for new submissions. We welcome continued input from the user community. Comments can be sent via the "contact us" link at www.icmje.org. The Committee will consider comments received before May 1, 2011, when we prepare the next iteration of the uniform conflict of interest disclosure form.

The complexity, subjectivity, and emotionality of conflict disclosure ensure that some will consider this vehicle for reporting to be excessively burdensome, while others will think it falls short in one area or another. We cannot, however, let the perfect be the enemy of the good. We hope that the revised ICMJE form will be another step toward simplifying and standardizing reporting of conflicts of interest. A more uniform reporting process will alleviate the confusion that prevails when multiple journals use different reporting formats and will ease the reporting burden on the members of the biomedical research community so they can pursue the research that will improve the care that we can deliver to our patients. With these thoughts in mind, we encourage all journals to adopt the new version of the uniform disclosure form.

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Editor's note: This editorial is being published simultaneously in all ICMJE member journals.

Disclaimer: Dr. Sahni's affiliation as representative and past president of the World Association of Medical Editors (WAME) does not imply endorsement by WAME member journals that are not part of the ICMJE.

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Testosterone Deficiency and Replacement in Older Men

William J. Bremner, M.D., Ph.D.

It is now clear that men have gradual declines in average serum testosterone levels as they age. These decreases begin by middle age and continue into old age.[1,2] Although the decreases are substantial in many men, they are quite variable. Some men, even in old age, maintain serum testosterone levels similar to those of healthy young men.

Many of the physical and behavioral changes that occur in men as they age are similar to those that occur in younger men with hypogonadism. These changes include decreases in muscle mass, strength, bone mass, and sexual function and increases in body fat, fatigue, and depressed mood. It is therefore reasonable to ask whether testosterone deficiency could be causing some of the adverse physical and behavioral changes of aging and whether these could be improved with the administration of testosterone.

The diagnosis of testosterone deficiency in older men is complicated by the fact that many older men (more than 20% in some studies) have testosterone levels that are lower than the normal range in younger men. In addition, the clinical presentation of male hypogonadism is nonspecific and overlaps with that of other illnesses and with the aging process itself. Therefore, it is frequently unclear in caring for individual older patients whether the diagnosis of hypogonadism is appropriate and whether testosterone administration might be helpful or might instead cause adverse effects.

Two articles in this issue of the *Journal* address these important issues.[3,4] Wu et al.[3] report on a population survey of 3369 men, 40 to 79 years of age, in eight European centers. Results of the survey with respect to subjects' general, sexual, physical, and psychological health were compared with morning measurements of total and free testosterone levels in the subjects' serum. Among many symptoms surveyed, three sexual symptoms (poor morning erection, low sexual desire, and erectile dysfunction) and three general symptoms (inability to perform vigorous activity, depression, and fatigue) were associated with low testosterone levels. Further analysis showed that the presence of at least three sexual symptoms in a man with a total testosterone level of less than 11 nmol per liter (3.2 ng per milliliter) could be used to define late-onset hypogonadism. This conclusion was validated in a second data set in the same study. These conclusions are a valuable addition to earlier research, as well as to society guidelines,[5,6] which have also proposed the combination of symptoms and low testosterone levels to establish the diagnosis of late-onset hypogonadism. The difficulty with using symptoms alone to define late-onset hypogonadism was highlighted by the finding that more than 25% of men with normal testosterone levels had similar sexual symptoms.

Among older men with testosterone deficiency, can we replace testosterone in an effective and safe manner? Many studies involving limited numbers of men have shown that the administration of testosterone results in improved muscle mass and strength, increased bone mass, and other positive effects.[7] None of the studies have been of sufficient size or duration to adequately address potential risks, such as the risk of prostate disease. The study by Basaria et al.[4] was designed to assess whether leg-muscle strength in older men with severe limitations in mobility was increased as a result of testosterone administration. Community-dwelling men 65 years of age or older with a testosterone level of 100 to 350 ng per deciliter (3.5 to 12.1 nmol per liter) were randomly assigned to receive a transdermal gel containing testosterone (to achieve testosterone levels of 500 to 1000 ng per deciliter [17.4 to 34.7 nmol per liter]) or placebo. The 209 participants had a high prevalence of hypertension, diabetes, hyperlipidemia, and obesity. During the experimental phase, the testosterone group showed greater leg and arm strength than did the placebo group but also had higher rates of cardiovascular adverse effects. The excess of cardiovascular events in the testosterone group led the data and safety monitoring board to recommend early termination of the study. Of initial concern was the fact that 10 of the 106 men receiving testosterone had adverse cardiac events, as compared with 1 of the 103 men receiving placebo. Further investigation at the request of the data and safety monitoring board showed excesses of "cardiovascular-related" events in the testosterone group. These results are surprising, since many studies with cumulative numbers of subjects greater than those reported here have not detected substantial increases in cardiovascular risk during testosterone administration (including many studies in which subjects achieved the same or higher serum testosterone levels, some for longer periods of time).[8] As the authors state, there is a clear possibility that their results are due to chance.

Many readers may disagree with the decision of the data and safety monitoring board to terminate the study early. Results of studies terminated early may differ from those of larger, longer-term studies. Also, readers will speculate that the higher rates of adverse events in the testosterone group may have been due to the fact that the two groups of men had different baseline char-

acteristics, with a higher rate of hyperlipidemia and statin use and of hypertension in the testosterone group before the experimental interventions. To me, the decision of the data and safety monitoring board seems reasonable. For whatever reason, there were higher rates of cardiovascular disease in the group of men who were receiving testosterone in this study than in their counterparts who were receiving placebo.

Although this result sounds a note of caution in general concerning testosterone administration in older men, it certainly should not deter investigators from proceeding with additional, larger studies of testosterone administration in well-characterized groups of older men to more clearly outline benefits and risks. Similarly, it should not prevent clinicians from prescribing testosterone replacement for well-established late-onset hypogonadism, although it should provide some new caution about the administration of testosterone in older men who have an extensive history of cardiovascular disease and immobility.

Ultimately, we will need large, carefully designed trials of testosterone administration, perhaps along the lines of the Women's Health Initiative. Such trials should include a sufficient number of subjects to allow the assessment of key clinical outcomes, such as bone-fracture rates, muscle strength, and avoidance of falls, and an assessment of the role of testosterone replacement in the prevention of psychiatric disease, as well as the risks for prostate, cardiovascular, and other adverse outcomes. The numbers of older men receiving testosterone are large and increasing. We owe it to our patients and their families as well as to our physician colleagues to have much better data and guidelines for the administration of this critical hormone.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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1. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. J Clin Endocrinol Metab 2001;86:724-31.
2. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. J Clin Endocrinol Metab 2002;87:589-98.
3. Wu FCW, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010;363:123-35.
4. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med 2010; 363:109-22.
5. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:2536-59.
6. Wang C, Nieschlag E, Swerdloff R, et al. Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. J Androl 2009;30:1-9.
7. Page ST, Amory JK, Bowman ED, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip, strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab 2005;90:1502-10.
8. Fernández-Balsells MM, Murad MH, Lane M, et al. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2010;95:2560-75.