

The results showed that there was an approximate doubling of nondisjunction for the 3 chromosomes considered together when sperm from men 18 to 29 years were compared with sperm from men 50 to 60 years of age. The numbers were small: 0.11% for the former and 0.27% for the latter. Most of the disomy involved the X and Y chromosomes, with disomic sperm containing XY outnumbering disomic sperm containing XX or YY by about 2:1.

The authors concluded that nondisjunction does occur during male meiosis. It mainly involves sex chromosomes and increases with age, approximately doubling between the ages of 20 to 60 years. However, they point out that the risk for producing trisomic offspring is low: In men over the age of 50 years, only 0.27% of sperm were disomic for the X and/or Y chromosome. The authors also caution that it is not known if disomic sperm compete equally with normal (monosomic)

sperm for fertilization. If not, then the clinical relevance of disomic sperm may be moot.

Griffin DK, et al. *Hum Mol Genet* 1995;4:2227-2232.

Editor's comment: *This is the first direct evidence that meiotic nondisjunction increases with age in males. As the authors mention, the effect is small, which probably explains why epidemiologic studies have failed to detect a paternal age effect. They rightfully point out that their results provide little basis for suggesting that older men, like older women, be offered prenatal testing for age-related trisomy. In reality, however, since older women are usually married to older men, such testing may be undertaken anyway.*

William A. Horton, MD

A Double-Blind, Placebo Controlled Study of the Effects of Low-Dose Testosterone Undecanoate on the Growth of Small for Age, Prepubertal Boys

Twenty-three short prepubertal boys (11 to 14 years of age) with heights at or below the 3rd percentile were randomized into a double-blind study comparing the effects of oral testosterone undecanoate (TU; 20 mg qd for 6 months) versus placebo on various growth parameters. Treatment was preceded and postluded for 6-month periods. The aim was to assess whether very low doses of TU could accelerate growth velocity (GV) without unduly advancing bone age (BA) in boys with constitutional delay of growth and puberty (CDGP).

The investigators reported that 11 boys taking TU showed a significantly greater GV compared with 12 boys receiving placebo (GV = 5.84 vs 3.38 cm/y), a difference of 2.46 cm/y attributed to 6 months of TU treatment. The effect on BA, axillary and pubic hair, lean body mass, and testicular volume was negligible. Nocturnal growth hormone (GH) concentrations measured over an 8-hour period (every 20 minutes) did not change with treatment. Measurement of serum testosterone, before and following testosterone administration in the morning, revealed an average 10-fold increase at 1-hour postingestion. Within 8 hours, the increase fell to less than 4-fold. There was a projected fall to base level by 16 hours. The authors appropriately emphasized that the efficacy of anabolic or sex steroids in promoting short-term growth and increasing final height is as yet unproven, and that carefully designed, controlled, prospective trials to determine the optimal regimen for growth acceleration would be of great potential therapeutic benefit to many children.

Brown DC, et al. *Arch Dis Child* 1995;73:131-135.

Editor's comment: *The authors are to be commended for designing a well-planned study of the type needed for the stated purposes. Unfortunately, this study was too brief to provide*

adequate information regarding how best to treat CDGP patients with TU. Specifically, 6 months of treatment that provided small alterations in GV is prone to quantitative misinterpretation. A GV increase of approximately 1.25 cm in 6 months (projected to be at a rate of 2.5 cm in 12 months) is at great risk of being in error. A 0.5 cm error at one measurement and a 0.5 cm error in the opposite direction 6 months later will produce an error of 1.0 cm/y or 2.0 cm/y projected. Some smoothing of the error may occur when groups of children are studied, but the error remains significant. This is not to say that low doses of TU do not increase GV. Nevertheless, errors in measurements taken over only a 6-month period of treatment can lead to erroneous conclusions. Even if one accepts that there may be no significant error, 6 months of treatment yielding a gain of 1.25 cm, is relatively insignificant in producing the alterations that are therapeutically effective in boys with CDGP. Therefore, a 12 month study would have been much more useful.

Another possible error in the protocol was the morning administration of TU and the nocturnal measurement of GH concentrations 12 to 16 hours later, when serum testosterone levels have fallen to essentially the projected level of untreated boys. TU given in the morning may have been associated with increased GH levels during the day that went undetected because GH was not measured at that time.

Another advantage of a 12 month study is that BA acceleration often requires more than 6 months of observation to be recognized. Twelve months of treatment might have demonstrated inappropriate advancement of BA. The authors are invited to write a letter of rebuttal if they wish.

Robert M. Blizzard, MD