

First Editor's Comment: A complete reprint of this article will be sent to those who request it by e-mail to rblizzard@compuserve.com.

Unfortunately in nearly all studies of this type it is difficult to separate cause and effect. For example, does malnutrition or illness produce wasting and/or stunting accompanied by zinc deficiency or is the zinc deficiency etiologic in malnutrition and/or illness and/or stunting and/or wasting? In spite of this excellent study, the answer to this question remains an enigma. Moreover, zinc supplementation seems indicated to a much greater extent than currently in use.

Robert M. Blizzard, MD

Second Editor's Comment: Recently Brown et al published a meta-analysis of randomized controlled trials of the effects of supplemental zinc on the growth and serum concentrations of prepubertal children. A total of 33 studies were compiled demonstrating that zinc supplementation produced a significant positive height response and an increase in serum zinc levels. Growth responses were greater in those children with low weight for age and low height for age. This paper was reviewed in *Growth, Genetics & Hormones* in 2002 (Vol. 18, No. 4) and the importance of recognizing the value of zinc nutrition in "at risk" populations was emphasized.

However the note of caution noted below by Dr. Tarim should be kept in mind.

Fima Lifshitz, MD

Reference

1. Brown KH, et al. *Am J Clin Nutr* 2002;75:1062-1071.

Letter to the Editor:

I would like to add a precaution before suggesting zinc supplementation to anyone with nutritional growth retardation who lives in places where zinc deficiency may be prevalent. Iron deficiency which may co-exist with zinc deficiency may be aggravated during zinc therapy because these two minerals may block the intestinal absorption of each other.¹ Consequently, iron deficiency may also worsen growth retardation. Therefore, I suggest excluding iron deficiency, which is easier to diagnose than zinc deficiency, before initiating zinc supplementation.

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Reference

1. Lifshitz F, et al. Nutritional Growth Retardation. In: Lifshitz F, ed. *Pediatric Endocrinology 3rd Edition*. New York: Marcel Dekker, 1996:103-120.

Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus

Because multiple laboratory tests are used in the diagnosis and management of this disease, the quality of the scientific evidence supporting the use of these assays varies. Therefore, an expert committee drafted evidence-based recommendations for the use of laboratory analysis in patients with DM. An external panel of experts (DB Sacks, DE Bruns, DE Goldstein, NK Maclaren, JM McDonald and M Parrott) reviewed a draft of the guidelines, which were modified in response to the reviewers' suggestions, and other steps were taken to gain a consensus of expert opinions. The guidelines, as published in *Clinical Chemistry*, consist of an Executive Summary of one page providing specific recommendations based on data published or expert consensus. Several analyses are of minimal clinical value at the present time and measurement of them is not recommended. The entire article is 42 pages. Those clinicians treating diabetics should at least scan the article and closely scrutinize the Executive Summary.

Highlights of the Executive Summary are now presented:

Glucose should be measured in an accredited laboratory to establish the diagnosis of DM and to screen high-risk individuals. Blood should be drawn after an overnight fast. Glucose should be measured in plasma. If plasma cannot be separated from cells within 60 minutes, a tube with glycolytic inhibitor should be used. On the basis of biological variation, glucose analysis should have analytical imprecision less than 3.3%, bias less than 2.5%, and total error less than 7.9%.

The OGTT is not recommended for the routine diagnosis of type 1 or 2 DM. The key limitation of the OGTT is its poor reproducibility. It is recommended for establishing the diagnosis of gestational DM.

Because of the imprecision and variability among glucose meters, they should not be used to diagnose DM and have limited value in screening. Noninvasive glucose analyses cannot be recommended at present as replacements for plasma glucose or measurements by an accredited laboratory. Glycated hemoglobin (GH_b) should be measured at least biannually in all patients with DM. US laboratories should use GH_b assays certified by the National GH Standardization Program

(NGSP) as traceable to the DCCT reference. GH_b levels should be maintained at <7% and the treatment regimen should be reevaluated if GH_b is >8% as measured by NGSP - certified methods.

Routine measurement of genetic markers is not recommended for the diagnosis or management of patients with DM. Likewise, autoimmune markers lack specificity and are not recommended for routine diagnosis or screening of DM.

An annual search for micro albuminuria should be performed on patients without clinical proteinuria. To be useful, semiquantitative or quantitative screening

tests must be shown to be positive in >95% of patients with micro albuminuria. Positive results must be confirmed by quantitative testing in an accredited laboratory.

All adults with DM should receive annual lipid profiles.

Sacks DB, et al. *Clinical Chemistry* 2002;48:3,436-472.

Editor's Comment: *This is only the very essential infrastructure of the Executive Summary. The article is endowed with significant substance.*

Robert M. Blizzard, MD

Mutations of the *Great* Gene Cause Cryptorchidism

The investigators previously identified a mutant strain of mice (*crsp*) with high intraabdominal bilateral cryptorchidism due to a 550 kb deletion of the proximal arm of mouse chromosome 5. Within the deleted region, the investigators identified a G-protein coupled receptor gene (GPCR) termed "G-protein coupled receptor affecting testis descent" or *Great*. *Great* was expressed in testis, brain, and skeletal muscle. In the current paper, the authors developed a mouse "knock-out" model of this gene. The phenotypes of the wild type mice and those who were heterozygous (*Great*^{+/−}) were normal. However, animals who were homozygous for the mutation (*Great*^{−/−}) were similar in phenotype to *crsp* mice. In (*Great*^{−/−}) mice, there was failure of development of the gubernaculum (the ligament whose shortening is partially responsible for the inguinal-scrotal phase of testicular descent). The investigators then cloned human *GREAT* (chromosome 13q12-13), an 18 exon gene encoding a GPCR, and analyzed its structure in 61 men with bilateral (N=31) or unilateral cryptorchidism. In one subject with bilateral cryptorchidism, a heterozygous loss-of-function mutation was identified (exon 8, A C, Tyr222Pro was identified). The authors concluded that mutations in *GREAT* are responsible for cryptorchidism in some human males but the frequency of a *GREAT* as a cause of cryptorchidism mutation remains to be determined.

Gorlov IP, et al. *Hum Molec Genet* 2002;11:2309-2318.

First Editor's Comment: *GREAT had been cloned by other workers and termed LGR8 - Leucine-rich repeat-containing GPCR. Relaxin had been identified as a ligand for GREAT. However, testicular descent is normal in the Relaxin "knock-out" male mouse. *Insl3* - insulin-like factor 3 - is a member of the relaxin family and is synthesized in the testes; its loss results in bilateral cryptorchidism due to maldevelopment of the gubernaculum. Thus, *Insl3* may be the natural ligand*

for GREAT. While homozygous loss of Great is needed for cryptorchidism in mice, apparently its heterozygous loss appears to be sufficient in humans to cause this malformation; the mechanism(s) of this species difference is/are not defined at present.

*There are two phases of testicular descent - transabdominal and inguinal-scrotal. The first phase is conditioned by failure of development of a cranial suspensory ligament mediated by testosterone. The second phase is stimulated by development of the gubernaculum, demonstrated to be related to the interaction of *Insl3* and *GREAT*. Mullerian duct inhibitory factor and its receptor also play a role in this phase of testicular descent. The manuscript also suggests that it would be inappropriate to tell another gentleman that he is "not so GREAT!"*

Allen W. Root, MD

References

1. Overbeek PA, et al. *Genesis* 2001;30:26-35.
2. Nef S, Parada LF. *Nat Genet* 1999;22:295-299.
3. Teixeira J, et al. *Endocrine Rev* 2001;22:657-674.

Second Editor's Comment: *This article is the best I have read concerning the development and descent of the testes. Work in mice and in humans is blended in describing the embryological development of both testes and ovaries. The 11 authors come from diverse and multiple fields - urology, genetics, pharmacology, embryology, molecular biology, etc., which largely accounts for the excellence of the article. Those interested in gonadal development, normal and/or abnormal, will be gratified in reading the article in its entirety.*

Robert M. Blizzard, MD