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### MANAGEMENT OF CHILDREN WITH INTERSEX CONDITIONS: PSYCHOLOGICAL AND METHODOLOGICAL PERSPECTIVES

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Pediatric medicine has undergone considerable upheaval in the past few years over the treatment of children with disorders of sexual differentiation. There have been challenges to all aspects of traditional practice, including sex assignment, genital surgery, the role of the patient and parents in decision-making, disclosure of medical details, the composition of the treatment team, and nomenclature. These challenges have been met with serious attention by pediatricians and other health professionals involved in the care of these children, and there has been considerable discussion of the merits of changes to current practice.<sup>1-8</sup> This report considers the status of the evidence relevant to treating children with intersex conditions, with particular emphasis on psychological and methodological issues.

#### BACKGROUND

For 50 years, treatment of children with intersex conditions was guided by the belief that gender identity results from social rearing rather than biological factors, provided that gender-confirming genital surgery is done early in life.<sup>9,10</sup> Although there have always been questions about this policy, anecdotal evidence generally suggested that it produced good outcome.<sup>11,12</sup> The policy and the evidence used to support it have recently been subject to detailed scrutiny because of several well-publicized reports. This includes a case of ablatio penis raised female who was unhappy with the assigned sex,<sup>13,14</sup> conference reports of XY males with absent or malformed penis due to cloacal exstrophy reared as females who declare themselves to be boys,<sup>15</sup> and reports of adverse outcomes from intersex patients.<sup>16,17</sup>

Several issues have emerged from recent discussions (Table 1). The focus has been on sex assignment and genital surgery, with traditional treatment and challenges often seen in polar terms (Table 2). Discussions have often been acrimonious, and recommendations based

on personal beliefs or anecdotes, although it is clear that the interests of patients are best served by careful application of evidence.

#### EVIDENCE REGARDING SEX ASSIGNMENT

##### Determinants of Gender Identity

Decisions regarding sex assignment require recognition of the complexity of gender identity. Gender identity cannot be simply predicted from any single factor; neither is it always consistent with sex of rearing, nor is it simply related to extent of prenatal hormone exposure. The publicized individual with ablatio penis<sup>14</sup> was reared as a boy early in life and it is unclear how this contributed to his gender identity. Another individual with a similar history but with earlier female reassignment had a different outcome, particularly female gender identity.<sup>18</sup> To date, there have been no published systematic studies of individuals with cloacal exstrophy, and case reports indicate variations in gender identity, with no clear indication of the percentage who identify as males or are unhappy as females.<sup>19,20</sup>

The most systematic evidence regarding gender identity comes from two conditions. Females with congenital adrenal hyperplasia (CAH) overwhelmingly identify as female.<sup>21-23</sup> The very small minority of females with CAH who are unhappy as females or live as males are not necessarily those with the greatest genital virilization or

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Table 1

**Controversies in Treatment of Children with Intersex Conditions**

**Sex assignment**

What criteria should be used?  
 What determines gender identity?  
 When (if ever) is gender identity fixed?

**Genital reconstructive surgery**

Is it necessary? (Why?)  
 When should it be done?  
 What are its benefits and risks?

**Decision-making**

Who makes the decisions?  
 When should decisions be made?  
 What information is used to make the decisions?  
 What support is available?

**Information-sharing**

What are the parents told at the time of diagnosis and decision-making?  
 What does the child learn and when?  
 What support is available?  
 What is the best way to share information?

**Involvement of mental health professionals**

Should psychologists or psychiatrists be part of the diagnosis and treatment team?  
 Does counseling to families facilitate decision-making?  
 Does routine and continuing counseling to patients and families improve outcome?

the most prenatal androgen excess. Males with micropenis have not been studied as extensively as females with CAH, but they identify as males when reared that way and appear to function well.<sup>24,25</sup>

There is little systematic evidence to guide decisions about sex assignment in other intersex conditions.<sup>20</sup> Recent studies of individuals with micropenis and those with ambiguous genitalia with perineoscrotal hypospadias of varying etiology suggest that gender identity is generally consistent with sex of rearing.<sup>26,27</sup> But, for several reasons, caution is necessary when generalizing from these studies. First, a substantial proportion of participants (about 25%) were dissatisfied or questioned their sex of rearing. Second, as is typical of retrospective studies, patients who were dissatisfied or atypical were probably underrepresented: 30% of eligible patients did not participate and some participants elected not to answer sensitive questions. Third, outcome was assessed with a few items of unknown sensitivity. Fourth, those reared as boys were subjected to more surgery than those reared as girls.

**Recommendations Regarding Sex Assignment**

Sex assignment for an intersex child is one of the most difficult decisions made by parents and health professionals, though it is natural to seek simple solutions. But just as it is no longer tenable to assume that gender identity is always consistent with the sex of rearing, evidence indicates that it is equally unwise to consider gender identity to result directly from fetal androgen exposure (inferred from genital appearance or another indicator). Although other aspects of behavior may relate to degree of fetal androgen exposure, gender identity does not. For example, among females with CAH, degree of prenatal androgen exposure (inferred from genetic mutation, salt-wasting status, and degree of genital virilization) is moderately associated with interest in boy-typical activities and sexual orientation.<sup>23,28-30</sup> but not gender identity.<sup>21-23</sup> Therefore, it is crucial to separate aspects of outcome (Table 3).

There is sufficient evidence to suggest that 46,XX CAH patients be reared as girls, given the documented good outcomes associated with such rearing. Nevertheless, there are no systematic studies of those reared as boys. It is reasonable to suggest that 46,XY micropenis patients be reared as boys, given the small studies of good outcomes in such cases and the need for surgery with rearing as girls, but it would be helpful to have more evidence comparing quality of life and sexual function in those reared as boys vs. girls. In all other cases, decisions will need to be made with the limited information available from case reports. All children should be assigned as boys or girls. Rearing children as intersex is not advocated by health professionals or activist organizations (including ISNA). Parents and health professionals should realize that an intersex individual may elect to change gender later in life. The accuracy of the sex assignment can only be judged by the patient. It is essential to recognize that gender identity is not synonymous with gender-role behavior or sexual orientation, so that childhood tomboy behavior in girls or homosexuality should not be taken as indications of incorrect sex assignment.

**EVIDENCE REGARDING SURGERY**

Decisions regarding genitoplasty should be considered in light of the evidence regarding the stated need for surgery. Current practice is predicated on several assumptions: (1) sex-typical genital appearance is necessary for gender identity development consistent with rearing sex and for healthy psychological adjustment; (2) adjustment is hindered by unusual-appearing genitalia, through disruption in parent-child bonding, reactions from caretakers and peers, and difficulty in forming sexual relationships; (3) corrected genitalia are necessary for sexual activity, particularly intercourse. But some intersex patients as adults have

Table 2

**Summary of Traditional Care and Current Challenges in the Treatment of Children with Intersex Conditions**

<b>Sex Assignment/Gender Identity</b>	<b>Traditional Practice</b>	<b>Challenge</b>
Determinant of gender identity	sex of rearing	prenatal androgen
Stability of gender identity	fixed by age 2	develops throughout life
Role of genitalia	crucial to identity & adjustment	reflect brain masculinization
Decision-maker	physician	family
<b>Genital Surgery</b>		
Rationale	anatomy to match rearing sex	surgery is for comfort of others
Consequences	facilitates gender identity	inhibits gender change
	facilitates adjustment	impairs sexual function
	facilitates sexual intercourse	
Decision-maker	physician	patient

Table 3

**Aspects of Outcome in Children with Intersex Conditions**

<b>Gender Identity</b>	Sense of self as male or female
<b>Gender-role Behavior</b>	Aspects of behavior that differ between males and females; is multidimensional
<b>Sexual Orientation</b>	Sex of target of sexual arousal
<b>Sexual Functioning</b>	Sexual sensitivity Potential for orgasm Capacity for intercourse, if desired
<b>Psychological adjustment ("quality of life")</b>	Happiness Absence of distress Satisfaction with specific aspects of life e.g., psychosexual adjustment

The surgical outcomes most often studied have been genital appearance and adequacy of genitalia for peno-vaginal intercourse. But the assumptions behind surgery and the concerns of patients make it clear that other outcomes need to be considered, particularly those related to the quality of sexual experience, including sensitivity and satisfaction, and general quality of life (Table 3).

**Physical Outcomes of Surgery**

There are no systematic outcome data regarding genital appearance and sexual function, especially for current surgical procedures. There are reports of suboptimal cosmetic outcome and self-reported sexual function, but they are based on limited assessments of selected patients with surgery of varying quality.<sup>26,27,31</sup> Therefore, it is difficult to know how surgery affects sexual function, and the factors that account for variations across individuals. Measures of clitoral responsiveness suggest normal nerve conduction after surgery,<sup>32</sup> but it is unclear whether this translates into normal sensitivity. It is also important to remember that intercourse is only one part of sexual activity, and surgery to facilitate intercourse might compromise orgasmic response.

There is optimism that current techniques used by skilled surgeons produce better cosmetic and functional outcomes now than in the past,<sup>33</sup> but confirming evidence is essential. Outcome studies require detailed assessments and comparisons with subjects without intersex conditions, given the complexity of sexual response, the variations in arousal and orgasm among typical individuals without genital surgery,<sup>34</sup> and the limitations of self-report in assessing sexual response.<sup>35</sup>

complained that surgery does not prevent problems and may actually exacerbate them, because of adverse cosmetic and functional outcomes from surgery. These critics further contend that problems arise from the undue focus on the genitalia and not their appearance per se.

## **Psychological Impact of Genital Appearance**

Both physicians and intersex advocates are concerned about psychological problems associated with intersexuality. Physicians suggest that children who look different will have difficulty forming a coherent self-concept, including gender identity, and receive negative reactions from others, with adverse effects on adjustment and life satisfaction. Some intersex advocates argue that problems result from stigma and shame induced by messages from physicians and parents that atypical genitalia are unacceptable.

Neither set of concerns have been empirically validated – or refuted. There are no data showing the relative importance or unimportance of normal-appearing genitalia for psychological outcome. The existence of gender dysphoria in individuals with and without intersex conditions indicates that normal-appearing genitalia are not sufficient for gender identity consistent with rearing sex, but there is no systematic study of the role (if any) that genital appearance plays in the development of gender identity. It is widely believed that boys with a small penis are teased, causing poor peer relationships and adjustment problems. Although this has not been systematically studied, males with micropenis appear to do well.<sup>24,25</sup> Relevant data from boys with hypospadias who had received genital surgery show psychological adjustment similar to that of control boys, with little relation between adjustment and genital appearance, but depression is associated with more surgery and hospitalizations.<sup>36</sup>

Evidence from individuals with other physical conditions reinforces the complex contributors to outcome. Problems in individuals with intersex conditions might not arise from specific aspects of the condition or treatment itself, but from the stresses they impose on the patient and the family.<sup>37</sup> Children's stress may arise from their own experiences, such as surgery, repeated physical exams and hospitalizations, responses to their unusual genital appearance, or from changes in parent-child interactions brought about by parents' stress. Parent stress may be independent of the child's physical illness or may result from it, for example, from concerns about the child's genital appearance, responsibilities of caring for a sick child, or financial burdens brought about by the child's illness. Additional risk may arise from children's problems with peer relationships,<sup>38</sup> but even here the cause is not simple. Peer problems are affected by more than physical appearance, such as frequent school absences and sex-atypical behavior.<sup>37,39</sup> Furthermore, the association between peer relationships and adjustment is bidirectional: poor peer relations place a child at psychological risk, but poorly adjusted children have difficulty making friends to start.

## **Psychological Outcome in Intersexuality**

Thus, there are many paths by which mental health might be affected in individuals with intersex conditions, but there is no evidence regarding any of them. Further, there is surprisingly little evidence about the ultimate mental health outcomes hypothesized to be affected by these paths, primarily because such studies are difficult. Scientific studies may undersample individuals with problems, but reports from intersex activists may overrepresent those with problems.<sup>40</sup>

The most systematic evidence regarding mental health in intersex individuals comes from females with CAH. Several studies show that their mental health is not different than that of controls, although they may have specific problems with body image and psychosexual function.<sup>41-46</sup> There are not enough data to know whether outcome is related to genital appearance or surgery.

These results on good adjustment might be surprising in light of assumptions described above. However, they are consistent with evidence that chronic illness, trauma, and other adverse life events have only transient effects on adjustment in the majority of people. Among individuals with a variety of physical disabilities (including quadriplegia), there is often an immediate period of depression, but after a short period (weeks to months), most report positive well-being.<sup>47,48</sup>

This mismatch between expectation and evidence is an example of the tendency to attribute outcome to the cause that is most salient, in this case, the appearance of the genitalia or the intersex condition itself. But, outcome is influenced by many factors, including temperament and life circumstances. People are not accurate at predicting factors that influence life satisfaction in others because they only focus on a small set of contributors.<sup>49</sup> This means that attributions about problems among intersex individuals must be validated empirically.

## **Recommendations Regarding Surgery**

The lack of systematic outcome data makes decisions about genital surgery very difficult. There are insufficient data regarding the functional consequences of genital surgery, but there are also insufficient data regarding the effects on a child of living with atypical genitalia. It is likely that the effects of both genital surgery and genital appearance are not the same for all individuals. Perceptions of and responses to the situation may be more important than its objective nature, and psychological support may help families develop coping strategies to foster mental health. It is important to remember that decisions should be made in the best interests of the child and not the parents.

## CONCLUSIONS

The discussions surrounding the treatment of children with intersex conditions have crystallized the assumptions and evidence underlying treatment. Changes to treatment must be informed by evidence or, consequently, dilemmas will arise again. Despite gaps in the evidence regarding outcome, there is some information available to guide treatment.

First, sex assignment cannot be based on the assumption that gender identity is determined by either sex of rearing or degree of fetal androgen exposure. Most individuals with 46,XX CAH do well when reared as girls, but there are no systematic studies of those reared as boys. Most individuals with 46,XY micropenis appear to do well when reared as boys, but this approach should be viewed cautiously until there is more evidence about psychological and sexual outcome with male vs. female rearing. There is insufficient evidence regarding other causes of intersexuality and cloacal exstrophy, but all children should be assigned as girls or boys, with the recognition that some may change gender later in life.

Second, decisions about surgery would benefit from systematic evidence regarding functional outcome of current procedures and consequences of atypical genitalia. Sexual function involves more than cosmetic

appearance and the ability to have intercourse. Given the dearth of evidence, assumptions and biases should be clearly articulated to families.

Third, there is a pressing need for additional systematic evidence that addresses the complex determinants of psychological outcome. It is not sufficient to examine outcome only in relation to characteristics of the intersex condition and its treatment. There must be recognition and consideration of the child's temperament, family situation, culture in which the child lives, and benefits of psychoeducational interventions to reduce stress and facilitate coping.

Outcome itself must be defined from the perspective of the patient, and include quality of life. The components of outcome are not interchangeable (Table 3).

Fourth, translation of findings to treatment requires that studies meet important methodological criteria regarding sampling, assessment, and inferences consistent with the limitations of the methodology (Table 4). It is important to avoid being swayed by studies that support preconceptions or provide simple solutions.

Recent debates have improved treatment of children with intersex conditions by forcing an articulation of assumptions and examination of evidence. Resolution of current controversies requires a commitment to

Table 4

### Considerations in Evaluating Outcome Studies of Children with Intersex Conditions

#### Sampling

- What was the population sampled?
- What proportion of potential participants were studied?
- How do the participants compare to the nonparticipants?
- How would results change if nonparticipants have different outcome?
- What was the comparison group?
- Were the samples of intersex and comparison individuals large enough to see effects of clinical significance, including group differences and predictors of outcome?

#### Outcome Assessment

- Were different aspects of outcome carefully differentiated?  
For example, was gender identity measured independently of gender role?
- Was each outcome assessed in detail with reliable and valid measures?
- Were patients compared to controls to be sure that outcome is specific to an intersex condition?
- Were hypothesized predictors of outcome assessed in detail with reliable and valid measures?

#### Inferences

- Were appropriate statistical comparisons made so that inferences can be made to the population?
- To what populations can results be generalized?
- Can outcome be empirically attributed to intersex condition itself?
- Can outcome be empirically attributed to specific factors related or unrelated to intersex condition?
- Are inferences appropriately qualified in light of (inevitable) methodological limitations?

evidence-based care and a recognition that outcome in intersexuality cannot be simply predicted from medical factors alone.

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## Commentary: Intersex Issues - A Series of Continuing Conundrums

Dr. Blizzard has abstracted and commented upon two extraordinarily important manuscripts by Migeon and colleagues. These investigators have provided the first analysis of the long-term outcome of 75 adults with male pseudohermaphroditism or micropenis (46XY or 45X/46XY) managed as children at Johns Hopkins Hospital. These children had been assigned to either the male or female gender. All of 18 patients with feminine external genitalia (androgen insensitivity syndrome or complete gonadal dysgenesis) were raised as females; 5/18 subjects with micropenis (stretched length <1.9 cm) without hypospadias were reared as females. In 39 subjects with ambiguous genitalia, 18 of whom were raised as female and in whom in depth information concerning their "sexuality" was sought, the assigned sex was at least "satisfactory" in the majority. Indeed, those reared as male had greater incidence of atypical external genitalia and greater dissatisfaction with perceived "body image". In general, however, the

outlook for normal adult heterosexual adjustment reared as either male or female was quite good in this group.

Until more complete data are available, these observations can serve as the basis upon which to counsel the parents of a neonate with male pseudohermaphroditism in regard to their choice in the gender assignment of their offspring. Dr. Blizzard correctly states that the "paternalistic" approach to medical practice is no longer tenable.

*In my opinion, in the context of this psychosocial emergency, it remains extremely important that the experienced physician assist, perhaps even guide, the parents through the decision making process. In the absence of androgen insensitivity, complete gonadal dysgenesis, deficiency of P450<sub>side chain cleavage</sub> or 17-hydroxylase/17-20 lyase, and related disorders, it seems most appropriate to rear the incompletely virilized male in the masculine gender if there is at all sufficient penile corpus to do so or to permit its surgical amplification.*

Dr. Blizzard critically analyzes the current thinking concerning the problem of when to perform reconstructive genital surgery in the patient with male pseudohermaphroditism assigned to the female gender.

*In my opinion, he correctly rejects the extremist position that no reconstruction be undertaken until the patient herself can consent. Clearly, this approach will lead to great duress in the lives of the patient and her parents. (One can barely imagine the stress that a parent would be under in raising a child whose gender may change or that of the child who will surely learn at a surprisingly early age that her genitalia differ from those of other girls.) While each child must be considered individually, cliteroplasty during infancy and vaginoplasty at adolescence seem reasonable in my opinion once feminine gender has been assigned until the long-term efficacy of earlier vaginal reconstructive techniques have been evaluated.*

Dr. Blizzard discusses the issue of intra-cultural differences in attitude toward the problem of intersex and the challenging question of whether all children with 46XX female pseudohermaphroditism should be reared as females.

*His thoughtful and insightful comments are seconded by this writer, although my inclination is to rear all females with virilizing congenital adrenal hyperplasia as girls. Individualization of care and informed parental choice*

*are the keystones upon which management of the neonate with atypical external genitalia must be based.*

*Readers who wish to be brought up-to-date concerning some of the conundrums of intersex issues and what the current concepts are concerning intersex issues will benefit from Dr. Blizzard's commentary.*

Blizzard RM. *Pediatrics* 2002;110(3):616-621.

Allen W. Root, MD

**Dr. Blizzard's Comment:** *Comments about one's commentary are not necessarily legitimate. However, I comment relating the above abstract and editorial comment by Dr. Root to the lead article in this issue by Dr. Sheri Berenbaum. Her studies and writings are always logical, intelligent, and scientifically based. In her article, Dr. Berenbaum demonstrates the applicability of my adjectives used to describe her approaches to solving the conundrums of intersex. I highly recommend each reader contemplate her description of the complexities in this field. Hopefully others will approach the conundrums of intersex in the same contemplative way as does she.*

Robert M. Blizzard, MD

#### Letter to the Editors:

In the December 2002 edition of *Growth, Genetics & Hormones* (Vol. 18. No. 4), two articles (Imaizumi K, et al. *Am J Med Genet* 2002;107:58-60; Kurotaki N, et al. *Nat Gen* 2002;30:365-366) were abstracted under the title *A Gene as a Major Cause of Sotos Syndrome Has Been Identified*. The authors are reported to state that the identification of a deletion or mutation of this mutated gene on chromosome 5 will sometimes help in the diagnosis of Sotos syndrome, etc. Both Dr. Judy Hall and Dr. William Horton gave cogent editorial comments.

However more recent evidence indicates that additional knowledge gained by Kurotaki and others should be considered by clinicians and investigators attempting to use identification of a deletion or mutation of this mutated gene (NSD1) to help in the diagnosis of Sotos syndrome. Specifically, at the ASHG meeting in October 2002, Kurotaki et al from Japan reported finding point mutations and deletions of the NSD1 gene in a large series of patients and Clech et al from Paris reported their findings in 39 patients. Only 14 were felt to have typical Sotos syndrome; four had a

NSD1 deletion of paternal origin. It had previously been suggested that based on similarity of the phenotypes, Sotos and Weaver syndromes might be allelic disorders. Rahman et al from the UK reported that >40% of patients with typical Sotos syndrome had intragenic mutations in NSD1 and 3 of 7 patients with Weaver syndrome had intragenic NSD1 mutations. In each of these series, patients with a combination of overgrowth and mental retardation, but without typical features of either Sotos or Weaver syndrome, were not found to have deletions or intragenic mutations of NSD1.

These reports collectively demonstrate that the majority of patients with typical Sotos and Weaver syndrome have intragenic mutations or deletions of NSD1, and thus, represent allelic disorders. However, the combination of overgrowth and mental retardation represents a heterogeneous phenotype in which only a portion is accounted for by abnormalities of NSD1.

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### Editorial Comment:

Sotos syndrome and Weaver syndrome are both overgrowth syndromes beginning usually prenatally. Such overgrowth continues during childhood. These two syndromes are similar in many respects; in respect to overgrowth, mental retardation, large hands and feet, advanced bone age, and tall stature but, usually, adult height within the normal advanced percentiles. However, they do differ in certain subtle respects. The patient with Sotos syndrome (cerebral gigantism) has a head that is dolichocephalic. The occiput tends to be flat in the patients with Weaver syndrome. The face tends to be smaller. There are hypoplastic facial bones and

macrognathia in Weaver syndrome, but pointed chin and normal mandibular development prompts one to think more of Sotos syndrome. The joints are limited in motion often in Weaver syndrome with limited elbow, ankle, wrist, hip, and knee extension. The long bones are widened or splayed in Weaver syndrome and camptodactyly is frequent. Further details concerning these two syndromes can be pulled from the pediatric database, although the update listed is 1994 (<http://www.icndata.com/health/pedbase/files/sotosynd.htm> - or - [weaversy.htm](http://www.icndata.com/health/pedbase/files/weaversy.htm)). Comparable data can also be found on the web at <http://www.nlm.nih.gov>. At this web site you will have a choice to enter "Weaver".

Robert M. Blizzard, MD

### Abstracts from the Literature

## Circulating Levels of IGF-1 Directly Regulate Bone Growth and Density

Previous studies by LeRoith and co-workers and Ueki et al have demonstrated that selective loss of liver-derived insulin-like growth factor-1 (IGF-1) or of acid labile subunit (ALS) does not substantially impair murine growth and development despite marked decline in circulating levels of IGF-1.<sup>1,2</sup> This has led to the suggestion that only the IGF-1 produced locally by bone is necessary for linear growth.<sup>3</sup>

In order to explore this question further, LeRoith and his colleagues developed double "knock-out" animals which were deficient in both liver IGF-1 and ALS (LID-ALSKO), and compared these with animals deficient only in liver IGF-1 (LIDKO) or ALSKO. As anticipated, serum concentrations of IGF-1 were decreased markedly, -65% in ALSKO, -75% in LIDKO, and -90% in LID-ALSKO relative to control animals with normal hepatic IGF-1 and ALS production. However, the rate of IGF binding protein-3 (IGFBP-3) degradation was also increased in these animals; thus free IGF-1 values were increased modestly in LIDKO (+150%), minimally in ALSKO (+108%), and markedly in LID-ALSKO animals (+350%). Growth hormone and insulin concentrations were greatly increased in LID-ALSKO mice. The clearance of IGF-1 was markedly accelerated in ALSKO (32 minutes) and LID-ALSKO (18 minutes) as compared with control (69 minutes) and LIDKO (73 minutes) mice, reflective of lack of binding of IGF-1 to IGFBP-3/ALS.

Intrauterine growth of all animals was apparently normal. By 3 weeks and 4 weeks of post natal age (Figures), the length and weight of the LID-ALSKO mice were less than those of the intact animals. Linear growth of the LIDKO and ALSKO animals did not differ from controls. However, the rate of weight gain of ALSKO mice was impaired to the same extent as that of the LID-ALSKO group. Tibial length, and heights of germinal, proliferating, and hypertrophic zones of the proximal

tibial growth plate, were significantly diminished in the LID-ALSKO mice but not in the two single "knock-out" groups. On the other hand, femoral length, total and cortical bone density, periosteal circumference, and cortical and trabecular bone volume were diminished in all "knock-out" groups, but to a substantially greater degree in the LID-ALSKO animals. Administration of exogenous IGF-I increased linear growth, femoral length, and size of the proximal tibial growth plate, as well as IGFBP-3 concentrations, in all groups. IGF-1 mRNA levels in bone were similar in all groups.

The investigators concluded that *circulating* IGF-1 was important for linear and appositional bone growth and bone mineralization and that its effects were mediated through actions on periosteal osteoblasts as well as upon chondrocytes within the epiphyseal growth plates.

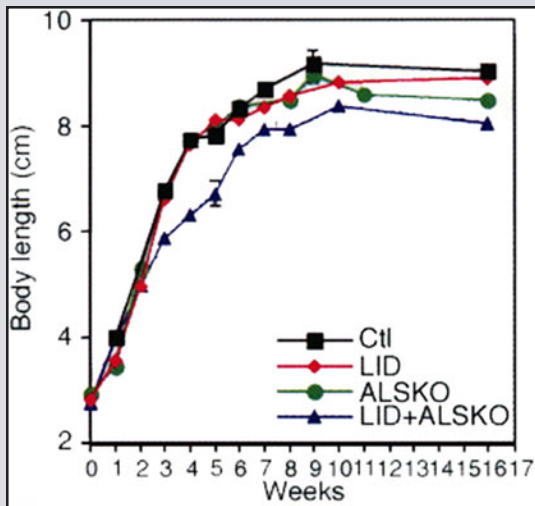
Yakar S, et al. *J Clin Invest* 2002;110:771-781.

**First Editor's Comment:** *This important paper establishes the necessity of circulating IGF-I for normal growth and bone mineralization. It demonstrates that osseous synthesis of IGF-I alone is insufficient for normal linear growth of bone and mineral deposition. Thus, reexamination of the "somatomedin hypothesis" suggests that both liver derived and locally synthesized IGF-I are necessary for normal bone metabolism. Interestingly, "knock-out" of any of the IGFBPs has little effect upon the phenotype of the mutant mouse, but their over expression results in inhibition of growth.<sup>4</sup> One wonders what the phenotype of the mouse that lacks IGF-I, IGFBP-3, and ALS might be ... possibly lethal?*

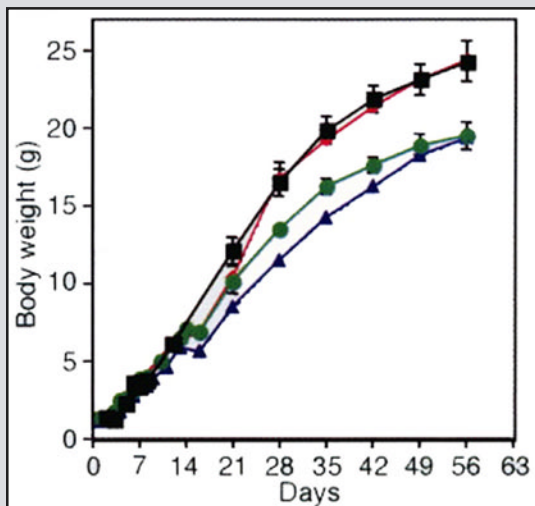
Allen W. Root, MD

Figures

Postnatal growth in LID+ALSKO mice



Body length was measured from nose to anus at weekly intervals ( $n = 20-30$  mice per group).



Body weight was measured at weekly intervals from birth to the age of 8 weeks ( $n = 30-60$  mice per group).

Reprinted with permission from Yakar S, et al. *J Clin Invest* 2002;110:771-781.

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1. LeRoith D, et al. *Endocrine Rev* 2001;22:53-74.
2. Ueki I, et al. *Proc Natl Acad Sci USA* 2000;97:6868-6873.
3. Kaplan SA. *Growth Genetics & Hormones* 2002;18:38-39.
4. Silha JV, Murphy LJ. *Endocrinology* 2002;143:3711-3714.

**Second Editor's Comment:** In *Growth, Genetics & Hormones* (Vol. 18, No. 3), an important lead article entitled *Somatomedin Hypothesis: Time for Reexamination* was written by Dr. Solomon Kaplan. He has been asked to write an editorial comment.

**Dr. Kaplan's Comment:** The paper by Yakar et al extends and amplifies the findings in a previous publication by the authors<sup>1</sup> on the role of circulating IGF-1 in promoting longitudinal growth in mice. They had already shown that despite inactivation of the IGF-1 gene in the liver, resulting in reduced concentrations of circulating IGF-1 by as much as 75%, the growth of the animals was not impaired. Their findings were consistent with the growing body of evidence against the validity of the somatomedin hypothesis, which holds that the effects of growth hormone on longitudinal growth are mediated through hepatic production of IGF-1.<sup>2</sup>

IGF-1 circulates in the serum largely as a 150-kDa complex comprised of the IGF-1 molecule, IGF binding proteins (mostly IGFBP-3), and the acid labile subunit (ALS). Others had previously shown that ALS knockout (ALSKO) mice experienced only mild growth retardation despite profound disruption of the circulating IGF system.

Yakar's current paper reported the effects of double gene disruption of the IGF system: inactivation of the hepatic gene for IGF-1 (LID) combined with ALSKO, on bone growth and density. In the mice carrying the double gene deletion, there was a reduction of circulating IGF-1 concentrations by as much as 85 to 90%; the animals also experienced significant growth impairment. There was a diminution in the amount of circulating IGFBP-3 protein and also in the free IGF-1 fraction. Loss of ALS led to more rapid disappearance of 125-I labeled IGF from the serum because absence of the ALS protein

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leads to proteolytic cleavage of IGFBP-3 and loss of its protective binding of IGF-1. The authors conclude that a minimum concentration of IGF-1 in the serum, higher than what they observed in the double gene-deletion mice, is necessary for normal bone and somatic growth.

Following administration of IGF-1 by injection, the animals with the double gene deletion experienced increased serum IGF and IGFBP-3 concentrations accompanied by restoration of normal bone growth and modeling, as well as increased somatic growth. These findings are consistent with their observation that the restoration of normal growth can be accounted for by increased serum IGF-1 concentrations above the minimal levels necessary for normal growth to occur.

This paper provides confirmatory evidence that hepatic derived IGF-1 and acid labile subunit are not necessary for normal growth provided minimal serum levels are maintained from non-hepatic sources including autocrine/paracrine production by target tissues.

Solomon A. Kaplan, MD

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1. Yakar S, et al. *Proc Natl Acad Sci USA* 1999;96:7324-9.
2. Daughaday WH, et al. *Nature* 1972;235:107.

## The BRCA2 Gene's Role in Fanconi Anemia and Various Cancers

Fanconi anemia (FA) is an autosomal recessive disorder in which affected subjects have great susceptibility to neoplasia early in life, including acute myeloid leukemia and squamous cell carcinoma. Bone marrow failure is also frequent, as well as mutations in at least 8 groups of FA patients (A, B, C, D<sub>1</sub>, D<sub>2</sub>, E, F and G) and germline mutations in six of these have been identified in 6 genes (A, C, D<sub>2</sub>, E, F and G). The FA cells manifest many broken and misshapen chromosomes reflecting that FA proteins participate in the repair of DNA damage, either stimulating or inhibiting normal repairs. Five of the 6 genes previously described combine in a multi-subunit nuclear complex which activates by ubiquitination of the protein product of a sixth gene (FANCD2) which is involved in the process of DNA repair. Howlett et al<sup>1</sup> identified a 7th gene by demonstrating that homozygous "loss of function" mutations occurring in the BRCA2 gene (causing breast cancer as does the BRCA1 gene) occurs in a subset of patients with FA.

Witt and Ashworth<sup>2</sup> stated in the introduction of their commentary; "Important discoveries are so neat and satisfying that, in retrospect, they seem obvious. Howlett et al disclosed that the inheritance of two defective copies of the BRCA2 breast cancer susceptibility gene can lead to FA. The BRCA2 protein is thought to be important in the repair of DNA damage. Cells lacking BRCA2 inaccurately repair damaged DNA leading to gene mutation and progression of tumors and are particularly sensitive to DNA cross-linking agents. Howlett et al demonstrated that one of the previously unidentified FA genes (FANCD1) is BRCA2." No BRCA1 mutations were found in the patients studied by Howlett et al. However, all the authors of all three papers speculatively agreed that the 6 previously cloned genes are linked in a common pathway with BRCA1 and BRCA2 genes.<sup>1-3</sup>

Venkitaraman<sup>3</sup> in his closing comments stated; "The network which connects BRCA and FA proteins in DNA

repair includes at least two other molecules - ATM (mutated in ataxia telangiectasia) and CHEK2 - whose inactivation is also associated with carcinogenesis in several tissues. Although the precise functional connections between the molecules in this network remain obscure, it is clear we are glimpsing an important tumour suppressor pathway whose disruption may underlie many different types of human cancer."

1. Howlett NG, et al. *Science* 2002;297:606-609.
2. Witt E, Ashworth A. *Science* 2002;297:534.
3. Venkitaraman AR. *Lancet* 2002;369:1343-1345.

**First Editor's Comment:** *Heterozygous inactivating germline mutations in BRCA1 and BRCA2 have been linked to increased susceptibility to breast and ovarian cancer in women.<sup>1</sup> In the tumors that develop in these patients, there is loss of heterozygosity of BRCA1 or BRCA2. Both BRCA1 and BRCA2 are important for repair of DNA damaged by exposure to ionizing radiation and cross-linking, and do so by interrupting the cell cycle while promoting repair of the damaged DNA strands.<sup>1-3</sup> The carboxyl-terminal domain of BRCA2 likely binds to single strands of DNA at the site(s) of a double stranded DNA break and facilitates the binding of other repair factors such as RAD51, an important member of this family. This article is of interest because it demonstrates the difference in phenotypes that result from heterozygous as compared to homozygous germline mutations in BRCA2. How this mutation affects somatic growth and the reproductive endocrine system is unclear. However, Wajnrajch et al<sup>4</sup> found aberrations of endocrine function in 44/54 primarily prepubertal patients with FA.<sup>4</sup> Abnormalities included short stature with mean height SDS -2.35 (due to growth hormone insufficiency in 44%), hypothyroidism (36%), hyperinsulinemia (72%), impaired glucose tolerance (25%), and diabetes mellitus (2%). Skeletal maturation*

was approximately one year delayed behind chronologic age; predicted adult height in 22 subjects was -1.24 SDS.

## References

1. Wilson JH, Elledge SJ. *Science* 2002;297:1822-1823.
2. Yang H, et al. *Science* 2002;297:1837-1848.
3. Witt E, Ashworth A. *Science* 2002;297:534.
4. Wajnrajch MP, et al. *Pediatrics* 2001;107:744-754.

**Second Editor's Comment:** The phenomena described in the papers given as references are phenomenal. The first 3 references read as a package will permit any reader not informed about such matters to advance into the upper elementary levels, both in respect to understanding the physiology and pathophysiology of Fanconi Anemia, breast cancer, and to the interactions of genes and gene products.

Allen W. Root, MD

Robert M. Blizzard, MD

## Serum Zinc in Infants and Preschool Children in the Jeddah Area: Effect of Diet and Diarrhea in Relation to Growth

Dr. Bahijri has written a thoughtful analysis of the etiology and effect of zinc deficiency on wasting and stunting of 728 children in 5 age groups (4-6, 6-<12, 12-<24, 24-<36, and 36-72 months). Using the concept of weight for height, the subjects were classified according to their grade of wasting, and using the concept of height for age, the subjects were classified according to their grade of stunting. The dietary, auxological, and chemical evaluations were carefully done in accord with the most modern standards and techniques. The study was undertaken to determine the prevalence of zinc deficiency in the Jeddah (Saudi Arabia) area among preschool age children, to see whether such a deficiency is a cause of retarded growth, to determine whether a relationship exists between height for age and serum zinc concentrations, and if possible to determine the causes of zinc deficiency.

The authors presented serum zinc levels in the various age groups for subjects: (1) without stunting and wasting, (2) with various grades of wasting, (3) with various grades of stunting, and (4) with both stunting and wasting. Many subjects in each group had zinc levels <10.4  $\mu\text{mol/L}$  which is frequently cited in the literature as the cut off for normalcy. However, the lowest mean serum zinc levels were found in the patients in the group with stunting and wasting. Whereas those who had neither stunting nor wasting had the highest levels. The older stunted children (group 3) had lower zinc levels than those found in the younger children. All patients with wasting (group 2) had hypozincemia.

The authors concluded that diarrhea rather than low dietary intake mostly accounts for the low zinc levels in infants (4-12 months). As the subjects passed the 24 month mark, diet deficiency became the presumed major cause of hypozincemia and this cause became more dominant as the etiology in the oldest age group (36-72 months).

The importance of zinc in biology is well reviewed, including that zinc is known to influence cell division, growth and development, as well as sexual maturation. It is needed also as a membrane stabilizer, and is

essential for the integrity of the immune system. More than 100 enzymes require zinc as a cofactor, and zinc seems to be involved in the proper storage and release of insulin, growth and repair of tissues, wound healing, ability to taste food, production of prostaglandins, mineralization of bone, blood clotting, function of vitamin A, and functions of the thyroid hormones.

Not commonly known, an important predisposing factor for zinc deficiency is the extensive use of cereal protein which limits the availability of zinc due to high phosphate and phytate content. The recommended dietary allowance of the Food and Nutrition Board and the National Academy of Sciences in the United States is 15 mg/day for adult males and 12 mg/day for adult females, with higher recommended levels during pregnancy and lactation. Requirements for infants and children are relatively high in relation to body size because of increased requirements for physical growth.

The best sources for zinc in the diet are meat and fish; the bioavailability of zinc from animal products is considered to be greater than that from plants. Diarrhea is associated with zinc deficiency and low serum zinc concentration. Suggestions have been made that growth retardation commonly seen in children in developing countries is related to zinc nutritional deficiency.

Unfortunately, it was not feasible to interpret the direct effect of zinc deficiency on wasting or stunting although a significant majority of subjects with wasting and/or stunting had severe deficiency. The author summarized: "The result of this work shows a high incidence of low serum zinc levels among Jeddah-area infants and young preschool children, which is associated with diarrhea and wasting in the first two years of life, and generally low dietary intake, wasting and/or stunting in older children. Zinc supplementation is recommended for certain categories of subjects to improve appetite and hence dietary intake, immunocompetence, and anthropometric measurements."

Bahijri SM. *Annals of Saudi Medicine* 2002;21:324-329.

**First Editor's Comment:** A complete reprint of this article will be sent to those who request it by e-mail to [rbizzard@compuserve.com](mailto:rbizzard@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.<sup>1</sup> 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.

Omer Tarim, MD  
Director of Pediatric Endocrinology  
Uludag University Faculty of Medicine  
Bursa, Turkey

#### Reference

1. Lifshitz F, et al. Nutritional Growth Retardation. In: Lifshitz F, ed. *Pediatric Endocrinology 3<sup>rd</sup> 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<sub>b</sub>) should be measured at least biannually in all patients with DM. US laboratories should use GH<sub>b</sub> assays certified by the National GH Standardization Program

(NGSP) as traceable to the DCCT reference.  $\text{GH}_b$  levels should be maintained at <7% and the treatment regimen should be reevaluated if  $\text{GH}_b$  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*<sup>+/−</sup>) were normal. However, animals who were homozygous for the mutation (*Great*<sup>−/−</sup>) were similar in phenotype to *crsp* mice. In (*Great*<sup>−/−</sup>) 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

## Kyphosis in Turner Syndrome

Elder and colleagues performed lateral thoracic spine and standing anterior-posterior scoliosis radiographs in 25 of 30 girls between the ages of 5 and 18 years with Turner Syndrome. Excessive kyphosis was defined as an A-P curvature greater than 40%, vertebral wedging as an A-P deformity greater than 5% at any vertebral body, and scoliosis as a lateral curve greater than 10%. Karyotype, age, height, weight, and body mass index percentile, and use and duration of growth hormone, oxandrolone (anavar), and/or estrogen were recorded and entered into a linear regression analysis to determine significant predictors of kyphosis or kyphosis and wedging. Of the 25 subjects studied, 15 (60%) had abnormal radiographic findings. Ten (40%) had excessive kyphosis, 10 (40%) had vertebral wedging, and 5 (20%) had scoliosis. All girls older than 14 years of age (N=8) had excessive kyphosis and wedging.

The subjects were  $12.0 \pm 3.6$  years old. Sixty percent had a 45X karyotype, 80% had received GH therapy, and 36% had received estrogen therapy. Logistic regression analysis revealed that chronologic age alone was predictive of excessive kyphosis/wedging, ( $P=0.053$ ). Stepwise linear regression analysis also showed that chronologic age was predictive of the degree of kyphosis ( $P=0.032$ ). None of the other variables were predictive. The authors remarked upon the high prevalence of vertebral wedging and excessive kyphosis in their study population. They noted that this is markedly increased compared with the reported prevalence of 3% in the general population. The cause of the scoliosis is apparently multi-factorial, but may include mechanical factors, osteoporosis, adolescent growth spurt, and intrinsic bone defect. Girls with Turner syndrome are known to have a significant number of bony abnormalities, including hypoplasia of cervical vertebrae, and hemivertebrae, although these were not found in the study population. The authors also note

that their inability to determine the contribution of age and hormonal therapies to the development of kyphosis may be the result of the small number of subjects studied.

PediaLink.org (Vol. 109) 6/2002. PPE 93.

**Editor's Comment:** *With such a huge number of Turner subjects (40%) with reported excessive kyphosis, it is surprising that there are not more reports of its prevalence. Indeed this study suggests all girls with Turner syndrome should have routine radiographic screening and should be evaluated by an orthopedist. It is also surprising that more information is not available regarding the probable pathogenesis of these deformities. Since the vast majority of subjects in the study had received or were receiving GH, its contribution to the development of the kyphosis is impossible to determine. However, information from subjects in larger multi-centered databases of individuals who have and have not been treated with GH, would be important to access in order to determine its possible role in the genesis of this deformity. Some information regarding the prevalence of kyphosis in children treated with GH who either had or did not have GH deficiency also could be an important comparison group. Unfortunately this study raises many more questions than it answers, but will probably stimulate other centers to evaluate girls with Turner syndrome. Perhaps a multi-centered survey could help provide a better understanding of this problem. The Growth, Genetics and Hormones Editorial Board welcomes a letter to the editor from readers who have knowledge of data pertinent to the questions raised.*

William L. Clarke, MD

## Cancer Risk in Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann Syndrome (BWS) is a well-known syndrome of overgrowth. Macrosomia, neonatal hypoglycemia, midline abdominal defects, macroglossia, ear pits and the predisposition to embryonic cancers in infants and young children, including Wilms tumor, hepatoblastoma and neuroblastoma are the important clinical features of BWS. It is now possible to correlate the phenotypic features with specific genetic disturbances. Most recently, alterations in the imprinting and methylation of several genes in the 11p15 region have been implicated in its etiology. Different patients have different involvement phenotypically and genetically.

De Baun et al have correlated anomalies of DNA methylation of one of the relevant genes, *H19*, in patients with cancer, as compared to those without. Those with cancer are less likely to have abnormalities of the methylation of another gene in the area, *LIT1*. Conversely, abnormalities of methylation of *LIT1* are more likely to be associated with abnormal wall defects and macrosomia. Affected individuals with paternal uniparental disomy of *11p15* are more likely to have associated hemihypertrophy, cancer, and hypoglycemia than those without uniparental disomy.

These findings suggest that all individuals with BWS deserve a precise molecular evaluation in order to be

able to appropriately screen for expected complications. The cluster of genes related to BWS has been studied extensively because of its involvement in the epigenetic phenomenon of imprinting. Abnormal and loss of imprinting of the *IGF2* gene found in this region is present in a number of tumors. *H19* plays a role in the methylation of *IGF2* and so its abnormal methylation or expression may increase the risk of cancer by its relation to *IGF2*.

In the evaluation of BWS, one would expect that cancerous tissue might have different imprinting or methylation than other easier to study tissues. This is particularly frustrating when hemihypertrophy is present. It is interesting to note that any hypertrophy observed in patients with BWS is suggestive of mosaicism. To date, all of the reported patients with paternal UPD of 11p15 are in fact, mosaic. Thus, the two sides of the body probably have different manifestations of the Beckwith-Wiedemann gene cluster.

The hypoglycemia that can be seen in Beckwith-Wiedemann Syndrome also is associated with

uniparental paternal disomy. Since hypoglycemia can result in secondary mental retardation, both screening and watching for hypoglycemia in patients with BWS is extremely important during infancy.

DeBaun, et al. *Am J Hum Genet* 2002;70:604-611.

**Editor's Comment:** *Most of the conditions recognized to be involved in genomic imprinting are associated with abnormalities of growth. Thus, the possibility of genomic imprinting must be considered in any syndrome of abnormal growth. Further evaluation can obviously lead to unique insights about pathogenesis as are being developed in the BWS. This work is allowing recognition of the heterogeneity existing in BWS that may predispose to severe complications.*

Judith G. Hall, OC, MD

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*GROWTH, Genetics, & Hormones Index for Volume 18 (2002)*

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