

Microphallus: Eventual Phallic Size Is Dependent on the Timing of Androgen Administration

Husmann and Cain produced 2 animal (rat) models of hypogonadotropic hypogonadism in utero. Persistent microphallus and sexual infantilism occurred. Treatment with dihydrotestosterone (DHT) in large doses was begun at 7, 28, 56, and 84 days of age. To evaluate the effect of treatment, the length (stretched) and weight (autopsied) of the penis was measured. The androgen receptor protein found in the penile corpora, which is necessary for penile growth and which disappears as the penis reaches end-stage growth, was measured immunohistochemically.

Early exposure to androgens (before 56 days) resulted in diminutive penile growth, apparently due to accelerated downregulation of the androgen receptor. Although late administration of androgen enhanced penile length significantly (Figure 1), penile weights (reflecting penile widths) remained subnormal (<2.5 standard deviations [SD] below the normal mean).

The authors believe, based on current clinical and experimental data, that brief androgen therapy of the neonate with micropenis is necessary to determine if the phallus will respond; this is necessary in considering the sex of rearing. Interval therapy during childhood is not recommended. Treatment with androgens to stimulate maximal phallic growth should be initiated when the child is >12 years of age. The statement is made that evaluation of the adult population with a history of micropenis reveals that interval androgen therapy during childhood does not result in any significant size advantage of the penis compared with that of the untreated child. Unfortunately, delaying pharmacologic therapy does not result in complete development of phallic growth (weight, therefore width). Further studies reportedly are underway using the 2 rat models.

Husmann DA, Cain MP. *Urol* 1994;152:734-739.

Editor's comment: Although published in 1994, this article only recently was called to my attention (by Dr. Dan Metzger

of the University of British Columbia, and British Columbia Children's Hospital, Vancouver). A subsequent abstract was presented at the American Academy of Pediatrics meeting in April 1995 dealing with analogous studies in humans (Cain et al. "Micropenis Secondary to Hypogonadotropic Hypogonadism: Clinical Evaluation of Early Versus Late Hormonal Therapy").

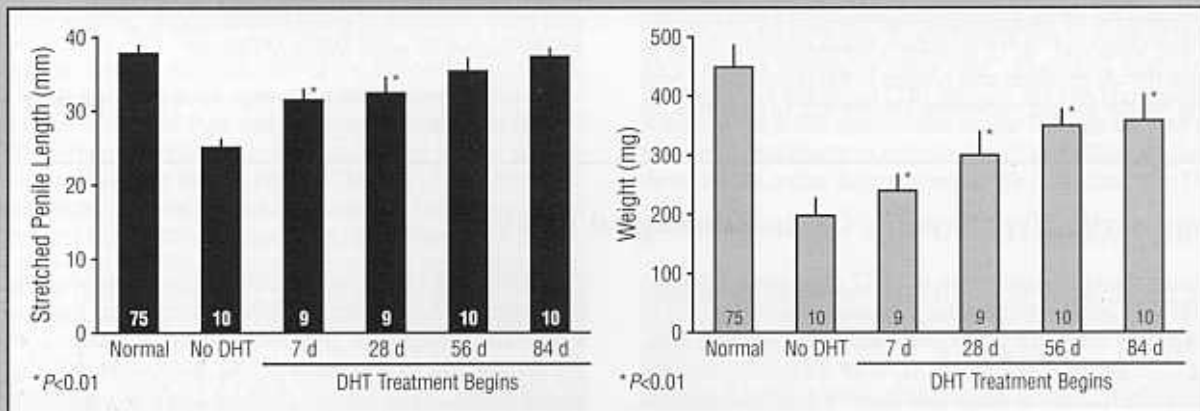
Twenty-five patients met the criteria of micropenis, ie, stretched penile length at diagnosis <2.5 SD below the mean and laboratory criteria consistent with gonadotropin hormone-releasing hormone deficiency. Early hormonal therapy was defined as >20,000 IU of human chorionic gonadotropin (HCG), <6 months treatment with testosterone cream, or combined HCG and testosterone treatment >3 months, by 7 years of age. Delayed treatment was defined as initiation of treatment after 11 years of age. Ten and 15 patients were categorized into each group, respectively.

The median age at diagnosis in the early treatment group was 4 years (range, birth to > 7 years). Final evaluation was at 20.5 years (16 to 28 years). All continued to have micropenis (<-2.5 SD). Fifteen received late treatment (median age, 15 years). Final evaluation was at 21.3 years (15 to 37 years). Stretched penile length was within normal range in 13 of the 15 patients treated late. The authors concluded that the clinical data support the following hypothesis: Improved phallic growth occurs with delayed hormonal therapy for micropenis secondary to hypogonadotropic hypogonadism.

These data from humans and the conclusions drawn are intriguing because of the similarity to the conclusions reached from studying the animal model.

Is the parallelism justified? My answer is: Possibly, but only possibly. The studies are important because of the attempt to study biochemical and anatomic science with treatment in the rat, and make clinical observations to support or reject the hypotheses derived from the animal studies. Congratulations are extended to the authors for their approach and efforts. However, questions to be raised include: (1) Were the phalluses

Figure 1



Penile length and weight are given for hypogonadotropic rats in relation to when dihydrotestosterone (DHT) treatment was begun. DHT treatment was effective in increasing length in all, but the increase was greater in rats treated late.

in the older age group relatively larger before treatment? The median age at diagnosis was 12 years, in contrast to 4.0 years for the early treatment group. (2) Were the widths of the phalluses greater in the late treatment group—before and/or after? Widths of the flaccid phallus could have been measured in the human, although this was not possible in the rat. (3) Were any of the children in the early treatment group deficient in growth hormone (GH)? GH deficiency is associated with micropenis, and particularly so when luteinizing hormone and GH are both deficient.

Regardless of the answers to these questions, extended delay of treatment (usually with androgens) for individuals

with micropenis is advisable. However, in my experience there are some young children who have significant psychological consequences as a result of not being able to bare themselves in the dressing room and/or stand to urinate with their peers. These children should be treated early, in my opinion, if they are being raised as males. Emphasis should be made in respect to interpreting these data that the subjects all allegedly had micropenis secondary to hypogonadotropic hypogonadism, and the observation and deductions should not be construed outside micropenis of this origin.

Robert M. Blizzard, MD

The Role of the Sulfonylurea Receptor in Insulin Secretion

Review of several articles permits the following deductions. In response to glucose, there is depolarization of pancreatic β cells, transient increase in cytoplasmic levels of Ca^{++} , and release of insulin. These processes are regulated by adenosine triphosphate (ATP)-sensitive K^+ channels that are blocked by glucose-induced increase in the cytosolic ratio of ATP:adenosine diphosphate (ADP), thus resulting in membrane depolarization and increased release of stored intracellular Ca^{++} .¹ Sulfonylureas stimulate insulin secretion by blocking ATP-sensitive K^+ channels, thus depolarizing pancreatic β cells. Aguilar-Bryan et al² have identified the genes for the endogenous sulfonylurea receptors (SURs) of the rat and hamster; they code for 1,582 amino acid proteins with a molecular weight of 177 kd and 13 transmembrane domains that share homology with the cystic fibrosis transconductance regulator (CFTR) and P-glycoprotein multidrug resistance (MDR) genes, both membrane transport proteins. The SUR is associated with but is not the K^+ receptor; it may regulate activity of this monovalent cation channel by affecting the phosphorylation of the K^+ channel or by sensing the ATP:ADP ratio.

In humans, the gene for the SUR is localized to chromosome 11p15.1, the same chromosomal location to which persistent hyperinsulinemic hypoglycemia of infancy (PHHI) has been linked. In patients with PHHI, an autosomal recessive disease of severe hypoglycemia and unregulated insulin secretion, Thomas et al³ demonstrated that the gene for the human SUR was abnormal. In 13 families, a homozygous guanine to adenine (G→A) mutation was present in the region of the gene coding for the second nucleotide binding fold (a portion of the

protein that interacts with cytosolic nucleotides), leading to an abnormal frameshift and inclusion of a stop codon, thus resulting in a truncated protein. In one family a G→A mutation in a codon preceding the exon coding for the second nucleotide binding fold region resulted in abnormal splice sites within this important region. These studies demonstrate the importance of the endogenous SUR in the regulation of insulin secretion. Inactivation of this receptor results in unregulated insulin secretion, implying that normally this receptor inhibits insulin release by maintaining the activity of the ATP-dependent K^+ channels within the pancreatic β cell.

1. Philipson LH, Steiner DF. *Science* 1995;268:372-373.
2. Aguilar-Bryan L, et al. *Science* 1995;268:423-426.
3. Thomas PM, et al. *Science* 1995;268:426-429.

Editor's comment: These articles illustrate the principle that many therapeutic agents reflect the action of endogenous substances as yet undiscovered. Thus, identification of the SUR implies the presence of an endogenous ligand for this receptor that must be involved in the regulation of insulin secretion and carbohydrate metabolism. One wonders about the chemical composition and source of this endogenous ligand and whether the endogenous ligand and/or its receptor might be aberrant not only in subjects with PHHI but also in patients with other disorders of energy homeostasis, perhaps with islet cell tumors or some forms of obesity.

Allen W. Root, MD

Lymphocytic Hypophysitis: Clinicopathological Findings

A clinicopathologic description of 16 (2 male and 14 female) patients with lymphocytic hypophysitis was presented. In 10 of the 14 female cases, the presentation was associated with pregnancy (2 in the second trimester, 2 in the third trimester, and 6 postpartum). Clinical presentations were diverse: 9 patients (56%) exhibited signs of expanding pituitary mass; 10 (63%) showed anterior pituitary hypofunction; 3 (19%) had diabetes insipidus; and 6 (38%) displayed hyperprolactinemia (4 associated with pregnancy and 2 attributable to a stalk effect). Three

(19%) died due to progressive unrecognized hypopituitarism. In 1 patient (6%), elevated growth hormone (GH) levels with a resultant increase in insulin-like growth factor 1 were demonstrated. In 4 patients (25%), autoimmune thyroiditis was found. In 10 patients (63%) a pituitary mass mimicking an adenoma on computed tomography scans or magnetic resonance images was demonstrated, with 8 showing evidence of suprasellar extension. Antipituitary antibody testing was performed in 2 patients and yielded negative results. The