

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: Clinicopathologic 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