

second 6 months of life) shown to have null mutations. Finally, males may be candidates in order to attain a greater adult height.

Adrenalectomized patients can be expected to attain full potential adult stature, as well as decreased virilization, less precocious puberty, and decreased obesity compared with conventionally treated controls. These patients may also be at decreased risk for adrenal crises during times of stress. Attempts to perform a "medical adrenalectomy" remain hypothetical, and it is not likely that it will become a candidate for gene therapy within the coming decades [32]. Thus, for specified cases, our database will elucidate the risks and benefits of adrenalectomy as compared to conventional medical treatment.

Specific Aim Ic: 1. To examine 128 children who were born from pregnancies at risk for CAH or who themselves are CAH-affected, and to compare dexamethasone (DEX)-exposed to DEX-nonexposed children in regard to cognitive (especially memory), psychiatric, and gender development. 2. To compare CAH girls with prenatal DEX exposure to those without, as well as to non-CAH children with or without DEX exposure in regard to the development of gender-role behavior and to brain lateralization as indexed by handedness.

Hypotheses: 1. As compared to non-DEX-exposed controls, prenatally DEX-exposed children may show: a) Impairments of cognitive development, especially of memory, b) Increased psychiatric symptomatology, especially of internalizing character (e.g., depression), and c) We have no theoretical reason to expect effects of DEX on gender development in non-CAH girls or in CAH boys, but want to explore these groups for such DEX effects. 2. As compared to prenatally DEX-unexposed CAH girls, DEX-exposed CAH girls will show: a) Decreased masculinized gender-role behavior, and b) Decreased non-right-handedness.

Background and Significance: On the psychological side, genetic females born with ambiguous genitalia who were not treated prenatally suffer consequences of the genital ambiguity: (1) Increased rates of gender-misassignment and -reassignment, with potential long-term consequences for gender identity development; (2) difficult genital surgery and frequent examinations of their genitalia during childhood, which renders trauma and may produce lasting psychologic sequelae; (3) characteristic behavioral changes.

Androgen effects on gender-related behavior and handedness. Excessive systemic androgen levels during prenatal development of female fetuses influence not only genital development but also brain differentiation and subsequent behavior. Corresponding shifts in gender role behaviors, as expected on the basis of animal models, and possibly enhanced by way of reactions of the social environment to the genital ambiguity, have been demonstrated in girls and women with CAH by a variety of interview- and questionnaire-based studies in several countries and were recently confirmed by systematic behavior observation. The spectrum of behavioral effects ranges from mild or marked tomboyish behavior of childhood [33-36] to increased adolescent/adult bisexuality and lesbianism [37, 38]; through full male identification with request for sex reassignment surgery and legal gender change in adolescence [39, 40] or adulthood [41]. The etiologic factors in the latter probably include prolonged ambiguity of the external genitalia, body image issues, and psychosocial factors in interaction with direct brain effects on hormones [41-43]. In addition, the genital abnormalities and often multiple corrective surgeries needed affect social interaction, self image, romantic and sexual life, and fertility. As a consequence, many of these patients, and the majority of women with the salt-losing variant, appear to remain childless and single [44, 45]. Prenatal androgens are also suspected of influencing the development of hemispheric lateralization of the brain. For instance, Geschwind and Behan (1981) emphasized the role of prenatal testosterone in increasing left-handedness in males [46]. Our previous finding of increased sinistrality in girls with CAH as compared to unaffected sisters [47] is compatible with such an effect of androgens on the brain.

Treatment of prenatal androgen excess and the prevention of its somatic and psychological consequences requires the capacity of prenatal diagnosis of CAH and of prenatal glucocorticoid replacement.

Prenatal diagnosis of CAH in at-risk fetuses is possible in the first trimester by HLA typing or by DNA analysis of genes within the HLA complex in chorionic villus cells, or, in the second trimester, by measurement of 17-hydroxyprogesterone or $\Delta 4$ -androstenedione in amniotic fluid [48, 49]. A pregnancy is thought to be at risk for CAH offspring if the mother has previously given birth to a CAH-affected child, if the parents or other close relatives are CAH-affected, or if the parents are known to be genetic carriers.

Prenatal treatment of a CAH-risk pregnancy must begin soon after diagnosis of pregnancy, because sexual differentiation of the genitalia occurs in human fetuses between 9 and 13 weeks of gestation [50, 51], and must continue until CVS or amniocentesis can be performed. In CAH-affected females, treatment is continued until birth. Treated females are born with normal or only slightly virilized external genitalia [49]

The existence of **behavioral effects** of DEX treatment cannot be simply derived from the genital outcome. In mammals, differentiation of genitalia and brain differ in timing, in their requirements for dose/duration interaction, and in the androgen metabolites involved. Thus, effects of prenatal DEX on androgen-influenced