gender role behavior in males. Dr. Paul Trautman, a child psychiatrist, Dr. Susan Baker, a psychoendocrinologist, and Dr. Heino Meyer-Bahlburg, a psychoendocrinologist who is a noted expert on gender disorders, will continue to collaborate with us in the cognition and behavioral studies (see letter of agreement from Dr. Trautman and Dr. Meyer-Bahlburg, **item i**).

Effects of early prenatal dexamethasone on the cognitive and behavioral development of young children. Animal studies have shown lasting effects of perinatal corticosteroid treatment on the nervous system and behavior in rodents and primates, including various aspects of both social and cognitive functioning [127]. Dexamethasone of human pregnancies needs therefore to be evaluated for possible behavioral side effects. In a 1992 study of the effects of early prenatal dexamethasone exposure on cognitive and behavioral development, behavior problems, and temperament, Trautman et al. studied 26 consecutively identified children aged 6 months to 51/2 years whose mothers had been dexamethasone-treated during pregnancy because their offspring was at risk for congenital adrenal hyperplasia (CAH), compared with 14 children from untreated CAH-risk pregnancies [127, 128]. Three children in each group were CAH-affected. Assessments were performed by way of mother-completed standard questionnaires. No significant differences in cognitive abilities or behavior problems were identified. On temperament questionnaires, prenatally dexamethasone-exposed children showed more "shyness" ($p<0.004$), greater "emotionality" ($p<0.03$), less "sociability" ($p<0.04$), and a trend for "greater avoidance" ($p<0.07$) than unexposed children. Prenatally dexamethasone-exposed infants also had significantly higher "internalizing" ($p<0.002$) and total "problem" behavior scores ($p<0.05$). The results should be considered preliminary until they have been replicated by a larger scale sample of children. We therefore propose to do such a replication study, and in addition, to reexamine the children previously studied, for stability of the effects over time. If the results are replicated, they would form the basis of a more in-depth study of the children by direct examination, which will require separate funding in a future grant.

Androgen effects on gender-related behavior and handedness. Excessive systemic androgen levels during prenatal development appear to 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, 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 [135-138] to increased adolescent/adult bisexuality and lesbianism [139]; through full male identification with request for sex reassignment surgery and legal gender change in adolescence [140, 141] or adulthood [142]. 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 [143, 144].

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 [145, 146]. Preventive prenatal dexamethasone exposure is expected to improve this situation. However, the existence of behavioral effects of dexamethasone treatment cannot be simply derived from the genital outcome. In mammals, the sexual differentiation of the brain largely occurs after that of the genitalia. In line with this is the finding by Dittmann et al. [147] that marked differences in behavioral masculinization between two subsyndromes of classical CAH (salt wasters and simple virilizers) cannot be explained by differences between the two groups in the degree of genital masculinization at birth. Finally, genitals and brain differ in their requirements for dose/duration interaction and androgen metabolites involved. Thus, effects of prenatal dexamethasone on androgen-influenced behavior must be assessed separately from its effects on the genitals. For this purpose, we had included very sensitive measures of gender role behavior in our side effect study [127], but the very small number of affected cases evaluated at that time precluded a preliminary analysis of that subsample. Now we propose to again include the gender scales in the side-effect replication study since our sample of affected children has increased sufficiently for statistical analysis of the combined sample. We will also examine the gender behavior of boys since nothing is known of the potential dexamethasone effects here.

We propose to Investigate the effect of androgens on hemispheric lateralization of the brain by the study of sinistrality. Geschwind and Behan emphasized the role of prenatal testosterone in increasing left-handedness in males [148]. As we have demonstrated increased sinistrality in girls with CAH as compared to unaffected sisters, we have shown an effect of androgens on the brain [149]. When we treat male and female fetuses (even for a short time) who are at risk for CAH with dexamethasone, we are suppressing prenatal testosterone levels. Sinistrality may be the most direct way to demonstrate clinically the effect of prenatal