

The investigators suggest that the impairment of respiratory function in PWS may be due in large part to an abnormality in the function of a hypothalamic respiratory regulatory center rather than to excessive weight, that rhGH may have had a direct central stimulatory effect on this structure, and that the hypoventilation of PWS may be amenable to treatment.

Lindgren AC, et al. *Eur J Pediatr* 1999;158:936-940.

**Editor's comment:** Although current data did not explore the possibility that the increased respiratory effort during rhGH treatment of PWS subjects was due, at least in part, to increase in lean body mass and improved muscle strength, these findings support the suggestion that rhGH may be useful in the management of PWS, which is a conclusion that this reviewer has been very reluctant to draw. Lindgren et al (*Acta Paediatr Scand* 1998;87:28-31) also have reported that in a controlled, randomized trial of rhGH in PWS subjects, rhGH led to increases in growth, lean body mass, physical activity, and endurance, and

improvements in behavior. Carrel et al (*J Pediatr* 1999;134:215-221) confirmed these findings and also observed that rhGH improved physical strength, agility, and inspiratory and expiratory muscle strength in PWS. Since chronic respiratory insufficiency often leads to pulmonary hypertension and right ventricular heart failure, and is a major cause of death in PWS, treatment of PWS may be expanded to include diet, exercise, and rhGH. Before rhGH becomes the standard of care for PWS, however, further controlled and, hopefully, double-blind studies must be conducted that confirm these reports and justify the large expenditures that such treatment will engender, as well as demonstrate that the quality of life of rhGH-treated PWS subjects is superior to that achieved by a rigorous residential dietary and exercise program alone.

Several abstracts and editorial comments regarding the treatment of PWS have appeared in *GGH* in 1999 (see Vol 15, pages 10 and 11).

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## Postnatal Sex Reversal of the Ovaries in Mice Lacking Estrogen Receptors $\alpha$ and $\beta$

The investigators developed mice in which both estrogen receptors (ERs)  $\alpha$  and  $\beta$  had been disrupted or "knocked out" ( $\alpha\beta$ ERKO) by breeding phenotypically normal mice heterozygous for loss of either one or the other ER.  $\alpha\beta$ ERKO mice were phenotypically intact and survived normally. Adult male mice in which both ERs had been eliminated had normal internal genitalia but slightly smaller testes than control animals, with loss of germinal epithelium and subnormal spermatogenesis; they were infertile, which is consistent with earlier reports of the  $\alpha\beta$ ERKO male—indicating that estrogen and the ER are necessary for complete spermatogenesis. Adult female mice in which both ERs had been disrupted also had normal but hypoplastic internal genitalia, indicating that neither ER is necessary for Müllerian duct differentiation. Having ER $\alpha$  is necessary for uterine response to estrogen. The ovaries of  $\alpha\beta$ ERKO adult female mice contained both healthy (with oocytes) and sex-reversed follicles; the latter were characterized by degeneration of the oocyte and "transdifferentiation" of follicles into seminiferous-like tubules, with Sertoli-like cells that expressed increased amounts of mRNA for *Sox9/MIS*. Similar changes are not observed in adult female mice who lack one or the other ER.

The authors suggest that the ovarian follicles of the  $\alpha\beta$ ERKO adult female mice "redifferentiated" into testes-like structures. Although

sex reversal of fetal rodent ovaries has been accomplished by their transplantation into an adult animal or one in which there is transgenic overexpression of *MIS* or by in vitro exposure to *MIS*, it previously has not been recorded in adult ovaries. The investigators suggest that in the absence of both ERs, the differentiated ovarian follicle is able to form a testes-like structure, possibly because of the loss of estrogen-mediated persistent repression of *MIS* and *Sox9*.

Couse JF, et al. *Science* 1999;286:2328-2331.

**Editor's comment:** This paper documents the need for both ER  $\alpha$  and  $\beta$  and therefore estrogen to maintain ovarian differentiation in the adult mouse. Wnt-4 recently has been shown to be necessary for ovarian and Müllerian duct differentiation and BAX regulates the longevity of the ovarian follicle. Future studies will be directed to elucidating the mechanism(s) of estrogen action and the identification of other factors involved in this complex process. If the reader has not read the lead article in this issue of *GGH* titled "Estrogen and Growth", he/she will miss a golden opportunity to integrate these 2 presentations regarding the actions of estrogen. Keep in mind, however, that mice and humans may not be identical in all actions of estrogen.

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## Directed Pharmacological Therapy of Ambiguous Genitalia Due to Androgen Receptor Gene Mutation

The authors report a 46,XY infant with ambiguous genitalia and undescended gonads due to the partial androgen insensitivity syndrome (PAIS). A T $\rightarrow$ C transition resulted in a missense mutation of codon 807 in the ligand binding region of the androgen receptor (AR). The mutated AR had only 15% of the binding capacity for testosterone and 15% of the in vitro transcription activating function as the wild-type AR. Yet this mutated AR bound dihydrotestosterone (DHT) with high efficiency and effective function. Topical periscro-

tal application of a preparation of DHT gel led to raised serum DHT concentrations, rugation of the scrota, descent of the gonads, and enlargement of the phallus. The authors conclude that functional assays as described of a mutated AR may identify subjects who are androgen responsive and thus could be reared in their genetic sex with DHT administration.

Ong YC, et al. *Lancet* 1999;354:1444-1445.