Editorial

Molecule for molecule, estradiol is the most potent of the steroid hormones. Its potency facilitated the design of bioassays for the early isolation and purification of the hormone. Furthermore, physiologically effective (and mean circulating) levels of hormones in general are in inverse proportion to the affinities of the hormones for their various receptors. The high affinity of estradiol for the estradiol receptor (K_d of ~ 0.1 nM) was an advantage in characterizing the receptor. As a consequence of these features, estradiol was one of the first steroid hormones to be purified and among the first for elucidation of the mechanism of action. The disadvantage of this high potency is that the hormone can act at concentrations that are not detectable by the best available assay procedures.

This problem is not so serious for analysis of estrogen physiology in the mature female because, at ovulation, estrogen levels are within the measurable range, and effective bioassays are available for estimating estrogen levels during the remainder of the menstrual cycle. However, in infants and prepubertal children of both sexes, adult men, and postmenopausal women, measurements of estradiol in plasma rarely provide information of biological or clinical significance. This problem is made worse by the fact that estradiol is both secreted by the gonads and formed by extraglandular aromatization from circulating 19-carbon precursors, so that tissue levels may not always be predictable by measuring plasma hormone.

By way of illustration, evidence obtained from metabolic studies indicates that gynecomastia in men is the result of any of several derangements in estrogen physiology, but plasma estrogen levels are rarely abnormal (1). For example, estradiol-secreting testicular tumors can produce feminizing syndromes that regress upon removal of the tumors but do not produce measurable levels of estradiol in plasma (2). Likewise, on physiological grounds estrogen is believed to play a role in premature thelarche in girls, the regulation of growth at puberty, the development of prostatic hyperplasia, and the growth of a variety of tumors, but the quantitative aspects of this relation have not been established. The physiology and pathophysiology of estrogen are probably less well understood than those of any other major hormone.

In this issue of *The Journal,* Klein et al. (3) describe the development of a new estradiol bioassay that has a detection limit that is two orders of magnitude lower than previous assays. This technique uses a yeast that has been genetically engineered to contain estradiol receptor and an estrogen-inducible reporter gene (β-galactosidase under the control of an estrogen-response element). The assay can be used for the measurement both of estradiol itself and of some pharmacological agents such as ethinyl estradiol and stilbesterol. As the first application of this methodology, the authors have demonstrated that estradiol levels are much lower in children than previously reported but are nevertheless eightfold higher in girls than in boys. This finding is of considerable potential interest for understanding the onset of puberty.

Because of its complexity, this new method may not be immediately applicable for routine clinical studies, but as a research tool it makes possible the investigation of the many puzzling, unsolved issues of estrogen physiology and pathophysiology. Indeed, the availability of this sensitive bioassay technique should serve as a stimulus for a renaissance in estrogen physiology. Because the assay uses the estrogen receptor for ligand recognition and contains a built-in amplification system, it may even be possible to adapt the technique for the measurement of fungal, phyto-, and other weak environmental estrogens (4) and thus make it possible to answer once and for all the question as to whether the current epidemic of gynecomastia in men (5) is due to suggogate estrogens.

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