

This Week's Citation Classic®

Ryan K J. Biological aromatization of steroids. *J. Biol. Chem.* 234:268-72, 1959.
[Boston Lying-in Hospital and Department of Obstetrics, Harvard Medical School, Boston, MA]

This paper described for the first time the preparation of an in vitro human placental enzyme system that could convert substrate levels of androstenedione and testosterone to estrone and estradiol, respectively. The reaction required placental microsomes, TPNH, and molecular oxygen and was therefore postulated to be a mixed function oxidase system. [The *SCI*® indicates that this paper has been cited in more than 450 publications.]

Conversion of Androgens to Estrogens

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This cited work was the first research project I undertook as a beginning resident in obstetrics and gynecology at the Boston Lying-in Hospital in 1957. I had just switched fields after completing a residency in medicine, at the Massachusetts General and Columbia-Presbyterian Hospitals, and biochemistry fellowships at Harvard Medical School, with Nobel laureate Fritz Lipmann and with the steroid chemist Lewis Engel. Since I had worked on estrogen metabolism as a medical student, the switch from medicine to obstetrics was not as irrational as it appeared to some of my medical colleagues at the time. In addition, the Macy Foundation provided support to encourage such studies in reproduction.

The pathway for estrogen biosynthesis was largely unknown until the late 1950s when tracer studies revealed conversion from androgens, utilizing crude tissue slice preparations of ovaries and placentas. At about the same time, it was discovered that hexahydrobenzoic acid could be aromatized by

liver enzymes. Prior to these observations, it had been postulated that the aromatic A ring of estrogens might need to be derived from the essential aromatic amino acids that were available only from the diet. Louis Fieser, the distinguished professor of organic chemistry at Harvard, speculated at one of his lectures that mammalian enzyme systems might not be able to develop the energy needed to synthesize an aromatic ring de novo.

In 1957, I published in the *Journal of Biological Chemistry*¹ on the adrenal enzyme system for 21-hydroxylase, which consisted of microsomes, TPNH, and oxygen, and its light reversible inhibition by carbon monoxide. When I was sufficiently freed of clinical residency duties, the subsequent discovery of an almost identical system for the placental synthesis of estrogen followed quickly and easily. Failure to find any trace of estriol synthesis in this system resulted in a sequel publication² the same year on the conversion of 16-hydroxylated androgens to estriol. Prior to that observation, it was believed that estriol was simply a metabolite of estradiol. Ironically, the new pathway for estriol synthesis via 16-hydroxylated androgen precursors was subsequently found to be the major source of estriol in human pregnancy in vivo, with the precursor coming to the placenta from the fetus.³ Evidence for the relationship of aromatase to cytochrome P-450 came later.^{4,5}

The principal use of this enzyme system has been to study the hormonal regulation of human reproduction, as a primary source for further purification of aromatase, and as a model system to test antagonists for blocking estrogen synthesis in hormone-sensitive malignancy. It is gratifying to know that after 31 years, the original, relatively simple system still has utility.⁶

1. Ryan K J & Engel L L. Hydroxylation of steroids at carbon 21. *J. Biol. Chem.* 225:103-14, 1957. (Cited 245 times.)
2. Ryan K J. Metabolism of C-16-oxygenated steroids by the formation of estriol. *J. Biol. Chem.* 234:2006-8, 1959. (Cited 115 times.)
3. Magendantz H G & Ryan K J. Isolation of an estriol precursor 16-alpha-hydroxydehydroepiandrosterone, from human umbilical sera. *J. Clin. Endocrinol. Metab.* 24:1155-62, 1964. (Cited 95 times.)
4. Canick J A & Ryan K J. Cytochrome P-450 and the aromatization of 16-alpha-hydroxytestosterone and androstenedione by human placental microsomes. *Mol. Cell. Endocrinol.* 6:105-15, 1976. (Cited 55 times.)
5. Hall P. Role of cytochrome P-450 in the biosynthesis of steroid hormones. *Vitamin. Hormone.—Advan. Res. App.* 42:315-68, 1985.
6. Cole P A, Bean J M & Robinson C H. Conversion of a 3-desoxy steroid to 3-desoxyestrogen by human placental aromatase. *Proc. Nat. Acad. Sci. USA* 87:2999-3003, 1990.

Received September 24, 1990

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LS, V. 34, #18, May 6, 1991

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