How the Hell Did We Get Here? Part III
The Role of Estrogen in Women's Health

T. Watson Jernigan, M.D., M.A.

Objectives of this Lecture

- The attendees should be able to:
  1. Outline the development of hormones starting in the 1880s.
  2. Discover the biochemical development of conjugated equine estrogens.
  3. Interpret the medical literature from 1975 and 2002.

Objectives of CME

“To enhance medical knowledge and give new and updated reports on research to area physicians, residents, medical students, and nursing and hospital staff.”

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Why Study Present Situation?

• Baby Boomers (born 1946-1964) still coming into menopause.

• **Reason:** Life Expectancy Increase
  - 1900 USA Female 49
  - 2007 USA Female 79.7

• **Reason:** Increase in Percentage of Older Population
  - 1900 USA 4% of population (3 million)
  - 2000 USA 12% of population (35 million)
  - 2030 USA Projection 70 million women >65 years of age
Early Pioneers in Hormonal Therapy

• 1889 Charles Brown-Sequard
  Reported the rejuvenating effects of self-administered injections of testicular extracts & theorized that ovarian extract would have beneficial effect in females.

• 1896 R. Chrobak
  Suggested use of ovarian grafts

• Ludwig Fraenkel
  1896 Described ovarian therapy with a substance obtained from cow or sow ovaries.
  1903 “Die Function des Corpus Luteum” Recognized symptoms of perimenopause but needed to investigate forms of treatment.
1920s Age of Biochemical Advancements

- 1922 Edgar Allen & Edward Doisy
  Jointly reported their experiments in extraction of follicular fluid of hog ovaries, and the demonstration of the extract’s estrogenic effect on the vagina & uterus of castrated mice & rats.

- 1926 A.S. Parkes & C.W. Bellerby
  Coined Basic Word, “Estrin” to designate the hormone that induces estrus in animals. The terminology was extended to include estrone, estradiol, estriol.

1920s (continued)

- 1929 Elmer L. Sevringhaus & J. Evans
  Use an estrogenic compound derived from amniotic fluid of cattle to treat menopausal symptoms. Compound named amniotin.

- 1929 Edward Doisy
  Isolated crystalline estrone from urine of pregnant females; subsequently isolated 17β estradiol from sow ovaries.

1930s & 1940s Development of Pharmaceutical Estrogen

- 1932 Girard
  Responded to complaints of scarcity of “ovarian hormones” by obtaining 20 grams of crystalline substance derived by use of a new reagent to treat mare’s urine.

- 1936 “Estrin” – significant amounts of pure estradiol finally isolated.
1930s & 1940s (continued)


- 1939  T.N.A. Jeffcoate published “Oestrogenic Hormone Therapy” British Medical Journal 2:671-676 (September 30)

• 1939  Gordon A. Grant
Working for Ayerst Company, he suggested use of urine from horses. The process involved production of sodium salts from the sulfate esters of various estrogens, yielding a water-soluble conjugate.

• 1941  Canada  1942 USA
Conjugated equine estrogens used for treatment of menopausal symptoms
Pre Mar In (Pregnant Mare’s Urine)

<table>
<thead>
<tr>
<th>Composition of Conjugated Estrogens (Promarin)</th>
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<tbody>
<tr>
<td>Sodium estrone sulfate</td>
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<tr>
<td>Sodium equinone sulfate</td>
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<tr>
<td>Sodium 17-hydroxyestrone sulfate</td>
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<tr>
<td>Sodium 17-estradiol sulfate</td>
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<td>Sodium 16α-hydroxyestrone sulfate</td>
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1930s & 1940s (continued)

- 1942  FDA approval for use of conjugate equine estrogens (CEE)

1960s Menopausal Age of 1920s Flapper

- Women’s Suffrage Movement 1910s
- “Roaring 1920s”
- Great Depression 1930s
- World War II 1940s
- Kinsey Report 1950s
- Great (?) 1960s
1960s (continued)

December 1975

- Retrospective Study (NEJM 293:1164-1167, 1975)
- Reviewed 317 patients with adenocarcinoma of endometrium versus 317 patients as matched controls who had other gynecologic neoplasms.
- **Results:** Estrogen-users: 152 patients with cancer Controls: 54 patients with endometrial cancer.

December 1975 (continued)

- Conclusions:
  1. Risk of endometrial cancer 4.5x greater in estrogen users
  2. Highest Relative Risk in patients without obesity or hypertension

December 1975 (continued)

- “Case-Control” study (NEJM 293: 1167-1170, 1975)
- 94 patients identified with endometrial carcinoma and matched with 94 control patients
December 1975 (continued)

- **Results**: 57% (54 patients) of cancer patients versus 15% (14 patients) of control patients had used estrogens (mainly conjugated equine estrogens)

- **Results**: risk-ratio estimate increased with duration of exposure. 1-4.9 years exposure = RR 5.6  7 or greater years of exposure = RR 13.9

- **Conclusion**: these data suggest that conjugated equine estrogens. Have an etiologic role in endometrial carcinoma

Impact of 1975 Articles

- Diminished prescriptions of estrogens particularly CEE

- Development of combination therapies particularly CEE + MPA (medroxyprogesterone acetate)

- Development of Transdermal Therapies 1986 Introduction of Estraderm®

1970s Post December 1975

- Schindle et al. (J. Clin Endocrinol Metab 35; 627, 1972.

  **Comment**: “These data and our findings of increased estrogenic activity in the vaginal smears; endometrial hyperplasia preceeding or associated with endometrial cancer; and a high incidence of obesity, diabetes and hypertension in these patients with endometrial cancer might be an indication that metabolism of certain steroid precursors in fat tissue plays a role extra-glandular estrogen, production and the development of endometrial malignancy.”
1980s & 1990s Resurgence of Estrogen

• 1996 PEPI Trial
  Effects of hormone replacement therapy on endometrial histology in postmenopausal women
* daily administration of CEE, enhanced the development of endometrial hyperplasia
* combining CEE with cyclic or continuous MPA or cyclic MP protected the endometrium from hyperplastic changes associated with estrogen-only therapy

1980s & 1990s Resurgence of Estrogen (continued)

• By 1990s, approximately 25% (to 40%) of all U.S. women aged 40 years or older were using some formulation of menopausal hormonal therapy

• Beginning of 2000, prevalence of hormone used peaked in European countries.
  France 35%
  Switzerland 40%
Data from National Abutoratory Medical Care survey for years 2001 through 2003

Results: number of visits with menopausal hormone prescriptions fell from 26.5 million visits to 16.9 million visits

Results: Rate of decline was highest among women 50 years of age and older

Results: no significant difference in the decline by hormone type (oral versus transdermal)
2000s Post-WHI (continued)

- **Wang et al.** presented “Trends in Prescribing Hormone Therapy Post-WHI by Physician Specialty” as a poster 2009 NAMS meeting.
- Retrospective database study
- 2002-2007 Pharmacy claims and eligibility data from MedImpact Healthcare System
- Claims Volume per 10,000 members was calculated by quarter from 2002 through 2007

2000s Post-WHI (continued)

- **Results:** Overall claims for HT prescribed by MDs of all specialties decreased 72% from 2Q 2002 to 4Q 2007
- **Results:** 94% of overall HT claims were standard-dose in 2Q 2002; by 4Q 2007 proportion of standard-dose HT claims decreased by 77%
- **Results:** Proportion of transdermal HT claims increased from 8% 2Q 2002 to 19% 4Q 2007

2000s Post-WHI (continued)

- Retrospective Cohort Study (Menopause, Vol. 16, No.5, 2009)
- 300,000 Inhabitants in Barcelona 1998-2007
- Women 50-69 years of age evaluated
- Age groups evaluated: 50-54, 55-59, 60-64, 65-69
2010: Future of Menopausal Therapy

- Estrogen: Oral, Transdermal, Transvaginal
- Other Therapies: Acupuncture, Herbal, SSRIs, SSNIs
- Compound Hormones: Custom Dosages, “Bioidentical” (saliva)
Leon Speroff

“The challenge for clinicians is to make decisions that are suitable and correct for individual patients. Clinicians are unique in bringing a special relationship with patients to the process of utilizing their store of knowledge. The process requires individualization, the application of knowledge in a modified form based upon the clinician’s experience and the clinician’s familiarity and understanding of the individual patient. I call decision-making in this clinician-patient interaction “medical judgement.”