Drug Development
-- ENOVID --

AL Chemistry Group Project

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What is Enovid?

- Enovid is the drug's trade name only
- A Combined Oral Contraceptive Pill (COCP)

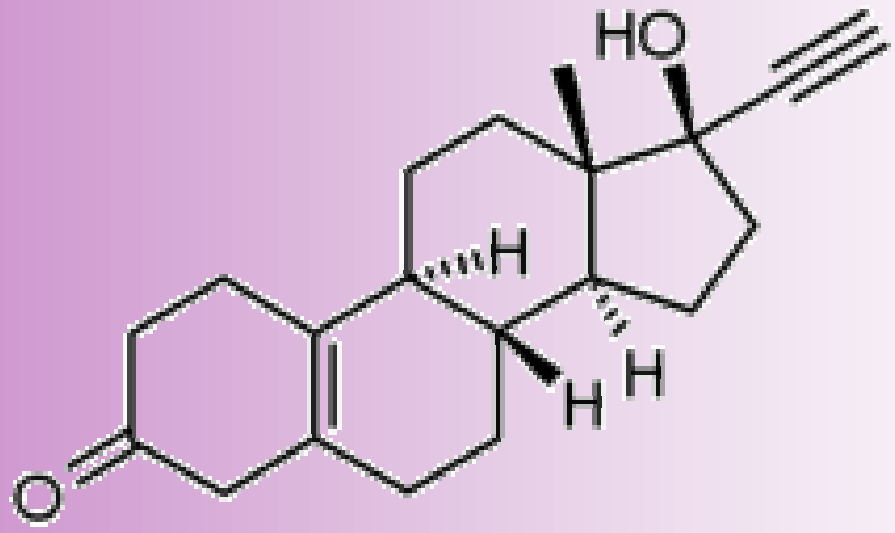
Norethynodrel ($C_{20}H_{26}O_2$)

+

Mestranol ($C_{21}H_{26}O_2$)

} Enovid

The Lead Compounds

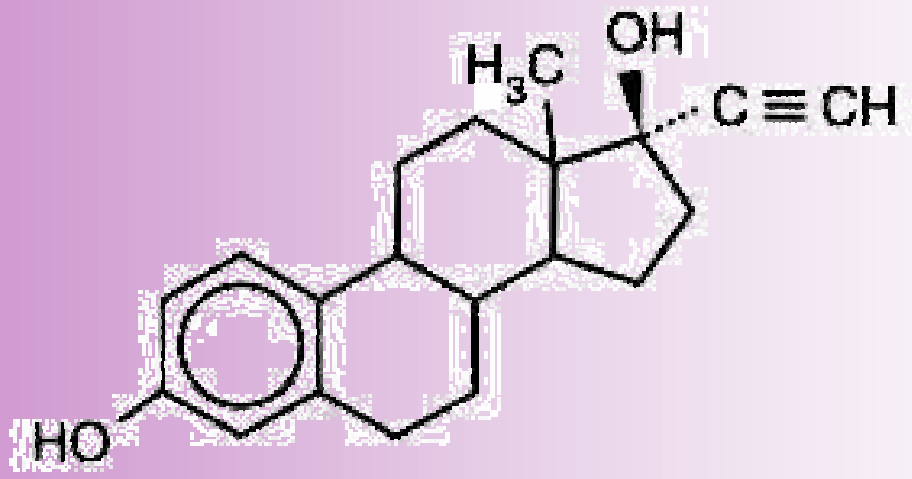


Norethynodrel

IUPAC: (17 β)-17-ethynyl-17-hydroxyestr-5(10)-en-3-one

- It's a progestational hormone, used especially in oral contraceptives

The Lead Compounds

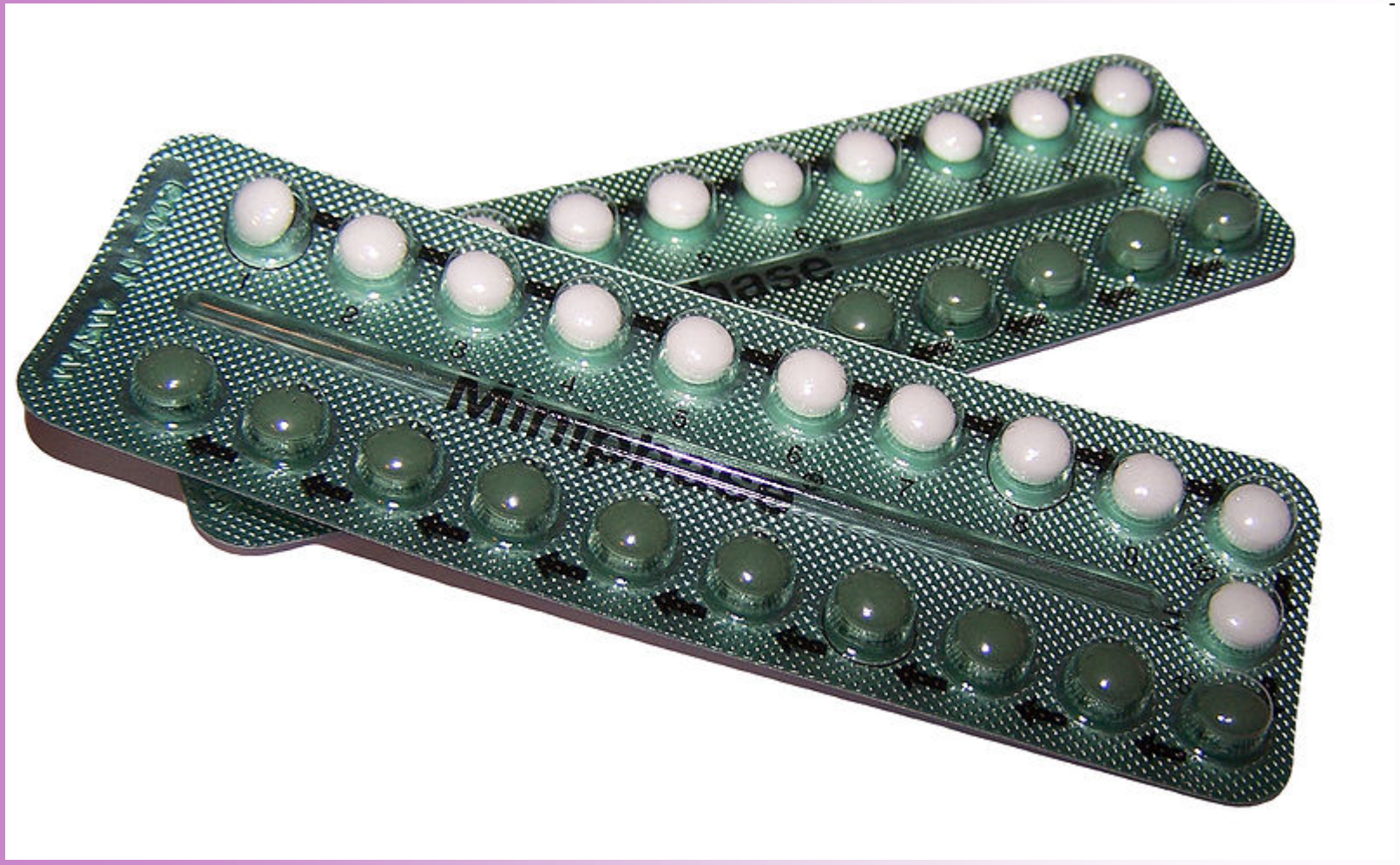


Mestranol

IUPAC: (17 β)-17-ethynyl-3-methoxyestra-1,3,5(10)-trien-17-ol

- It's a synthetic estrogen, used in oral contraceptive preparations

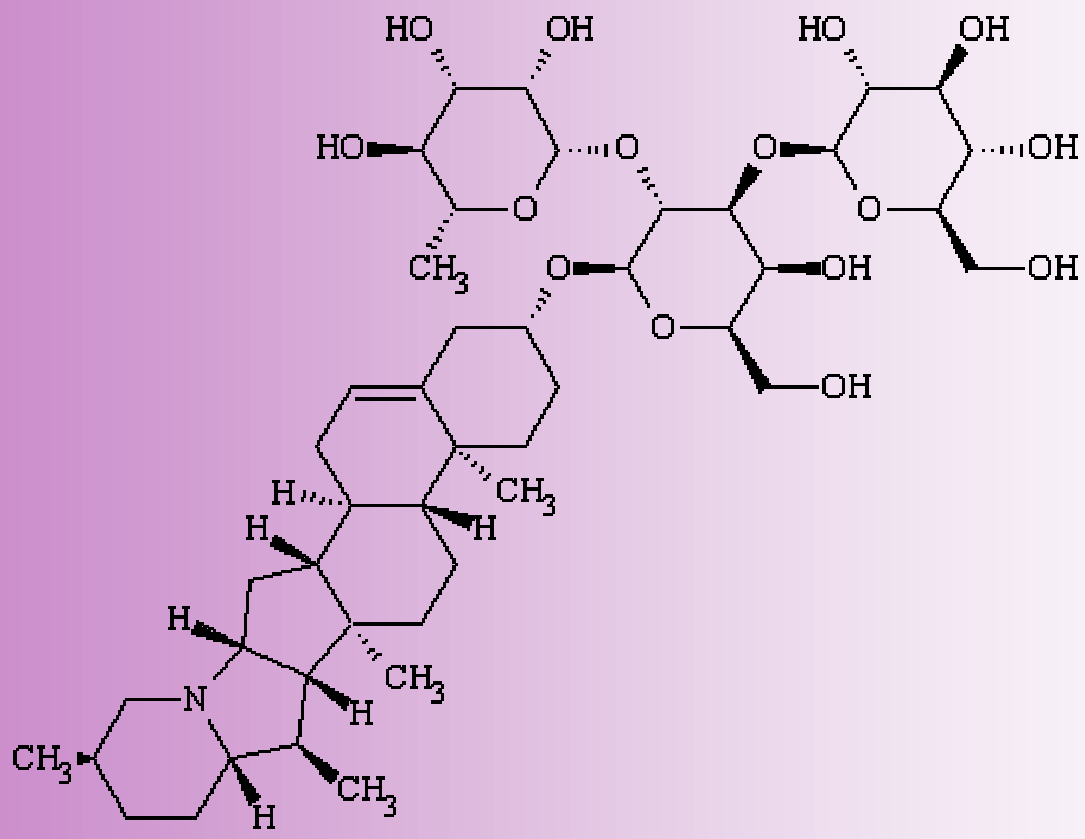
Photo of Enovid Pills



Lead Compound Discovery

- 1930s found ***androgens***, ***estrogens*** or ***progesterone*** inhibited ovulation
- 1939, Russell Marker synthesized progesterone from plant steroid *sapogenins*
- 1942, he discovered a better starting material, the ***saponin***, which can be converted to **sapogenins** in laboratory

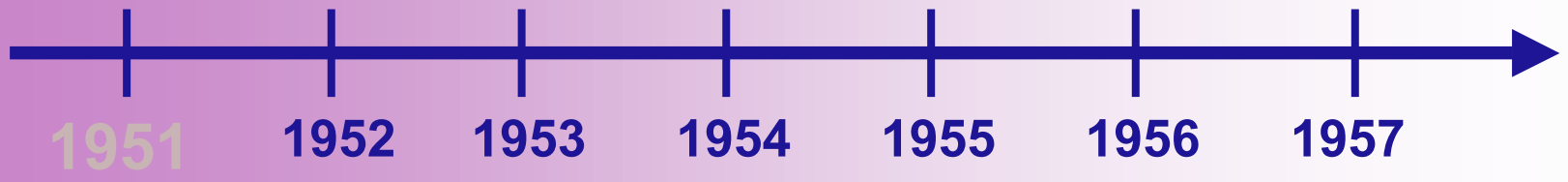
Lead Compound Discovery



Structural formula of Solanine, a kind of saponin

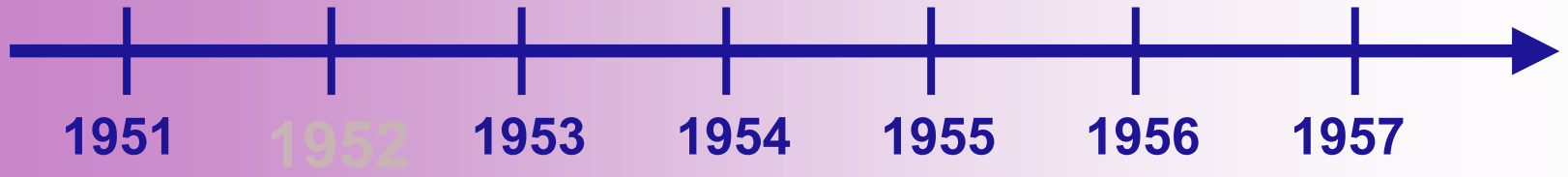
Molecular Modification

- *Gregory Pincus* with *Min Chueh Chang* began hormonal contraceptive research.
- Experiment showed injections of **progesterone** suppressed ovulation in rabbits.



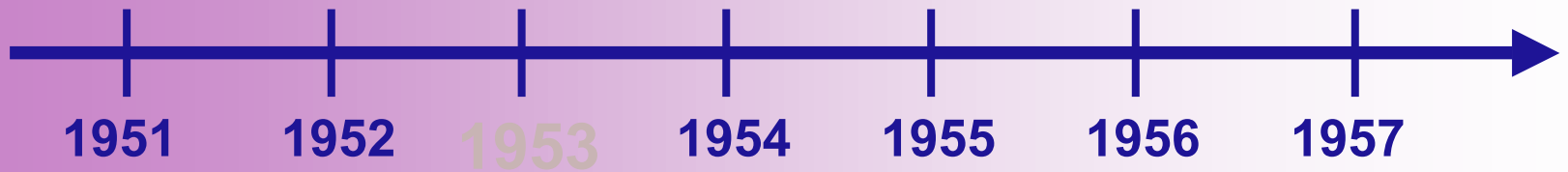
Molecular Modification

- *John Rock* induced anovulatory pseudo-pregnancy state in 80 infertility patients with continuous increasing oral doses of ***estrogen*** and ***progesterone.***
- However, this method brings along the troubling absence of menstrual period.



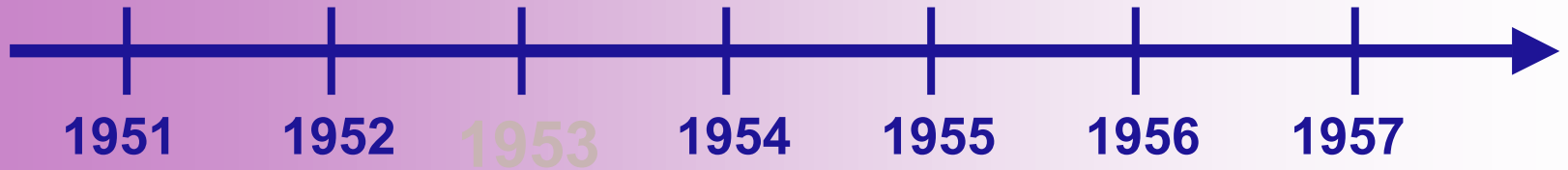
Molecular Modification

- *John Rock* again induced anovulatory pseudo-pregnancy state in 27 infertility patients with *progesterone*-only regimen to produce withdrawal bleeding.
- This obtains the same result as the previous trial without any absence of menstrual period.



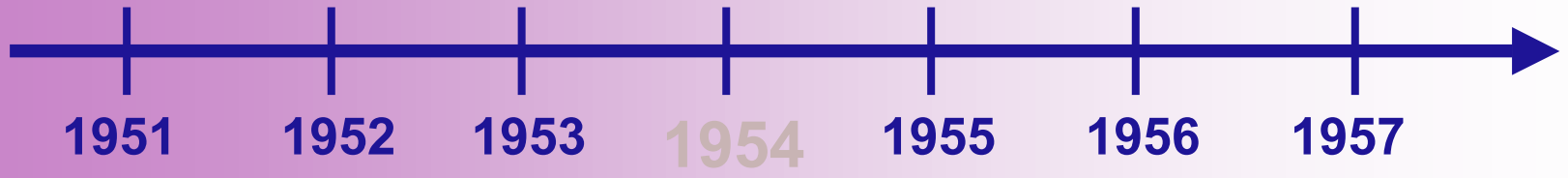
Molecular Modification

- *Pincus* discovered that the three most promising oral **progestins** were Syntex's **norethindrone**, and Searle's synthesized ***norethynodrel*** and **norethandrolone**



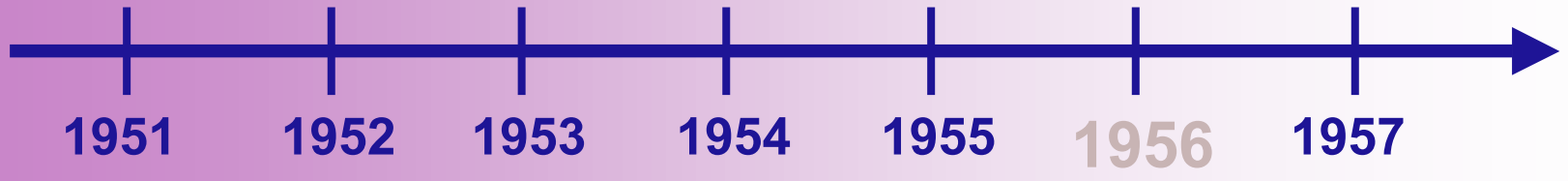
Molecular Modification

- *Rock* began the studies of the ovulation-suppressing potential the three oral **progestins**.
- He discovered that 10 mg or higher doses of ***norethindrone*** or ***norethynodrel*** suppressed ovulation without breakthrough bleeding.
- While all doses of ***norethandrolone*** caused breakthrough bleeding, so he abandoned the use of ***norethandrolone.***



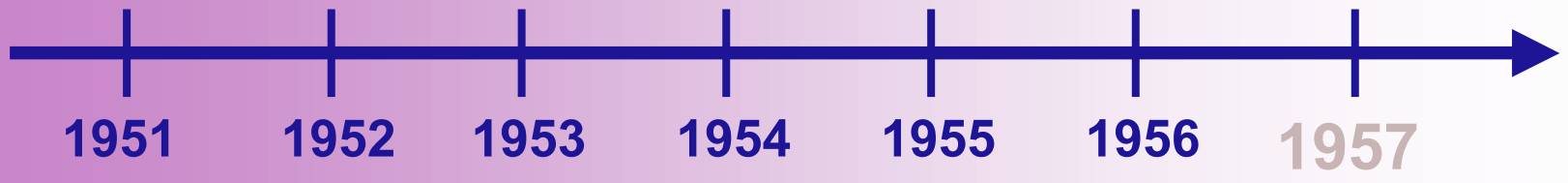
First Human Trial

- ***Mestranol***, an intermediate in their synthesis *contaminated* ***Norethindrone*** or ***norethynodrel***.
- When ***mestranol*** = 1%, breakthrough bleeding occurred.
- When ***mestranol*** = 2.2%, no breakthrough bleeding.



Second Human Trial

- Searle concluded that estrogen content could be reduced by 33% to lower the incidence of estrogenic gastrointestinal side-effects without significantly increasing that of breakthrough bleeding.



Approval For Marketing

In **1965**

- The Food and Drug Administration (FDA) approved **Enovid** 10 mg to married women for contraceptive use in the US.

In **1972**

- The FDA approved **Enovid** to unmarried women for contraceptive use in the US.