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TIARELLA CORDIFOLIA	Coolwort
TRILLIUM ERECTUM	Beth Root
TUSSILAGO FARFARA	Colt's Foot
TILIA SPECIES	Linden
TROLLIUS EUROPEAUS	Globe Flower
URTICA DIOICA	Nettle

Beth root

•**Common Names/Synonyms** - Birth Root, Wake Robin, Nodding Wakerobin, Indian Shamrock, Lamb's Quarters, Indian Balm, Ground Lily, Cough Root, Jew's Harp Plant, Milk Ipecac, Pariswort, Rattlesnake Root, Snakebite, Three-Leaved Nightshade, Trillium.

•**Description** - Beth Root is an herbaceous perennial which grows in rich soils and shady woods of the central and western United States and grows to a height of 40cm. The simple stem arises from an oblong, tuberous rootstock and bears at the top a whorl of three round-ovate acuminate leaves. In May and June a single yellow-white to reddish-white flower appears above the leaves. It grows in rich woodland in the central and western states of the USA. Trilliums are remarkable in that the leaves and flower petals are always in 3's.

•**Properties/Uses** - Astringent, antihemorrhagic (with particular action on the female reproductive system), mild expectorant, uterine tonic, antiseptic, diaphoretic, emmenagogue. Beth Root contains a natural precursor of the female sex hormones, which the body may utilize or not, thereby having a normalizing effect. It is used for menorrhagia and metrorrhagia and against complications arising during labor, including post-partum hemorrhage. It is considered to be a specific for excessive blood loss associated with menopausal changes, and is a palliative remedy for blood loss from the urinary tract. It is also used to treat coughs, bronchial problems and pulmonary hemorrhage, as well as gastrointestinal bleeding, diarrhea and dysentery. The underlying causes of any blood loss should be treated with the appropriate remedies. Beth Root may be administered as a douche for leucorrhoea or as a poultice or ointment for varicose and other ulcers. As a poultice or salve it is an effective application for insect bites and stings.

•**Cautions** - No side effects or contraindications with normal use.

- Plants - major impact on modern medicine- providing important steroids
- Cortisone originally had to be obtained from animals
- For example, in 1935 chemists were isolating cortisone from bile acids in the urine of oxen
- Elaborate chemical procedures, involving 38 steps, were then required to make important human steroids
- **In 1938, a gram of natural cortisone was worth \$100 (1938 dollars!)**
- For many years ethnobotanists* had known that certain plants had been used by primitive peoples as fish poisons, soaps, and shampoos
- Produce foam in water and are called **saponins**, which are steroids
- Saponin destroys red blood cells on contact
- Causes the fish to be stunned and then float to the surface
- Fish are not poisonous to humans when eaten.
- Some of these saponin-bearing plants were also used by societies as oral contraceptives
- Mexico and Central America: several plants were taken to stop female ovulation
- Matto Grosso Indian women in Brazil took plant products daily to prevent pregnancy

*Study of plants used by primitive people

- Russell Marker - biochemist interested in plants
- 1939 - published a study on sarsasapogenin
 - saponin in *Smilax* used to make sarsaparilla
- 1940 - published studies on diosgenin, a saponin* isolated from a Mexican yam species of the genus *Dioscorea*
- Synthesized the human hormone testosterone in eight steps
- Progesterone in just five steps
- Made plans to use yams for mass production of human steroids,
- Proposals rejected by the pharmaceutical companies
- 1942 - Marker got an indefinite separation from his wife
 - Went to live in Mexico
 - Set up a laboratory in his room
 - Made steroids from yams
 - Worked round-the-clock for several weeks to make progesterone
 - Offered the progesterone for sale to a businessman in Mexico City
 - Businessman offered him \$80 per gram

*Surfactant glycoside

**GUESS
WHAT
HAPPENED
?**

- Marker handed him two kilograms of the stuff (\$160,000), which he had produced in two weeks

- A company called Syntex was then organized to make steroids from Mexican yams, using the syntheses invented by Marker
- After a while Marker left the company, but he left also with the secret of a crucial step in the process
- Syntex hired Dr. George Rosenkranz, who went to Mexico and figured out the missing step
- Rosenkranz took yams and was able to make progesterone then testosterone, and finally the female hormone estrone
- Rosenkranz is credited with the saying
"Adam goes into the test tube and Eve comes out."

- All of this work in Mexico occurred while major pharmaceutical companies in the United States were trying to make several grams of hydrocortisone from the adrenal glands of 2,200,000 hogs
- Marker made another important discovery - identified a yam saponin called botogenin
 - Has an oxygen located at the carbon-12 position
 - Upjohn chemists used microorganisms to convert this compound into a useful form
 - Could easily move the oxygen to the C-11 position
 - Opened the door for advanced cortico-steroids
- About 66 pounds of fresh yams could yield one pound of diosgenin and two ounces of cortisone
- In the 1960s, a gram of cortisone cost two dollars to produce
- At this cheap price the industry could produce cortisones, human sex hormones, and human steroids inexpensively and also produces huge profits
- This was the start of inexpensive oral contraceptives, fertility drugs, and a wide assortment of cortisone drugs

Russel Earl Marker

- The Marker Lectures were established in 1984 through a gift from the late Russell Earl Marker, professor emeritus of organic chemistry at Penn State, whose pioneering synthetic methods revolutionized the steroid-hormone industry and opened the door to the current era of hormone therapies, including the birth-control pill. The Marker endowment allows the Penn State Eberly College of Science to present annual Marker Lectures in astronomy and astrophysics, the chemical sciences, evolutionary biology, genetic engineering, the mathematical sciences, and the physical sciences.

PHARMACOLOGY OF STEROID COMPOUNDS

- Estradiol is most potent natural estrogen
- Inactive when given orally
- Ethinyl group at 17 position made it orally active (EE)
- Older pills had used 3-methyl ester (mestranol) of ethinyl estradiol
- Mestranol will not bind to receptor and must be converted to EE
- Currently used compound is EE

PHARMACOLOGY OF STEROID COMPOUNDS

- Metabolism of EE
 - Varies from person to person
 - Varies with sampling time in the same person
 - Same dose may cause different side effects in different individuals
 - Thrombosis is related to estrogen dose

PHARMACOLOGY OF STEROID COMPOUNDS

- Success of EE led to development of ethisterone (oral derivative of testosterone)
- Removal of 19 carbon from ethisterone to form norethindrone
- Changed properties from androgenic to progestogenic
- Progestational derivatives of testosterone are referred to **19-nortestosterone**
- Androgenic properties not totally eliminated

PHARMACOLOGY OF STEROID COMPOUNDS

- Norethindrone can be converted to EE in small amounts
- Also has very weak binding to estrogen receptor
- Serious side effects related to high dose of progestational agents now minimal
- Another compound (Norgestrel) is racemic mixture of d- and l- norgestrel (only d-norgestrel is active)

Northethindrone Family

- Norethindrone
- Norethynodrel
- Norethindrone acetate
- Lynestrenol
- Norgestrel
- Norgestimate
- Desogestrel
- Gestodene

Desogestrel & Norgestimate

- Requires two degradative steps before they express progestational properties
- Active metabolite is 3-keto-desogestrel
- Differs from levonogestrel by a methylene group in 11 position
- Several metabolites contribute to norgestimate activity
- Considered a second generation progestational agent because of metabolite (levonorgestrel)

Definitions of Dose

- Low-Dose Oral Contraceptives
 - Product containing <50 ug EE
- First Generation Oral Contraceptives
 - Products containing 50ug or more EE
- Second Generation Oral Contraceptives
 - Products containing levonorgestrel, norgestimate and other norethidndrone family and 30 or 35 ug EE
- Third Generation Oral Contraceptives
 - Product containing desogestrel or gestodene with 20 or 30 ug EE

Ethinyl Estradiol

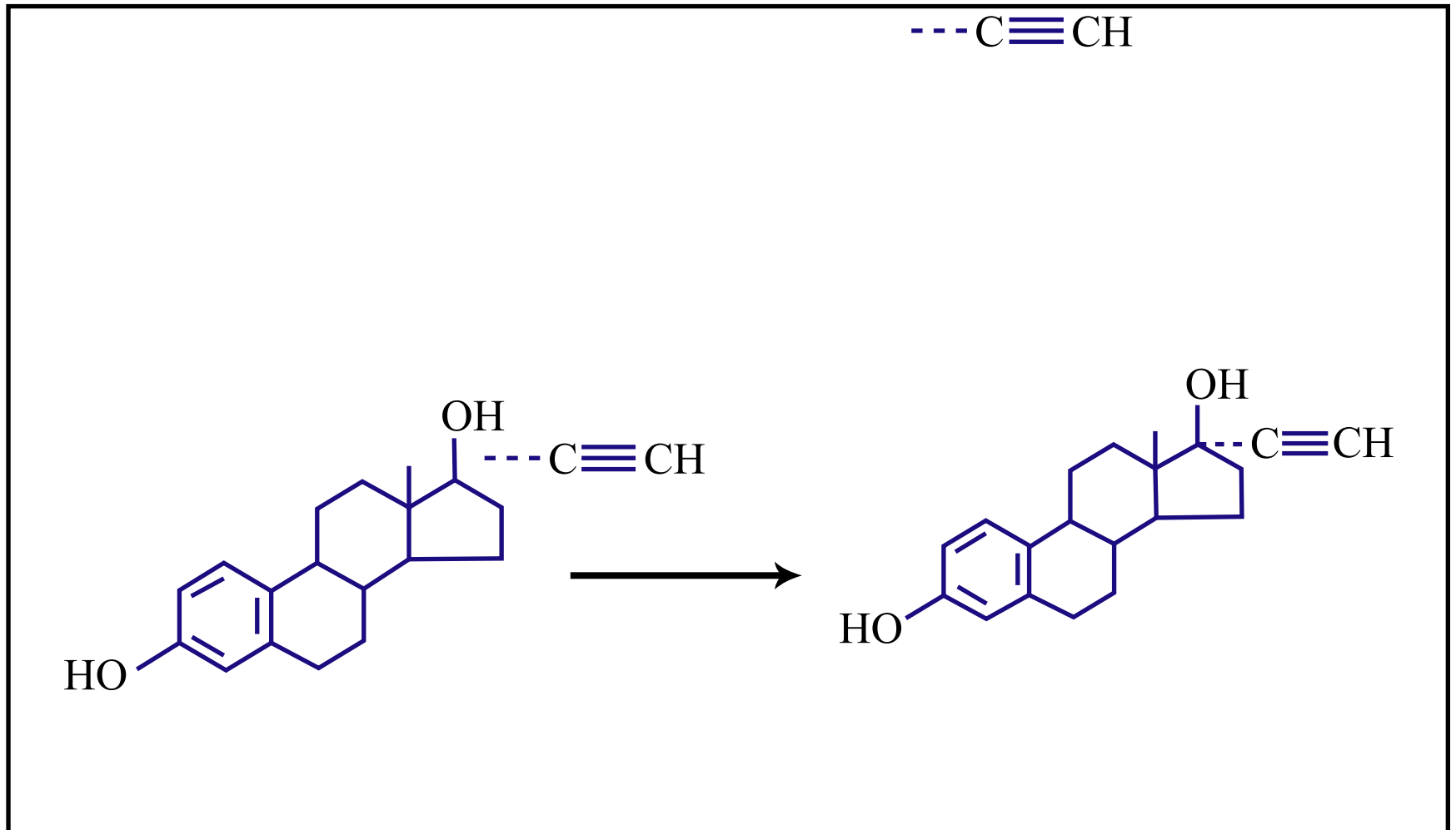


Figure by MIT OCW.

Testosterone to Esthisterone

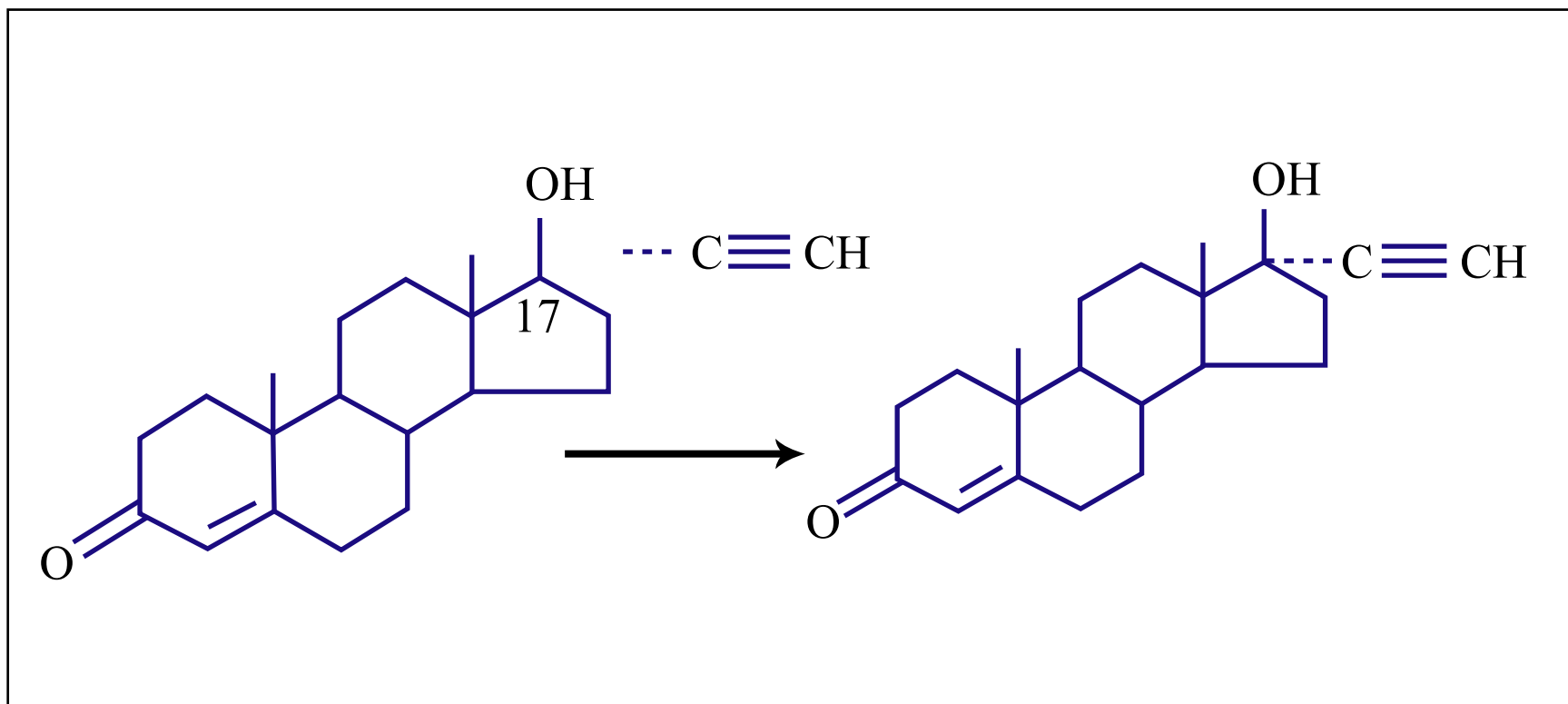


Figure by MIT OCW.

Gestodene

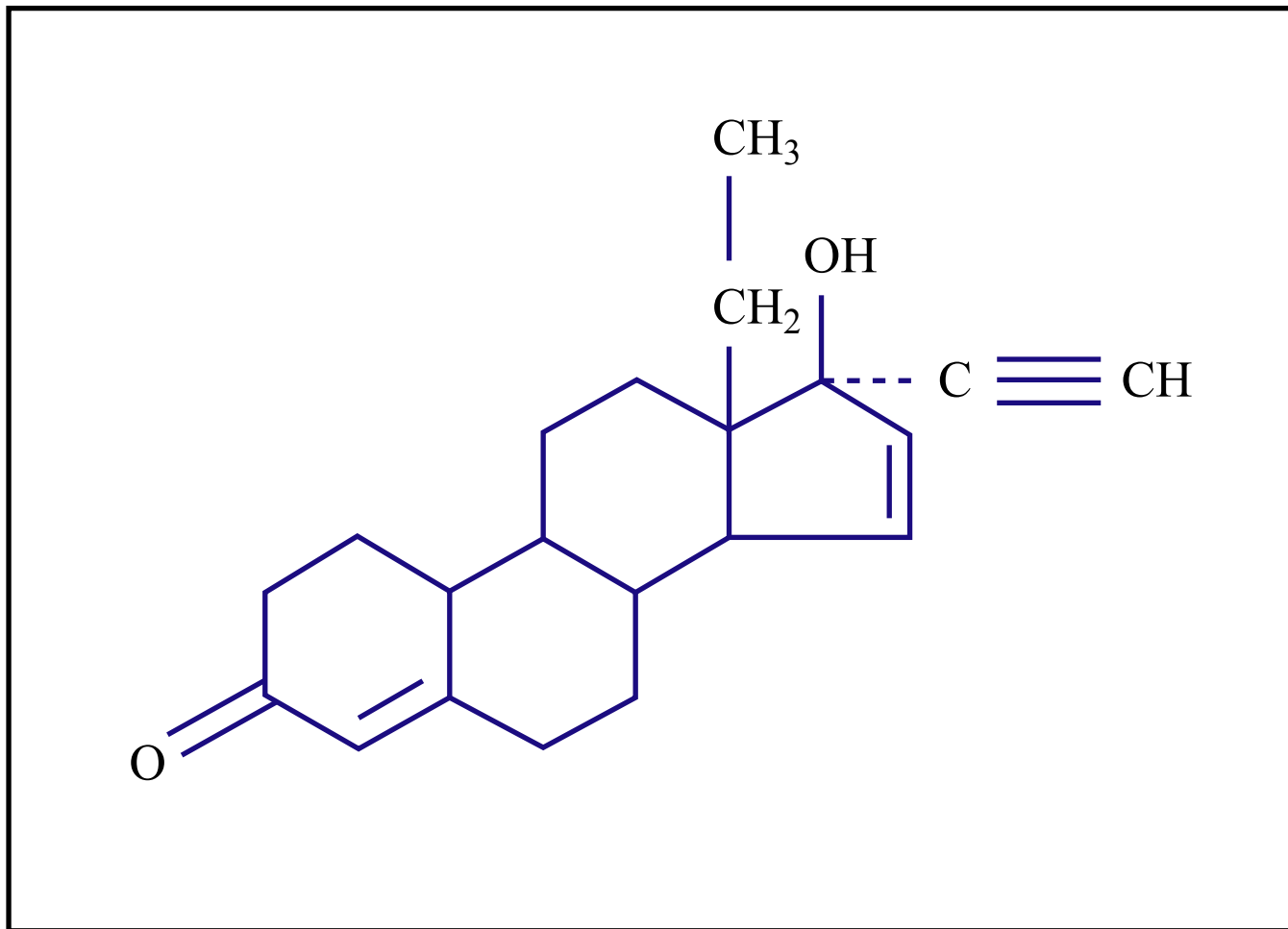


Figure by MIT OCW.

Dienogest

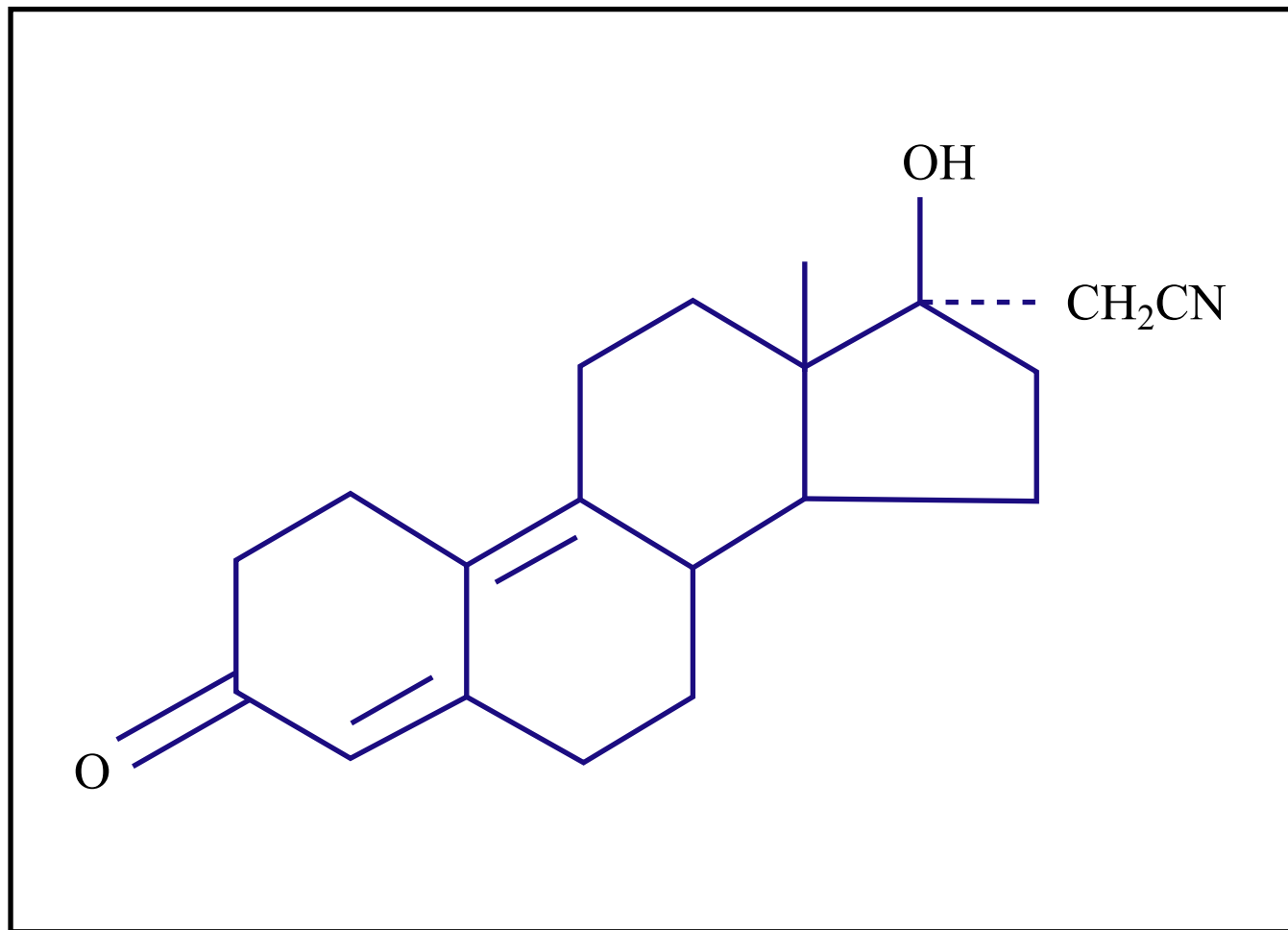


Figure by MIT OCW.

Desogestrel

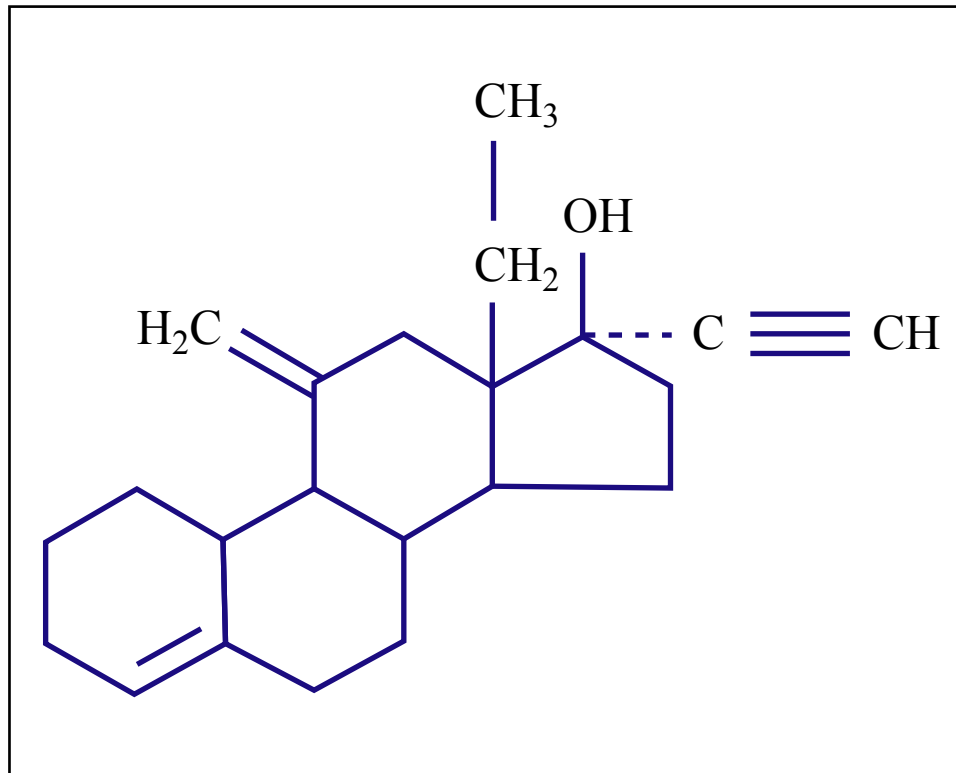


Figure by MIT OCW.

Potency

- Historically used term
- Different responses in
 - Uterus
 - Breast
 - Liver
- Animal and human responses differ as well
- ***Need to speak of Biologic efficacy*** in humans
- Clinical characteristics
 - Efficacy
 - Side effects
 - Risks
 - Benefits

New Progestins

- Old belief – androgenic progestins caused heart disease
 - (Actually due to coagulation facilitation by estrogen)
- New Progestins
 - Desogestrel
 - Gestoden
 - Norgestimate
- All are comparable to old products with regard to
 - Cycle control, bleeding, amenorrhea
- They produce increased SHBG
 - Reduced free testosterone
 - Used for acne and hirsutism control

Formulations

- Polyphasic pills
 - Attempt to reduce side effects, BTB
 - No real difference noted over monophasic
 - 7 day pill free
 - 4 days pill free
 - 2 days pill free
 - Estrophasic approach – low early estrogen
 - Reduced nausea initially
 - As estrogen rises the SHBG rises
 - Reduced androgenic effects
- No difference in efficacy

Mechanism of Action

- Combined pill is given daily for 3 weeks of 4
- Prevents ovulation
 - Pituitary
 - Hypothalamic
- Progestational effect suppresses LH (no surge)
- Estrogenic effect suppresses FSH (no dominant follicle)
- Even if follicle developed there would be sufficient inhibition to prevent ovulation (as demonstrated in the minipill)

Mechanism of Action

- Purpose of the estrogenic component
 - Stability to the endometrium
 - Prevent irregular shedding (breakthrough bleeding)
 - Potentiates the action of progesterone
 - Allowed reduction in dose of progestational agents
 - Probably increases intracellular expression of P receptors
 - Minimal level of estrogen is required to maintain efficacy of combined pill
 - Effect of progesterone always exceeds that of estrogen
 - Endometrium (decidualized, exhausted glands)
 - Cervical mucous (thick and impervious to sperm)
 - Tubal function (? Reduction in motility – alteration in tubal fluid)

Efficacy of Oral Contraceptives

- Most failures occur because of delay in initiation of next cycle
 - Allow *escape ovulation*
- Use of placebo pills to avoid “forgetting to restart” is a good idea
- Most prevalent problem associated with failure
 - Vomiting
 - Diarrhea
 - Use backup method after bout of gastroenteritis
 - Place pill in vagina
- .1% failure rate if motivated, 7.6% during first year

David Wagner - Package Designer

David P. Wagner invented his dispenser to help his wife remember to take her Pill. Doris Wagner began taking the Pill after their fourth child, Jane, was born on November 14, 1961, and the Wagners decided that their family was complete. The only oral contraceptive on the market in 1961 was Enovid, from G. D. Searle & Co. Prescriptions for Enovid were dispensed as tablets in a small brown bottle. Instructions for taking the Pill seemed straightforward: Doris was to take the first tablet on the fifth day after beginning menstruation, continue with one tablet every day for 20 days, and then stop; she would begin menstruating in two to three days, and on the fifth day of menstruation she was to start another 20-day cycle of tablets. The 20-pill regimen originated in the 1940s, when hormones were first used to treat menstrual problems. It was selected for the oral contraceptive clinical trials so that the hormonally controlled cycle would conform to the average or “normal” 28-day menstrual cycle and would encourage women to view the method as “natural.”

The Package

- Compliance packaging for the Pill
- Based on prototypes of the first container designed to hold the oral contraceptive
- The packaging prototypes came to the Smithsonian's collections as the result of a case study of the birth control pill in the Museum's *Science in American Life* exhibit, which opened in April 1994.
- David P. Wagner of Geneva, Illinois (the inventor) donated his prototypes and a small but fascinating collection that includes his design drawings, patent, correspondence, legal documents, and examples of oral contraceptive packages that either did or did not fall within the claims of his patent.

David Wagner

David Wagner recalled, “there was a lot of room for error in whether ‘the Pill’ was actually taken on a given day.” He said, “I found that I was just as concerned as Doris was in whether she had taken her pill or not. I was constantly asking her whether she had taken ‘the Pill’ and this led to some irritation and a marital row or two.” To resolve their frustrations, Wagner listed the days of the week on a piece of paper, put the paper on the dresser in their bedroom, and placed one pill over each day. When Doris removed a pill, the day of the week would be revealed and they could both tell, at a glance, whether she had taken her pill. “This did wonders for our relationship. It lasted for about two or three weeks until something fell and scattered the pills and the paper all over the floor.”

The Inventor

Still, he liked the basic idea, but he needed some kind of container to keep the pills oriented to the day of the week, yet prevent them from spilling, even if his wife carried them in her purse. He started “noodling around,” and sketched variations of such a pill box.

David Wagner was more than a clever spouse: he was educated to take a technological approach to problem solving. He worked as a product engineer developing new fasteners for Illinois Tool Works, and he already held one patent at the time he invented his dispenser.

He recalled:

At this point, I felt I had a pretty good idea, but if I was going to interest anyone in it, I felt I needed several models. So, with just a 1/4" electric drill, a fly cutter to be used in the drill, paper, a saw, a staple, pencil, double-faced transparent tape, several drill bits, a snap fastener that I took off of a child's toy, and several flat, clear sheets of either acrylic or polycarbonate plastic, I fashioned the first pill box for packaging birth control pills. My model is dated 5-15-62. I simulated the pill by sawing thin slices from a wooden dowel rod.

Wagner applied to patent his invention on July 27, 1962, with the help of a friend who was a patent attorney. Soon afterwards, he paid a visit to the Director of Advertising for G. D. Searle & Co. He said that Searle “felt basically my pill box was a good idea, but at that particular time they were preoccupied with establishing a market.

Series of images with examples of various types of birth control package removed due to copyright reasons.

Percent Pregnant in 1 Year

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Package Insert

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Benefits of OC

- **Benefits**

- Decreased cancer - ovarian and endometrial cancer risk decreases by 40% after 1 year of total OCP pill use and 80% reduction after 10 years of use (*JAMA 1987; 257:796-800*). This protection lasts at least 15 years and most likely persists for a lifetime. Conversely, if a woman has been ovulating for 35 or more years then her risk of ovarian cancer increases by 300% (from 1% to 3%) lifetime risk. The protection against ovarian cancer is thought to be from the reduction in ovulation and the use of progestin induces apoptosis or cell death of abnormal ovarian epithelial cells.
- Decreased breast changes like cyclic and fibrocystic complaints, fibroadenoma
- Decreased benign ovarian tumors and cysts
- Decreased pelvic inflammatory disease
- Decreased rheumatoid arthritis
- Regulates and reduces menstrual bleeding
- Decreased endometriosis
- Decreased osteoporosis
- Decreased anemia
- Decreased menstrual cramps, ovulation pain & premenstrual tension
- Decreased acne and hirsutism
- Can adjust menses for vacations or if conditions require amenorrhea
- No interference with coitus

Risks of Death (Various Fun Things)

- Risk of death in a year for men and women who participate in...
 - Motorcycling 1 in 1,000
 - Automobile driving 1 in 5,900
 - Rock climbing 1 in 7,200
 - Playing football 1 in 25,000

- Risk of death per year for women aged 15 to 44 from:
 - Using tampons 1 in 350,000
 - Having sexual intercourse (PID) 1 in 50,000

- Risk of death per year for women from:
 - Undergoing sterilization 1 in 38,500
 - Continuing a pregnancy 1 in 10,000
 - Legal abortion:
 - Before 9 weeks 1 in 262, 800
 - Between 9 and 12 weeks 1 in 100,100
 - Between 13 and 15 weeks 1 in 34, 400
 - After 15 weeks 1 in 10,200

- Using oral contraceptives:
 - Nonsmoker 1 in 66,700
 - Age less than 35 1 in 200,000
 - Age 35-44 1 in 28,600