

Progestin: Synthetic Progesterone

Progestin is a synthetic form of progesterone, a naturally occurring hormone, which plays an important role in the female reproductive cycle. During the 1950s two types of progestin that were later used in birth control pills were created, norethindrone and norethynodrel. In 1951 Carl Djerassi developed norethindrone at Syntex, SA Laboratories located in Mexico City, receiving a patent on 1 May 1956. In 1953 Frank Colton developed norethynodrel at G.D. Searle and Company Laboratories located in Chicago, receiving a patent on 29 November 1955. These two types of synthetic progesterone are important to the history of embryology as part of the birth control movement, because they facilitated the development and creation of the birth control pill, which changed the way people viewed birth control and revolutionized women's birth control methods.

During the 1940s there was a strong desire among chemists and pharmaceutical companies to develop synthetic steroids because of advances in basic knowledge of hormones and endocrinology. Also, the development and commercial success of cortisone, a steroid used for the treatment of arthritis, encouraged the exploration of steroids for treatment of other medical problems. It was believed that sex hormones in particular would hold great potential for possible treatments. The steroid research programs of commercial laboratories at this time focused on simply creating synthetic steroids and then supplying them to researchers and physicians to discover and develop uses for them.

Djerassi was the first to develop a synthetic progestin known as norethindrone. He had long been interested in steroids and came to Syntex because of the opportunity to focus on steroid synthesis. Russell Marker, who also worked at Syntex, had discovered in 1943 that progestin could be synthesized in large quantities from diosgenin, a steroid found in Mexican yams, through a process known as "marker degradation." Although this work was not directly related to Djerassi's development of norethindrone, it established Syntex as a major site for hormone research and production, facilitating Djerassi's later work.

At the same time, Frank Colton developed norethynodrel at G. D. Searle and Company in Chicago. Norethynodrel is a potent, orally active progestin that differs from norethindrone only in the location of one of its carbon double bonds. Both synthetic progestins, norethindrone and norethynodrel, function in birth control by elevating progesterone levels and preventing ovulation, mimicking the conditions during pregnancy. Norethindrone was considered to induce more masculine tendencies and was prescribed to women who had problems such as tender breasts prior to menstruation. Norethynodrel was considered to have more feminizing tendencies and was prescribed to women who had problems with acne.

Neither Djerassi nor Colton had intended for the compounds to be used in birth control pills, assuming instead that they would be used to treat gynecological disorders such as irregular menstrual cycles and endometriosis, which causes painful menstruation and infertility. However, both Searle and Syntex, unaware of Gregory Pincus' research agenda, had supplied samples of their compounds to him at the Worcester Foundation, where Pincus and others were actively developing a hormonal birth control pill. In October 1955 at the Fifth International Conference on Planned Parenthood, Pincus reported that based on tests in rats, the two compounds norethindrone and norethynodrel were the most promising for use in a birth control pill based on their ability to prevent ovulation. These findings were also published in *Endocrinology and Science*.

Ultimately norethynodrel was chosen for use in Enovid, the first hormonal birth control pill, which was marketed in 1960. This selection was because of Pincus' ties to Searle through his past consulting work, as well as Searle's enthusiasm for the birth control pill. On the other hand, Syntex

laboratories was associated with Parke-Davis Pharmaceuticals, who were reluctant to produce a birth control pill due to concern over religious and moral backlash. In 1962, norethindrone was marketed by Ortho, a division of Johnson and Johnson, as the birth control pill Ortho-Novum. Despite initial hesitation in selling birth control, in 1964 Parke-Davis gained rights to norethindrone acetate, a derivative of norethindrone, from Syntex, giving Syntex a large share of the birth control market.

By 1969 there were twenty-two different brands of pills marketed in the US, and they differed by the amounts of progestin and estrogen they contained. At this time the most commonly used progestin was still norethindrone. Enovid had contained very large doses of norethynodrel and some estrogen, but due to the side effects from such large doses of hormones, it was no longer prescribed as an oral contraceptive. Ortho-Novum was still used in 1969 because it contained much smaller doses of hormones and did not have the same side effects.

The creation of progestin is important to understanding and controlling development because of the role it played in the development of the hormonal birth control pill. Although this was not its intended purpose, progestin and synthetic estrogen (specifically ethinyl estradiol) are essential components of the birth control pill and other birth control technologies, such as Plan B.

Sources

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