

Yams of Fortune: The (Uncontrolled) Birth of Oral Contraceptives

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Russell Marker hated wasting time. Upon qualifying for a doctoral degree in chemistry as a twenty-three-year-old student at the University of Maryland in 1925, all that stood between him and his degree were several required physical chemistry courses. But Marker didn't want to take physical chemistry, as he already had a master's degree in the subject. The university refused to modify its graduation requirements and Marker's own advisor threatened him with the dead end career of "urine analyst" if he didn't complete his coursework. Marker refused and left the university without his degree, an independent scientist in search of a job.

Despite his advisor's lack of optimism, Marker did indeed go on to make tremendous scientific contributions throughout his career. While not the only scientist or social visionary involved, Marker's work formed the scientific cornerstone for the development of oral contraceptives, among the most socially significant scientific discoveries ever made. Yet despite such professional achievements, Marker's story remains marked by the combination of independence, good fortune, and ingenuity that led him to walk away from a Ph.D. because of a disagreement over coursework.

In the words of Steven Weintraub, the Russell and Mildred Marker Professor of Natural Products Chemistry at Pennsylvania State University, "There are more stories told about Russell Marker than perhaps any chemist. Although many of these stories are apocryphal, they are so fascinating that most of us cannot bear to stop repeating

them. This is the oral history of our profession that we pass to our colleagues and our students. They are the campfire stories that bind our profession together."

Following his less-than-glorious send-off from the University of Maryland, Marker's interest in hydrocarbon research led him to Ethyl Corporation. While at Ethyl, he developed an octane rating system for gasoline that is still used today.

However, after a few years Marker's chemical interests changed, and he left Ethyl to work as an organic chemist at the Rockefeller Institute. Here too he met with success; over a six-year period he produced many publications focusing on molecular configurations and their relationship to reaction chemistry. Eventually, Marker's background in hydrocarbon chemistry and molecular orientation led him to the developing field of steroid research. In 1938, he accepted a funded position at Pennsylvania State University.



Russell Marker during his years at Pennsylvania State University

Courtesy of [Pennsylvania State University](#)

The power of hormones

Of particular interest at this time in chemical history were the recently

discovered sex hormones, or androgens, molecules such as testosterone, estrogen, and progesterone (see Figure 1). Of these,

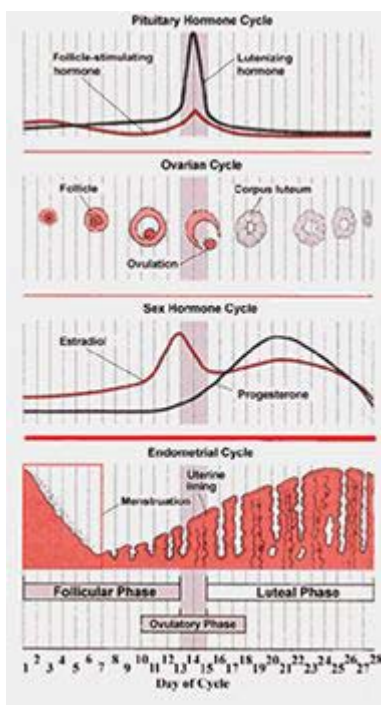


Figure 1: An overview of the menstrual cycle. Progesterone is critically important in controlling this progression of events and thus the ability to medically manipulate progesterone led to the development of birth control.

Courtesy of [Holistic Online](http://HolisticOnline.com)

ry responses vital to a functioning immune system, maintenance of blood hydration, pH and salt levels, as well as sexual development and function all rely on the proper functioning of various steroids.

The vast power of such hormones was not lost on physicians, and by the 1930s, progesterone was used to treat menstrual disorders, problem pregnancies, and gynecological cancers. However, progesterone was so expensive to purchase that both research and medical endeavors were often stymied. The only known way to isolate the hormone involved laborious and inefficient synthesis exploiting the byproducts of cholesterol oxidation. In a price comparison, at today's market value,

gold sells for about \$11 a gram; in the 1930s, progesterone sold for \$80 a gram. And so, despite the potential medical benefits of steroid hormones, progress in the field remained frustratingly slow.

It may have been his unusual academic background or work experience that contributed to Russell Marker's breakthrough in the field of hormone synthesis. In 1938 he presented a chemical hypothesis that contradicted prevailing chemical beliefs of the time. He proposed that the side chain of sarsasapogenin, a plant steroid derived from the sarsaparilla plant, was not chemically inert but actually chemically reactive. As a result, if chemical groups were removed from the sarsasapogenin side chain, then what remained was no longer sarsasapogenin but progesterone (see Figure 2). In a series of reactions now known as Marker degradation, Marker had found a way to synthesize progesterone.

There was only one problem - sarsasapogenin was also extremely expensive. However, rather than give up on his idea, Marker began studying botany, trying to find a less-expensive chemical relative of sarsasapogenin with which to further his studies. His search led him south, to the Mexican-American border in the Southwest, and finally into Mexico itself.

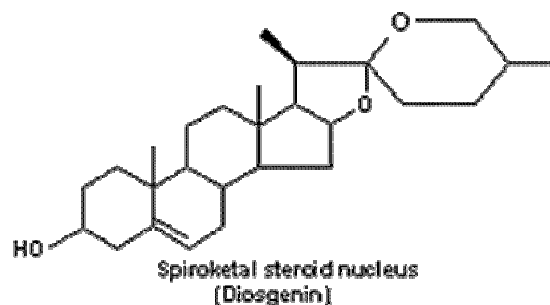


Figure 2: The molecular structure of diosgenin, the precursor for progesterone isolated from yams

Courtesy of www.friedli.com/herbs/phytochem/glycosides.html

A trip to Veracruz, Mexico

In November 1941, he found his steroid source in the most unlikely of plants, the wild yam *Dioscorea* that grows near the city of Orizaba in the state of Veracruz. Marker went on a field trip, collecting two large sacks of the tuber in the mountains of Veracruz. With this precious luggage he headed back to Orizaba to return to his position at Penn State.

Unfortunately, when he went to claim his

yams, he discovered that they had disappeared from the top of the bus; luckily he was able to bribe a police officer for their release. He later smuggled the yams across the border. Once back in Pennsylvania, Marker demonstrated that diosgenin, the compound extracted from the yams, could be efficiently synthesized into progesterone. Yet despite this achievement, not a single American pharmaceutical company wanted to commercialize Marker's process. In a 1979 interview, Marker recounted his tale of frustration:

"After I was convinced that Parke-Davis would not go into it, I tried other companies to get support. For instance, I tried Merck and they said that since Parke-Davis turned me down they would not go into it. ... Then I decided that I was going to have to go into it myself."

And so, with the determination that had once led him to walk out on a Ph.D., Marker resigned his position at Penn State, withdrew all of his savings, and moved to Veracruz. He soon became an expert on yams, harvesting 10 tons of them from the Mexican jungle. The yams were dried and reduced to a syrup that was easily transported back to the United States. Marker borrowed a friend's lab to convert his yam syrup into three kilograms of progesterone, at that time the largest batch ever produced, with a 1943 market value of about \$240,000. Convinced that his idea was commercially viable, Marker decided to return to Mexico in search of partners in industry.

Arriving in Mexico City, he turned to the phonebook. In 1944 a small company called Syntex was formed as a result of a partnership between Marker, Emerik Somolo, a Hungarian immigrant to Mexico, and Dr. Federico Lehmann, a German-trained scientist. Unfortunately, this relationship was not to last. Following disputes over profits, Marker pulled out of Syntex by the end of 1945 and established his own company. For personal reasons he retired from this position, and from

Oral Contraceptives Timeline

The development of the first oral contraceptives was a cumulative event following the work and visions of many people on an international scale - men and women as well as scientists and social activists. This timeline is an attempt to place Russell Marker, credited with inventing "the pill," in historical and scientific perspective.

1916	Margaret Sanger opens the first birth control clinic in the United States.
1921	Austrian endocrinologist Ludwig Haberlandt begins experiments on the role of progesterone.
1925	Russell Marker leaves his doctoral work and begins a career in industry.
1938	Marker proposes the Marker degradation for the synthesis of progesterone from plant products.
1942	Marker demonstrates that diosgenin, extracted from wild yams, can be used to synthesize progesterone.
1944	Syntex, a joint venture between Marker, Emerik Somlo, and Federico Lehmann, is launched.
1945	<ul style="list-style-type: none"> • Marker leaves Syntex. • Syntex recruits Dr. George Rosenkranz, a Hungarian émigré in Cuba, as research director.
1949	<ul style="list-style-type: none"> • Marker retires from chemical research. • Carl Djerassi, a chemist at Ciba Pharmaceutical Company in New Jersey, is recruited by Rosenkranz to go to Mexico as director of steroid research at Syntex
1951	<ul style="list-style-type: none"> • Norethindrone, an orally active variant of progesterone, is discovered in a Syntex lab under the direction of Rosenkranz and Djerassi. • Sanger challenges her friend Dr. Gregory Pincus to find an oral contraceptive. Katherine McCormick, a friend of Sanger, donates research funds.
1953	<ul style="list-style-type: none"> • Carl Djerassi leaves Mexico but retains a research connection with Syntex. • Dr. Gregory Pincus begins testing oral contraceptives using G.D. Searle's norethynodrel.
1960	The Food and Drug Administration approves the first oral birth control pill using the norethynodrel produced by G.D. Searle.
1962	The FDA approves a birth control pill containing norethindrone, the Syntex compound.
1970	Senate hearings held on the safety of oral contraceptives.

chemical research itself, in 1949 at the age of 47.

Continuing on Marker's foundation

Yet Syntex as well as other companies were able to continue on the foundation Marker had pioneered. Back in the early 1920s when Marker was still a graduate student, experimental manipulation in rats proved that an unknown compound secreted from the ovaries of a pregnant mammal prevented ovulation, in a process called [hormone regulation](#).

By 1950 two additional discoveries had been made. First, the "magic substance" first described in 1921 was properly identified as progesterone. Second, following the achievements of Russell Marker and succeeding chemists, progesterone had become one of the cheapest and most readily available of all hormones. Thanks to Syntex, the price of progesterone had plummeted from \$80 to \$1 per gram.

These discoveries became reality just as social consciousness was beginning to explore the concept of contraception; hormonal manipulation of the female reproductive system seemed an ideal possibility for birth control. However, progesterone itself wasn't the best candidate because it required injection; an orally-active mimic of progesterone was a better alternative.

In 1951, Carl Djeressi, the scientist who succeeded Marker at Syntex, filed for a patent on a compound he called norethindrone, a modification of progesterone. In 1953, the pharmaceutical company G.D. Searle obtained a patent on the work of Frank Colton, a chemical variant they dubbed norethynodrel. The irony of this dual discovery is that neither scientist had a birth control pill in mind when developing the compounds. There was greater interest in using progesterone mimics to synthesize cortisol, a compound

already in use as a treatment for inflammatory disease.

However, eventually the connection was made between orally active "progesterone" and birth control. After several years of testing, G.D. Searle obtained the first FDA patent for an oral contraceptive in 1960. This was followed in 1962 by a Syntex patent now marketed as part of Johnson & Johnson. Norethindrone, the chemical that got its start in a small lab in Mexico, is the active ingredient in nearly half of all oral contraceptives used today.



Oral Contraceptives - "the Pill" that developed out of Marker's work

Courtesy of [University of Arizona Campus Health](#)

The birth control pill today

The work that began with the study of sex hormones in the early 20th century involved many research scientists, physicians, and social visionaries. Indeed, there is a dialogue that continues today concerning the long-term effects of hormonal manipulation (see a timeline of the history of oral contraceptives). However, it cannot be denied that the science begun by Russell Marker has had tremendous repercussions

in many different fields. With more than 10 million users in the United States alone, "the pill," as it is commonly known, is the most common form of non-surgical birth control. Also used in the developing world, the ability to control pregnancy and family development has had an undeniable affect on women's health and social opportunities. Says Susan Scrimshaw, dean of the University of Illinois public health school:

"In the U.S., I believe, this led to more certainty in women's careers and was part of women's really growing in stature and influence in the professions. Internationally, I think, it also helped women with the sense of control over their lives and is still part of transformations in women's independence and growth in education and leadership."

In addition, beyond social influences, the scientific relationships formed in Mexico have led to beneficial growth in that country's research endeavors and scientific community. In 1951, following the patent on norethindrone, *Fortune* magazine headlined an article: "Syntex makes the biggest technological boom ever heard south of the border." Further developments needed to sustain scientific growth led to the establishment of what is now Mexico's leading research institute, the Instituto de Quimica of the National University. Noriega Bernechea, the president of the Mexican Sociedad de Quimica, says, "the debt of gratitude that Mexican research and education owe Syntex cannot be

overshadowed by anything."

It would be impossible to tally the lives affected by Russell Marker's contribution to chemistry. It would also be impossible to estimate the odds that his discovery and the steps it entailed - walking out on a Ph.D., conducting three completely different kinds of chemical research before age 40, resigning a prestigious faculty position, and spending life savings in pursuit of Mexican yams - would be made at all. And that is what makes science fun. Great discoveries are often made by those willing to see things in a slightly different way. Even a remote, inedible wild tuber has value for those willing to search for it.

References

Adams, Lisa. Mexico Celebrates Local Discovery that Led to the Pill.
http://www.canoe.ca/Health0111/26_mexico-ap.html
[Link current as of February 1, 2003]

Raber, Linda. "International Historic Chemical Landmark acclaims success of Mexican steroid industry and a U.S. chemist who made it possible." *American Chemical Society* 77 (43): 78-80, 1999.

Roberts, Royston. *Serendipity: Accidental Discoveries in Science*. Wiley and Sons: New York, 1989.

Snider, Sharon. *The Pill: Thirty Years of Health Concerns*. FDA online 1990. www.usagold.com [Link current as of February 1, 2003]

Voet, Donald and Judith Voet. *Biochemistry*. Wiley and Sons: New York, 1995.

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