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Perspectives on the History of Oral Contraceptives: Popular, Progesterone and Personal

by

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For my parents

Patricia Dutt

A selfless activist for the rights of all

And

Stephen Komor

Who taught me to ask why

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Introduction: A Revolutionary Pill

The oral contraceptive is one of the greatest and most influential developments of the twentieth century. It is the most reliable method of contraception, and one of the easiest. Today over 100 million women worldwide use a birth control pill to prevent unwanted pregnancies. Of those 100 million women, very few would recall a time when it was not only difficult to find an effective contraceptive, but it was illegal as well. Thanks to the work of thousands of scientists, doctors and women's rights activists, women can now limit the size of their families with regard to their wishes and economic constraints. No longer must they choose between sexual relations and freedom, between intimacy and good health.

Written histories of the development of oral contraceptives are many, but the perspectives they take are few. The standard history of oral contraceptives is a legal, political and social battle for women's rights. It is the story of the Comstock laws, which essentially made contraceptives illegal, and the subsequent half a century of work by the women's rights activist Margaret Sanger, philanthropist Katherine McCormick and their allies. Scientists are far less popular than the Sanger/McCormick/Comstock triad that dominates this history. In the popular press at least, biographies are by far the most prevalent form of history, and are most commonly focused on Comstock or Sanger. Each has over half a dozen biographies devoted to his or her lifetime, as well as substantial entry in general histories of sex, American politics and women's rights. By contrast, very little has been written about Gregory Pincus, the scientist who had a major role in bringing the scientific and women's rights communities together to ultimately produce the oral contraceptive as

we know it today. The first biography of Pincus, titled *A Good Man*, is scheduled for release in late 2009.[1]

Likewise, legislation is more popular than chemicals, and arrests and protests are more newsworthy than scientific developments. Recent publications on the birth control pill show the beginning of a movement toward a more complete history; Lara Mark's *Sexual Chemistry: A History of the Contraceptive Pill* is one of the newest and most comprehensive examples of the new wave of "pill biographies".[2] But most of the science behind the pill remains unavailable to the popular audience and available to the academic audience only by carefully tracing the pill's development through the scientific literature.

One exception might be books such as John Bennett's *Chemical Contraception*, written in 1974 when oral contraceptive technology was new and changing rapidly.[3] His book details the science behind different kinds of chemical contraception, including spermacides and several generations of contraceptive pills. He begins with a chapter on population control, an attempt to attract a wider audience that is indicative of the popularity of population control research throughout the 1960s and 1970s. Scientists had succeeded in extending life expectancies, a.k.a. "death control", by eradicating diseases and improving medicine and nutrition. Now, to fix the imbalance in birth and death rates, they had to produce an equally effective birth control. The importance of population control was driven by many interests: citizens' worry that they would lose their upper and middle class lifestyles due to overcrowding and insufficient resources, humanitarians' concern for impoverished and overpopulated third world nations, and western governments' concern over the

growing populations in communist nations, or nations that had the potential to become communist. These concerns would ultimately result in substantial government funding for population control, though that funding did not appear until after the pill had already been developed and was on the market in the United States.

Aside from biography, the writings of the main players are an important resource in constructing the history of oral contraceptives. Just by the titles one can see why Pincus, and numerous other scientists who worked on oral contraceptives, have faded into the historical background. While Sanger's writing credits include *Motherhood in Bondage*[4] and *The Pivot of Civilization*[5], and Comstock's include *Frauds Exposed Or How The People Are Deceived And Robbed, And Youth Corrupted*[6], Pincus's books were obviously directed towards a much narrower audience. His titles include *Uterine Changes in the Rabbit With the Advent of Pregnancy*[7] and *Hormones and the Aging Process*[8].

The scientist most commonly associated with the history of oral contraceptives is usually Carl Djerassi, an organic chemist whose work in chemical synthesis produced the second oral contraceptive to be marketed in the United States. He is far better known than Pincus, almost entirely of his own making. He has written an autobiography, as well as several other works detailing and reflecting on his contribution to oral contraceptives, and has proclaimed himself the mother of the modern birth control pill. "The organic chemist", he writes in *A Pill for People, Pets and Bugs*, "symbolizes the mother, with the chemical entity representing the egg." Within his analogy, Pincus, as the biologist, is the father and those scientists who refined the pill through clinical trials were the obstetricians and pediatricians.[9]

The problem with Djerassi's historical analysis is that there were hundreds of developments that paved the way for the initial "birth" of the oral contraceptive, and they build on one another such that it would that it would be futile to try to assign relative importance. The development of oral contraceptive contains very few grand 'aha' moments, very few great jumps in knowledge. It took 50 years to amass the hundreds of bits of information that led Pincus to choose the hormone progesterone as the active component in the first oral contraceptive, and led Djerassi and other organic chemists to synthesize orally active progesterone in their laboratories.

Some might ask, why record the history of oral contraceptives at all? Both the laws allowing birth control and the chemical recipes for creating oral contraceptives are already on the books. Recording the past will not provide us with better birth control in the future. The reason for recording the social and political history is clear, not only to myself but to the many historians who have written biographies or legislative histories on this subject. This history must exist so that we as a society don't take oral contraceptives for granted, so that we understand what kinds of laws can be used as weapons against a woman's right to choose whether or not she becomes pregnant, and so that we work to maintain this freedom, recognizing that the fight against oral contraceptives was instigated by a small group of men, and that it took almost 100 years of grassroots work by (largely) women for this freedom to be reinstated.

The argument for the recording of the scientific history may be less obvious, but is no less important. As I will show in later chapters, the early developments that provided the knowledge base for the first oral contraceptive and its successors were

produced by scientists who were not specifically looking for an oral contraceptive. Up until the 1950s, the majority of scientists who contributed to the development of oral contraceptives were practicing basic, not applied, research. Often basic research involves asking the question "what happens if we do x" – for example, remove the ovaries of a pregnant rabbit, or administer ovarian hormones. Success has a broader definition in basic research, including adding to knowledge base, making unexpected discoveries and, possibly, providing an answer to the research question. Applied research, on the other hand, is done with the intent of solving a specific problem, and success is measured by the solution or product produced. Applied research questions did not come until the last 10 or 15 years of oral contraceptive research. Such questions included: what hormone or combination of hormones makes the best oral contraceptive? What is the minimum effective dosage? Will this treatment impact fertility?

Finding funding for those later applied questions, is naturally easier because the funding organizations – be it the government, industry or private philanthropic foundations – are more generous when a tangible application is promised to follow the research. Developments such as that of oral contraceptives show how important basic research is because the applied research questions would never have been asked, and thus solved, if it were not for the knowledge base provided by basic research. The general population often fails to see how a white-coated chemist mixing chemicals in a laboratory benefits them – and ask why their tax dollars are funding his or her research. By this case study of oral contraceptives I hope to show that supporting scientific research, especially basic research, may be an act of faith in

science, but it is so incredibly important in ways that we, necessarily, cannot yet define. I also hope to honor the scientists who worked toward one of the greatest scientific developments of the twentieth century, whether they realized at the time or not.

With all due respect to this revolutionary technology, this thesis emerged from a point far from the usual women's rights focus that surrounds the history of oral contraceptives. It began one fall afternoon in Upstate New York. My mother and I had just returned from Little Tree Apple Orchards with a bushel of apples. We were perched on twin stools in the kitchen, peeling apples for apples pies and applesauce. I always cook sitting on a stool, a habit I picked up from my mother, which she in turn picked up from her grandmother. Whenever we cook with apples she always tells me – as she did that afternoon - about her grandmother, Viola Dutt, the wife of a farmer, who could skin an apple in seconds with a hand sharpened knife, leaving behind one continuous curl of peel per apple. She had to be a quick cook; she prepared three meals a day for her husband and my grandfather's eight brothers and sisters.

I had always been interested in family history, and although my grandfather didn't talk much, my grandmother made up for it by supplying little tidbits about each family member: Woody, who was killed in World War II, had a building at Penn State named after him; Robley's wife was schizophrenic, and once tried to poison the family by adding rat poison to the pies meant for dessert (she confessed before the pies were eaten).

As a scientist, one sibling who especially interested me was grandfather's older brother Ray Dutt, about whom I knew two things: he worked with sheep and he

worked on the precursor to the birth control pill. Perhaps, I thought, Dutt is a forgotten link in the translation of oral contraceptives from initial animal studies to a pill taken by millions of women worldwide. I could see how complicated assigning credit was when it came to scientific developments: does it go to the person who had the idea, who designed the experiment, or who performed the experiment? What about the work of scientists whose work sparked the original idea? Or, perhaps in my uncle's case, to the man who did the experiment, first, but on sheep, or the man who did the experiment next, on humans?

In my attempt to decipher Dutt's role in the development of oral contraceptives I dove into the scientific literature, and in an attempt to understand the impact of oral contraceptives on society I consulted the biographies and social histories. I found countless ways to look at the history of oral contraceptives. To name a few, one could consider the history as a story of advancement of women's rights, or a mission of the eugenics movement, or a fight for funding and acceptance for controversial research, or a revolution in synthetic chemistry, or the discovery of the endocrine system, or a great American invention.

In following chapters I present three versions of the history of oral contraceptives. The first is the most popular of such histories, explaining the legal obstacles to contraception against which women's rights activist worked, and eventually triumphed over, in the first half of the twentieth century. The second attempts to show that oral contraceptives represent one of the most collaborative and complex inventions in the history of the science. The third tells the story of reproductive physiologist Dr. Ray Dutt, who stands both as an everyman for the

thousands of scientists that will never receive credit for their work on oral contraceptives and as an influential scientist in his own right, who made significant contributions to the field of animal science.

Popular History: A Triumph for Women's Rights

"I wonder if you will kindly give me some advice on birth control? I have been married not quite four years and have four children…I feel I must conserve my strength for a few years for the sake of my children. My home is ninety miles from a hospital and too far from a physician to ever have assistance at childbirth."[10]

"I am a slave…If it hadn't been for people giving me cast off clothes I don't know what I would do. If you would only help me prevent from having anymore [children] I would be more than thankful. I don't think I could stand to have anymore." [11]

"After marriage I lived in the country on a farm and since I was from town many neighbors thought I knew [how to prevent pregnancy]. It was almost with tears that I had to refuse to aid the poor creatures." [12]

"I am writing in the interest of my two daughters…I think the oldest one and her husband are trying the thing they did with no success, since their fourth baby was born before their oldest one was old enough to go to school. Her husband is a mechanic and can't make enough to keep them going now, so I wish for their sakes you would write me and tell me what to do." [13]

The above quotes are taken from letters sent to the women's rights activist Margaret Sanger.[†] Written in the late 19th and early 20th century, these letters frame the traditional representation of the history of birth control in America. Due to the Comstock Laws, a series of federal and state laws enacted in the 1870s, the sale, advertisement, and in some cases the use, of contraceptives was illegal in the United States. At that time birth control methods on the (black)market included condoms, abortifactants, intrauterine devices, vaginal suppositories and diaphragms (womb veils, in early 20th century vernacular), but only those who could find the illicit contraceptive businesses and afford the various products would have benefitted, and few of the devices were known for sufficiently preventing pregnancy. Poor women

[†] These quotes are taken from a collection of letters complied and prefaced by Sanger. No names, dates or locations are given with the letters, many of which are excerpts. The collection was first published in 1928.

and those who lived in rural areas were still living in the dark ages, contracepetively speaking, relying on "natural" methods: prolonged lactation, the rhythm method and withdrawal. For all women one hundred percent effective contraception was a combination of privilege and luck.

The Comstock Laws were the work of Anthony Comstock, a writer and activist who lived and worked in New York City in the late 19th and early 20th century. Born into a devout Congregationalist family in Connecticut in 1844, he moved to New York City in 1868 after his service during the Civil War. Having grown up in a small community in traditionally conservative Connecticut he was unprepared for the diversity of lifestyles embraced by such a large metropolitan center, and he quickly became outraged by what he saw as amorality decorating every corner: brothels and pornography shops, strip shows and prostitutes.[14] For his first four years in New York City Comstock worked as a clerk and independently pursued his mission of eradicating amorality. One of his first victims was a book dealer who had sold one of Comstock's friend a "lewd" books. This friend claimed that the book had enticed him into visiting a brothel, where he subsequently contracted a venereal disease. Comstock purchased a similar book from the dealer under false pretences, and then turned the book dealer into the police under anti-obscenity statues that had been recently passed by the New York State Legislature.[15]

Comstock's assent into the highest echelons of the anti-birth control movement began in 1872 with the death of William Hayes, a book dealer as well as a pornography printer and well-known surgeon. After his death, Hayes's stock of bookplates, engravings and printing supplies, valued at $30,000, were put up for sale.

Comstock saw removing these items from the market as a step toward cleaning up New York City. He approached the Young Men's Christian Association (YMCA), an organization that had been fighting vice for a number of years, for help in obtaining Hayes's stock. They granted Comstock the $30,000, as well as man power to transport the stock to the Polytechnic Institute of Brooklyn. There Hayes's life work was systematically destroyed in one day by hand-poured acid.[16]

News of Comstock's zealotry soon reached the ears of Morris Ketchum Jesup, a wealthy merchant, financier and founding member of the YMCA. In 1872 Jesup helped Comstock establish the New York Society for the Suppression of Vice (NYSSV), of which Comstock served as director. Backed by substantial manpower and funds Comstock was now poised to pour a much more debilitating and tenacious acid on the birth control movement: The Comstock Laws.

Comstock objected to contraceptives on two accounts. As a deeply religious man he rejected birth control as "unnatural", an interference with God's will. His religious reverence for human life was magnified by his own experiences with fertility and mortality. His beloved mother died had when Comstock was 10 years old, and 18 years later, Comstock saw his first and only child die less than a year after she had been born. Worse still, he and his wife were unable to have any more children. These experiences surely fueled his anger at couples who, in his mind, were flouting their fertility by intentionally preventing pregnancy.

Secondly, Comstock was convinced that the availability of contraceptives amplified sexual promiscuity, and that the mere presence of contraceptives caused "morally weak" men to be overcome by immoral desires. Not only were most sexual

relations immoral, they were also dangerous, as shown by the example of his friend who had contracted an venereal disease after being "lured" into a brothel.

In his campaign to outlaw contraceptives Comstock took advantage of a pair of loosely enforced anti-obscenity laws already on the books. The first was the Tariff Act of 1842, which outlawed the importation of "indecent and obscene prints, paintings, lithographs, engravings, and transparencies."[17] The second, the 1865 Postal Act, was more stringent; it prohibited sending any obscene materials through domestic mail. Comstock saw that the sale and advertisement of such items would become greatly reduced if he could legally define contraceptives as "obscene". Financed by the YMCA, he spent the first three months of 1873 lobbying for such a law in Washington, D.C. Congress enacted the Comstock Law on March 3rd 1873, defining contraceptives, as well as educational material on contraceptives and reproductive health, as obscene. Three days later Comstock was appointed Special Agent to the United States Post Office, a new position provisioned by the new law. He oversaw a group of postal inspectors whose sole duty was to enforce the new law by monitoring the mail and performing raids on the businesses of suspected violators.[18]

The new law also contained a prohibition against advertising obscene material, which gave Comstock and the NYSSV the ability to prosecute anyone who published or distributed information on contraception or reproductive health, even if the publications were not sent through the mail. After passing the federal law in 1873 several states followed up with laws that made the *use* of contraceptives illegal as well. Although the Comstock Laws became less and less aggressively enforced as the

United States moved through the 20th century, they remained on the books until 1970 when Congress removed contraceptive devices from the list of obscene materials. The last of the Comstock laws did not die until 1972, when contraception for unmarried people became legal in Connecticut and Massachusetts.

Despite the Comstock laws the sale and use of contraceptives continued during the late 19th and early 20th centuries. Contraceptive manufacturers and merchants circumvented the laws in a number of creative ways. One method was to give contraceptives code names or bill them as sanitary products in public advertisements. Many in the business adopted aliases, and distributed their stock throughout the city so that a single raid could not destroy their business. As a result, the birthrate in the United States, which had been falling since 1820, remained on the decline even after 1873.[19]

The burden of enforcing the obscenity laws fell on Comstock's band of postal inspectors, of which there were only 63 in 1873. Simply bringing violators to court was difficult due to insufficient staffing and once there, Comstock and his supporters in the NYSSV were in general met with, if not opposition, non-cooperation by the courts. In many cases the courts ruled that searching mail was an invasion of an American's right to privacy. In the early days of the law Comstock and his cronies posed as contraceptive seekers to identify contraceptive merchants. The courts ruled this practice was illegal, defining it as entrapment through inducement.

The Comstock laws were increasingly weakened by the beginning of the twentieth century because the courts tended to side with the contraceptive manufacturers and consumers when they were prosecuted. A landmark 1882 case in

which a newspaper owner was arrested for advertising vaginal syringes in his newspaper significantly redefined the laws when the judge ruled that contraceptives could be sold and used for medical or hygienic purposes. By the time of Comstock's death in 1915, not one person had served the full sentence for violation of his law.[20]

Although the Comstock laws didn't have as grave an effect as they might have if Comstock hadn't been such an unlikable "religio-monomaniac", or if the courts were more conservative, they certainly contributed to the poor state of birth control in early and mid 20th century America. The laws enforced outdated Victoria morals and gave a small interest group a strong legal standing. They also made discussion of sexual and reproductive health a taboo topic, a taboo that persists even today. By the time the founder of the modern birth control movement, Margaret Sanger, came along women were vastly undereducated about their own health and contraception options, and often suffering physically, emotionally and financially due to several unwanted pregnancies. Although much of Sanger's work took place after Comstock's death in 1915, his laws, ideology and followers provided sufficient opposition for Sanger.

* * * *

Margaret Sanger was born in 1879 in Corning, NY, the sixth child of a devout Roman Catholic family. Trained as a nurse, she became an advocate for a universally available and effective birth control method after her mother died at 50 from tuberculosis, aggravated by a lifetime of weakness that had resulted from 18 pregnancies and 11 live births. Sanger too experienced poor health after just one

pregnancy and was told by her doctor that she would be risking her life if she had anymore children. Lacking sufficient contraception she had a second and a third, and spent many years in poor health. Her devotion to the birth control movement was solidified by her experiences working a nurse in immigrant neighborhoods in New York City, where she saw problems of poverty and poor health exacerbated by large families and overpopulation.

Sanger was an activist for women's rights, not just population control or women's health. Cheap, effective and widely available contraception would allow women control over their bodies, and their lives. She recognized the importance of having a method in which men did not have to be involved, to further the independence of women. Sanger, who had two husbands, and at least as many additional lovers in her lifetime, also saw oral contraceptives as a way to improve sexual relations.

Sanger's extensive and courageous work made it possible for oral contraceptives to eventually be sold commercially. Years after the pill was on the market, Sanger recalled her struggle. "I bumped up against this very, very arrogant, old fashioned, stupid law, which had to be changed… And I decided the best way to change it was to break it."[21] Her first act of protest against the Comstock Laws was to establish the *Woman Rebel* in 1914, a publication that provided information to women about preventing pregnancy. It was there that she coined the term "birth control".[22]

Entire books have been written about Sanger, and it is not my intention to try to chronologize her life in a few spare paragraphs. A list of *some* of her

accomplishments, however, gives one a feeling for her dedication. From 1914 to 1950 her work included publishing pamphlets, journals and books on the women's rights and birth control, opening the first birth control clinic in Brooklyn in 1916, organizing national birth control conferences, and establishing the American Birth Control League, which was renamed Planned Parenthood in 1942. For her efforts she endured constant public ridicule and several stints in jail, prosecuted for violation of the Comstock Laws. The following excerpt from a 1931 New York Tribune article – less than halfway through her career – characterizes the importance of her work.

> "Mrs. Margaret Sanger, founder of the Birth Control Union, has been awarded the annual medal of the American Women's Association which cites her for qualities of "vision, honor and valor"…Mrs. Sanger has carved, almost single-handed and in the face of every variety of persecution a trail through the densest jungle of human ignorance and helplessness. She has many times been arrested, assaulted and covered with mud, which remains perhaps the most substantial tribute to her pioneering genius. Pretty nearly everything and everyone had been against her… But such is the common sense of what she has been saying and great the courage and conviction of her way of saying it that people have at last begun to listen and believe. Her victory is not by any means complete but the dragons are on the run."[23]

The necessary meeting of science and politics occurred in 1951 when Sanger invited reproductive biologist Gregory Pincus to dinner.[24] Pincus was no stranger to opposition to his work. He had started his career as an assistant professor at Harvard University, and in 1934 he was the first person to achieve in-vitro fertilization of a mammalian egg.[†] His research was made public in 1936 by a reporter from the New York Times who happened to be in the audience when he presented his paper at a conference of the Federation of American Societies for Experimental Biology.[25] In an article titled "Brave New World" the reporter referred to Pincus's achievement as a "striking success", but misjudged the implications of his work:

> "Dr. Gregory Pincus of Harvard is not exactly a novelist's Bokanovsky, but he has gone far towards realizing Huxley's social order by developing rabbit's eggs in glass with the aid of nothing but strong salt solution or high temperature. The more imaginative biologists are not dismayed by the prospect of looking at a glass vessel and saying: 'That's my mother'. Serenades will still be strummed on guitars, Romeo and Juliet will still part reluctantly on the balcony, Leander will still swim the Hellespont to his Hero. Love will simply be divorced from parenthood if the biologists are right."[26]

The article was picked up by newspapers around the country, inciting a public backlash against Pincus and fertility research. In 1937 he was denied tenure at

[†] In-vitro fertilization was first achieved in 1900 by German-born American physiologist Jacques Loeb. He used ultra-violet light to stimulate development in sea-urchin larvae.

Harvard, ostensibly due departmental reorganization, though the more likely cause was a combination of the negative reaction to his research and anti-Semitism.[27] Pincus was then invited to Clark University by endocrinologist Hudson Hoagland, who he had met in graduate school. In 1939 Pincus made national news again, drawing similar "Brave New World" comparisons for engineering the first mammal parthenogenesis.

In 1944 Pincus and Hoagland left Clark to establish the Worcester Foundation for Experimental Biology in Shrewsbury, Massachusetts. Both scientists were sick of, as Pincus put it, "bickering faculty meetings, futile committees, jealous colleagues and teaching…to indifferent students." So determined were they to escape the academic life that Pincus worked as a janitor and Hoagland mowed lawns to support their research before outside funds were obtained. [28] The foundation allowed Pincus and Hoagland to devote all their time to studying the physiological effects of steroids.

By the time Pincus and Sanger met in 1951, Pincus's outside funds had come and gone. The American pharmaceutical company Searle, which had employed Pincus as a consultant since his Clark University days, had granted the foundation money to develop a financially feasible synthetic method for the steroid cortisone. When scientists at the pharmaceutical company Upjohn beat Pincus to the synthesis, Searle cut Pincus's funding. Pincus's subsequent request for funding to research the possibility of a hormonal oral contraceptive was denied by Searle. Given Pincus's interest in fertility and steroid research, and the promise of research funding from the Planned Parenthood Federation of America, Sanger had little trouble convincing Pincus and his team to turn their interests towards developing an oral contraceptive.[29]

Sanger's major source of funding for the studies came from fellow women's rights activist Katherine McCormick. As well as a philanthropist and suffragist, McCormick was the second woman to graduate from MIT, in 1904, and the first to receive a science degree from the institution.[†] She relocated from sunny California to frigid Boston to oversee the research, her training as a biologist allowing her to remain closely involved in the research progress.

After nearly ten years of research and clinical trials by Pincus's lab, and over two million dollars of McCormick's personal funds, the world's first modern oral contraceptive was released in 1960.[‡][30] If there can be any one person to whom the development of oral contraceptives can be attributed, that person is Gregory Pincus. He was the person who put the biological and chemical pieces together, the person who designed a pill fit for human use, and the person who was brave enough to first orchestrate clinical trials of his proposed pill, and then seek out a pharmaceutical company to market the pill in the United States.

As I will show in later chapters, however, one cannot identify a single inventor of oral contraceptives. It's often hard to identify even the major players, because there were so many small, but necessary, victories. Studies that lead up to the development were made in the laboratories of reproductive biologists,

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[†] Like Comstock and Sanger, McCormick had a personal relationship to questions of fertility. Her husband was a schizophrenic and during his lifetime she devoted hers to looking for a cure for his disease. For fear of giving birth to a similarly ill child, she vowed not to have any children. This conviction likely affected her intimate relationship with her husband, and influenced her position on birth control.

[‡] The distinction "modern" is used to refer to today's pill because oral contraceptives have existed at least since 500 AD. Such contraceptives were usually in the form of potions, but sometimes made into a pill. A Greek physician of the Byzantine Court by the name of Aetius recorded several such potions in his medical encyclopedia titled *On Medicine in Sixteen Books or Discourses*. Examples of these potions include "cyrenaic sap, of the size of a pea in two glasses of winy water" and "copper water in which one extinguishes hot iron, drunk continually and above all immediately after the end of menstruation, is anti-conceptional."

endocrinologists, and organic chemists. It took 50 years of gathering scientific knowledge for Gregory Pincus to decide that a hormonal oral contraceptive was a feasible pursuit.

Progesterone History: A Scientific Journey

Documenting the Scientific Studies

The scientific version of the history of the oral contraceptive pill is the discovery, purification and modification of progesterone. This history spans over 60 years, from the end of the 19th century until the first birth control pill was released in 1960. The literature on this topic is voluminous. Documenting every development in the history of progesterone is beyond the scope of this study, and, I would argue, a nearly impossible task. I provide instead an outline of the important discoveries to give the reader a sense of the complexity of the science behind oral contraceptives, and a taste of the many scientific obstacles that were overcome.

Identifying the necessary advances in scientific and technological knowledge is relatively easy; assigning responsibility for the discoveries proves much more difficult. Dr. Goldzieher, a physician and historian, characterizes the development of oral contraceptives control thus:

> "It is an appealing and romantic notion to think that great discoveries spring full-blown from the brow of a genius, catalyzed by trivial events such as an overflowing bathtub or a falling apple; indeed, some great discoveries may have happened this way. However, in today's world, with its virtually instant information access and the living presence of nine-tenths of all the scientists who ever existed, discoveries are more likely to arise from a coincidence of information,

technological advances, intellectual and societal timelines and financial support."[31]

There are hundreds of experiments associated with the development of oral contraceptives. The scientists behind those experiments will be, at best, remembered by a one-liner in a review article written in the 1960s. Others on the periphery, like those in the Animal Sciences, will probably never be connected with the oral contraception revolution. One of those scientists, Dr. Ray Dutt, is profiled in the third chapter of this thesis. When I began research on Dutt I was asking, did he get the credit he deserved for his contributions to science? After months of research that focused on reading papers from scientific journals, determining who contributed what to a scientific advancement became increasingly difficult and vague. I now ask a simpler question: what credit does he deserve?

No matter how original and innovative the results produced by a single scientist were, they were always built on developments that had come before. To make matters worse, nearly identical experiments and results frequently appear within a few years of one another. It is often unclear whether the second author is replicating the experiments of the first, or if he was simply unaware of the other's studies, as researchers in the early and mid 20th century lacked the immense data sharing capabilities that exist today. This ignorance of another's work was especially prevalent when scientists were experimenting on opposite sides of the Atlantic, so when given the choice, I opted to highlight the work of American scientists over their European counterparts. I chose to recognize scientists based on their prevalence in

summaries of oral contraceptive history that had been written by scientists, their prolificacy on hormonal research and their proximity to the important developments.

Biological Inquires

The history of progesterone begins right before the turn of the 20th century, when the scientific community clued into an observation that farmers and veterinarians had been privy to for at least half a century. In 1898 a Swiss veterinarian by the name of E. Zschokke reported that in order to restore fertility in sterile cows it was common practice to manually crush the persistent corpus lutea of those cows.[32] Corpora lutea, it had been known for some time, appeared as temporary bodies in the ovaries of pregnant cows. If the corpora lutea did not decay after the pregnancy was completed, as was normal, they would become "persistent" and impede fertility. According to Zschokke, this rudimentary infertility technology had been in use since at least the mid 19th century. Zschokke concluded that as long as the corpus luteum was present, none of the ovary follicles could mature.

Observations of this kind were translated into scientific experiments by a number of scientists. German physiologist C.H. Stratz published an 1898 study of the changes that took place in the ovaries during the pregnancies of two species of Insectivores and one of Lemurid (lemur). Stratz reported that following copulation the ovarian follicles became undeveloped. British biologist John Beard was the probably the first to articulate that the presence of the corpus luteum not only inhibited follicle growth, but also inhibited ovulation. It is unclear if earlier scientists merely neglected

to mention this obvious continuation of effects, or if they were unaware that ovulation occurs after a single ovary follicle is allowed to mature. In any case, Beard's speculations about the function of the corpus luteum, however simple, would eventually be proven true. The corpus luteum, he writes, undergoes an "increase in size during gestation that would appear to be a contrivance for diminishing the nutrition of the ovary and the ova and thus preventing a normal ovulation."[33]

Although Beard is most well known for his later work with cancer cells, his observations and theories about pregnancy and birth gave direction to the study of these topics in the beginning of the 20th century. His impact is largely due to his 1897 book titled *The Span of Gestation and the Cause of Birth* in which he catalogs his anatomical investigations, and those of his colleagues. His interest in the topic was primarily one of scientific curiosity. "The coming into being of an organism is the most wonderful phenomena in nature," he wrote. "Our knowledge of this, even in the commonest animals, is lamentably deficient."[34]

Another important early contribution is that of French histologist Auguste Prenant. He too had noticed the ovulation inhibition abilities of the corpus luteum, and proposed that that the corpus luteum was an endocrine body, imparting its effect through the release of hormones. The concept of endocrine bodies - glands that secrete hormones into the circulatory system - had been around since the eighteenth century, and experimental proof for such chemical messengers began accumulating in the mid 19th century.[†] One of most influential of such experiments, completed in 1849, showed that castration of a rooster caused atrophy in the comb, but that the

[†] The word "hormone", from the Greek "impetus", was coined in 1902 by British physiologist Ernest Henry Starling.

comb could be regenerated if the testes were transplanted to another part of the rooster's body. It was concluded that the testes released some sort of chemical messenger that acted on a completely different part of the body, demonstrating the "action at a distance" characteristic of hormones.[35]

By the end of the 19th century all of the major endocrine glands had been identified by biologists, even if their endocrine function was not yet known. The major glands include (in order of discovery): the gonads (ovaries and testes), the thyroid, the pineal gland, the pituitary gland, the adrenal glands, the pancreas and the parathyroid gland.[‡] By the mid 20th century most of the hormones released by these glands had been identified, and the endocrine system was recognized as one of two main control systems of the body. The second control system, the nervous system, responds to outside stimuli, such as heat or pressure, by sending an electrical signal through the body's extensive network of neurons. In contrast the endocrine system usually responds to a change in the internal environment of the body such as a change in the concentration of glucose in the blood. The response of the endocrine system is to secrete hormones into the circulatory system, which then distributes the hormone throughout the body so that it can act on the appropriate organs. For example, if the body senses the level of glucose in the blood is too high the pancreas will secrete insulin into the blood stream. Insulin causes the body's cells to take up glucose and store it for later use.

Studies of the corpus luteum lay dormant for over a decade until American pathologist Leo Loeb picked them up in the early 20th century. In 1911 he published the first comprehensive study of the cycles of the ovary, truly setting the investigation

[‡] See Appendix B for a diagram of human endocrine glands.

of the function of the corpus luteum into action. In his introduction he notes that since 1898 "no more detailed investigation into the processes taking place in the ovaries under various conditions has appeared as far as we are aware. Within recent years, however the question has been raised whether a new ovulation can take place during pregnancy."[36]

Loeb's study of hundreds of pairs of ovaries from guinea pigs in all stages of life and fertility sought to answer this question, as well as create a detailed picture of ovarian cycles. He allowed guinea pigs to become pregnant naturally and then surgically removed their corpora lutea. After observing ovulation in several of the guinea pigs he concluded that pregnancy itself was not an inhibitor of ovulation. Rather, the corpus luteum, active during pregnancy, was influencing ovulation.[34] Early studies on the impact of the corpus luteum on reproduction in mammals would rely heavily on the scientific knowledge base Loeb had built. One such paper acknowledges his influence thus: 'It has been shown by Loeb that one function of the well developed corpus luteum in the mammalian reproductive cycle is to inhibit ovulation. This fact appears to be firmly established for mammals by his observations and experiments.'[37] †

In 1914 Raymond Pearl and Frank M. Surface at the Maine Experiment Station published a study that set a number of precedents in corpus luteum research. Instead surgically implanting or removing whole corpora lutea, as was the strategy of

† Similar work occurred in labs across Europe, though communication across the Atlantic was not good, and Loeb's developments were independent of such work. In Innsbruck, Austria professor of physiology Ludwig Haberlandt surgically planted ovaries from pregnant rabbits under the skin of normal adult rabbits, rendering them infertile. In Vienna Otfried Fellner showed that ovarian (estrogen) extracts inhibited pregnancy by preventing the formation of the corpus luteum

Loeb, they injected animals with corpus luteum extract (or "luteal extract").[‡] Secondly, they used livestock fowl as their test animal, instead of the more traditional rabbit or guinea pig. Birds have no corpora lutea, nor do they have any analogous organ, so there was no reason to believe a corpus luteum extract - a mammalian product – would have any impact on the reproductive systems of birds. Despite this, Pearl and Surface found it scientifically valid to inject bovine corpus luteum extract into two groups of twenty actively laying fowl. Stranger still, the injections prevented ovulation.

This study is one of the earliest to seriously consider the findings for real life applications. These were not experiments done on laboratory animals, but on farm animals that were an economic commodity. As researchers at a state experiment station, Pearl and Surface would have been more concerned with the marketable applications and economic benefits of their research than with amassing a wider knowledge base, as was a primary interest of Leo Loeb. The researchers hypothesized that if there was a chemical that could prevent ovulation, there might also exist a chemical that could enhance ovulation, and thus enhance the egg laying capabilities of birds. This would have obvious economic benefits for Maine farmers. "We hope shortly to undertake experiments in this direction," they concluded.[38]

This study's application of corpus luteum research to such an unlikely test subject, the bird, shows the level of scientific interest in the corpus luteum in 1914. Often when a scientific development is particularly innovative – such as the ability to prevent contraception - scientists from every discipline will attempt to apply that

[‡] Pearl and Surface were probably the first American group to use corpus luteum extract. The first experiment that injected corpus luteum extract into mammals was performed by Herrmann and Stein in Europe in 1916.

development to their work. When carbon nanotubes were discovered in 1991, for example, researchers proposed applications of nanotubes ranging from sunscreen[39] and tennis rackets[40], to electronics[41] and cancer drug delivery systems[42]. Alas, unlike luteal extract, carbon nanotubes have not yet found a revolutionary application akin to oral contraceptives. If the history of the development of oral contraceptives is any indicator however, at least 30 years of research remains before such an application emerges.

Isolation of the Corpus Luteum Hormone

One of the major challenges faced by researchers performing reproductive hormone studies in the 1910s and 1920s was that luteal extract was not a standardized preparation. It could include one or more hormones, and because most of the sex hormones were not characterized until the mid 1930s, researchers could never be sure which hormone(s) they were working with. Content of the extract varied with starting material, which could be the entire ovary or hand-harvested corpora lutea, and with extraction method. Even if the scientist successfully isolated the hormone he wished to target, the medium with which the extract was mixed could determine its efficacy. Injections in a lipid medium usually worked, injections in an aqueous medium were less reliable.[43] Oral administration was never successful.

By the 1920s ovulation inhibition and other effects characteristic of early pregnancy had been attributed to luteal extract. Several research groups, including those associated with Leo Loeb, showed that luteal extract produced proliferation in

rabbit endometria and that guinea pigs responded to the extract by preparing their uterus for placenta development. Another group working on similar animal studies was the team of F.L. Hisaw, R.K. Meyer and C.K. Weichert at the University of Wisconsin. The group primarily tested the impact of luteal extract on the guinea pig's symphysis pubis, a cartilaginous joint that unites the two pubic bones near the base of the pelvis. During pregnancy in guinea pigs, and in humans, the symphysis pubis relaxes and expands measurably, usually two to three millimeters. Hisaw et al. found that luteal extract did produce a relaxed symphysis pubis as well as inhibition of ovulation and the alteration of the endometrium. Scientists suspected that the effects of the luteal extracts were the result of a single hormone, but they weren't positive. The next logical step was to isolate and characterize the hormone, or hormones, having these effects.

In 1929 Willard Allen, a young researcher at the University of Rochester Medical School, entered the luteal extract debate. Allen was one of the largest contributors to the development of oral contraceptives, second only to Gregory Pincus, and perhaps Leo Loeb. In 1930 he called for the purification of progesterone, highlighting the difficulties caused by the undefined mixture of corpus luteum hormones. "The fact that [multiple] hormones must have been present in the corpus luteum extracts of earlier workers, before the specific tests were discovered, [renders] it not impossible that still other hormones may be concerned in the different effects described, for example, by Hisaw and ourselves. For this reason it is important to purify the potent substances as far as possible and to determine their respective chemical characteristics and physiological effects."[44]

Allen was unique because of his flexibility across disciplines; he performed both chemical and biological studies with ease and he was the driving force behind the isolation of the corpus luteum hormone. He entered medical school on a whim, it seems, for he recalls he approached the Dean's Office at Rochester in the fall of 1926 without an appointment and having made no formal application. "To make matters worse," he recalls in his memoirs, titled *Recollections of My Life With Progesterone*, "classes had already commenced. Admissions processes were clearly quite different from today, as he was quickly interviewed and admitted. Allen concludes, "I recommend this irregular approach to Medical School; it attracts attention."[45]

In 1927, Sydney Asdell and F.H.A. Marshall of Harvard University had shown that the hormone estrogen does not produce the same effects that luteal extract imparts, thus proving that estrogen was not the corpus luteum hormone.[†46] In 1929 Allen and his mentor George Corner further showed that placental extract did not have the same effects as luteal extract.[47] That same year they published a study in which they allowed rabbits to become pregnant and then removed their ovaries 18 hours later. With the injection of luteal extract the embryos grew and implanted in the uterus as normal; without the extract the embryos died within four days. The authors concluded "The evidence is now complete that in the rabbit the corpus luteum is an organ of internal secretion which has for one of its functions the production of a special state of the uterine mucosa (endometirum) and that in turn the function of the proliferated endometrium is to nourish or protect the free blastocytes and to make

[†]Estrogen had been isolated in 1924 and was purified in 1928 by E. Allen et al. at the University of Washington. Not incidentally, Leo Loeb was at that time a member of the faculty at the University of Washington. Although Loeb's name is not on that particular paper, the names of several of his collaborators are.

possible their implantation."[48] In other words, the corpus luteum was essential for maintaining pregnancy. They applied this information to develop a standardized bio-assay for the corpus luteum hormone that was instrumental in both the isolation of the hormone and in future studies that assessed the hormone's physiological impact.

Having thus personally confirmed the effects of luteal extract Allen heeded his own call to isolate the hormone. By 1930 he had succeeded in removing all the known lipids (fats) from the luteal extract, leaving only a yellow, hormone rich oil.[42] After asking around the biochemistry department at the University of Rochester for assistance in further purifying the hormone, and receiving none, he recalls "I realized then I was in unchartered territory."[43] He decided to try using vacuum distillation.[†] This was an unprecedented application of the technology, and his eventual success afforded him the honor of being the first person to use vacuum distillation to purify a biologically active compound. Kodak Laboratories, the facility in which he performed the distillation, went on to use his application to distill vitamins A and D out of cod liver oil.

In 1934 Allen and Oskar Wintersteiner, a chemist at Columbia University with whom Allen collaborated, published a paper characterizing the several different compounds that appeared in luteal extract and identifying one as the anovulary hormone. The isolation method they used was a slight variation on the distillation method Allen had developed at Kodak and published in 1932.[49] Incidentally, three other research groups published reports of isolation of the hormone in the summer of

[†] Distillation is a process that separates liquids based on their boiling points. In traditional distillation liquids are boiled by heating, causing the liquids of lower boiling point evaporate, or distill, from the mixture. Vacuum distillation incites boiling by using a vacuum to lower the air pressure on the liquid. This technique is especially helpful when removing liquids of high boiling points, such as oils.

1934: two German groups, Butenandt and Westphal; and Slotta, Rushchig and Fels; and a Swiss group, Hartmann and Wettstein.

The nearly simultaneous isolation success touched off a scramble for recognition, disguised as a debate over the name for the newly isolated hormone. In his 1930 paper Allen had proposed the name "pro-gestin" for its function of encouraging gestation, or the carrying of the fetus. In 1934 Slotta and Butenandt informed their American counterparts that they had agreed to call the hormone "luteo-sterone", or yellow steroid. Allen recalls, "This development did not appeal to us, as we had named the hormone progestin in 1930. On January 14, 1935 Corner dispatched a masterful letter to Slotta in which we suggested progesterone and progestenone as suitable names for the hormone. By giving up our name progestin we hoped Slotta would give up his."

Given Allen's presumptuous "application" to medical school, it is no surprise that his name became the international standard. That summer Allen was invited to attend a special conference of the Health Organization of the League of Nations whose purpose was to standardize the use of several sex hormones, including the recently isolated anovulary hormone, as well as give each a standard name. These standards would have a positive impact on future sex steroid research; from then on when one scientist used one unit of progesterone in his experiment the rest of the scientific community would know exactly how much of which hormone was being used. One evening, having retired to a pub with Alan Parkes, the secretary of the conference, Allen mentioned that Slotta and Butenandt would be proposing luteo-sterone as a name for the anovulary hormone. Parkes, Allen recalled, "Blew his stack.

The three of us then settled down during our midnight supper to a serious discussion of possible names for the new corpus luteum hormone. I was armed with the names progestenone and progesterone. Parkes…convinced me that progesterone was the better word and so the name was born." To drive home his success Allen published his 1935 paper "Nomenclature of the Corpus Luteum Hormone" in not one, but four journals, in two different languages: English [50] and German[51].

With the successful purification of progesterone scientists now needed to verify progesterone's responsibility for effects that had been formerly attributed to luteal extracts. At the University of Pennsylvania A. W. Makepeace, along with George Weinstein and Maurice Friedman, used Allen and Corner's bioassay to publish the first paper to confirm that progesterone inhibited ovulation in the rabbit.[†]

The paper also investigated the mechanism of inhibition, for which the authors proposed three possible scenarios, all concerning modification of the gonadotropic hormone, follicle stimulating hormone (FSH), which is released from the pituitary and causes ovulation.[52]

In the first scenario progesterone was proposed to decrease the sensitivity of the ovary follicle to FSH, so that the ovary would not recognize the "message" to ovulate. Makepeace at al. tested this by simultaneously administering a large dose of progesterone and an ovulating dose of FSH. Most of the rabbits in the test did ovulate, and the authors concluded that ovaries in the presence of FSH would release an egg regardless of whether or not progesterone was present. Thus progesterone did not reduce the sensitivity of the ovary to FSH and must intercept FSH prior to reaching the ovary.

The next step was to determine if FSH is destroyed en route to the ovary after being released by the pituitary. Weinstein had tested this hypothesis in an unpublished study by injecting several different gonadotropic hormone preparations, including FSH, into rabbits with active corpora lutea. The injections were given at levels only slightly above the normal ovulating dose, so the amount of each hormone present in the rabbit was approximately equal to physiological levels. Weinstein observed ovulation in almost all the rabbits, showing that progesterone does not intercept FSH after has been released into the bloodstream.

Finally, having ruled out the previous two scenarios, the authors concluded that progesterone must somehow inhibit the release of FSH from the pituitary. Based again on unpublished work, this of Freidman, the authors note that progesterone does not interfere with synthesis of FSH in the pituitary; the amount of FSH available in the pituitary at the time when the corpus luteum is active in the body would be sufficient to prevent ovulation were it released. Thus they conclude "There remains…only one likely mechanism of the progesterone inhibition of ovulation: this is, some interference with the post-coital release of the pituitary hormone [FSH]."[49]

That group was one of the first to try to elucidate the mechanism and in the coming decades they would be proven correct. Today scientists have mapped out the many roles of the corpus luteum. It functions to prepare and maintain the uterus for pregnancy, and to prevent contractions of the uterus prior to the full development of the fetus. The corpus luteum forms from the mature ovary follicle that erupts when an egg is released, i.e. when ovulation occurs. It then releases progesterones and estrogens that thicken the endometrium, the inner layer of the uterus, in preparation

for receiving and nurturing an egg. The progesterone released also prevents a second ovulation, as Beard observed. This allows the body to concentrate its resources on a single fetus. Within about five days of fertilization the ovum becomes a blastocyst, which releases a hormone called human chorionic gonadotropin (hCG) that tells the corpus luteum to continue releasing progesterone. This positive feedback cycle maintains the thick endometrial layer necessary to support a developing organism, and continues to repress ovulation. If the egg is not fertilized hCG is not produced, the corpus luteum eventually decays, and a new ovulation occurs.

Hormone Chemistry

In some sense the elucidation of the mechanism of action was unimportant to the development of progesterone as an oral contraceptive. Based on animal studies scientists now knew the minimum dose necessary to prevent ovulation, and that was really all that was necessary for use as an oral contraceptive. There were, however, two roadblocks, which would occupy the next 15 years of oral contraceptive development.

The first problem was that progesterone was still prohibitively expensive and difficult to produce. All hormones, not just progesterone, were expensive in the early 20th century because the only source was other mammals. Some of the first hormone production facilities were offshoots of slaughterhouses; previously unmarketable parts of livestock like ovaries, testicles, and other endocrine glands suddenly became very valuable as sources of hormones. Human and mammal urine was an additional

source for researchers. Hormones are a very potent class of molecules, which means that only a small amount is necessary to have the intended effect. As a result only a small amount is present in the body at any one time, and thus yields from hormone harvests were very low. For example, the testosterone extraction method of German scientist Ernst Laquer produced five milligrams of hormone from one ton of bull testicles.[53] In 1935 it took approximately 2500 pregnant sows to produce one milligram of progesterone.[54] With these methods the price for progesterone remained at $1000 per gram.[55]

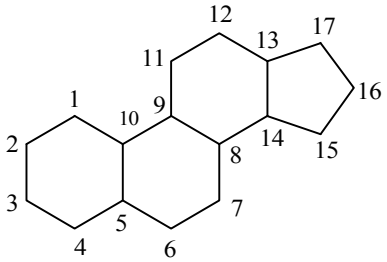
Allen's "simplified" method of progesterone production began with a large vat of cow or sow ovaries which were "finely minced and then ground with sea sand." The hormone was then separated from proteins and other large molecules present in the ovary mixture by extraction with a boiling solvent, such as benzene or alcohol. Extraction uses essentially the same technology as making a cup of tea. The ovary mixture, akin to tea leaves, was placed in a in a porous bag, similar to the tea bag, and left to seep the boiling solvent. The hormone molecules are quite small and dissolve easily in the solvent, while the protein and other molecules that provide structure to the ovary remain in the bag. Just as a tea bag can be used multiple times because not all of the tea oils are removed in the first cup of boiling water, the bag of ovary mixture too was extracted multiple times. The procedure stated that "three extractions are sufficient to extract all of the progestin, provided that the tissue in the bags is broken up by kneading between each extraction and the alcohol is kept boiling vigorously."[56]

To complicate matters, hormones aren't the only molecule soluble in the solvents; phospholipids (fats) which make up the cell walls, and other small molecules also entered the solvent. The removal of phospholipids required several more extractions, and then Allen's vacuum distillation method was applied. Maximum yield, when beginning with 1500 grams of ovary, was 0.3-0.4 grams of progesterone.

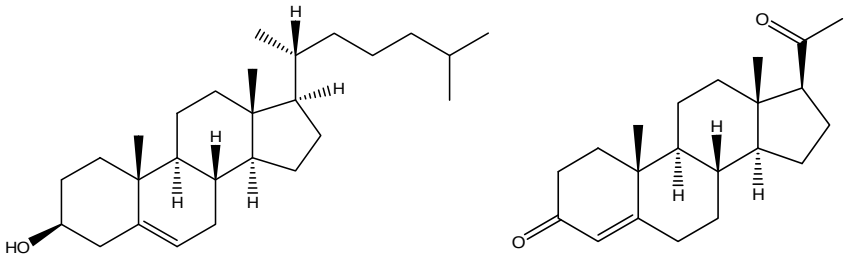
Performing the extraction on a large scale - production of a gram or more, the amount necessary to do large scale physiological studies - brought additional complications. Rochester slaughterhouses could not fill Allen's need for ovaries, so he sent his assistant, Carl Goetsch, down to Chicago for fresh ovaries. Allen writes, "Putting 200 lbs of ovaries through an ordinary meat grinder seemed to be a big job. We solved this one by using the power meat grinder in the hospital kitchen, but I must say that the personnel in the kitchen were not happy about it. I suspect, however, that our ovaries were fresher than some of the meat which normally went through the grinder."

The extraction process began as soon as the ovaries left the grinder. Large vats of boiling alcohol are neither pleasant nor safe, and the approach to ventilation was simplistic, and indicative of their devotion to the project. "We were concerned about the methanol fumes in the laboratory but we had no choice; extraction of the hormone had to be done in methanol. Since it was summertime we opened all the windows, turned on the electric hot plates and boiled methanol for days until the entire lot of ovaries had been extracted. Fortunately neither Carl Goetsch nor I suffered methanol poisoning."[57]

In the mid-1930s European scientists developed a way to synthesize progesterone from cholesterol. Cholesterol is the natural starting material from which the mammalian body biologically synthesizes all steroid hormones, progesterone included. Both cholesterol and progesterone are steroids, a class of organic (carbon based) molecules that have four fused carbon rings. (The "sterol" in the name cholesterol indicates that cholesterol is a steroid alcohol). The method was not widely used in the United States, however, because it required large amounts of cholesterol, harvested from the brains and spinal cords of bovine mammals.[58]



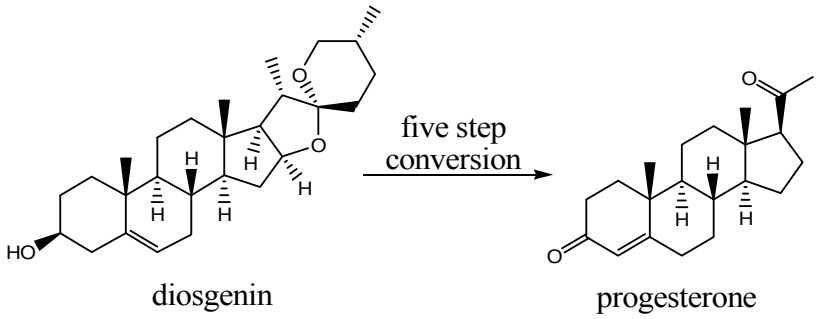
Basic steroid structure: Each line indicates a bond between two atoms and each point where lines intersect indicates a carbon atom. Traditional numbering of the carbon atoms is shown. The addition, through bonding, of different atoms or groups of atoms, called substiuents, create the different steroids.



cholesterol progesterone

Comparison of cholesterol and progesterone: Modifications of the basic steroid structure give cholesterol and progesterone distinct physiological functions. In the diagram traditional representation of stereochemistry is indicated. Solid triangles indicate a bond that is coming out of the page, while dashed triangles indicate a bond going into the plane of the page. Solid lines indicate bonds and atoms parallel to the plane of the page. Unless the end of bond (line or triangle) is specifically marked with an atom, such as 'H' for hydrogen, the bond is assumed to end with a methyl (CH_4) group.

A breakthrough in progesterone synthesis finally occurred in 1940. American biologist Russell Marker came across a paper by Japanese scientists that described isolating the plant hormone diosgenin from *Dioscorea tokoro*, a species of wild yam. Inspired by diosgenin's similarity to cholesterol he developed a relatively simple five step process to convert the plant hormone into progesterone. Unable to get sufficient support for continuing studies of diosgenin, he abruptly left his post at Pennsylvania State University, and in 1942 moved to Mexico, where he set up a laboratory in an old pottery shed. Marker spent the nest two years traveling all over Mexico collecting wild yams. By the time he had found the wild yam he believed had the highest diosgenin content, the Cabeza de Negro, he had tested over 400 different species in his makeshift laboratory.[59]



Comparison of diosgenin and progesterone.

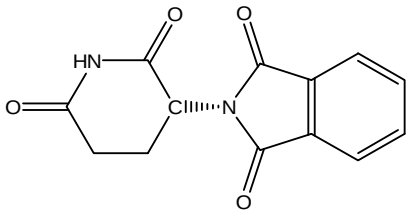
In 1944 Marker co-founded the chemical company Syntex in central Mexico with Hungarian businessman Emeric Somlo. The sole purpose of the company was to synthesize steroids using the Cabeza de Negro as a starting material. Although Marker's work originally began with progesterone, his discovery would have impacts far beyond the production of a single hormone; by 1955 80-90% of all steroid synthesis worldwide began with the Barbosa, a cousin of the Cabeza de Negro that had been found to have an even higher diosgenin yield.[60]

* * * *

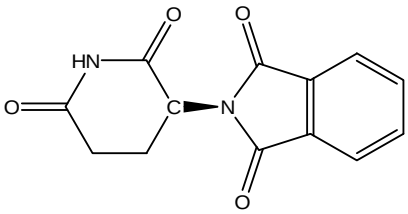
The second major obstacle that stood in the way of oral contraceptives was the fact that natural progesterone was not orally effective. Taken by mouth, natural progesterone is metabolized and deactivated by the liver and then excreted in the urine. Progesterone had debuted as a drug in the late 1930s, given to women as treatment for habitual abortion and dysmenorrhoea (painful menses).[61] Unfortunately,

administration was either by large and painful injections or by less potent, and messy, direct vaginal insertion.

Creating an orally effective progesterone was a problem attacked by synthetic organic chemists, chemists whose specialty is modifying and synthesizing chemical compounds. One of the shocking and amazing things about biochemistry is that two molecules that differ by one atom, or even the placement of one atom, can have vastly different functions. The thalidomide tragedy is an example of this phenomenon. Thalidomide was a morning sickness drug sold from the late 1950s until the early 1960s, when it was linked to serious birth defects in the children of mothers prescribed the drug. Further investigation showed that the drug had two enantiomers, each of which had a different physiological effect. Enantiomers are two molecules that have the same number and type of atoms; only the orientation of those atoms differs. They are mirror images of one another, and like one's hands, enantiomers are similar but not the same. One enantiomer of thalidomide was suppressing morning sickness, while the other was producing often serious birth defects.



(S)-thalidomide

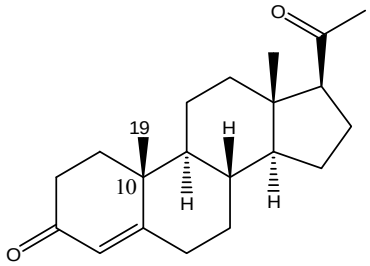


(R)-thalidomide

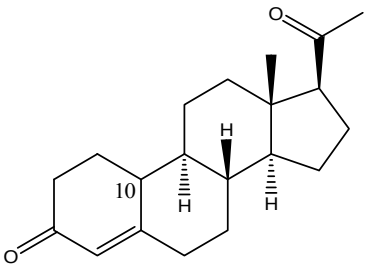
Comparison of (S)-thalidomide and (R)-thalidomide: The above molecules are enantiomers. The only difference between the two molecules is the direction of the central carbon-nitrogen bond. The (S)-enantiomer causes severe birth defects while the (R)-enantiomer helps prevent morning sickness.

In the 1940s Max Ehrenstein of the University of Pennsylvania began investigating the effect of slight structural modifications on the function of progesterone. At that time several biologically active estrogens had been synthesized that had little structural similarity with natural estrogen.[62] This essentially means that scientists had made, in their laboratories, a series of molecules that acted like estrogen but did not look like estrogen. "The question arises," the authors wrote, "at what stage simplifications in structures of the naturally occurring hormones are accompanied by the loss of physiological activity."

With that question in mind Ehrenstein attempted to synthesize 10-norprogesterone, meaning he removed the methyl group from progesterone's number 10 carbon. He was only mildly successful with the synthesis - the product was impure and the yield was a dismal 0.07% - but when he, under the tutelage of Willard Allen, injected the material into two rabbits he found that it had the same biological activity as progesterone. This small scale experiment was hardly scientific proof of 10-norprogesterons's functions, and due to the low yield there was not enough material for subsequent studies. The small success, however, was enough to turn scientists' attention towards norporgesterones as a potentially cheaper or orally effective alternative to natural progesterone.[63]



progesterone



10-norprogesterone

Comparison of progesterone and 10-norprogesterone: The only structural difference between the two hormones is the presence of a methyl group at the 10 spot. 10-norprogesterone is also known as 19-norprogesterone, because the methyl group removed is number 19.

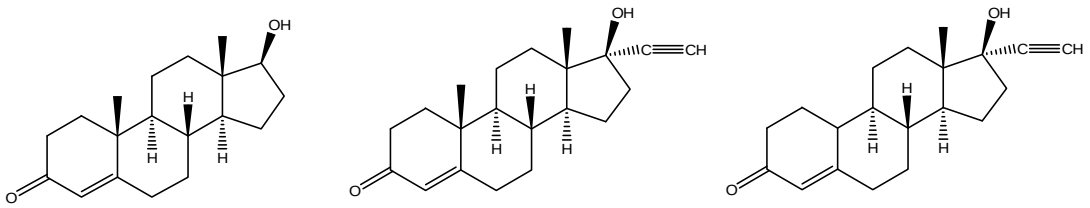
In 1953 Carl Djerassi, who had joined Syntex in 1948, and his colleagues at the Syntex laboratories, L. Miramontes and G. Rosenkranz, published a simplified synthesis of 10-norprogesterone. They modified a method developed by English chemist A. J. Birch in 1950 and use the hormone hecogenin, found in agave plants, as their starting material.[†] Whereas previous 10-norprogesterones had been a mix of stereoisomers, the product produced by Syntex had identical stereochemistry to natural progesterone. The substance, named 19-norprogesterone because the methyl removed was number 19, was found to be four to eight times as potent as natural progesterone when injected, by far the most potent progesterone known at that time.[64]

With the knowledge that the simple removal of a single methyl group could increase biological activity four to eightfold, the team at Syntex turned their attention to another hormone: 17-α-ethynyltestosterone. Birch had reported that the androgenic effects of this testosterone analogue were reduced when the methyl group was

[†] Both hecogenin and diosgenin, used by Marker to synthesize progesterone, are members of a class of plant hormones called sapogenins.

removed from carbon 10. (Androgens enhance and maintain masculine characteristics.) Many years earlier, in 1938, German scientist Hans Herloff Inhoffen had reported that 17-α-ethyltestosterone was an orally effective progesterone, though not as potent as injection of natural progesterone. Djerassi's team successfully synthesized 19-nor-17-α-ethyltestosterone in 1951, renaming it a more manageable norethisterone.

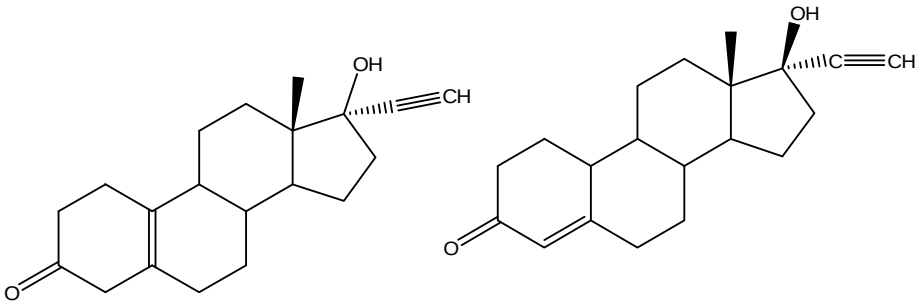
In 1954 human clinical trials of norethisterone were completed by Dr. Roy Hertz at the National Institutes of Health, who was interested in the compound's ability to treat menstrual disorders such as dysmenorrhea (painful menses), endometriosis (growth of endometrial tissue outside of the uterus), and functional uterine bleeding (irregular cycles with excessive bleeding). The studies showed that not only was new compound was several times more potent than 17-α-ethyltestosterone, but it was orally effective as well.[65]



testosterone 17-a-ethynltestosterone 19-nor-17-a-ethynltestosterone

Comparison of (A) testosterone, (B) 17-α-ethyltestosterone and (C) 19-nor-17-α-ethyltestosterone: A is converted to B by the addition of ethnyl to the 17 carbon; this structural change reduces the androgenic effects of testosterone and imparts weak progesterone-like activity. B is converted to C by the removal of the 19 carbon, which significantly increases the progesterone-like activity of the hormone.

A year after Syntex reported the synthesis of norethisterone, Searle, a Chicago based pharmaceutical company, synthesized another orally active progesterone analogue. The Medical Director at Searle had asked his chemists to produce an orally active progesterone for treatment of menstrual disorders in the summer of 1952, and by the end of the fall Searle chemist Frank Colton had produced norethynodrel.[66] The compound's structural similarity to norethisterone would eventually cause bad feelings between Colton and Djerassi, especially because Colton's compound became the first FDA approved oral contraceptive. In later years Djerassi would note that the 1952 directive, and Colton's synthesis, came after his successful synthesis was reportedly complete. It is worth noting, however, that Syntex's news of norethisterone was only provisionally announced in April of 1952 and wasn't published in a scientific journal until 1954.[†67]



norethynodrel norethisterone

Comparison of norethynodrel and norethisterone: Norethisterone (Djerassi's compound) is converted to norethynodrel (Colton's compound) in the laboratory when reacted with acid, or in the stomach when reacted with gastric juices. Due to this reaction, by the time the hormone reaches the blood stream it is the norethisterone isomer, regardless of which hormone was originally ingested,.[68]

[†] Djerassi's patent for norethisterone was filed in Mexico on November 22nd, 1951. Colton's patent for norethynodrel was filed in the United States on August 31st, 1953.

From Hormone to Hormonal Contraceptive

The concept of a hormonal oral contraceptive originated in 1924 when Austrian biologist Ludwig Haberlandt stated that placental and ovarian hormones could be used for fertility regulation in female animals and humans. In 1931 he explicitly suggested these hormones for *Geburtenregulung* (birth control), but his death a year later precluded any further work.[69] In 1936 another Austrian, obstetrician R. Kurzrok, presented a paper on "The Prospects for Hormonal Sterilization" at the Contraceptive Research and Clinical Practice conference held in New York City. His ideas were ignored. Ten years later, in 1945, Dr. Fuller Albright specifically described the ovulation-inhibiting qualities of estrogen, and suggested it as a contraceptive.[70] He too was ignored. By the time Sanger and Pincus joined forces in 1951, the idea of a hormonal contraceptive had been around for at least 25 years. For this reason we must recognize the complexity of the development of oral contraceptives, which was dependent on a convergence of scientific knowledge, technological ability, legal allowance, financial resources and the people to put it all together.

Pincus's role in the final seven years of oral contraceptive development was as the conductor is to an orchestra. All the pieces of knowledge were present, but it was up to Pincus to orchestrate putting them together. He had to reconcile the biological information – which hormones prevented ovulation when taken orally, but had the least side effects – with the chemical – which hormones were quick, easy, and inexpensive to produce. He organized the first large scale human clinical trials, and coordinated the efforts and concerns of women's rights activists, pharmaceutical

companies and the religious right. Endocrinologist Egon Diczfalusy writes, "The development of different scientific disciplines follows its own characteristic zigzag type of evolution along different dimensions, which must be connected in form by some sort of chicken wire by a creative mind – Gregory Pincus – in order to provide a real breakthrough."[71]

Due to undesirable side effects of estrogen Pincus decided to focus his work on progesterone. The first study he directed – most of the laboratory work was done by his partner, biologist Dr. Min-Chueh Chang – was a repeat of Makepeace's 1937 work with rabbits. After proving to himself that progesterone did inhibit ovulation, he wrote to pharmaceutical companies, requesting samples of their synthetic progesterones. Under Pincus's direction Chang and a group of researchers at the Worchester Foundation tested over 200 compounds, eventually selecting three as the most potent: Syntex's norethindrone and Searle's norethynodrel and norethandrolone.[72]

To carry out clinical trials Pincus partnered with Dr. John Rock, who was in the interesting position of being a well-respected member of the Catholic community and a proponent of birth control. Trained as a gynecologist, Rock had devoted his career to both curing infertility in sterile women and developing contraceptive methods to help women whose health or wellbeing would be endangered by a pregnancy. In 1924 Rock had established the first infertility clinic in the United States in Brookline, Massachusetts, and in 1936 he established a second clinic to teach the rhythm method, which he had developed. The rhythm method, though of variable reliability as a contraceptive method, proved to be helpful in treating infertility.[73]

The first human clinical trials began in 1953 with the small-scale administration of one of the three synthetic progesterones to infertile women and nurses at the Worcester State Hospital. Much was demanded of the women who participated in this study. First, control data was taken of their menstrual cycles to confirm that they were ovulating normally. Progesterones were then administered orally, vaginally or by injection for 20 days of each cycle. During and after the cycle women were instructed to take their temperature and vaginal smears daily, and undergo monthly painful endometrial biopsies during each cycle. No doubt that these measures were necessary for scientific completeness, but the time and comfort these women donated, not to mention the possibility of adverse effects that always accompanies testing a new drug therapy, was a great contribution to millions of women.[74]

The study was a success. All three compounds inhibited ovulation, and side effects were minor and rare. In addition seven of the 48 women tested conceived within five months of the last treatment. The authors concluded, in a statement that sounds both relieved and victorious: "Hence it appears in these seven instances, at least, that the steroids not only did not damage the ovaries but, on the contrary, may have been helpful in the relief of sterility."[75]

Having thus shown that synthetic progesterone was both an orally effective ovulation inhibitor and non-toxic Pincus and Rock were ready for large scale clinical trials. They faced a problem, however, because contraceptives were still illegal in Massachusetts, and, under the anti-obscenity laws, so was contraceptive research. They could no longer disguise their research as infertility research – which was legal

– because they needed to test the hormones on fertile women. As a result all three large scale trials were performed outside of the United States; two were conducted in Puerto Rico and one in Haiti. Physician Edris Rice-Wray, one of the few women in a position of power during progesterone's long history, was the on-site supervisor to the clinical trials in Puerto-Rico, while Celso-Ramon Garcia coordinated the efforts between the United States and Puerto Rico. Data from the studies helped Pincus and his colleagues set the dosage at ten milligrams of norethynodrel (Colton's hormone), with a small amount (150 micrograms) of an estrogen called mestranol to prevent breakthrough bleeding. By the end of the trials in 1958 over 800 women had taken the pill.[76]

The Food and Drug Administration (FDA) approved the Pincus/Colton pill, named Enovid, in 1957 for gynecological disorders, and in 1960 for contraceptive use. The Djerassi/Syntex pill was also approved as therapy for gynecological disorders, but Syntex's marketing partner in the United States, Parke Davis, refused to market the pill as an oral contraceptive for fear of a backlash from Catholic Americans and other conservative groups. Pincus's pill had avoided this fate by having Rock on board. The presence of Rock – a Harvard faculty member, a well-respected gynecologist and a Catholic – was largely responsible for Searle's agreement to market Enovid as an oral contraceptive. Even with Rock's collaboration Pincus and his group concealed their research aims to avoid condemnation before their experimental results were complete. In the fall of 1956 Pincus, Rock, and Garcia had attended the Laurentian Hormone Conference to present a lengthy paper on the laboratory and clinical studies of synthetic progesterones, without once mentioning

their contraceptive potential. After the presentation one of the attendees commented "One fact that stood out in this study is that Dr. Rock has unwittingly… given us an excellent oral contraceptive which may be applied with little untoward effect." None of the three authors said one word in reply, although the first clinical trial had been underway for some months.[77]

Syntex resolved their problem by choosing Ortho as its new marketing partner, but because Parke-Davis refused to release the necessary clinical trial data that proved the safety and the efficacy of the pill, Syntex was forced to spend the next two years redoing the trials to meet FDA approval. Syntex's pill was finally put on the market in 1962

The birth control pill was first major advance in contraceptive technology since the introduction of the condom in 1869. In other words, it had been almost 200 years since progress had been made in the field of contraception.[78] Legally the contraceptive pill could only be prescribed to married women, but, fortunately, the version of the pill prescribed for gynecological disorders was chemically identical. Unmarried women thus skirted the law by "developing" serious gynecological disorders. By 1965 the pill was the most popular form of birth control, prescribed to 6.5 million married women and untold number of unmarried women in the United States.

Personal History: Dr. Ray Dutt

In 1948 a young graduate student in animal science published a study on progesterone's ability to regulate fertility. In the past such experiments had been done on the rabbit or the guinea pig, which served as a model of the human system. This time the study's author, Dr. Ray Dutt, chose to perform his experiments on sheep with the intent of better understanding the reproductive physiology of sheep. Dutt hoped that progesterone would control the reproductive cycle of the sheep, and more specifically, control it in such a way that fertility would be enhanced.

Up until the mid 20th century the study of progesterone was focused on humans. The scientists from the previous chapter used animals as a model for the human system, performing experiments so that they could better understand how the human body functions. John Beard, Willard Allen and Leo Loeb were trained as medical doctors. Carl Djerassi, Frank Colton and the other chemists who helped develop orally effective progesterone did so with the comfort of their human consumers in mind. If livestock had been the focus the chemists would not have bothered with an orally effective progesterone; injections are often preferable to orally delivered drugs when dealing with livestock because the drug dosage is easier to control. The possible benefit of an orally effective progesterone would have been outweighed by the cost of research incurred by pursuing such a drug.

By mid-century, however, a large enough knowledge base on progesterone and reproductive physiology had developed so that scientists could now conceive of a number of applications for the knowledge. Dutt's 1948 study came at a time when 50 years of progesterone research was diverging into two research programs: in humans

the ultimate goal became the suppression of fertility, while in animals the goal was enhancement of fertility. As a result, Dutt's study had an impact on both programs of study. In his role as a minor contributor to the first he serves as an everyman to all the scientists who were essential to the development of oral contraceptives, but whose contribution cannot be quantified and can only be discussed as a part of the larger body of progesterone research.

As a major contributor to the field of reproductive physiology in animal science he represents the animal scientists who pioneered the field of livestock reproductive physiology. He is completely unknown outside of the animal science community, although his work on progesterone impacts millions of meat-eating Americans every day. In this way Dutt is also a representative of the animal science field, a discipline about which the general public knows little, but that has a significant impact on our society today. Finally Dutt's 1948 study, and the rest of the research that comprised his career, show that the history of the development of oral contraceptives may begin with progesterone, but the history of progesterone does not end with oral contraceptives.

* * * *

Dutt's story begins on the farm, the birthplace of animal science and of nearly all the animal scientists of his generation and the generation that preceded him. He was born Ray Horn Dutt on August 26th, 1913 in Bangor, Pennsylvania.[†79] Bangor is

[†] Biographical information on the Dutt family and Dr. Ray Dutt was obtained through personal interviews with Dr.Dutt unless otherwise noted.

located in the northeastern corner of Pennsylvania Dutch Country, 75 miles due west of New York City.[‡] His father, Elmer James Dutt, was a farmer, and his mother, Viola Horn, was a former schoolteacher. Dutt was the third of nine children; the youngest was my grandfather George. Dutt remembers George being born, at home of course, with a doctor there to help with delivery and one of his mother's sisters coming for a week or two until Viola had regained her strength. That was 1927 and Viola was 41 years old. The first Dutt child, Jim, was born in 1910 when Viola was 24, which means she had nine children in the span of 17 years. Large families were not unusual at that time, especially on the farm when extra hands lightened the work in the fields and the barns.

Many children, too, softened the blow of the loss of one or two children to illness at an early age. The Dutts are made of strong stock though; the family did not lose anybody until World War II. They are known for living long lives, and keeping their hair until the end. Elmer Dutt lived until age 81, and died with a full head of black hair. My grandfather was one of the youngest to die; he died in 2005 at age 83 of cancer caused by a lifetime of smoking and exposure to coal dust, at Bethlehem Steel, were he worked as an engineer. Ray Dutt is 95 and still living in Lexington, KY. When my mother and I visited him in the summer of 2008 he easily rattled off the birth dates of all his siblings, and recalled his studies on sheep in acute detail. His hair had turned white but it was thick and neatly parted to one side.

[‡] The Dutts have been farmers in Pennsylvania at least since the beginning of the 19th century, if not earlier. Ray's brother Carl, who still lives in the Dutt farmhouse, believes that the farmhouse was built around 1800 because all the beams in the house are hand hewn. If the house had been built much later the beams would have been cut by a circular saw.

Elmer Dutt was a successful farmer. He kept cows for milk, chickens for eggs and pigs for meat, an apple and peach orchard that had a couple of hundred trees, and a large vegetable garden. Everything that family did not eat was sold at the market. Even during the Depression the Dutts prospered, partially due to the fact they were on a farm and could provide all their own food, and partially due to Elmer's business acumen. Somewhere along the line he had decided that strawberries would be a good investment because it would be easy to have the kids help with the propagation and harvest. The strawberry crop brought in 700 to 800 dollars a year, even during the Depression. "Without that you know it would have been tough," Dutt said. "If my father had just dealt with his cattle I don't think he could have made it. He diversified where he could take advantage of the kids helping, like picking strawberries."

Elmer did well enough that in 1929 he was able to put up $1000, which made the difference between the cost of running electric lines into the neighborhood and the funds provided by a government grant for which he had applied. That year the Dutts got indoor plumbing, a refrigerator, a new kitchen to accommodate the new electrical stove and a radio. Before 1929, it was frontier days. Dutt remembers taking baths before 1929, Saturday nights in a big washtub that sat in front of the fireplace in the kitchen. Before they had a refrigerator food was stored in what Dutt referred to as "the cave", a root cellar in back of the farm house. I saw the cave one summer, and it was just as Dutt had described: about 20 slate steps that descend steeply to an underground cellar fifteen feet from the front door of the house. Today the steps have decayed into a treacherous, mucky ramp, so I viewed the cellar the best I could from

ground level. It was inconceivable to think that 200 years ago someone – my great great, or great great great grandfather, had hacked 10 feet down into the earth, and then created an underground room, with only hand tools.

Elmer and Viola may have been successful, but theirs was a hard farm life. They recognized that it didn't have to be that way for their children, and so were both strong proponents of education. Despite the sacrifice of sending the children to school while work built up on the farm, Viola and Elmer insisted that all their children, boys and girls, get a high school education, and go to college if they wanted. Education was particularly important to Viola, who had been a schoolteacher in her early twenties but was prohibited by law from continuing her work after she married Elmer. Dutt and his siblings did their farm chores around school, in the mornings and the evenings, and on the weekends. At the age of eleven Dutt became responsible for driving the farm's team of horses to harrow and drag the fields. When Dutt came back from college for Christmas vacations he says his father "insisted I go along with him to market so that he could show me to his customers. I think he wanted to show me off as a student."

The value of education was instilled in the Dutt children at a young age. When Dutt was in third grade the one room school he attended, close enough to be seen from the Dutt's house, closed due to low enrollment. He transferred to a two room school in nearby Johnsonville, to which he had to walk a mile and a half every day. The walk didn't bother Dutt, but he was upset about being set back in his education as a result of the switch. "The [new] teacher gave me a geography book," he recalls, "and I already had that book. She said 'you just pitch in and keep quiet'. She kept me

in the third grade because she wanted to keep an equal number of students in each grade. She did the same thing to another boy, John Harsing, kept him in the third grade instead of letting us go ahead in the fourth grade."

Dutt entered high school in 1928 and graduated four years later in 1932, in the midst of the Depression. He spent the next four years working on the farm and at part time jobs around Bangor. He also played the trombone in the East Bangor Band, which he enjoyed, because the band traveled around the area and allowed him to get off the farm from time to time. In 1936 Dutt got a job driving a truck for road construction efforts near Bangor. When the job finished he had saved $360, and decided to go to college because he "wasn't doing anything else", and he had enough for a year of tuition at Pennsylvania State University in State College, Pennsylvania. In the fall of 1937 Dutt went down to State College with his brother Jim, who had been at Penn State for the past two and half years. He enrolled in the Animal Science program, a natural choice as he had grown up on what was primarily a dairy farm. That was the rationale Dutt gave when I asked why he chose the major. "My farm background, I guess," he said.

All the animal scientists I spoke to during the course of my research, both of Dutt's generation and of the generation after him, grew up on farms or ranches. (Even though family farms are rapidly disappearing, this remains the case today). It was clear that Dutt's farm background led him to the agricultural sciences, but he could have chosen plant sciences, or agricultural economics, or any number of majors for which he would have been equally qualified. My grandfather George went into engineering, Dutt's older brother Jim went into horticulture. Dutt, however, really

liked being with the farm animals. When I asked his children for an anecdote about their father they both independently recalled a childhood Christmas morning when Dutt left before breakfast and presents to attend to some of his sheep that were ill. Dutt's graduate students would have tended to the sheep in Dutt's absence, but it was important to Dutt to personally care for the sheep.

Agriculture and animal science are relatively new as academic disciplines, although agriculture has been around for millennia. Institution of agriculture as a field of higher education within which advanced scientific research occurs started with the Morrill Land Grant Act of 1862. The federal government recognized that strong agricultural and technological industries, and knowledgeable scientists and engineers to run those industries, would be highly beneficial to the United States. The government provisioned public lands to each state of the union to be used to establish public colleges - so-called land grant colleges - to teach "agriculture and mechanical arts" (engineering).[80] Any extra land not being used as a physical part of the college campus was to be sold off to private buyers; the funds from the sale would take care of the colleges' yearly expenses. Land was given to states in proportion to their populations, 30,000 acres for each Congressional senator and representative, so there was sure to be extra land.

The new colleges were successful at disseminating knowledge, however no new information was being produced through research, so no significant advancement in agriculture was made. What states needed was a research establishment to perform the scientific experiments that farmers, who were forced to turn a profit every year or perish, had neither the time nor the money to carry out. In 1887 that need was

recognized and answered by the Hatch Act, which granted $15,000 a year to states for the establishment and maintenance of an agricultural experiment station. The stations would both conduct scientific research and disseminate that research to area farmers.[81] Except in the case of a few states that already had research stations, the new stations were established as wing of the state's land grant college.[82]

Pennsylvania State Agricultural Experiment Station 1890

From Pennsylvania State University Archives[83]

Pennsylvania State University was, and continues to be, one of the largest land grant institutions in the nation. Their Animal Science program (called Animal Husbandry during Dutt's undergraduate years) was formed in 1907 as a part of the Pennsylvania experiment station.[84] The program served Dutt well, even providing him with housing. When Jim graduated, Dutt, left without a roommate, moved into the sheep barn to save money. He lived there for a year and half before moving to the cattle barn as a senior. Each barn had a room outfitted like a dormitory, with beds for

four students and in exchange for taking care of the animals the students were allowed to live in the barns free of charge. Between taking care of the livestock and taking summer jobs, by the time he graduated in 1941 he had about $360 to his name – the same amount with which he had entered school. "I got a scholarship. I studied in college. I wasn't a playboy at all," he said, by way of explanation.

And he was smart. Even among what had to be a group of exceptionally smart and hardworking young men and women – you wouldn't leave the farm in those days unless you had one, or more likely, both qualities– Dutt was exceptionally smart and hard working. He was awarded the Alpha Zeta scholarship in 1937, which was given to the freshmen who had the highest grade point average in the College of Agriculture. While at Penn State Dutt received two additional scholarships given to exceptional students in the animal sciences, the Arthur Bigelow Scholarship (1939) and the Louise Carnegie Scholarship (1939-1941).[†]

The cup the school gave him when he won the Alpha Zeta award sits on the table next to his television set in his living room in Lexington. Next to the Alpha Zeta cup is a one nearly identical cup, this one awarded in 1940 for *High Individual Meat Judging and Identification Contest*. "This is for being a good judge?" I asked Dutt when I noticed the cup. "That's what the professor said, I guess," he replied. I later discovered that the award was given at the International Livestock Exhibition in Chicago, the World Series of livestock shows. It was an honor even to be picked for the exhibition team – Dutt went to Chicago along with five of his classmates – not to mention winning an honors.[85] It is possible that Dutt, given his age, had forgotten the

[†] What goes around comes around. Penn State currently awards the Ray H. Dutt scholarship, endowed by Dr. Dutt and given to outstanding students in the animal sciences department.

circumstances under which he won the award, but it is equally likely that the omission is due to his humility. In any case having kept the awards for nearly 70 years shows how much they meant to Dutt.

Cattle Judging Class in the 1930s at Penn State

From: The History of the Department of Dairy and Animal Science[86]

Dutt '41 Wins Trophy

Ray H. Dutt '41 was declared winner of the National Merit Trophy Award at the International Livestock Exposition in Chicago Tuesday. Dutt won the award last year given by the Penn State Block and Bridle Club for being the outstanding senior in animal husbandry.

An announcement in *The Daily Collegian*, Penn State student newspaper, Dec 4th 1940

Dutt's final accomplishment at Penn State was winning the John W. White Fellowship, which provides funds for one year of graduate study at any university the student chooses. In 1941 Dutt went out to the University of Wisconsin in Madison, which was, and still is, one of the largest, and arguably the best of the land grant institutions. Wisconsin was one of the few states to establish an "experimental farm" prior to the 1887 Hatch Act, and it was one of the first experiment stations to embrace dairying, which set the precedent for a well established animal science department.[87]

Dutt's advisor at Wisconsin was Dr. Lester E. Casida, a young geneticist and a pioneer in the new field of reproductive physiology. [†] This relationship would later be fruitful to Dutt when he began his job search; Casida's graduates were aggressively recruited by animal science departments across the country.[88] Casida had trained under Dr. Fred F. McKenzie, a founder of the reproductive physiology field who was on the faculty of the University of Missouri from 1924-1941. McKenzie performed some of the first research on artificial insemination technology, work that Casida continued and expanded on during his tenure at Wisconsin from 1934 to 1970.[89] Casida's work, primarily in cattle, laid the groundwork for understanding hormonal control of livestock estrous cycles and for identifying environmental and genetic factors that impact ovulation and embryo survival. Dutt, as an early member of the third generation of reproductive physiologists, would carry on much of Casida's work during his 30 year career.

[†] It may now seem inappropriate that a geneticist would be working on reproductive physiology and endocrinology, but 1941 there was no such thing as an endocrinology department at the University of Wisconsin, and genetics research was, of course, much more rudimentary than it is today. The original proposal for an endocrinology department was submitted in 1959 by Casida and three other faculty members, Dr. E.S. Gordon (medicine), Dr. W.H. McShan (zoology), and Dr. R.K. Meyer (zoology).

Dutt began research with Casida as soon as he got out to Wisconsin. Casida's previous work had been to test the impacts of various hormones on the reproductive tracts of sheep, cattle and pigs, and in 1942 the pair began to look for a hormone that would bring a herd of sheep into estrus at the same time, known as synchronizing estrous. "Estrus", commonly known as "heat" is the period of the female mammal's sexual receptivity to the male. The estrous cycle refers to the time period between the beginning of one estrus and the beginning of the next. This cycle ranges from 4-5 days (rat and mouse) to 21-22 days (horse). The estrous period also varies for different species. At the short end of the spectrum are the guinea pig and the rat, which have an estrus period of 8 and 14 hours respectively, and at the long end is the dog, at 7-9 days. The rabbit, notorious for exponential reproduction, is in constant estrous. Most mammals undergo an estrous cycle, although humans and great apes undergo the analogous, but not identical, menstrual cycle. Ovulation occurs during or immediately after estrus. This ensures that the sperm enters the body at the same time the egg is available for fertilization.

Synchronizing estrous has multiple benefits for livestock breeders. First, it allows the breeder to know exactly when his herd will go into estrous. This in turn allows him to plan for insemination, and then inseminate the entire herd at the same time. As is the case today, in the 1940s farmers did not rely on chance to get their livestock inseminated. They did not allow their co-ed sheep to mill around in green pastures and mate as the mood struck them. Farmers paid large sums for prize rams that were known for producing hearty offspring, and brought that ram into the ewes' pasture for a short period of closely controlled breeding. If they could predict when

the ewes would be in heat within a day or so they could reduce the amount of the ram's time they had to pay for, and ensure that the entire herd was impregnated. In later years, when artificial insemination became the standard method of breeding many livestock species, estrous control became essential for timing the insemination.

The second benefit would be a uniform lamb crop. If all the ewes became pregnant at the same time, they would also all give birth at the same time. This ensured that all the lambs would be approximately the same size when it came time to bring them to market, making it easier to negotiate a desirable price. Although the sheep was used in this experiment, Dutt and Casida expected their results to extrapolate to the cow and the pig, more popular and profitable livestock with similar reproductive cycles. The benefit of the sheep as a test animal is economical; not only is the animal inexpensive, but it can be housed in small quarters and can tolerate low quality feed.

As important as being able to identify estrus was, no fail-safe method had yet been developed to do so consistently. In the 1940s farmers relied on experienced herdsmen who could detect behavioral changes that indicated estrous. For example sows will exhibit an "immobility response", or stand still, when pressure is applied to their back. Farmers also had the option of releasing into the female flock an aproned ram equipped with a device that would mark the females he mounted. Only females that were in estrous would allow a male to mount, and thus the estrual females would be marked. This method was useful for livestock that did not demonstrate distinctive estrual behavior, like the ewe, whose only behavioral change is "restlessness".[90]

In 1942 Dutt and Casida attempted to synchronize estrus using gonadotropic hormones.[‡91] Gonadotropic hormones, as explained in Chapter Two, induce ovulation by stimulating the ovaries, a type of gonad. Dutt and Casida hypothesized that simultaneous injections of the hormone would cause simultaneous stimulation of the ovaries, and thus the herd would ovulate at the same time. For the experiment to be a success, however, the herd would all have to go into estrous at the same time as well.

The 1942 experiment tested two different gonadotropic preparations, unfractionated anterior pituitary extract and follicle-stimulating extract (FSH).[†] The hormones did exactly the opposite of what the researchers hoped they would do. The effect of the FSH was barely distinguishable from the effect of the control except that in some cases it shorted the estrous, giving researchers a smaller window in which to inseminate the animals. The unfractionated extract increased both the length of the estrous cycle and the variation in start date, making it harder to predict when an ewe would be in estrous. Gonadotropic hormones would not answer the cycle control problems of animal scientists.

The resulting paper was not published until 1945 due to Dutt's entrance into the US Army in late 1942. Rather than wait to be drafted into the infantry, he preemptively enlisted in the Marines because he could get a commission after only 10 weeks in service. "I could have probably stayed out of the service awhile longer," he said, due to an offer to work for the Hercules Powder Plant, "but I had brothers in the

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[†] The authors chose the first because they know that the hormone came from the pituitary, and the second because they knew that the hormone acted on the ovary follicles. At that time no pure preparation of gonadotropic hormone was available.

service."[†] He served for two years as part of a marine unit that was performing security on a navy base in Trinidad. The navy base was in place to protect American Liberty ships that were transporting bauxite from Venezuela to the United States.

Dutt met his wife Louise during the war on a blind date. Louise was a psychologist in the WAVES who helped develop IQ tests for the navy.[‡] She was stationed in Washington, D.C., where Dutt was sent for a month to complete his discharge. Dutt was rooming with a friend who was dating his future wife's sister. The couple set up a blind date for Dutt and Louise, but the night before the date the war ended. Both Dutt and Louise were partying until the early hours of the morning and didn't feel up to a date that night, but, fortuitously, neither managed to get in touch with the other to cancel.[92] They went on the date and were married six months. Their ceremony was in Johnston, Pennsylvania, Louise's hometown. Dutt couldn't find any suits that fit in the stores around Johnston because the war had just ended, so he got married in a borrowed jacket.

* * * *

When Dutt returned to Wisconsin in 1946 he picked up his work on synchronizing estrous. After reading the literature on hormonal control of reproductive cycles, he decided to try progesterone in the place of gonadotropic hormone extracts. Dutt knew that the lifetime of luteal tissue was about 14 days, so he

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[†] Of the seven Dutt brothers, five went to war, and three returned. The two that remained in the United States, Carl and Robley, were exempt because they were working on the family farm in Bangor.

[‡] WAVES is an acronym for Women Accepted for Volunteer Emergency Services.

decided he would perform 14 consecutive days of injections, with the goal of eradicating all functional corpus lutea from the previous estrous period. After 14 days all the sheep would be at the same point in the estrus cycle, that is, the point when no luteal tissue remained. Dutt's hope was that the sheep would then all enter their natural estrus cycles at the same time and thus ovulate at the same time.

Dutt obtained 30 sheep at the beginning of the 1947 breeding season and divided them into two groups: 12 sheep would receive ten milligrams of pure progesterone a day and 18 sheep would receive five milligrams a day. Each of those groups was divided evenly into three subgroups to begin their injections on either the fourth, eighth or twelfth day after the first day of estrous. Prior to the start of the injections each ewe was allowed to go through one natural estrous cycle so that Dutt and his researchers could take control data. Dutt recorded the occurrence and length of estrus by releasing an aproned ram into the ewe hold twice daily. An ewe was recorded "in heat" if "she allowed the ram to mount and remained standing if he had mounted."[93]

After the suite of injections was complete each ewe was subject to an observational laparotomy to check for silent ovulation (ovulation when estrous is absent). Ewes were then allowed to go through an estrous cycle, artificially inseminated, and then slaughtered 36 to 48 hours after the artificial insemination. Their reproductive tracts were removed and "immediately taken to the laboratory where a thorough search was made for ova". Dutt and his team wanted to make sure the progesterone hadn't interfered with the fertility and viability in the ova. The ability to synchronize estrous would be worthless if it rendered infertile eggs.

All the injections, surgeries, and monitoring of behavior was done by Dutt with little assistance from herdsmen or lab technicians. While it was not – and still is not – unusual for a graduate student to do hands on, often tedious data collection, Ph.D. researchers often pass most of the hands on work off to laboratory assistants. Even in later years, as he prospered in his professional career and rose in the ranks at the University of Kentucky, Dutt preferred to do his own data collection.

This time the experiment was a success. The authors reported that they had controlled the time of onset of estrous for 100 percent of the ewes on the higher (10mg) dose and 67 percent on the lower (5mg) dose. Regardless of whether the treatment began on the fourth, eight or twelfth day of estrous, all of the ewes began estrous within 0.1 day (2.4 hours) of each other. By comparison the control variance was observed to be 0.5-1.4 days (12-32 hours).

With the success of the study Dutt was able to complete his Ph.D. thesis, and apply for positions that would allow him to continue his research in sheep fertility. He had two options for employment: either work for a pharmaceutical company, developing drugs to enhance livestock fertility and productivity, or work at a land grant university. He chose a university position because of the independence it would allow. Although animal science is an applied science, within the context of animal science research Dutt's scientific interests were considered "basic" because his research goals were not solely focused on finding solutions to a specific problem. I once asked Dutt what he would do if he were active in the field now. He replied that he was interested in sex determination, and the ability to choose sex of an offspring.

"But do you think that is a good idea," I asked, "To be able to choose the sex of your child? Would you want to choose the sex of your child?"

"It would be interesting to know how it works," he replied. He preferred to ask 'what if', and elucidate the mechanisms and reasoning behind scientific phenomena. Although he appreciated the benefits his research conferred on livestock breeders, he saw the scientific knowledge as more valuable than any pill or potion that resulted from his work.

Dutt eventually chose the University of Kentucky in Lexington because of his interest in sheep research. At that time Kentucky had a flourishing sheep industry, and, as a result, the Kentucky experiment station conducted a lot of sheep research.[†] A letter written in 1951 to UK College of Agriculture Dean Frank Welch by Richard Miller, a sheep specialist at the UK extension, describes the sheep industry in Kentucky. "Kentucky lambs are widely known in the trade as the best lambs produced. For a number of years…Kentucky farmers received a higher price per pound for their lambs than any farmers of any other state…The sheep industry [in Kentucky], which grossed better than 25 million dollars last year could well be increased to double this amount in a few years time."[94]

In addition to the economic importance of sheep to the state of Kentucky, they were a source of pride. The UK archives contain announcement after announcement of UK sheep winning national and international titles. One announcement commemorated the death of "Champ", also known as "Old Champ", "the finest Southdown sire ever born". Champ was named reserve grand champion at

[†] The sheep industry was mostly devoted to lamb, not wool production. For example meat sales accounted for over 93% of the proceeds of sale of the UK's sheep crop in 1960. The remaining percentage was proceeds from wool.

the Chicago International at the young age of 10 months and sired a legacy of prizewinners. He died at the ripe old age of seven, and in 1957, three years after his death, Southdown sheep breeders, state and UK officials unveiled a monumental gravestone to honor Champ. The announcement state that, as far as UK knows, "Champ is the first sheep for whom such an honor has been accorded."[95]

Given UK's devotion to sheep, Dutt clearly made a good career choice. As he tells the story, UK wanted Dutt just as badly. "Garrigus [then the head of the Animal Industry Department at UK] wanted a nutritionist. I wrote and told him that my training was in reproductive physiology and that I wanted to work in that field, not in nutrition. And then a couple weeks later he wrote me a letter and said that he had a position here for a reproductive physiologist. Would I come down and look at it?" Dutt was hired as an assistant herdsman and quickly moved up the ranks to be named associate professor in 1954.

Dutt's first paper in conjunction with the UKY experiment station was published in 1953.[96] That its publication comes less than a year before he was promoted from herdsman to professor may be coincidence, but at the very least Dutt's thorough and productive research proved to the university his competency as an independent researcher. This study displays the three major characteristics of Dutt's work. One, he valued his independence and often worked alone, as he did in this study. Two, he preferred studies that were structured with a basic, rather than applied, knowledge goal. Three, he most commonly worked with sheep, although in later years he also worked with swine.

The second and third characteristics can be explained by the short summary of the experiment; the first characteristic – independence - needs a longer explanation, which follows after the summary. The purpose of the study was to the test the impact of progesterone on anestrous ewes. Many mammals, ewes included, only exhibit the estrous cycles during certain times of the year. Sheep exhibit estrous only in late summer and early fall. The rest of the year do not ovulate and are not receptive to sexual advances from rams. This is referred to as the anestrual period, and is a problem for breeders because it means they only get one crop of lambs per year. Dutt's research was based on two developments from several earlier studies. The first was his discovery that progesterone synchronized estrous in estrual ewes. Secondly, had several studies showed that Pregnant Mare Serum (PMS, a gonadotropic preparation) reliably induced ovulation in anestrual ewes, but that ovulation was accompanied by estrous in only a small number of cases. Dutt hypothesized that some combination of PMS and progesterone injections would consistently produce ovulation *and* estrous in anestrous ewes.

The test herd was divided into eight groups of nine ewes each. One group received no injections, one group received only PMS, one group received only progesterone and the remaining five groups received one to five progesterone injections on three day intervals, followed by a single PMS injection three days after the last progesterone treatment. The data was consistent with Dutt's hypothesis. The no injection control group exhibited neither estrous nor ovulation and the PMS-only group exhibited only ovulation, as expected. About half the ewes in the progesterone-only group ovulated and showed estrous. Among the sheep that received both

hormones, all but one ewe ovulated. The occurrence of estrous increased with the number of progesterone doses. At the highest dose, five injections of progesterone, all the ewes showed estrous.

The importance of this study for Dutt was the clues this provided about the ewes anestrual cycle. Based on his results Dutt concluded that pre-treatment with progesterone somehow prepared the body for estrous when the ovulation was induced a few days later. This would later be valuable information for researchers who were trying to understand the natural reproductive cycle of livestock, and trying to control that cycle with hormones. Notably absent was any mention of possible applications to lamb breeding for this research, the most obvious of which is increasing lamb production by inducing ovulation and impregnating ewes during the winter or spring, a time of year that ewes do not naturally become pregnant.

Dutt was the only researcher named on the paper. He generally preferred to work alone on his studies, even to the point where he took care of his own sheep, instead of letting technicians and farms hands do what other researchers viewed as mundane grunt work. Part of this independence comes from Dutt's farm background. Farm life had trained him to endure, and to expect, long hours of hard and often mundane work. In Bangor if the farm was not cared for the family did not eat; as a professor at UK the consequences were not so severe, but Dutt clearly did not make that distinction. Work was a way of life. Dr. George Mitchell, a friend and former UKY animal scientist, told me that Dutt put a new roof on his house when he was 79 or 80 "just to show that he could do it. For a couple of months he skipped about half

or two thirds of his golf rounds.[†] He did everything: he took the old shingles off, he carried the new shingles up the ladder and put them on the roof, hammering them in by hand. I don't think he had one of these power hammers like they use nowadays." Dutt thinks he was younger, probably in his early 70s, but really, putting on your own roof is impressive at any age.

I did not know Dutt in his earlier days, but the stories of his hardworking, humble attitude reflect my personal experiences with his brothers. My grandfather George was the kind of man who would come visit his daughter, my mother, and fix the kitchen sink, the garden fence, the wiring for the stereo, prepare dinner, and then sit around afterwards looking jumpy with the lack of activity. One of the first things he did when he retired was get a job at the local golf course, where he worked for the next twenty years. He worked up until two weeks before he died. My great-uncle Carl, who still lives on the farm, is now 83. Carl was a postman in his younger years, spending the mornings and evenings working on the farm. Ten years ago he planted a small orchard, 30 apple and peach trees. In addition to maintaining the orchard he plants a large garden every year, mostly tomatoes and peppers. When my mother and I visited last summer we left with a gift of 25 pounds of fresh picked vegetables, the extraction of which hardly made a dent on the bounty of the garden.

Dutt's independence comes also from a scientist's attention to detail that some might call perfectionism. Dr. Lee Edgerton, a reproductive physiologist at UK and a mentee of Dutt's, recalled a time when Dutt felt that the UKY herdsmen weren't

[†] Dutt's absence from his thrice-weekly golf get-togethers was often the only indication that something was going on in his life. He had back surgery in his early 60s and told no one about it, even his closest golf buddies, which included Dr. Mitchell. He simply did not show up to golf rounds one day, and then reappeared on the green a few weeks later, standing a bit straighter.

taking proper care of his research sheep.[97] In the most quiet and respectful way possible Dutt told the chairman of the animal science department that he refused to continue his research until he got a private sheep unit. His request was quickly granted, which indicates the value of Dutt as a faculty member at UK.

This attention to detail would serve Dutt during his service as editor of the *Journal of Animal Science*, the most prestigious journal in the field. The editorial job was described to me as a labor of love, vastly unpaid and overworked. Dutt was the last volunteer editor for the journal; when his three year stint ended in 1966 the journal hired a full time editor to do the job Dutt had been doing in addition to teaching and research. Dutt credits his wife with his success as an editor; he reviewed the papers for scientific accuracy while his wife corrected for style and grammar. His daughter Kathy said that as children, if she and her brother Phil wanted to find their parents the best bet was to check their bedroom, where one would be hunched over the typewriter while the other was dictating or correcting a paper copy. The hardest part of being an editor was turning down a paper. "It wasn't pleasant to know that when you say this paper is not acceptable, it doesn't meet the standards of the journal, you're making an enemy."

Dutt also served as the vice-president and president of the American Society of Animal Science in 1967 and 1968, respectively. The year that Dutt was president the annual meeting was held in Tulsa, Oklahoma, near the Acoma Native American reservation. For some reason that is lost to all those that were present, the Indian chief conferred honorary tribal membership on Dutt. That was the meeting where Edgerton first met Dutt, and his first sighting was of Dutt doing the tribal dances that were part

of the induction ceremony. Edgerton noted that such behavior was very uncharacteristic of Dutt, which, based on my other interviews, seemed largely true. On the other hand, while many of his colleagues told me he was very quiet, his niece Susan remembers him as a story teller. Susan's recollection accurately reflected my personal experience with Dutt; I visited him for several days in a row, during which he told hours of fascinating stories about his work and his life.

Dr. Dutt at the American Society of Animal Science annual meeting in 1968, the year he was president of the society. The photograph shows Chief Wayne Wolfrobe Hunt conferring membership in the Acoma Indian Tribe on Dr. Dutt, far left.

Photograph courtesy of Kathy Dutt.

Edgerton, who was a graduate student in the 1960s, told me that the atmosphere of mid-century scientific research, especially in reproduction, also contributed to Dutt's predilection for independence. Today researchers, especially in

large universities, tend to work together so that they can pool money and manpower, thus producing quicker and more comprehensive results. Researchers can then put their names on a greater number of papers, resulting in personal advancement, and universities can leverage large amount of research into prestige and grants.

Mid-century agricultural research was conducted differently. Researchers were responsible for research, not obtaining funding through grants. Funding was the responsibility of the heads of the department. Although the shift towards collaboration began in the 1940s, scientists from the early 20th century were trained to work independently or in small groups, and were often secretive. At Purdue University, for example, many of the older offices in the agricultural school have walk-in vaults, like bank vaults, that allowed researchers to keep their research a secret until the paper was published. Researchers trained by scientists who had themselves been trained in the early 20th century, as Dutt was by Casida, would have likewise been if not secretive, reticent about their work.

This was compounded by the fact that reproductive physiology was a relatively new field that offered ample opportunity for new and prestige-conferring discoveries. Reproductive physiology, too, could be a taboo topic in the prudish mid-century, not something to be brought up in polite conversation. The United States would eventually pump money into reproduction research due to the fear of a population explosion in communist countries, but prior to the late 1950s finding funding for such work was fraught with religious and political pitfalls. Dutt's department head was able to find funding for his studies because his research

ultimately increased the food supply. Most of Dutt's funding came either from the USDA or from the livestock industry.

Dutt's independence, was not, however, due to anti-social tendencies. Edgerton described Dutt as a bit of loner, "not an introvert, but a person who was about doing his task." He would work with others if collaboration would augment the research, and work alone if it would not. One group of researchers Dutt enjoyed working with under any circumstance was graduate students. Mentoring graduate students was one of Dutt's favorite parts of the job. Like Casida, Dutt had the reputation for being a tough but fair mentor to his students, and his graduate students were aggressively courted by industry and universities alike. In 1971 he was awarded the Sang Award, and a prize of $3000, for his outstanding contribution to the UK graduate program.

Dr. Ray Dutt (left) receiving the Sang Award in 1971

Photograph courtesy of Kathy Dutt

Within the animal science community Ray Dutt was a well-known name for several decades, and even early in his career. In 1957 he received a Fulbright Grant he had not even applied for. A researcher at Canterbury Agricultural College in Lincoln, New Zealand, suffering from low sheep yields, had put Dutt's name into a Fulbright application. Dutt and his family, which by then included the two children, spent nine months in New Zealand as a result.

Today, however, research in reproductive physiology has progressed and specialized such that only those students studying reproductive endocrinology in sheep would recognize his importance. Currently there are very few of such students due to the substantial decline in the sheep industry that has occurred since the mid-twentieth century. When Dutt started his work at Kentucky in 1948 the state had one million sheep, today there are 35,000.[98] The decline in the industry results from a combination of decreased demand for sheep products and insurmountable fertility barriers. Lamb and mutton, which were never popular with Americans to begin with, have been edged out by cheaper, more widely available and leaner meats. Wool was largely displaced by synthetic fibers in the mid 20th century.

As for the reproductive obstacle, sheep have only one natural breeding season a year, in late fall. Cattle and pigs, on the other hand, are similar to humans and have estrous cycles throughout the year, although they are more fertile in the spring. Several attempts to increase lamb production have been successful, but production is nowhere near that of calves or piglets. Many farmers use a sheep breed that is a cross between the Dorsset, which has a less seasonal cycle, and the Finn,

which is highly prolific. Breeds and crosses are also selected for their ability to give birth to twins.

Hormonal fertility control is practiced very little in regard to sheep, at least in the United States.[†] The purpose of synchronizing estrous through the use of hormones is to provide a known opening for fertilization by a superior sire through artificial insemination (AI). The small genetic benefit conferred by using AI with sheep, coupled with the relatively small US sheep flock, does not offset the cost of AI. By contrast the benefit of cattle AI is so great that 70% of the cattle production in the United States uses this technology.[99]

* * * *

Although Dutt was popular in the animal science community, and some of his earlier papers were even cited by scientists outside of the animal sciences, he is not what we would call a well known scientist. His work was not flashy, in fact, it deals with something most prefer not to think about: killing farm animals and turning them into steaks and hams. In addition, he was humble. Dr. Gary Cromwell, a swine specialist at UK, noted that Dutt never engaged the public through speeches or publications in more popular scientific journals, and "was never one to promote himself."

Certainly, Dutt's name is not usually associated with the development of the oral contraceptive. Passing judgment on my family's pride in Dutt as "the one who

[†] In New Zealand and Australia, where sheep are a more popular, a limited amount of hormonal fertility control occurs.

worked on the precursor to the birth control pill" is difficult. Who am I to issue a verdict on what this esteemed animal scientist did over 60 years ago? I, who have had no training in animal science or reproductive physiology. I want to believe it is true, both because Dutt's role would confer a familial pride and because I would have been the one to expose it to the world beyond the Dutt dinner tables. As a scientist, however, I can only analyze the data, and use that analysis to present the clearest conclusion possible.

The story about Dutt contributing to the development of the oral contraceptive began, in my family anyway, with a mystery article titled: *Basic Research Discovery by Agricultural Experiment Station Workers leads to Development of The Pill for Human Birth Control*. A bold statement. In such a case one wants to compare the data with the source, but, alas, there is no author or date on the article, nor do I know where – or if – it was published. It was written sometime after the pill had been released and had been deemed a success, but before computers succeeded typewriters. It reads like a press release, probably from the USDA or another governmental agency overseeing the agricultural experiment stations. It is possible, though I think highly unlikely, that Dutt wrote it himself.

The article states that Dutt's 1948 paper was the first to "show that progesterone could be used effectively to control ovulation and fertility in mammals." Prior to 1948 progesterone was well studied but was not being considered for fertility control; Dutt and his advisor Casida brought that application to the attention of scientists in general and, specifically, to Pincus. The article concluded "The basic study of Dutt and Casida in 1948 has become a classic, because the concepts they

developed from a fundamental research finding have led to the practical application of the pill as a method of birth control."

Dutt's colleagues agreed with the article's claim in vague enough terms that, in retrospect, I suspect they were responding to my leading questions about Dutt's role in the development of oral contraceptives. Dr. Cromwell stated that "everybody [in the animal science community] knew him and recognized what he had done in terms of initial groundwork and birth control." An animal scientist I spoke to at Cornell University had heard of Dutt and generally of his work, but was not aware of any connection between him and the pill.

In conjunction with the article, there is proof that Pincus was inspired by Dutt's work. Pincus cited the 1948 study twice, first in *Effects of Certain 19-Nor Steroids on Reproductive Processes in Animals* (1954) and *Effects of Progesterone and Related Compounds on Mating and Pregnancy in the Rat* (1956). In the 1954 study Dutt's paper was one of 7 cited, and in the 1956 study, one of 15 cited. It is unclear, however, how inspiring Dutt was to Pincus. Pincus could have merely cited Dutt as proof that progesterone controlled ovulation in sheep. As far as I know, Dutt was the first to report the anovulary effects of progesterone on any livestock animal since Pearl tested luteal extracts on birds in 1914. Another possibility is that Dutt's only contribution was to dig Makepeace's 1937 study out of the literature vault, and by publishing a reference to it in 1948, make it more available to Pincus.

Pincus must have chosen progesterone based on his literature searches but the pivotal source he accessed might have been Dutt's, or could have been Makepeace's or any number of earlier studies from the 1930s and 40s that tested

progesterone on different mammals. The announcement of orally active progesterone, however, was probably not the impetus. The patent application for Djerassi's progesterone was filed in November 1951. According to Pincus's biographer, the decision to test progesterone "supposedly" occurred on Pincus's drive home from his spring 1951 meeting with Sanger.[100] In other words, nobody knows where Pincus's inspiration came from.

The most convincing proof of Dutt's contribution comes from the insight he exhibited during the 1948 study. He and Casida had collaborated with a third scientist, R.K. Meyer, on their previous experiment. Meyer had contributed significantly to the literature on progesterone in the late 1920s and early 1930s. He was the first researcher to test the effects of luteal extract on the symphysis pubis of the guinea pig, as reported in Chapter Two. By the mid 1930s, however, he had turned his interest toward gonadotropic hormones– hence the 1942 study testing gonadotropic effects on the reproductive system. It is curious that Meyer did not suggest progesterone as a method of estrous synchronization after the gonadotropic preparations failed. One possible explanation is that progesterone was prohibitively expensive in 1942; it would be two years before Russell Marker discovered that progesterone could be synthesized from diosgenin in wild yams. Dutt recalls that it was very difficult to get progesterone before the war. Although it is possible Meyer served as a consultant to Dutt and Casida, his name is not on the 1948 paper. This oversight by an experienced reproductive endocrinologist shows that progesterone was not an obvious choice for hormonal cycle control in the 1940s and early 1950s. Whether or not Dutt's work was Pincus's reason for choosing progesterone, Dutt

deserves significant recognition for his insight in choosing progesterone for estrual synchronization.

Regardless of his contribution to oral contraceptives, Dutt had made a significant impact on the animal science. Over the course of his career he published 40 journal articles that explored the effect on livestock fertility of different perturbations, including hormone injections, changes in temperature, and varying patterns of exposure to light. His research in 1948, deemed a "pioneer study" by the American Society of Animal Science, laid the way for all future research in synchronization of estrous. He was the first person to use progesterone to synchronize estrous in a livestock species and his work was a model for livestock species that would lead to developments of large scale estrous control and fertility treatments for cattle.

By his impacts on the field of animal science Dutt has greatly contributed to the development of the meats industry in the United States. The original creation of the animal science discipline is responsible for the industries that provide our meat and dairy. Animal scientists have made it possible for these commodities to be available at any time of the year, regardless of the breeding season. In the 1920s on the Dutt farm one litter of piglets was born in the spring and that fall Elmer and his sons would slaughter four or five grown pigs. Those four pigs would provide all the pork that the family of eleven would eat for the entire year. Some was eaten right after the slaughter, but most was cured or smoked and saved for the lean winter and spring months. By contrast, today pork is available at any time, in any stage of preservation. Dutt's work in hormonal estrous synchronization made it for animal

scientists to modify the pig's reproductive cycle – and to a greater extent the cycle of the cow – to fit the demands of the customer.

Conclusion: The Pill as a Triumph for Good Science

This thesis reexamines the history of oral contraceptives to take into account the numerous and impressive scientific accomplishments, and the complex interactions that led to the development of the pill. These events are traditionally excluded from the history of oral contraceptives in favor of the stories of Anthony Comstock and Margaret Sanger. As the women's rights version is the privileged form of oral contraceptive history, we might ask why this is the case. One factor is the common misconception that scientists are one-dimensional, white coated brains that produce abstract information. In fact, their discoveries can be very interesting, for example in the case of Pearl and Surface using a mammalian hormone to prevent ovulation in a bird. Scientists are humorous, such is the case with Allen's reminiscences of isolating progesterone, and dramatic, as seen by the debate over the naming of progesterone. The moments of drama and the humor in scientific developments may be initially difficult to locate, but once uncovered these stories are just as interesting as those of Comstock and Sanger.

To further its popularity, the women's rights version of this history is linear and easy to understand. Sanger's motivations are clear and we can tell her story by moving her from event to event on the way to her envisioned goal and then celebrate in the triumph of achieving that goal. That presentation is largely coincident with the way the actual history played out. Sanger had sought an effective and cheap contraceptive since the beginning of her career, and the story concludes when her

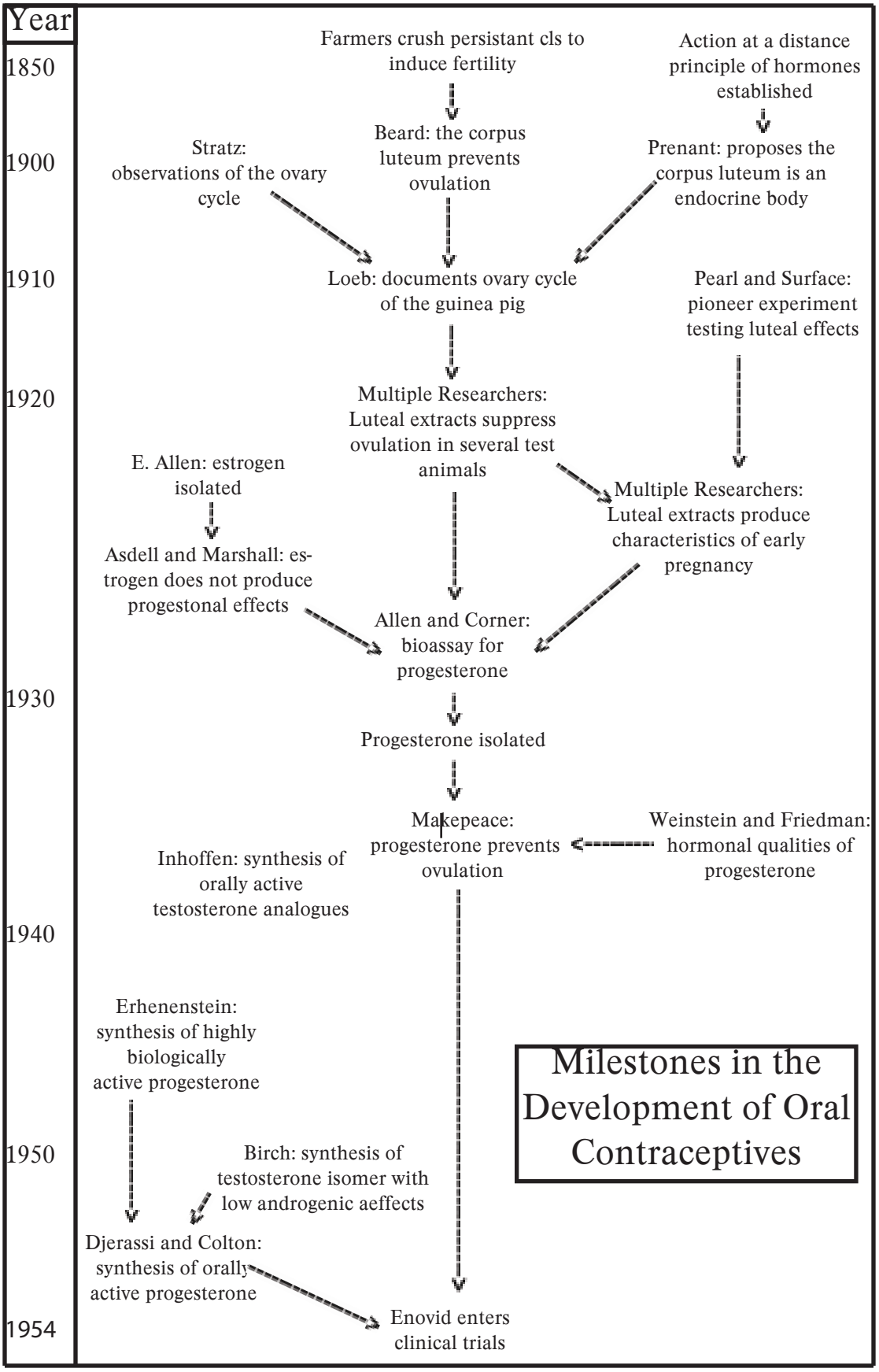
dream is fulfilled. Furthermore it is an uplifting story, one that we value as a symbol of hard work and moral conviction rewarded.

The goals of the scientists are much more disparate. Some were interested in clinical applications of their work, some worked in science to satisfy their own curiosity. For others, research was merely a job. Dutt entered research because he wanted to get off the farm, and use his brain as well as his hands. He stayed in research because he liked figuring things out, and he was innately curious. The scientific story only has the direction we can now give it by looking back through the literature and picking out those accomplishments that eventually led to the pill. We have given those hundreds of studies an end point in the pill but the end point might as well be the emergence of a centralized and massive beef industry. A hundred million women worldwide take the pill daily. By contrast, on average, *every single* American eats a quarter pound of beef daily, not to mention pork and lamb.

This new perspective of the history is distinctly non-linear, and cause and effect is not always clear. The isolation of progesterone is analogous to the scientific history of progesterone at large. For years chemists had been trying to reduce the yellow, oily luteal extract down to a crystalline solid, and then, all of a sudden, in one summer, four different laboratories had the crystals. It was the chance emergence of four exceptionally intelligent scientists, but the fact that all the pieces were in place, so that anyone with sufficient knowledge of chemistry and hormones could now isolate the hormone. Perfection of vacuum distillation technology by Allen led to purification of progesterone, but also purification of vitamins, and a new nutrition industry. Every single factor that collided when Sanger and Pincus met in 1950

ricocheted off, leaving a mark on the pill, but also continuing on a new trajectory. None of these scientific achievements found their "end point" in oral contraceptives because there were still experiments to be done, questions to be answered – and to be asked.

Dr. Ray Dutt never gave a thought to the possibility of human oral contraceptives during his study of progesterone in 1948. It was only many years later, in the 1960s, that he realized that Pincus had applied to humans a technology Dutt had pioneered in sheep. His reaction was likely similar to that of the dozens, maybe hundreds, of researchers who saw a piece of their research in the pill: proud and content, but not smug or over-excited. These scientists had achieved something in their contributions to the pill that they had not sought. Some might call them lucky, but above all they are good scientists, people who practiced science in a detail-oriented and objective manner to produce knowledge that others could rely on and use in their own inventions for decades to come.


Year
1850
1900
1910
1920
1930
1940
1950
1954
Farmers crush persistant cls to induce fertility
Action at a distance principle of hormones established
Beard: the corpus luteum prevents ovulation
Stratz: observations of the ovary cycle
Prenant: proposes the corpus luteum is an endocrine body
Loeb: documents ovary cycle of the guinea pig
Pearl and Surface: pioneer experiment testing luteal effects
Multiple Researchers: Luteal extracts suppress ovulation in several test animals
E. Allen: estrogen isolated
Multiple Researchers: Luteal extracts produce characteristics of early pregnancy
Asdell and Marshall: estrogen does not produce progestonal effects
Allen and Corner: bioassay for progesterone
Progesterone isolated
Makepeace: progesterone prevents ovulation
Weinstein and Friedman: hormonal qualities of progesterone
Inhoffen: synthesis of orally active testosterone analogues
Erhenenstein: synthesis of highly biologically active progesterone
Milestones in the Development of Oral Contraceptives
Birch: synthesis of testosterone isomer with low androgenic aeffects
Djerassi and Colton: synthesis of orally active progesterone
Enovid enters clinical trials

Biological Diagrams: The Ovarian Cycle[101]

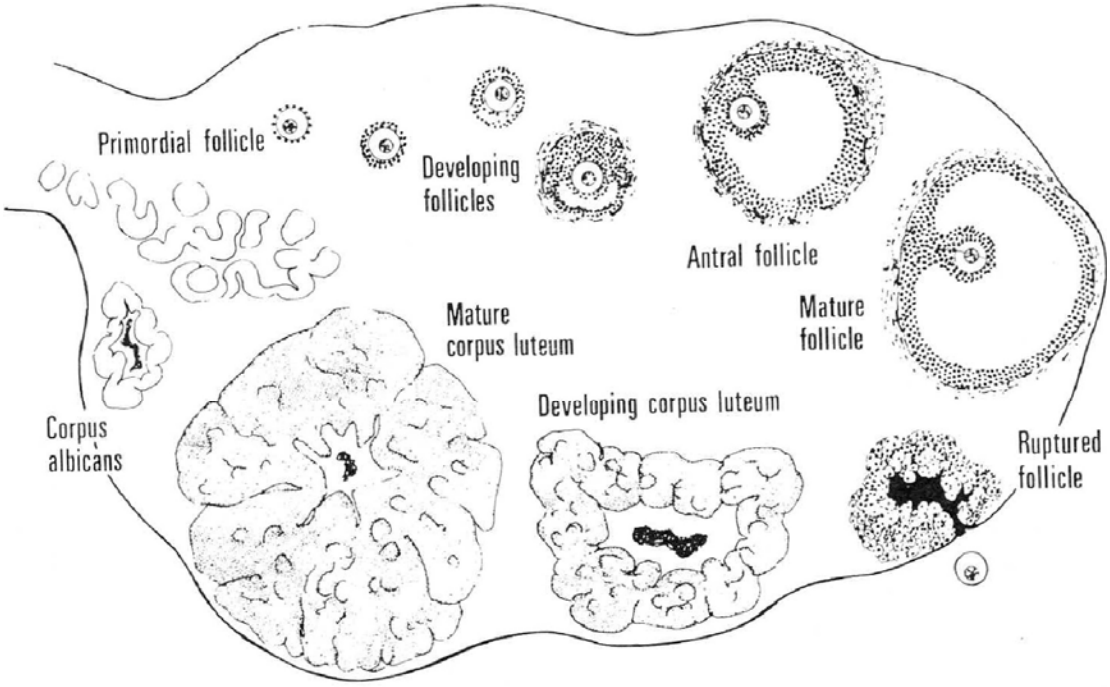
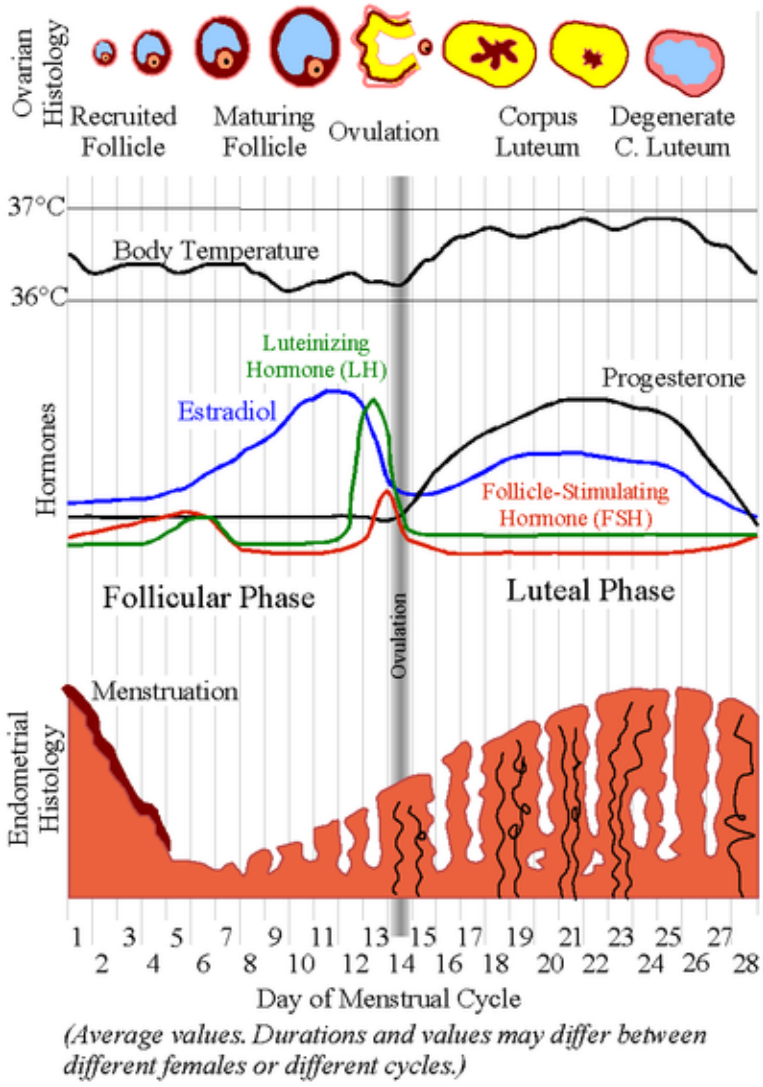


Fig. 1. Schematic illustration of maturation of ovarian follicle and corpus luteum. From M. R. Abell and J. R. G. Gosling, "Pathology of the Female Reproductive Tract," to be published.

The Ovarian Cycle: The ovary cycle begins at the top left, when primordial egg follicles, present in the female since birth, begin to develop. Once the follicle has sufficiently matured, it ruptures and releases its egg into the fallopian tube. The ruptured follicle then becomes the corpus luteum, which releases hormones that maintain a uterine environment appropriate for nourishing the egg. If the egg is not fertilized the corpus luteum will eventually decay, and the cycle will begin anew.

Biological Diagrams: The Menstrual Cycle[102]



The Menstrual Cycle: Different levels and combinations of hormones regulate the state of the endometrium (uterine lining) during the menstrual cycle. Progesterone levels surge immediately following an ovulation. Modern oral contraceptives use progesterone to trick the body into thinking it has already ovulated, thus preventing ovulation.

End Notes

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