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The Pill at 50 (in Germany): Thriving or Surviving?

Djerassi C

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The Pill at 50 (in Germany): Thriving or Surviving? *

C. Djerassi

This article describes in detail the history behind the chemical development of oral contraceptives, notably the synthesis of norethindrone, which represents the chemical template from which virtually all subsequent oral contraceptives are derived. Attention is also paid to the introduction of the most recent oral contraceptives in Germany and reasons are provided for the dim overall prognosis about the future of contraception, namely that nothing fundamentally new is on the horizon. **J Reproduktionsmed Endokrinol 2011; 8 (Special Issue 1): 14–31.**

Key words: norethindrone, norethynodrel, levonorgestrel, chemistry of oral contraceptives, Ludwig Haberlandt

■ Which 50th Birthday?

How many people – other than those trying to hide their age – celebrate the same birthday in successive years? And why should that happen to a drug? Yet in 2001, several people (starting with Carl Djerassi [1]) celebrated the 50th birthday of the Pill, while 9 years later a media frenzy exploded all over the world with another 50th anniversary celebration of the Pill. And now, in 2011, we are doing it again by commemorating the date, 50 years ago, when the Pill was introduced in Germany. In terms of this article's title, this would clearly mean that the Pill is thriving. And in a way it is, especially in light of two overwhelming facts of the last half century – the global population explosion and the rise of women's rights – without which oral contraceptives would just have been another medical advance and not an invention with enormous societal consequences. Yet in this article, I shall also make the contradictory argument that the Pill is only surviving, because nothing else is on the horizon in terms of fundamentally new methods of birth control.

During those years, I have been interviewed, filmed, and encouraged to pontificate on the occasion of various birthdays of the Pill, perhaps because one of the ironies of the Pill's career is that its own conception has been so hard to pin down. It all depends (as any obstetrician will tell you) on who is counting. In 1997, I spoke at a medical congress in Vienna commemorating the 35th anniversary of the Pill in Austria – not an inappropriate geographic choice as I will demonstrate shortly – while in May

2010, I was bombarded by requests from many American print, radio, and TV reporters to comment on the “50th birthday” of the Pill, because the media were dating the Pill's debut to the formal approval by the Food and Drug Administration (FDA). While such dates may be occasions for celebrations, “birthdays” they are not. The Viennese event was equivalent to celebrating a baby's arrival in a town far away from its original birthplace and the 50th “birthday”, especially hyped by the American media, could be equated to the date on which the baptismal certificate was issued in Washington. As far as I am concerned (and I was concerned), the real birth date of the Pill was October 15, 1951, the day we completed at Syntex in Mexico City the first synthesis of a steroid eventually destined to be used for oral contraception. A few days later, the first few precious milligrams of “norethindrone” – the generic designation of the formally named “17 α -ethynyl-19-nortestosterone” – was already in the mail from Mexico City to Dr. Elva G. Shipley at Endocrine Laboratories Inc., a commercial establishment in Madison, Wisconsin, with the request that the substance be tested for oral progestational activity.

■ Mothers of the Pill?

I mention Dr. Shipley here primarily because her early participation in the Pill's history impinges on a claim often heard – that the scientists involved in the development of oral contraceptives were uniformly males. This belief has grated on women for decades. As Margaret Mead [2] put it in the late 1960s: “[The

Pill] is entirely the invention of men. And why did they do it? ... Because they are extraordinarily unwilling to experiment with their own bodies ... and they're extremely willing to experiment with women's bodies ... it would be much safer to monkey with men than monkey with women.” While Mead's irritation may well be understandable, it nevertheless represents a gross oversimplification that ignores that nature had provided scientists with a crucial hint on which to build – women do not get pregnant during pregnancy because of the continuous secretion of progesterone – whereas no such clue exists in male reproductive biology. Dr. Shipley's contribution is significant for an additional reason that may explain some of Mead's indignation: fifty years ago women were still largely excluded from many areas of scientific research. In a field that was undeniably a male province, Dr. Shipley had to do her work in a commercial laboratory she had founded next door to the University of Wisconsin where her husband, Roland K. Meyer, was Professor of Zoology at a time when nepotism rules were still inviolate.

A pervasive sense of the ironies of this historic male bias has caused various writers and journalists to search far and wide for female heroes in the record of the Pill. Margaret Sanger is the favorite, probably for reasons stated in the final paragraph of David Kennedy's definitive biography [3]: “Yet the praise Margaret Sanger received often seemed out of proportion to her achievement. Part of the hyperbole, undoubtedly, derived from her personal magnetism, which rarely failed to bring those who met her

* Portions of this article come from [1].

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into her orbit. But a larger part reflected Mrs. Sanger's symbolic satisfaction of a pervasive psychological need. American society in this century has not realized its frequently stated ideal of equal status for women. Perhaps, therefore, the apotheosization of a feminist heroine like Margaret Sanger reflects society's recognition of the continuing victimization of women, and the desire, in some way, to find a redemptress. For that role Margaret Sanger, at her best and at her worst, was well suited."

Still, Sanger's historic, though certainly not scientific role in fostering the birth control movement in the USA would validate her choice as one of the grandmothers of the Pill. A more romanticized candidate is Katherine McCormick, a wealthy philanthropist, who was persuaded by Sanger in the early 1950s to subsidize some of the biological work at the Worcester Foundation for Experimental Biology that under the leadership of Gregory Pincus contributed heavily to the development of the Pill. However commendable such philanthropy is, anointing Katherine McCormick as one of "the indisputable mothers of the Pill" (as was done by one journalistic author, Bernard Asbell, in "A Biography of the Drug that changed the World" [4] and then repeated by many others), is as far-fetched as calling John D. Rockefeller one of "the fathers of the Pill". (The Rockefeller Foundation and its offspring, the Population Council, supported much more research in reproduction and contraception than Mrs. McCormick ever did and has continued to do so over the course of many decades). A curious fact, not commented upon by any other writers (e.g. [5]) on the role of Gregory Pincus is that Pincus, though dedicating his opus magnum, "The Control of Fertility" [6] to "Mrs. Stanley McCormick" for "her steadfast faith in scientific inquiry ..." did not mention any financial support on her part in his acknowledgment section in spite of a lengthy list of funding agencies, individuals, and companies, notably G. D. Searle and Co.

Financial support, valuable as it may be, can never be equated with creativity; otherwise, the Medicis would be considered the greatest artists of the Renaissance. Instead, let me add the name of Elva G. Shipley as literally the first biologist – male or female – who estab-

lished the high progestational activity of orally-administered norethindrone. If her results had been negative, we would have dropped the project and would never have sent the material to other biologists, including Gregory Pincus, who, as I will demonstrate below, can rightfully be called a "father of the Pill".

Since the Pill is so intimately connected with human reproduction, albeit in terms of preventing it, let me pursue the Pill's genealogy through the metaphor of reproduction. Call the Pill the baby and follow its birth through (1) the first (unsuccessful) attempts at conception, (2) the ovulation of a fertile egg, (3) the ejaculation of various sperm, (4) the successful fertilization, (5) the implantation of the embryo, (6) the fetal development, and finally (7) the birth of the baby. Geographically, the first step occurred in Austria, the second in Mexico, the next 3 in the continental United States, and the last in Puerto Rico – not untypical for a baby in the present highly mobile society.

■ The Overlooked Role of Ludwig Haberlandt

The least-known character in the Pill's story is not a woman after all. It is Ludwig Haberlandt, professor of physiology at the University of Innsbruck. As early as 1919, he carried out a crucial experiment, in which he implanted the ovaries of a pregnant rabbit into another rabbit, which, in spite of frequent coitus, remained infertile for several months – a result that Haberlandt called "hormonal temporary sterilization". (Partisans of Mrs. McCormick might take note that this and subsequent work of Haberlandt's was supported financially by the Rockefeller Foundation.) The problem with this method, of course (other than its reliance on surgery), as well as with subsequent attempts to avoid surgery by the use of "glandular extracts", was that these extracts were not the pure hormone responsible for its contraceptive effect. A mixture of hormones and other proteins, they constituted a potential problem of toxicity for the recipient. Attempts to "purify" these extracts presented the next hurdle to overcome on the way to a practical oral contraceptive.

In numerous subsequent experiments and publications over the course of ten

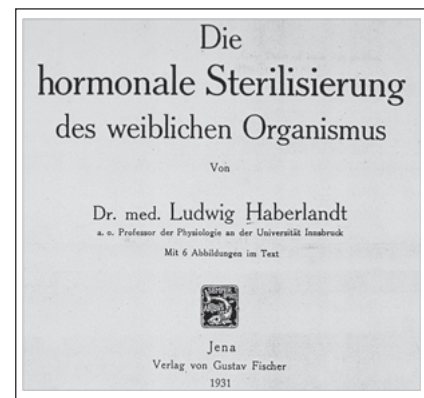


Figure 1. Title page of Haberlandt's book.



Figure 2. Newspaper headlines (1927) about Pill for Women.

years, Haberlandt – invariably using the first person singular, so strikingly different from today's insistence by scientists on the royal "we" – emphasized the obvious applicability of his animal experiments to human contraception. He fully recognized that the responsible factor was a constituent of the corpus luteum and in 1931, in a remarkable book [7], "The Hormonal Sterilization of the Female Organism" (Fig. 1), of less than 15,000 words that hardly anyone now living seems to have read, Haberlandt outlined in uncanny detail the contraceptive revolution of some thirty years later. He pointed out that oral administration, which he actually demonstrated in mice, would be the method of choice as well as the necessity for periodic withdrawal from the hormone to allow menses to occur. He called for the use of such contraception on clinical and eugenic grounds, arguing that it would enable parents to have the desired number of healthy children. Objections by people like the sexologist van de Velde that too many women would take advantage of hormonal contraception was dismissed by Haberlandt with the argument that such preparations would require a physician's prescription and would not be made available over the counter. He ended his manifesto with a visionary claim: "Unquestionably, practical application of the temporary hormonal sterilization in women would markedly con-

tribute to the ideal in human society already enunciated a generation earlier by Sigmund Freud (1898). Theoretically, one of the greatest triumphs of mankind would be the elevation of procreation into a voluntary and deliberate act”.

Haberlandt did not limit his publications to the scientific literature. He also published in the popular press and gave interviews that led to huge newspaper headlines (Fig. 2) like “*My aim: fewer but fully desired children!*” (in the January 20, 1927 issue of the *Acht Uhr Abendblatt, Berlin*) complete with commentary by the now-familiar chorus of physicians, lawyers, and theologians. His obsession with the therapeutic potential of corpus luteum extracts was so well known that his students hung a banner by his home with the couplet, “*Verdirb nicht Deines Vaters Ruhm mit Deinem Corpus Luteum*” [Don’t mar your father’s renown with your corpus luteum]. But Haberlandt was not content with the visionary’s role only. He contacted several pharmaceutical companies in an attempt to obtain consistently active and nontoxic corpus luteum and placental extracts for human clinical experiments. In his 1931 book, he finally reported success in the following words: “*I have been in contact for over three years with the therapeutic firm Gideon Richter in Budapest [to this day, a company active in the steroid field] and it is likely that in the near future a suitable ‘sterilizing preparation’ under the name ‘Infecundin’ will be available for systemic administration in clinical experiments as I had already announced in Vienna [September 1930]*”. He confirmed that experiments in mice with orally-administered “Infecundin” had demonstrated temporary infertility without toxic reactions, “*since only in this manner does the new method have any chance for clinical success*”. A year later, the 47-year old Haberlandt committed suicide [8] as a result of the incessant criticism of his work in conservative Austria, but the name “Infecundin” survived. In 1966, it became the trade name of the first oral contraceptive produced in Hungary by the very same company Haberlandt had contacted 40 years earlier.

Within 2 years of his death, pure progesterone was isolated in no less than four laboratories in Germany, the US and

Switzerland; its chemical structure established by Karl Slotta (a Hitler refugee eventually settling in Brazil); and its synthesis from the soyasterol stigmasterol accomplished by Fernholz in Göttingen and by Butenandt in Danzig. Had Haberlandt lived, there is no question that he would have pursued his dream of temporary hormonal sterilization in humans without resorting to corpus luteum extracts. But even with pure progesterone, he could have shown only that ovulation can be inhibited by injection as the appropriately named American investigator A. W. Makepeace demonstrated in 1937 in rabbits and E. W. Dempsey in guinea pigs. For oral administration, Haberlandt would have needed another steroid – not naturally occurring, but waiting to be synthesized – and that took 20 more years. Thus, nothing further happened, and Haberlandt’s work fell into such oblivion that the next biologist to take it up, Gregory Pincus (who clearly should have known better), did not even feel obligated to cite Haberlandt among the 1459 references in his own book [6]. Nor for that matter did Pincus’s clinical collaborator, John Rock, whose book *The Time has Come* [9] quotes Makepeace’s work but none of Haberlandt’s pioneering earlier research. Yet if there ever was a grandfather of the Pill, the Austrian Ludwig Haberlandt above all others deserves that honor. Aside from not mentioning Haberlandt’s work, these 2 books by Pincus and Rock, who are often called the 2 fathers of the Pill – an interesting variant of parthenogenesis contain a surprising lacuna: zero reference to the chemical invention of the Pill, without which, of course, no biological or clinical research on today’s Pill could even have started.

Since the term “father of the Pill” carries reproductive connotations, the development of oral contraceptives might well deserve some reproductive metaphor. Thus one might ask why the metaphoric fathers, Pincus and Rock, did not refer to the usual missing partner in such a process, namely a metaphoric mother? In my own writings, I have frequently made the point that for any synthetic drug – oral contraceptive, antibiotic, anticancer or anti-anything – the organic chemist assumes the irreplaceable maternal function. I anoint the chemist with the maternal role, because I consider the

synthetic chemical – by definition invented and synthesized by the chemist – as the egg that needs to be fertilized. The biological experiments that are subsequently conducted are then the father’s sperm, with the key biological experiment representing the crucial seminal event that caused fertilization of the egg. Only then does the clinician enter the picture as midwife. It is this triad, in which each component is indispensable, that deserves consideration and it is amazing to what extent the maternal role of the chemist is often downplayed or ignored outright in medicine. Consequently, much of what I have to say in this article will focus on chemists and the underlying chemistry.

■ What was the Real Role of Russell Marker?

For mostly journalistic reasons, many accounts of the Pill’s early genealogy start with the name of Russell Marker, a research professor at Pennsylvania State College in the late 1930s and early 1940s. Perhaps what attracted the journalists and TV filmmakers to add Marker to the list of fathers of the Pill was Marker’s status as a maverick. Lacking the formal union card of a Ph.D., Marker’s true rank as one of the giants of steroid chemistry was recognized only two decades after his sudden and total withdrawal from chemistry while still in his forties. But despite his genuine claim to greatness in the larger field of steroid chemistry, in terms of oral contraception in particular he contributed nothing.

Which is not to say that Marker wasn’t important, albeit indirectly, for making the raw materials of contraceptive research more readily available. Until the mid-1940s, virtually all clinically useful progesterone was prepared in one way or another from soyasterols or cholesterol in processes that required conversion of such sterols into intermediate products prior to final transformation into progesterone. These intermediate steps represented a bottleneck, as only limited quantities of the necessary substances could be generated at one time. Not surprisingly, this poor yield kept the price of progesterone very high (approximately US\$ 80/gram in the early 1940s). All this changed dramatically when Marker revolutionized the chemical production of progesterone. Within a few

years, as a result of his process, the cost of progesterone dropped sufficiently that it became inexpensive enough to be used as the starting material for the synthesis of other steroids (for instance cortisone), rather than just serving as a clinically useful drug for menstrual disorders. But what, precisely, was the nature of Marker's discovery?

In the late 1930s and early 1940s, Marker conducted research on a group of steroids called "sapogenins", compounds of plant origin. They got their name because, in their naturally-occurring form (where they are linked to sugars in compounds called "saponin") they form soapy lathers in water. Natives of Mexico and Central America had long used them for doing laundry and to daze or kill fish. Marker concentrated on the chemistry of a member of this group called diosgenin, which was present in certain types of inedible yams (*Dioscorea* species) growing wild in Mexico. He succeeded in developing a five-step, high-yield conversion of diosgenin into progesterone. All kinds of apocryphal stories have been written about Marker's departure from Pennsylvania State College during World War II and his move to Mexico, many embellished with mysterious disappearances into the Mexican jungle, newspaper-wrapped parcels containing the equivalent of the world's supply of progesterone, and the like. But in 1979 (approaching the age of 80), he visited me at Stanford University and permitted a taped interview, excerpts of which have appeared in book form [1].

The interview ended on a poignant note. A driver had come to take Marker from my Stanford office to the San Francisco airport from where he was supposed to fly to Mexico City for a brief visit. He asked for the men's toilet and as I led him there, he suddenly turned to me, "Tell me, where am I? What am I doing here? What did we talk about?" Fearing that he had suffered a sudden memory loss, I reached into his jacket and drew out his plane ticket. After explaining gently where he was, I gave the ticket to the driver, asking him not to just drop off Marker at the airport, but rather see to it that he boarded the plane. A few weeks later, I learned that Marker had suffered a mild heart attack and had been taken off the plane in Texas to a hospital. I had conducted my taped interview in the

presence of my colleague, the late Harry Mosher, then Emeritus Professor of Chemistry at Stanford, who had been a graduate student at Penn State and had worked in the same laboratory as Marker. After Marker departed, Mosher turned to me. "There are other versions as well". And sometime later, after I had published an autobiography [10] in which Marker was mentioned, I received a letter from a reader, an American chemist then living in Israel, who had also worked in the same laboratory at Penn State. It was a startlingly bitter letter, citing evidence to support his view that Marker had been virulently anti-Semitic around the outbreak of World War II, a claim that was subsequently confirmed by another independent witness from the early 1940s.

In terms of the chemical history of the Pill (though not in the eyes of a refugee from Hitler, like myself), Marker's purported anti-Semitism would appear to be irrelevant. But there is an intriguing aspect to Marker's alleged prejudice. His Ph.D. supervisor at the University of Maryland was Morris Kharasch, one of the very first Jewish professors in the WASP-dominated university chemistry faculties of pre-World War II America. For reasons that have never been completely clarified, Marker never finished his doctorate at Maryland, but, following a short industrial stint at Ethyl Corporation, he spent 6 years at the Rockefeller Institute working under another well-known Jewish chemist, Phoebus Levene. That collaboration broke off so bitterly that Marker – in a last gesture of defiance to a superior – removed the labels of virtually all the research samples that he left behind when he departed for his new position at Pennsylvania State College. Among chemists, only burning one's laboratory notebooks would be a worse act of vandalism.

The only subsequent time I met Marker was in 1984, when the annual Russell Marker Lectures in the Chemical Sciences at Pennsylvania State University were inaugurated through his own funds. He requested that I present the first series and I used that opportunity to pay homage to him by paraphrasing "Marker-at-Stanford" in front of Marker. Physically and mentally, he was in fine fettle and I was pleased that he wanted me to initiate the annual event established in

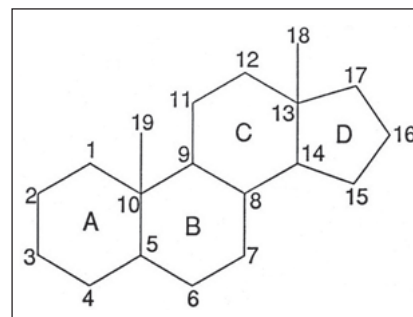


Figure 3. Steroid skeleton

his honor. Still, Marker's enduring contribution to contemporary chemistry, and indirectly also to pharmacology and medicine, lies in his discovery that steroid hormones could be synthesized from a naturally occurring and cheap plant source – research that I considered so important that on one occasion I nominated Marker for a Nobel Prize.

■ Partial vs Total Synthesis

To appreciate the significance of Marker's work it is necessary to understand the difference between "total" and "partial" synthesis. To a chemist, "total synthesis" is making a molecule from scratch – essentially from air, carbon sources (such as coal or petroleum), water and other elementary substances – not unlike building a house from clay and timber, iron and sand. "Partial synthesis", on the other hand, involves starting with an advanced structure – say a barn – and then converting it into a habitable house with plumbing and central heating. In Marker's synthesis, the building to be constructed was a "steroid" – a term that one hears often enough in contemporary life, but rarely (outside of organic chemistry classes) in its proper definition as the tetracyclic chemical skeleton known generically by the forbidding name "perhydrocyclopentanophenanthrene" (Fig. 3).

Tens of thousands of synthetic, and several thousands of natural compounds are based on this fundamental steroid skeleton made up of carbon and hydrogen atoms only differing minutely in chemical structure by the attachment of some additional atoms (usually oxygen) at various locations. The variations, however minute, produce dramatically different biological results. Many of the most important biologically active molecules in nature represent slight varia-

tions on the steroid skeleton: the male and female sex hormones, bile acids, cholesterol, vitamin D, the cardiac-active constituents of digitalis, the adrenal cortical hormones (related to cortisone and usually referred to generically as “corticosteroids”) and many plant-derived and marine natural products.

When Marker started his research in the 1930s, the total synthesis of steroids had not yet been accomplished. All steroid hormones then known (e.g. progesterone and testosterone) were produced only by “partial” synthesis from naturally occurring steroid precursors, mostly from cholesterol and bile acids – both of animal origin. By pursuing synthesis from such a starting point, chemists were simply imitating nature, which uses cholesterol as the starting material for the synthesis of steroids in the body. And although kilogram quantities of steroid hormones such as progesterone were produced since the late 1930s by some European drug companies, the methods were unwieldy. Marker’s contribution was to show that compounds derived from plant sapogenins could be transformed much more cheaply into the desired steroid “house” (e.g. progesterone) than could be generated from a more cumbersome “barn” such as cholesterol.

■ The Mexican Connection: The Role of Syntex

As he recounted in his interview with me, after he was unable to convince any American pharmaceutical firm of the commercial potential of diosgenin, Marker formed in Mexico in 1944 a small company, Syntex, in partnership with two European immigrants, the Hungarian Emeric Somlo and the German Federico Lehmann. A few months later, Syntex started to sell to other pharmaceutical companies (but not to the general public) pure, crystalline progesterone prepared by Marker’s process in five chemical steps from diosgenin. Within a year the partners had a disagreement, and Marker left the company, taking his technical expertise with him. For a time, Syntex was without its most profitable product.

Early in his academic career, however, while still at Pennsylvania State College, Marker had published a description of

his chemical processes in the *Journal of the American Chemical Society* [11]. Since no one had taken out patents in Mexico for his discoveries, the commercial production of progesterone from diosgenin was up for grabs in that country. Somlo and Lehmann, looking for another chemist who could re-establish the manufacture of progesterone from diosgenin at Syntex, recruited George Rosenkranz from Havana. A Hungarian like Somlo, Rosenkranz had immigrated to Cuba a few years earlier from Switzerland, where he had received his doctorate under the Nobel laureate Leopold Ruzicka (one of the giants of early steroid chemistry) and was already familiar with Marker’s publications. Within two years, Rosenkranz had re-instituted the large-scale manufacture of progesterone from diosgenin. Even more important, he had achieved the large-scale synthesis, from those same Mexican yams, of the commercially more valuable male sex hormone testosterone. Both syntheses were so much cheaper than the methods used by the European pharmaceutical companies then dominating the steroid hormone field – such as CIBA in Switzerland, Schering in Germany, and Organon in Holland – that in a short while tiny Syntex broke the international hormone cartel. As a result, prices fell, and these hormones became much more available. In the late 1940s, Syntex served as bulk supplier to pharmaceutical companies throughout the world, but few people outside these firms even knew of the existence of this small chemical manufacturing operation in Mexico City, which was soon to revolutionize steroid chemistry and the steroid industry all over the world. By the late 1950s, over half the world’s supply of steroid hormones originated from Mexico, where in the meanwhile other American and European pharmaceutical companies had also started to establish manufacturing subsidiaries based on the commercial exploitation of diosgenin.

So why do I relegate Marker at best to the role of a distant maternal grand-uncle in the genealogy of the Pill? Because the availability of progesterone on an industrial scale did not contribute in any way whatsoever to the development of oral contraceptives. Certainly a source of pure progesterone was necessary, and in sufficient quantities to investigate its therapeutic use. But the need of pro-

gesterone for contraception had been Haberlandt’s insight, not Marker’s, and the provision of pure progesterone had already been achieved long before Marker in the 1930s, shortly after Haberlandt’s death, through the work of German scientists like Erhard Fernholz and Adolf Butenandt, who won a Nobel Prize in 1939 for his steroid research. But nothing had happened, not because progesterone was expensive, or in short supply, but simply because it was not sufficiently active by oral ingestion to be taken as a pill. By the time Marker appeared on the scene with a new and better synthesis of progesterone, the progesterone contraceptive boat had already sunk. It took two other maternal uncles and a mother to construct a new one, and a father to make it seaworthy.

Without Marker, of course, there would not have been any Syntex – the physical site in Mexico where the maternal role was played out. But there is no question that some other mother would have appeared elsewhere soon thereafter, because in the chemical sense, two older German maternal relatives (Maximilian Ehrenstein and Hans Herloff Inhoffen), often completely ignored, had inadvertently pointed the way for a chemical mother to produce the requisite ripe egg – in other words, the creation of a synthetic steroid mimicking the biological role of progesterone, but being active by mouth. Before describing that “maternal” process, a brief detour from oral contraceptives to cortisone is warranted because, while cortisone has no biological connection to the Pill, cortisone was nevertheless the molecule that brought me to Syntex in Mexico and hence to the Pill.

■ Some Autobiographical Observations: Cortisone and Oral Progestins

By the fall of 1945, a 22-year-old, newly-naturalized American citizen with a Ph.D. degree from the University of Wisconsin and a wife, I returned to CIBA (the pharmaceutical firm in New Jersey where I had worked for one year after graduation from Kenyon College) for another four years, to resume work on antihistamines and other drugs. One day in the spring of 1949, I received an unsolicited employment offer from Syntex, a company I had never heard of.

Although the position, as associate director of chemical research, seemed tempting to me, the location of Syntex in the scientific backwater of Mexico made the offer seem ludicrous. Fortunately, I am a tourist at heart; when I heard the invitation, “Come and visit us in Mexico City, all expenses paid”, I went. And as a bonus decided to include a visit to Havana in my itinerary.

George Rosenkranz, then technical director of Syntex and barely past 30, impressed me enormously as a sophisticated steroid chemist; he also charmed me personally. Rosenkranz showed me rather crude laboratories, but he promised lots of laboratory assistants and substantial research autonomy to devise a practical synthesis of cortisone and to pursue other aspects of steroid chemistry that might interest me. Furthermore, even though the labs were primitive, Syntex could boast of some advanced equipment such as an infrared spectrometer at a time when neither CIBA nor my alma mater, the University of Wisconsin, had such an instrument, which proved to be enormously useful for steroid research.

I arrived at Syntex in the late autumn of 1949, just around my 26th birthday. I have never regretted that decision, even though at that time my American colleagues considered me mad to move to a country that, although famous for mariachi music, bull fights, and pre-Columbian ruins, had only generated the barest of blips on the radar screen of international chemical journals. Yet I was convinced that the best route to the academic job still eluding me was to establish a reputation in the scientific literature. I felt intuitively that Mexico was the right place for me. Syntex had the same objective I did: to establish a scientific reputation. Our common goal – the “partial” synthesis of cortisone from a plant raw material – was one of the hottest scientific topics in organic chemistry at that time. I was young and willing to gamble on a few years in Mexico – partly because living in another country and learning another language appealed to me, but also because I thought that any scientific achievement from a laboratory in Mexico was likely, upon publication, to make a much bigger impression on academia than one coming from the usual elite laboratories in North America

or Europe. Consequently, I really had only one requirement before I accepted the Syntex offer, and that was to publish any scientific discoveries promptly in the chemical journals. Syntex agreed to this and stuck to its bargain. From my previous industrial experience, I fully understood that discoveries have to be patented by the firm in whose laboratory the work is performed before they are written up for publication. But instead of having patent attorneys deciding whether and when to publish, at Syntex Rosenkranz and I called the shots – extraordinary for a pharmaceutical company. As a result of this policy, during my first two years at Syntex we published more rapidly in the chemical literature than did any other pharmaceutical company, or even many university laboratories.

Until 1951, the only source of cortisone was through an extraordinarily complex process of 36 different chemical transformations starting from animal bile acids – a tour de force pioneered by Lewis Sarrett of Merck and Co. For many years, this had proved to be the longest and most complicated synthesis of any chemical on an industrial scale. Now that cortisone had emerged as a wonder drug, developing an alternative partial synthesis from a plant raw material became one of the most acclaimed scientific projects, with a number of powerful academic and industrial research groups competing to be first. At the outset, nobody even realized that a small research team in Mexico City had entered the race. But when we completed ahead of everyone else in June of 1951 our synthesis of cortisone from diosgenin, the resulting publicity was astounding. Thus, long before Syntex sold drugs under its own name to the medical profession, its international scientific reputation in chemistry was well established. Ten years after my temporary move to Mexico, when Professor Louis F. Fieser of Harvard analyzed in 1959 the references in the latest edition of his text *Steroids* [11], the recognized bible of steroid research, he found that no laboratory in the world – academic or industrial – had published as much in the steroid field as Syntex had in that time. Chemistry south of the Rio Grande had finally made the grade.

Which finally brings me back to the Pill and to a discussion of the maternal (i.e.

chemical) role in the birth of oral contraceptives as well as my personal involvement in the first synthesis of a steroid oral contraceptive. Within the confines of the present article, it would be superfluous to go into detail since I have described that story extensively in two autobiographical works [1, 10] addressed to a wider public and have cited all relevant chemical and biological literature references in an earlier review article [12].

At the time that I became interested in the chemistry of progestational steroids, one of the dogmas of steroid chemistry was that almost any chemical alteration of the progesterone molecule would either diminish or destroy its biological activity. This belief seemed puzzling in light of the fact, well known at the time, that estrogenic steroid hormones, which occur naturally in a variety of forms, as well as synthetic chemicals not even based on the steroid skeleton, display marked estrogenic potency. In 1944, Maximilian Ehrenstein (another emigrant from Nazi Germany), then working at the University of Pennsylvania, published a paper that was mostly overlooked, but had made a deep impression on me while still a graduate student. By an extremely laborious series of steps, Ehrenstein had transformed the naturally-occurring steroid cardiac stimulant strophanthidin into a few milligrams of impure oily 19-norprogesterone (actually called “10-norprogesterone” at that time). To return to my earlier metaphor, Ehrenstein had transformed a very elaborate mansion (strophanthidin) into a funky little vacation house. While he had obtained only enough material for biological testing in two rabbits, in one of them his compound had displayed higher progestational activity than the parent hormone. A positive test in one animal out of two could, of course, have been just a fluke. What made Ehrenstein’s results so unusual was what that “19-nor” in the compound’s name signified. It meant that Ehrenstein had removed carbon atom No. 19 (between rings A and B of the steroid skeleton depicted in Fig. 3) from the most inaccessible site of the steroid molecule to replace it with a hydrogen atom. On paper – or in words – the change sounds trivial. Given the state of the art of organic synthesis at the time, however, this was so difficult an operation that it had required

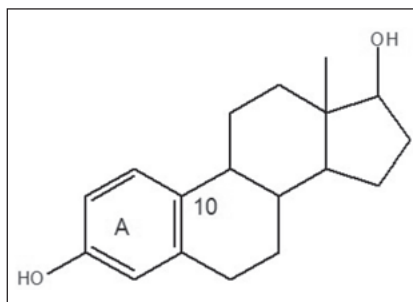


Figure 4. Chemical structure of estradiol.

several years for completion. Moreover, if the biological results were real, Ehrenstein's observation demolished the previous assumptions about the inviolability of the progesterone structure. But there was another problem: Ehrenstein's oily product was, as I indicated, impure: a mixture of at least three "stereoisomers" – molecules that, while structurally identical, were, like mirror images, as alike – and fundamentally different – as your left hand and your right. In biochemistry, which often requires molecules to fit together like a hand in a glove, such a difference can be crucial. Which one of the components, if any, was responsible for the putative progestational activity? It took seven years for someone to come up with an answer. Our ability to do so led us almost straight to the Pill.

Part of my Ph.D. thesis at the University of Wisconsin in the early 1940s had dealt with the partial synthesis of the then-inaccessible estrogenic hormones from the more readily available androgens, such as testosterone. For years, the estrogens were only available by isolation from the urine of pregnant women (and later of pregnant mares, the source of one of the more-frequently prescribed estrogen compositions in use today for hormone replacement therapy). In fact, the estrogenic hormones, such as estradiol and estrone, were the last steroid types to yield to partial synthesis, because no obvious precursor for them existed in nature. All of the other naturally-occurring steroids are based on the skeleton in Figure 3; the estrogens, however, are based on the structure for estradiol shown in Figure 4. Here, ring A has changed from the ordinary six-sided form to an "aromatic" form, where half the carbon-carbon bonds are double. You don't need a Ph.D. in organic chemistry to note the other difference between the estrogens and all other steroids. This is

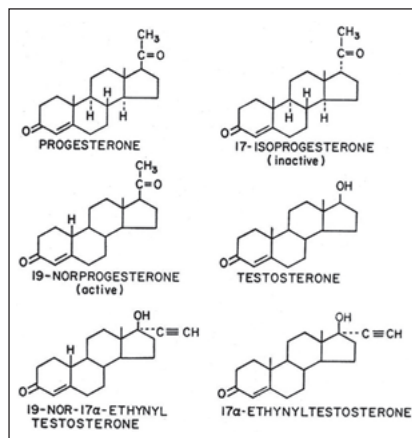


Figure 5. Chemical structures of key steroids leading to the Pill.

the absence of carbon atom 19 usually attached at position 10, which makes possible the doubling-up of carbon-carbon bonds in ring A. Chemically speaking, the only difference between testosterone (a conventional steroid with carbon atom 19) and the estrogens ("aromatic" steroids lacking C-19) – between men and women – is that one carbon, but what a difference it makes!

The partial synthesis of steroid hormones such as testosterone and progesterone could be extended to the estrogens if a process could be devised that would eliminate the key carbon atom No. 19 and thus effect the "aromatization" of ring A so typical of the estrogens. Hans H. Inhoffen, at Schering A.G. in Berlin, had demonstrated the practical feasibility of such a chemical conversion, but the work had been performed during World War II and experimental details were scant and had to be partly reconstructed. Syntex had started to use the Inhoffen process (which had not been patented in Mexico) for the production of modest quantities of estrone and estradiol. Upon assumption of my research position there, I suggested to Rosenkranz that Syntex examine another and potentially proprietary route to the estrogens directly from testosterone. In less than three months we succeeded in accomplishing this aim, which in chemical jargon would be described as the "aromatization of ring A of conventional steroids".

Our partial aromatization studies turned into the impetus that led us in a fairly straight path to the first synthesis of an oral contraceptive. From a technical standpoint, I felt that the time was ripe to

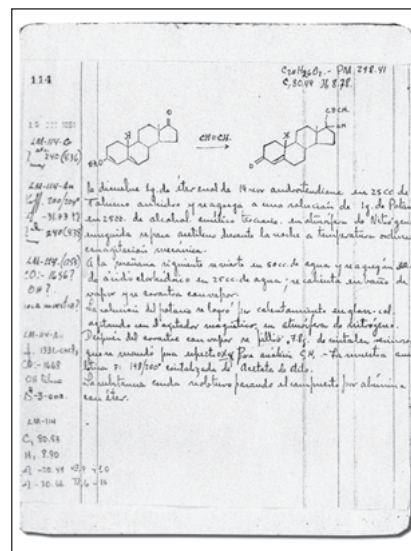


Figure 6. Syntex lab notebook (15 Oct. 1951) describing last step in synthesis of norethindrone.

follow up on Ehrenstein's lead of 1944. Using various chemical methods developed as part of our estrogen synthesis as well as methodology perfected by the Australian chemist, Arthur J. Birch (subsequently a long-term Syntex consultant), my Syntex colleagues and I prepared for the first time in 1951 pure, crystalline 19-norprogesterone (a steroid that like the estrogens lacked carbon atom 19) which, when assayed in rabbits at Endocrine Laboratories in Wisconsin, was found to be four to eight times as active as natural progesterone. In other words, Ehrenstein's observation with an oily mixture tested in one rabbit was more than confirmed: replacement of carbon atom 19 by one hydrogen had produced the most active progestational steroid known at that time. This observation was crucial, because Ehrenstein's mixture of stereoisomers had also the wrong configuration at C-17 – a change that was known to destroy progestational activity in progesterone itself (see top 2 compounds in Fig. 5) – and from an experiment in a single rabbit, it was not clear whether the beneficial effect of removing the angular methyl group between rings A and B was real.

With that lead in hand, we turned to another accidental discovery that had been made in 1939 [12] in Germany, where chemists at Schering, again under the leadership of Inhoffen, found that if acetylene is added at position 17 of the male sex hormone testosterone (see 17 α -ethynyltestosterone in Fig. 5), its biological activity is changed markedly:



Figure 7. Maximilian Ehrenstein

for unknown reasons this androgenic compound has weak progestational activity. Far more important, it also proved to be orally active. On the reasonable assumption that removal of the 19-carbon atom increases progestational potency and addition of acetylene confers oral efficacy, we at Syntex put both these observations together. On October 15, 1951 (see notebook page reproduced in Fig. 6), Luis Miramontes, a young Mexican chemist doing his undergraduate bachelor's thesis work at Syntex under my tutelage, completed the synthesis of the 19-nor analogue of Inhoffen's compound – that is, 19-nor-17 α -ethynyl-testosterone (bottom left structure in Fig. 5) or, for short, “norethindrone” – which turned out to be the first oral contraceptive to be synthesized.

We immediately submitted the compound to our favorite commercial testing laboratory in Wisconsin for biological evaluation and gloated happily when Dr. Elva G. Shipley reported back that it was more active as an orally effective progestational hormone than any other steroid known at that time. In less than six months, we had accomplished our goal of synthesizing a superpotent, orally active progestational agent! Returning to my reproductive metaphor, I classify our synthesis of norethindrone as the release of the fertile egg waiting now to be fertilized. Once that is understood, the roles of Ehrenstein and Inhoffen as older maternal uncles become obvious. Since Ehrenstein (Fig. 7) lived in the States, our paths crossed in the 1950s at several scientific meetings. I know that he was

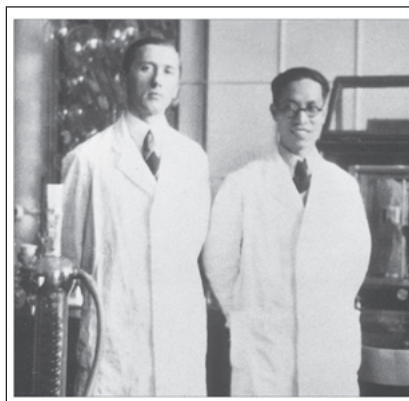


Figure 8. Hans Herloff Inhoffen and Huang Minlon at Schering, Berlin.

pleased at our elevation of his original 19-norprogesterone work from a piece of chemical esoterica to one of seminal significance; we actually published [12] a joint paper in 1958 to establish the nature (“wrong” stereochemistry at C-14 and C-17 compared to that of natural progesterone) of one of the components of his original 19-norprogesterone mixture.

My encounter with Inhoffen was different. We met only once at an international scientific congress. There, his comments seemed frosty, leaving the impression that my work as a graduate student at the University of Wisconsin had constituted an intrusion into his early work on the partial synthesis of estrogens. But in 1999, our paths crossed again, twice, though on his part posthumously. Early that year, I received the Inhoffen Medal at the Technical University of Braunschweig, but a more moving event occurred later that year in Graz. I had given a typical academic talk on the History of the Pill and had done so in German, which meant that it moved slower than it would have in English. When I realized that I would be running out of time, I decided to skip some slides. One of them was a picture of Inhoffen together with the father of Chinese steroid chemistry, Huang Minlon (Fig. 8). The room was crowded and I had to cope with many questions before the audience broke up. Suddenly a tall, serious man, probably around 60 years old, approached me to ask quietly, “Did you know Inhoffen and his work?” Before explaining what I had intended to say about Inhoffen, I produced the slide (Fig. 8) I had brought with me but had skipped during my talk. That's when I found out that I was speaking to Peter Inhoffen, a Catholic theo-



Figure 9. First page of U.S. patent of norethindrone.

logian and only son of Prof. Inhoffen, from whom he had become estranged. I couldn't read his expression: was his question prompted by curiosity or by still smoldering filial pride?

Our patent application (Fig. 9) for norethindrone was filed on 22 November 1951 (it is the first patent for a drug listed in the National Inventors Hall of Fame in Akron, Ohio), and I reported the details of our chemical synthesis, together with the substance's high oral progestational activity, at the April 1952 meeting of the American Chemical Society's Division of Medicinal Chemistry in Milwaukee. The abstract [12] of this report under the names of Djerassi, Miramontes and Rosenkranz was published in March 1952, and the full article with complete experimental details appeared in 1954 in the *Journal of the American Chemical Society* [12]. Readers may well be irritated by such an avalanche of dates, but chronological precision is the baggage of scientists preoccupied with priority – a foible I would be disingenuous to hide.

A few weeks after having synthesized the substance and having received from Dr. Shipley confirmation of its anticipated oral progestational activity, we sent it to various endocrinologists and clinicians: first to Roy Hertz at the National Cancer Institute in Bethesda, Maryland and to Alexander Lipschutz in Chile; later to Gregory Pincus at the Worcester Foundation in Shrewsbury, Massachusetts, to Robert Greenblatt in Georgia, and to Edward Tyler of the Los

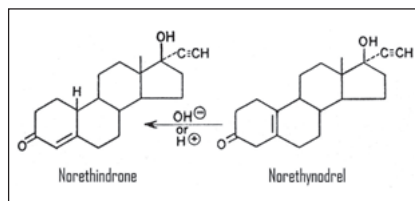


Figure 10. Conversion of norethynodrel into norethindrone.

Angeles Planned Parenthood Center. It was Tyler who, in November 1954, presented the first clinical results of using norethindrone for the treatment of various menstrual disorders and fertility problems. All of these biological investigations can be equated to sperm that is surrounding the egg. But since this is a record of the history of the Pill, we need to address the source and origin of the particular sperm that led to the fertilization of our chemical egg and thus to the ultimate birth of an oral contraceptive.

While we were aware of Haberlandt's work, initially, we were not focusing on contraception when we developed an oral progestational compound, because contraception was of no interest in 1951 to the pharmaceutical industry. Our research was undertaken because at that time the natural hormone progesterone was used clinically for treatment of menstrual disorders, for certain conditions of infertility, and at a research level, for the treatment of cervical cancer in women by local administration of a high dose of the hormone. Such administration was extremely painful because it involved injecting a fairly concentrated oil solution of large amounts of progesterone into the cervix. What drove us was the desire to create a more powerful progestational compound that would be active orally. As it happened, the progesterone treatment of cervical cancer did not pan out, but the clinical use of our norethindrone (under the trade name Norlutin and licensed to Parke, Davis and Company – at that time a large American pharmaceutical company) for the treatment of menstrual disorders was approved by the FDA in 1957 and is one of its therapeutic indications to this day.

Each of the biologists mentioned above had his own area of expertise and interest in the field of progestational activity. Gregory Pincus and his colleague Min-Chueh Chang of the Worcester Foundation for Experimental Biology in Shrewsbury, Massachusetts, were focus-

ing on how progesterone worked to inhibit ovulation (the mechanism behind Haberlandt's "temporary hormonal sterilization" and Makepeace's confirmation). Among the many steroids tested in 1953 by the Worcester Foundation group for such activity two substances (Fig. 10) stood out: our norethindrone and another substance, norethynodrel, that had been synthesized by Frank Colton at G. D. Searle, a pharmaceutical company in the Chicago area. The chemical history of norethynodrel is worth telling, since it illustrates one of the less attractive features of scientific research: the drive for scientific priority and the attempts to circumvent patent priority. In this instance, the stakes were higher than usual, since commercial considerations and financial returns quickly entered the equation.

■ Norethindrone vs Norethynodrel

For historical accuracy and appropriate credit, it is important to note that even though norethynodrel was only synthesized well over a year following the publication of our successful synthesis of norethindrone, it was norethynodrel that first entered the market as an oral contraceptive. M. C. Chang had found norethindrone and norethynodrel to have been the two most promising candidates in his initial animal studies. But his boss, Gregory Pincus, who was a consultant for Searle, selected the Searle compound for further work. Syntex, not having any biological laboratories or pharmaceutical marketing outlets at that time, licensed Parke-Davis & Co. of Detroit to pursue the FDA registration and market the product in the United States. (That choice itself was ironic, since it was Parke-Davis that had sponsored the original research work of Marker's at Pennsylvania State College, but had then refused continued support in Mexico, thus leading to the foundation of Syntex). It was only after 1957, when both norethindrone and norethynodrel had received FDA approval as drugs for non-contraceptive, gynecological purposes, that the paths of the two companies diverged.

Searle deserves full credit for reaching the market first with an oral contraceptive, norethynodrel, under the trade name Enovid, but its repeated claim to

have synthesized the substance independently and concurrently with Syntex's norethindrone constitutes a blatant misrepresentation of the facts. The record based entirely on published data is unambiguous. On August 31, 1953 – well over one year after our first publication (March 1952) dealing with the synthesis of norethindrone, and 21 months after our own November 1951 patent filing date (Fig. 9) – Frank Colton of G.D. Searle & Company filed a patent application for the synthesis of a steroid that differed trivially from norethindrone through the position of one double bond (Fig. 10). Trivially different, because treatment of Colton's isomer, norethynodrel, with acid, or just human gastric juice, converts it to some extent into Syntex's norethindrone – a conversion that among others [12] was established by Gregory Pincus and his collaborators. Is synthesis of a patented compound in the stomach an infringement of a valid patent? (Interestingly, years later, a similar suit with a related oral contraceptive was pursued by Wyeth, Inc. against Ortho Pharmaceuticals and initially resolved in favor of the plaintiff). I urged that we push this issue to a legal resolution, but Parke-Davis, our American licensee, did not concur.

Searle was selling a very successful anti-motion-sickness drug, Dramamine, which contained Parke-Davis's antihistamine Benadryl. Given that the only FDA-approved uses of our norethindrone in 1957 was the treatment of menstrual disorders and certain conditions of infertility, the issue seemed small potatoes to Parke-Davis, over which it was not worth fighting with a valued customer.

In the mid-1950s, Searle actively supported clinical trials of the contraceptive efficacy of norethynodrel. The work was conducted in Puerto Rico, under the direction of Pincus and especially John Rock, a clinical endocrinologist and gynecologist from Harvard. Around the same time in Mexico City and Los Angeles, Syntex sponsored contraceptive trials with norethindrone. But fearing a possible religious backlash, Parke-Davis suddenly chose not to pursue these results through the FDA approval process, and returned the contraceptive (but not gynecological) marketing license to Syntex. Alejandro Zaffaroni, Syntex's Executive Vice President, eventually ne-

gotiated a favorable marketing arrangement with the Ortho Division of Johnson & Johnson, a company with a long-standing commitment to the birth-control field, but the shift to a new company meant a delay of nearly two years before Syntex's norethindrone received FDA approval as a contraceptive. By 1964, three companies – Ortho, Syntex, and Parke-Davis (having changed its mind after realizing that no Catholic-inspired boycott had developed) – were marketing 2.0-milligram doses of Syntex's norethindrone (or its acetate), which by then had become the most widely used active ingredient of the Pill.

There is no question that Searle deserves kudos for marketing noethynodrel first – despite a possible consumer backlash by opponents of contraception. But given the extraordinary importance of these steroids, why does the Searle group to this day not disclose in the peer-reviewed literature any of the chemical research that led them to their pill? The only date supporting the claim for “independent simultaneous discovery” is Searle's patent filing date of August 31, 1953, a date that sounds “simultaneous” only without juxtaposition to the October 15, 1951 lab book entry (Fig. 6) describing the completion of the synthesis of norethindrone and the November 21, 1951 filing date (Fig. 9) of Syntex's patent application.

Colton and other researchers from Searle had not otherwise been reluctant to publish their steroid research. Indeed, in 1957, they published an article [13] in the *Journal of the American Chemical Society* about a new steroid anabolic, 17 α -ethyl-19-nortestosterone (Nilevar), that was produced in one step from our 17 α -ethynyl-19-nortestosterone (norethindrone). In their article, the Searle chemists cited quite properly our earlier publication, which predated theirs by over three years. Thus, their unaccountable shyness about the most significant product in their corporate history, norethynodrel, can only raise questions. Why, for instance, did Gregory Pincus, the person most responsible for persuading Searle to market norethynodrel, make not a single reference to any chemist (not even Frank Colton) in his 1965 opus magnum, “The Control of Fertility?” Why does his book make no mention of how the active ingredient of the

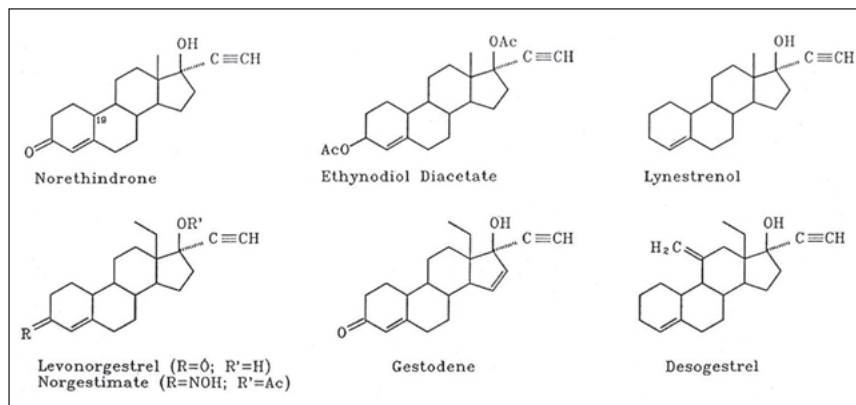


Figure 11. Chemical structures of oral contraceptives.

Pill actually arrived in his laboratory? And even worse: why did Pincus drop Haberlandt's name into a black hole of anonymity?

■ Pincus and the Chemists

My preoccupation with establishing unequivocally the priority – and thus the metaphoric maternal identity – is not just my admittedly strong competitive drive. I am realistic enough to acknowledge that it really does not make any difference to the world who does what first. But giving credit to Syntex as the corporate institution where it all first started is important to me (even though I severed all connections with that company in 1972), because institutional memories are so short. Syntex was the first and possibly the only significant example of important research in such a highly competitive and technically sophisticated field being conducted in a developing country. Both qualitatively and quantitatively, the research output of Syntex during the ‘fifties has never been matched in the steroid field; the pride and self-assurance it provided to a cadre of Mexican organic chemists, virtually all of them trained at Syntex, was moving to witness. Yet that company does not exist anymore, because in 1994 it was acquired by the Swiss pharmaceutical colossus Roche and promptly swallowed and digested. In that digestive process, the entire research division of Syntex in Mexico, which had just moved into new quarters in Cuernavaca, was closed and all research personnel dismissed. To me, the cold-bloodedness of this corporate amputation seems unforgivable: I know of no other pharmaceutical company in Mexico that has currently any significant research presence.

Syntex, as a company, and Mexico, as a country, deserve full credit as the institutional site for the first chemical synthesis of an oral contraceptive steroid – a statement that is not meant in any way to denigrate Searle's successful drive to be the first on the market with a steroid oral contraceptive. But there is a more charming end to this story. In the process of swallowing Syntex, Roche not only closed the Mexican research laboratories where norethindrone was first synthesized. Roche also decided to distance itself from any involvement in the contraceptive field, and promptly sold the entire Syntex oral contraceptive line, still based in its entirety on norethindrone. Who was the purchaser? None other than G. D. Searle – the company that went to heroic lengths to circumvent the Syntex patent on norethindrone and now had to pay good money to market it as its lead oral contraceptive long after the original patent had expired. But the story does not end there. G. D. Searle itself was acquired several times – first by Monsanto, but eventually by Pfizer, now the largest pharmaceutical company in the world. Few are aware of the fact that around 1954, Pfizer had an option from Syntex to market norethindrone, an option the company had not exercised because its president, John McKeen, an active Roman Catholic layperson, felt that Pfizer should not touch any agent even potentially related to birth control. Yet half a century later, Pfizer entered the contraceptive market with norethindrone! What a closure to an historical circle!

Interestingly, Syntex-developed norethindrone is still a widely used active ingredient of oral contraceptives, whereas Searle's norethynodrel disappeared from the market many years ago, to be super-

seded by other 19-nor steroids, which, as shown in Figure 11, are close chemical relatives of norethindrone. The second and third structures in Figure 11 are further examples of steroids, whose chief *raison d'être* was that they were not covered by the original Syntex patent (Fig. 9) of norethindrone, yet are converted to a considerable extent in the body into norethindrone and hence can all be considered qualitatively as “pro-drugs” of norethindrone.

On first glance, another alteration of the norethindrone molecule by addition of one methyl group in position 18, leading to levonorgestrel (Fig. 11) also seems to be just another example of a minor chemical change prompted by the desire to circumvent Syntex's norethindrone patent. Though seemingly trivial, chemically this was a drastic change since no naturally occurring steroids were known that possessed an angular ethyl group at position 13. Hence this substance could only be prepared by total synthesis and this was accomplished in 1964 [14] by Herchel Smith and collaborators at the University of Manchester. The patent rights to this higher homolog of norethindrone were acquired by Wyeth, a company that was active in hormone replacement therapy, who developed levonorgestrel into the “mother substance” of a second series of oral contraceptives (e.g. gestodene and desogestrel in Figure 11). In fact, for the first forty years of the clinical use of steroid contraceptives, all of the hundreds of “Pills” sold all over the world under different trade names were basically derivatives (see Fig. 11) of norethindrone or levonorgestrel.

It should not be surprising that I, as a chemist, in terms of my reproductive metaphor that equates any synthetic drug to an egg, spent the bulk of this chapter examining the maternal lineage of the Pill. But just as it is clear that Ludwig Haberlandt merits attribution as the paternal grandfather, Gregory Pincus – despite the uncertainties of paternity generally – deserves to be called a father of the Pill. The initial rabbit experiments by M. C. Chang in Pincus's laboratory clearly were the sperm that fertilized the chemical egg, and the subsequent implantation of the embryo and eventual fetal growth can largely, though not entirely, be ascribed to further experiments

conducted in Pincus's laboratory. But Pincus was not only a prolific and highly experienced endocrinologist, he was also a charismatic entrepreneur. Many times, this latter quality is more difficult to find than mere scientific brilliance; it took entrepreneurship of Pincus's caliber to bring the steroids provided by the chemist to the stage where clinical trials of the Pill could be initiated and where John Rock, as leader of the clinical team, could assume the mantle of metaphoric obstetrician for the eventual birth of the Pill. While Rock's name is inexorably connected with that role, others, notably Celso-Ramon Garcia (the first professor of OB/GYN at the University of Puerto Rico Medical School) and Edith Rice-Wray (Medical Director of the Puerto Rican Family Planning Association) contributed heavily to the planning and implementation of the first clinical trials in the San Juan area. Rice-Wray subsequently directed a Family Planning clinic in Mexico City where she continued her clinical studies, this time with Syntex's norethindrone.

Of the numerous talks and interviews that I have presented over the course of decades on the birth of the Pill, three stand out in my mind. Two of them were formal occasions directly associated with Pincus's memory: the Gregory Pincus Memorial Lecture and Award presented in 1982 on his home turf, the Worcester Foundation for Experimental Biology, and the last Gregory Pincus Memorial Lecture at the 50th and final Laurentian Hormone Conference in 1993. Ironically, this event was held in Puerto Rico – the site of the first oral contraceptive clinical trials – although these annual meetings, founded by Pincus, usually met in the Laurentian Mountains of Quebec. In the same year, I also gave the first A. S. Parkes Memorial lecture at Cambridge which commemorated a British pioneer in reproductive biology. But the most relevant event to my story is an unusual session held Friday morning, May 5, 1978, in an old New England mansion on the outskirts of Boston, the headquarters of the American Academy of Arts and Sciences. The Academy was holding a closed two-day session on “Historical Perspectives on the Scientific Study of Fertility”. The purpose of the meeting was to have a free-flowing dialogue among some of the key scientists who had been active in

the field of fertility in the United States during the previous 40 years (therefore, it was not surprising that, as far as I could tell, at age 55, I was the youngest of that group) in order to collect a record that historians of science might draw upon in the future.

The unedited transcript of that Friday morning session reads awfully: Nouns do not match verbs, tenses get mixed, punctuation is lost, and many words are misspelled or appear to be inaudible. Nevertheless, one gets a real flavor of excited human dialogue and interruptions, of hurt egos, of hitherto undisclosed vignettes. Here are 2 samples.

Hechter: *May I take a couple of minutes?*

Djerassi: *I haven't finished. I'd like to continue because I've only gotten to the first half of my story.*

Reed: *He can have my time. This is the first really fruitful ... (inaudible)*

Greep: *This is history from the horse's mouth, and I think it's very good.*

Djerassi: *I misunderstood. Did you want me to continue?*

Greep: *Yes.*

The scientific co-chairman of the Boston Academy's May 1978 meeting was Roy O. Greep, a distinguished endocrinologist at Harvard, who had known personally most of the actors in this play. Another key participant was Oscar Hechter, who for many years had been senior scientist of the Worcester Foundation for Experimental Biology. Though not directly involved in the development of oral contraceptives, he had been an intimate collaborator of Gregory Pincus. James Reed of Rutgers University was a historian studying the birth control movement in America.

I felt that this was the one opportunity, years after Pincus's death, where I could find out why he had been so ungraciously selective in not acknowledging work of others that was crucial to the development of the Pill. John Rock, who had not behaved very differently, was in the room, but he had reached an age where it was not any more possible for him to contribute to the dialogue. His

was a silent, poignant presence. But Celso-Ramon Garcia, Rock's and Pincus's closest clinical colleague, was present, which led to the following exchange:

Garcia: Basically, the monograph "Control of Fertility" that Pincus wrote expresses in detail what his feelings were about who contributed to what.

Djerassi: Why did he not mention any chemists, do you happen to know that?

Garcia: He was a biologist, the same way as you are principally presenting your story as a chemist.

Djerassi: That's not true. That's why I submitted a paper here with biological references, including yours.

Garcia: Well, okay, but the fact is that principally you are a chemist and your major contribution has been that of a chemist.

Djerassi: But this would be like my describing the history of oral contraceptives without a single reference to Pincus or Rock or yourself!

In other words, Garcia – and by inference Pincus – felt that it is sufficient to focus on the paternal role in discussing the history of the Pill. Hence as a chemist, I have tried to illuminate the equally indispensable "maternal" role of the chemist. But since in 2011 we are celebrating the 50th anniversary of the Pill in Germany, let me end with a discussion of the "German" role.

■ The 50th Birthday of the Pill in Germany

It is curious, yet understandable, that in 1961 Germany proved to be the third country after the USA and Australia to allow the use of an orally active progestational steroid for contraceptive purposes. Curious, because Germany at that time was as conservative in the area of family planning as many other European countries where the Pill was only permitted years later; but also understandable, since in terms of scientific research and medical applications of steroids, Germany was in many respects the most advanced country in the world and especially so in steroid chemistry with the

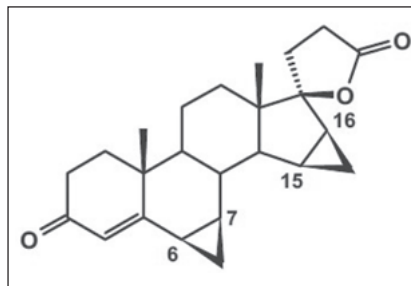


Figure 12. Chemical structure of drospirenone.

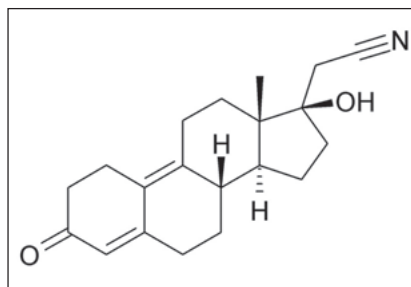


Figure 13. Chemical structure of dienogest.

Nobel laureates Windaus, Wieland, and Butenandt heading the list. Similarly, among pharmaceutical companies, Schering AG played a lead role in medical applications of steroid hormones. So it was not surprising that Schering was also the company that introduced the first Pill into Europe. However, in contrast to the USA, it was not norethynodrel (Fig. 10) but rather the acetate of norethindrone, which in the body is primarily metabolized into the parent norethindrone, thus constituting a pro-drug of the latter. But in contrast to the Syntex-G. D. Searle commercial competition outlined above, in this instance Schering marketed norethindrone acetate under the trade name Anovlar under license from Syntex, which in turn had another amusing historical consequence: Parke Davis, the American pharmaceutical company who first distributed norethindrone under Syntex license for menstrual disorders, but had then returned the rights to market is as contraceptive for fear of a Catholic boycott, subsequent to Schering's launch of norethindrone acetate (Anovlar) changed its mind and also marketed the substance as an oral contraceptive in the mid 1960s.

When Wyeth introduced Herchel Smith's levonorgestrel (Fig. 11) into the American market, Schering licensed it for distribution in Germany. Thus for the first twenty years, Schering's increasingly powerful position worldwide in the field of contraception was based on externally

licensed steroids from Syntex and Wyeth. Only in the middle 1980s, when a levonorgestrel analog with an additional double bond in ring D (see Fig. 11) was synthesized and introduced under the generic name Gestodene did Schering market a proprietary steroid as a contraceptive, an achievement that was repeated twice more during the last decade with drospirenone [15] (Fig. 12) and dienogest (Fig. 13). A possible rationale and commentary for these decisions follows below in the final section.

■ The Future: Reflections and Prognosis

The subtitle of this article – *thriving or surviving* – implies some prognostication and this is the theme with which I wish to conclude: specifically do we need new methods of contraception and if so, who is "we?" The answer is clear, once we accept that demographically speaking, instead of dividing the world into "more developed" and "less developed" nations, we need to accept that the division is now between geriatric and pediatric countries.

As seen in Table 1, with the exception of Afghanistan, all of the top pediatric countries are African, whereas with the exception of Japan, the most geriatric countries (Tab. 2) are found in Europe. By examining Table 3, which lists the ten world-wide most populous countries expected in 2050, Pakistan, Nigeria, Bangladesh, Ethiopia and partly also India fall into the pediatric category.

Clearly, the contraceptive needs of the pediatric countries, which are of no commercial interest to the large international pharmaceutical firms, are not only urgent but also totally different from those of the geriatric countries. What most of Africa and parts of Asia and Latin America need is not newer birth control methods – in other words new "birth control hardware", but rather improvements in "birth control software" – meaning improvements in education, public health, and foremost changes in the status of women, because improving those will cause an explosion in the use of existing methods of family planning.

The only market that could afford new methods of birth control are the geriatric countries, but those populations have al-

Table 1. Countries with youngest populations (2010)

Country	% ages < 15
Niger	50.1
Uganda	48.7
Burkina Faso	46.4
Congo, Dem. Rep.	46.4
Zambia	46.2
Malawi	45.9
Afghanistan	45.9
Chad	45.6
Somalia	44.9
Tanzania	44.7

Table 2. Countries with oldest populations (2010)

Country	% ages 65+
Japan	22.6
Germany	20.5
Italy	20.4
Sweden	18.3
Greece	18.3
Portugal	17.9
Bulgaria	17.6
Austria	17.6
Latvia	17.4
Belgium	17.4

ready learned how to limit their families by existing methods. In the large majority of European countries, the average sized family (ca. 1.5 children) is far below replacement level (2.1 children). For those countries, the leitmotiv “contraception” in the field of reproductive medicine has been replaced by “conception”, whereas exactly the reverse applies to the pediatric countries. I do not wish to imply that the geriatric countries would not be better off if there were a much wider choice of contraceptive options, including in those countries where birth control is already practiced by a substantial portion of the population. So what new ones might make sense in Europe or Japan?

In 1989 [16], I listed 6 fundamentally new methods (Tab. 4) – not piddling improvements in existing ones – that, if implemented, would vastly expand the choice for human fertility control for all constituencies: poor and affluent, pro-choice and anti-abortion, female and male. They would also make a difference in convenience, economic savings to the consumer, and possibly even safety.

Table 3. Most populous countries (2050)

Country	Population (Millions)
India	1,748
China	1,437
United States	423
Pakistan	335
Nigeria	326
Indonesia	309
Bangladesh	222
Brazil	215
Ethiopia	174
Congo, Dom. Rep.	166

Table 4. A priority list of new contraceptive methods [C. Djerassi, Science 1989; 245: 356].

1. Spermicide with antiviral properties (effective during normal coitus)
2. Once-a-month pill effective as menses inducer
3. Reliable ovulation predictor (“red” & “green” light)
4. Easily reversible and reliable male sterilization
5. Male contraceptive pill
6. Antifertility vaccine

Note that improved efficacy is hardly an issue any more.

Twenty-two years later, only ovulation prediction (3. in Tab. 4) has been realized – in part because it required no toxicity expenses and could focus entirely on diagnostic efficacy and accuracy. But in terms of usage, it is employed much more widely for purposes of conception rather than contraception. Work on an antiviral spermicide (1. in Tab. 4) is still progressing – primarily because of its applicability to the AIDS pandemic rather than for reasons of improved contraception, but so far with little success. Easily reversible and reliable male sterilization (4. in Tab. 4) would be of great advantage in both pediatric and geriatric countries, since vasectomy is practiced widely – notably in China and the US, though not in Germany – but mostly by men who are already fathers and wish no more children. If reversibility were guaranteed – a very expensive proposition, requiring large numbers of volunteers and many years of observation then vasectomy, since it is simple as well as safe, might well be practiced by many

young men before they ever had fathered any children. For pharmaceutical companies, this approach would be of zero financial interest.

This leaves alternatives 2, 5 and 6, which would represent fundamental advances that would also fill enormous lacunae in our contraceptive armamentarium. But the costs for developing such agents would be enormous (each easily exceeding US\$ 1 billion), very time consuming [17] and very likely also prone to litigation. Only the largest pharmaceutical companies would have the necessary scientific and financial resources for such an endeavor, and given their focus on the diseases of aging and deterioration that afflict the ever increasing geriatric populations of these rich countries, it is not surprising that not a single of the 20 largest pharmaceutical companies is currently pursuing research and development work on a male contraceptive or a fertility vaccine. So what is left?

The few major drug companies that continued after 1975 to pursue any research in female contraception were those that had a significant market share of the Pill. The two most important ones (Schering in Germany and Organon in Holland) were both swallowed up in recent years by German (Bayer) and American (Merck-Schering-Plough) pharmaceutical giants, not unlike what happened in the 1990s with Syntex and the Swiss drug firm Roche. But since we are now celebrating the 50th anniversary of the arrival of the Pill in Germany, let us examine what has happened during the past decade when two more new steroids – drospirenone (Fig. 12) and dienogest (Fig. 13) were added to the list of the seven 19-norsteroids of the norethindrone and levonorgestrel type (Fig. 11). But before doing so, it is necessary to emphasize the main motivation in developing the five new chemical modalities in Figure 11 aside from norethindrone and levonorgestrel. Clearly, it was to carve out a proprietary position vis a vis these two 19-norsteroid prototypes by creating minor chemical modifications that would offer patent protection.

Because of the huge cost of developing even such minor chemical variants, a considerable effort was also directed by these companies as well as some non-profit organizations such as the Popula-

tion Council toward introducing new delivery vehicles, such as injectables, silastic implants, vaginal rings, skin patches and the like. In my opinion, such applied research is well justified in extending the use of these steroid contraceptives to a wider population. But what about continuing to create “new” oral contraceptives? Aside from narrow marketing considerations, is there a societal need and would the money expended on such endeavor not be better justified if it addressed the development of some fundamentally new methods of the type illustrated in Table 4? Again from a societal standpoint, the answer must be a resounding affirmative, but what about commercial economic considerations on the part of a pharmaceutical company? In that regard, I am afraid that the answer must be negative. In fact, the market has spoken because none of the major pharmaceutical companies is spending any money on such new areas for the obvious reason that in terms of urgency in the geriatric countries, birth control cannot and possibly even should not have a high priority. Few will argue that spending a few billion dollars on a new contraceptive would be more useful – societally or commercially speaking – than a drug preventing Alzheimer’s disease.

It is for this reason that in 1994 [18], I proposed with Stanley Leibo a different approach to birth control in males that would not involve research nor marketing by pharmaceutical giants. But since male contraception is not the focus of this article, I shall conclude with some personal reflections on the introduction of the two latest oral contraceptives, drospirenone (Fig. 12) and dienogest (Fig. 13) – both developed in Germany – which are sometimes called “fourth generation” oral contraceptives. Are they really new and why were they developed?

Chemically speaking, drospirenone (Fig. 12) is indeed unique among oral contraceptives, since all the others (Figs. 10, 11) are based on the ubiquitous 19-norsteroid skeleton, whose origin I have described in excruciating detail through the history of norethindrone; all of these substances were designed specifically to act as orally active progestins. Drospirenone, on the other hand, was developed nearly 40 years ago as an aldosterone antagonist and only much later discovered to possess ovula-

tion inhibiting properties. The reason for taking an old chemical, whose patent coverage had virtually expired, and then to launch it two decades later as a contraceptive was based on extensive biological scrutiny which showed that in terms of potential side effects, it seemed to offer some advantage over all the other 19-norsteroids because of its mild anti-androgenic and anti-aldosterone properties. These became the basis of a successful marketing campaign in 2000 which quickly propelled drospirenone under the trade name Yasmin into a top selling contraceptive. One might, therefore, reach the conclusion that such an emphasis on ancillary hormonal attributes – separate from the contraceptive properties – would constitute a logical rationale for bringing a new steroid contraceptive to the market.

While logical, it ignored a crucial lesson from history. As I described in great detail [1, 11], the first three oral contraceptives (norethynodrel, norethindrone, and levonorgestrel) were scrutinized medically over a period of ca. 20 years to an extent that has never been equaled by any other drug in medicine, primarily because these were potent drugs that were given for years to “healthy” people for preventive rather than curative purposes, which carried with it an almost unrealistic emphasis on safety. Among the main side effects studied were potential thromboembolisms and cancers. It took at least two decades in the post-marketing phase to carry out these huge epidemiological studies, which would be impossible to perform in a pre-marketing period, because it would require unrealistically high numbers of experimental subjects for financially too burdensome time periods. In the process, one of the most significant positive side effects was uncovered, namely a protective action against ovarian cancers in nearly 50% of the user population. Because such studies required many years, these were based on the then only existing three Pills – norethynodrel, norethindrone, and levonorgestrel. Indeed, the recent report by Hannaford et al [19] summarizing the results from a mammoth study comparing 339,000 woman years of never-users with 744,000 woman years of ever-users of the Pill, contains the statement: “Many women, especially those who used the first generation of oral contraceptives many

years ago, are likely to be reassured by our results. Our findings might not, however, reflect the experience of women using oral contraceptives today, if currently available preparations have a different risk to earlier products.”

This limitation applies even more dramatically to a second article by the same authors [20] based on 46,112 women observed for up to 39 years which concludes that ever-users of oral contraception had a significantly lower rate of death from any cause, including all cancers, all circulatory diseases, and some other diseases than the never-users. I would claim that from an overall public health standpoint, it is these conclusions that should carry much more weight than relatively minor differences in some of the hormonal effects of the newest compounds for whom such epidemiological studies are not and most likely never will be available.

Thus, in the case of drospirenone (Fig. 12) in 2010 a series of law suits were initiated against Schering claiming an increased risk of thromboembolic disorders and other vascular problems in women using Yasmin compared to those in women on oral contraceptives containing the older 19-norsteroids (Fig. 11). While this increased incidence of thromboembolic problems is small, it clearly was enough to tarnish the reputation of Yasmin. Was that the reason that Schering introduced still another new oral contraceptive in 2009, this time based on the 19-norsteroid dienogest (Fig. 13)?

Under the trade names Natazia and Qlaira, the substance was touted as the first oral contraceptive to use as companion estrogen estradiol valerate instead of the conventional ethynylestradiol – the implication being that these were new chemicals. In point of fact, dienogest had already been synthesized in 1979 [21] by Kurt Ponsold and colleagues and launched under the tradename Valette in 1990 by Jenapharm in combination with ethynylestradiol as an oral contraceptive. Its commercial success was apparently one of the reasons why Schering then acquired this East German concern. Estradiol valerate has been known for well over half a century. Natazia is claimed to be more effective than other oral contraceptives in controlling heavy

Table 5. Monthly cost in £ of oral contraceptives [NHS New Drug Evaluation No. 98, November 2009].

– Norethindrone	0.51–0.92
– Levonorgestrel	0.96–1.32
– Desogestrel	2.19
– Drospirenone	4.90
– Dienogest	8.39

menstrual bleeding. Is that really a reason for replacing the virtually identical Jenapharm product Valette with its 20-year long history of wide use with still another oral contraceptive containing a 50-year old estrogen and at the same time making it the most expensive oral contraceptive on the market?

In my opinion, contraception is too important a public health feature world wide to have minimal marketing advantages be the reason to resurrect old drugs and claim them to be new “fourth generation” advances, albeit in a more complicated polyphasic formulation. Since the National Health Service in the UK covers contraceptives, its cost of the various steroid contraceptives is of concern as summarized in Table 5.

Does it really make sense to pay 10 to 15 times more for such “new” agents by comparison with oral contraceptives that are still consumed by millions of women and have been the subject of decades-long epidemiological studies [19, 20]? For the pediatric countries of the world, the answer is a resounding no. But is it even justified for the geriatric countries – especially in these days of nearly unsustainable increases in medical care during economically troubled times?

In the long run, it will probably not make any difference for two reasons. First, the only entities with the scientific and financial resources to create new chemically-based contraceptives are the large pharmaceutical firms. Continuing to dabble with minor modifications of existing steroid progestins combined with estradiol derivatives does not seem to me to be of overriding societal benefit. A focus on improvements in postcoital agents – the “morning after pills” – might well be more useful for consumers, but hardly to drug firms. Among the twenty largest in the world, not one is working on new methods for fertility control of the type summarized in

Table 4, with the possible exception of a viral spermicide as a side issue related to research on drugs effective against AIDS. As I pointed out, the reasons are logical because these companies are focusing on the crucially important and unsolved problems of an increasingly geriatric population where the illusory “totally safe” criterion does not apply nor does the enormous potential of liability suits. A cancer patient is unlikely to sue as a result of side effects that a user of contraceptives or vaccines would consider unacceptable. Pharmaceutical companies are not philanthropic organizations, who can afford to ignore the financial bottom line.

But there is a second reason why I believe that significant new work on contraceptives will not occur as the emphasis in Europe and other geriatric countries shifts from “contraception” to “conception.” As I argued in both a book [1] and two plays [22, 23], within a few decades the option of preserving one’s gametes at a young age, say the early twenties, followed by resorting to IVF for the one or two children that European families now have, would become a realistic option – especially for those women who now postpone child bearing and thus would be in a position to operationally extend their fertile life time. The obvious corollary would then be to consider early sterilization which would make contraception unnecessary for effective and desired family planning. None of these shifts would involve the pharmaceutical industry and hence can be implemented as a matter of public policy as has been illustrated for a male contraceptive alternative [18].

As a scientist, who at one time was also an executive of a pharmaceutical company and who has turned into a playwright of “science-in-theatre” plays, it seems only fitting that I present my prediction of the divorce of sex from reproduction in dramatic form through a brief dialogic excerpt [22] from “An Immaculate Misconception” between Dr. Melanie Laidlaw, a reproductive biologist and (in the play) the inventor of intracytoplasmic sperm injection (ICSI), and her clinical colleague, Dr. Felix Frankenthaler.

Melanie: *Now, if ICSI works in humans... think of those women – right now, mostly*

professional ones – who postpone child-bearing to their late thirties or even early forties. By then, the quality of their eggs... their own eggs... is not what it was when they were ten years younger. But with ICSI, such women could draw on a bank account of their frozen young eggs and have a much better chance of having a normal pregnancy later on in life. I’m not talking about surrogate eggs.

Felix: *Later in life? Past the menopause?*

Melanie: *You convert men in their 50s into successful donors.*

Felix: *Then why not women? Are you serious?*

Melanie: *I see no reason why women shouldn’t have that option ... at least under some circumstances. But think beyond that ... to a wider vision of ICSI. I’m sure the day will come – maybe in another 30 years or even earlier – when sex and fertilization will be separate. Sex will be for love or lust.*

Felix: *And reproduction under the microscope?*

Melanie: *And why not?*

Felix: *Reducing men to providers of a single sperm?*

Melanie: *What’s wrong with that ... emphasizing quality rather than quantity? I’m not talking of test tube babies or genetic manipulation.*

Felix: *And then what?*

Melanie: *Each embryo will be screened genetically before the best one is transferred back into the woman’s uterus. All we’ll be doing is improving the odds over Nature’s roll of the dice. Before you know it, the 21st century will be called “The Century of Art.”*

Felix: *Not science? Or technology?*

Melanie: *The science of... A... R... T: assisted reproductive technologies. Young men and women will open reproductive bank accounts full of frozen sperm and eggs. And when they want a baby, they’ll go to the bank to check out what they need.*

Felix: *And once they have such a bank account... get sterilized?*

Melanie: *Exactly. If my prediction is on target, contraception will become superfluous.*

Felix: *I see. And the pill will end up in a museum... of 20th century ART?*

Melanie: *Of course it won't happen overnight... But A... R... T is pushing us that way... and I'm not saying it's all for the good. It will first happen among the most affluent people... and certainly not all over the world.*

■ Conflict of Interest

No financial conflict of interest.

All figures kindly provided by Carl Djerassi.

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