Reflections on the 50th Anniversary of the Birth Control Pill

The story of the development of “The Pill” really begins with Margaret Sanger, whom I like to call “Mother One” of the Pill. She was a social worker in New York City in the 1930s and was constantly dealing with poor immigrant families who would have ten or more children with no access to family planning due to the Comstock Laws that had been established by Congress in 1873. This Law made the advertising, the sale, or the procurement of contraceptive devices, a federal crime. In fact, it was not repealed in the states of Massachusetts and Connecticut until 1965, five years after The Pill was approved by the FDA as a contraceptive for women. In her struggle to help poor families, and in defiance of the Comstock Laws, Margaret Sanger opened family planning clinics, for which she was arrested and the clinics were shut down. Eventually, the authorities allowed her to operate clinics on public health grounds. As she gained recognition, she became president of the International Planned Parenthood Federation (IPPF) but she was always on the lookout for new methods of population control that would give women more control of their own fertility. During her quest for a better contraceptive she heard about Gregory Pincus who was one of the foremost reproductive biologists at that time. As a result of a meeting with Pincus in New York City in 1951, she provided a small sum of money to Pincus from IPPF, whose resources were very limited, to fund a small project on hormonal contraception at the Worcester Foundation for Experimental Biology (WFEB) in Shrewsbury, Massachusetts.

Mrs. Katharine McCormick, whom I like to call “Mother Two” of the Pill, was heir to Stanley McCormick’s share of the International Harvester fortune. She was the second woman to graduate from the Massachusetts Institute of Technology, and the first woman to graduate in science with a bachelor’s degree in biology. A friend and sponsor of Margaret Sanger, she learned about IPPF’s support of a small birth control project awarded to Gregory Pincus at the WFEB. Mrs. McCormick was already sponsoring a project on schizophrenia at WFEB and knew Gregory Pincus very well. So, to learn more about the birth control project, she arranged a meeting with Pincus and Sanger at the WFEB in 1953. According to accounts by Mrs. Pincus, the two ladies were very demanding, more or less pounding on Pincus’s desk, in their quest for a “magic bullet.” With his characteristically calm demeanor, Pincus outlined his thoughts to the ladies. He pointed out that, from work done in 1937 by Makepeace et al., and also by Dempsey, progesterone was known to block ovulation in laboratory animals, but progesterone was very expensive and had to be given in very high doses by mouth or by injection thus making it unsuitable for routine use as a contraceptive. However, Pincus related that a medicinal chemist from the United States had emerged from the jungles of Mexico with bags of progesterone synthesized from a plant, thus reducing the cost of progesterone from about $500.00/gm to eventually less than $5.00/gm. Pincus also indicated that many pharmaceutical companies were making synthetic analogs from this cheap progesterone so he proposed to test these analogs in laboratory animals to see if any were active by mouth. As Pincus was outlining this scenario, the story goes that Mrs. McCormick kept interrupting him, wanting to know how much this research would cost. Pincus initially ignored the interruptions but was thinking at the back of his mind that about $75,000 would cover the costs for laboratory animals, a technician, and a post doc. But on reflection, he realized that Mrs. McCormick was very wealthy, so when she interrupted again, he said that he thought that $150,000 would cover the cost of the project, a considerable sum in 1953 dollars! Whereupon, Mrs. McCormick reached into her pocket book and wrote out a check for $20,000, saying “Here is the first installment Dr. Pincus—now get on with it!!” Over the ensuing years Mrs. McCormick would donate two million dollars to the project and to the WFEB. After years of testing in rats and rabbits by research assistants Anne Merrill and Mary-Ellen Fitts, supervised by M.C. Chang the ovulation expert at WFEB, two compounds were found to be the most effective when given by mouth to laboratory animals - Norethynodrel from Searle and Nor- ethisterone from Syntex. However, testing had to be performed in women. John Rock, a colleague of Pincus from his Harvard days, agreed to do tests in women. John Rock was running a clinic in Boston to improve fertility in women by giving very large amounts of progesterone by mouth supplemented with Diethyl Stillbestrol, the first non-steroidal synthetic estrogen which was originally promoted for clinical use by Sir Charles Dodds in the U.K. The rationale was that withdrawal of these hormones would cause a surge of gonadotrophins and thus increase conception rates—the so-called Rock rebound effect. Because the Comstock laws that prohibited the promotion of contraceptive devices, there were potential problems associated with investigating a birth control pill. For this reason and other religious concerns, trials of a potential oral contraceptive were carried out under the category of menstrual regulation. Pincus and Rock eventually chose to use Norethynodrel in women because early results showed it to be more effective than Norethisterone in blocking ovulation, probably due the presence in Norethynodrel of ethinylestradiol that enhanced its progestogenic effect. In fact, the 3-methyl ether of ethinylestradiol (Mestranol) was subsequently added to both Norethynodrel and Norethisterone, the latter being introduced by Ortho Pharmaceuticals three years later as an oral contraceptive. Norethisterone, synthesized by Carl Djerassi at Syntex, was the first orally active 19-nor progestin to be produced but, for various reasons, its use as an oral contraceptive was not established until three years after the introduction of Norethynodrel by G.D. Searle. None-the-less, Djerassi made an important contribution to the evolution of The Pill by pioneering the development of synthetic analogs of progesterone. Of the twenty five women who completed Rock’s trials using very high oral doses of progesterone, all showed inhibition of ovulation.