

Two pills, two paths: a tale of gender bias

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In Japan, it took over 30 years to register the contraceptive Pill, but it took only six months to approve Viagra. The Pill was developed in an academic institution and no large pharmaceutical manufacturer wished to market it. Viagra was developed inside a big company and actively promoted. In the USA, the Pill was almost removed from the market because of widely publicized reports of deaths, but mortalities associated with Viagra do not make the headlines. Viagra has been promoted by the famous, whilst those who use the Pill do not appear in advertisements. Even theologians have treated these two drugs according to different standards. It is suggested that this asymmetry is not accidental, but is an expression of a deep-seated dual standard that is ultimately driven by biosocial differences in male and female power, and reproductive agendas rooted in human evolution.

In 1921 in Vienna, Austria, Ludwig Haberlandt described how the hormones released in pregnancy might be made into a practical contraceptive. 'It needs no amplification,' wrote Haberlandt, 'of all methods available, hormonal sterilization based on biological principles, if it can be unobjectionably applied in the human, is an ideal method for practical medicine and its future task of birth control.' Yet it took until 1960 in the USA and 1962 in Europe before oral contraceptives (OCs) were developed and on the market. In the case of Japan, it took almost three more decades, until 1999, before OCs were approved for sale.

In 1996, Boolell, Ballard and their colleagues published a clinical study of a type-5 phosphodiesterase inhibitor (sildenafil) they had researched to treat angina. In a small series of 12 men they demonstrated sildenafil also improved penile response to sexual stimulation: Viagra had been discovered. The marketing application was submitted to the US Food and Drug Administration in September 1997 and Viagra was approved for commercial sale in March 1998 [1].

Are these differences in timing an accidental consequence of the processes of drug development and research, or are they symptomatic of a more profound division of the way in which the world treats drugs related to male and female reproduction? If so, is there a plausible explanation of why the Pill, which has changed the lives of hundreds of millions of women, and a tablet that brings some extra

sexual pleasure to a relatively small group of men, should be treated so differently (Fig. 1)?

Research perspectives

Viagra was discovered in the laboratories of the Pfizer Company and developed by a large team of well-funded researchers vividly aware of the commercial potential of the product. For a drug developed at the end of the 20th century, Viagra secured FDA approval rapidly. The development of the Pill was carried out in an academic institutions on shoestring budget by tiny group of researchers who had not intended to work in this field. In 1951, Margaret Sanger, the American family-planning pioneer, and International Harvester fortune heiress Katherine McCormick had dinner in New York with Gregory Pincus. Pincus was a highly competent reproductive physiologist from at the Worcester Foundation outside Boston. Sanger and McCormick understood the crying need for a 'simple, cheap, safe contraceptive to be used in poverty stricken slums.' Although 'Goody' Pincus, as he was known, would not have initiated research in contraception of his own volition, he realized it should be possible to create an OC based on progesterone – the hormone of pregnancy. McCormack wrote a check for \$116 000. Pincus recruited his colleague Min Chueh Chang and excited the interest of John Rock, the leading gynecologist in Boston. The first clinical studies were published in *Science* in 1956.

The thirty years between Haberlandt's initial publication and the Pincus, Rock and Chang research had been taken up by two issues. One was the lack of a low-cost source of steroid hormones and the other an overt hostility to contraceptive research. The first sex hormone (estrogen) had been isolated in milligram amounts from four tons of cow ovary in 1936, but then in the 1940s, Russell Marker found he could synthesize steroids from the Mexican yam



Fig. 1. The contraceptive pill and Viagra.

at 100th the cost of animal sources. But even if cheap steroids had been available earlier, it is exceedingly unlikely they would have been used in contraceptive research. In the 1920s, Dr J.R Baker was expelled from his laboratory for investigating spermicides [2], and he was able to continue his work only when he was rescued by an Australian pathologist called Howard Florey – later Lord Florey, who received a Nobel Prize for his work on penicillin and was at one time President of the Royal Society. Even when the Pill reached Britain, the Ministry of Health and the Medical Research Council refused to sponsor clinical studies because it was ‘too politically and morally sensitive for them to handle,’ [3] and it was left to a charitable group, the Council for the Investigation of Fertility Control (an offshoot of the British Family Planning Association) to conduct clinical trials. In the USA, the National Institute of Child Health and Human Development was explicitly barred by Congress from studying contraception until 1958.

Commercial perspectives

Remarkable as it may seem today, when the ‘Pincus Pill’ was shown to work, it was illegal to use it in Massachusetts. In the 1870s, Anthony Comstock (1844–1913) had lobbied the US Congress to pass a series of laws that defined contraceptives and related literature as pornography. Comstock was a rigid puritan (Fig. 2), and in 1917 the Comstock Laws were used to shut down the first American family planning clinic in Brooklyn, New York, which Margaret Sanger had opened 10 days previously. Although some US states had overturned the infamous ‘Comstock Laws’ prior to the Supreme Court ruling that made contraceptive legal in every state (*Griswold vs Connecticut, 1965*) [4], Massachusetts was not among them. When OCs were developed, the clinical trials had to be done outside Massachusetts, in Puerto Rico, Los Angeles and Haiti.

In such a hostile atmosphere, all the large pharmaceutical manufacturers were extremely hesitant to market the Pill. Finally, G.D. Searle, then a relatively small company in Chicago, agreed to distribute the first OC, called *Enovid*, by marketing them as a treatment for ‘menstrual irregularities,’ and warning women about the ‘possible side effects of contraceptive activity.’ Every thing about the trials proved controversial. Writing in 1969 a Washington Post reporter, Morton Mintz, claimed that the FDA had approved oral contraception on an inadequate 132 cases. Nearly four decades later, there were still claims that the Pill had been approved as a result of the ‘most cursory trials of any pharmaceutical ever licensed by the Food and Drug Administration.’ Truth be told, the Searle company submitted over 10 000 cycles of exposure and 20 volumes of literature submitted to the FDA, which for the period was the largest body of information ever presented to the agency [5]. By contrast, the sexual implications of Viagra had begun as a genuine side effect that soon became the driving force in development, and the key clinical trials were done in the US without controversy by clinicians eager to undertake the research. Perhaps the only similarity on the commercial development of the two drugs was in the enthusiasm of the volunteers, whether



Fig. 2. Anthony Comstock, who lobbied the US Congress to pass a series of laws that defined contraceptives and related literature as pornography.

poor Puerto Rican women suddenly released from the burden of unintended pregnancy, or older men restored to a few hours of youthful pleasure.

By 1959, two years later, half a million American women were using the Pill. A decade after *Enovid* went on the market, a Searle spokesperson remarked, ‘If anyone had told us that the Pill was going to be discussed at bridge parties and across dinner tables, well, frankly, we would have disbelieved them.’ Nearly a half a century later, 100 million women worldwide use OCs.

Side effects and the media

Typically, the appropriate dosage for new pharmaceuticals is determined by starting off at a very low dose and slowly increasing the amount until the desired therapeutic effect is achieved. However, because the risk for ineffective birth control dosages would have led to an unacceptable pregnancy rate (during a time when abortion was not only illegal but unthinkable), the first pills had exceptionally high doses of hormones. In time, the dosages were slowly lowered to the levels of the highly effective and safe pills that we have today, but in the interim, the high-dose Pills were associated with some severe and in a small number of cases, fatal side effects. Cases of thrombo-embolic disease among Pill users occurred shortly after the occurrence of birth defects due to the use of thalidomide among pregnant

women hit the headlines. The media, on a wave of reproductive health news, publicized every actual or perceived death related to OCs. The press coverage of the risks associated with OCs nearly led to the withdrawal of the Pill from the market altogether, when Senator Gaylord Nelson in the 1970s held a hearing of the U.S. Senate Select Committee on Small Businesses, Subcommittee on Monopoly on Pill side effects. During this same period, a book titled *The Doctor's Case Against the Pill* was written by journalist Barbara Seaman [6]. The introduction to the book, written by Dr Hugh Davis, stated, 'Never in history have so many individuals confidently consumed such a powerful medication with so little information as to potential hazards and alternatives.' The irony of his comment was that Davis was at the same time promoting the Dalkon Shield IUD he had recently invented, whose poor design led to numerous deaths and continues to cast a shadow over IUD use today.

By contrast, the media have been relatively absent in reporting any negative news regarding Viagra, including the 130 related deaths that had been recorded by the end of 1999 and the death of one head of state. At this time, the drug had been on the market for less than two years. The fatalities associated with OCs were far fewer at a similar stage of marketing, whereas the fatalistic press on these incidents was unrelenting.

The power of the media is also used for positive endorsements of health technology. Again, this is a benefit afforded Viagra and not the Pill. Despite the stigma associated with the serious problem of erectile dysfunction, Senator Robert Dole, a former US presidential candidate, has bravely confronted the jokes and endorsed the pharmaceutical in national print and broadcast advertisements (Fig. 3). By contrast, however, there is yet to exist an endorsement for the Pill by anyone of celebrity status. Imagine the effect on young people if Madonna were to put her name behind the Pill.

Theological perspectives

John Rock, the clinical member of the triumvirate of scientists who developed the Pill was a devout Roman Catholic who went to Mass every morning. His 1963 book

titled, *The Time Has Come: A Catholic Doctor's Proposal to End the Battle Over Birth Control*, argued that OCs should be considered morally acceptable because they were an extension of naturally occurring processes.

In the same year, Pope Paul created a 13-man Pontifical Commission to discuss contraception, an entity that was later expanded to include 53 men and 5 women. As the Pope perceived that the Commission was likely to provide a favorable interpretation of the Catholic position on 'artificial contraception', he decided to go to a more reliably conservative source and asked the 15 bishops to decide. Even the bishops voted 9-3 (with 3 abstentions) in favor of OCs [7]. Ultimately, the Pope rejected the Commission's findings and endorsed a minority report by a group of cardinals and priests who strongly opposed contraception. This was essentially a marketing decision, that as they had condemned so many women to hell for using contraception, the Church could not credibly reverse its decision. In 1968, Pope Paul issued the encyclical *Humanae vitae* (Of Human life), which stated:

'...Similarly excluded [as a lawful means of controlling the birth of children] is any action, which is, either before, at the moment of, or after sexual intercourse, specifically intended to prevent procreation – whether as an end or a means.'

The shattering impact of Pope Paul's declaration penetrated all levels of Catholicism: theologians were discharged, priests abandoned the Church, and attendance at weekly Mass throughout the US dropped from 71% to 50%. At the same time, American Catholic women began using contraceptives at the same rate as Protestants, and by the 1970s, family size was 2.27 among Catholics and 2.17 among non-Catholics [8].

Theologically, *Humanae vitae* owed a great deal to the writings of Saint Augustine, who proposed that Original Sin was transmitted from generation to generation. According to Augustine, the only moral justification for sex was that it could lead to procreation, and it was this thinking that Pope Paul reaffirmed in the encyclical. However, what is overlooked is that Augustine had buttressed his arguments concerning the intrinsic sinfulness of sexual intercourse with the notion that man's disobedience toward God was manifest in male spontaneous erections; they were, noted Augustine, 'not moved by the will', but 'excited by lust.' [9] Although Viagra merely reinforces this evidence of man's sin, the Vatican has been silent on Viagra, while not sparing its criticism of the Pill.

The Japanese experience

While estrogen-progesterone combinations were marketed in Japan for menstrual irregularities, in 1967 the Japanese Ministry of Health forbade their use as contraceptives. It was claimed that Japanese women were physiologically different from Western women. When several pharmaceutical companies in 1990 presented clinical data on Japanese women in another attempt to register the Pill, the Japanese government rejected the petition on the grounds that its availability would accelerate the spread of HIV. The registration was postponed yet again in 1998, when the MOH demanded additional

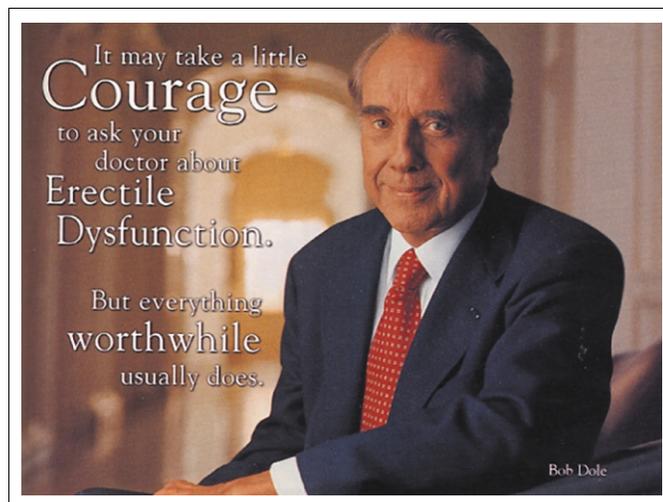


Fig. 3. Viagra in the media.

studies on the possible relationship between endocrine disrupting chemicals in the environment and the Pill. It is no coincidence that the relevant MOH department reviewing the case was composed of 198 men and only six women.

A year later, in 1999, Viagra was approved for Japanese men in the record time of six months. Concerns about Japanese physiological differences or the spread of HIV were never mentioned. Eventually, when the asymmetry between the Pill and Viagra became so blatant, OCs were approved later that year. Whilst Viagra had been approved in just six months, the Pill was approved only after more than 36 years. Studies show that the decades of negative propaganda circulated about the Pill has left 70% of Japanese women afraid to use it. Even today, only one in 150 fertile women uses OCs in Japan [10].

The battle between the sexes

The contrast between the way specialists and society as a whole have handled Viagra and OCs differs at every step of the way. It cannot be explained as an accident of history, because the asymmetry in response invades every aspect of laboratory research, pharmaceutical development, drug regulation, media response, public statements of people with name recognition, and even theology. What is going on?

Evolutionary biologists suggest that reproductive strategies are strongly influenced by the relative investment each parent makes in the offspring, and they predict that individuals of the sex that makes the least investment in reproduction will compete among themselves for access to the sex that makes the greater investment. Thus, among mammals where in many species the males supply only sperm and females carry and breastfeed their young, males tend to fight for access to females. Among that minority of species where the males not only inseminate the female but actually invest in the next generation, as do for example gibbons or beavers and human beings, behaviors have evolved that function to reduce the possibility of investing in unrelated young. Even in human beings, while such behaviors need not be conscious, they are found across virtually all cultures. Evolutionary psychology predicts that sexual infidelity by wives will be more likely to lead to divorce than a sexual infidelity by husbands, and studies bear this out. A plausible explanation of the consistently different ways in which professions, lawmakers, and even scientists have treated the Pill and Viagra is that it is an expression of a natural, hard-wired male drive to control paternity. The Pill does give women a degree of sexual freedom that could threaten an

evolved desire of men to control female sexuality, whilst Viagra merely enables men to be more sexually active.

The behaviors that evolution has implanted in us evolved to deal mainly with the long-lost world of hunter-gatherer communities in which our ancestors spent hundreds of thousands of years, compared with the few thousand years we have lived in cities or the hundreds of years since the industrial revolution. Evolutionary psychology does not tell us how to behave in the modern world, but it sometimes has the power to provide rational explanations of seemingly irrational behaviors. Biology cannot – and should not – be used to guide our morals, and most reasonable people believe the world would be a happier place if the sexual dual standard did not exist.

Explorations and achievements in the biological sciences, specifically, have enabled human beings to manage the cyclical hormone changes controlling reproduction, to understand the structure, function and interaction of the gametes, the unfolding complexity of embryonic development, and the remarkable interactions between the mother and her offspring that characterize pregnancy.

The application of our knowledge of reproductive physiology has given us OCs, the control of postpartum hemorrhage, and the promise of stem cell research, and it has rekindled erectile mechanisms that age or pathology can erode. Civilization, at its best, should help us overcome the worst of our evolutionary heritage. Appropriately used, the insights of evolutionary psychology may be able to help us in that process.

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