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Is the Pill Natural?

by MALCOLM POTTS

"The pill reflects the triumphs, the crises and the confusion of the century to which it belongs. Its mere production remains a masterpiece of industrial chemistry . . ."

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Oral contraceptives containing artificially synthesized hormones are the only truly 20th-century method of contraception. Many of today's popular contraceptive methods have existed, in one form or another, for as long as 100 years. The first literary reference to the condom dates from 1717, and pessaries with intracervical stem, forerunners of intrauterine devices, were widely promoted during the 19th century. In 1863, Queen Victoria's obstetrician, James Young Simpson, described what is now called menstrual regulation. — Tubal ligation is known to have been used in 1880, with the practice of vasectomy following about ten years later. However, oral contraceptives were only first sold to treat gynaecological disease in 1957 and were marketed as a contraceptive shortly after. Yet, despite its recent birth, the pill is older than many of the women taking it.

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Oral contraceptives cause widespread and profound changes in a woman's body, from increased earwax to an increased likelihood of heart disease; they can also cause death. They were approved by the US Food and Drug Administration (FDA) on limited evidence that would probably

not be acceptable if presented today. Pills still have not been licensed for use as a contraceptive in Japan.

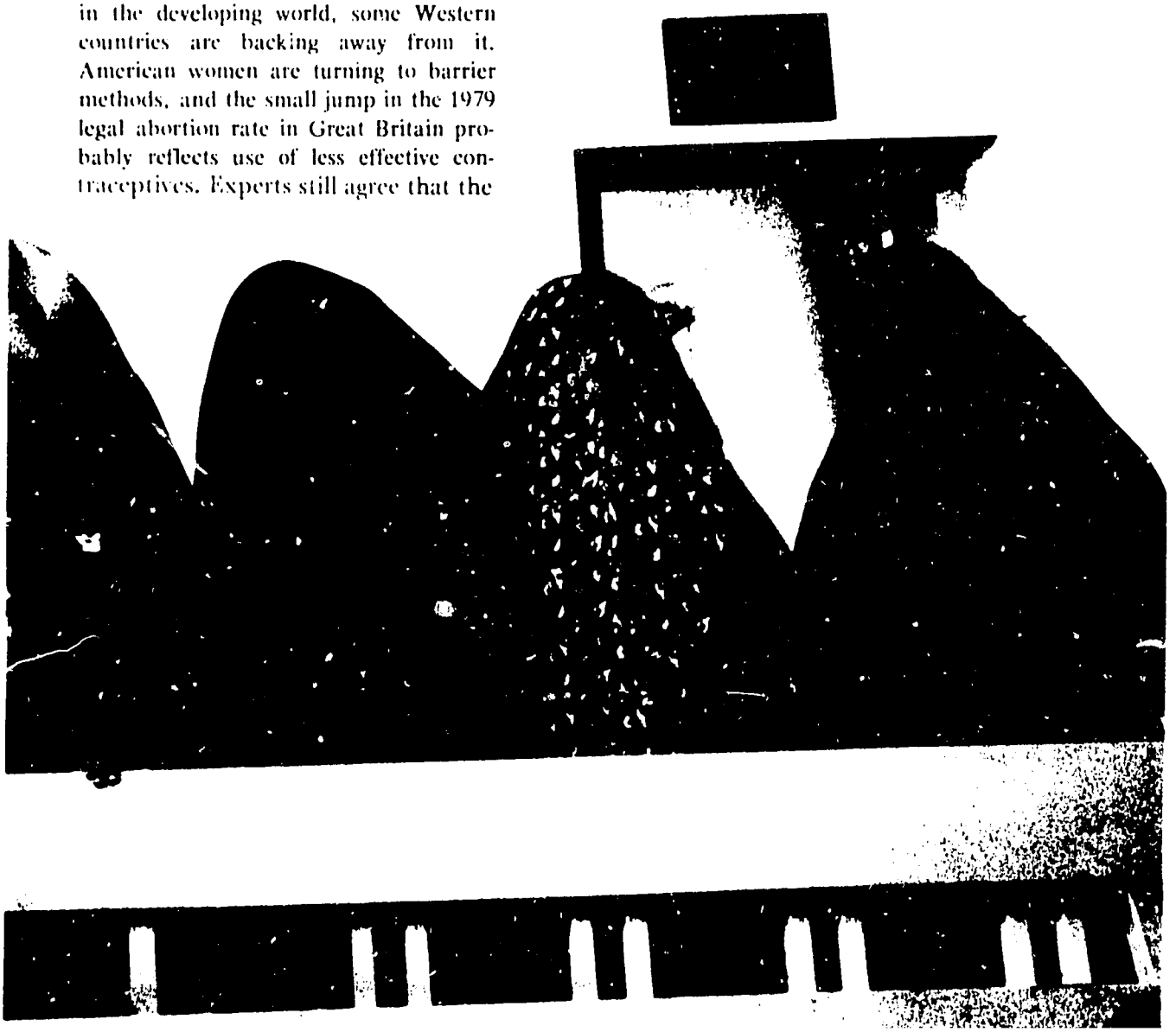
In the mid-1960s, the pill was hailed as a miracle. Dr. John Rock, the Catholic obstetrician from Boston who did the original clinical work on the pill, wrote

> . . . pills, when properly taken . . . do not mutilate any organ of the body, nor damage any natural process. They merely offer to human intellect the means to regulate ovulation harmlessly, means which hithertofore have come only from the ovary and, during pregnancy, from the placenta.[2]

But the late 1960s and early 1970s saw the accumulation of adverse facts about pill use combined with a great deal of media comment, so that by the mid-1970s at least one section of the Western public was willing to see the pill as a disaster. In 1966, Dr. Roy Hertz, then with the National Institutes of Health, Washington, DC, called the suppression of ovulation by the pill "an unequivocal abnormality."[3]

Today, while use of the pill still spreads in the developing world, some Western countries are backing away from it. American women are turning to barrier methods, and the small jump in the 1979 legal abortion rate in Great Britain probably reflects use of less effective contraceptives. Experts still agree that the benefits of pill use outweigh the risks for most women, but some imply that the method is second best—perhaps not as nasty as thalidomide or PCB, but something that is "unnatural" and best avoided.

The pill is a Western invention that has been seen through Western eyes. Although not a perfect imitation, the hormonal changes the pill induces in a woman's body are more like those of pregnancy than of regular ovulation followed by menstruation. For example, thrombotic disease is less common among pregnant women than among pill users. However, as any physician in the developing world knows, many women only menstruate infrequently, since they are either pregnant or lactating for many of their fertile years. Therefore, the suppression of ovulation is in large part natural. Modern living is associated with fewer pregnancies, briefer lactation and (probably as a result of improved nutrition) a decline in the age at menarche, giving women an even longer exposure to menstrual changes. The contemporary woman who lives in London or Los



Angeles may menstruate before she becomes a teenager, marry in her twenties and have only two children. Consequently, she is exposed to the endocrine turmoil of perhaps 350 ovulatory cycles between menarche and menopause, while the housewife in Bangladesh or Brazil may ovulate only 50 times or fewer in her fertile lifetime.[4]

This contrast is more than a piece of armchair biology. It is one measure of the change modern living has thrust upon women. Women may no longer die from having too many babies, but the new way they are using their reproductive systems does have serious penalties. Several diseases that affect the middle-aged woman are associated with delayed childbearing, such as endometriosis and other types of pelvic disease, including ovarian cancer.

Most important of all, the Western world is suffering an epidemic of breast cancer. It is a disease women rightly fear, and, despite brave campaigns for its early diagnosis, treatment remains disappointing. Cancer of the breast kills one out of every 20 Western women. It is the single most common form of cancer among women in Europe and in the USA, accounting for one quarter of all female deaths due to cancer. In the USA about 60,000 cases a year are diagnosed and 30,000 women die of the condition. Breast cancer is by no means a homogeneous disease, and to most generalizations there are numerous exceptions. But unlike, say, cancer of the cervix or lung, the cause and progress of breast cancer are usually strongly influenced by circulating ovarian hormones.

Cooperative international studies conducted by MacMahon and colleagues have shown that the age when a woman has her first child and the risk of developing breast cancer later in life are closely related. The older a woman is when she first becomes pregnant, the greater the risk of breast cancer later in life.[5] In the developing world, where childbearing still takes place at an early age, breast cancer is less of a problem, reaching only one seventh of the incidence in Taiwan that it does in Boston. Japanese women who migrate to the USA cease to enjoy the relative rarity of breast disease characteristic of the Orient; in two generations they reach the high level of risk to which American women are exposed. As the third world advances economically, breast disease will no doubt become more common.

The pill contains artificial hormones, and the influence of steroidal contraceptives on the development of cancer probably remains the most important issue concerning the use of these drugs. The problem is a complex one. Not all cancers can be expected to respond to hormones in the same way. Information about the commonly used combined pills does not necessarily apply to pregestogen-only pills, nor to the injectable contraceptives, such as Depo-Provera. It is possible, although not likely, that different combined pills could have different effects. In theory, the pill could have different effects on a developing cancer than on an already established cancer. The hormonal changes associated with pregnancy early in life reduce the risk of breast cancer later, but the same disease can progress particularly rapidly in a woman with breast cancer who falls pregnant.

Dr. Hertz may have been overemphatic in describing the pill as unequivocally abnormal, but he was right to caution in 1971: "When a carcinogenic agent is applied to a human subject, the full expression of the effect of that carcinogenic agent usually requires on the average about a decade."[6] The first epidemiologic studies of the pill provided evidence of blood clotting, because the changes the pill induces in this area occur as soon as the method is adopted. Only now are we beginning to get information about benign tumors and about cancer.

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There has been a suspicion since the early 1970s that women who use the pill have fewer diseases of the breast than those who do not. This finding has been confirmed from several localities. The oral contraceptive study by the Royal College of General Practitioners in the United Kingdom has shown that pill users are at a reduced risk of developing benign breast

disease.[7] In Britain and America, the source of most of our information, physicians usually examine women and take a medical history before prescribing pills. Some physicians are reluctant to prescribe the pill to women with a personal history of breast tumors (or sometimes even a family history), and they almost certainly would not recommend oral contraception to women in whom they had found lumps in the breasts. Therefore, when large numbers of women are followed, it is likely that this screening process will result in pill users reporting a lesser occurrence of breast disease than nonusers. However, the fact that breast disease becomes less and less common the longer a woman takes the pill and the fact that the effect may be more marked with higher doses of progestogen both suggest the relationship is a genuine, causal one and not just the effect of chance.

The data on breast cancer come from some of the same authorities who have documented the increase of cardiovascular disease among pill users. A study done by the Royal College of Physicians in Britain of over 40,000 pill users and controls is the basis of much of our information on the pill's side effects. Howard Ory of the US Department of Health, Education and Welfare's Center for Disease Control in Atlanta and Brian McMahon mailed a questionnaire to 100,000 women in the Boston area to determine how many were pill users; they then evaluated the incidence of breast disease. Those who had used the pill for two years or more had a 65% reduction in fibrocystic breast disease.[8]

The development of breast cancer later in life is known to be more common in women who have had certain types of benign breast disease. Certainly, the pill does not, as once feared, increase the probability of developing breast cancer. In 1975, Sir Richard Doll and Professor Vessey from Britain showed that when 322 women with breast cancer were compared to 502 women without breast cancer, the use of the pill was not greater among those with the disease.[9] Recently, Dr. Gambrell, using computerized data from the US Air Force Data bank, assembled evidence suggesting that women using the pill have 17 chances in 100,000 of developing breast cancer each year, while those not using it have 53 chances in 100,000. Their results also suggested that those women using the pill who did develop breast cancer suffered a less invasive form of the disease than those not using oral contraceptives.[10]

American women usually have a breast examination at the time of oral contraceptive prescription (at which time they are generally taught to examine their breasts monthly). If lumps are discovered during breast examination, the women are not normally given oral contraceptives. In the long term, this practice may prove a counterproductive precaution. For the epidemiologist, it complicates the study of the relationship between pill use and breast cancer and could be a factor influencing Gambrell's results.

Although ovarian cancer is not as common as breast cancer, it is still the fourth most common form of cancer among women in the USA. Like breast cancer, its incidence is related to women's reproductive history. The more children a woman has, the less the risk of ovarian cancer. In this case, there is strong evidence that taking the pill reduces the risk of developing ovarian cancer. In a study from the University of Southern California, researchers calculated the number of anovulatory years (due to pill use and/or pregnancy) for 150 women with ovarian cancer and 150 controls. They found that the relative risk of developing ovarian cancer fell by half if the woman had used the pill, or was pregnant and had not ovulated, for at least nine years.[11]

Other studies are being conducted, and in the next few years additional results should be forthcoming. If oral contraceptives do prove to protect against certain types of ovarian cancer, they might still have different and adverse effects on certain types of breast cancer, or on all cancers, depending on the evolutionary stage of the disease when the pills are taken. Finally, the pill might reduce the risk of breast cancer but still increase the risk of other types of hormone-influenced cancer, such as cancer of the uterus. However, if the initial trends in relation to breast cancer are confirmed, then the whole picture of pill use will alter. Fortunately, the occurrence of heart disease among women of the age who take oral contraceptives is rare, so even if the pill multiplies that risk several times, it will re-

main uncommon. Breast disease, on the other hand, is so common that a reduction in incidence due to taking the pill might outweigh the proven disadvantages of oral contraceptive use. Even the need for using the pill would change. If the need changed, so would the theology and ethics of oral contraceptive use: it is the woman who never marries and never has children who is at greatest risk of developing breast cancer.

Good news travels slowly: it is also easy to overstate. It would be misleading to claim that the pill, as we have known it for 20 years, is the optimum way to restore the hormone balance to something approaching the pattern naturally found when women bear many children and breast-feed for long intervals. The risk of cardiovascular disease is serious, and it's a disease that does kill. Benign tumors of the liver are another potentially dangerous, although exceptionally rare, adverse side effect of oral contraceptive use. Although they are not malignant, they can cause death by bleeding.

However, it is reasonable to emphasize that oral contraceptives may well belong to a category of drugs that will allow a woman to have the children she wants when she wants them and will ensure a lower probability of developing breast cancer, endometriosis, ovarian cancer or other diseases to which the contemporary woman who delays childbearing is at risk. In short, perhaps the pill is not about to disappear but is rather the preface to a drug that women will still be using in the year 2080 and beyond. It is not the pill that is "unnatural" but modern living and the way we use our bodies. The modern woman who was *not* pregnant as a teenager and who may only spend a few months of her life lactating is in a unique and "unnatural" position.

The complete equation of oral contraceptive risks and benefits is hardly within sight of completion. In 1964 the President of the British Medical Association said that women using pills were "taking part in a mass experiment," adding, "call them guinea pigs if you like." He was right. It is important to realize what authorities who regulate the use of drugs can, and more important, cannot do. In nearly all countries, governments require extensive data from animal tests and carefully controlled clinical studies before they will license a drug for general use. Some of the administrative procedures developed in the past 20 years are a direct result of experience with the pill.

However, observations on animals over several (up to ten) years of use and on a few hundred, or even several thousand, human volunteers cannot prove safety: they can only demonstrate whether it is responsible to make a particular drug or device available for public use. Rare adverse side effects are only uncovered by widespread use. In the case of the pill, studies of approximately 1 million women who had used the pill for several years were required before associated cardiovascular risks, which affect only a few of every 100,000 women, could be proven or disproven. People are not beagle dogs or rhesus monkeys; in a very real sense, every new drug licensed for use is ultimately an experiment on our species. There are no shortcuts. Any new method of contraception may look attractive to the public when first introduced, but to the cautious physician, familiarity breeds assurance. The pill has the increasing attraction that it has been widely used for a long time.

It is worth noting that nearly all the findings concerning the bad and the good side effects of oral contraception diminish the significance of its availability by prescription only. Today, we know that the Western physicians who carefully examined women before prescribing the pill in the 1960s and early 1970s did not know, and did not ask, about the two factors subsequently found to be most powerfully associated with increased risks: Does the woman smoke and is she over 40? Now that we know these questions, they can be as usefully asked by a village distributor in Thailand or a schoolteacher distributor in Brazil as by a gynaecologist in Stockholm or Buenos Aires.

The injectable contraceptive Depo-Provera has been in use for about half the time of the pill and has been used by about 1 million women. A good deal is known about it, and, so far, its record is probably better than that of oral contraceptives at a similar stage in their history. No deaths from the use of injectable contraceptives have been reported, and, as they contain only progesterone without the addition of estrogen found in the combined pill, they have fewer widespread effects on the body. Although twice recommended as a con-

traceptive by an FDA expert committee and already registered for the treatment of cancer, Depo-Provera has not yet been approved as a contraceptive in the USA. It is, however, licensed as a contraceptive in many European and developing countries. The FDA is, in effect, refusing to license the drug because the agency perceives the drug to be surrounded by too many unanswered questions; yet those questions *cannot* be answered until the drug is licensed for widespread use. This dilemma will occur with all new methods of contraception that are systematically, rather than locally, active.

Some authors have implied that the pill is a chauvinistic invention of male scientists who did not wish to tamper with the male reproductive system. In fact, there are biological reasons why development of a pill for use by men has lagged several decades behind the female counterpart. All the eggs that a woman's ovaries will release throughout her fertile life are present in her ovaries even before birth. During the monthly cycle of hormonal changes, the eggs are released, one at a time, and the hormonal changes of pregnancy and lactation are a natural way of interrupting their release. In the man, millions of new sperm are produced every day, and there are no natural pauses in production to imitate. Put metaphorically, ovulation is like removing a bottle of soda from the refrigerator once a month, and the pill is a method of keeping the door closed. In men, an oral contraceptive would throw a monkey wrench into the machinery of sperm production. No doubt, someday, the problem will be overcome and a pill for male use will be developed—but it is still a long way off.

The perspective we have on the pill is always some years out of date. It takes time to collect data on side effects, time to analyze and publish those data and time for information to percolate through to the medical profession and the media. In the 1960s, perhaps 8 million women were using the pill in the USA, a couple of million in Europe and a few hundred thousand in the developing world. Today, 15 years later, 100 million are using, or have used, oral contraceptives. Perhaps the pendulum of criticism that swung rather markedly against the pill in the West in the late 1970s will now start to drop back to a more neutral position. The pill is a uniquely effective, reversible method of contraception. However, it has complex, good and bad effects on the user and carries a small but measurable risk of death.

For most Western women, and for nearly all women in developing countries, the adverse risks are offset by reduction in the risks of death due to unwanted pregnancy. The health benefits of pill use have not been fully evaluated. However, there is a reduction in breast disease (and in some gynaecological diseases). A reduction in the incidence of breast cancer is possible and has been suggested in one study. If confirmed, it will be one of the most exciting medical discoveries of the 20th century.

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