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Doctor Hume, an Australian physician, prepared the following paper for a seminar on family planning at the Academy of Science, Canberra, Australian Capitol Territory, in November, 1983, and updated it this past summer for publication in Linacre Quarterly. *He notes that the three studies at the end of the paper, from the Centres for Disease Control Cancer and Steroid Hormone Study are of particular interest to U.S. readers. They were not available until after the paper was completed, so Doctor Hume summarized them as they are presented here.*

The DES Problem

Diethylstilbestrol, although a synthetic estrogen, is not a steroid and has a potency only 1/25 that of ethinyl estradiol, the estrogen most commonly used in the combined estrogen-progestogen Pill. Nevertheless the story of DES is very relevant in any examination of the subject of the relationship of oral contraceptives and neoplastic changes in women.

The combined Pill was launched in 1958 after very inadequate trials in Puerto Rico in the mid 1950s and was given limited approval by the Food and Drug Administration (FDA) of the U.S. in 1960. The drug company mainly responsible for its early promotion, G.D. Searle and Co., conducted a tremendous advertising promotion campaign and very soon women on the Pill in the U.S. were being numbered in millions. This put indirect pressure on the FDA which, when the extent of the thalidomide disaster was revealed by the findings of McBride in 1961, should have called for caution. However, the Pill got the green light and, on the reassurance of the Family Planning Association that it was safe, was introduced into Britain in 1962. Since then we have seen a succession of new formulations of the Pill, each proclaimed to be "safe" and indeed "safer" than its predecessor.

The dose of the ingredients has been progressively lowered till it is now only a fraction of what it was in the original Pill. Some of the ingredients have quietly disappeared altogether, as have the so-called sequential formulations, much hailed in the late '60s and early '70s. The reason, of course, is that the Pill, in practice, was shown to be not so safe. While

increasing animal experimentation was carried out to test n eroids, the real guinea pigs have always been the actual users, the wor emselves. Generally speaking, the victims have been young, healthy w , although, needless to say, the casualty rate rose sharply in the old e groups.

The DES experience was very similar. However, as it ed earlier, there has been more time to see the long term results, givi a foretaste of things to come. DES was first synthesized by Dodds a lleagues in 1938. Its most prominent use followed studies in 1948 and 9 by Smith, who suggested that DES was beneficial in both the treatme f threatened abortions and the prevention of abortions in patients wh previously had repeated pregnancy losses. Between the late 1940s and 1 an estimated two to three million women (mostly in the U.S.), were presc DES during their pregnancies, thereby exposing 1 to 1.5 million fetus each sex to the drug. Later studies showed that DES was not only uccessful in benefitting women suffering from the disorders for which i s prescribed, but was actually associated with significant increases in ab on, neonatal deaths and premature births. In addition, serious long te onsequences of in utero exposure to DES have continued to come to nt.

In 1970, Herbst and Scully reported the occurren of clear cell adenocarcinoma of the vagina in seven girls, aged 14 to years. These seven cases exceeded the total of all previously reported ch cancers in this age range. In 1971, an epidemiologic study demonst ed the link of vaginal clear cell adenocarcinoma to in utero DES exp re which had occurred 15 to 20 years earlier. The FDA banned the e of DES in pregnancy the same year. However, the legacy of in ute DES exposure has continued to grow.

Although the most serious side effect to DES-exposed da ghters has been the induction of neoplasia (with over 300 cases reported up to 1979), such daughters are also more likely to have minor vagi al and uterine abnormalities. Their fertility is affected resulting from abnormalities of anatomical development with cervical mucus effects and cervical incompetence, as well as structural abnormalities of the uterus and Fallopian tubes, leading to menstrual and reproductive dysfunction, e.g., infertility, spontaneous abortion, ectopic pregnancy, premature delivery and perinatal death.

In male progeny there has so far been no evidence of malignancy. However there have been structural developmental abnormalities of the genitalia affecting the penis, epididymal cysts and underdeveloped and undescended testes.[1]

The major risk of DES exposure may turn out to be not of the development of clear cell adenocarcinoma, but of vaginal and cervical squamous metaplasia. The prevalence of dysplasia in such cases is reportedly 2.1%, whereas there is an estimated five-fold increase in the incidence of carcinoma-in-situ, with the possibility of a vast increase in squamous malignancy.

A case of a 23-year-old single woman, who was exposed to DES as a fetus and affected by cervico-vaginal adenosis and as a result presented with

carcinoma-in-situ, was reported by Shepherd, Dewhurst and Pryse-Davies in the *British Medical Journal*.[2] Of particular interest was the fact that she was taking the Pill, resulting, in her case, in double exposure to estrogens, albeit 24 years apart.

At this time, there is no substantial evidence that DES taken during the pregnancy has had an adverse effect on the health of the mother. However, the well known epidemiologist, Dr. Valerie Beral and Linda Colwell, reported a link between the taking of DES during pregnancy and the appearance 18 to 22 years later of breast cancer.[3] It is recommended that women who have taken DES in pregnancy be subjected to regular breast checks and Pap smears associated with colposcopy.

There have now been seven patients with vaginal clear cell cancer discovered in Australia; six of these patients had a history of maternal ingestion of DES. In 1972, the *Medical Journal of Australia* published a statement from the Australian Drug Evaluation Committee outlining the danger of maternal DES therapy and also the risk of the DES content of the "morning after" Pill. DES Referral Centres have been set up in Australia – at Prince Henry's Hospital in Victoria and King George V Hospital for Mothers and Babies in Sydney.

A recent study by Greenberg et al, supported by a grant from the US National Cancer Institute, compared the incidence of breast cancer in 3,033 women who had taken DES in pregnancy during the period from 1940 to 1960, with the incidence in a comparable group of unexposed parous women.[4] They found a crude relative risk of 1.4 in the exposed group, which had a slightly higher breast cancer mortality (relative risk 1.1) than in the unexposed. The authors concluded that the incidence of breast cancer was moderately but statistically significantly increased in women given DES, but were unable to exclude the possibility that some unrecognized concomitant of DES exposure accounted for this increase.

The findings of this study showed that DES-exposed women clearly appeared to be at an increased risk of breast cancer which, while less than that associated with a positive family history of the disease, seemed to become more pronounced with time and may prove to be of greater concern in the future. The frequency of breast cancer among the controls in this study dropped after the age of 60 years, when the difference between exposed and unexposed women was most pronounced.

The long-term effects of DES exposure on mothers, daughters and sons are not known and there is a continuing need for well-documented and long-running studies to identify new problems and increased health risks associated with exposure to DES, as well as to allay anxiety among DES-exposed persons and their families.

In one recent study, Depue et al noted that testicular cancer was more frequent among males with intra-uterine hormone exposure (9 of 106 patients with testicular cancer vs. 2 of 107 controls had been exposed to hormones). However, in this series, five of the nine exposed mothers had received oral hormone pregnancy tests and only two had taken DES.[5]

Endometrial Cancer — The Oracon Story

The incidence of cancer of the endometrium in women bel the age of 50 years is quite low at 14 cases per 100,000 women. It is icularly rare in this age group where there are normal regular menst cycles.

Those at special risk are the obese and the infertile and e cially in polycystic ovarian syndrome and in women having estroge roducing tumors and failure of ovulation and dysfunctional bleeding. of these conditions produce a situation where the endometrium is posed to prolonged stimulation by estrogen unopposed by progestero

Women who ultimately develop endometrial adenocar ma have frequently shown signs of hypothalamic-pituitary-ovarian dysfu on in their reproductive years, manifested as oligomenorrhea, hyper- or h menorrhea and polymenorrhea. These dysfunctional bleeding patterns oc frequently because of failure to ovulate, causing problems of infertility he triad of hypertension, obesity and diabetes is a common finding ir ients with endometrial cancer.[7]

Estrogen, whether endogenous or exogenous may, ove ong period of time, produce endometrial hyperplasia if not interrupte opposed by progesterone. This entity has been shown to advance t lenomatous hyperplasia, carcinoma-in-situ or eventually, endometri ncer. Post-menopausal estrogen use has also been associated with th currence of endometrial carcinoma. The overall risk has been shown t six-fold for estrogen users as opposed to non-users. Long-term use o er five years carries a 15-fold risk.

In 1963, sequential oral contraceptives were first mar d in the U.S. Their use was promoted, in part, by an effort to simulate re clearly the natural sequence of estrogen, followed by estrogen-proge one, as found during the normal menstrual cycle. The scheme involved king 80 to 100 mcg. of estrogen alone for 14 to 16 days, followed an estrogen-progestogen combination for five to six days, the progestoge content varying from as little as 3mg to 25mg.[8]

Silverberg, Makowski and Lyon, in 1975, first repor the occurrence of endometrial carcinoma in young women takin sequential oral contraceptives. These reports were quickly followed by others. By June, 1976, 30 cases of verified invasive carcinoma of the endometrium had been identified, occurring in women under the age of 40 who had a documented history of oral contraceptive use. Twenty had used sequential type preparations, nine had used combined formulations, and one patient used an unknown type. Nineteen of the 20 using sequentials had used one preparation containing 100 mcg of ethinylestradiol as the estrogen and 25 mg of dimethisterone, a weak progestogen, and marketed under the trade name of Oracon. Before further studies could be carried out, the sequential oral contraceptives were voluntarily withdrawn from the market by the manufacturers.[9]

Progesterone competes with estrogen for binding sites in the endometrial cells and may reduce the estrogen-stimulating effect. The exposure of the normal estrogen-primed endometrium to progesterone converts this tissue to the typical secretory type seen during the luteal phase of the menstrual cycle. This cyclic effect of progesterone prevents the normal proliferative endometrium from progression to hyperplasia. The addition of a potent progestogen to the estrogen produces a decidual pattern of endometrial response with a tendency to atrophy rather than progress to hyperplasia. This property of progestogens is used therapeutically in the treatment of endometrial cancer, which, incidentally, has a good prognosis with a cure rate of 90%. Depo-Provera, (Medroxyprogesterone acetate), in large and repeated doses, appears to be the drug of choice.

However, predictions that the simultaneous administration of estrogen and progestogen might reduce endometrial cancer risk should be regarded with caution. While they do reduce the incidence of endometrial hyperplasia, there is no direct evidence that this applies to endometrial cancer as well.[10]

All estrogens seem to increase endometrial cancer risk, irrespective of their formulation or mode of administration. Initially it was thought that conjugated or "natural" estrogens, particularly estrone, were primarily responsible for the association, but recent work has implicated synthetic compounds such as DES as well. Similarly it was thought earlier that estrogens were more hazardous when given continuously rather than cyclically, but this, too, is unsupported by newer investigations.[11]

The addition of a powerful progestogen may protect women in older age groups who take estrogen for prevention of osteoporosis or prolongation of the "youthful look", but it introduces all the hazards of thrombo-embolism, hypertension and myocardial infarction which characterize the taking of the Pill by women in older age groups. The mortality rate accompanying Pill use in this group is 22 per 100,000 women and this exceeds that of endometrial cancer by far.[12]

The Pill and Breast Cancer

In 1950, a trial was set up in England to evaluate the effects of large doses of stilbestrol (DES) and ethisterone, a progestogen, on rates of fetal loss in pregnant diabetic women. Eight women were allocated at random to receive the hormonal treatment and 76 to receive inactive tablets. The aim was to establish the efficacy of this treatment in reducing fetal loss, the rates of which were exceptionally high in diabetic women. Identical rates of spontaneous abortion (8%) and perinatal mortality (23%) were noted in both the hormone and non-hormone treated groups. Similar results were obtained for non-diabetic women in a randomized trial of stilbestrol conducted in Chicago. That both studies failed to show a beneficial effect of hormonal treatment during pregnancy did much to curb the administration of sex hormones to pregnant women, although the practice continued during the 1960s.

In 1978, Bibbo and colleagues reported the results of the 25-y follow-up of the mothers who had participated in the Chicago-based al. They found an excess of breast cancer in the group treated with stilbest although the difference was not statistically significant.[13]

In 1980, Valerie Beral and Linda Colwell, who was involved i original English trial, reported on the long term follow up of mothers w ook part. Information about all but four of the women was obtained (97%) ie overall mortality was 4.5 times that of comparable women in Englan d Wales, most deaths being from complications of diabetes. More tu s, mostly benign, were reported in the hormone-exposed than the non-e sed group (14-18% and 2-3% respectively). Four cases of malignant b st disease were reported in the hormone-exposed women and none in the -exposed.

Beral and Colwell concluded that these findings supported r evidence linking estrogen treatment and breast cancer and suggested the latent period before the tumor becomes clinically apparent may b 5 years or longer.

In a commentary on the findings of Beral and Colwe Vance and Millington drew attention to the fact that most studies on oral traceptives found no increase in breast cancer in Pill users and perhaps, e a decrease. However, they pointed out that a delayed appearance of brea ancer, such as that noted by Beral and Colwell, might have been missed b use younger women predominated in these investigations. They were pro ed to review these studies and prepared a table summarizing data from f case-control studies of breast cancer according to "young" and "old" s groups. Age categories differ among studies and for two studies, they esumed that premenopausal patients were younger than postmenopaus [14]

The data in their table indicate an increased risk of brea ancer among women with a positive history of oral contraceptive use, bu nly after they have passed into their fifth or sixth decade. Most Pill us have not yet reached the critical age.

Relative Risk of Breast Cancer in Women with a History of Contraceptive Use Compared with Controls in Published Studies.

	Definition (y)		No. of cases		Relative risk		
Reference	Young	Old	Young	Old	Young	Old	OC use
1	15-39	40-49	104	348	0.72	1.31	Ever
2	pre	post	126	160	0.80	1.66	Ever
3	16-40	46-50	301	115	0.8	2.4	Ever
4	pre	post	768	1090	1.09	1.24	Ever
5	31-45	46-55	31	24	1.2	3.2	Past
5	31-45	46-55	23	26	0.8	8.0	Present

Breast cancer is more common among women who have never borne children than among parous women and the longer a woman delays her first pregnancy, the more she increases her risk of developing the disease. Recently, it has been suggested that prolonged use of oral contraceptives before the first full-term pregnancy may increase the risk of breast cancer, although after this pregnancy the risk is probably unaffected by taking the Pill.

Clearly, the first full-term pregnancy does something to alter a woman's risk of developing breast cancer. Whether or not she breastfeeds is probably irrelevant, but there is good evidence that the breast epithelium is permanently changed by pregnancy. Although histological change occurs in the ductules, the physiological change in the epithelium, shown by its altered response to hormones, is more striking. Possibly the high progesterone concentrations of late pregnancy induce progesterone receptors which can then respond to the lower concentrations of a normal menstrual cycle. If these receptors are inadequate before the first full term pregnancy, then during normal cycles, the breast will therefore be exposed to "unopposed" estrogen, despite the presence of normal concentrations of progesterone in the circulation.[15]

The effects of the Pill may be different among nulliparous and parous women as is now being suggested by epidemiological surveys. Although the combined Pill provides estrogen balanced by progesterone, if the breast of the nulliparous woman cannot respond to the progesterone component, then a young girl taking the Pill is exposing her breast epithelium to "unopposed" estrogen, although in a low, but steady, concentration.

Early menarche, nulliparity and late menopause are also important risk factors in the development of cancer of the breast. The sooner the cycles begin, the sooner the "unopposed" estrogen begins to act on the breast epithelium. In the premenopause, there is an increased frequency of anovular cycles, again exposing the breast to "unopposed" estrogen. A further, but as yet unconfirmed, risk factor, is that identified by Pike and colleagues, namely an early miscarriage before the first full-term pregnancy. Although concentrations of both estrogen and progesterone increase in early pregnancy, in the nulliparous woman only the estrogen will affect the breast. Women having first trimester-induced abortions before their first full term pregnancy were shown to be similarly at risk, with a 2.4-fold increase.[16]

In the R.C.G.P. study of the Pill, initiated in 1968, the findings in regard to breast cancer were reported in 1981.[17] One hundred thirty-three cases of breast cancer were recorded. There were 19 deaths among ever-users of the Pill and 10 in the controls. Analysis showed a significant increase in the incidence of breast cancer among women aged 30 to 34 at diagnosis if they had ever used the Pill. By 1979, less than 5% of the original 23 – 611 women — were current, if intermittent users. No figures are given for how many of the 18,755 women, enrolled when they were already using or had used the Pill, had developed breast disease during their previous use of the Pill, thought to amount to 25,570 women years (R.C.G.P. 1974). This previous use was excluded from the final analysis because it had not been observed in use.

In 1981, Pike et al collected records of 293 women with br st cancer under the age of 33 between 1972 and 1978; 48 had died an f the 163 interviewed, 83% had used the Pill. Those who had taken it fore their first full-term pregnancy had an increased risk which rose with duration of Pill use.[18] In 1977, Passenbarger et al found that 15 out 5 women under the age of 30 with breast cancer had used the Pill.[19]

Pike also found a significant increase in breast cancer in men with a history of benign breast disease. Hoover et al, in 1976, found t estrogen use was related to an especially high risk of breast cancer if the ign disease developed after the women had started the drug.[20] The fi g of large epidemiological trials that the Pill reduced benign breast dise has always seemed anomalous to some clinicians whose observations s ed just the opposite.[21]

The study of Pike et al gave rise to extensive correspondenc the *British Medical Journal*, especially challenging their concept of the lassification of oral contraceptives according to "progestogen potency" at of Swyer is typical. However Swyer said: "My competence in epi iology does not allow me to criticize the general contention by Pike et a at long-term use of oral contraceptives by young women may increase t isk of breast cancer. . ."[22]

Meanwhile, the FDA, having reconsidered its posi about oral contraceptives and cancer, made a firm statement that ther no increased risk of breast cancer in oral contraceptive users of an tegory or in association with any particular formulation of oral cont ptives.

However the FDA felt somewhat uneasy about Pr sor Vessey's findings. It was planning to revise the labeling of oral traceptives to include a warning that their use may be associated with increased risk of cervical cancer.[23]

More recently, a group of Swedish researchers has ad d its support to the findings of Professor Pike and his Los Angeles grou n a preliminary report of a study about to be published. A case control st dy was done on 80 consecutive cases of breast cancer in women born in 939 or later and diagnosed at the age of 45 or earlier, who were intervie ed personally by their physician. These were matched with 225 control

When the data were analyzed by conditional logarithmic regression, women who had started to use the Pill at 20-24 years of age had three times the risk of developing breast cancer prior to 46 years of age compared with non-users.

The relative risk increased with earlier age of starting the Pill. Women beginning to use the Pill after their first pregnancy had a lower relative risk than others, although the difference was not significant. In this investigation, both a low age at menarche and a high age at first full-term pregnancy were related to increased breast cancer risk.

The authors conclude: "Our results, taken together with earlier reports linking early O.C. use with breast cancer, are a matter of great concern in respect of O.C. use by young women".[24]

The Pill and Liver Tumors

The association between taking the Pill and the development of non-malignant liver tumor hepatoma was first suggested in 1972 by Horvath.[25] The following year, Baum et al described seven women, all oral contraceptive users, who developed benign hepatic adenomas.[26] Subsequently a number of reports have appeared supporting these findings, although the histopathologic diagnosis has been variously reported as focal nodular hyperplasia, adenoma, hamartoma, benign hepatoma, solitary hyperplastic nodule and focal cirrhosis. Prior to 1970, benign liver tumors in young women were very rare.

The risk of developing these liver conditions increases dramatically with duration of use of the Pill, particularly after 5 years. The majority of affected women had been taking mestranol-containing compounds, mestranol being a synthetic estrogen metabolized in the body to ethinylestradiol. Nevertheless significant numbers of these lesions have been reported in patients taking ethinylestradiol-containing compounds. A few patients have taken DES, conjugated equine (natural) estrogens and progestogen-only compounds.

Benign hepatoma is a very vascular tumor and subject to spontaneous rupture, death often resulting from massive hemorrhage. A carefully conducted national survey, carried out by the American College of Surgeons' Commission on Cancer, showed the frequency of benign lesions indicated a large peak in the 26 to 30-year age group. This peak corresponds to the increased use of oral contraceptives in this age group. The increase is true only for Pill users and benign lesions. Vana et al in another study showed that 40% of tumors were diagnosed in women exposed for five years or less. Hemorrhage was most frequently associated with adenomas and almost exclusively confined to the oral contraceptive users. A significant number of patients present with signs of intraperitoneal hemorrhage and shock, the lesions seeming most prone to rupture at or about the time of menstruation.

A number of the reported deaths have occurred secondary to attempts at resection. For those lesions which are asymptomatic, the best and safest course would appear to be to discontinue the Pill, urge the patient to avoid pregnancy and await spontaneous resolution of the lesion. Pregnancy, with the resultant high levels of sex steroids, may have a particularly stimulating effect and increase the propensity for these lesions to hemmorhage.[27]

Individual case reports have appeared in the literature, particularly in *Lancet*, linking oral contraceptive use, some compounds containing mestranol and others ethinylestradiol, with malignant liver tumors in young women. For instance, two cases of cholangiocarcinoma in women on the Pill, aged 21 and 29 years respectively, were reported. This malignant tumor has its peak incidence in the sixth decade, being very rare in the third.[28,29]

An added risk factor in the development of primary hepatocellular carcinoma is infection with hepatitis B virus which is endemic in Asia and Africa. Nevertheless this liver malignancy is rare among women of childbearing age (15-40) in Singapore. However Chong-Jin Oon et al from

the Hepatoma and Liver Study Group of Singapore General Hospit reported primary hepatocellular carcinoma in a 29-year-old woman who ad been on two different formulations of the Pill (both containing ethiny stradiol) for seven years. They considered the administration of the Pill ay well have resulted in the earlier development of primary hepatocellular rcinoma in this case.[30]

The Pill and Malignant Melanoma in Australia

Valerie Beral and her associates have reported on a case co rol study of 287 women aged 15-24 years with malignant melanoma and 5 matched controls conducted in Australia.

Their findings indicated that, after a lag of 10 years, oral co raceptive use for a total of five years or longer was associated with a 50 increase in risk. This relationship persisted after adjusting for a number potential confounding factors, including complexion, sunbathing activities ccupation and education.

Beral et al note that relative risk estimates reported by thei study and several others which considered long term use of the Pill, were the range of 1.4 to 4.4. While these relative risks were not large, they ere of the same order of magnitude as the relative risks for blond hair colo RR = 1.6) or fair skin (RR=2.1), noted by them for Australian women Both these factors are widely accepted as being important determinants o melanoma.

In conclusion the authors state: "If, as our data and that of oth rs suggest, a lag period of 10 years or more is involved, it may still be sev al decades before the effects of oral contraceptives on malignant melan ma can be properly evaluated."[31]

The Pill and Cancer of the Cervix

One of the most fascinating stories of modern medicine is the gradual unfolding of the epidemiology of cancer of the cervix. While ultimately linked with the intricacies of behavior (perhaps misbehavior would be the better word) of human beings in regard to sexual activity and the not-unexpected influence of sexually transmitted diseases, the Pill has managed to find its way into the labyrinth, together with the ubiquitous ciagrette. While the epidemiological jig-saw is not yet complete, enough pieces have been fitted into the picture to provide a good idea of the general landscape.

It is an ill wind that blows no one any good. We have to thank the advent of the Pill for the tremendous stimulus it has provided to epidemiological research and the crop of outstanding researchers who have risen to the occasion in elucidating its many ill effects and its occasional health benefits. The accompanying rise in sexually transmitted diseases has provided another rich field for research with many interesting discoveries. All of which, it pays one to reflect, has been an expensive ongoing exercise. Chastity may, in the eyes of modern liberated humanity, be a very dull virtue, but its cost-effectiveness is undoubted. It also sets the standard in public health and preventive medicine. Its cost to the taxpayer is nil, in sharp distinction to the legacy of sexual liberation. While it may be cynically pointed out that it is simply a case of a virtue bringing its own reward, it should be considered worthy of a civic award — perhaps even a Nobel prize.

The suggested solutions take no account of the possibility that the promotion of chastity may provide the answer. No, man's ingenuity will find a way by producing some marvelous new polyvalent vaccine, dealing a death blow to gonorrhea and syphilis, as though they were as controllable as diphtheria and tetanus. Among the ranks of man's brilliant modern researchers is waiting another Salk or Sabin who can produce a vaccine to eliminate the villainous Herpes virus II and its partner in crime, the genital wart virus. Chastity, like modesty, is a term soon to be dropped from the dictionary as obsolete, belonging to the Victorian era of sexual suppression and frustration. Sexual liberation is here to stay, a much-venerated sacred cow. It is unthinkable that it be open to challenge. Yet all the findings point to sexual promiscuity as the culprit in the epidemic of pelvic inflammatory disease, of herpes genitalis, of cervical neoplasia and even of acquired immune deficiency syndrome — AIDS.

Up till about 30 years ago, mortality figures for endometrial and cervical cancers were combined for statistical purposes. Only since that time has it been possible to study cervical neoplasia in any detail. There are two principal hypotheses considered in the etiology of cancer of the cervix:

(1) the association of cervical cancer with factors related to an early age at first intercourse and first pregnancy. It proposes that during adolescence, the cervical epithelial cells are especially vulnerable to carcinogens (the Coppleson theory).

(2) the association of cervical cancer with factors related to the multiplicity of sexual partners, not only of the woman herself but also of her husband, proposing that malignant change is induced by a sexually transmitted infection. Herpes virus type II, the cause of genital herpes, has been long regarded as the specific agent.[32] However, more recently, human papilloma virus, responsible for genital warts, has been joined with the herpes virus as a cofactor.[33]

Cancer of the uterine cervix is almost unknown in nuns. The list of epidemiological factors associated with cancer of the cervix have been known for a number of years. They constitute a formidable list indeed: broken marriage, multiple marriages, extramarital sexual activity, premarital sexual activity, early age of first marriage, early age of first intercourse, multiple induced abortions, illegitimacy, multiple sexual partners of the woman, multiple sexual partners of her husband, history of prostitution, history of sexually transmitted disease, low socio-economic status, and urban residence.

On the other hand, common denominators of the low risk groups are: restrictive codes of sexual conduct (chastity), and religious endogamy, e.g., those who marry within their religious faith, particularly of the Jewish faith.

A study of 750 Taiwan prostitutes by Sebastian et al provided strong

support for Coppleson's theory.[34] Their women subjects did n tart their trade until they were aged 18. They showed a low yield of cervi dysplasia of 10.7 per 1,000, indicating that it is sexual activity during th iolescent phase of active metaplasia which predisposes to cervical d lasia and neoplasia. Many authors feel that there is a continuum betwe dysplasia and neoplasia, including invasive cancer of the cervix.

A new hypothesis of the etiology of cancer of the cervix has b proposed by Skegg et al, underlining the importance of the male factor.[3] ie authors point out that concentration on female sexual behavior fails to e in several epidemiological features of cervical cancer, e.g.:

1. the extremely high incidence in parts of Latin America re female chastity before marriage and fidelity within marriage are hig valued in some of these societies;
2. the large decline in mortality in many western countrie er the past half century or more which started long before screening pr ams began in 1965;
3. the low risk in Jewish women;
4. the association with cigarette smoking, which appears to l ndependent of sexual risk factors, and
5. the possible association with oral contraceptives.

If cancer of the cervix is caused by an infectious age transmitted venereally the sexual background of each male partner m be of great importance. In one study of cervical dysplasia and carci a-in-situ in women who claimed to have had only one partner, the relati sk increased with the number of sexual partners their husbands reported. he husbands of affected women were also more likely to have had vene l disease, to have visited prostitutes and to have had affairs during m age.

In some Latin American societies, women are expected t ave only one partner, whereas their husbands may have many. Such ehavior was characteristic of European societies in the Victorian era d favors the flourishing of prostitution. Cali in Colombia and Recife in B zil both have incidence rates of cervical cancer four to six times high than United Kingdom registries. It has been suggested that this could be due to deficiency of Vitamin A in South American countries. However prostitution has been a prominent feature of life in these countries and visits to brothels by men may account, at least in part, for the high risk of cervical cancer in their wives.

The decline in mortality in cervical cancer, which has characterized the present century, was interrupted by increased rates in women born between 1911 and 1926, who spent part of their early adult lives during the 1939-45 war, when the incidence of gonorrhea was high. This suggested "the presence of an infective agent which was increased by the changes in customary sexual partnerships brought about by war and its aftermath."[36]

The general decline in mortality may involve changing patterns of sexual behavior in men from Victorian and Edwardian patterns which resembled those of contemporary Latin America where there is a "double standard"

of sexual morality with much resort by men to prostitutes.

In contemporary western society, the so-called permissive society, marked by increasing premarital sexual activity, particularly in women — both men and women tend to have several sexual partners. Cervical cancer mortality rates in young women have begun to rise again, at least in Britain and New Zealand.

Another important etiological factor is related to the husband's occupation. There is a high mortality in the wives of men in specific occupations which involve travel and absence from home. There is also evidence which suggests that, if cervical cancer develops in a man's first wife, his subsequent wife may be at an increased risk. This might reflect transmission of a virus from the male, the identity of which virus is as yet unknown.

Malignant disease is the most common cause of death in women aged 25 to 50. While the immediate effect of the Pill on vascular disease was accepted fairly quickly, the increased risks of malignant disease and mental illness have taken longer to be acknowledged and quantified by large scale trials.[37] In the Oxford/F.P.A. contraceptive study of 17,032 women aged between 25 and 39, there were twice as many deaths from neoplasms (25.3) as compared with circulatory disorders (12.3).[38,39]

A 1978 report of this same study was entitled "Neoplasia and dysplasia of the cervix uteri and contraception: a possible protective effect of the diaphragm". Sixty-five of the women developed cervical neoplasia, the incidence rate in diaphragm users being 0.17 per 1,000 women years of observation as against the much higher rates of 0.95 in Pill users and 0.87 in those fitted with an I.U.D. All six women who developed invasive cancer had been using the Pill at the time of entry to the study. For the first time, cigarette smoking was reported as a major risk factor in cervical neoplasia in this study. Also, as compared to Pill and IUD users, diaphragm users were less likely to have had coitus at an early age and had had materially fewer sexual partners.[40]

In 1980, Harris et al showed that the risk of cervical dysplasia or carcinoma-in-situ increased with duration of Pill use, while the risk decreased with prolonged use of barrier methods. They also found that the number of partners exerted effects independently of age at first intercourse. Cigarette smoking once again showed up as a significant risk factor.[41]

Meissels et al, in a study of French Canadians in Quebec, found in 2,017 women with mild and moderate dysplasia highly significant correlations between early age at first coitus and oral contraceptive use. When corrected for age at first coitus, there was a significant excess of dysplasias in Pill users. Dysplasia of the uterine cervix behaves epidemiologically like carcinoma-in-situ and invasive squamous carcinoma, they stated — in other words, essentially as a venereal disease. It remained to be seen whether all dysplasias form one continuum or whether there are two morphologically similar but biologically distinct forms of dysplasia — one more frequent, regressing spontaneously; the other relatively rare, progressing to carcinoma-in-situ and invasive carcinoma of the cervix.[42]

Stern et al, in a study of 300 women with cervical dysplasia ›mpared to 300 with negative smears, found that those using the Pill had increase in both severity of dysplasia and in the incidence of conversion to cinoma-in-situ. The probability of progression from dysplasia to cancer 'ill users was 0.3 after seven years, compared with 0.05 in non-users.

In the American Walnut Creek study of 16,638 women, 61 nad used the Pill while 50% of those aged 50 to 54 had taken estrogen he major cause of the 170 deaths were malignant neoplasms (45%), comp d to only 15% of deaths due to vascular causes. Cancer of the cervix was nificantly increased for those under 40 years of age. Malignant mela nas were significantly increased as was lung cancer in Pill users who ›ked. All six cases of urinary tract neoplasms and six of the seven thy l cancers occurred in users.

Registration rates for carcinoma-in-situ have increased from 86 to 15.2 per 100,000 between 1965, when registration began, and 197 he largest increase in new cases is in the 15- to 24-year-olds (ten times) 2 34 group (five times) and in the 35- to 44-year-olds (twice). These ures show considerable increases in the incidence of both breast and ce cal cancer since the early 1960s when the Pill was introduced estrogen "replacement" therapy became fashionable. The largest inc se is in the 15- to 24-year-olds who, although they still have a low incide of cancer, have only recently become the main age group to start using Pill. This age group has a risk of double exposure to exogenous ho nes. Their mothers may have taken them during pregnancy or lactation (., the mini-Pill or Depo-Provera).[44]

A very recent study by Holst and Abyholm[45] looked at a oup of 318 women with tubal infertility in Norway. Women with tubal fertility due to pelvic inflammatory disease tend to have many of the risk ctors which characterize women who develop cervical neoplasia. Thirt one of these women (9.7%) had dysplasia of varying degree or carc oma-in-situ. Fourteen (4.4%) had severe dysplasia or carcinoma-in-situ. This was 44 times the national average for women in the age group (20-39). Among 200 unselected infertile controls, one patient had moderate and one severe dysplasia. Both of these were found to have tubal infertility. The authors conclude, therefore, that women with tubal infertility represent a comparatively high risk group for the development of precancerous lesions of the cervix.

In the U.S.A. the use of the Pill fell by 25% between 1974 and 1977 but increased by 25% in the U.K.[46] The Pill is the contraceptive method of choice for young unmarried girls who are now at much greater risk of becoming promiscuous than they were 20 years ago and having unplanned pregnancies, abortions, sexually transmitted disease and abnormal babies.

The prestigious medical journal, *Lancet*, is noted for the number of papers it has published which have aroused a furor in the media because of consistently dramatic discoveries concerning the Pill's ill effects. The *Lancet* on Oct. 22, 1983, published not one, but two such papers, one by Prof.

M.C. Pike and his group in Los Angeles[47] on breast cancer and the Pill and the other by Prof. Martin Vessey and his colleagues on the possible adverse effect of the Pill in cervical neoplasia.[48] The reaction of the media and of medical leaders in the field of family planning to this "bombshell" was characteristic — one of startled dismay and, in the case of many of the doctors, disbelief. In fact both studies confirmed evidence which had been mounting for some time.

As these papers were published when mine was well advanced I shall deal with them both at this point as what one might call a Stop Press item.

The Breast Cancer Study

Pike and his colleagues carried out a case-control study of 314 breast cancer patients aged less than 37 years at diagnosis and 314 individually matched controls to assess the influence of the Pill on the risk of the disease. They found that long term use of the Pill, before age 25, of the combination type containing a "high" content of the progestogen component, was associated with an increased risk of breast cancer. The relative risk was approximately four after five years of such use, and nine cases and no controls had used Pills of this type for more than six years before age 25.

Previous studies of this type had few data on long term Pill use before the first full-term pregnancy.

Pike et al postulate that, as the combination Pill suppresses ovulation, there is a lack of rupture of the surface of the epithelium of the ovary and, hence, a decrease of mitotic activity in this area where ovarian cancer arises. A similar lack of activity characterizes the effect of the Pill on the endometrium, the peak of mitotic activity taking place in the follicular phase of the normal cycle.

In the breast, the reverse occurs, mitotic activity reaching a peak in the luteal phase due to the effect of progesterone acting in combination with estrogen. Combination oral contraceptives, with their mixture of estrogen and progestogen, may therefore stimulate breast tissue mitotic activity. The higher the estrogen and progestogen content of the Pill, the greater the mitotic activity and hence the increase of risk of breast cancer. If Pill use begins at an early age, when long and frequently anovular cycles are still common, then the longer the time and the more intense the stimulation before the first pregnancy.

The authors point out that the use of the Pill during similar cycles experienced during the pre-menopausal period is also associated with increased risk of breast cancer.

As an interesting sequel to Professor Pike's study, a letter signed by both Professors Vessey and Pike as well as two other researchers and published in the following issue of *Lancet*, announced that they were joining forces to conduct a large case control study of breast cancer and the Pill in young women in the U.K.

The Neoplasia of the Cervix Study

The Oxford-based group carried out a 10-year followup of 8 parous women who entered the Oxford-FPA contraceptive study w using the Pill and 3,154 parous women who entered the study while u an IUD, to determine the incidence of biopsy-proven cervical neoplasi 13 cases of invasive cancer, which were of squamous type, occurred vomen in the oral contraceptive group. Both carcinoma-in-situ and cer dysplasia also occurred more frequently in this group than in those usi UDs. The incidence for all three forms of neoplasia combined, rose fro per 1,000 woman-years in those with up to two years Pill-use to 2.2 per 0 woman-years in those with more than eight years Pill use. There wa such trend among IUD users, where the rate remained constant, around per 1,000 woman-years. The great majority of cases of invasive cance e detected by means of cervical smears. The aggregated data for all for of cervical neoplasia provided considerable evidence for an associa with oral contraceptive use — a disturbing finding.

Vessey and colleagues had already pointed out from result the Oxford FPA study published in 1978 that the use of the diaphrag might offer protection against cervical neoplasia and that all six wom n the study in whom invasive cancer of the cervix had developed at that e, had been using the Pill.[49] Hence, women using a diaphragm are un sfactory as a comparison group in view of the relatively low incide of cervical neoplasia among them.

Unfortunately data about age at first intercourse and nu rs of sexual partners were not collected for the women under study. W n with long durations of Pill use were slightly more likely to be hea mokers and to have married and had their first full term pregnancy at a rly age than women with short durations of use. Similar small differe s were also apparent in the IUD group.

Cervical neoplasia was not found to be associated with a sp cific estrogen or progestogen or with any particular dose of estrogen or br nd of the Pill.

A large number of epidemiological studies conce ned with oral contraception and the risk of cervical neoplasia have been published, some showing negative results while others showed a positive asso iation between risk and duration of use. The negative studies included very few long-term users of the Pill. In the Oxford group study, no association would have been apparent if the data had been restricted to women of up to 48 — or even 72 — months of exposure.

The possibility that prolonged oral contraceptive use is making a contribution to the steadily rising death rates from cancer of the cervix and the incidence of invasive cervical cancer and carcinoma-in-situ in England in women under 34 in the last decade, should be borne in mind. These trends have generally been considered to be attributable to changes in sexual behavior.

It is uncertain by what mechanism the Pill might have an unfavorable influence on the risk of cervical neoplasia, but cervical tissues are known to be responsive to the influence of contraceptive steroids. Furthermore, if the Pill does indeed speed up the "transit time" from cervical dysplasia to more serious neoplasic lesions as described by Stern et al,[50] this might explain why the Oxford group observed a substantial relation between Pill use and invasive cancer. The authors conclude that their data offer considerable support to the view that long-term use of the Pill may increase the risk of cervical neoplasia, while not overlooking the influence of sexual factors. They recommend that women who have accumulated more than, say, four years of Pill use should regularly have cervical smears to enable serious disease to be detected and treated while it is curable.

Now, almost two years later, the significance of the study by Vessey and his colleagues remains, although attempts have been made to discredit it on the grounds that it did not identify age at first intercourse and numbers of sexual partners. Early age at first intercourse is recognized as an important factor in the etiology of neoplasia of the cervix, while the sexual history of male consorts has also come to be accepted as of considerable significance.

The possible confounding effect of cigarette smoking, which was unknown as a co-factor in cervical neoplasia at the time the Oxford study began, has also been put forward to weaken the impact of its findings.

Further evidence in support of a Pill-cervical neoplasia hypothesis has come from a WHO study, largely based on women in developing countries whose preliminary findings show an increase in the relative risk for invasive carcinoma of the cervix in women who have ever used the Pill. The relative risk of 1.19 for ever-users increased to 1.53 after five years of Pill use.[51]

The limited levels of screening procedures for cervical cancer in developing countries was considered important as it overcame the problem of a bias in favor of early diagnosis in Pill-taking women who tend to make frequent use of these procedures in countries where they are more readily available.

Only 31% of the cases gave a history of multiple sexual relationships. As in the Oxford study, information on cigarette smoking was not collected. However the researchers pointed out that this is unlikely to be an important contributing factor. Cigarette smoking is uncommon among the older women in developing countries who made up the bulk of those studied in this survey.

The weight of evidence from what are now numerous studies dealing with prolonged use of the Pill and the development of neoplasia of the cervix is considerable. The implication of this for women currently using the Pill, however, is somewhat uncertain because the findings are based in part on exposure to preparations which contained higher doses of estrogens and progestogens than many products now in use.

As with the findings showing the cardiovascular risks associated with taking the Pill, efforts have been made to undermine the findings of this WHO study by emphasizing the importance of cigarette smoking as a co-factor in the causation of cancer of the cervix. It seems that the protagonists of the Pill would have us believe that the Pill is harmless and it is only a matter of persuading women not to smoke. There does not appear to be any doubt,

however, that cigarette smoking and taking the Pill are a etty lethal combination.[52,53]

Smoking and Cervical Cancer

An association of cigarette smoking and cervical neoplasia is recently been recognized. A study by Trevathan et al in the U.S.[54] has sh n cigarette smoking to be significantly associated with carcinoma-in tu, severe dysplasia and mild to moderate dysplasia with relative risks o .6, 3.3 and 2.4 respectively. Cumulative exposure to cigarette smoking measured by pack-years smoked) was strongly related to risk of the conditions. Women with 12 or more pack-years of exposure had relative ks of 12.7, 10.2 and 4.3 respectively for the three conditions, with some idence that the risk was greatest in women who began smoking in their rly teenage years.

Generally the results of this survey support the data from pr ous studies. It is suggested that cervical cells may be exposed to compone of cigarette smoke that are absorbed into the blood and then secreted h the cervical epithelium.

The possibility of a causal association between cigarett moking and cervical neoplasia does not exclude the possible, or even es itial, role of other factors such as herpes simplex type II and multiple s ual partners. Perhaps the cervical epithelium, especially while undergoing ne metaplasic changes of puberty, is particularly sensitive to the carcinog s of cigarette smoke. Alternatively a systematic effect of smoking, conc vably related to vitamin A metabolism, could be the mechanism.

By way of conclusion I could do no better than to quote om the *JAMA* editorial on the subject of smoking and cervical cancer:

"Cervical carcinoma in situ is a disease of young women. The risk imparted by smoking is especially large for young women. Given that the treatment for this disease may result in sterility it is obvious that in addition to jeopardizing their lives, smoking has resulted in an inability to bear children for thousands of women."[55]

Conclusion

With the news in 1970 that DES in mothers had caused genital cancer in their daughters, the scenario was set for the eventual recognition of an association between the Pill and cancer. By the mid 1970s, the occurrence of new growths of the liver, albeit mostly benign, had already been discovered. These were related, not surprisingly, to length of exposure to the Pill.

About the same time, the news that endometrial cancer had been discovered in women taking sequential oral contraceptives containing high dose estrogen and a weak progestogen, demethisterone, caused the immediate withdrawal of Pills of this type from the market. However it was realized that all

estrogens seemed to increase the risk of endometrial cancer, irrespective of their formulation or mode of administration.

By the late 1970s, the etiology of breast and cervical neoplasia had become much clearer. The work of Pike and Passenbarger and their colleagues highlighted the possible effect of the Pill in the cause of breast cancer. Although large epidemiological trials appeared to show that the Pill reduced benign breast disease, many clinicians gained the opposite impression. As time went by, more women entered long-term categories of Pill-taking, or even just aged to the point where carcinogenic agents could exert their effect. The most recent findings of Professor Pike's research put the spotlight squarely on women who had taken high potency progestogen Pills from an early age, drawing attention to the concentration of the Pill's carcinogenic effects in adolescence and early adulthood. They also showed that progestogens, as well as estrogens, had carcinogenic potential.

The rapidly rising incidence of cervical neoplasia in young women, at a time when mortality from this disease in older women was declining, worried the epidemiologists. The etiology of cervical cancer is complex and multifactorial, involving such factors as early commencement of intercourse, multiplicity of partners who themselves may have been promiscuous, viral infections, with Herpes virus II and the Papilloma virus acting as cofactors; and now the recognition of an association between cigarette smoking and cervical cancer. Meanwhile, the Pill during the late 1970s had entered the list, gradually establishing its claim to be recognized as an important etiological factor.

Finally, Vessey and his colleagues from Oxford confirmed the findings of others. As the *Lancet* editorial said, in commenting on their recent paper: "The relation reported by them and others of an increasing incidence of cervix cancer with increasing duration of oral contraceptive use is strong and consistent and the progression of dysplasic lesions to in-situ carcinoma seems to be accelerated by the Pill".[56]

The effect of the Pill in causing thrombo-embolism, stroke and heart attacks, together with its disturbance of lipid metabolism, are well known. Cigarette smoking, although the mechanism of its action is obscure, is clearly recognized for its synergistic action in increasing the incidence of cardio-vascular pathology in women on the Pill. It is of more than passing interest that cigarette smoking has now taken its place as a contributing factor in neoplasia of the cervix. It remains to be seen whether there is a similar synergism of action with the Pill in this area.

That the Pill could theoretically be an important cause of immuno-suppression offers an interesting area for research in the immediate future. As Ellen Grant has said: "Most women who are allergic to the 20th century are previous Pill users."[57] The Pill's disturbance of liver function could interfere with enzyme removal of mutagens and carcinogens.

The responsibility for the harmful effects of prescribing the Pill for adolescents needs to be sheeted home to those in our community who openly and consistently advocate it on the grounds of being "realistic" towards

the needs of the young. It seems that, to them, the ultimate evil pregnancy which is to be avoided at all costs, whatever the consequ es. Those advocates feel that parental rights should be overridden and law either flouted, twisted or changed; that the young must have their and have it now, unrestricted, but always "protected" against pregna . Surely it is time, in the interests of the health of the women of our n n, for too long the guinea pigs of the oral contraceptive industry, for eappraisal of this disastrous policy.

The Centres for Disease Control Cancer and Steroid H one Study

Oral Contraceptive Use and the Risk of Endometri Cancer
(JAMA 1983. 249. pp. 1600-1604)

This study showed a protective effect for women had used combination oral contraceptives (OC) for at least 12 month heir relative risk being 0.5 that of never users. The protective effect w nost notable for and largely confined to nulliparous women, whose ris was only 0.4 that of nulliparous never users. This has not been previo y reported.

However, users of sequential OCs and all other OCs wer greater risk of endometrial cancer developing than never users, with k ratios (RR) of 2.1 and 1.8 respectively. It appears that at least six days progestogen treatment per month are necessary for it to exert its protecti effect against the carcinogenic effects of the estrogen of the Pill.

The authors estimated that 39,000 women with endometri cancer would be diagnosed in the U.S. in 1982 with 3,000 deaths, th disease having the third highest incidence of all cancers. It was consider that more than 40 million women in that country have used OCs. Appr imately 2,000 potential new cases of endometrial cancer would be avert by the use of combination OCs in 1982, according to the authors of the report.

The Centres for Disease Control Cancer and Steroid Hormone Study

Long-Term Oral Contraceptive Use and the Risk of Breast Cancer
(JAMA 1983. 249. pp. 1591-1595)

The authors of this report state that OCs have been used by more than 25 million women in the U.S. and 150 million world wide. Breast cancer is the leading cause of cancer mortality among women in the U.S., the disease affecting 7% of American women.

Most published studies of the effects of OC use on breast cancer were conducted in the early 1970s and hence were unable to look at the influence of long-term OC use or the delayed effects of OC use on the risk of breast cancer, said the authors.

This study reports the initial 6 months of a 25 month study based on data for 689 women with newly diagnosed breast cancer and 1,077 controls. The women were aged 20 to 54. Those with breast cancer, when compared with controls, were more likely to be nulliparous, be older when their first child was born, have a history of breast cancer in first degree relatives (mother, sister, daughter) and a history of benign breast disease. They were also more likely to be premenopausal.

Compared with women who never used OCs, the relative risk of breast cancer for women who used the Pill for at least one month sometime in their lives was 0.9. The duration of OC use, up to 11 years or more, did not influence a woman's risk of breast cancer.

A lack of association between OC use and the risk of breast cancer was noted for women of all ages studied. Even long-term use (11 years or more) which began more than 15 years ago, did not alter the risk. Women who used the Pill before their first full term pregnancy showed a risk ratio of 1.3 when compared to controls. The authors did not consider this to be a materially increased risk, but suggested further analyses of such cases — because of their importance. Use of the Pill did not increase the risk of breast cancer among women with benign breast disease or a family history of breast cancer.

The authors make no claims of any cases of breast cancer being averted by use of the Pill.

The Centres of Disease Control Cancer and Steroid Hormone Study

Oral Contraceptive Use and the Risk of Ovarian Cancer
(JAMA 1983. 249. pp. 1596-1599)

Ovarian cancer ranks as the fourth leading cause of cancer mortality among women in the U.S. An estimated 18,000 cases and 11,400 attributable deaths will occur among American women in 1983. Almost one-third of the cases will occur among women aged 20 to 54 years. Pregnancy appears to exert a protective effect, several studies having noted an increased risk of ovarian cancer among women of low parity.

The authors report their analysis of ovarian cancer data collected during the first 10 months of a study of 179 women, aged 20 to 54, with newly diagnosed ovarian cancer, compared to 1,642 women with intact ovaries.

Compared with controls, women with ovarian cancer were more likely to be younger than 30 years of age, to have never married or been pregnant and to have a diagnosed infertility problem.

The authors found that the age-adjusted relative risk of ovarian cancer developing for ever-users compared with never-users was 0.6, the risk

decreasing with increasing duration of OC use to 0.4 in wo who had used the Pill for five years or more. This lower risk appea o persist long after OC use ceased.

The authors consider that whether ovarian cancer is c d by the "incessant ovulation" of the nulliparous woman or by the alt ve theory that high levels of circulating pituitary gonadotrophins omote its development, both are consistent with a protective effect of ill, which both inhibits ovulation and suppresses gonadotrophin rele

They estimate that the incidence of ovarian cancer in w n 20 to 54 might be about 30% higher if women had never used OCs. her words about 1,700 cases of ovarian cancer in this age group wi averted in 1983 by the use of the Pill. Further investigation of the e miology of ovarian cancer and its relationship to OCs is clearly wa ed in their opinion.

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