Editor: There are about 10 million American women and 50 million women world-wide who now take oral contraceptives. In the 18 years since the Pill was first marketed, more and more has become known about its potential health hazards, and fear has arisen about a possible link to cancer. Is there any convincing evidence that oral contraceptives are associated with breast cancer, for example?

Dr. Kretzschmar: No, there isn’t. There is no evidence that the Pill increases the risk of breast cancer and in fact, it has been shown that oral contraceptives may offer some protection against benign breast disease. For example, when Vessey and his group compared 345 women admitted to London teaching hospitals with breast lumps (90 malignant and 255 benign) against a matched control group admitted for acute medical or surgical conditions, it was found that oral contraceptives were in no way related to the risk of breast cancer. It was discovered that the risk of admission to a hospital for a breast biopsy among Pill-users was reduced by about 75 percent, compared to those women who had never used the Pill at all.

The Boston Collaborative Drug Surveillance Program did another retrospective study, and had similar findings. One hundred twenty-one patients with breast disease (cancer, fibrocystic disease, fibroadenoma and miscellaneous problems such as fibrolipoma or benign duct ectasia) were compared to 842 patient controls. Among the women with newly diagnosed breast cancer, three of 23 (13 percent) had received oral contraceptives, compared to 20 percent who had received oral contraceptives among the controls. Of the patients with benign breast tumors, six percent had received oral contraceptives, compared to the 20 percent among the controls. When these findings were analyzed for the patients’ ages, it was revealed that at each age level, Pill usage was less common in those with benign breast tumors. According to their data, hospital admissions in the Boston area for breast diagnosis were reduced by almost half for those women using oral contraceptives.
The prospective study being done by the Royal College of General Practitioners in Great Britain has also ruled out an association between breast cancer and oral contraception. Their 1974 interim report showed that of 46,000 women — 50 percent using the Pill continuously, and 50 percent not — 11 cases of malignant neoplasm of the breast were found in Pill-takers, four cases in ex-takers, and 16 among the non-taking control group. A lower incidence of benign breast neoplasm became apparent after two years of continual Pill usage.

Editor: Aside from causing cancer de novo, is there any evidence that the Pill might exacerbate existing tumors?

Dr. Kretzschmar: As far as the belief that women with benign breast tumors have a higher risk of developing breast cancer, the apparent protective effect of oral contraceptives against benign breast tumors could be considered a protection against subsequent development of breast malignancy as well. Also, prolonged use of oral contraceptives simulates pregnancy in some ways, and we know that, relative to other women, those who become pregnant early in life are at a lower risk of developing breast cancer.

There is some evidence that women who have fibroids may have enlargement of their fibroids related to the Pill. Of course, women with a strong family history of breast cancer should be followed with caution, and should have careful breast examinations at frequent intervals; women with known or suspected carcinoma of the breast should choose another form of contraception. But I am quite convinced that oral contraceptive intake is in no way responsible for breast carcinoma, de novo or otherwise.

Editor: Have oral contraceptives been linked to ovarian cancer?

Dr. Kretzschmar: No. There is no relationship. If anything, the Pill has an inhibitory effect on the development of ovarian cancer. In the British study of 46,000 women, there have been fewer deaths from both breast and ovarian cancer among those women using the Pill than among those who did not.

Editor: Is there a relationship between the Pill and uterine cervical cancer?

Dr. Kretzschmar: No. Among women receiving estrogen from a combination-type oral contraceptive, no convincing relationship to cancer of the uterine cervix has been established. In a case-control study done at the State University of New York-Downstate Medical Center in Brooklyn between 1969 and 1975, 689 consecutive patients with cervical carcinoma were interviewed and compared with a control group of 1,300 with normal cervical smears. Each case subject was matched with a control subject for age, ethnic origin, age at first coitus, age at first pregnancy, and socioeconomic status. The findings: no significant
difference between the case and control subjects in the use of oral contraceptives.

This conclusion duplicates the results of many other studies as well. Worth and Boyes compared the use of oral contraceptives among 310 women, 20 through 29 years of age, who had carcinoma in situ of the cervix with 682 control subjects matched for age who had negative smears. Again, there was no significant difference in the use of oral contraceptives. Thomas compared 324 women who had positive cervical smears showing dysplasia or carcinoma in situ of the cervix with 302 women from the same locality. No difference was found in their use of the Pill.

Although there has been a significant increase in recent years in pre-invasive lesions of the uterine cervix, this increase has been found in both users and non-users of the Pill. This brings out one of the more positive aspects of the Pill. Just think of the number of women who routinely see their physicians now and obtain a Pap smear because they are on the Pill. Women who are on the Pill have a much better chance for earlier diagnosis of changes in their cervical epithelium than those who are not—and that's certainly a plus factor in the relationship of cancer to oral contraception.

**Editor:** You discount a link between oral contraceptives and uterine cervical cancer. But if a Pap test reveals cervical dysplasia in a patient, would you advise her to stop taking the Pill?

**Dr. Kretzschmar:** No, I would manage the dysplasia with selective biopsies and appropriate treatment. I would not advise her to stop taking the Pill.

**Editor:** Are oral contraceptives associated with endometrial cancer in your view?

**Dr. Kretzschmar:** No, there is no relationship. The sequential tablets, which provided estrogen alone for 14 days, and then estrogen and progestogen in combination for seven more days, were taken off the market when controversial evidence linking estrogen with possible cancer of the uterus came to light. In 1975, 21 cases of endometrial cancer among Pill-taking women under the age of 40 had been recorded, but in eight of the cases, factors were found which militated against a close relationship between oral contraceptives and carcinoma, and of the remaining 13 cases, 11 had taken sequential agents. So, there is absolutely no evidence to link endometrial cancer with combination or progestin-only oral contraceptives. In fact, since only about eight percent of women taking oral contraceptives at that time used sequential agents, the unduly high incidence of sequential agent therapy in these 21 cases might suggest that women who are predestined to develop this tumor are actually protected against it by the combination pills.

If you wish to discuss replacement estrogen, exogenous long-term estrogen for menopausal women, that's controversial. According to an article published in the *New England
Journal of Medicine in 1975, the use of these exogenous estrogens in menopausal and post-menopausal women was associated with a 4.5 times greater risk of endometrial cancer. However, some physicians do not believe that there is a connection, and there are many knowledgeable people on both sides of the fence. Women taking estrogens should have frequent pelvic cancer-screening examinations and physicians should be on guard if abnormal bleeding develops. I would point out, in this respect, that the Pap smear is not a totally effective screening device for endometrial cancer; in fact, 40 to 60 percent of patients with adenocarcinoma of the uterus will have negative Pap results. An evaluation of the endometrial cavity with a suction curette, or an endometrial biopsy should be performed on all patients at high risk, or on those with a suspicious history. If a physician then feels he has not gotten a sufficient sampling, a dilation and fractional curettage should be done under local or general anesthesia. Our diagnostic procedures in this area should be further developed.

Editor: Would you comment on the evidence linking oral contraceptive use to benign liver tumors?

Dr. Kretzschmar: Yes, this was looked at carefully, and in April 1977, the American College of Surgeons released documented evidence on the increased incidence of benign hepatomas related to oral contraceptives. Their survey material consisted of 543 cases of primary liver tumors among both sexes; 378 in females and 165 in males. Among the males, 8.5 percent were benign, while among the females, 56.1 percent were benign. A positive history of oral contraceptive use was reported in 49.5 percent of the female patients, and in 29 percent the contraceptive history was unknown. However, it is reasonable to assume that a certain number of these “unknowns” included Pill-users; therefore, among the female patients in this study, more than 50 percent of primary liver tumors occurred in users of oral contraceptives.

The majority (73.8 percent) of the liver tumors diagnosed in Pill-users were benign. On the other hand, among non-users, the percentages of benign and malignant tumors were roughly equal. This difference in the proportion of benign to malignant tumors among users and non-users is substantial, and further supports the association between Pill use and the occurrence of benign liver tumors. Also, the frequency of malignant tumors in this study increased with age, and resembled the distribution of malignant liver tumors in the various age groups of the general population. But the distribution of benign liver tumors peaked in the age group of 26-30 years, and this parallels the age distribution of oral contraceptive use in the general population.

Editor: What were the histologic types of these benign liver tumors?

Dr. Kretzschmar: The survey showed that among non-users, the benign tumors were proportionately divided among four histologic types. But
among users, there was a preponderance of hepatic cell adenomas and focal nodular hyperplasia; together, these two types represented 82.6 percent of all benign tumors in users. So it appears that the association between oral contraceptives and benign liver tumors applies only to these two types. The incidence of adenomas peaked significantly in the 26-30 year-old group, and then declined sharply; the incidence of focal nodular hyperplasia peaked in the 31-35 year-olds and then remained rather constant in the older groups.

Editor: Do the statistics vary with different types of oral contraceptives?

Dr. Kretzschmar: Two synthetic estrogens are used in oral contraceptives: ethinyl estradiol and mestranol. (Mestranol is demethylated in the liver to ethinyl estradiol.) Where information was available on the type of synthetic estrogen used, 66.7 percent of the tumors were found in women who had used mestranol. But that correlation should be interpreted rather cautiously, since mestranol was marketed first, and until 1970, was used more frequently than ethinyl estradiol by the general population.

Editor: What were the most common presenting symptoms, and how were these tumors treated?

Dr. Kretzschmar: Many presented with symptoms of intraperitoneal bleeding, although masses and pain were generally the most frequent presenting symptoms in the survey. It would appear that contraceptive users had highly vascularized tumors, and this might suggest that oral contraceptives exacerbate clinical symptomatology of these tumors. But it should be noted that a high proportion of these benign liver tumors were asymptomatic and were discovered incidentally. I think clinicians should be especially aware of this diagnostic possibility when examining young women who appear otherwise healthy.

Most hepatic cell adenomas studied in this survey were treated by surgical resection, but 13 percent were untreated, and of the cases of focal nodular hyperplasia, 14 percent were untreated. There may be a spontaneous regression of these tumors once oral contraceptive use has been discontinued.

These two types of benign liver tumors have not been shown to be precursors of hepatocellular carcinoma, and there is no evidence that because of different pathogenic mechanisms, the benign tumors in patients on oral contraceptives have any proclivity for malignant degeneration. But benign hepatic lesions can suddenly and unexpectedly rupture, and hemorrhage into the abdominal cavity. Emergency resection of the tumors has not always prevented fatalities. Clinicians should be aware that oral contraceptive users are at risk in relation to these benign liver tumors, and should follow their patients accordingly.

Editor: Do you recommend the use of DES as a morning-after pill, given its proven correlation with vaginal carcinoma in female
children of women who received the drug early in pregnancy?

Dr. Kretzschmar: I think that for any patient who is fully aware of the controversies about it, DES is an appropriate management for the morning-after situation, as is menstrual extraction.

Editor: What are the major contraindications to the use of oral contraceptives?

Dr. Kretzschmar: Women with present or past thrombophlebitis or thromboembolic disorders should not take the Pill. Similarly, patients with a history of cerebrovascular and coronary artery disease should use another form of contraception. Impaired liver function, known or suspected carcinoma of the breast or estrogen-dependent cancers are other contraindications. The Pill should not be used when pregnancy is suspected, and any undiagnosed abnormal genital bleeding should be investigated and treated before an oral contraceptive is prescribed.

Editor: In your experience, what is the most common side effect of the Pill, and how should it be treated?

Dr. Kretzschmar: The most common side effect is breakthrough bleeding, and this should be treated with an increased dosage of estrogen. As a general principle, a patient should begin with the lowest level of estrogen that will prevent ovulation. If breakthrough bleeding persists, the estrogen dosage can be gradually increased. And I'm sure the physician can find another oral contraceptive—assuming the patient is healthy—that will not cause this side effect.

Editor: Should the Pill be prescribed for uses other than contraception?

Dr. Kretzschmar: This is done, and I think it's acceptable. For example, it's effective and relatively safe in the management of severe dysmenorrhea.

Oral contraceptives also provide an effective control of prolonged or excessive bleeding. When there is no pathologic basis for the menorrhagia—such as leiomyomas, polyps, and the like—combination agents are very successful in reducing the blood flow. The advantage of this is obvious.

Editor: To sum up, for whom is it safe to prescribe the Pill?

Dr. Kretzschmar: A safe candidate for the Pill is any healthy young woman who wishes to have temporary control of her fertility. And I emphasize the word temporary. Neither patients nor physicians should avoid the Pill out of fear of carcinogenicity. There is simply no convincing evidence that the Pill causes cancer.

Editor: Thank you Dr. Kretzschmar