INTRODUCTION

Widespread use of oral contraceptives and the public controversy over changing sexual behavior and social values which has accompanied it have focused the attention of medical researchers on this method of fertility control, making the users of orals probably the most scrutinized group in the history of medical science. This scrutiny has inspired a plethora of medical controversies, among them the question of the relationship of oral contraceptive use to the development of neoplasms, both benign and malignant. Indeed, the issue of neoplasia may be the longest standing and least resolved of all these controversies.

Researchers have devoted a great deal of attention to looking for relationships between oral contraceptive use and neoplasms for several reasons:

- experimental evidence that ovarian hormones can sometimes alter tumor incidence in certain laboratory animals;
- epidemiologic evidence suggesting that endogenous hormones (those produced by the body) affect the development of neoplasms of the breast and endometrium;
- reports that women using estrogen alone or oral contraceptives have developed neoplasms;
- the ready availability of data on neoplasia (and other diseases) in users of oral contraceptives—from the records of family planning clinics, hospitals, cancer screening programs, and private physicians;
- widespread public concern about cancer.

This issue of Population Reports begins with a discussion of the methods and difficulties of studying whether and how factors influence the occurrence of neoplastic diseases in humans. This report emphasizes epidemiologic studies of oral contraceptives and neoplasia because such studies are the source of most of the available information on the subject. Also, epidemiologic studies produce the most clearly relevant information, its meaning unclouded by the problems of extrapolating from one species to another, from one type of hormonal treatment to another, from one age group to another. This is not to say that the meaning of findings from epidemiologic studies of users of oral contraceptives is clear. On the contrary, their interpretation is extremely difficult, complicated by the nature of neoplastic diseases, our lack of knowledge about their causes and their development, and disagreements about the diagnosis and classification of lesions.
Experiments with animals provide some of the clearest evidence that hormones may somehow affect the development of some neoplasms in reproductive organs, at least in certain species. For this reason, this report summarizes the results of experiments with animals and hormones and, at the same time, discusses the difficulty—indeed, often the inadvisability—of extrapolating findings in animals to humans.

This report also summarizes findings on breast and endometrial cancer in older women who have taken estrogens alone (not oral contraceptives) to treat symptoms of menopause. These studies, many of which are recent, are of interest in themselves. However, like animal studies, their relevance for users of oral contraceptives is questionable; oral contraceptives contain a progestin as well as an estrogen, and these two components interact to affect the body in ways different from those attributable to either component administered separately.

In this report, a discussion of the uses and problems of both epidemiologic and animal studies sets the stage for a presentation of evidence on hormones and neoplasia in the sites which have received the most attention from researchers—breast, uterine cervix, uterine corpus, liver, pituitary, and ovary. Each section reviews the epidemiologic evidence concerning oral contraceptives and presents briefly, where appropriate, what is known or hypothesized about the roles of hormones in neoplastic diseases in both humans and animals. The strength of the evidence varies greatly among sites. The strongest evidence suggests that users of oral contraceptives are less likely to develop benign breast neoplasms and more likely to develop benign liver tumors than are nonusers. Some evidence also suggests that older women who use estrogen alone may be more likely than nonusers to develop preneoplastic and malignant neoplasms of the endometrium. The same may be true—the evidence is much more limited—of young women who use sequential oral contraceptives, now no longer marketed in many countries and never popular. Combined oral contraceptives have not been associated with increased incidence of endometrial neoplasia. Evidence concerning cancer of the breast, the most common malignancy in women in most developed countries, and cancer of the uterine cervix, the most common malignancy in women in many developing countries (see Table 1), is less clear. Cervical and breast cancers are diseases clearly influenced by sexual and reproductive behavior, which in turn influences and is influenced by choice and use of contraceptive method. This makes studying associations between these cancers and oral contraceptives especially difficult. A few studies have found statistically significant differences in the use of oral contraceptives between some groups of women with these diseases and similar women without them, but these findings seem inconsistent and are difficult to explain biologically. The differences observed seem most readily explained by research limitations or chance variations.

In summary, this issue of Population Reports responds to two questions: (1) what is the evidence concerning relationships between oral contraceptive use and the occurrence of neoplasia? (2) why do answers to questions about possible relationships remain elusive?

### Table 1—Reported Annual Incidence of Cancers of Selected Sites per 100,000 Women in Selected Countries and Regions, 1960s and 1970s

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Indonesia, Nigeria</th>
<th>Saskatchewan, Canada</th>
<th>California, USA</th>
<th>Kinghorn &amp; St. Andrews, Jamaica</th>
<th>Connecticut, USA</th>
<th>Bombay, India</th>
<th>Israel, Jerusalem, Israel only</th>
<th>Japan, Japan</th>
<th>Italy, Italy</th>
<th>Netherlands, Netherlands</th>
<th>Germany, Germany</th>
<th>Greece, Greece</th>
<th>Hungary, Hungary</th>
<th>Scotland, Scotland</th>
<th>Poland, Poland</th>
<th>Austria, Austria</th>
<th>Slovenia, Slovenia</th>
<th>Yugoslavia, Yugoslavia</th>
<th>New Zealand, New Zealand only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>5.8</td>
<td>73.0</td>
<td>26.4</td>
<td>89.9</td>
<td>11.3</td>
<td>96.7</td>
<td>14.1</td>
<td>69.0</td>
<td>53.1</td>
<td>22.7</td>
<td>42.0</td>
<td>68.6</td>
<td>36.3</td>
<td>23.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>7.0</td>
<td>11.4</td>
<td>39.9</td>
<td>29.5</td>
<td>11.4</td>
<td>14.3</td>
<td>4.8</td>
<td>15.2</td>
<td>37.9</td>
<td>42.1</td>
<td>12.9</td>
<td>22.0</td>
<td>36.5</td>
<td>13.6</td>
<td>22.0</td>
<td>18.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>0.5</td>
<td>20.4</td>
<td>2.8</td>
<td>4.3</td>
<td>22.4</td>
<td>11.2</td>
<td>1.3</td>
<td>16.5</td>
<td>21.0</td>
<td>8.2</td>
<td>8.1</td>
<td>10.6</td>
<td>11.7</td>
<td>10.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chorionepithelioma</td>
<td>3.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.8</td>
<td>0.1</td>
<td>0.3</td>
<td>0.6</td>
<td>0.6</td>
<td>0.62</td>
<td>1.0</td>
<td>0.6</td>
<td>0.1</td>
<td>0.5</td>
<td>0.0</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterus, unspecified</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ovary, etc.</td>
<td>3.0</td>
<td>12.6</td>
<td>5.1</td>
<td>6.4</td>
<td>15.5</td>
<td>2.7</td>
<td>16.4</td>
<td>20.9</td>
<td>19.3</td>
<td>6.5</td>
<td>10.5</td>
<td>7.9</td>
<td>13.1</td>
<td>12.7</td>
<td>6.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other female genitalia</td>
<td>0.4</td>
<td>3.1</td>
<td>1.4</td>
<td>1.5</td>
<td>3.4</td>
<td>1.0</td>
<td>1.9</td>
<td>0.5</td>
<td>3.4</td>
<td>5.2</td>
<td>1.4</td>
<td>2.8</td>
<td>4.1</td>
<td>2.8</td>
<td>3.1</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Various periods, but all encompass several years during 1960s and or early 1970s.

*Other uterus, including chorionepithelioma.

*Ovary only.

NR = Not Reported

SOURCE: Waterhouse et al. (591).
Epidemiology, the study of the distribution and determinants of disease in humans (358), provides researchers with the methods for exploring possible associations between oral contraceptives and neoplastic diseases in women. Four of these methods yielded most of the evidence discussed in this issue of Population Reports: case reports, examination of disease rate trends, case-comparison studies, and cohort studies. Each method is appropriate in certain circumstances, and each can contribute to an understanding of neoplastic diseases and the factors which influence them (see Table 2). However, they cannot by themselves determine whether oral contraceptives—or any other environmental factor—cause neoplasms. The evidence they produce must be carefully evaluated on the basis of its internal strength and its consistency with other evidence (see Fig. 1). For the present, assessment of cause and effect remains a matter of judgment.

Special Problems

The nature of neoplastic diseases makes epidemiologic investigation into their causes particularly difficult. First, neoplastic diseases are usually rare, so it is difficult to collect a large enough number of cases for study. At the same time, the rates at which most neoplastic diseases occur do not change rapidly, making it difficult to attribute changes in rates to specific causes. Second, neoplasms probably develop over many years before being detected. Researchers dealing with cancer cases must depend on old memories and old records when looking for possible causes, and researchers dealing with suspected causes must wait many years—possibly decades (270)—to see whether neoplasms develop. Third, neoplastic diseases seem to result from a complex interaction of genetic, environmental, and behavioral variables. The more variables which must be taken into account, the more difficult study becomes; and the possibility persists that unknown factors could be important. Fourth, there is much deep-rooted disagreement over the definition and classification of neoplasms, especially when tissue samples are the basis for classification. Researchers often cannot be sure

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Functions</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case reports . . .</td>
<td>Describe patients, their illnesses, and exposures to environmental factors; discuss suspected inter-relationships.</td>
<td>Often the source of first suspicions about disease causes; encourage more rigorous study.</td>
<td>Few conclusions are made on the basis of case reports alone.</td>
</tr>
<tr>
<td>Disease rate trends . . .</td>
<td>Examine the incidence or mortality of a disease in a large population.</td>
<td>Can be compared with trends in exposure to environmental factors; help assess impact of disease on public health.</td>
<td>To produce detectable changes in rates, exposure to environmental factor must be widespread in the population and must alter the chances of developing the disease considerably.</td>
</tr>
<tr>
<td>Case-comparison studies . . .</td>
<td>Compare exposure to environmental factor in groups with a disease with that in similar groups without the disease.</td>
<td>Determine relative differences in exposure between those with and those without a disease; appropriate when the disease is rare or quick results are desired.</td>
<td>Do not determine the incidence rate in either group; depend on memory and records of participants, which may be faulty.</td>
</tr>
<tr>
<td>Cohort Studies . . .</td>
<td>Compare disease incidence in groups exposed to an environmental factor with that in groups not exposed.</td>
<td>Appropriate when fullest information, least subject to unavoidable possibilities of methodological bias, is required, or when information on more than one disease is sought.</td>
<td>Often require study of large groups over long periods of time, especially with rare diseases.</td>
</tr>
</tbody>
</table>

[For further discussion of these methods, see Cornfield & Haenszel (105), Doll & Vessey (128), Dorn (130), Hardy & White (240), Hill (254), Hines & Goldzieher (259), MacMahon & Pugh (358), Sartwell (505), Schlesselman (510), Seigel & Corfman (517).]

Fig. 1. Criteria for assessing the likelihood of causal relationships between exposure to an environmental factor and a disease.

1. Strength of association between factor and disease
2. Consistency of results with other studies using different methods
3. Specificity of association between factor and disease
4. Logical temporal relationship (exposure must precede disease)
5. Relationship between quantity or duration of exposure and the likelihood of developing disease (dose-response)
6. Ability of a single theory of disease causation to account coherently for all the evidence
7. Analogy with similar diseases and their causes
8. Consistency with broader knowledge about diseases and about human biology

whether the neoplasms they are studying are in fact the same as or different from the neoplasms studied by others. Furthermore, how lesions are classified bears upon judgments of their seriousness, causes, and treatment.

Evidence from a number of sources suggests that under certain circumstances some hormones can affect the development of certain neoplasms. The problem is whether and how such evidence can be applied to the use of oral contraceptives—for example:

- Some breast cancers are influenced by estrogen; they grow in its presence and regress in its absence.
- Under certain conditions, some hormones alter the development of neoplasms of the mammary glands or genital organs in some animal species or strains.
- According to some recent epidemiologic studies, menopausal and postmenopausal users of estrogens alone may be more likely to develop endometrial cancer than are women who do not take these hormones (77, 219, 382, 375, 537, 611).
- The pattern of endogenous hormones in women with breast or endometrial cancer may be or may have been different from that in women who do not develop these types of cancer.

Such evidence suggests that the subject of oral contraceptives and neoplasia merits study. But much knowledge is lacking concerning the relevance of this evidence to oral contraceptive use. Among the unresolved issues are these:

- What are the relationships between benign and malignant neoplasia in the female reproductive organs and liver?
- What importance should be attached to differences between neoplasms in tissues influenced by hormones and those in tissues not greatly influenced? Can we apply what is known about nonhormonal cancers to hormonal cancers?
- How important is the cyclic nature of oral contraceptive use and the fact that orals contain two interacting components—an estrogen and a progestin? Can evidence concerning estrogens alone be applied to oral contraceptives?
- How important might differences and changes in the content and dose of oral contraceptives be?
- Should the results of experiments with animals be applied to humans even though there are important differences in the reproductive systems among species and in the types of neoplasms which develop in them?
- From the time of exposure to a suspected causal factor, how long should we expect to wait for detectable neoplasms?
- Could hormones affect tumors differently at different stages of their evolution?
- How long should we expect to wait for neoplasms to develop from the point of detection from the time of exposure to a suspected causal factor?
- How does the behavior of oral contraceptive users differ from that of nonusers? How might these differences affect their likelihood of developing neoplasms?

Because important questions such as these are unresolved, and because there are no fully accepted specific theories of neoplasia in humans, the researcher’s ability both to design studies which account for all relevant variables and to interpret study results is limited.

ANIMAL STUDIES

Results of studies involving laboratory animals have raised concern about the role of ovarian hormones in the development of tumors, and therefore these studies deserve careful assessment. Although results are often conflicting, in general they agree that hormones, including those used in oral contraceptives, affect the development of neoplasms in several animal organs, particularly the breast, uterine corpus and cervix, ovary, liver, and pituitary. The specific nature of this effect is unknown, due mainly to a lack of basic knowledge about mammalian reproductive systems and the mechanisms of tumorigenesis.

Uses and Problems

Much of what is known about human metabolism and physiology is derived from animal studies. The reasons for reliance on animal studies are clear:

- Some laboratory animals, particularly rodents, are small and have short life spans, so they can be easily cared for and observed through entire life cycles.
- Variables which affect disease rates, like heredity, mating patterns, and diet, can be controlled.
- Ethical considerations sometimes preclude experiments using human subjects.
- They provide valuable clues for investigators to follow in human studies.
- When data on humans are inadequate, they often serve as the basis for policymaking by government drug regulatory agencies.

Animal studies, however, have certain limitations. One is the unsettled question of how well animal studies will predict human response: if a substance causes neoplasms in animals, will it necessarily cause them in humans? If it does not cause neoplasms in animals, will it therefore be safe for human use? Although these questions are far from being answered at this time, the little comparative information available suggests that no one species, not even the monkey, is similar to humans in enough respects to indicate definitively whether oral contraceptives cause neoplasms in humans (58, 138, 172, 212, 257, 314, 327, 436, 463). Unfortunately, species differences among reproductive systems may be greater than differences among many other organ systems. For example, humans and Old World monkeys are the only animals which menstruate cyclically (478). The likelihood of a correct prediction may be increased by examining several species and looking for trends that cross species lines. In many cases trends are not apparent, however, and the problem of relevance persists.

Another limitation is the lack of standardization in study design and analysis of results. Studies of the effects of estrogen, progesterone, and other sex hormones on neoplasms have been conducted since the 1930s (319), and many variables have been found to affect their results—for example, dosage, duration of exposure to hormone and of observation period, animal strains employed, the sex of the animals, various modes of administration and regimens, administration with or without a known carcinogenic agent, and age at time of exposure. When many of these factors differ, comparisons among studies become difficult. At best, only general trends can sometimes be detected.
<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Ref. No.</th>
<th>Description</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Col­laborative Drug Sur­veillance Program 1973</td>
<td>54</td>
<td>Case-comparison study. Comparison of OC use by 98 women with BBN and by 842 women who might use OCs who were admitted to same hospitals for acute illness or elective surgery.</td>
<td>6% (n=6) with BBN had used OCs compared with 20% of controls—a significant difference. Age-standardized rate ratio: 0.47. For each 5-year age group between 20-44, OC use was less common in women with BBN. Negative association most pronounced in fibroadenoma cases. Data insufficient for evaluating influence of duration of use.</td>
</tr>
<tr>
<td>Fasal &amp; Paffen­barger 1975</td>
<td>164</td>
<td>Case-comparison study. Comparison of OC use by 446 women with BBN under age 50 with 446 surgical patients and 446 medical service patients matched for religion, race, age, hospital of admission, and time of hospitalization.</td>
<td>9.4% of women with BBN were current users of OCs compared with 15.7% of surgical controls and 10.4% of medical controls. 40.4% with BBN had used OCs at some time compared with 43.5% of surgical controls and 47.8% of medical controls. &quot;Relative risk&quot; rate ratio, 0.8, &quot;of borderline significance.&quot; Risk of BBN decreased with increasing duration of OC use: e.g., &quot;relative risk&quot; for women who had used OCs for 8 years or more, 0.2. Limitations of study: Patients with [BBN in this study] are somewhat older than the universe of patients from which they truly come.</td>
</tr>
<tr>
<td>Kelsey et al. 1974</td>
<td>300</td>
<td>Case-comparison study. Comparison of OC use in 364 women aged 20-44 with BBN and in 364 controls, matched for age, marital status, race, education, hospital of admission, and admission dates.</td>
<td>More controls than cases had used OCs, but difference not statistically significant. Average duration of OC use significantly higher for controls in general than for cases in general, and for cystic hyperplasia and fibroadenoma subgroups. OC use for more than 2 years significantly more common among controls than among cases in general and in fibroadenoma subgroup. Use for more than 4 years significantly more common among controls in general and in cystic hyperplasia and fibroadenoma subgroups.</td>
</tr>
<tr>
<td>Nomura &amp; Comstock 1976</td>
<td>447</td>
<td>Case-comparison study. Comparison of use of OCs or estrogens alone in 320 women age 20-49 with BBN and in 320 controls matched for race, age, and residence in Washington County, Maryland (USA). All cases and controls had participated in 1963 census of county. Average duration of use: for OCs, 6 months for cases, 7 months for controls; for estrogens alone, 48.5 months and 50.0 months, respectively.</td>
<td>23.7% of cases had used OCs, compared to 22.2% of controls. 42 case-control pairs were nonuser/user; 48 were user/nonuser, for a relative risk of 1.14, not statistically significant. Use of estrogen alone, particularly diethylstilbestrol, was more common among cases whose first use of estrogen was 4 or more years before biopsy than among controls.</td>
</tr>
<tr>
<td>Ory et al. 1976</td>
<td>456</td>
<td>Cohort study. Rates of hospitalization for BBN in OC users and nonusers among 97,789 Boston area women. 499 cases of fibrocystic disease and 83 of fibroadenoma diagnosed in 30 month period.</td>
<td>Hospitalization rate for cystic disease lower in OC users than nonusers. No significant reduction in rate for users of 1 year or less, but continued use progressively reduced rate. Age-standardized rate ratio for users of more than 2 years compared with nonusers: 0.4. Reduction of risk appeared to persist for several years after OC use discontinued. OC users were less frequently hospitalized for fibroadenoma, but difference was not statistically significant.</td>
</tr>
<tr>
<td>Royal College of General Practitioners 1974</td>
<td>488</td>
<td>Cohort study. Compares rate of clinically-diagnosed BBN during 34,875 woman-years of OC use to rate during 42,306 woman-years of observation of never-users matched to users for age and marital status, and to rate during 9,803 woman-years of observation of women who stopped using OCs during the course of the study.</td>
<td>290 cases of BBN reported among users, or 8.51 per 1,000 woman-years; 106 cases reported among ex-users, or 11.4 per 1,000 woman-years; 463 cases reported among controls (nonusers), or 10.63 per 1,000 woman-years. Ratio of rates, standardized for age, parity, social class, and cigarette consumption, for users to controls: 0.80, which is statistically significant. Higher progestin doses and longer duration of use associated with lower rates of BBN. Negative association &quot;only becomes apparent after 2 years of continual use.&quot;</td>
</tr>
</tbody>
</table>
The lack of standard definitions of terms like lesion, hyperplasia, tumor, nodule, and, most importantly, malignant and benign poses another problem. Definition is fundamental because the induction of malignant tumors is more serious than induction of benign tumors. Disagreement over the classification of tumors occurred in early studies (196, 197, 445) and persists today (332, 555).

Animal studies will continue because they provide information where other data would be difficult or impossible to obtain. However, this information must be used with full awareness of its limitations.

**Table 3—(cont.)**

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Ref. No.</th>
<th>Description</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sartwell et al. 1973</td>
<td>506</td>
<td>Case-comparison study. Rate of OC use among 416 women with BBN (306 with cystic disease, 71 with fibroadenoma, 39 with other conditions) compared with use rate in 416 women admitted to same hospital for other reasons, matched for age, race, single or ever-married, and hospital pay status.</td>
<td>Long-term OC use significantly more common among controls than among cystic disease cases—34 controls had used OCs for more than a year, compared with 14 cases. Fibroadenoma cases and their controls showed no marked differences in hormone use rates. &quot;Our data do not seem to us to allow... an inference [that OCs protect against BBN], but they do provide further evidence that OCs... are not causative factors in this group of conditions.&quot;</td>
</tr>
<tr>
<td>Vessey et al. 1972</td>
<td>587</td>
<td>Case-comparison study. Rate of OC use in 255 ever-married women aged 16-39 who had BBN compared with use among 255 ever-married women admitted to same hospitals for other reasons and matched for age, parity, and time of hospital admission.</td>
<td>66.7% of cases had never used OCs, compared with 54.6% of controls; difference due almost entirely to higher number of current, long-term (more than 2 years) users found among the controls. &quot;... there is some evidence that OC use may actually protect against [BBN]... this protective effect is largely confined to women who continue to use OCs more than 2 years. Such women appear to have only about 25% as great a risk of being admitted to hospital for a breast biopsy as women who have not used [OCs] at all. The protective effect seems to apply both to fibroadenoma and to chronic cystic disease of the breast...&quot;</td>
</tr>
<tr>
<td>Vessey et al. 1976</td>
<td>586</td>
<td>Cohort study. Reports incidence rates of BBN in 17,032 white British women aged 25-39. 56.6% used OCs at time of entry into the study (followed for 31,076 woman-years), 24.8% used diaphragms (followed for 14,739 woman-years), and 18.6% used IUDs (followed for 10,014 woman-years).</td>
<td>Incidence per 1,000 woman-years of follow-up, standardized for age, social class, parity, and smoking habits:</td>
</tr>
</tbody>
</table>

**Benign Breast Neoplasms.** Benign neoplasms of the breast seem to appear less frequently in users of oral contraceptives than in nonusers. Of 9 studies, all published since 1970, 7 concluded that users faced significantly less risk of developing benign breast neoplasms than nonusers; 2 found the difference in oral contraceptive use between women with benign breast neoplasms and similar women without the disease was not statistically significant (see Table 3).

Studies have placed the risk of benign neoplastic breast disease in oral contraceptive users at between 25 and 50 percent of that in nonusers. The longer a woman uses orals, the less her risk of developing benign breast neo-

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**BR EAST NEOPLASMS**

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Long-term OC use significantly more common among controls than among cystic disease cases—34 controls had used OCs for more than a year, compared with 14 cases. Fibroadenoma cases and their controls showed no marked differences in hormone use rates. "Our data do not seem to us to allow... an inference [that OCs protect against BBN], but they do provide further evidence that OCs... are not causative factors in this group of conditions."
Breast Cancer. Most epidemiologic studies to date have found no evidence of either a positive or negative association between breast cancer and short-term (up to 4 years) use of oral contraceptives. Of special interest are two 1975 reports which noted contrasting results. A relatively large case-comparison study conducted in California (USA) found more oral contraceptive use than expected in a few subgroups of breast cancer patients (164, 464), but a large British study which looked at some of the same subgroups failed to find any significant differences in use of orals between women with breast cancer and those without (585). When researchers compare many subgroups, some statistically significant differences may well occur by chance (2, 164, 584). (See Table 4.)

Most studies of postmenopausal women receiving only estrogens have revealed no relationship to breast cancer (see Table 5). However, a large 1976 study, which compared breast cancer incidence rates in a group of postmenopausal estrogen users with an expected incidence rate calculated from those for large populations of similar women, found a relationship between estrogen use and an increased incidence of breast cancer in women who were followed for 12 years or more (265). Some of the earlier studies suffered from small sample sizes or other methodological weaknesses (265).

Other evidence suggests that estrogens, whether endogenous or exogenous, play some role in the development of breast cancer—for example:

- Epidemiologic evidence has been interpreted to suggest that higher breast cancer risk is associated with longer exposure to endogenous estrogens: breast cancer is rare in men and rarely develops before puberty in women (324); women whose ovaries are removed at a young age are less likely to develop breast cancer than are women who undergo natural menopause (168, 260, 330); early menarche and late menopause seem associated with higher breast cancer risk (572), although nutrition may be an intervening variable affecting both menarche and breast cancer risk (548).
- Under certain conditions, breast tumors have developed in some test animals given estrogens (see Mammary Neoplasms in Animals).
- One-third of breast cancers are estrogen-dependent; they will regress, at least temporarily, if deprived of estrogen (556).
- Case reports note the development of breast cancer in transsexuals (genetic males) who were taking estrogens to bring about breast development (561).

Estrogens alone are not analogous to oral contraceptives, however, since orals also contain a progestin, which interacts with the estrogen.

A number of epidemiologic studies of breast cancer and oral contraceptives, including several cohort studies, are now underway in the USA and the UK. They involve more subjects than do most of the published studies and may provide better evidence about what relationships, if any, exist between oral contraceptive use and breast cancer.

Role of Hormones

Because in most developed countries breast cancer is the most common malignancy in women, the disease has been extensively studied. Research has revealed a complex pattern of epidemiologic associations (355, 467) (some of which are mentioned above) and conflicting information about hormonal patterns in women with breast cancer. So far, however, research has not fully explained what role various hormones play in breast cancer development.
<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Ref. No.</th>
<th>Description</th>
<th>Findings and Researchers' Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthes et al. 1971</td>
<td>17</td>
<td>Case-comparison study. Use of OCs or postmenopausal estrogen replacement therapy by 119 women aged 15-75 with breast cancer, compared with use by 119 controls, women in hospital at same time as cases and matched for age within 5 years, race, ever-or never-married, and hospital pay status (as an indicator of socioeconomic status).</td>
<td>6 cases and 7 controls had used OCs. 18 cases and 14 controls had used estrogens only. 5 cases and 17 controls had used an unnamed or several hormonal products. Among women under 50, comparisons were: 2 cases and 7 controls using OCs only, 1 and 10 using other, unnamed, or multiple products. In matched pairs of cases and controls, there were more pairs in which only controls had used hormones. &quot;Neither in the total series nor in those under 50 years of age was there an indication of greater use of estrogens or contraceptive products than among the controls.&quot; 13% (n=3) of cancer patients used OCs compared with 20% of controls.</td>
</tr>
<tr>
<td>Boston Collaborative Drug Surveillance Program 1973</td>
<td>54</td>
<td>Case-comparison study. Use of OCs during previous 3 months in 23 breast cancer patients aged 20-44, found through surveillance of area hospitals, compared with use in 842 women of childbearing age admitted to hospitals for acute illness or elective surgery but otherwise healthy.</td>
<td>Rates of breast cancer per 1,000 women per year: ( \text{nonusers: } 1.0 ) users for &lt; 25 months: 0.6 users for &gt; 25 months: 0.7 No dose-response relationship. Differences not statistically significant.</td>
</tr>
<tr>
<td>Ory et al. 1976</td>
<td>456</td>
<td>Cohort study. Rates of hospitalization for breast cancer compared in OC users and nonusers among 97,769 Boston area women. 137 cases diagnosed in 30 month period.</td>
<td>50% of cancer patients had used OCs compared with 45.6% of controls, not a significant difference. Significantly higher use of OCs was found among cancer patients who had used OCs for 2-4 years ( 10.9% \text{ (n=49) v. 6.2}% \text{ (n=53)} ); who had had BBN and had used OCs for more than 6 years ( 13.3% \text{ (n=8) v. 1.5}% \text{ (n=1)} ); who had used OCs before first childbirth ( 4.6% \text{ (n=17) v. 1.4}% \text{ (n=10)} ); but not among those who were nulliparous. &quot;The data presented here shed little new light on whether or how OCs may be carcinogenic, but neither do they clear these drugs of complicity.&quot;</td>
</tr>
<tr>
<td>Paffenbarger et al. 1975</td>
<td>164</td>
<td>Case-comparison study. Past or present OC use in 453 women under age 50 with breast cancer compared to use in 672 patients in medical and surgical departments in same hospitals, individually matched (2 controls per case) for age within 5 years, race, and religion.</td>
<td>38.8% (n=125) of cancer patients had used OCs compared with 38.6% (n=156) of controls. No significant differences in OC use among case and comparison groups as wholes or by length of use, by time since first use, by parity (nulliparous or parous), by age (under 36 or older), or by OC brand. Only 7.5% had begun OC use 6 or more years before developing cancer. Only 14.3% had used OCs for more than 2 years.</td>
</tr>
<tr>
<td>Royal College of General Practitioners 1974</td>
<td>498</td>
<td>Cohort study. Compared 34,875 woman-years of OC use to 42,306 woman-years of experience in nonusers matched to users for marital status (all married) and age (within 3 years), 9,853 woman-years of experience by women who stopped taking OCs during the course of the study were also analyzed.</td>
<td>11 cases of breast cancer observed in current users—standardized rate: 0.36 per 1,000 woman-years. 4 cases in ex-users—rate: 0.42. 18 cases in controls—rate: 0.34. &quot;The number of cases of breast cancer, though still small, is not negligible and shows no evidence of an association with pill usage.&quot;</td>
</tr>
<tr>
<td>Vessey et al. 1975</td>
<td>585</td>
<td>Case-comparison study. OC use by 322 married cancer patients aged 16-45 compared with use in 412 controls chosen from acute medical or surgical patients at same London hospitals and matched for age within 5 years and parity (groups of 0, 1-2, and 3 or more births).</td>
<td>No statistically significant trend. &quot;Certainly . . . the present investigation provides no evidence of any carcinogenic effect of OCs.&quot;</td>
</tr>
<tr>
<td>Vessey et al. 1976</td>
<td>586</td>
<td>Cohort study. Reports frequency and incidence rates of breast cancer in 17,032 white British women aged 25-39. 56.6% used OCs at the time of entry into the study (followed for 31,076 woman-years), 26.8% used diaphragms (followed for 14,735 woman-years), and 18.6% used IUDs (followed for 10,014 woman-years).</td>
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</tr>
<tr>
<td>Author &amp; Date</td>
<td>Ref. No.</td>
<td>Description</td>
<td>Findings</td>
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<tr>
<td>Boston Collaborative Drug Surveillance Program 1974</td>
<td>53</td>
<td>Case-comparison study. Estrogen use among 51 postmenopausal women aged 45-69 identified through area hospital surveillance compared with use among 774 controls aged 45-69 admitted to the same hospitals during the surveillance period for acute illness, elective surgery, or orthopedic treatment.</td>
<td>4 of 51 cancer patients used estrogens (age standardized rate: 9%) compared with 63 of 774 controls (age standardized rate: 8%), not a significant difference.</td>
</tr>
<tr>
<td>Burch et al. 1976</td>
<td>66</td>
<td>Cohort study. Occurrence of breast cancer in 1,000 hysterectomy patients who received estrogens, most for over 5 years, and who were followed for a total of 14,318 woman-years, compared with expected incidence based on data for another region of the southern USA.</td>
<td>33 developed breast cancer compared with 23.7 expected; 6 died of breast cancer, compared to 7.8 expected.</td>
</tr>
<tr>
<td>Casagrande et al. 1976</td>
<td>77</td>
<td>Case-comparison study. Use of exogenous estrogens compared in two sets of cases and controls: 100 women aged 50-64 at diagnosis of breast cancer, each matched by age and socioeconomic status with a woman chosen from the files of the case's physician, and 47 cases aged 50-59 at diagnosis and neighborhood controls in same age group (no controls found for 16 patients).</td>
<td>Limiting analysis to only those with natural menopause, in first group, 57% (24/43) of cases used estrogens compared to 74% (39/53) of controls; in second group, 79% (25/33) of cases were users compared to 59% (16/27) of controls. For groups combined, relative risk was 1.2. Duration of use about the same in cases and controls. Likelihood of using estrogen depended on age and age at meno¬pause, reflecting increasing use of estrogen in southern California (USA) area where study was conducted.</td>
</tr>
<tr>
<td>Hoover et al. 1976</td>
<td>265</td>
<td>Cohort study. Occurrence of breast cancer in 1,981 menopausal users of conjugated estrogens [all patients seen in a Louisville Kentucky (USA) private practice since 1939], followed for an average of 12 years, was compared to expected incidence among women of same race and age (5-year age groups) based on data from 2 surveys of incidence in U.S. cities.</td>
<td>49 cases observed, 39.1 expected. Risk increased with &quot;interval from first exposure, particularly after 10 years' follow-up ... &quot; (n=23 observed, 14.1 expected). No relationship to total dose detected. &quot;The risk among women with [benign breast] disease diagnosed after they started taking estrogen&quot; 7 times that of general population. Risk greater for those following regimens of other than daily administration and for those using higher doses. Relative risk (rate ratio) compared to white Southern (USA) women: 1.2 after 10-12 years follow-up; 1.9 after 13-16 years follow-up; 2.0 after 17-24 years follow-up.</td>
</tr>
<tr>
<td>Mustacchi &amp; Gordan 1958</td>
<td>415</td>
<td>Cohort study. Occurrence of breast cancer in 120 white women, average age 61.8 at beginning of therapy, who received cyclic estrogen therapy for osteoporosis and were followed for 601 woman-years, compared with expected incidence as calculated from age-specific cancer rates for 2 areas in USA, 1947-1948.</td>
<td>5 or 6 cancers of all sites would have been expected, but no cancers occurred.</td>
</tr>
<tr>
<td>Teter 1976</td>
<td>566</td>
<td>Occurrence of breast cancer in 2,211 menopausal women receiving a variety of estrogens cyclicly, with a progestin given at the end of each cycle, during 11,055 patient-years, compared with expected rate based on incidence rates for Warsaw, Poland.</td>
<td>3 cases of breast cancer and 1 of endometrial cancer occurred, whereas 31.3 were expected.</td>
</tr>
<tr>
<td>Wilson 1962</td>
<td>604</td>
<td>Cohort study. Occurrence of breast and genital cancers in 304 women aged 40-70 who received estrogen for an average of 7.8 years (total: 2,387 woman-years of exposure for breasts) compared with expected number based on data from Mustacchi &amp; Gordan (415).</td>
<td>18 mammary and genital cancer cases expected, but none occurred.</td>
</tr>
<tr>
<td>Author &amp; Date</td>
<td>Ref. No.</td>
<td>Hormone</td>
<td>Description</td>
</tr>
<tr>
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<td>-------------</td>
</tr>
<tr>
<td><strong>MICE</strong></td>
<td></td>
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</tr>
<tr>
<td>Coezy 1976</td>
<td>90</td>
<td>Enovid®, Ovulen®, Lutestral®, and components</td>
<td>daily oral doses, various doses; groups of 30-35, high incidence strain</td>
</tr>
<tr>
<td>Coezy &amp; Rudali 1970</td>
<td>91</td>
<td>Ovulen</td>
<td>daily oral doses, 7.5 µg; groups of 60-70; high incidence strain</td>
</tr>
<tr>
<td>Committee on Safety of Medicines 1972</td>
<td>94</td>
<td>OC components, separately and in combination</td>
<td>daily oral doses, 2-5 µg; 50-150, 200-400 times human body weight equivalent dose, for 90 weeks; 7,000 mice; groups of 40; low incidence strain</td>
</tr>
<tr>
<td>Drill 1974</td>
<td>133, 134</td>
<td>Enovid, Enovid-E®, Demulen®, and components</td>
<td>daily oral doses, 2-5-200 times human body weight equivalent dose, for 56 weeks; groups of 40; low incidence strain</td>
</tr>
<tr>
<td>Heston et al. 1973</td>
<td>253</td>
<td>Enovid</td>
<td>daily oral doses, 10, 20, 40 µg from age 4 weeks; 5 high and low incidence strains; groups of 56</td>
</tr>
<tr>
<td>Rudali et al. 1972</td>
<td>500</td>
<td>Enovid, Ovulen, Lutestral, and progestins</td>
<td>daily oral doses, various doses; from age 4 weeks; groups of 30-35; 3 high incidence strains</td>
</tr>
<tr>
<td><strong>RATS</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Committee on Safety of Medicines 1972</td>
<td>94</td>
<td>OC components, separately and in combination</td>
<td>daily oral doses, 2-5 µg; 50-150, 200-400 times human body weight equivalent dose, for 304 weeks; 6,500 rats; groups of 40</td>
</tr>
<tr>
<td>Drill 1974</td>
<td>133, 134</td>
<td>Enovid, Ovulen, Demulen, Enovid-E, and components</td>
<td>daily and cyclic oral doses, 2-1,000 times human body weight equivalent dose, for 90 weeks; groups of 35-60</td>
</tr>
<tr>
<td>Gruenstein et al. 1964</td>
<td>227</td>
<td>Enovid</td>
<td>intragastric doses, 5 mg, for up to 50 weeks, alone or prior to and concurrent with 3-MCA treatment; groups of 21-54</td>
</tr>
<tr>
<td>McKinney et al. 1968</td>
<td>380</td>
<td>ethinyl estradiol, megestrol acetate, BDH-2700, separately and in combination</td>
<td>average daily and cyclic oral doses, 53 µg (BDH-2700, ethinyl estradiol), 2.63 µg/kg (megestrol acetate); groups of 40</td>
</tr>
<tr>
<td>Rieche 1971</td>
<td>492</td>
<td>C-quinns® [chlormadinone acetate (CA) + mestranol (ME)]</td>
<td>intragastric doses, 50 µg (CA), 1.7 µg (ME) for 6 months after DMBA treatment; groups of 78-98</td>
</tr>
<tr>
<td>Schardein et al. 1970</td>
<td>508</td>
<td>Norlestrin®</td>
<td>daily oral doses, 10 and 100 times human body weight equivalent dose, for 2 years; groups of 50</td>
</tr>
<tr>
<td><strong>DOGS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drill 1974</td>
<td>133, 134</td>
<td>Enovid-E, Ovulen</td>
<td>cyclic dosages, 1, 10, and 25 times human body weight equivalent dose; groups of 16</td>
</tr>
<tr>
<td>Finkel &amp; Berliner 1973</td>
<td>170</td>
<td>several OCs and components</td>
<td>cyclic oral doses, 1-10, and 25 times human body weight equivalent dose, for 5 years; groups of 12-20</td>
</tr>
<tr>
<td>Wazeter et al. 1976</td>
<td>594</td>
<td>ethynodiol, mestranol, Wy-4355, anages tone acetate, separately and in combination</td>
<td>cyclic doses, 2, 10, and 25 times human body weight equivalent dose, for 7 years</td>
</tr>
</tbody>
</table>
Certain endogenous estrogen fractions have been cited as carcinogenic and another as anticarcinogenic \( (93, 325, 530, 531) \) on the basis of several factors: the epidemiology of breast cancer, including the observation of some protective effect against breast cancer conveyed by first birth at a young age \( (357) \); the results of animal studies \( (113, 317, 318) \); and by basic biological data about the availability of estrogen fractions \( (306, 615) \), by a recent epidemiologic study \( (291) \), and by comparisons of hormone levels in women with cancer and those without \( (326, 366) \) and among populations with differing breast cancer incidence rates \( (125, 356) \). This theory has received much attention from researchers studying exogenous hormones and breast cancer (as well as endometrial cancer), but it is contradicted by other comparative studies of hormone levels \( (306, 615) \), and by basic biological data about the availability of estrogen fractions to breast tissue \( (341) \). While the three estrogen fractions may play differing roles in the development of breast cancer, the nature of those roles is far from determined \( (306, 341, 615) \). The application of theories about endogenous estrogen fractions to exogenous estrogens or to oral contraceptives seems premature. Three other hormones—andro gens \( (65, 66) \), progestrone \( (525) \), and prolactin \( (539) \)—have all been suspected of playing a role in breast cancer development, but none has been confirmed \( (306, 341) \). Much more study is needed before theories about the role of hormones in breast cancer can be applied to help prevent breast cancer or to predict which women are at high risk \( (355) \).

### Mammary Neoplasms in Animals

Although it appears certain some hormones can effect the development of breast neoplasms in animals, the results of the many studies published are conflicting. Thus, definitive general statements are not possible. Some studies have reported changes in mammary tumor incidences after the administration of estrogen or oral contraceptives to mice, rats, and dogs, but not monkeys \( (136, 367) \) (see Table 6). It can be argued that species differences make rodents and dogs poor models for human breast cancer. The Old World monkeys, which menstruate cyclicly like humans, may be better models, but their mammary development differs from that in humans. Tumor types in humans also differ from those in other species. For example, the most common form of breast cancer in women—scirrhous carcinoma—does not occur in rodents or dogs \( (555) \).

#### Table 6—(cont.)

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Ref. No.</th>
<th>Hormone</th>
<th>Description</th>
<th>Effect on Tumor Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drill et al. 1974</td>
<td>139</td>
<td>Enovid-E</td>
<td>cyclic oral doses, 1, 10, and 50 times human body weight equivalent dose, for 5 years; groups of 16</td>
<td>no increase</td>
</tr>
<tr>
<td>Finkel &amp; Berliner 1973</td>
<td>170</td>
<td>several OCS and components</td>
<td>cyclic oral doses, 1, 10, and 50 times human body weight equivalent dose, for 5 years</td>
<td>no increase</td>
</tr>
<tr>
<td>Kirschstein et al. 1972</td>
<td>307</td>
<td>Enovid</td>
<td>daily oral doses, 1 mg, for 18 months; 8 animals</td>
<td>1 tumor, similar to human breast cancer, in 1 treated animal; possibly spontaneous</td>
</tr>
<tr>
<td>Wazeter et al. 1976</td>
<td>594</td>
<td>ethinylerone, mestranol Wy-4355, anagastro acetate, separately and in combination</td>
<td>cyclic doses, 2, 10, and 50 times human body weight equivalent dose, for 7 years</td>
<td>no increase</td>
</tr>
</tbody>
</table>

* Incidence of tumors in control groups varied \( (94, 138) \).
* 3-methylcholanthrene (known chemical carcinogen).
* 7,12-dimethylbenz(a)anthracene (known chemical carcinogen).

**Mice.** Three factors appear to be important in the induction and growth of breast tumors in mice: virus, heredity, and hormonal environment \( (136) \). The Mammary Tumor Virus (MTV) is transmitted from one generation to the next through the milk of the nursing mother \( (43, 44) \). Strains of mice which harbor the virus exhibit a high incidence of spontaneous breast cancer—as much as 100 percent—while virus-free strains have a low incidence \( (43) \). Similar viruses have been found in human milk and breast cancer tissue \( (402, 511) \), but no direct evidence links them to human breast malignancies. A hereditary factor, operating independently of the virus, also seems important in mice \( (29, 39, 41, 42, 154, 251, 252, 409, 526) \), but little is known of its mechanism. The hormonal factor was first recognized in 1916, when A. Lathrop and L. Loeb reported that ovariectomy greatly decreased the incidence of spontaneous tumors in mice \( (322) \). In the 1930s A. Lacassagne discovered that ovarian extracts could induce mammary cancer in males of some strains \( (316, 317, 318) \). His studies were followed by many experiments \( (34, 126, 185, 193, 367) \) showing that estrogens will induce mammary cancer in a significant number of males of high incidence (virus-carrying) strains \( (40, 48, 69, 70, 94, 109, 133, 134, 136, 182, 194, 394, 501, 526, 527, 559, 575) \). Females of high incidence strains already exhibit a high incidence, and it is not affected by estrogen. Both males and females from low incidence (virus-free) strains develop few spontaneous tumors, and incidence is not affected by estrogens \( (48, 409, 559) \). With progesterone administered alone varied effects have been observed \( (71, 133, 134, 245, 318, 409, 571) \).

Oral contraceptives such as Enovid® and Ovulen®, with several exceptions, have elicited no significant increase in the incidence of mammary tumors in either high or low incidence mouse strains (see Table 6).
Rats. The etiology of mammary neoplasia in rats is not as well understood as that in mice. Strain differences can be observed (150, 151, 152, 523) and viruses may play a role (14, 47), but the only factor studied extensively has been hormone administration (115, 193, 353, 523). Results of these studies varied widely. Estrogens have induced tumors in most strains (80, 94, 112, 113, 145, 146, 147, 148, 149, 150, 152, 158, 196, 197, 198, 353, 377, 433, 444, 445). Changing certain variables—dosage, administration of estrogen along with a known carcinogen, or combination with progesterone—may result in an indication of no effect on tumor incidence or even of suppression of tumor growth (59, 73, 227, 275, 277, 522, 560). Oral contraceptives have not been found to alter tumor incidence in rats except in two studies, where an increase was observed under some conditions (see Table 6).

Unlike mouse mammary tumors, tumors in rats, whether spontaneous, carcinogen-induced (112, 113, 115, 118, 272, 274, 433, 441, 442, 444) or estrogen-induced, tend to be hormone dependent, as are some human breast cancers (556). Since some rat and some human breast tumors are similar in their hormone dependence, studies on rats may help researchers understand and treat these tumors in women (116, 117, 273). At the same time, there are species differences in breast tissue response to sex hormones and in tumor growth characteristics (444).

Dogs. Several progestins used in oral contraceptives have been removed from the market or their use limited in several countries (1, 4, 33, 170) due to reports that female dogs given these compounds showed an increase in mammary tumor incidence (see Table 8). The decisions, and the reports which prompted them, have caused much controversy. The debate centers on two issues. The first concerns the susceptibility of beagles to progestin-induced tumors.

It has been argued that species differences in the effect of progesterone on target tissues and in the metabolism of progestins are so great that beagles are unreliable as predictors of human neoplastic response to progestins (58, 256, 314, 427, 426, 463). The second issue concerns the type of mammary tumors which appear in the progestin-treated dogs. Although some tumors in the beagle, both spontaneous and progestin-induced, seem comparable to human tumors (106, 555), the most common progestin-induced lesion—the mixed mammary tumor—is very rare in humans (6, 428, 555) and other animals (430). The unique appearance of the mixed mammary tumor in the dog raises the possibility of differences between humans and dogs not only in the endocrine system but also in the origin and nature of breast neoplasms.

WHO MEETING

A World Health Organization (WHO) Scientific Group will meet in Geneva, Switzerland to review the results of ongoing studies involving the possible relationships between hormonal contraceptives and benign, as well as malignant, tumors of the breast, cervix, uterus, and liver.

The meeting is scheduled for December 5-9, 1977.

Monkeys. All neoplasms in monkeys are of special interest due to their close phylogenetic relationship to humans. They are not the perfect laboratory animals, however. The problems of housing and caring for them limit the number of subjects, so that only large differences in incidence could be detected. And, while Old World monkeys menstruate cyclically, as do humans, there are species differences in breast development—the breasts of monkeys develop at pregnancy, not at puberty (479). Furthermore, spontaneous and induced tumors are relatively rare in the nonhuman primate, leading some to suggest that monkeys are impractical as laboratory animals (170). Both estrogens (159, 199, 200, 241, 279, 471) and oral contraceptives have failed to elicit an observable increase in tumor incidence in monkeys (see Table 6). A case of mammary carcinoma very similar in appearance and clinical progression to human breast cancer has been reported in an animal treated with an oral contraceptive (307). It is not possible to determine whether the tumor was spontaneous or hormone induced.

CERVICAL NEOPLASMS

Malignant and Premalignant Lesions. Studies of cervical cancer and its precursors in users of oral contraceptives have produced varied results. Most found no link between the use of orals and the risk of developing malignant or premalignant cervical neoplasms, but several have reported a positive relationship and several, a negative relationship. The special difficulties of epidemiologic studies of cervical cancer may help account for the variability in the results. At first glance, cervical lesions would appear easy to study, since Papanicolou smears make possible rapid screening of large populations. This may be one reason that cervical cancer and its precursors are the most studied of lesions in oral users—over 30 epidemiologic studies have been published (388). However, the lack of agreement about the diagnostic definitions (459) and progression of precancerous lesions makes interpretation of results difficult and introduces the potential for bias, as does the inability, in most studies to date, to account for the most important variable known to affect the risk of developing cervical cancer—age at first coitus (388).

Women whose first coital experience takes place during adolescence are more likely to develop cervical cancer than those who begin intercourse later (25, 368, 495). If women who begin intercourse at an early age are more or less likely to choose oral contraceptives than women who start intercourse when they are older, studies which do not account for age at first coitus would be biased. The only study of age at first coitus and contraceptive choice found little difference in average age at first coitus among groups using different contraceptive methods (387), but contraceptive choice among those who had their first coital experience during the apparently most critical years—early adolescence—was not analyzed separately. Other studies have raised the possibility that, for unknown reasons, women at higher risk of cervical lesions tend to choose oral contraceptives more often than other women (190, 552). Still, other studies have found no such relationship (457, 529). (See Table 7.)
Table 7—Neoplasms of the Uterine Cervix and Oral Contraceptive (OC) Use, Selected Studies, 1970-1976

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Ref. No.</th>
<th>Description</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Weber & Boyce et al.  | 1972     | 55 Case-comparison study: Frequency of OC use in 196 women with cervical cancer compared to frequency in 196 controls without cervical cancer matched for age, ethnic group, age at first coitus, age at first pregnancy, and socioeconomic status.                                                                 | “The frequency of abnormal cytologic findings, epithelial dysplasia, carcinoma in situ, invasive carcinoma in the cervix uteri, as well as of false positive cytologic findings . . . did not differ significantly between users of [OCs] and users of other contraceptive methods” as a whole or when divided by 5-year age groups, number of pregnancies, age at first pregnancy, or all these factors combined with socioeconomic status. Only significant difference was higher frequency of abnormal cytology in middle-class OC users than in nonusers, probably a chance finding. 93 controls had used OCs compared to 103 cases; duration of OC use among controls—2,262 woman-months; among cases—2,239 woman-months. Average duration of use, 22 months in both groups. Differences not statistically significant. 2,249 changed status at least once; progression among OC users—55.5%; among nonusers—55.2%. 1,265 changed status at least twice; progression among users—37.5%; among nonusers—47.1%. 650 changed status 3 times; progression among users—46.1%, among nonusers—47.1%. “There was no significant difference in the pattern of progression and regression between oral and non-oral groups. Oral contraceptives do not aggravate the conditions which lead to development of premalignant lesions in the uterine cervix.” Significantly higher rates of carcinoma in situ were found in 2 groups—women who had 2 or more children, were under age 30, and had used OCs (2.3 times rate in similar nonusers), and women who had 2 or more children, were over age 40, and had not used OCs (2 times rate in similar users). A significantly higher rate of invasive cancer was found in women over age 30 who had not used OCs (2.9 times rate in similar users; only 3 invasive cases occurred in women under age 30). “It is not known why the young multiparous women on [OCs] should show a significant increase in prevalence of carcinoma in situ, but it is tempting to suggest that the increase is due to an increase in early and possibly sustained sexual activity.” New cases of carcinoma in situ (after true negative smears): 0.15 per 1,000 users, 0.38 per 1,000 nonusers.  
Incidence per 1,000 woman-years of use: |
<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Ref. No.</th>
<th>Description</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller 1973</td>
<td>393</td>
<td>OC users (n=2,394) from a Connecticut (USA) town were matched with non-users of same age (within 2 years) otherwise chosen at random from 16,175 nonuser residents of the same town. Although most women were screened more than once, the most abnormal cytologic finding for each woman was recorded and the number of users and non-users of each cytologic status was compared. Average duration of OC use: 49.1 months.</td>
<td>Found remarkable similarities between the test and control group in each age bracket.</td>
</tr>
<tr>
<td>Ory et al. 1975</td>
<td>459</td>
<td>Case-comparison study. Incidence and duration of OC use among 147 women with carcinoma in situ and 854 with dysplasia after 2 previous normal Pap smears were compared with incidence and duration of use of OCs in 8,553 with at least 3 consecutive normal smears. All women were aged 15-44, black, and used either OCs or IUDs.</td>
<td>No significant differences in occurrence or duration of past or present OC use between cancer patients and controls. 28% of the OC users or former users with cancer had used OCs for 3-6 years, compared to 15.3% of OC users among controls. Difference is not significant due to small numbers.</td>
</tr>
<tr>
<td>Sandmire et al. 1976</td>
<td>504</td>
<td>Case-comparison study. OC use by 76 women with abnormal Pap smears who were later found to have cervical cancer (invasive or in situ) compared to OC use in 780 controls selected at random from records of 40,211 consecutive smears.</td>
<td>The findings here should not imply this hormonal therapy is completely safe. The data do indicate that if there is an adverse effect, the incidence is low and the potential lesion may require many years to develop.</td>
</tr>
<tr>
<td>Thomas 1972</td>
<td>569</td>
<td>Case-comparison study. Frequency of OC use among 378 women aged 15-50 with cytology suggestive of cervical neoplasia (Paps III, IV, or V) but without invasion compared to OC use in 360 controls, a 1 in 30 probability sample of the white women aged 15-50 living in the same Maryland (USA) county who had smears taken during the same time period (1965-1969).</td>
<td>No significant differences in occurrence or duration of past or present OC use between cancer patients and controls. 28% of the OC users or former users with cancer had used OCs for 3-6 years, compared to 15.3% of OC users among controls. Difference is not significant due to small numbers.</td>
</tr>
<tr>
<td>Vessey et al. 1976</td>
<td>586</td>
<td>Cohort study. Reports incidence rates of carcinoma in situ and dysplasia and number of cervical cancer cases in 17,032 white British women aged 25-39, 56.6% of whom used OCs at the time of entry into the study (followed for 31,076 woman-years), 24.8% used diaphragms (followed for 14,739 woman-years), and 18.6% used IUDs (followed for 10,014 woman-years).</td>
<td>Incidence per 1,000 woman-years of follow-up standardized for age, social class, parity, and smoking habits:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytology</th>
<th>Users</th>
<th>Nonusers</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>1,800</td>
<td>1,775</td>
</tr>
<tr>
<td>mild atypia</td>
<td>580</td>
<td>603</td>
</tr>
<tr>
<td>suspicious</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>malignant</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

"The findings here should not imply this hormonal therapy is completely safe. The data do indicate that if there is an adverse effect, the incidence is low and the potential lesion may require many years to develop."

"When data were controlled for possible confounding variables, likelihood of OC use associated with carcinoma in situ rose linearly with duration of use. For those who had used OCs for more than 36 months, likelihood was almost 5 times that of IUD users. Risk of dysplasia rose somewhat linearly with duration of use. For those who had used OCs for 2-3 years, likelihood was 1.9 times that for IUD users. Both trends significant. "The substantial variation in the histologic diagnosis of carcinoma in situ prevents us from making any firm biologic interpretations...""
The association of high risk of cervical malignancy with coitus during adolescence and with several partners (368, 495) suggests the possibility that factors other than hormones play the primary role in the development of cervical cancer. The epidemiologic patterns of cervical cancer have encouraged a search for some carcinogenic agent which might be transmitted by coitus and for explanations of the apparent high susceptibility of cervical epithelium during adolescence. Under suspicion as sources of DNA which might initiate malignant changes in cervical cells are the virus herpes genitalis (HSV 2) (5, 19, 20, 28, 104, 239, 419, 420, 421, 423, 424, 482)—a venereally transmitted virus which causes sores on the genitals (482)—and the sperm head itself (28, 104, 536). If cervical cancer is caused by a venereally transmitted agent, barrier methods of contraception may protect against it, as several epidemiologic studies suggest (56, 384, 385, 586). A hypothesis about susceptibility during adolescence is that active metaplasia—the normal process of squamous epithelium developing in the place of columnar epithelium exposed to the vaginal environment (see Fig. 2) (75, 171, 589)—takes place at this time, as well as prenatally and during the first six months of pregnancy (101, 102, 535), and that during this period of cellular activity contact between cellular and foreign DNA is more frequent (104, 490, 536). Metaplasias showing signs of premalignancy have recently been observed in adolescents (101, 345, 534, 535).

While a venereally transmitted agent may prove to be the primary cause of cervical cancer, a secondary role for oral contraceptives has been hypothesized. One theory is that cervical mucus could serve as a more effective shield against a carcinogen when thickened by the action of oral contraceptives (57, 99, 101, 451). This effect might be especially important in adolescence when, because of a high proportion of anovulatory cycles, cervical mucus often remains thin and perhaps is structurally conducive to transporting a carcinogen (287). On the other hand, it has been suggested that, if oral contraceptives cause swelling of the cervix and consequent cervical "eversion," or turning out of the endocervix at the external os (see Fig. 2) (176, 180, 285, 287, 404, 585), this could trigger metaplasia (102, 104, 107) and increase tissue susceptibility. Limited data suggest that metaplasia may occur more often among users of oral contraceptives than among nonusers (see Benign Lesions). It is possible that both changes in cervical mucus and increased eversion would take place in users of oral contraceptives, and would cancel out each other's hypothesized influence on susceptibility to cervical cancer (99).

### Table 7—(cont.)

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Ref. No.</th>
<th>Description</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worth &amp; Boyes</td>
<td>505</td>
<td>Case-comparison study. OC use in 310 British Columbia (Canada) women aged 20-29 who had preclinical cervical cancer (all but 2 cases were carcinoma in situ) compared to OC use in 682 controls chosen because they were the next 3 patients of same age group with normal smears seen by each cancer patient's doctor. Mean interval from first OC use to entry into study was over 5 years for both cases and controls.</td>
<td>Percent who had used OCs:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20-24</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>25-29</td>
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<td></td>
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</tbody>
</table>

No significant differences. No significant difference by type of OC (combined or sequential).

### Benign Lesions

A variety of benign cervical lesions—some involving largely squamous cells, some largely columnar cells—have been reported in users of oral contraceptives. Four of five published epidemiologic studies suggest a positive relationship between oral contraceptive use and squamous metaplasia (see Table 8). Metaplasia is a normal process (171), possibly occurring under the influence of endogenous hormonal or physical changes (101, 102, 535), and probably not inherently a precursor of malignancy (75, 171). It has been theorized, however, that the fast-growing metaplastic cells, while sometimes remaining benign, could sometimes develop malignant changes (18, 64, 100, 269, 438, 588), possibly on exposure to a carcinogen (104, 176, 278, 438, 489, 534). Both the role of oral contraceptives in metaplasia and the relationship of metaplasia to malignancy must be better defined before conclusions can be drawn.

Adenomatous lesions, which consist mainly of mucus-containing cells like those of the columnar epithelium, may develop under the influence of the progestins in oral contraceptives (214, 437). They range in severity from polyps measuring up to several centimeters long, which are similar to those seen in pregnant women (76, 214, 435) and are rare, to gland-like cell arrangements, which may

---

**Fig. 2. Structures and tissues of the uterine cervix.**
be relatively common (437). The tissue structure of adenomatous lesions may look like cancer (72, 217, 468, 564, 602), but an examination of the cells shows that they are benign (11, 72, 564). Adenomatous lesions usually (11, 217, 468, 602), but not always (437), regress soon after oral contraceptive use stops.

### Cervical Neoplasms in Animals

Little evidence exists, thus far, relating the administration of oral contraceptives to laboratory animals to the development of cervical neoplasms.

**Mice.** Breeding has little effect on cervical cancer incidence in mice, implying less hormonal influence on the cervix than on the breast in this animal (514). However, induction of cervical neoplasms by estrogen has been reported since the mid-1930s (7, 110, 132, 181, 184, 187, 188, 193, 319, 347, 348, 394, 465, 466). The reported tumors appeared at low rates, were of questionable malignancy, and occurred for the most part only after direct application to the cervix (181, 184, 191, 193). Since cervical carcinoma is rarely seen in control animals, it is reasonable to assume that estrogen played some role in the promotion of these neoplasms. The effect of progesterone on tumor incidence has varied (155, 207, 296, 488), but some studies suggest that it may have an effect on the type of tumor which appears (207, 296). Oral contraceptives have not generally increased the incidence of cervical cancer with the exception of possibly malignant lesions induced in one strain by Enovid (see Table 9).

**Rats.** The few studies available involving the rat indicate that neither estrogen (208, 380) nor oral contraceptives (see Table 9) stimulate tumor growth.

**Monkeys.** Cervical cancer, like other neoplasms, is rare in the monkey (302), and oral contraceptives have not thus far produced any neoplasms (see Table 9). As with breast cancer, cervical cancer in monkeys seems very similar, histologically and developmentally, to human cervical cancer (263), with metastases to the bladder, lymph nodes, and lungs. Early studies with natural estrogens produced some reports of squamous metaplasia arising in the cervix of monkeys and of some lesions diagnosed as precancerous (159, 161, 241, 264, 279, 462). Many metaplasias regressed after hormone treatment stopped. They may not have been as ominous as early investigators supposed (216). Estrogen, however, used in conjunction with a chemical carcinogen, produced dysplasia—considered possibly precancerous—in four out of eight rhesus monkeys (294).

### NEOPLASMS OF THE UTERINE CORPUS

**Endometrium.** Suspicions that endometrial cancer might be linked to the sequential form of oral contraceptives have been aroused by recent case reports from the USA (92, 297, 299, 350, 532, 533). Sequential, consisting of estrogen alone for most of the cycle with a progestin added for a few days at the end of the cycle, were used by most of the women whose cases have been reported. In the USA, however, sequentials comprised only 5 to 10 percent of the oral contraceptives sold in recent years (3). The association between endometrial cancer and use of sequential oral contraceptives in some of the reported cases may be explained by the fact that they were often prescribed to control abnormal uterine bleeding—bleeding perhaps due to undiagnosed endometrial neoplasia. However, in a series of 30 cases of endometrial cancer in oral users under age 40, few of the sequentials users had any of the common characteristics of premenopausal women who develop endometrial cancer—nulliparity, obesity, and cystic ovaries. Users of combined orals, on the other hand, exhibited these traits about as frequently as did nonusers under age 40 whose cases were reported in other series, implying that endometrial cancer and use of combined orals was coincidental (533). Of all reported cases involving sequentials, nearly all occurred in women using one particular regimen—100 µg daily of the estrogen ethinyl estradiol for 21 days, with 25 µg of the progestin medroxyprogesterone added during the last 5 days. Analytic epidemiologic studies which could provide stronger evidence about the role of sequentials have not been published, and they will now be more difficult to conduct, at least in North America, because pharmaceutical companies have withdrawn sequential contraceptives from U.S. and Canadian markets (533) as a result of the case reports and because sequentials are less effective in preventing pregnancy than combined orals.
A recent investigation found that the incidence of endometrial hyperplasia may increase with the length of time sequential oral contraceptives have been used (315). Hyperplasia is a proliferation of the endometrium which seems to take place under continued stimulation with estrogen. If estrogen stimulation does not stop or is uninterrupted by progesterone or progestin, hyperplasia may proceed to atypical adenomatous hyperplasia, carcinoma in situ, and eventually endometrial cancer (234, 309, 543); about 10 percent of adenomatous hyperplasias proceed to cancer (232).

Menopausal Use of Estrogens

Recent U.S. studies suggest that estrogen taken alone during and after menopause increases the risk of developing endometrial cancer. These studies, conducted by the case-comparison method, found that women with endometrial cancer were several times more likely to have used estrogens than were similar women who did not have endometrial cancer (see Table 10). Three found that the longer the estrogen use, the higher the risk of cancer (352, 375, 611). Increasing use of estrogen to treat symptoms of menopause has been blamed for the increasing incidence of endometrial cancer in older women noted by some U.S. cancer registries (596).

Although some of the case-comparison studies on endometrial cancer have been criticized on several grounds, including possible case-finding bias (213, 268, 541), insufficiently matched controls (96, 213, 541), misdiagnosis (96, 213, 220), prescription bias (if estrogens were prescribed to treat bleeding irregularities which were symptoms of undiagnosed disease) (213), and lack of sufficient time between estrogen exposure and detection of the disease (211, 519, 520), there is, nonetheless, other evidence consistent with the results of the case-comparison studies which suggests that administration of estrogens alone may play some role in the development of endometrial cancer. Such evidence includes:

- case reports of endometrial cancer in women who had taken estrogens for many years because they lacked functioning ovaries (124, 283, 321);
- case reports of endometrial hyperplasia in other women treated with estrogens for long periods (61, 174, 231, 582);
- suggestions that women who often fail to ovulate may face a higher than usual risk of hyperplasia and of endometrial cancer, possibly because of a lack of progesterone to counteract estrogen stimulation (167, 309, 349, 542);
- case reports suggesting that endometrial cancer may occur more frequently than usual in women with ovarian tumors which produce estrogen (233).

While data on estrogens alone are not directly relevant to oral contraceptives, they do suggest the importance of hormonal balance to avoid endometrial malignancy.

Progestins and Cyclic Administration

Progesterone and progestins, when given cyclically along with estrogens, may interfere with the development of cancer. While no epidemiologic studies have yet been conducted to compare endometrial cancer or hyperplasia rates in women using estrogens alone to rates in women using combined regimens, there is other evidence to suggest a protective role for progestins:

### Table 9—Effects of Oral Contraceptive (OC) Hormones on Cervical Tumors in Animals, Selected Studies, 1965-1976

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Ref. No.</th>
<th>Hormone</th>
<th>Description</th>
<th>Effect on Tumor Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MICE</strong></td>
<td></td>
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</tr>
<tr>
<td>Committee on</td>
<td>94</td>
<td>OC components, separately and in combination</td>
<td>daily oral doses, 2-5, 50-150, 200-400 times human body weight equivalent dose for 60 weeks; 7,000 mice, groups of 40</td>
<td>no increase in most groups; small increase in ethinyl estradiol groups</td>
</tr>
<tr>
<td>Safety of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drill</td>
<td>132</td>
<td>Enovid, Enovid-E, Ovulen, Metrulen, Demulen, and components</td>
<td>daily oral doses, 2.5-200 times human body weight equivalent dose for 18 weeks; groups of 40 males and 40 females</td>
<td>no increase in most groups; from 0 to 8% increase for ethinyl estradiol high dose groups</td>
</tr>
<tr>
<td>1976</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heston et al.</td>
<td>253</td>
<td>Enovid</td>
<td>daily oral doses, 10, 20, and 40 µg from age 4 weeks; 5 strains; groups of 56</td>
<td>increase in 1 strain only, high dose</td>
</tr>
<tr>
<td>1973</td>
<td></td>
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</tr>
<tr>
<td><strong>RATS</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Committee on</td>
<td>94</td>
<td>OC components, separately and in combination</td>
<td>daily oral doses, 2-5, 50-150, 200-400 times human body weight equivalent dose for 104 weeks; 6,500 rats, groups of 40</td>
<td>no increase</td>
</tr>
<tr>
<td>Safety of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drill</td>
<td>132</td>
<td>Enovid, Ovulen, Demulen, Enovid-E, and components</td>
<td>daily and cyclic doses 2-1,000 times human body weight equivalent dose for 80 weeks; groups of 35-60</td>
<td>no increase</td>
</tr>
<tr>
<td>1976</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schardein</td>
<td>508</td>
<td>Norlestrin</td>
<td>daily oral doses, 10 and 100 times human body weight equivalent dose for 2 years; groups of 50</td>
<td>no increase</td>
</tr>
<tr>
<td>et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1970</td>
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<tr>
<td><strong>MONKEYS</strong></td>
<td></td>
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</tr>
<tr>
<td>Kar et al.</td>
<td>295</td>
<td>Enovid</td>
<td>cyclic oral doses of 10 mg/60 kg body weight; 14 monkeys; up to 1,095 days</td>
<td>no increase</td>
</tr>
<tr>
<td>1965</td>
<td></td>
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</tr>
</tbody>
</table>
Table 10—Endometrial Cancer in Postmenopausal Women and Estrogen Use, Selected Studies, 1954-1977

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Ref. No.</th>
<th>Description</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunn &amp; Bradbury 1967</td>
<td>142</td>
<td>Case-comparison study. Estrogen use by 56 postmenopausal women with endometrial cancer (average age, 63.9 years) was compared to use by 53 women who had also appeared at the same U.S. hospital primarily for treatment of postmenopausal bleeding but who were diagnosed as having atrophic endometria (average age, 61.3 years). No adjustment for obesity and fertility differences.</td>
<td>28.6% of cancer patients recalled using estrogens, compared with 27.5% of comparison group. No relationship detected between cancer and duration of use or time of administration relative to menopause. Participants' recall not confirmed.</td>
</tr>
<tr>
<td>Gray et al. 1977</td>
<td>219</td>
<td>Case-comparison study. Estrogen use compared in 205 women with endometrial cancer and in 205 women, matched for year of diagnosis, age, and parity, who had had hysterectomies for benign uterine diseases. All women were patients in a single physician's practice between 1947 and 1976.</td>
<td>55 of cases and 31 of controls had used estrogen-containing medications (relative risk: 2.1). 32 and 12, respectively, had used conjugated estrogens (relative risk: 3.1). Relative risk increased with duration of use and strength of dose.</td>
</tr>
<tr>
<td>Jensen &amp; Østergaard 1954</td>
<td>284</td>
<td>Case-comparison study. Estrogen use by 105 women with endometrial cancer was compared to use by 52 women with diseases unrelated to endometrial cancer admitted to the same 2 Danish hospitals. 72 of the cancer patients were postmenopausal.</td>
<td>33.2% of the cancer patients “from whom such information was available” had used estrogens, compared with 21.2% of the controls.</td>
</tr>
<tr>
<td>Mack et al. 1976</td>
<td>352</td>
<td>Case-comparison study. 63 postmenopausal women with endometrial cancer were each matched by age, marital status, and date of entry into the community with 4 women without endometrial cancer and not hysterectomized (252 controls). Both cases and controls were residents of a retirement community with one medical care facility and one pharmacy.</td>
<td>Women with endometrial cancer were more likely to have used estrogen than were those without cancer. Risk ratios: any estrogen—8.0; conjugated estrogen—5.6; other estrogens—3.3. Risk increased with dose. Risk was lowest with cyclic administration of low doses. Risk ratio: 1.8.</td>
</tr>
<tr>
<td>McDonald et al. 1977</td>
<td>375</td>
<td>Case-comparison study. 145 women developed endometrial cancer in Olmsted County Minnesota (USA), between 1945 and 1974. Each was matched to 4 other female residents of the county with intact uteri who had received medical services at the county's medical facilities. Records of cases and controls were searched for prior estrogen use and other variables.</td>
<td>No significant difference in proportions of cases and controls using estrogen (27% v. 28%), but user-controls were short-term users, taking estrogens in pregnancy or for lactation suppression. Cases tended to be longer users, taking estrogens for menopausal symptoms and menstrual dysfunction. Cases more likely than controls to have used conjugated estrogens (CE). Risk increased with duration of CE use and size of daily dose. CE use more strongly associated with less aggressive cancer than with more aggressive.</td>
</tr>
<tr>
<td>Nachtigall et al. 1975</td>
<td>418</td>
<td>10-year prospective double blind study of 84 women receiving estrogen replacement therapy (included 10 mg daily of the progestin medroxyprogesterone acetate for 7 days a month) and of 84 controls, matched for diagnosis and age but receiving placebo.</td>
<td>No endometrial cancer in estrogen users, 2 cases in placebo users, both diabetic and obese (risk factors for endometrial cancer), but matched users were also diabetic and obese.</td>
</tr>
<tr>
<td>Smith et al. 1975</td>
<td>537</td>
<td>317 women over age 48 with endometrial adenocarcinoma were matched by age (within 4 years) with an equal number of women with other gynecological neoplasms who attended the same 2 Washington State (USA) hospitals. Information came from medical records. Dosage, specific estrogen, and treatment schedule not studied.</td>
<td>152 of the cases had used estrogens compared with 54 controls. (Relative risk: taking into account year and age at diagnosis, 7.5.) Estrogen users with endometrial cancer were less likely to be obese or hypertensive than nonuser cases. (Obesity and hypertension are considered risk factors for endometrial cancer.) Cancers were less likely to be severe in estrogen users, perhaps because they were detected earlier (96, 220).</td>
</tr>
<tr>
<td>Teter 1976</td>
<td>566</td>
<td>Occurrence of endometrial cancer in 2,211 Polish women using estrogens for 11,055 woman-years in a variety of regimens, most of them cyclic and including a progestin at the end of each cycle, compared to the expected rate calculated from incidence rates for women aged 40-69 in Warsaw, Poland.</td>
<td>1 case of endometrial cancer and 3 of breast cancer were observed, whereas a total of 31.3 were expected. &quot;The possible explanation for the observed low incidence of cancer is that progesterone or synthetic progestogen was always routinely added in the second part of the therapeutic cycle.&quot;</td>
</tr>
</tbody>
</table>
Women with apparently normal functioning corpora lutea, which produce progesterone, probably are less likely to develop endometrial cancer than women with ovulatory failure and, thus, no corpus luteum (230,349).

Progestins can cause the regression or disappearance of endometrial hyperplasia or carcinoma in situ (309); combined oral contraceptives have been used successfully to treat hyperplasia in premenopausal women (308).

Large doses of progestins cause remission of metastatic endometrial cancer in approximately 30 percent of cases (349). Among the progestins used this way is medroxyprogesterone acetate, also used as the injectable contraceptive Depo-Provera [see Population Reports K-1, "Injectable Progestogens—Officials Debate But Use Increases," March 1975].

The apparently beneficial effect of progestins has not been completely explained. At the cellular level it appears to result from the ability of progestins to reduce the number of molecular sites in the endometrial cell to which estrogens can bind, thus reducing estrogen's growth stimulus to the cell (349,573,574). On the tissue level, the relationship of cell lines to their environment may be analogous to the evolution of species as influenced by their environment (484). Some cells are likely to survive and reproduce better in one environment than in another. If the hormonal environment is unbalanced and unchanging, as happens in women with ovulatory failure or women who are taking estrogens alone continuously, lines of cells which respond to that environment by growing and reproducing at extremely rapid rates—malignant cell lines, in other words—would have a survival advantage over other cells. If progesterone or progestins are also present, however, the balance and interplay of the two hormones would discourage any one line of cells from obtaining an advantage and beginning uncontrolled growth (485). With combined oral contraceptives, cyclic administration assures periodic shedding of the endometrium, which may serve as "a physiological eraser of endometrial neoplasia" (484).

### Table 11—Effects of Oral Contraceptive (OC) Hormones on Endometrial Tumors in Animals, Selected Studies, 1965-1973

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Ref. No.</th>
<th>Hormone</th>
<th>Description</th>
<th>Effect on Tumor Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>MICE Committee on Safety of Medicines 1972</td>
<td>94</td>
<td>OC components, separately and in combination</td>
<td>daily oral doses, 2–5, 50–150, 200–400 times human body weight equivalent dose, for 80 weeks; 7,000 mice, groups of 40</td>
<td>no increase in most groups; increase for ethinyl estradiol and megestrol acetate, high dose</td>
</tr>
<tr>
<td>Heston et al. 1973</td>
<td>253</td>
<td>Enovid</td>
<td>daily oral doses, 10, 20, 40 μg, from age 4 weeks; 5 strains, groups of 56</td>
<td>no increase</td>
</tr>
<tr>
<td>RATS Committee on Safety of Medicines 1972</td>
<td>94</td>
<td>OC components, separately and in combination</td>
<td>daily oral doses, 2–5, 50–150, 200–400 times human body weight equivalent dose, for 104 weeks; 6,500 rats, groups of 40</td>
<td>no increase</td>
</tr>
<tr>
<td>McKinney et al. 1968</td>
<td>380</td>
<td>ethinyl estradiol, megestrol acetate, BDH-2700, separately and in combination</td>
<td>average oral doses, 53 μg–BDH-2700, 263 μg/kg—megestrol acetate, for 2 years; groups of 40; continuous daily or cyclic administration</td>
<td>no increase; adenomatous polyps observed</td>
</tr>
<tr>
<td>Schardein et al. 1970</td>
<td>508</td>
<td>Norlestrin</td>
<td>daily oral doses, 10 and 100 times human body weight equivalent dose, for 2 years; groups of 50</td>
<td>no increase</td>
</tr>
<tr>
<td>MONKEYS Kar et al. 1995</td>
<td>295</td>
<td>Enovid</td>
<td>cyclic oral doses of 10 mg/60 kg body weight, 14 monkeys, up to 1,095 days</td>
<td>no increase</td>
</tr>
</tbody>
</table>
Other Uterine Neoplasms. The Royal College of General Practitioners' cohort study in Great Britain found that users of oral contraceptives developed uterine fibroids at less than half of the rate of nonusers (498). Fibroids are benign tumors of the uterine musculature, without any tendency toward malignancy, which can cause heavy uterine bleeding and jeopardize the course of pregnancy. While not ruling out the possibility of a real protective effect from oral contraceptives, the study noted that women with fibroids are often subfertile and so would be less likely than other women to use orals. Also, oral contraceptives often reduce heavy menstrual bleeding, so fibroids might go undetected. These two factors may account for the observed difference in rates. Another British cohort study failed to find any significant difference in the incidence of uterine fibroids among users of orals, of diaphragms, and of IUDs (586).

Use of oral contraceptives soon after treatment of hydatidiform mole may increase the likelihood of developing a trophoblastic tumor, a recent British study suggests (557). Hydatidiform mole is an abnormality of early placentation development. In the USA, it occurs in approximately 1 in 2,000 pregnancies. It is treated by evacuating the contents of the uterus, after which some trophoblastic cells (those from the tissue surrounding the embryo) commonly persist in the uterus, occasionally for many months. The trophoblast usually regresses, but in 2 to 3 percent of cases carcinoma develops. For this reason women who have been treated for hydatidiform mole are monitored by analysis of urine levels of human chorionic gonadotropin (HCG). The fall of HCG to levels normal for nonpregnant women signifies regression of the trophoblast. In a series of 611 women treated for hydatidiform mole, almost 25 percent of 65 who took oral contraceptives before HCG levels had returned to normal required cytotoxic chemotherapy for trophoblastic tumor, compared with about 9 percent of the 464 who did not. Taking orals after HCG levels had returned to normal apparently did not affect the need for treatment.

Endometrial Neoplasms in Animals

The administration of oral contraceptives has not increased the incidence of endometrial neoplasms in any research animals, according to studies published to date.

Mice. The etiology of endometrial neoplasms in most laboratory animals is not known. Levels of estrogen and progesterone probably affect development of this type of cancer, but there is no agreement among researchers as to their exact effects (199, 190, 238, 296, 337, 348, 381, 394, 465, 466, 522, 601). Progesterone may affect the type of neoplasm induced by a known carcinogen (298). Oral contraceptives have had no tumorigenic effect (see Table 11).

Rats. Attempts to induce endometrial cancer in rats by administering estrogens (23, 45, 204, 237, 376, 379, 518, 603) or oral contraceptives (see Table 11) have been unsuccessful.

Guinea Pigs, Hamsters, and Rabbits. No studies of oral contraceptives and endometrial neoplasms have yet been reported. Some authors have observed that estrogen administration preceded the appearance of benign lesions, some of which were hormone dependent, in these species (21, 334, 335, 339, 392, 383, 403, 431, 432, 470, 473, 474, 483, 561, 597), while progestins caused the regression of existing tumors and inhibited induction of tumors by a known carcinogen in rabbits (225). Rabbits are of interest because spontaneous endometrial carcinoma is common and progression from hyperplasia to neoplastic growth, apparently similar to progression in humans, has been observed (222, 386). However, in other ways the reproductive system and process of the rabbit are quite different from those in humans (386).

Monkeys. As with all neoplasms in the monkey, few spontaneous endometrial carcinomas have been reported (302). Studies involving estrogen administration, even in high continuous doses, have been negative (111, 159, 160, 161, 199, 241, 261, 262, 279, 471, 513, 580, 614) with the exception of one group that reported tumors in the squirrel monkey. Some of these tumors were diagnosed as malignant (373). Similarities in the menstrual cycle—e.g., menstruation occurring on the average every 27 days and lasting for 3 to 5 days (263)—and possibly in hormonal interactions make some species of monkey promising models for the study of human uterine carcinoma.

Liver Tumors

Over 100 cases of benign liver tumors in women using oral contraceptives have been reported in the last 5 years (8, 9, 15, 18, 22, 26, 27, 31, 38, 78, 84, 87, 95, 119, 210, 247, 258, 267, 301, 311, 343, 360, 361, 369, 370, 371, 386, 399, 460, 461, 486, 509, 550, 570, 577, 579). Two case-control studies (156, 157, 454, 494), as well as other epidemiologic evidence (412, 579), suggest that certain types of benign liver tumors occur more frequently in users of orals, especially long-term users, than in nonusers. Despite the apparently much higher risk for long-term users, the actual number of women developing tumors remains quite low (588). The annual incidence of all types of benign liver tumors in U.S. women, both users and nonusers, has been roughly estimated at 0.5 per 100,000 (579). An estimate of 0.04 per 100,000 for an eastern U.S. urban area has been made (131).

The types of liver tumors apparently linked to oral contraceptive use are frequently referred to as hepatocellular adenomas and focal nodular hyperplasias (476, 524, 579). Adenomas are large vascular tumors. Tissue in them appears normal, but blood flow is abnormal. Focal nodular hyperplasia consists of multiple, gland-like nodules, also with abnormal blood flow (439, 546). Adenomas can be life-threatening because they can rupture, causing heavy bleeding into the peritoneal cavity (439). Focal nodular hyperplasia, on the other hand, often produces no symptoms (280, 546) and seldom leads to complications (312, 313, 546).

The risk of developing a benign tumor is greatest for long-term users of oral contraceptives (156, 157, 454, 494). In a series of 58 women for whom information was available, average duration of use was almost 5 years, and 85 percent had used orals continuously for more than 4 years (439). A U.S. national survey found that 40 percent of the cases in 110 years of orals involved more than 5 years of use (579).

Liver tumors have been reported in women who have used orals for as short a time as 4 months (85, 579), but whether short exposures could have a causal effect is questionable.
Both case-comparison studies have suggested that the risk of developing a hepatocellular adenoma increased consistently with duration of use of orals (156, 157, 454, 494), while the U.S. survey found that results concerning the duration of use associated with focal nodular hyperplasia divided into two categories: of 31 cases, 15 were associated with less than 2 years of use; 12, with more than 5 years of use (579).

In addition to the dose-response relationship involving hepatocellular adenoma observed in the case-comparison studies, evidence of a link between oral contraceptive use and hepatocellular adenoma and focal nodular hyperplasia includes:

- The age distribution of users with benign liver tumors approximates that of oral contraceptive users in the USA, with peak incidence occurring in the 20s; incidence among nonusers increases gradually with age (579).
- In the U.S. national survey of all types of liver tumors, three-quarters of those found in users were benign, whereas only about half were benign in female nonusers (579).
- Over 50 percent of all tumors reported in the survey occurred in users of oral contraceptives, while the proportion of women of reproductive age using oral contraceptives may be from one-quarter to slightly more than one-third (579).

- Characteristics which are associated with hepatocellular adenomas in nonusers—hospitalization for gall bladder disease, uterine fibroids, and removal of benign breast lumps—are not found as often in users who develop these liver tumors (494).
- In at least 4 women, who resumed use of oral contraceptives after surgery, hepatocellular adenomas recurred (370, 454).
- Benign liver tumors rarely occur in men (280, 546, 579), suggesting that female hormones are important to development of the tumors (546).

Several hypotheses are proposed to explain how oral contraceptive steroids could cause benign liver tumors (332, 440, 524, 545), most involving the metabolism of steroids by the liver, but just what role steroids play is not yet clear (85). Suspicion has focused on estrogens as the responsible agent (85, 157), and cases have been reported in users of estrogens alone (85, 524, 549). However, at least four cases have involved progestins alone (440), although, of course, any of them may be coincidental. Several reports have hypothesized that mestranol was more likely to cause liver tumors than ethinyl estradiol (157, 440), but the preponderance of mestranol use among users of oral contraceptives with benign liver tumors may reflect commercial market shares of the two estrogens during the 1960s (24, 85, 156, 163, 412, 576, 579).

### Table 12—Effects of Oral Contraceptive (OC) Hormones on Liver Tumors in Animals, Selected Studies, 1968-1976

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Ref. No.</th>
<th>Hormone Description</th>
<th>Effect on Tumor Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>MICE</td>
<td>Committee on Safety of Medicines 1972</td>
<td>94 OC components, separately and in combination</td>
<td>daily oral doses, 2-5, 50-150, 200-400 times human body weight equivalent dose for 80 weeks; 7,000 mice, groups of 40</td>
</tr>
<tr>
<td>Heston et al. 1973</td>
<td>253 Enovid</td>
<td>daily oral doses 10, 30, 40 μg from age 4 weeks; 5 strains, groups of 56</td>
<td>no increase, 4 strains; decrease, 1 strain</td>
</tr>
<tr>
<td>RATS</td>
<td>Committee on Safety of Medicines 1972</td>
<td>94 OC components, separately and in combination</td>
<td>daily oral doses, 2-5, 50-150, 200-400 times human body weight equivalent dose for 104 weeks; 6,500 rats, groups of 40</td>
</tr>
<tr>
<td>McKinney et al. 1968</td>
<td>380 ethinyl estradiol, megestrol acetate, BDH-2700, separately and in combination</td>
<td>average daily and cyclic doses, 53 μg (BDH-2700, ethinyl estradiol), 2.63 μg/kg (megestrol acetate) for 2 years; groups of 40</td>
<td>no increase, 4 strains; decrease, 1 strain</td>
</tr>
<tr>
<td>Schardein et al. 1970</td>
<td>508 Nortestren</td>
<td>daily oral doses, 10 and 100 times human body weight equivalent dose, for 2 years; groups of 50</td>
<td>increase in regenerative nodules and hepatocellular adenomas</td>
</tr>
<tr>
<td>DOGS</td>
<td>Wazeter et al. 1976</td>
<td>594 ethynodiol, mestranol, Wy-4355, anastrozol, acetate, separately and in combination</td>
<td>cyclic doses 2, 10, and 25 times human body weight equivalent dose; 7 years</td>
</tr>
<tr>
<td>MONKEYS</td>
<td>Wazeter et al. 1976</td>
<td>594 as above</td>
<td>cyclic doses 2, 10, and 50 times human body weight equivalent dose; 7 years</td>
</tr>
</tbody>
</table>
Roughly two dozen cases of primary malignant liver tumors have been reported in users of oral contraceptives (84, 86, 121, 205, 370, 389, 512). Data do not permit a conclusion about whether or not oral contraceptive use is associated with higher risk of primary liver malignancy. Malignant liver tumors have been found in men and children using anabolic androgens, which are chemically similar to the progestins used in oral contraceptives (35, 63, 286). Neither hepatocellular adenoma (280) nor focal nodular hyperplasia (280, 546) has been considered a precursor of malignancy, although the evidence on focal nodular hyperplasia is probably stronger (546). Nonetheless, malignant tissue has been seen in a hepatic adenoma in a user of oral contraceptives (121) and, in one of 79 cases of hepatic adenoma reported to the Armed Forces Institute of Pathology in Washington, D.C. (USA), repeat surgery was required because malignant hepatoma developed (494). This woman was not a user of oral contraceptives.

Liver Tumors in Animals

Oral contraceptives may increase the incidence of liver tumors in mice and rats, but no tumorigenic effect has been seen in dogs or monkeys, according to the available evidence.

Mice and Rats. Hepatic tumors generally considered malignant (hepatomas) occur spontaneously in mice and rats (555). Incidence varies according to factors such as strain, diet, hormonal changes, and even housing environment (108, 202, 327, 555). Some studies have indicated that exogenous estrogen can damage the liver or impair liver function (491, 538, 601), but only a few studies have found evidence that estrogen had stimulated tumor development (37, 547). Oral contraceptives have elicited conflicting results (see Table 12).

Table 13—Effects of Oral Contraceptive (OC) Hormones on Pituitary Tumors in Animals, Selected Studies, 1965–1973

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Ref. No.</th>
<th>Hormone</th>
<th>Description</th>
<th>Effect on Tumor Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>MICE</td>
<td>94</td>
<td>OC components,</td>
<td>daily oral doses 2-5, 10-150; 200-400 times human body weight equivalent dose, for 60 weeks; 7,000 mice, groups of 40</td>
<td>differing percentage increases for various compounds; control groups varied</td>
</tr>
<tr>
<td>Committee on Safety of Medicines 1972</td>
<td></td>
<td>separately and in combination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heston et al. 1973</td>
<td>253</td>
<td>Enovid</td>
<td>daily oral doses, 10, 20 and 40 μg from age 4 weeks; 5 strains; groups of 56</td>
<td>no increase, 4 strains; increase in 1 strain, dose-related</td>
</tr>
<tr>
<td>RATS</td>
<td>94</td>
<td>OC components,</td>
<td>daily oral doses 2-5, 10-150; 200-400 times human body weight equivalent dose, for 144 weeks; 6,500 rats, groups of 50</td>
<td>no general increase; some increase with some compounds; control groups varied</td>
</tr>
<tr>
<td>Committee on Safety of Medicines 1972</td>
<td></td>
<td>separately and in combination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McKinney et al. 1969</td>
<td>390</td>
<td>ethinyl estradiol, megestrol acetate, BDH-2700, separately and in combination</td>
<td>average daily and cyclic oral doses; 53 μg (BDH-2700, ethinyl estradiol), 2.63 μg/kg (megestrol acetate) for 2 years; groups of 40</td>
<td>no increase; control groups varied</td>
</tr>
<tr>
<td>Kar et al. 1965</td>
<td>295</td>
<td>Norlestrin</td>
<td>daily oral doses, 10 and 100 times human body weight equivalent dose, for 2 years; groups of 50 rats</td>
<td>increase with high dose; decrease with low dose</td>
</tr>
<tr>
<td>Schardein et al. 1970</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONKEYS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dogs and Monkeys. No liver abnormalities in dogs or monkeys receiving oral contraceptives in various dosages have been found in the ongoing experiments of F. X. Wazeter and associates (592, 593, 594) (see Table 12).

NEOPLASMS OF OTHER SITES

Pituitary. Amenorrhea (the absence of menstruation) is an occasional side effect following use of oral contraceptives. Because amenorrhea is also a common symptom of pituitary dysfunction or tumor (236), there has been some concern that oral contraceptives might in some cases affect the pituitary adversely or even induce tumor growth. A recent study of 191 women with secondary amenorrhea (i.e., who have previously menstruated but have ceased to do so) diagnosed the cause of amenorrhea as pituitary tumors in 26 percent of the 69 former users of oral contraceptives. However, in only 13 percent of those whose amenorrhea was not associated with oral contraception. The difference is statistically significant (364). Further studies are being planned to determine what relationship might exist between oral and pituitary tumors (30).

Studies with animals—particularly mice—suggest that oral contraceptives may induce pituitary tumors. The Committee on Safety of Medicines (94) found a definite increase in the incidence of pituitary tumors in mice given several components of oral contraceptives (see Table 13). These results prompted the Committee to suggest that women taking oral contraceptives be watched for amenorrhea or other indications of hypothalamic-pituitary dysfunction (94). The effect of orals on the pituitary of the rat.
is uncertain due to incidence differences among control groups in several studies.

Estrogen-induced pituitary tumors in mice and rats have been reported since 1936 (80, 94, 109, 151, 182, 195, 203, 379, 433, 434, 445, 613). The initial effect of exogenous estrogen is an enlargement of the pituitary gland. This is accompanied or followed by development of a tumor, either benign or malignant as evidenced by metastases.

**Ovary.** Several studies have produced no grounds for suspicion that oral contraceptives are associated with a higher than expected incidence of ovarian neoplasms in women. Two studies detected no link between oral contraceptive use and benign ovarian neoplasms, while finding that oral contraceptive use seemed to provide some protection against functional ovarian cysts, which are not true neoplasms (455, 586). A third study found clinically diagnosed ovarian tumors, most of which were ovarian cysts, occurred at one-third the rate in users of oral contraceptives as in nonusers (498). Functional cysts may not have been distinguished from true neoplasms in this study.

In the few animal studies available, evidence does not suggest that oral contraceptives significantly increase the incidence of ovarian tumor development in mice, rats, or monkeys (see Table 14).

A series of reports in the 1960s noted that progesterone and two progestins—norethindrone and norethynodrel—were associated with an increase in tumor incidence in the ovaries of one strain of mice (336), but subsequent experiments with the same strain failed to confirm these findings (253) (see Table 14). Hormone-dependent tumors have been induced in several breeds of dogs by administration of the estrogen stilbestrol both alone and in combination with progesterone (281). In monkeys, no tumorigenic effects were found with administration of estrogen (159), estrogen plus progesterone (111), or oral contraceptives (295).

### Table 14—Effects of Oral Contraceptive (OC) Hormones on Ovarian Tumors in Animals, Selected Studies, 1965–1973

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Ref. No.</th>
<th>Hormone</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
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<td>94</td>
<td>OC components, separately and in combination</td>
<td>daily oral doses 2-5, 50-150, 200-400 times human body weight equivalent dose, for 80 weeks; 7,000 mice, in groups of 40</td>
<td>small (statistically insignificant) increase in some strains</td>
</tr>
<tr>
<td>Heston et al. 1973</td>
<td>253</td>
<td>Enovid</td>
<td>daily oral doses 10, 20, 40 μg from age 4 weeks; 5 strains; groups of 56</td>
<td>no increase</td>
</tr>
<tr>
<td>RATS</td>
<td>94</td>
<td>OC components, separately and in combination</td>
<td>daily oral doses, 2-5, 50-150, 200-400 times human body weight equivalent dose, for 104 weeks; 6,500 rats; groups of 40</td>
<td>small increase (statistically insignificant)</td>
</tr>
<tr>
<td>Schardlein et al. 1970</td>
<td>508</td>
<td>Norlestrin</td>
<td>daily oral doses, 10 and 100 times human body weight equivalent dose, for 2 years; groups of 50 rats</td>
<td>no increase</td>
</tr>
<tr>
<td>MONKEYS</td>
<td>295</td>
<td>Enovid</td>
<td>cyclic oral doses of 10 mg/60 kg body weight; up to 1,095 days; 14 monkeys</td>
<td>no increase</td>
</tr>
</tbody>
</table>

### CONCLUSIONS

There is no clear evidence to date that oral contraceptives cause any form of cancer. There is increasing evidence that oral contraceptive use does affect the occurrence of benign neoplasms of the breast and liver. A variety of epidemiologic studies conducted in the USA and Great Britain have consistently demonstrated a lower incidence of benign breast tumors in users of oral contraceptives when compared to nonusers. This "protective" effect appears to be related to progestin dose and duration of use—observations which reinforce the conclusion that this is a pharmacological effect of oral contraceptives. The use of oral contraceptives—particularly long-term use—seems to be associated with a higher incidence of certain types of benign liver tumors. This conclusion is based on case reports, two case-comparison studies, and the differing epidemiologic patterns of liver tumors in users and nonusers. Despite the increase which may be attributable to oral contraceptives, these tumors remain rare.

While there is to date no evidence that combined oral contraceptives are associated with an altered incidence of endometrial neoplasia, case reports of endometrial cancer in young women using sequential oral contraceptives were sufficiently worrisome that these products have been withdrawn from the market in the USA and other countries. Sequential use has always constituted a small portion of the oral contraceptives used and have demonstrated no advantages over the more popular combined orals. Recent case-comparison studies suggesting that older women with endometrial cancer are more likely than women without the disease to have used estrogens alone may reinforce suspicions about the estrogen-dominated sequentials, but they do not seem relevant to combined orals.
The cervix and the breast are the two most important cancer sites studied for possible effects of oral contraceptives because in nearly every country one or the other is the most common site of cancer in women. At the same time, the relationships of oral contraceptive use to cancers of the cervix and breast are exceedingly difficult to study. Indeed, all the neoplasms discussed in this report, cancer of the cervix seems to be the most studied and the most difficult to study well.

The differences in breast cancer occurrence between users of orals and nonusers have in most studies been small and most readily explained as chance variations. Some of these studies have been relatively small and involved short-term use of oral contraceptives, so how much reassurance they provide is difficult to assess. A few studies have found statistically significant relationships between oral contraceptive use and increased breast or cervical cancer, but problems of diagnosis and biological interpretation make their meaning ambiguous. Perhaps further studies, several of which are now in progress, will define and establish the meaning of associations between oral contraceptive use and neoplasia.

Oral contraceptives have brought millions of women relief from the burdens of childbearing and the fear of unwanted pregnancy and have contributed to happier family and sexual lives, better health, and an improved standard of living. Oral contraceptives have helped reduce illness and death due to childbearing and, in many places, have facilitated the slowing of population growth. These benefits are clear and large. No known adverse effects on the incidence of neoplasia outweigh these benefits or argue for restricting the availability of orals. Lack of basic knowledge about neoplasia and hormones and the difficulties of studying relationships between them discourage predicting the results of future research. Nonetheless, it is encouraging that over the last 17 years, the use of combined oral contraceptives by hundreds of millions of women in virtually every nation has produced no clear evidence that "the pill" causes cancer.
98. COPELAND, M.M., The treatment of mammary dysplasia with
99. CHRISTOPHERSON, W. M., and MAYS, E. T.
1963.
108. CRAIN, R. C., Spontaneous tumors in the Rochester strain of
94. COEZY, E., and RUDAU, G. Action d’un contraceptif
91. COEZY, E. and RUDAU, G. Action d’un contraceptif
90. COEZY, E. and RUDAU, G. Action d’un contraceptif


1977 IUSSP GENERAL CONFERENCE

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