

Drug-Induced Cancer

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This report reviews the medicinal agents that have been linked to human cancer, with emphasis on recent evidence implicating estrogenic compounds such as DES, menopausal estrogens, and oral contraceptives. Attention is also given to drugs that have fallen under suspicion and requires further epidemiologic evaluation. The detection of drug-cancer associations not only influences clinical and public health practice, but may also provide insights into mechanisms of carcinogenesis. The clinician contributes to the prevention of drug-induced cancer by being alert to iatrogenic hazards and cooperating in epidemiologic investigations, by weighing risks versus benefits in individual cases, and by discussing with patients the rationale and risks of proposed forms of therapy.

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BY DESIGN, DRUGS are substances which are biologically and chemically active, and are given at doses designed to alter physiologic or pathologic processes in humans. It is not surprising that unintended reactions are commonplace. Acute side effects have always been of great concern to those marketing, prescribing, consuming, or regulating drugs, and for that reason they are usually well documented through toxicity studies and clinical trials. Long-term side effects, including cancer, are much more difficult to evaluate and still remain largely unknown. This paper summarizes the epidemiologic evidence for drug-induced cancer in man. The few agents discussed—both those with human evidence of carcinogenicity, and those evaluated and thus far exonerated—are a testimony to the limited information available on long-term effects. Revelations of even larger gaps in our knowledge can be expected as serious concerns about particular drugs are raised almost on a monthly basis. With the help of clues from clinical and experimental studies, the epidemiologist has a major task in clarifying relationships that have been suggested, and in uncovering new hazards.

A convenient way of categorizing information on the carcinogenicity of drugs is as follows:

- (1) Drugs associated with cancer in humans.
- (2) Suspect drugs for which human evidence of carcinogenicity is inconclusive or conflicting.

- (3) Suspect drugs for which human studies have not yielded evidence of carcinogenicity.

- (4) Suspect drugs as yet unevaluated in humans.

The last category is the largest, and includes a wide variety of medications suspected on the basis of laboratory experimentation, chemical structure or action, or clinical impression. Review of this category is best done by laboratory scientists, and is mentioned here only to illustrate ways in which a drug may fall under suspicion.

Drugs Associated with Cancer in Humans

Table 1 lists those drugs that increase the risk of human cancer. Some have been withdrawn from clinical practice, while others are still used, since risk-benefit estimates may warrant their administration in certain disorders. However, as different conditions are added to the therapeutic indications for a drug, new assessments of risk-benefit must be made.

Radioisotopes exert carcinogenic effects by release of ionizing radiation at deposition sites in the body. For example, radioactive phosphorus increases the risk of acute non-lymphocytic leukemia in patients with polycythemia vera.¹ Radium and mesothorium, bone-seeking isotopes once used for bone tuberculosis and other illnesses, produce a high rate of osteogenic sarcoma and carcinoma in mucous membranes near bone, notably the paranasal sinuses.² Radioiodine used in high doses for thyroid cancer probably increases the risk of leukemia,³ but no effect has yet been seen when lower amounts are used for hyperthyroidism.⁴ Thorotrast, deposited in the reticuloendothelial system after use in radiographic studies, is a cause of hepatic angiosarcoma and acute non-lymphocytic leukemia.⁵

Chlornaphazine was withdrawn from use in 1964 when high doses for polycythemia vera and Hodgkin's

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TABLE 1. Drugs Established as Human Carcinogens

Drug	Malignancy
Radioactive drugs (phosphorous (P-32), radium, mesothorium, thorotrast)	Organs where concentrated (acute leukemia, osteosarcoma, nasal sinus carcinoma, angio- sarcoma of the liver)
Chlornaphazine	Bladder cancer
Arsenic	Skin cancer
Methoxypsoralen	Skin cancer
Phenacetin-containing drugs	Renal pelvis carcinoma Bladder cancer(?)
Alkylating agents (melphalan, cyclophosphamide, chlor- ambucil, dihydroxy- busulfan, and others)	Acute nonlymphocytic leukemia Bladder (cyclophosphamide) Other sites(?)
Immunosuppressive agents (Azothioprine)	Lymphoma Skin cancer Soft-tissue sarcoma Melanoma(?) Liver and gall bladder(?) Lung adenocarcinoma(?)
Androgen-anabolic steroids	Hepatocellular carcinoma
Estrogen-containing drugs Prenatal (DES) Postnatal (DES, conjugated estrogens, oral contra- ceptives)	Vaginal adenocarcinoma Endometrial carcinoma Breast cancer(?) Cervical cancer(?) Ovarian cancer(?) Choriocarcinoma(?) Melanoma(?) Liver tumors (benign)

disease were found to cause bladder tumors.^{6,7} This drug is a derivative of β -naphthylamine, previously known to be a bladder carcinogen for workers in the chemical industry.

Inorganic arsenicals have not been shown carcinogenic in experimental animals, but when taken internally (*e.g.*, Fowler's solution) they can induce skin cancer in humans.⁸ The skin cancers following arsenical use are characteristically multiple, involve unexposed parts of the body and unusual locations (*e.g.*, palms of

the hand), and are associated with arsenical pigmentation and hyperkeratosis.

Methoxypsoralen, used in combination with ultraviolet light in the treatment of psoriasis, has been related to an increased risk of squamous cell carcinoma of the skin.⁹

Analgesic mixtures containing phenacetin, when taken in very large amounts, can cause chronic pyelonephritis and papillary necrosis. Reports from various countries, most notably Sweden, indicate that patients with "analgesic nephropathy" are prone to transitional cell tumors of the renal pelvis, and perhaps the bladder also.^{10,11}

Alkylating agents, used primarily for the treatment of malignant neoplasms, have been under suspicion for some time.¹² These drugs, including melphalan, cyclophosphamide, and chlorambucil, may exert their action in part by breaking chromosomes. This mechanism mimics an effect of ionizing radiation, which is carcinogenic to a variety of organs. Indeed, the radiogenic tumor with the shortest latent period—leukemia—has now been convincingly linked to the use of alkylating agents. The early reports linking leukemia to the use of melphalan or cyclophosphamide in multiple myeloma were skeptically received; it was assumed that improvements in survival might have enhanced the development of a hematopoietic neoplasm related to the origin or natural history of myeloma.¹³ However, the drugs themselves were implicated by subsequent studies, including the long-term follow-up of patients participating in randomized clinical trials, and surveys of patients treated for tumors not involving the hematopoietic system.

Reimer *et al.* studied 5,455 patients with ovarian cancer from several institutions.¹⁴ Thirteen developed acute non-lymphocytic leukemia, and all had received alkylating agents. The risk of leukemia in the patients given chemotherapy was 36 times the expected value, rising to 171 times that expected in those surviving two years or more. No excess risk of leukemia was seen among a group of ovarian cancer patients who were not treated with these drugs. An excess of similar magnitude was estimated from a long-term follow-up of patients in a clinical trial of multiple myeloma.¹⁵

In the ovarian cancer and myeloma studies, it was estimated that the attack rate of leukemia among patients surviving ten years from treatment with alkylating agents may be on the order of 12–20%. This risk of leukemia may be acceptable when treating conditions with a poor prognosis such as advanced ovarian cancer or myeloma. However, these drugs are often recommended and used for conditions with a considerably better long-term prognosis, and in these circumstances the benefits of treatment should be carefully weighed

TABLE 2. Suspect Drugs for Which Human Evidence of Carcinogenicity is Either Inconclusive or Conflicting

Drug	Malignancy
Chloramphenicol	Leukemia
Iron Dextran	Soft tissue sarcoma (site of injection)
Dilantin	Lymphoma
Phenobarbital	Brain tumors; liver cancer
Amphetamines	Lymphoma
Reserpine	Breast cancer
Progesterone (Depo-Provera)	Cervical cancer
Phenylbutazone	Leukemia
Crude tar ointment	Skin cancer
Clofibrate	Gastrointestinal and respiratory malignancies

against the risks. Only acute leukemia has been conclusively linked to the use of alkylating agents, but, probably through immunosuppressive effects, an excess of non-Hodgkin's lymphoma has been reported recently among patients treated for Hodgkin's disease.¹⁶ However, since the latent period for the appearance of solid tumors is probably much longer than that of leukemia, it is important to continue surveillance of the increasing numbers of long-term survivors receiving alkylating agent therapy.

Cyclophosphamide has been related to an increased frequency of bladder cancer.^{17,18} The effect appears specific for this particular alkylating agent, which induces acute toxic effects in the bladder mucosa.

Many of the drugs in Table 1 seem to induce tumors in the classical manner associated with chemical carcinogenesis. The immunosuppressive and hormonal agents are also causally related to certain cancers, but the mechanisms of action appear somewhat different.

Immunosuppressive agents have been assessed primarily by follow-up studies of renal transplant recipients.¹⁹⁻²¹ Nearly all transplant patients have had azathioprine and corticosteroids, but cancer risk is likely to be similarly altered by other immunosuppressants. In a survey of 16,290 transplant patients, the risk of non-Hodgkin's lymphoma was increased 32-fold, and was related primarily to histiocytic lymphomas.²¹ The excess risk of lymphoma appeared within months of transplantation, and about one-half of the lymphomas arose in the brain, which is generally a rare site for this tumor. For all other cancers combined, the excess risk was on the order of twofold and first became evident about two years after transplantation. This was not seen for all tumors across-the-board, as might be predicted by the hypothesis of "immunologic surveillance." There were modest increases in risk for cancers of the liver, bile duct and gallbladder, and urinary bladder, and for soft tissue sarcoma, leukemia, adenocarcinoma of the lung, squamous carcinoma of the skin, and malignant melanoma. No increases were seen for such common neoplasms as colon or breast cancers, or squamous carcinoma of the lung. Recently, other groups of patients taking immunosuppressive drugs have shown an excess of lymphoma, although at a lower rate than that seen in transplant patients.²²

It is noteworthy that the array of neoplasms following drug-induced immunosuppression resembles that seen with the genetically determined immune deficiency syndromes,²³ with chronic lymphocytic leukemia,²⁴ and with other conditions associated with immunodeficiency.^{25,26} Further epidemiologic and laboratory studies should clarify the mechanisms by which immunosuppressants predispose to certain cancers, including the possible role of oncogenic viruses.

Androgenic-anabolic steroids in the form of oxymetholone or methyltestosterone derivatives were first linked to hepatocellular carcinoma by case reports of patients undergoing long-term therapy for aplastic anemia.²⁷ Cases of Fanconi's anemia seem at special risk, in accord with their heritable predisposition to acute leukemia and other cancers. Liver tumors occur also when the steroids are used for conditions other than aplastic anemia, and some tumors have regressed upon drug withdrawal.²⁸ An association with hepatic angiosarcomas has recently been reported.²⁹

While the drug-cancer associations discussed so far are clinically important and may offer insights into basic mechanisms of carcinogenesis, relatively small numbers of individuals have been exposed to the medications in question. Also, in some instances, the patients are quite ill and willing to accept the risk of serious side effects for the potential benefits of treatment. The public health ramifications are much greater for estrogen-containing drugs.

Estrogen-containing drugs, despite laboratory evidence of carcinogenicity, have been, and continue to be, widely used in high doses for long periods of time by large numbers of healthy women. It is estimated that between four and six million Americans (mothers, daughters, sons) have been exposed to diethylstilbestrol (DES) during pregnancy.³⁰ A recent survey indicates that as many as 50% of all menopausal women in one area of the United States were given estrogens for a median duration of ten years.³¹ It is also estimated that 80 million women in the reproductive age range throughout the world use oral contraceptives.³² Thus, not only is the human species participating in a massive natural experiment to evaluate the potential carcinogenicity of these compounds, but the public health significance of even small alterations in carcinogenic risk due to these drugs is substantial. During the last ten years, studies of the carcinogenic potential of estrogen-containing drugs have led to a substantial increase in our knowledge of drug-induced cancer. Prior to the early 1970s, the numbers of persons exposed to estrogens, particularly long-term users, were too few for an adequate evaluation to be made by case-control studies. Although follow-up studies of heavily exposed individuals had been conducted, each was so deficient in conduct or analysis that the results were uninterpretable.^{33,34}

DES during pregnancy

In 1971 an unusual cluster of a rare form of vaginal cancer was reported in females aged 14-22 years, and was linked to intrauterine exposure to diethylstilbestrol (DES) given to pregnant women.³⁵ Further case-control

studies confirmed these results and related the *in utero* exposures to an excess risk of clear cell adenocarcinomas of the vagina and cervix.³⁰ Shortly thereafter, a registry of this disease in young women was established, and now contains reports of over 350 cases of clear cell adenocarcinomas of the genital tract.³⁶ Among those cases with an available maternal pregnancy history, approximately two-thirds indicated *in utero* exposure to DES or similar synthetic estrogens such as hexoestrol and dienestrol.

It appears that the incidence of clear cell adenocarcinoma is between 1/1000 to 1/10,000, through the age of 24, among exposed daughters. Since the use of DES during pregnancy was not common prior to the early 1950s, accurate estimates for what occurs beyond the age of 24 are not yet available. However, the rates rise very sharply at age 14, peak at age 19, and decline rapidly. The steepness of the ascending limb of this curve is noteworthy, considering that the relevant exposure was 15 to 20 years earlier. Usually if the latent period for a disease is long, it tends to have a wide range. In this circumstance, while the average latent period is 19 years, the range is quite constrained. This suggests that some event associated with puberty (the surge of endogenous estrogens?) is needed to promote the development of this cancer.

With the great interest in describing various features of clear cell adenocarcinoma following DES exposure, it is easy to forget that the effects on other hormonally sensitive organs have not yet been evaluated adequately. Recent reports suggest that intraepithelial squamous cell neoplasia of the cervix and vagina may be more common in DES exposed women,³⁷ but this has not been confirmed.³⁸ The women exposed to DES *in utero* are just now entering the age range when cancers of the cervix and breast begin to appear, and it will be a number of years before they reach the usual age for cancers of the endometrium and ovary. The need for continued evaluation of this exposure is obvious.

Although no clear excess risk of cancer has yet been documented among males exposed *in utero*, two small case-control studies of testicular cancer have suggested an effect.^{39,40} Concern about male offspring has been increased by the high rate of genital anomalies observed after prenatal exposure.⁴¹

Often overlooked is the fact that the mothers who took DES during pregnancy also had a substantial, albeit short-term, exposure to exogenous estrogen. The dose regimen most popular in the late 1940s and early 1950s called for 10 to 12 grams of DES to be administered during the pregnancy. The data on cancer risk among such women are sparse and conflicting; some excess risk of cancers of the breast and reproductive organs was suggested by one large follow-up study,⁴² but not confirmed by a subsequent smaller study.⁴³

Menopausal Estrogens

Late in 1975, two case-control studies indicated that the use of conjugated estrogens for the climacteric was associated with an increased risk of endometrial cancer.^{44,45} One study, conducted in a cancer clinic, observed a fourfold to eightfold increased risk of endometrial cancer among estrogen users compared to non-users.⁴⁴ The other study, involving a large prepaid health plan, found an eightfold excess risk overall for users of estrogen, and a dose-response relationship with duration of use, rising to 14-fold among those who used estrogens seven years or more.⁴⁵ Both studies were based on record reviews. A subsequent study in a large retirement community utilized both health plan records and personal interviews, and obtained similar results.⁴⁶ A comparable relative risk is seen following the use of nonconjugated estrogens, along with a dose-response relationship with the dose of the tablet usually used. Since these initial reports, eleven independent investigations have had similar findings, using a wide variety of study designs.^{33,34,47-55} Methodologic criticisms of these studies have been raised and addressed adequately,⁵⁵⁻⁵⁷ and there is no question that a cause-and-effect relationship exists. This is consistent with the rising incidence of endometrial cancer in the United States following the dramatic increase in the use of menopausal estrogens.⁵⁸

At least two aspects of the relationship between estrogens and endometrial cancer deserves further study. First, what happens when progestational agents are added to estrogenic compounds used for hormonal replacement therapy? It has been suggested that these agents might at least partially offset the risk associated with estrogens.^{59,60} Second, what happens to the risk among women who have stopped using estrogens? Preliminary data from recent studies suggest a persistent elevation in risk, even among former users who stopped some time ago.^{54,55} However, after standardization for the amount of estrogen received, there appears to be a meaningful reduction in the excess risk of endometrial cancer very soon after the women stopped using the medications. These observations are exciting for their immediate relevance to cancer prevention, and their biological implications in understanding the role of promoters in carcinogenesis.

The relationship between menopausal estrogen use and the risk of breast cancer has been debated for some time. Two recent follow-up studies have suggested that the risk of breast cancer may be elevated among long-term estrogen users.^{61,62} In one of these studies, 49 breast cancers were observed among 1891 women followed for an average of 12 years, whereas 39 such cases were expected based on rates in the general population.⁶¹ The relative risk of breast cancer increased with

duration of follow-up in this study, reaching about two-fold after 15 years. Several case-control studies of breast cancer reported no significant association with respect to estrogen use. However, only recent studies can address the question of long-term use, and preliminary findings suggest a positive association.^{63,64}

Although menopausal estrogens have been reported in association with other cancers, the observations have usually been isolated or preliminary in nature. The risk of ovarian cancer was significantly high among a small group of women treated both with DES and conjugated estrogens for menopausal symptoms,⁶⁵ and a follow-up of mothers exposed to DES during pregnancy revealed an excess of ovarian cancer compared to a control series.¹² On the other hand, case-control studies using record-linkage and interview approaches did not find an association between conjugated estrogen use and ovarian cancer.^{66,67} Some studies have suggested that users of conjugated estrogens might actually have fewer than the expected numbers of cancers other than those of the breast and reproductive system.⁶² While the lack of a dose-response relationship weakens the argument for a protective effect, additional studies are needed.

Oral Contraceptives

Prior to 1960, these potent combinations of estrogens and progestins were not used outside of clinical trials. The subsequent abrupt and widespread use by a healthy population of oral contraceptives, which show carcinogenic activity in laboratory animals, has raised serious concern.

To date, endometrial cancer is the only malignancy that has been clearly linked to the use of oral contraceptives, and this association may be limited to one type of oral contraceptive, and perhaps a single brand. In a series of young women with endometrial carcinoma and a history of oral contraceptive use, the proportion of users of sequential oral contraceptives was much higher than expected from national rates of use of sequential versus combination agents.⁶⁸ This finding has recently been confirmed by a case-control study which identified an excess risk of fourfold to fivefold for users of the sequential type of oral contraceptive.⁶⁹ A particular brand, Oracon, was the primary, and perhaps only, culprit. The relative risk of endometrial cancer among Oracon users was approximately sevenfold. Sequential oral contraceptives involve the use of estrogen alone during the first half of the menstrual cycle, followed by a progestin in the second half. In this manner, women are exposed at some time to unopposed estrogen in a manner resembling exposure to menopausal estrogens. It is noteworthy that Oracon involved unopposed estrogen for two days longer each month than the other sequentials, and consisted of the most potent estrogen

and weakest progestin of any of the sequentials. By contrast, there is evidence that combination oral contraceptives (in which estrogens and progestins are given together) may be associated with a reduced risk of endometrial cancer.⁶⁹

The relation of oral contraceptive use to cancer of the uterine cervix remains unsettled. Few data are available on the risk of invasive cancers, and the observations are concerned mainly with cervical dysplasia and/or carcinoma *in situ*. The evidence is complicated by uncertainties in the pathologic and epidemiologic characteristics of these lesions. Four case-control studies have been conducted—three found no association,⁷⁰⁻⁷² while the fourth, among Black women attending a screening program in Atlanta, Georgia, noted a positive association with some evidence of a dose-response relationship.⁷³ Four follow-up studies have thus far been reported—two found no significant differences in cancer, carcinoma *in situ* or precancerous lesions between oral contraceptive users and users of methods other than the diaphragm.^{74,75} The third study, among 17,942 women enrolled in a prepaid health plan, detected a significantly increased relative risk of *in situ* cancer among oral contraceptive users, a risk which increased with duration of exposure.⁷⁶ The fourth study, involving patients with dysplasia, found higher rates of progression to carcinoma *in situ* among users of oral contraceptives, particularly after extended use of six years or more.⁷⁷

The studies of cervical neoplasia and oral contraceptives have been numerous, conflicting, and difficult to interpret. The complex methodologic issues have been summarized elsewhere.^{32,33} Despite these limitations, there is some evidence suggesting that the risk of cervical dysplasia and carcinoma *in situ* is increased among long-term oral contraceptive users who have other risk factors for these conditions. This conclusion is very tentative, however, since all of the potential sources of bias and confounding in these studies have not been controlled adequately.

In 1973, several young women receiving oral contraceptives were reported with benign liver tumors.⁷⁸ These tumors were highly vascular and often presented as emergencies with abdominal hemorrhage and shock. Two case-control studies have linked these tumors to the use of oral contraceptives.^{79,80} The risk for users of three to five years was about 100 times that of nonusers, and the risk for users of seven or more years about 500 times that of nonusers. The risks also appeared to be higher for users over age 30, and for users of pills containing greater doses of estrogen and progestin. While the relative risk is high, the absolute risk does not appear to be large for this rare tumor. Preliminary calculations suggest that the risk of hepatocellular adenoma among women under age 30 is no more than 3 per

100,000 contraceptive users per year.³² Over age 30 the absolute risk is greater, but not estimated. Several cases of hepatocellular carcinoma have been reported among women using oral contraceptives,⁸¹ but no controlled study has yet been conducted to evaluate risk.

Numerous evaluations of breast cancer among oral contraceptive users have shown no clear-cut evidence of either increased or decreased risk.³²⁻³⁴ Some studies have suggested a hazard for high-risk women, such as those with benign breast disease, nulliparity, or familial predisposition.⁸²⁻⁸⁴ A recent study indicates that use of oral contraceptives may have a beneficial effect on tumor growth and spread.⁸⁵ Further work is needed to evaluate the effects of long-term use and exposures in early reproductive life.

Several case-control and follow-up studies have documented a lower risk of benign breast disease among oral contraceptive users.^{32-34,86} This "protective" effect is related to duration and apparently restricted to current users and those who stopped less than a year prior to diagnosis.⁸⁶ For current users of oral contraceptives with a total exposure of longer than two years, the risk of being hospitalized for benign breast disease is only 25% of those who have never used oral contraceptives.⁸⁷ Since benign breast disease predisposes to breast cancer, it has been thought that oral contraceptives might eventually protect against this cancer. However, in a recent study of benign breast disease, the protective effect associated with oral contraceptives applied primarily to the form of the disease with the least ductal atypia.⁸⁸ On the other hand, oral contraceptives were associated with a slightly increased risk of benign disease with marked atypia.

Three recent studies have suggested that patients with ovarian cancer have a less frequent history of use of oral contraceptives than controls.^{87,89,90} This apparent protective effect is felt to be consistent with epidemiologic characteristics suggesting that women with "incessant" ovulatory activity are at higher risk than those with less ovulatory activity.⁹⁰ However, any protective effect on ovarian cancer may be relatively short-term with the late consequences yet to be evaluated.

Recent reports have also related use of oral contraceptives to cutaneous melanoma, pituitary adenoma, and invasive hydatidiform mole.^{32,33} There is some evidence to indicate that these associations might not be causal, but the data are insufficient to draw conclusions at this time.

Suspect Drugs for Which Human Evidence of Carcinogenicity is Inconclusive or Conflicting

Table 2 lists drugs about which serious concern of carcinogenicity has been raised by human observa-

tions. However, because of the scarcity of epidemiologic studies, conflicting results, or uncertain interpretations, the associations are considered to be unsettled.

Case-reports have implicated various marrow-depressing drugs, notably chloramphenicol and possibly phenylbutazone, in the development of leukemia.⁹¹⁻⁹³ A causal relationship would be consistent with the potential of leukemogenic agents (radiation, benzene, alkylating agents) to produce aplastic anemia.^{93,94} The chromosomal defects caused by chloramphenicol are noteworthy, since similar defects are seen in various inborn and acquired conditions at high risk of leukemia.⁹⁴

Several patients have been reported with sarcomas arising at sites of previous iron-dextran injections.^{95,96} These preparations have induced sarcomas in laboratory animals, but the excess risk in man appears to be extremely small, if present at all.

Diphenylhydantoin (Dilantin) occasionally induces lymphoid reactions that regress on cessation of therapy. However, transformation to malignant lymphoma has occurred in several patients.^{97,98} The nature of this association remains to be defined, but may be related to the capacity of Dilantin to concurrently depress and stimulate immune responses. Three separate studies indicate that if there is an excess risk of lymphoma associated with this drug, it is almost certainly of small magnitude.⁹⁸⁻¹⁰⁰

Phenobarbital, a widely used sedative, has been brought under suspicion by studies in laboratory animals. Large follow-up studies of epileptics treated with this agent have not yielded clear evidence of a carcinogenic effect, despite some excesses of brain and hepatobiliary tumors.^{99,100} The association with brain tumors was dismissed as being related to treatment for early symptoms of the disease. However, a recent study has related childhood brain tumors to *in utero* and early life exposures to phenobarbital, so that further evaluation of this drug is indicated.¹⁰¹

Amphetamine intake, mainly for weight reduction, was linked to an excess risk of Hodgkin's disease in two case-control studies.^{102,103} With the problems involved in obtaining a reliable history, and with one negative study,¹⁰⁴ this relationship remains in doubt.

Reserpine was suggested as a risk factor for breast cancer by three studies reported in 1974.¹⁰⁵⁻¹⁰⁷ Subsequent investigations have failed to confirm these observations.^{108,109} While an association cannot be entirely dismissed, particularly in view of positive studies in laboratory animals, a cause-and-effect relationship is currently in doubt.

Injectable progesterone (Depo-Provera) was linked to an excess risk of *in situ* cervical cancer in one study population,¹¹⁰ but the comparison rates used to calcu-

late an "expected" number of such tumors may have been inappropriate. However, the magnitude of the risk reported and the carcinogenicity of progestogens in the laboratory call for further studies.

Although the relation of crude tar ointments (containing polycyclic hydrocarbons) to the development of skin cancers has been argued for some time,¹¹¹ a recent study has indicated an excess risk of skin cancers following their use in psoriasis.¹¹²

An excess of certain cancers, particularly of the gastrointestinal tract, has been reported in clinical trials to evaluate the efficacy of clofibrate in preventing morbidity or mortality from coronary artery disease, but the findings are inconclusive because of the small numbers involved.¹¹³

Suspect Drugs for Which Human Studies Have Not Yielded Evidence of Carcinogenicity

Table 3 lists those drugs that have been under suspicion of carcinogenic potential, but which thus far have been evaluated in humans without positive findings. The brief list attests not to the rampant carcinogenicity of suspect drugs nor to the lack of drugs suggested for evaluation; rather, it attests to the paucity of epidemiologic studies and the difficulty in ruling out significant but rare long-term side effects. This is illustrated by a recent follow-up study of metronidazole (Flagyl) users, which was interpreted as showing no hazard.¹¹⁷ It is noteworthy, however, that four lung cancers were observed in this group while less than one was expected, and that the excess risk was confined to persons followed over ten years. Although based on small numbers, the finding seems consistent with the capacity of metronidazole to induce lung tumors in rodents.

Suspect Drugs as Yet Unevaluated in Humans

Table 4 presents a sample of many drugs that have been suspected of carcinogenic activity, but which are unevaluated in humans. They illustrate the various ways in which a drug can fall under suspicion. Both dapsone and griseofulvin, used widely in particular geographic areas, have produced tumors in laboratory animals.^{121,122} The phenothiazine drugs as a class stimulate prolactin release, which may affect the risk of cancers of the breast and gynecologic organs. Oxytetracycline, a commonly prescribed antibiotic, is suspected by virtue of its chemical structure—a tertiary amine, which may combine in the body with dietary nitrites to form carcinogenic nitrosamines.¹²³ Chloroquin, commonly used to prevent malaria in endemic areas, has a side effect of inhibiting DNA repair,¹²⁴ and through this mechanism might possibly increase the risk of cancer.

Thus, leads to suspect drugs may come from several

TABLE 3. Suspect Drugs for Which Human Studies Have as Yet Not Yielded Evidence of Carcinogenicity

Isoniazid ¹¹⁶⁻¹¹⁹
Metronidazole ^{117,118}
Antimetabolites (methotrexate, 5-fluorouracil) ^{119,120}

sources, including clinical observations, drug surveillance programs, studies in laboratory animals, mutagenicity testing, a suspect chemical structure or a capacity to alter immunologic, hormonal, molecular, or other mechanisms that may be involved in carcinogenesis. The discovery of drug-cancer associations may have major impact on clinical practice, public health measures, and etiologic insights into carcinogenesis, so that every credible lead should be aggressively pursued by epidemiologic investigations.

Opportunities for Prevention

There is a time-honored recommendation given to those prescribing or consuming drugs, which should lead to the prevention of side effects or late effects, including cancer. That is, any drug should only be used when necessary, and then at the lowest dose and for the shortest period of time required to achieve the desired result. However, in practice this is often difficult advice to follow due to varying criteria for what is "necessary" and the definition of "desired result." Recent events surrounding the use of estrogens as replacement therapy have underscored the fact that critical evaluation of the efficacy of a drug for various conditions is often not performed until after an untoward effect is identified.

The clinician has an important role in the prevention of drug-induced disease (including cancer) by being alert to new iatrogenic hazards, by encouraging epidemiologic investigations to detect and clarify risks, by weighing risks versus benefits in individual cases, and by adopting a critical stance in requiring objective evidence of benefits before incorporating a drug into practice. In this process the clinician is aided by research and regulatory agencies that ensure appropriate investigations into drug efficacy and hazards, including the use of premarketing laboratory screens and epidemiologic surveillance systems.

The consumer also should become more knowledgeable about the dangers, known or potential, in taking or

TABLE 4. Suspect Drugs as Yet Unevaluated in Humans

Dapsone
Griseofulvin
Phenothiazines
Oxytetracycline
Chloroquin

not taking a particular medication. The clinician has a responsibility in providing this kind of information and discussing the rationale and risks of proposed forms of therapy. This course of action is not specific for the prevention of drug-induced cancer, but is simply part of good medical practice.

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