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DRUGS

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Western societies are often called "medicated" or "over-medicated," because of their massive use of prescription and over-the-counter drugs. Intrinsically, these substances are biologically and chemically active, so that unintended reactions are relatively common. Acute side effects have always been of great concern to those marketing, consuming, or regulating drugs; 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 remain largely unknown. This chapter summarizes the epidemiologic evidence for drug-induced cancer in man. The limited number of agents implicated to date signifies not that other drugs are innocuous, but that the need for study is urgent.

Drug-cancer relationships in laboratory animals and man may be classified as follows:

- 1) Drug exposures associated with cancer in man.
- 2) Drug exposures carcinogenic in laboratory animals that with investigation have thus far demonstrated no carcinogenicity for man.
- 3) Drug exposures carcinogenic in laboratory animals that have not been evaluated in man.
- 4) Drug exposures either not carcinogenic in laboratory animals or whose carcinogenicity is unknown.

This presentation emphasizes the first two categories. Although the last two categories include the vast majority of pharmacologic compounds produced, a review of laboratory research with these agents is beyond the scope of this

report. However, some criteria are presented for selecting which drugs should be evaluated in man.

DRUGS ASSOCIATED WITH HUMAN CANCER

Agents related to cancer in man, recently reviewed by Fraumeni and Miller [1], are listed in Table 1. Some agents were removed from clinical use when their carcinogenic potential was recognized, but others are still used because estimates of risk-benefit ratios warrant their administration in certain diseases. However, as different conditions are added to the therapeutic indications for a drug, new assessments of risk-benefit ratios 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 myelocytic leukemia (AML) in patients with polycythemia vera [2]. 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, particularly the paranasal sinuses [3,4]. The same effect results from occupational exposures among radium-dial painters and radium chemists. Radioiodine used in high doses for thyroid cancer probably increases the risk of leukemia [5], but no effect is evident when lower amounts are used for hyperthyroidism [6]. Thorotrast, deposited in the reticuloendothelial system after use in radiographic studies, is a cause of hepatic hemangioendothelioma and AML [7].

Immunosuppressive agents (antimetabolites, corticosteroids, antilymphocyte serum) are suspected of being contributing factors to the high cancer risk experienced by recipients of renal transplants. The mechanism undoubtedly involves some alteration of immunologic processes rather than chemical induction of malignant change. In a recent follow-up study [8] of over 6,000 recipients of renal transplants, the risk of lymphoma was about 35 times normal—derived almost entirely from a risk of reticulum cell sarcoma that was 350 times higher than expected. Skin and lip cancers occurred up to four times more often than expected, whereas the risk of other cancers was 2½ times more frequent, due largely to soft tissue sarcoma and hepatobiliary carcinoma. Recent data [9] suggest that the risk is increased also for adenocarcinomas of the lung. Since persons with heritable immunodeficiency syndromes are susceptible to lymphoma and possibly other cancers [10], immunosuppressive drugs most likely are involved in posttransplant carcinogenesis. Despite case reports of cancer developing in patients with other conditions treated with these drugs, no study has as yet determined whether there is any excess of malignancy. Perhaps the predisposition to neoplasia in transplant recipients results from an interaction between immunosuppression and immunostimulation by antigens from the grafted kidney. The mechanism will be

TABLE 1
Cancers Related to Drug Exposures in Man

DRUG	RELATED CANCER
Radioisotopes	
Phosphorus (P^{32})	Acute leukemia
Radium, mesothorium	Osteosarcoma, sinus carcinoma
Thorotrast	Hemangioendothelioma of liver
Immunosuppressive drugs (for renal transplantation)	
Antilymphocyte serum	Reticulum cell sarcoma
Antimetabolites	Soft tissue sarcoma, other cancers (skin, liver)
Cytotoxic drugs	
Chlornaphazine	Bladder cancer
Melphalan, cyclophosphamide	Acute myelomonocytic leukemia
Hormones	
Synthetic estrogens	
Prenatal	Vaginal and cervical adenocarcinoma (clear-cell type)
Postnatal	Endometrial carcinoma (adenosquamous type)
Androgenic-anabolic steroids (for aplastic anemia)	Hepatocellular carcinoma
Others	
Arsenic	Skin cancer
Phenacetin-containing drugs	Renal pelvis carcinoma
Coal-tar ointments	Skin cancer
Diphenylhydantoin?	Lymphoma
Chloramphenicol?	Leukemia
Amphetamines?	Hodgkin's disease
Reserpine?	Breast cancer

important to establish. Although the cancer risk associated with immunosuppressive drugs is considered acceptable for renal transplantation, similar risks for less serious disorders might be unacceptable.

Cytotoxic agents used in cancer chemotherapy are often carcinogenic in laboratory animals, and some may induce cancer in man [11]. Chlornaphazine was withdrawn from use in 1964 when high doses for treating polycythemia

vera and Hodgkin's disease (HD) were found to cause bladder tumors [12]. This drug is a derivative of β -naphthylamine, previously known to be a bladder carcinogen in industrial workers. Certain alkylating agents also seem to elevate the risk of acute leukemia, especially the myeloblastic and myelomonocytic types. Most striking is the increase in leukemia among patients with multiple myeloma treated with melphalan or cyclophosphamide [13], although one cannot yet exclude the possibility that improved survival permits the development of a hematopoietic neoplasm related to the origin or natural history of myeloma.

Another effect of cytotoxic drugs was suggested by a recent follow-up study [14] of HD, which showed that intensive chemotherapy enhanced the risk of second cancers originating at heavily irradiated sites.

Synthetic estrogens, particularly diethylstilbestrol (DES), triggered much recent concern about the carcinogenic effects of drugs. First evidence for a human transplacental carcinogen came in 1971, when a link was reported between DES and a cluster of vaginal adenocarcinoma in Boston among eight women between 14 and 22 years of age [15]. At present, prenatal exposure to synthetic estrogens has been linked to clear cell carcinomas of the vagina and cervix in over 100 patients 7 to 29 years of age [16]. However, based on a recent follow-up study [17], the rate for the cancers after in utero exposure to estrogens has been estimated thus far to be no greater than 4 per 1,000 and probably considerably less [16]. Synthetic estrogens given after birth may also induce cancer. In a study of 24 patients receiving DES for at least 5 years for gonadal dysgenesis, endometrial carcinoma developed in two and possibly three cases [18]. Along with three cases in the literature, the tumors were diagnosed between 28-35 years of age, and most were of an unusual mixed or adenosquamous type.

Androgenic-anabolic steroids have been implicated by several reports of patients developing hepatocellular carcinoma after long-term treatment of aplastic anemia, mainly the Fanconi type, with oxymetholone or methyltestosterone derivatives [19]. Further evaluation is needed, particularly in groups receiving these medications for other reasons.

Inorganic arsenicals have not been shown carcinogenic in experimental animals, but when taken internally they are a cause of skin cancer in man [20, 21]. 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. Instances of lung cancer and liver hemangioendothelioma have been attributed to medicinal arsenic. These occurrences may not be in excess of expectation [21, 22], but would be compatible with what is known about cancer risks in occupational studies of arsenic exposure [22, 23].

Phenacetin in analgesic mixtures, when given in large doses, can cause chronic pyelonephritis and papillary necrosis. Reports from various countries [24-26] indicate that patients with "analgesic nephropathy" are at high risk of developing transitional cell tumors of the renal pelvis.

Coal tar and creosote preparations that contain polycyclic aromatic hydrocarbons have been reported to cause skin cancer in laboratory animals, in exposed workers, and in patients using these preparations [27].

Diphenylhydantoin (Dilantin) is one of four drugs under suspicion, along with chloramphenicol, amphetamines, and reserpine. There is some evidence of carcinogenicity in humans, but epidemiologic testing is inadequate. Dilantin occasionally induces lymphoid reactions that regress on cessation of therapy, but transformation to malignant lymphoma has occurred in several patients [28]. The nature of this association remains to be defined, but recent evidence [29, 30] in man and laboratory animals suggests that Dilantin may predispose to lymphoma by its capacity to concurrently depress and stimulate immune responses. Three separate studies [31-33] make it obvious that if there is an excess risk, it is almost certainly of small magnitude and perhaps acceptable, given the drug's efficacy in the treatment of epilepsy.

Chloramphenicol and other bone marrow-depressing drugs have been implicated by case studies in the development of leukemia [34, 35]. A causal relationship would be consistent with the potential of leukemogens (radiation, benzene, alkylating agents) to produce aplastic anemia [35, 36]. The production of chromosomal defects by chloramphenicol supports the possibility of a leukemia hazard, since such defects are seen in various conditions at high risk of leukemia [35, 36].

Amphetamine intake, mainly for weight reduction, was linked to a sixfold excess risk of Hodgkin's disease according to a recent case-control study [37]. With the problems involved in obtaining a reliable drug history, and with a subsequent negative study [38], this relationship needs further investigation.

Reserpine is indicated in three recent surveys [39-41] as a risk factor in breast cancer and possibly other tumors in persons treated for hypertension. Reserpine may be linked to breast cancer by its known capacity to stimulate prolactin release in humans [42]. But further studies are needed to evaluate the role of hypertension, social class, obesity, and other variables that may influence the association.

Often a drug with carcinogenic potential cannot be replaced by an equally effective, safe agent, so that some sort of risk-benefit decision must be made. To effectively make such a decision, the risk of cancer should not only be quantified, but also characterized with respect to dose-response, latent period, susceptibility factors, and the effect of cocarcinogens. In only a few cases, however, has the magnitude of excess risk been estimated in absolute or relative terms. Only very rarely are the "finer points" of an association delineated.

DRUGS CARCINOGENIC IN LABORATORY ANIMALS BUT SHOWING NO EFFECT IN MAN

Exactly which drugs are placed in this category depends on how rigorous an epidemiologic evaluation is expected. Adequate analytic studies of reasonable numbers of exposed persons followed over time have been conducted on only two drugs: *isoniazid* [43] and the *female steroidal sex hormones (including contraceptives)* [44-48]. This short list attests to the difficulties in evaluating cancer risk in man and in teasing the various components of risk (e.g., age, latent period, and cocarcinogen exposures) which also complicate the laboratory assessment of carcinogenicity.

The long latent period between exposure to a carcinogen and manifestation of the cancer is perhaps the single most important obstacle to adequate evaluation. This is illustrated by the apparent relation of alkylating agents to acute leukemia. In 26 reported cases of leukemia complicating multiple myeloma, the average latent period was about 4½ years [13]. Since the primary indication for this therapy is a usually fatal malignancy, the identification of risk was dependent on following up a large number of relatively long-term survivors.

If the latent period and other risk variables are not taken into account, the recognition and interpretation of relationships may be obscured. These variables may also interact with each other, as illustrated by the capacity of DES to cause genital tract adenocarcinomas. In this situation, the neoplasms are caused by a specifically timed prenatal exposure (probably first trimester), a latent period usually over 10 years, and possibly a concomitant surge of endogenous estrogens during puberty (acting as a promoting factor).

Because of the problems involved in evaluating drugs in man, any negative findings must be considered with caution. With *oral contraceptives*, three recent well-designed and executed analytic studies [46-48] to assess the risk of breast cancer showed either no association or perhaps slight protection. However, oral contraceptives have been available only since 1960 and in widespread use since 1965. Thus, the "latent period" that has now elapsed between exposure and the evaluation for disease is limited to 10 to 15 years for even the earliest of users.

Adequate assessment of a drug-cancer relationship requires knowledge of the epidemiology of the cancer in question. This information helps in distinguishing a drug effect from the natural history of the underlying disease and in identifying groups of people that might be particularly susceptible to a drug. It is known, for example, that a woman who has her first child before 18 years of age has one-third the risk of breast cancer of a woman having her first child after the age of 35 [49]. Perhaps younger women are also more susceptible to the effects of steroidal hormones.

In a recent survey [50] of Boston-area women of predominantly middle and upper social class, those entering the breast cancer age range had not used oral contraceptives in early reproductive life, because the drugs were not available. The exposure being studied in these women, therefore, may not be as relevant as exposure at a younger, more susceptible age. These difficulties, coupled with recent reports that oral contraceptive users are prone to liver tumors [51] and in situ cervical cancer [52], point to the need for continued monitoring.

OTHER DRUG EXPOSURES

The last two categories of drug exposures concern agents not yet evaluated in man. Experimentalists are better equipped to evaluate laboratory evidence of carcinogenicity. However, in assessing priorities for epidemiologic study of these drugs, it would seem prudent to weigh: 1) relative carcinogenicity in the laboratory, along with 2) the magnitude of population exposure, and 3) various parameters of this exposure (e.g., age, length of treatment, reason for treatment). Mentioned here are only a few drugs that would qualify for epidemiologic study at the earliest opportunity.

Various agents in *cancer chemotherapy* show carcinogenic potential in the laboratory. They have enabled some young people with cancer to survive long periods [53, 54] and are used in combination much earlier in the natural history of various malignancies. Furthermore, the agents are employed increasingly in nonmalignant conditions [55, 56], so that a major effort is now required to assess the long-term risks.

Laboratory research has raised concern about a group of drugs classed as *tertiary amines*. Included in this group are a number of widely prescribed drugs such as oxytetracycline and chlorpromazine. Experimentally, these agents, in the presence of a large amount of nitrite and an appropriately acidic medium, form highly carcinogenic nitrosamines [57]. In man also, the drugs may produce nitrosamines after interacting with dietary nitrites in an acid stomach. Widespread population exposure over many years and chronic use by some people dictate the need for epidemiologic evaluation. Study of chlorpromazine and other phenothiazines may be justified by an entirely different rationale. These agents are potent stimulators of prolactin release in females [42]. Since prolactin may be a risk factor in breast cancer, the risk of this neoplasm should be estimated among a group of women treated with heavy doses.

Iron dextran should be investigated because of its carcinogenicity in animals, widespread use, and case reports of malignancies at the site of injection [58, 59].

It has been claimed in the public press that women receiving *Depo-Provera* for contraception have a risk of in situ cervical cancer higher than that of

the general population as determined by the Third National Cancer Survey. The results are in doubt since the exposed (and not the comparison) group comes from a highly screened population. However, the magnitude of the risk reported and the carcinogenicity of progestogens in the laboratory [60] indicate the need for further studies.

ESTIMATES OF POPULATION EXPOSURE TO DRUGS

In determining which drugs to evaluate by epidemiologic study, it would be useful to know the magnitude and characteristics of exposure to various drugs in the population. Marketing and prescription surveys have provided marginally useful data. For example, 500 drugs account for approximately 85 percent of all prescriptions [61]. However, estimates are needed of population exposure to drugs by type, duration of use, and therapeutic indication. Data specific for age, race, sex, social class, and possibly other risk factors would be desirable. This type of information was collected at least once by the National Health Survey [62], but publication of the survey was economically oriented and did not identify particular drugs or conditions. The best available information is probably that collected by a commercial drug information service [63]. Prescription data are given according to age, sex, and therapeutic indication; but there are serious limitations to this resource, and a more useful information system should be developed [64]. In addition, special surveys should be conducted of detailed characteristics of consumption of very commonly used drugs. The patterns of drug usage in "special risk" populations, such as pregnant women, also should be studied.

These surveys would help not only in selecting drugs for evaluation, but also in quantifying the population risk and designing control programs when an association has been established. This information would be critical to risk-benefit decisions.

IMPLICATIONS AND RECOMMENDATIONS

Cancer Etiology

Identification of drug-associated cancers helps not only by indicating medicinal hazards, but also by providing information on possible occupational, dietary, or other environmental dangers from the same agents (e.g., inorganic arsenic, coal-tar derivatives, DES). In this manner, the role of nitrosamines in human carcinogenesis could be clarified by a study of users of the tertiary amine drugs. In addition, drug-cancer associations may provide insight into carcinogenic mechanisms. Immunologic determinants, for example, have been clarified by the study of cancer in immunosuppressed transplant recipients.

Despite widespread population exposure to drugs that physiologically might be expected to increase the risk of malignancy, only limited knowledge of drug-induced cancer has been accumulated. For one reason the source of productive clues has been primarily clinical observations. The alert clinician usually detects an environmental hazard through clusters of unusual, rather than common, events. The initial observation is often a cluster of patients with a rare tumor type, such as clear cell adenocarcinomas, or adenosquamous carcinomas of the genital tract (DES), liver hemangioendotheliomas (arsenic, Thorotrast), or myelomonocytic leukemia (alkylating agents). More common tumors may be recognized by unusual sites of presentation (e.g., brain lymphomas in transplant recipients, palms of the hands for arsenical skin cancer), or by associations with known toxic manifestations (e.g., arsenical dermatosis, analgesic nephropathy).

Recognition of drug relationships may also be enhanced by short latent periods (excess lymphoma risk within 1 year of renal transplantation). Thus, it is unlikely that a clinician would be able to link a drug to a common neoplasm occurring 10 to 50 years after exposure. This may be the situation for reserpine, which is under suspicion not on the basis of clinical observations, but from a systematic survey of cancer risk following drug exposures.

The clinical approach, obviously productive in the past, should be encouraged. Practitioners providing etiologic clues should be able to consult the National Cancer Institute, the International Agency for Research on Cancer, and other agencies. Promising leads should be pursued by epidemiologic study. However, with the increasing exposure of our society to a large battery of pharmacological agents, many taken by healthy individuals, some mechanism is needed to determine which drugs to evaluate systematically in man, rather than waiting for a risk large enough to become clinically obvious.

With the advances in comparative physiology and laboratory carcinogenicity testing, some decisions can be made on an interdisciplinary basis. Perhaps a first step would be a meeting of laboratory scientists, epidemiologists, and clinical pharmacologists to decide on drug exposures needing human evaluation. Priorities may be ranked on the strength and relevance of laboratory results, magnitude of population exposure, duration of drug use, special characteristics of consumers, and the ease or difficulty with which appropriate groups could be identified for evaluation. High priority should be given to studies of patient groups exposed to drugs known to be carcinogenic in other groups (e.g., DES for the menopause, androgens for male infertility).

Another recommendation is to incorporate drug histories into case-control studies of cancer and to conduct cohort studies concerned with any outcome. The format of the drug histories could vary, but might as a minimum be a checklist of suspected drugs. Drug surveillance programs, such as the one at Boston University [38, 39], are concerned with these studies and show great potential

for identifying long-term, as well as short-term, effects. These systems should continue to be used to generate and test hypotheses. To date, however, they have evaluated only those drugs taken recently (within 3 months of hospitalization for the Boston program). Perhaps the programs can be expanded in the future to include earlier drug histories.

Record-linkage systems, while much discussed, have contributed little to our understanding of the long-term effects of drugs. Theoretically, they seem to be ideal mechanisms to use for drug evaluation. Linking prescription information with subsequent hospital and diagnostic data for groups of people within prepaid health plans should be a relatively easy and inexpensive way of screening drugs for associations needing more intensive evaluation. With the likelihood of some form of national health insurance imminent, the opportunity for this type of study should be increased. The reasons for the failure of such record-linking efforts in the past need to be explored to determine if this is a feasible mechanism for drug screening.

Finally, a change in government policy might greatly facilitate studies of drug-induced cancer. The drug industry should be assigned some responsibility for evaluating long-term effects of drugs in man, just as it is now responsible for demonstrating safety regarding acute or toxic effects. A promising drug should not necessarily be withheld from general consumption until long-term follow-up studies have been done. A drug company, however, might be required to construct a surveillance mechanism in order to conduct a follow-up study, if warranted, on the first 50,000 to 100,000 individuals who received significant amounts of a new drug. This information would be furnished on demand to the FDA for appropriate evaluation up to 60 years after the introduction of a drug. Although the financial feasibility of this recommendation needs to be explored, it should not be inordinately expensive, particularly in terms of total drug sales; therefore, it should not substantially increase the cost of drugs. In fact, the money saved by not having to initiate such studies from scratch some 20 years after significant exposure could be great.

Cancer Control

Although the human data on drug-induced cancer is sparse, some steps can be taken in the areas of prevention, early diagnosis, and treatment. Control activities would benefit from the surveys previously outlined that could provide adequate data on drug-consumption patterns in this country. For instance, in the early 1960's DES was still being given to a surprisingly large number of pregnant women years after its efficacy in preventing spontaneous abortion had been disproved [65]. Even with the recent publicity about carcinogenic hazards to the fetus, within the past year prescriptions for DES were still being written for pregnant women [63]. Other illustrations of drug abuse (e.g., anabolic steroids given to athletes, chloramphenicol for upper

respiratory infections) should prompt action in the form of professional education or drug regulation.

Two types of screening programs are possible. First is a coordinated local or national program of periodic screening for patient groups exposed to known carcinogenic drugs who are no longer being seen for the condition that led to such therapy (e.g., women exposed in utero to Di.S. long-term survivors of malignancies). A second type of screening is continuous monitoring by physicians of patients being seen for the conditions that led to their drug exposure (e.g., renal transplant recipients, reserpine-treated hypertensive women). This approach should not be restricted to only those patient groups with proved carcinogenic exposures, but should also include those taking "suspect" drugs. However, the effectiveness of this continued monitoring for cancer depends on the physician's awareness of the possible risk involved. While for some physician groups this awareness may be high, for others it will require an intensive program of professional education.

Last year, dermatologists wrote 99,000 prescriptions for methotrexate for severe psoriasis, and urologists wrote 125,000 prescriptions for androgens for such conditions as the male climacteric and sterility [63]. These groups, and others like them, who may not be aware of the potential hazards of these drugs, should receive the emphasis in campaigns for professional awareness. Similarly, it is not clear how many of the over 300 groups performing renal transplants are aware of the high risk of skin cancer in transplant recipients and the unusually malignant course of this neoplasm if not treated early [66].

Finally, while it is important to discourage the inappropriate use of carcinogenic drugs and to encourage screening and early treatment of exposed patients, it is also imperative to identify the biochemical mechanism of drug carcinogenesis through experimental research. In this way, new drugs may be developed that are equally effective but not carcinogenic, and agents may be added to therapeutic regimens that would block the carcinogenic action [67].

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DISCUSSION

The relationship of birth-control pills and hepatoma was considered by some participants to be a serious public health threat. **Dr. Shubik** supported Richard Doll's opinion that birth-control pills are definitely related to the development of hepatoma in treated women. Furthermore, **Dr. Henderson** stated that 19 of 21 cases of liver adenoma studied by Edmundson in Los Angeles were associated with oral contraceptives.

With respect to the nitrosation problem in the gastrointestinal tract, **Dr. Shubik** felt this might be avoided by the addition of ascorbic acid to drugs susceptible to nitrosation. This has been done for tetracycline and should be used routinely. **Dr. Shubik** also reported that Flagyl, Meridazol, phenobarbital, and griseofulvin have produced tumors in animals and need to be studied in man. Studies of veterans who received griseofulvin while in Vietnam may yield valuable information. Perhaps the use of Flagyl and Meridazol should be restricted to life-threatening situations.

Dr. Davies commented that we must not lose sight of the vehicles used in drug compounding, since these vehicles may have carcinogenic or other toxic effects. An example might be the toxicity associated with vinyl chloride used in aerosol propellants. **Dr. Mulvihill** emphasized the potential importance of

genetic factors in evaluating responses to drugs. Screening for known genetic traits, such as α -1-antitrypsin deficiency, may identify persons who would respond abnormally to drugs or who should not work with certain substances.

Dr. Henderson pointed out that case-control studies of Hodgkin's disease (with respect to amphetamines) and breast cancer (with respect to menopausal estrogens) have produced conflicting results, due apparently to the difficulty in obtaining appropriate controls. **Dr. Hoover** concluded the discussion by agreeing with Dr. Shubik that the relation of birth-control pills to hepatoma is a major problem to be solved. He hoped that the National Health Insurance currently under consideration might improve the opportunities for record linkage and discovery of adverse drug effects.

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