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search can have great public health implications. Risk factors that are unimportant for individuals may be important when the effect is multiplied over the population as a whole, especially if the disease is common. For example, the Lipid Research Clinics trial showed that using cholestyramine to lower serum cholesterol about 9 percent in middle-aged men with high cholesterol levels reduced their seven-year risk of coronary events from 8.6 to 7 percent.⁸ Although such a reduction may not seem worthwhile to an individual, when spread over the estimated 1 to 2 million Americans with similar cholesterol levels, it could account for up to 32,000 fewer coronary events over the first seven years. Furthermore, discovering associations between exposures and disease, even when the effect is small, may be important in elucidating the pathogenesis of the disease. Certainly, defining the epidemiology of the acquired immunodeficiency syndrome was crucial in leading researchers to the cause.

There is no question that epidemiologic studies of risk factors for disease are of growing interest and importance, both for individuals and for the public health. It is important, however, to remember the pitfalls in interpreting them and to be cautious in advising patients on the basis of single or conflicting studies. This is particularly true of studies that purport to show only weak associations between exposures and disease. These should be evaluated more critically, by researchers and clinicians alike.

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COMING OF AGE — THE CHEMOPREVENTION OF CANCER

WITH the aging of the population and the continued fall in rates of mortality from cardiovascular diseases, cancer will emerge soon after the year 2000 with the dubious distinction of being the leading cause of death in the United States. Unfortunately, dramatic therapeutic successes in the treatment of cancer plateaued in the mid-1970s, and advances since have been incremental. Whether the remarkable progress in our un-

derstanding of the biologic and genetic underpinnings of normal and transformed cellular growth in the past 15 years will be translated into substantial therapeutic benefit remains to be demonstrated. Alternatives to therapy of late disease need to be developed for the control of cancer; chemoprevention, or the chemical prevention of cancer formation, is one such novel approach.

The process of cancer formation, or carcinogenesis, has been more and more precisely defined with the availability of increasingly sophisticated molecular and biochemical tools. Increased understanding of the genetic milieu that predisposes certain persons to cancer will offer an opportunity to define the risk of cancer in individuals and to modulate that risk with the use of inhibitors of biochemical alterations in incipient cancer cells. The expression of tumor transformation in vitro and in vivo can be inhibited by a variety of compounds. Normal dietary constituents and pharmacologic agents may be candidates for chemopreventive activity; their prototypes are beta carotene and synthetic retinoids, such as isotretinoin (13-*cis*-retinoic acid), respectively. In the early 1980s, clinical studies with small numbers of patients established that synthetic retinoids could inhibit the progression of many preneoplastic conditions and some neoplastic states (reviewed in Lippman et al.¹). Dietary epidemiologic studies provided substantial support for the notion that certain vitamins, micronutrients, and other components of food enhanced or inhibited the development of cancer in humans.^{2,3} Prominent among the dietary constituents implicated as preventive agents for cancers of the lung and other organs was beta carotene, a substance that has frequently been suggested for human use because of its easy availability and low toxicity, even in very high doses.³

In this issue of the *Journal*, the results of two large randomized clinical trials of chemoprevention are presented.^{4,5} They have been carefully designed and impeccably conducted, but they have led to different conclusions. Beta carotene did not lower the rate of development of new basal-cell or squamous-cell cancers of the skin in subjects with previous skin cancers. In contrast, isotretinoin did lower the rate of development of second regional tumors in patients with a previous oral cancer.

Why these opposite results? The most obvious explanation is that beta carotene and isotretinoin represent two quite different inhibitors of carcinogenesis. In most model systems beta carotene is a weak anticarcinogen, whereas isotretinoin is a potent inhibitor of cancer formation. However, since beta carotene has recently been demonstrated to reverse a preneoplastic condition in humans — a step rather late in the pathway to cancer — other explanations should be sought.⁶

In the beta carotene study, the authors thoroughly address possible reasons for the negative results, but they do not consider an important alternative possibility: that the high levels of beta carotene may have

interfered with the actions of other key micronutrients. Recently, Xu et al.⁷ found that the administration of beta carotene to normal subjects led to a 40 percent decline in plasma alpha tocopherol levels over a period of eight months. The administration of beta carotene to mice with hair that were being irradiated with ultraviolet light also led to a 40 percent decline in plasma alpha tocopherol levels and a decrease of more than 80 percent in cutaneous-tissue concentrations as compared with untreated controls, but it did not prevent photocarcinogenesis (Gensler H: personal communication). The protective effect of antioxidants against cancers induced by ultraviolet light may depend on the total antioxidant pool, and the cell may lose the protective advantage of elevated beta carotene levels when exposed to ultraviolet light if levels of other antioxidants that work through other mechanisms are decreased. Measurement of plasma alpha tocopherol levels in subjects in the current trial would therefore be of great interest. The design of future chemoprevention trials using beta carotene, and for that matter any other natural dietary or pharmacologic compound, will need to consider whether the level of alpha tocopherol or other key micronutrients will be adversely affected. The pharmacology of micronutrients has been surprisingly little explored, and other unsuspected negative effects are likely.

In contrast, the trial of isotretinoin for the prevention of second regional primary tumors in patients with a first primary oral cancer was strongly positive. Indeed, with the strong experimental and clinical data already available about the chemopreventive and therapeutic activity of isotretinoin, a negative result would have been quite unexpected. The results also imply, but do not prove, that since isotretinoin can prevent the development of second tumors, it probably can prevent the development of a primary cancer as well. The trial directly addresses the subject of "field cancerization," the idea that an entire area has been exposed to carcinogenic insult (such as cigarette smoke in the upper aerodigestive system or aniline dyes in the genitourinary system), and therefore the entire "field" is conditioned for the development of malignant cells. The concept of field cancerization is of general importance, since this property is probably applicable to carcinogenesis and chemoprevention in many major tumor sites in humans: gastrointestinal, gynecologic, genitourinary, and perhaps even in the breast.

The second primary tumor is a good model in which to conduct chemoprevention trials, since lesions are easily measured, the time to the appearance of the second malignant tumor is short, and biologic changes or biomarkers used as intermediate end points can be correlated. The use of biomarkers as intermediate end points, although not addressed in either study, is important,⁸ since using cancer as the end point of a chemoprevention study ensures very slow progress. Genetic, biochemical, and immunologic indexes can all

serve as intermediate end points. Their validation as true intermediate end points of cancer development will be critical to the rapid development of new clinical chemopreventive agents and in the design of future intervention trials.

The initial choice of chemopreventive agents for clinical trials has been limited to a few compounds and has been dictated by epidemiologic and laboratory data available in the late 1970s and by the rigid requirement of the use of a "safe" compound in normal or nearly normal populations.⁹ The safety level required should be related to the level of risk. For example, if the study population is composed of normal or nearly normal subjects (such as volunteers with a history of one polyp), very few or no side effects will be tolerated by either the subjects or the staff. In contrast, if the subjects are at high risk (e.g., have a history of familial polyposis, or second tumor), considerable side effects may be acceptable. Another major consideration in the development of chemopreventive agents is the assessment of efficacy. Unless at least a few side effects are manifest, one might argue that there is no biologic activity. The determination of levels of the compound in serum or relevant tissues or the modulation of relevant biomarkers will therefore be important.

Only beta carotene, the retinoids, folic acid, and vitamins C and E have so far been used to any extent in Phase III clinical chemoprevention trials. The development of new classes of compounds with minimal toxicity, targeted pharmacologic distribution, and the ability to modulate relevant biomarkers used as intermediate end points will be a major achievement that may lead to even more effective compounds.

On the basis of promising preclinical anticarcinogenic activity, hundreds of potential chemopreventive compounds have been identified from dietary sources (such as vegetables and garlic). A formal decision-making network has been organized by the National Cancer Institute to deal with the large numbers of compounds that will be turned up by screening.⁹ There are at present about 12 large Phase III or IV cancer-control clinical chemoprevention trials being conducted in the United States and another 5 elsewhere. These studies involve subjects at high risk for cancers of the skin, colon, cervix, breast, lung, and other organs, who are being treated with retinol, beta carotene, isotretinoin, 4-hydroxy-phenyretinamide, and other compounds. These trials involve more than 100,000 subjects. If even a few provide positive results, the manner in which we view the management of cancer is likely to undergo a fundamental change. The next few years will see the maturation of many of these clinical chemoprevention trials. Results are eagerly anticipated.

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MANDATORY MONITORING FOR SIDE EFFECTS

The "Bundling" of Clozapine

CLOZAPINE is a new neuroleptic drug that was released for clinical use in the United States in February 1990 under the trade name Clozaril. Its availability is limited by an expensive mandatory system for distributing the drug and monitoring side effects — a marketing practice known as "bundling." The cost of the clozapine "bundle" is \$172 a week, or approximately \$9,000 a year, making it one of the most expensive therapeutic drugs in the United States. The unusually high cost of the drug plus the monitoring system may make it difficult, if not impossible, for many patients with schizophrenia to receive clozapine, especially if they are indigent and are treated at public institutions. In addition to limiting the availability of clozapine, this unusual marketing practice raises other complicated questions: What factors contribute to unusually high drug costs? Who should control a drug's distribution? What are acceptable levels of risk for drug treatments? Who assumes liability for a treatment-associated risk? And what are the processes by which these questions should be resolved?

BACKGROUND

Schizophrenia is a chronic illness with a prevalence rate of 1 percent,¹ and it leaves many patients unable to live independently in the community. Although there is no cure for schizophrenia, neuroleptic drugs have been used for more than 30 years to control psychotic symptoms. The therapeutic efficacy of neuroleptic agents is moderate, leaving many patients with chronic disabilities. Recent research suggests that clo-

zapine offers better control of psychotic symptoms, especially for some patients whose symptoms are resistant to standard neuroleptic drugs.^{2,3} Unfortunately, clozapine has produced agranulocytosis in 1 to 2 percent of patients during their treatment. This potentially fatal condition can develop over the course of a few days, without any warning signs, and at any time during treatment. There have been fatalities in Europe, but no patient in the United States is known to have died of clozapine-induced agranulocytosis. Recent experience suggests that when clozapine is discontinued, the white-cell count rapidly returns to normal, so early detection can prevent a fatal outcome. If the drug is given again, however, this side effect is likely to recur.⁴

PROBLEMS WITH THE BUNDLE

In order to prevent fatalities due to rapidly developing agranulocytosis, the Food and Drug Administration required that the distribution of clozapine be linked to close monitoring of the white-cell count, even after years of continuous use. In response, the manufacturer (Sandoz) established a national drug-distribution and monitoring system, registered as the Clozaril Patient Monitoring System (CPMS). Under this system, which is already in operation, a weekly blood specimen is obtained by venipuncture in order to detect an early decline in the white-cell count. Patients receive a week's supply of clozapine only after the blood specimen has been obtained ("no blood, no drug"). Should a decline in a patient's white-cell count be detected during weekly monitoring, the clozapine is immediately discontinued.

Bundling — linking the availability of a drug to a mandatory distribution and monitoring system — is an unusual practice that is not currently used for any other drug in the United States. Drug distribution, phlebotomy services, and laboratory analyses are provided by two private, for-profit companies under an exclusive contract with Sandoz.

Although the risk of death from agranulocytosis may be substantially reduced by linking drug availability to weekly monitoring of the white-cell count, controversy has arisen over the mandatory use of the CPMS. The ability of the system to track large numbers of patients throughout the United States each week has yet to be demonstrated. Centralized monitoring and distribution may be difficult, especially in large, mostly rural states with dispersed populations and in inner cities, where patients' addresses may change frequently and where some patients are homeless. It is not certain that the CPMS is superior to existing resources for blood monitoring in major medical centers or at university and Veterans Affairs hospitals.

WHO WILL PAY FOR THE CLOZAPINE BUNDLE?

For the first time, the purchase price of a drug includes both the manufacturer's cost and profit and the cost and profit of bundled services as well. The high