mation, smoking cessation, legislation, price policy, and taxation.

We have to create much more awareness of the smoking problem among health professionals than before, and one of the most important messages is the following: smoking cessation treatment is not only a matter of prevention, it is also a part of regular treatment of diseases and rehabilitation.3

At the 6th World Conference on Smoking and Health (November 1987), it was stated that cessation now has enough scientific background to be implemented much more than before. Cessation means offering a wide variety of techniques and methods for different target groups and different organizational structures with different levels of assistance for the smoker.3

A diversified system of techniques to help the smoker to stop includes: (1) methods to help the already highly motivated, low-dependent smoker (mass media assisted techniques, simple brochures, self-help techniques); (2) methods to help the motivated, rather highly dependent smokers (nicotine replacement therapy); and (3) basis for all the other intervention techniques are methods to create and maintain motivation (health education, public information, public education).

The 1988 Report of the US Surgeon General4 states very clearly that the use of tobacco products is not a matter of free choice, but is the result of an addiction as scientifically valid as addiction to heroin and other narcotics.

Many pharmaceutical approaches have been tried to treat nicotine dependence in man (tranquilizers and stimulants, anti-cholinergic drugs, Lobeline and Anabasine, alkalizing the urine with sodium bicarbonate, silver acetate).

Early work on fluoxetine (a serotonin reuptake-blocker) has started, and some work has been done with clonidine, an α2-adrenoceptor. Nicotine itself has, however, so far been the only drug found to be effective in treating nicotine dependence according to scientific standards and many controlled studies.5.6

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Chemoprevention of Lung Cancer*
Problems and Progress
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Laboratory and epidemiologic research findings of the past several decades have provided strong evidence that lifestyle and environmental factors contribute significantly to cancer incidence. Cancer sites which account for over 70% of all cancer mortality in the US—lung, colorectal, breast, prostate, pancreas, stomach, ovary, bladder, and liver—are all thought to be influenced by dietary factors.

International correlation studies comparing dietary intake to cancer rates, studies of migration and time trends from areas with low cancer to or from areas with high cancer rates; comparison of certain low-risk US populations (Seventh Day Adventists, Mormons) with the general US population; and case control studies comparing dietary patterns in cancer patients to controls in the study population, and cohort studies tracing populations forward in time have all shown differences in human cancer thought to be related to diet.

The epidemiologic and basic research of the 1970s gave us important leads on the relationship of diet to cancer. With the approach of this decade, the National Cancer Institute (NCI) recognized that its efforts in the prevention of cancer would have to be expanded into human intervention research and programs, specifically: chemoprevention, smoking prevention and nutrition research programs. From the experimental studies of the mechanisms of "initiation" and "promotion," substantial gains had been made in understanding the mechanism of carcinogenesis. This increased understanding of the carcinogenesis process was particularly important to the development of a successful chemoprevention effort.

Chemoprevention is a relatively new concept which postulates that, where it may not be practical to prevent cancer by removing the carcinogenic substances from the environment, it may be possible to interfere with the phases of carcinogenesis by introducing into the body certain specific micronutrients—selected vitamins, chemicals, and trace elements—or other cancer inhibitors which will block one or more of the steps by which cancer develops and progresses.

EVIDENCE FOR CHEMOPREVENTION RESEARCH

As an example of epidemiologic evidence for cancer inhibition, about 20 reports have evaluated cancer incidence and intake of foods high in vitamin A or β-carotene. In 9 retrospective studies, a significant increase in cancer risk at various sites was associated with diminished vitamin A intake. Most other retrospective data confirm the inverse association between vitamin A or β-carotene-containing foods and relative cancer risk.

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Laboratory research supports the hypothesis that retinoids, and perhaps β-carotenoids, can inhibit or modify the expression of cancer. Retinoids are of special interest for chemopreventive use because they can exert their antineoplastic activity in cells that are already dedifferentiated. The study of retinoid activity has been facilitated by the concerted development of synthetic analogues designed to enhance potency and minimize toxicity.

Carotenoids are interesting because they do not exhibit any serious toxicity, and their blood levels are directly related to dietary intake, unlike the retinoids, which are subject to strict homeostatic control. A direct chemopreventive role for β-carotene has been suggested by virtue of its efficient ability to deactivate singlet oxygen and trap organic free radicals and kidney studies have also suggested lower risks associated with foods high in other nutrients, such as folate, vitamin C, and selenium.

**Rationale for Chemoprevention of Lung Cancer**

The concept of offering protection against lung cancer by adding micronutrients or other substances to the diet must be put in perspective. Chemoprevention is not the primary or preferred line of defense against lung cancer. Thousands of studies have demonstrated that the use of tobacco is the foremost cause of lung cancer; the most effective prevention of lung cancer is not to smoke. Research on strategies to reduce tobacco use are being aggressively pursued at the National Cancer Institute through 60 prevention trials in over 200 communities comprising 10 million people.

Nevertheless, there is a sound basis for research on chemoprevention of lung cancer. Former smokers, even years later, remain at higher risk than those who have never smoked. Smokers and former smokers with occupational or environmental exposure to radon and asbestos also carry an increased risk for lung cancer. Finally, there are smokers who, for a variety of reasons, cannot be persuaded to quit. In the interest of offering maximum risk reduction to these groups, research in chemoprevention of lung cancer is being conducted.

**Preclinical Studies in Chemoprevention of Lung Cancer**

During the past 3 years, the chemoprevention program at NCI has conducted preclinical chemoprevention evaluation studies in cells and animal models of lung cancer. The goals of these studies are to identify and determine the relative efficacy and relative toxicity of chemopreventive agents that would potentially be active in preventing lung carcinogenesis in humans. A number of principles help insure relevance and serve as useful indicators in selecting preclinical models:

1. The intervention must begin when the host has no histologic evidence of neoplasia, even though the intervention may be used subsequently to inhibit events in the carcinogenic process.
2. The agent used to induce the cancer in the animal model should work by mechanisms that are similar to mechanisms by which suspected human carcinogens act, e.g., carcinogens in cigarette smoke induce free radicals.
3. The neoplasia induced in the experimental model should be histologically similar to the human cancer in question.

4. The model should provide reproducible, measurable results; the cancers produced should be dose-related to the carcinogenic agent used; and the latent periods should be short enough to allow completion of the study in a reasonable time.

Two models have been chosen which include N-methyl-nitrosurea induced squamous cell carcinoma of the bronchus and diethyl-nitrosamine induced squamous cell and adenocarcinoma (including small cell) of the lung and bronchus. These two models compose the histologic spectrum of the predominant human lung cancers: (1) Both models show excellent dose-dependent kinetics of carcinogenesis. (2) They use an etiologic agent that induces cancer by mechanisms which may be similar to those operating in human carcinogeneses. (3) Both models allow for intervention at different stages of the carcinogenic process, and for a biologically relevant carcinogenesis process to proceed from one transformed cell in a way similar to the pathogenesis of human lung cancer.

By virtue of practical experimental design, the animal model is exposed to the carcinogen in an amount many times the adjusted dose in man. Therefore, when a potential chemopreventive agent results in a positive outcome—the inhibition of carcinogenesis—in the animal model, its potential for efficacy in human lung cancer is promising.

Several chemopreventive agents have shown promise in prevention of experimental lung cancer in animals:

4-Hydroxy-phenylethylretinamide, a potent retinoid exhibiting low toxicity, is being studied to determine if its effects on differentiation can result in prevention or inhibition of lung cancer. It has already been found effective in preventing experimental breast and bladder cancer in rodents.

β-Carotene, which has a molecular structure that makes it an excellent "trapper" of free radicals, is found at reduced levels in the serum of lung cancer patients. It is being tested in combination with retinol for its ability to inhibit both squamous cell and adenocarcinomas of the lung.

Difluoromethylnorlithine, an ornithine decarboxylase inhibitor, is being examined to determine whether its potential antiproliferative effects can be used to intervene in the late stages of lung carcinogenesis.

Oltipraz (a glutathione-S-transferase enhancer) is an effective detoxicant of potential chemical carcinogens. Sodium molybdate is also an effective modulator of detoxifying enzymes. Both are being examined to determine if their detoxifying activities can be used against certain chemical carcinogens.

All of these agents are in different stages of preclinical and clinical development. Early results have provided optimism that significant chemoprevention of human lung cancer may be possible in the next decade.

**Current Status of Clinical Prevention Research**

The predictive ability of animal models and epidemiology in the evaluation of a cancer preventive regimen is limited. Only through a controlled clinical trial can the efficacy and safety of an agent be clearly established. First, data from epidemiologic and laboratory studies are evaluated to determine whether a chemopreventive regimen is a promising
and acceptable candidate for a clinical trial. Once this step is completed, a clinical trial is initiated in which a safe and effective dose level for humans is established.

Both cancer prevention and cancer treatment trials are designed to rigorously evaluate the efficacy and safety of an intervention strategy in a clinical setting. Features of a sound research design such as randomization, appropriate controls, blinding when feasible, precise definition of patient eligibility, dose and treatment schedules, assurances of subject compliance, and accurate data collection and processing are important for both types of trials.

The two types of trials differ significantly, particularly with regard to the choice of study population and protocol. A treatment study population consists of cancer patients, while a prevention trial can select healthy persons, persons at high risk, or those with precancerous lesions, in addition to currently disease-free subjects previously treated for cancer who are at high risk for another new cancer. The duration and size of a prevention trial is usually greater than that of a treatment trial.

A further difference is the level of acceptable agent toxicity. Moderate to severe toxicity is considered reasonable in the treatment of malignant disease. In contrast, a cancer prevention intervention should be devoid of notable adverse side effects.

The study design of a treatment trial generally consists of a treatment group and an alternate treatment to placebo group. Complex designs are often used in intervention trials that evaluate more than one intervention. A chemoprevention regimen requiring multiple agents can usually be administered safely in combination.

The final phases of the clinical linear array are concerned with implementation of a chemoprevention regimen once its efficacy has been established. Research conducted to devise the most effective and appropriate application to target populations is then followed by a demonstration program.

Due to the enormous commitment of resources required for large-scale human intervention trials, studies with the potential for broad public health impact generally have been limited to situations of cancers with the greatest morbidity and mortality rates. If these large studies confirm the efficacy of specific chemopreventive interventions in high-risk groups, the broader application of these results to healthy individuals would have wide impact for reducing overall cancer incidence in this country.

NCI Clinical Trials in Chemoprevention of Lung Cancer

Pilot Studies

A two-year pilot study to assess the efficacy and toxicity of long-term retinoid/β-carotene treatment was conducted by the University of Washington in subjects with a smoking history of 20 pack-years or more. The 1,022 participants in the trial were randomized to daily treatment with 25,000 units of retinol, 30 mg β-carotene, retinol plus β-carotene in the same doses, or placebo. Compliance was considered excellent as measured both by self-reporting and periodic pill counts. Symptoms attributable to the intervention were negligible.

The same group of investigators conducted a second pilot study among subjects with asbestos exposure as well as a history of cigarette smoking. These subjects are at high risk for developing both malignant mesothelioma and lung carcinoma. To date, 764 men have been randomized to receive 25,000 units retinol plus 15 mg β-carotene daily or a placebo. There is no evidence that toxicity in the treatment group exceeds that of the placebo group. Compliance in both study groups has been equivalent. The investigators propose to integrate these two cohorts into a single large scale trial, monitoring them closely for an additional 5 years to further assess long term compliance, toxicity, and efficacy. Their ultimate goal is to launch a full-scale efficacy trial among 13,000 smokers and 4,000 asbestos-exposed subjects.

Another pilot study was conducted by the University of Pittsburgh among male and female cigarette smokers to determine the feasibility of using β-carotene in a chemopreventive trial. Approximately 400 subjects over the age of 55 were randomized to 15-30 mg β-carotene daily or to a placebo. Data from the third year of the study showed that the administered agent led to the expected increase in serum β-carotene levels. It also demonstrated that the trial was feasible, the compliance excellent, and the toxicity acceptable.

Finally, a six-month pilot study in China has investigated 350 active and retired tin miners who, by virtue of at least 10 years of underground mining experience, are at high risk for lung cancer. The miners received β-carotene, retinol, vitamin E, and selenium to determine if these agents might reduce lung cancer incidence. A full-scale study to test the protective potential of this intervention is scheduled to begin in 1989.

Intermediate End Point Studies

A trial has been initiated to determine whether markers of early lung carcinoma can be identified and whether β-carotene can modify either their frequency or progression. The 400 high-risk cigarette smokers entered into the aforementioned β-carotene pilot study will be studied to determine if quantitative DNA analysis of sputum epithelial cells can be used as a marker of premalignant abnormalities, to compare such analyses with standard sputum cytology, and to determine the effect of β-carotene administration on these parameters. If quantitative DNA analysis appears to be a marker which can be modified via a chemopreventive intervention, it might be possible to obtain stronger evidence of the efficacy of the intervention in reducing cancer risk, as well as identifying groups at particularly high risk for cancer.

Another intermediate end point trial at the University of Texas analyzes the incidence, prevalence, and modification of sputum atypia in high-risk asbestos workers. A second end point of this trial is the incidence of lung cancer. Six hundred thirty subjects have been enrolled and randomized to receive 50 mg β-carotene daily and 25,000 units retinol every other day or to placebo. This trial is ongoing and no data are available concerning the validity of the putative intermediate end point.

Preliminary data have been published on the results of a randomized trial conducted at the University of Alabama comparing 10 mg folic acid plus 0.5 mg vitamin B₆ daily for
Genetic Events in the Pathogenesis of Lung Cancer*

John D. Minna, M.D.

Ultimately, the prevention and treatment of lung cancer will be based on knowledge of the molecular and cellular events underlying the pathogenesis of this disease. A description of the pathogenesis must take into account the known etiologic factors, including smoking, exposure to other carcinogens such as radon or workplace chemicals, the presence of chronic obstructive airway disease, the role of diet, and, possibly, familial predisposition. We have found that lung cancer cells produce autocrine growth factors which are capable of promoting their own growth early in pathogenesis, allowing accumulation of a series of genetic lesions involving the activation of the dominantly acting cellular proto-oncogenes and the inactivation of the recessive (chromosomal deletion) or "tumor suppressor" genes.* Together these lesions participate in the transformation of bronchial epithelial cells to malignant lung cancer cells.4,4

Lung cancer patients have had considerable exposure to agents which can damage DNA. Lowering this exposure provides our first target in preventive efforts. Recently, P-post-labeling techniques have allowed the detection of covalently bound DNA adducts in normal lung. These studies have shown higher levels in DNA of cigarette smokers than nonsmokers and a linear relationship between adduct levels and daily or lifetime cigarette consumption, while people who have given up smoking for 5 or more years have adduct levels comparable with those of nonsmokers.5 We have found that lung cancer cells exhibit a large (almost bewildering) number and type of lesions in oncogenes and tumor suppressor genes, in the order of 10-20 lesions per tumor. Perhaps we should not have been surprised by this. Experimental systems show that even the dominantly acting oncogenes require the cooperation of more than one oncogene to transform normal cells (eg, such as a combination of c-myc and a mutated ras gene)6 and that cancer cells can use many different genetic motifs in the activation or inactivation processes.

The identification and characterization of the genetic events caused by this carcinogenic exposure has rapidly progressed over the past decade. This has come about because of the development of the field of cellular proto-oncogenes4 and the establishment of chromosomal deletion analysis using restriction fragment length polymorphism (RFLP) probes.7 The development of methods to culture lung cancer cells in vitro led to the establishment of a large panel of lung cancer cell lines.8,9 These lung cancer cell lines have allowed the systematic characterization of cyto-genetic changes including chromosomal deletions and translocations, oncogene status at the DNA and RNA level, and the production and response of lung cancer cells to highly

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Full-scale Trials

A large-scale trial has been undertaken in collaboration with the National Public Health Institute of Finland. Investigators are comparing the effect of oral synthetic β-carotene and vitamin E, separately and in combination, vs placebo, in reducing lung cancer incidence among approximately 29,000 male smokers, aged 55-69. Begun in March 1984 at five health centers throughout Finland, the study is expected to end in 1992.

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