Preface

In the industrialized world, deaths from cancer are increasing at a rate which cannot be explained by the aging of the population [1]. In the United States, cancer remains the second leading cause of death—22.4% of total deaths based on 1988 statistics [2]. Although stomach cancer deaths have declined approximately 80% since 1930, mortality from cancers of the prostate, breast, and lung have increased.

Most laboratory and epidemiological data suggest that approximately three-fourths of all cancers are attributable to lifestyle factors, such as diet, tobacco use, and occupational carcinogen exposure. The most obvious association is that between tobacco use and lung cancer; it has been estimated that 80% of lung cancers occur in smokers [3]. Despite efforts at primary prevention, i.e., cessation of tobacco exposure, the lung and upper aerodigestive tract will harbor approximately 226,000 new cancer cases in 1992 [2]. When both lung and stomach cancer are excluded, cancer incidences in industrialized nations are still increasing in males over age 45 [4]. These data suggest that efforts at secondary prevention strategies, such as chemoprevention, should be agressively pursued in addition to primary prevention.

Cancer chemoprevention may be defined as intervention with chemical agents between initiation and invasion in order to halt or slow the carcinogenic process. The testing of drugs for this purpose differs from that of testing for cancer treatment. The latter involves cancer patients as the study population in which increased patient survival or decreased tumor size are the endpoints. In contrast, cancer chemoprevention trials involve healthy populations, although these may be populations at higher risk for cancer, in which cancer incidence reduction is the endpoint. Since cancer may not develop for 20-30 years, the design of clinical chemoprevention trials involves large sample populations (tens of thousands), lengthy duration and follow-up, and high cost. For example, the National Institutes of Health-funded trial to determine the efficacy of tamoxifen in preventing breast cancer will involve 16,000 patients and $68,000,000 [5]. Several candidate chemopreventive agents that block testosterone activity in the prostate gland [6] are subject to many of the same trial dilemmas as tamoxifen.

The use of intermediate biomarkers as surrogate endpoints may circumvent the long and expensive problems in chemopreventive drug trial design. Intermediate endpoint biomarkers as defined here refer to biological alterations in tissue (histological, genetic, biochemical, proliferative, differentiation-related) occurring prior to malignancy. Although none have been validated to date, it is hoped that modulation of these biomarkers by potential chemopreventive agents will correlate with decreased cancer incidence. The use of intermediate biomarkers as trial endpoints will allow smaller sample populations, shorter trials, and less cost.

This special issue of the *Journal of Cellular Biochemistry* is the second in a series that represents manuscripts from conferences sponsored by the Chemoprevention Branch of the National Cancer Institute (NCI). The purpose of the conferences is to bring together basic and clinical research scientists to design clinical trial strategies involving intermediate biomarkers. In a previous issue, Supplement 16G, the idea of intermediate endpoint biomarkers as surrogate trial endpoints was introduced, using the colon as a representative organ.

This second issue, Supplement 16H, addresses chemoprevention of prostate cancer, the site of the highest incidence of cancer (22%) and the second highest cause of cancer deaths (12%) in males in the United States. The design of chemoprevention trials for the prostate presents problems in addition to those enumerated previously, such as competing causes of mortality in an older study population and the lack of dependable methods for detecting microscopic cancers. In this conference, the concept of biomarkers was expanded to include markers of the progression of microscopic to clinically relevant prostate cancer. The subject of a third special supplemental issue will be chemoprevention of bladder cancer.

The potential benefits of chemoprevention are substantial. The Chemoprevention Branch, NCI, which has as a major objective the development of promising chemical agents as chemopreventive drugs for humans, and the editors of the *Journal of Cellular Biochemistry* hope that exposure to the idea of intermediate biomarkers as surrogate endpoints in trials of chemopreventive drugs will stimulate better understanding and research. An additional, and possibly more wide-reaching, benefit of research in this area may be an increased understanding of the basic mechanisms of carcinogenesis and tumor progression.

REFERENCES

1. Hoel DG, Davis DL, Miller AB, Sondik EJ, Swerdlow AJ: Trends in cancer mortality in 15 industrialized countries, 1969-1986. J Natl Cancer Inst 84:313–320, 1992.
2. Boring CC, Squires TS, Tong T: Cancer statistics, 1992. CA 42:19–38, 1992.
3. Williams GM: Causes and prevention of cancer. Stat Bull 72:6–10, 1991.
4. Davis DL, Hoel D, Fox J, Lopez A: International trends in cancer mortality in France, West Germany, Italy, Japan, England and Wales, and the USA. Lancet 336:474–481, 1990.
5. FDC Reports: Nolvadex breast cancer prevention trial will be subject of hill hearing. "The Pink Sheet" 54:T&G 1, 1992.
6. Henderson BE, Ross RK, Pike MC: Toward the primary prevention of cancer. Science 254:1131–1138, 1991.