Preface

While stomach cancer deaths have decreased approximately 80% since 1930, cancer deaths in general are increasing in the industrialized world at a rate that cannot be explained by population demographics alone [1]. Based on 1988 statistics, cancer is the second leading cause of death in the United States, accounting for 22.4% of all deaths [2].

Many laboratory studies and most epidemiological data suggest that the majority of cancer deaths, approximately three-fourths, are attributable to so-called lifestyle factors: diet, tobacco use, and occupational exposure. Excluding lung cancer deaths, worldwide death rates for men in industrialized nations has increased 9% since 1950 [1]. Ten percent of cancer rates in the United States are attributable to cancers of the urinary tract. Occupational exposure to chemicals, particularly to aromatic amines, has long been implicated as an etiologic factor in elevated risk for bladder cancer [3]. Other studies have convincingly demonstrated an increased risk of bladder cancer in smokers as compared to nonsmokers [4]. These data suggest that efforts at secondary prevention (intervention) strategies including chemoprevention, should be aggressively pursued, as should new and existing primary prevention (avoidance) strategies.

The concept of cancer chemoprevention is based on the long-held model of the cancer process as a continuum. Chemoprevention is the intervention with chemicals (drugs) to either abolish or delay the development of those processes which begin with normal-appearing tissues and progress from clonal expansion through invasion and to eventual metastasis. Methods for testing potential chemopreventive drugs differ substantially from testing methods used for chemotherapeutic drugs. Efficacy for testing of chemotherapeutic drugs involves cancer patients as the study population and uses reduction in disease and/or improved mortality as study endpoints. Testing of chemopreventive agents, on the other hand, involves basically healthy individuals who may or may not be at increased risk for cancer, and uses the reduction of cancer incidence as the endpoint. Since an individual cancer may develop over decades, the design of clinical trials requires extremely large study populations, lengthy timeframes, and high cost [5,6].

Surrogate endpoints, particularly intermediate biomarkers, may help circumvent the length and expense involved in chemoprevention trials. Intermediate biomarkers are understood here to be morphological and/or molecular alterations in epithelial tissues associated with a phase of carcinogenesis preceding malignancy and have been classified as histological, genetic, proliferation-related, and differentiation-related.

Experimental studies on the development of intermediate biomarkers and their modulation by putative chemopreventive agents will focus on the degree of reliability and on their predictive value as measured by such factors as specificity, sensitivity, and overall correlation with cancer endpoints. The benefits of the application of intermediate biomarkers in cancer chemoprevention clinical trials include reduced time intervals necessary for the trial since the study endpoints are correlated with earlier stages in the carcinogenesis process. Efficacy trials will also require smaller study populations. As a direct result of the first two considerations, chemoprevention trials should be lower in cost than other clinical trials. Finally, the results of efficacy trials for the modulation of biomarkers may serve as rationale for performing further clinical trials with cancer incidence as the endpoint.

This special issue of the *Journal of Cellular Biochemistry* is the third in a series to be published in 1992, representing manuscripts from conferences sponsored by the National Cancer Institute (NCI). The purpose of these conferences is to bring together basic and clinical research scientists to design clinical trial strategie. The concept of intermediate endpoint biomarkers as surrogate trial endpoints was introduced in Supplement 16G, with the colon as the representative organ. The second issue, Supplement 16H, addressed 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 the additional problems of competing mortality in older study populations and the lack of dependable methods for detecting microscopic cancers. For this organ, the concept of biomarkers was expanded to include markers of progression.

This issue, Supplement 16I, addresses the chemoprevention of bladder cancer. Over 50,000 new cases of bladder cancer will be diagnosed this year alone [1]; the vast majority of these will be transitional cell carcinomas. The natural history of transitional cell carcinoma of the bladder presents many opportunities for intervention by chemopreventive agents. Trials designed for chemoprevention of bladder cancers involve all considerations enumerated previously, as well as strong components of lifestyle factors (smoking in particular) and occupational exposures. A forthcoming report will be an outgrowth of presentations from a meeting devoted to chemoprevention of aerodigestive tract cancers [7].

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