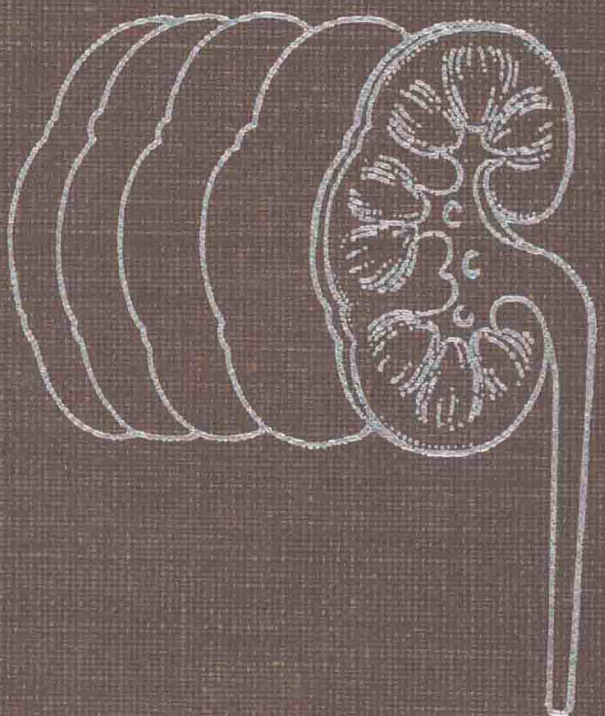

Cancer and the Kidney

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This volume contains much information about cancer therapy, particularly regarding drugs. The authors, editors, and publisher have taken meticulous care to insure the accuracy of the drugs, dosages, and schedules recommended. Since the law requires that information about changes in accepted indications and methods of drug use be printed in the package insert, the reader is advised to consult this document before using a drug. The physician then can be certain that new data have not led to altered instructions.

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Cancer and the Kidney

To our families

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FOREWORD

In 1963 a 19-page review article was published entitled "Renal Complications of Neoplastic Disease."* This constituted the first extensive consideration in the literature of the interaction between cancer and the kidney and was viewed as a comprehensive discussion of the subject. Major topics covered were hyperuricemic, hypercalcemic, myelomatous, and obstructive nephropathy. Several complications of antineoplastic therapy as well as tumor infiltration of the kidney also were considered briefly. This publication serves as a benchmark for an assessment of the current status of our knowledge relating to the interaction of cancer and the kidney.

Over the past two decades, knowledge relating to both cancer and the kidney has accrued rapidly. Enormous strides have been made in clinical oncology and, most particularly, in medical oncology. Similarly, the basic sciences, including cell growth and regulation, virology, immunology, and cell membranology, have become integrated into the coherent discipline of tumor biology. Thus, major advances have been achieved, not only at a clinical level, but at a basic level in oncology as well. Simultaneously, our understanding of kidney structure and function in health and disease has increased greatly. The impact upon the kidney of disturbances due to immunologic, infectious, vascular, and metabolic injury has become increasingly apparent. Although our ability to prevent or to modify these processes is not well developed, remarkable progress has been achieved in treatment of end-stage renal disease through dialysis and transplantation.

The present volume, with its 25 chapters and 50 contributors, reflects the expanded body of knowledge currently available relating to cancer, the kidney, and their interaction. Integration of this knowledge now is particularly important if the patient with cancer is to benefit maximally from these advances. I will elaborate subsequently upon the relationship between cancer and the kidney, citing specific examples of areas that are particularly important with regard to integration of knowledge. First, however, it would be informative to enhance the reader's historical perspective by highlighting in more detail some of the advances in clinical oncology and nephrology which have occurred during the past two decades.

The early 1960s represented a critical time for the development of medical oncology. The principles of combination chemotherapy in acute lymphocytic leukemia were developing, as applied to both remission induction and remission maintenance. These investigations, along with pharmacologic studies of meningeal leukemia, and the application of chemotherapy and radiotherapy to the prophylaxis

*Frei, E., III., et al.: Renal complications of neoplastic disease. J. Chron. Dis., *16*:757, 1963.

of meningeal leukemia, ultimately led to the curative treatment of that form of leukemia. A number of important agents, such as the fluoropyrimidines, the Vinca alkaloids, cyclophosphamide, and procarbazine, were discovered in the late 1950s and early 1960s. Immediately derivative of the aforementioned studies in acute lymphocytic leukemia were the prospectively designed curative-intent studies with combination chemotherapy in Hodgkin's disease and non-Hodgkin's lymphoma. Thus began medical oncology, which had been relegated to palliative attempts at treatment of patients with advanced disease and, since so little could be offered, had interrelated minimally with the established disciplines of surgery and radiotherapy. The scientific community was skeptical as to whether medical oncology, and chemotherapy particularly, represented a reasonable professional and resource investment. The transition from palliative to curative intent treatment for a few diseases in the late 1950s and early 1960s established the clinical potential for chemotherapy, led to the recognition in 1971 of medical oncology as a subspecialty of the American Board of Internal Medicine (there are now some 1,700 certified medical oncology subspecialists), and led to an increasing number of young investigators coming into the field.

Meanwhile, a new era in clinical nephrology was launched in the spring of 1961 with a dramatic presentation by Dr. Belding Scribner at the Annual Meeting of the American Society for Clinical Investigation. He described a new technique for chronic vascular access which was to mark the beginning of an advancing technology in dialytic support of patients with end-stage renal disease. Soon to follow were effective techniques in renal transplantation utilizing both living and cadaver kidney donors. The foregoing clinical achievements were accompanied by a major acceleration in kidney-related research. While A.N. Richards and co-workers developed the micropuncture technique prior to World War II, in the 1960s this technique was further developed in laboratories throughout the world. Its modifications and expanded applications led to advancement of our concepts relating to the functional anatomy of the nephron. Increasing application of the clearance methodology initially developed by Homer Smith and his colleagues also contributed to our expanded understanding of both normal and abnormal renal physiology. Concomitantly, percutaneous renal biopsy techniques evolved, thereby allowing easy access to kidney tissue for morphologic and immunologic studies at various stages of disease. Subsequent development of electron and immunofluorescence microscopy permitted the description of previously obscure pathologic processes, allowed classification of glomerulopathies into more meaningful categories, and elucidated the pathogenesis of immunologically mediated renal disease. This unprecedented progress in our understanding of the kidney served to stimulate intense interest on the part of clinicians as well as basic investigators. Nephrology was established as a subspecialty of the American Board of Internal Medicine in 1972; there are now some 1,400 Board-certified nephrologists in the United States. The membership of the International Society of Nephrology now numbers more than 4,000, whereas the American Society of Nephrology now has approximately 3,200 members.

From the foregoing, it is apparent that this major expansion of knowledge and interest in the disciplines of oncology and nephrology provides the potential for significant advances in the care of the cancer patient with associated renal disease, through integration of this knowledge and its bedside application. Realization of this potential has become increasingly important in recent years with the increased incidence of urinary tract complications in the cancer patient.

The patient with cancer is unusually vulnerable to the development of renal disease because of complications of therapy and the basic manifestations of cancer. Today there are some 14 forms of systemic neoplastic disease that can be cured either by chemotherapy alone or in the adjuvant setting, where chemotherapy is combined with localized forms of treatment. In addition, even in the absence of curative therapy, major benefit may be derived from chemotherapy. Thus, a high percentage of cancer patients are candidates for chemotherapy. Cancer is a vigorous disease and multimodality cancer treatment must be vigorous in order to control the tumor. Unfortunately, this vigorous therapy often affects normal host tissue, including the kidney. This applies not only to chemotherapy, but to radiotherapy as well. Since many chemotherapeutic agents are both immunosuppressive and myelosuppressive, and since intensive chemotherapy may be optimal for selected tumors, infectious complications are a major part of the medical oncology scene. The antibiotics employed to control the spectrum of organisms most likely to cause infections in cancer patients frequently cause renal damage. The complexity of the problem is highlighted by the fact that the average hospitalized cancer patient is receiving seven to eight different drugs at any one time.

In addition to therapeutic complications, immunologic abnormalities relating to the tumor may adversely affect renal function. Antibodies may develop to certain tumor antigens leading to formation of circulating immune complexes which may cause various glomerulopathies. Multiple myeloma and other neoplasms may result in the production of large quantities of paraproteins (immunoglobulins or subunits thereof), often a cause of severe renal damage. Metabolic abnormalities associated with cancer may also result in renal damage. Hypercalcemia due directly to destruction of bone by neoplastic cell invasion or due indirectly to ectopic parathyroid hormone or other tumor products may result in elevation of serum calcium with resultant nephropathy. Tumors with a high proliferative thrust, and particularly tumors that are markedly sensitive to chemotherapy and/or radiotherapy, may be associated with marked purine catabolism thereby causing hyperuricemic nephropathy. Indeed, prior to the 1970s this was the major concern of the medical oncologist with respect to risk of renal damage. Knowledge of the pathogenesis of this lesion has led to the development of highly effective measures for prevention and therapy. A variety of fluid and electrolyte imbalances may occur in cancer patients. Recognition, prevention, and treatment of these disorders require a comprehensive understanding of renal function. Finally, the cancer process may involve the kidney per se, or may produce obstruction of urine flow. The latter most commonly occurs with gynecologic and other pelvic neoplasms. The recognition and management of such disorders require knowledge of the pathology of urinary tract obstruction.

The foregoing examples underscore the importance of the kidney to the clinical oncologist. Although an appreciation of the interaction of cancer and the kidney is important for all physicians involved in the care of the cancer patient, it is essential that the medical and pediatric oncologist and radiation therapist, because of their frequent role as primary care physician for the cancer patient, possess a comprehensive knowledge of clinical nephrology. This involves an understanding of renal diagnostic techniques, including radiography, ultrasonography, and nuclear medicine; pharmacologic principles related to the kidney; pathogenesis and management of acute and chronic renal failure; and contemporary nutritional concepts. Furthermore, nephrologists and urologists increasingly will be called upon to participate in the care of cancer patients,

owing to the growing incidence and complexity of renal complications encountered in these patients. It is essential that these subspecialists develop an appreciation for the aspects of oncology to be considered in depth within this volume.

Thus, a compilation of the vast body of knowledge relating to the interaction of cancer and the kidney which has developed, predominantly over the past two decades, is a most important and worthy goal at this time. The editors have presented and integrated this knowledge into a single volume which is intended to serve as a reference source to all physicians caring for cancer patients. The intent is that pediatric and medical oncologists, nephrologists, and urologists; radiation oncologists; gynecologists; general surgeons; and primary care physicians have a single resource which comprehensively deals with the interaction between cancer and the kidney and thus facilitates the integration of their clinical efforts. I believe this goal has been met by *Cancer and the Kidney*, edited by experienced and highly accomplished clinician-investigators representing oncology (Marc B. Garnick) and nephrology (Richard E. Rieselbach).

Boston, Massachusetts EMIL FREI III

PREFACE

The goal of this volume is to provide a comprehensive view of the interaction between cancer and the kidney, a frequent concern of the diversity of physicians who care for patients with cancer. Although a substantial body of knowledge relating to this area has developed within recent years, heretofore a single comprehensive integrated source of clinically relevant data addressing this subject has been unavailable.

Cancer and the Kidney provides such a volume, and thus serves to advance the multidisciplinary approach that constitutes the foundation of contemporary care for the cancer patient. Principles derived from many disciplines are incorporated into a comprehensive consideration of both the impact of cancer or its treatment upon the kidney as well as the influence of kidney failure or its treatment upon the etiology and treatment of cancer. Contributing authors represent the disciplines of adult and pediatric nephrology, medical and pediatric oncology, diagnostic radiology, pharmacology, radiation therapy, urology, general surgery, gynecology, immunology, and endocrinology. The information presented represents both an extensive synthesis of appropriate American and world literature and the seasoned experience of clinicians and investigators who have been on the forefront of improving the care of patients with cancer and/or kidney disease.

Cancer and the Kidney is divided into five sections, each addressing a specific area as described in more detail within the preface for each individual section. First, basic concepts in nephrology that have relevance to the cancer patient are covered to develop a basis for subsequent consideration of specific interactions between neoplastic processes (and their treatment) and the urinary tract. Section II discusses neoplastic processes that involve the kidney via immunologically mediated disease, tumor products, or tumor metabolites, whereas Section III addresses those neoplastic processes that directly involve the kidney or produce renal failure via obstruction of urine flow. The renal complications of antineoplastic and associated therapy are discussed in Section IV. While Sections I to IV describe the manner in which cancer and its therapy affect the kidney, Section V considers the impact of kidney disease upon cancer. The chapters in this section discuss the contribution of primary renal disease and uremia (and its therapy) to the pathogenesis of cancer.

It is the editors' intent that the broad approach and primary clinical orientation of *Cancer and the Kidney* facilitate its utilization by clinicians of many disciplines who care for the patient with cancer. We hope that the multidisciplinary approach of this volume will serve as a stimulus for its readers to pursue collaborative care, in that this approach frequently offers the

most effective management for the cancer patient with kidney involvement. We believe that the complex interaction of cancer and the kidney has been elucidated to a major degree in recent years. In many instances, the challenges of previous years may now be met successfully by the multidisciplinary team prepared to apply the knowledge presented herein at the bedside of patients whose problems involve cancer and the kidney.

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