CRC

THE PATHOLOGY *of* BLADDER CANCER

Volume I

George T. Bryan
Samuel M. Cohen

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Editors

George T. Bryan, M.D., Ph.D.
Professor
Department of Human Oncology
Wisconsin Clinical Cancer Center
University of Wisconsin Center for
Health Sciences
Madison, Wisconsin

Samuel M. Cohen, M.D., Ph.D.
Professor and Vice Chairman
Department of Pathology and
Laboratory Medicine
Eppley Institute for Research
in Cancer
University of Nebraska Medical Center
Omaha, Nebraska

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PREFACE

Pathology, in a broad sense, is that branch of medicine dealing with structural and functional changes of cells, tissues, or organisms that cause or are caused by disease. Clearly, any branch of science or any approach that contributes to knowledge concerning the nature and evolution of disease may be considered as an element of pathology. The interdisciplinary character of the investigations of disease is well exemplified by the wide variety of scientifically diverse specialists that have contributed to present knowledge concerning bladder cancer. In several countries in recent years groups of specialists have been drawn together to form study groups to coordinate and communicate advances in the study of bladder cancer. In the U.S., the National Bladder Cancer Project, under the scientific leadership and guidance of Dr. Gilbert H. Friedell, and the support of the National Cancer Institute, has fostered and encouraged interdisciplinary approaches to studies of bladder cancer.

There are many reasons why scientists are attracted to investigate bladder cancer and its tissues of origin. The bladder is an easily accessible organ to direct visualization. Samples of tissue are relatively easy to obtain, though often in small quantities. Biologic variables can be studied in vivo and in vitro. Excellent animal models that replicate many recognized features of human bladder cancer exist. Defined chemical substances are known as etiologic determinants of human bladder cancer. And finally, much still needs to be learned in order to effectively deal with individuals at high risk of development of bladder cancer, or patients that have developed bladder cancer.

Present classification schemes of bladder neoplasms are based on structural analyses of histologic material, primarily at the light microscopic level. Attempts to identify histologic variables of certain bladder lesions as biologic precursors of malignancy are in progress. Efforts to relate functional attributes of altered bladder tissues to preneoplastic and neoplastic structural changes are in active development. These advances do require a common recognition and communication of histologic patterns that are used as standard benchmarks.

This volume is offered to present in detail descriptions of histologic characteristics of bladder cancer in humans and animals. Areas of recent research advances that may extend our knowledge of the pathobiology of bladder cancer are emphasized. Observations derived from experimental animals are related to the pathogenesis of bladder cancer in humans. This book is intended for pathologists, urologists, oncologists, radiation therapists, epidemiologists, environmental scientists, toxicologists, public health scientists, and regulatory officials.

George T. Bryan
and
Samuel M. Cohen

THE EDITORS

George T. Bryan, M.D., Ph.D., is Professor of Human Oncology at the University of Wisconsin Center for Health Sciences, and Clinical Consultant, William S. Middleton Veterans Administration Hospital at Madison, Wisconsin.

Dr. Bryan obtained his training at the University of Wisconsin, Madison, receiving the B.S. degree in 1954, the M.D. degree in 1957, and the Ph.D. degree in 1963. He served as an Instructor from 1961 to 1963, as an Assistant Professor from 1963 to 1967, as an Associate Professor from 1967 to 1969, and as a Professor from 1969 to 1975 all in the Division of Clinical Oncology, Department of Surgery at the University of Wisconsin (Madison). It was in 1975 that he assumed his present position.

Dr. Bryan is a Fellow of the American College of Physicians. He is a member of the American Association of Pathologists, American Society of Biological Chemists, The Society of Surgical Oncology, American Society of Clinical Oncology, American Association for Cancer Research, American Medical Association, American Chemical Society, American Association for the Advancement of Science, New York Academy of Sciences, Japanese Cancer Association, and the honorary society Sigma Xi. He has served or is serving on several expert review and advisory committees for the World Health Organization, National Cancer Institute, Food and Drug Administration, Environmental Protection Agency, National Academy of Sciences, and the American Association for Cancer Research. He has been the recipient of U.S. Public Health Service Postdoctoral Fellowships, and of The Gordon Y. Billard Award for Research in Environmental Sciences from the New York Academy of Sciences (1973). He has served as Principal Investigator of many research grants from the National Institutes of Health and the American Cancer Society.

Dr. Bryan is the author of more than 180 papers, and has been the editor or co-editor of two books. His current major research interests relate to bladder carcinogenesis and its modulation by interventive or therapeutic approaches.

Samuel M. Cohen, M.D., Ph.D., is a Professor and Vice-Chairman of the Department of Pathology and Laboratory Medicine and Professor of the Eppley Institute for Research in Cancer and Allied Diseases at the University of Nebraska Medical Center in Omaha, Nebraska.

Dr. Cohen obtained his B.S. degree in 1967 and his M.D. and Ph.D. degrees in 1972 from the University of Wisconsin in Madison. His Ph.D. was in experimental oncology from the McArdle Institute for Cancer Research. He served a residency in Pathology from 1972 to 1975 at St. Vincent Hospital in Worcester, Mass. and became board certified in Anatomic and Clinical Pathology in 1976. He was an instructor at the University of Massachusetts Medical School in Worcester, Mass. beginning in 1974 and became Visiting Professor at Nagoya City University Medical School in Nagoya, Japan sponsored by the United States — Japan Cooperative Cancer Research Program in 1976 to 1977. From 1977 to 1981 he was Staff Pathologist at St. Vincent Hospital and Associate Professor of Pathology at the University of Massachusetts Medical School. He assumed his present position in 1981.

Dr. Cohen is a member of the American Association for Cancer Research, the American Association of Pathologists, the Japanese Cancer Society, the American Association for the Advancement of Science, and the Nebraska Association of Pathologists. He has been the recipient of many research grants from the National Institutes of Health, is currently on an NIH Study Section, and is an Associate Editor for *Cancer Research*.

Dr. Cohen is the author of more than 80 papers and the author or co-author of 7 chapters of books. His current research interests relate to clinical carcinogenesis, particularly involving the urinary bladder, and including the study of carcinogen metabolism and mechanism of carcinogenesis. He is also active in developing clinical applications for electron microscopy.

To Mary and Jan for steadfast encouragement and support

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CONTRIBUTORS

Joseph Alroy, D.V.M.
Department of Pathology
Tufts University School of Medicine and School of Veterinary Medicine
Boston, Massachusetts

George T. Bryan, M.D., Ph.D.
Professor
Department of Human Oncology
Wisconsin Clinical Cancer Center
University of Wisconsin Center for Health Sciences
Madison, Wisconsin

Samuel M. Cohen, M.D., Ph.D.
Professor and Vice Chairman
Department of Pathology and Laboratory Medicine
Eppley Institute for Research in Cancer
University of Nebraska Medical Center
Omaha, Nebraska

Mohamed Nabil El-Bolkainy, M.D., Ph.D.
Professor
Department of Pathology
The National Cancer Institute
Cairo University
Cairo, Egypt

George M. Farrow, M.D.
Professor and Chairman
Department of Pathology
Mayo Clinic and Mayo Foundation
Mayo Medical School
Rochester, Minnesota

L. M. Franks, M.D., F.C.A.P., F.R.C. Path.
Head
Department of Cellular Pathology
Imperial Cancer Research Fund Laboratories
London, England

Gilbert H. Friedell, M.D.
Medical Director
Department of Pathology and the Central Pathology Laboratory
National Bladder Cancer Collaborative Group A
St. Vincent Hospital
Worcester, Massachusetts

Peter J. Hepburn, M.I. Biol.
Graduate Research Assistant
Department of Pathology
St. Paul's Hospital
Institute of Urology
London, England

Jerome B. Jacobs, Ph.D.
Director of Electron Microscopy
Department of Pathology
St. Vincent Hospital
and
Instructor
Department of Pathology
University of Massachusetts Medical School
Worcester, Massachusetts

Eileen B. King, M.D.
Clinical Professor
Departments of Pathology and of Epidemiology and International Health
University of California
San Francisco, California

John R. W. Masters, Ph.D.
Lecturer in Pathology
Department of Pathology
St. Paul's Hospital
Institute of Urology
London, England

George K. Nagy, M.D.
Staff Pathologist
Department of Pathology and the Central Pathology Laboratory
National Bladder Cancer Collaborative Group A
St. Vincent Hospital
and
Associate Professor
University of Massachusetts Medical School
Worcester, Massachusetts

A. Mahir Pamukcu, D.V.M., Ph.D.
Former Chairman and Professor
Department of Pathological Anatomy
Faculty of Veterinary Medicine
University of Ankara
Ankara, Turkey
and
Adjunct Professor, Emeritus
Department of Human Oncology
Wisconsin Clinical Cancer Center
University of Wisconsin Center for Health Sciences
Madison, Wisconsin

Bendicht U. Pauli, D.V.M.
Professor and Director of Research
Department of Pathology
Rush Medical College
Rush-Presbyterian-St. Luke's Medical Center
Chicago, Illinois

David C. Utz, M.D.
Professor of Urology
and
Chairman
Department of Urology
Mayo Clinic and Mayo Foundation
Mayo Medical School
Rochester, Minnesota

Ronald S. Weinstein, M.D.
Professor and Chairman
Department of Pathology
Rush Medical College
Rush-Presbyterian-St. Luke's Medical Center
Chicago, Illinois

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Chapter 1

ETIOLOGY AND PATHOGENESIS OF BLADDER CANCER

George T. Bryan

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I. INTRODUCTION

The pathology of bladder cancer is really the study of benign and malignant neoplasms arising in the renal pelves, ureters, bladder, and urethra. More appropriately these neoplasms should be called lower urinary tract tumors. However, by convention and custom, and perhaps because by far the majority of these tumors first present in the urinary bladder, they are called bladder tumors. The lining epithelial surface of the lower urinary tract, called the transitional cell epithelium or urothelium, is the tissue of origin for about 90 to 95% of lower urinary tract tumors. Thus, with a predominant location in the bladder and with an origin from epithelial surfaces, bladder tumors are commonly called bladder cancers.

International incidence rates of bladder cancer exhibit wide variation. In Egypt, bladder cancer is the most frequent human malignancy. In the U.S., bladder cancer accounts for about 4% of malignant diseases. It has been estimated by the American Cancer Society[1] that in 1982 in the U.S., 37,100 new cases of bladder cancer will be diagnosed, with about 27,000 occurring in males and 10,100 appearing in females. These incidence estimations exclude carcinoma *in situ*. It also has been estimated[1] that about 10,600 people, 7,300 males and 3,300 females, will die in 1982 of bladder cancer. Thus, bladder cancer is a significant and important public health problem in the U.S. and in other countries.

Incidence rate trends of bladder cancer in males, and to a lesser extent in females, have displayed a consistent increase in several countries since 1960, with a single registry in Japan showing a decrease.[2] It is not yet clear whether these trends represent a real increase or whether they may be due to changes in uropathologic criteria of cancer diagnosis, more complete histopathologic examination, or more accurate and complete diagnostic registration.

With bladder cancer representing a significant human cancer problem and with evidence suggestive of increasing incidence rate trends over recent time, it is reasonable to begin our inquiry of the pathology of bladder cancer with a brief discussion of etiology and pathogenesis. Aspects of these topics have been reviewed recently.[3-12]

Human and animal bladder cancer etiology and pathogenesis have been the subjects of intensive study for several decades. Early studies were descriptive and largely anecdotal and centered on unusual time-space clusterings of bladder cancer cases in workers exposed to occupational arylamines. Latter studies involved the development and use of animal models to extend tissue, cellular, and molecular investigations of bladder cancer pathogenesis. From these studies, knowledge has developed concerning how and why bladder cancer develops, leading to an enhanced mechanistic comprehension. Despite these advances, we still do not have complete analyses of the processes involved in bladder cancer pathogenesis. Though additional studies are yet required, data are now available to permit the conceptualization, planning, and assessment of more rational approaches to the prevention, early detection and diagnosis, and therapy of bladder cancer.

II. HISTORICAL BACKGROUND

In most human subjects, bladder cancer appears to be multifactorial in origin and multistage in evolution.[3-10] Chemical substances of natural as well as synthetic origins appear important in the etiology and pathogenesis of bladder cancer.[7,8,11] Chemical carcinogens are part of the natural environment in which humans reside.[12] It is likely that humans have been exposed to combustion products, carcinogens in edible plants, and background radiation for the approximately 4 million years of human evolution. Some of these substances have been implicated recently as contributors to bladder cancer etiology. For example, bracken fern (*Pteridium aquilinum*), now recognized as a potent plant bladder carcinogen, was used by several tribes of Pacific Northwestern Indians as an edible staple as long ago as 14,000 B.C.[13] It continues to be used as a human food and veterinary feed in several parts of the

world.[13,14] Schistosomiasis, a parasitic disease caused by *Schistosoma haematobium*, was connected by early Egyptians about 3000 B.C. to lesions now regarded as bladder cancer.[14] In Egypt and other areas of Africa, many individuals from an early age are subjected to repeated infestations by this parasite. In 1911 Ferguson[15] again suggested that schistosomiasis was associated with bladder cancer. The role of this parasite, if any, in the pathogenesis of bladder cancer is not clear, although recent data from certain animal studies seem to support an etiologic relationship.[16]

The first report of bladder cancer is generally attributed to Schuchardo in 1718.[17] For several decades, bladder tumors were identified only at necropsy. The discovery of the cystoscope in 1879 by Nitze provided a new method for the study and treatment with relative ease of urologic diseases in the living patient.[18] These early approaches led to developments that we presently use in evaluating bladder cancer.

The smoking of tobacco is presently believed to be a major contributor to the etiology and pathogenesis of bladder cancer. Tobacco was used for many centuries by North American Indians in tribal ceremonies. Tobacco smoking was introduced into Europe in 1519 by Spanish explorers, and its use spread rapidly to Asia and Africa.[10,12] Dr. John Hill in 1761 reported a relationship between tobacco use and cancer.[10,12] However, it remained until the 1950s for the development of evidence that cigarette smoking was etiologic for human bladder cancer.[10,12] To date, the constituents in tobacco smoke responsible for bladder carcinogenesis are unknown.

The urinary bladder was among the first visceral organs for which specific chemicals were proposed as etiologic agents of human cancer.[12] In 1895, the German clinician Rehn[19] reported that workers employed in the dyestuffs industry were at increased risk of bladder cancer development. This report was followed over the next 50 years by many reports of other investigators in several countries who identified similar clusterings of industrial exposures to arylamines and the development of bladder cancer in exposed workmen.[20] A major and significant epidemiologic study was reported in 1954 by Case and associates,[21] who demonstrated that dyestuff workers were at a 10- to 80-fold increased risk of dying from bladder cancer. The magnitude of risk varied with the particular arylamine handled and with the duration and intensity of exposures. In selected exposure circumstances, as many as 100% of exposed workers developed bladder cancer.[20] Benzidine and 2-naphthylamine were implicated as especially potent human bladder carcinogens.[20,21] 1-Naphthylamine was associated with a low risk of bladder carcinogenesis possibly due to contamination with 2-naphthylamine.[20,21] In 1955, data were presented by clinical investigators that workers exposed to 4-aminobiphenyl were at increased risk of bladder cancer formation.[22] Thus, by the mid-1950s conclusive evidence was available implicating at least three industrial arylamines as potent human bladder carcinogens.[4,8,10,14,20] With these data, several industrialized countries took steps to limit or abolish manufacture of these chemicals.[4,20] At that time it was believed generally that no more than 1% of human urothelial neoplasms were etiologically related to exposures to one or more of these chemicals.[20] Thus, studies by clinicians concerned about causes of bladder cancer in their patients developed important leads for other investigators.

The second major advance in studies of the etiology of bladder cancer came in 1938 when Hueper and co-workers[23] demonstrated the production of bladder cancer in dogs administered 2-naphthylamine. This major achievement led to the development of methods to study in the laboratory under controlled conditions the carcinogenicity of known or suspected chemical bladder carcinogens. It also permitted investigations of the cellular and molecular temporal pathogenesis of bladder cancer in efforts to elucidate these phenomena and construct rational approaches to their inhibition or reversal.[4-6] Initial studies with experimental animal systems progressed slowly as bladder tumor yields were generally low; latent periods of generation were lengthy; and biological evidences of invasive, metastatic, or lethal qualities were often

Table 1
ATTRIBUTABLE RISK PERCENT F FACTORS ASSOCIATED WITH HUMAN BLADDER CANCER CAUSATION

	Massachusetts (U.S.)[7]		Canada[24]		England[25]	
Factor	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
Cigarette smoking	39	29	56	29	85	27
Hazardous occupations	18	6	35	1	—	—
Unknown	43	65	9	70	15	73

lacking.[5] Early studies were descriptive rather than mechanistic. During the past 20 years, more workers have been attracted to study the causes of bladder cancer and as a result, significant new data and progress have occurred. Aspects of this topic have been extensively reviewed recently.[3-6,8,14,20]

III. EPIDEMIOLOGICAL STUDIES

Incidence rates for bladder cancer in many countries are increasing to variable degrees.[2] For example, in the U.S., these rates per 100,000 population during the period 1950 to 1954 were males, 14.1, and females, 4.4.[9] By 1970 to 1974, comparable incidence rates were males, 23.7, and females, 6.1.[9] Recently, several studies have attempted to quantitate the attributable risk percent of various factors associated with human bladder cancer causation[7,24,25] (see Table 1). These studies[7,24,25] demonstrate that cigarette smoking is significantly associated with bladder cancer causation in men, and to a lesser extent, in women, in the areas studied. Occupational exposures are also responsible for augmented risk of bladder cancer, especially in men. However, factors for a significant fraction of bladder cancers, especially in women, are not yet identified.[7,24,25] Attributable risk percent of bladder cancer varies with age.[7] For example, in men in Massachusetts, the attributable risk percent for ages 20 to 59, 60 to 74, or 75 to 89, respectively, are cigarette smoking, 54, 41, 19; hazardous occupations, 23, 20, 7; and unknown, 23, 39, 74.[7] It is possible that new factors responsible for bladder cancer causation have entered our environment since 1900 and that these may be related to smoking or hazardous occupations. In Massachusetts, hazardous occupations identified were dyestuffs, rubber, leather, painting, and other organic chemcials.[7]

Shown in Table 2 are the sources of exposure, chemical names, and animal species demonstrating bladder carcinogenesis to chemicals or substances generally accepted as human bladder carcinogens. Presented in Table 3 are available data concerning exposure sources, latency periods, minimum exposure times, and estimated relative risks for several accepted human bladder carcinogens. It appears from these data that prolonged exposure to these agents need not necessarily precede the expression of clinical bladder cancer. They suggest that brief, intense exposures to potent bladder carcinogens are sufficient to produce clinical disease. On the other hand, these observations also suggest that bladders of susceptible individuals may harbor cells previously initiated or promoted by other, more ubiquitous bladder trophic agents and that the final exposure provides a "milieu" sufficient for clinical malignancy.

From the standpoint of prevention, it is important to ask does age of initial exposure have any influence on the excess risk of bladder cancer development? In one study,[28] all of the excess risk of bladder cancer in men with occupational exposures was limited to those whose exposures began prior to age 25. On the other hand, a recent study by Ohkawa and associates[29] reports that Japanese men introduced into benzidine manufacturing industries had a significantly shorter latent period of bladder cancer development after age 40 (14.4 ± 6.0 years)

Table 2
ACCEPTED HUMAN BLADDER CARCINOGENS[3,4,7,8,10-12,14,20]

Source	Chemicals	Experimental bladder carcinogen[a]
Occupational	4-Aminobiphenyl	Yes — D, M, Rab.
	Auramine	No
	Benzidine	Yes — D
	2-Naphthylamine	Yes — D, Mon., H, R
Medicinal	Cyclophosphamide	Yes — M, R
	N,N-bis (2-chloroethyl)-2-naphthylamine	No
	Phenacetin	Yes — R
Habit — tobacco smoke	Unknown	No

[a] D, dog; M, mouse; Rab., rabbit; Mon., monkey; H, hamster; and R, rat.

Table 3
EXPOSURE SOURCES, LATENCY PERIODS, MINIMUM EXPOSURE TIMES, AND RELATIVE RISKS FOR ACCEPTED ETIOLOGIC FACTORS IN HUMAN BLADDER CARCINOGENESIS[3,4,7,8,10-12,14,20,26-29]

Chemical	Exposure[a]	Latency period (years)		Minimum exposure time (months)	Relative risk (O/E)[b]
		Range	Mean		
4-Aminobiphenyl	Occ.	15—35	?[c]	4.5	200
Auramine	Occ.	9—28	?	15	13
Benzidine	Occ.	1—45	14.4—23.6	?	14
N,N-bis (2-chloroethyl)-2-naphthylamine	Med.	2.5—10	5.5	?	?
2-Naphthylamine	Occ.	5—45	16—18	6—12	80

[a] Occ., occupational; Med., medicinal.
[b] O/E, observed-to-expected ratio.
[c] ?, data not available.

than did men who began working in the same industries prior to age 39 (23.6 ± 9.7 years) ($p < 0.01$). Several other studies[28] also suggest that older individuals are more susceptible than younger ones to cancer induction. At this time, it does not seem prudent to advocate that only older workers should be placed in potentially carcinogenic work environments.

Duration of exposure is another important issue. Several studies using data from occupational sources and from patients exposed to antineoplastic alkylating agent therapy showed that relatively short exposures of 4.5 to 12 months appreciably increased bladder cancer risk (see Table 3). Host capabilities to biotransform procarcinogens to ultimate molecular species, as well as relative susceptibilities of target tissues, may be important variables in determining increased susceptibility.[10]

Other factors in humans that may predispose to bladder malignancies include anatomic abnormalities, e.g., extrophy, patent urachus, diverticulum, etc.; persistent infections, e.g., in young females; schistosomiasis, etc.; urinary sources of natural carcinogens from plant food sources or abnormal tryptophan metabolism; or pelvic radiation in women.[3,6-8,11,12,14]

Table 4
EXAMPLES OF CHEMICALS WITH SOME EXPERIMENTAL EVIDENCE FOR BLADDER CARCINOGENESIS[3-6,8,10,11,14,20,27,31,32]

Class	Exposures[a]	Representative chemicals
Amine or azo dyes	Occ. User Environ.	3,3′-Dimethoxybenzidine, 3,3′-dichlorobenzidine, *o*-tolidine, *m*-cresidine, *p*-cresidine, *o*-anisidine, *o*-toluidine, *o*-aminoazotoluene, diacetylaminoazotoluene, *p*-dimethylaminoazobenzene, Citrus Red No. 2, Oil Orange SS, Ponceau 3R, Sudan I, Sudan II, *N*-phenyl-2-naphthylamine, 4-amino-2-nitrophenol, 3,2′-dimethyl-4-aminodiphenyl, 2-methoxy-3-aminodibenzofuran, 3-methoxy-2-aminodibenzofuran, *N*-2-fluorenylacetamide, dimethylazobenzene, 4,4′-methylene-*bis* (2-chloroaniline), 2-aminofluorene, 4-chloro-*o*-phenylenediamine, 3-methyl-2-naphthylamine
Nitrosamines	Bact. Inf. Foods Bev. Occ.	*N*-Methyl-*N*′-nitrosourea, *N*,*N*-dibutylnitrosamine, *N*-butyl-*N*-hydroxybutylnitrosamine, *N*-butyl-*N*-(3-carboxypropyl)-nitrosamine, *N*-methyl-*N*-dodecylnitrosamine, *N*-ethyl-*N*-(4-hydroxybutyl)nitrosamine
Nitroaryl	Occ. Med.	4-Nitrobiphenyl, 2-nitronaphthalene, *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide, formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide, *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide, 2-amino-4-(5-nitro-2-furyl)thiazole
Miscellaneous	Occ. Med.	4-Ethylsulfonylnaphthalene-1-sulfonamide, diethylene glycol, 3-phenyl-5β-dimethylaminoethyl-1,2,4-oxadiazole, 4′-hydroxy-2,3′-dimethylazobenzene, 2-(*N*-butyloxycarbonylmethylene)-thiazolid-4-one, 2-*p*-methoxybenzenesul-fonamido-5-isobutyl-1,3,4-thiadiazole, phenacetin, 4-ethoxyphenylurea, saccharin, cyclamate, quercetin, *p*-quinone dioxime, *o*-toluenesulfonamide

[a] Occ., occupational; Environ., environmental; Bact. Inf., bacterial infection; Bev., beverage; and Med., medicinal.

There are significant geographic international variations in bladder cancer incidence rates of more than tenfold in males.[30] For example, reported[30] rate variations per 100,000 population were from 28.7 in Bulwayo, Africa to 2.8 in Maori, New Zealand. Individuals migrating from Japan (a low incidence area) to Hawaii (a high incidence area) develped incidence patterns of bladder cancer intermediate between those of native Japanese and U.S. whites.[30] These data suggest that environmental determinants play a major role in bladder cancer causation in humans. Many of these determinants remain to be identified.

IV. SUSPECT SYNTHETIC CHEMICAL FACTORS

In addition to the synthetic chemicals described above that have been accepted as human bladder carcinogens or those chemicals that are produced commercially and are close structural analogs of recognized human bladder carcinogens, more than 50 chemicals have been reported to display bladder carcinogenicity for experimental animals[3-6,8,10,11,14,20,27,31,32] (see Table 4). In some circumstances, evidence supporting bladder carcinogenic effects is sparse, stemming from a single study. In other instances the evidence is strong, supported by multiple studies or consistent observations in several species. Some of these chemicals, e.g., *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide or *N*-butyl-*N*-hydroxybutylnitrosamine, etc. have been used to develop animal models of experimental bladder carcinogenesis.[5,6,33] Human exposures to these chemicals may be quite variable. The use of some of these chemicals is restricted to scientific laboratories and may provide potential exposures only to the persons working with them.[5] With other chemicals, occupational, distributive, or consumer exposures may be significant. In other cases, as with the artificial sweeteners, cyclamate and saccharin, commercial synthesis, distribution, or consumption involve the majority of individuals in a given society.[34] Such ubiquitous usage creates much difficulty in the design of appropriate epidemiological studies in human populations. Both cyclamate and saccharin have dem-