Cancer Treatment and Research 6

WILLIAM L. MCGUIRE, *series editor*

Genitourinary Cancer 1

edited by

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Foreword to the series

Where do you begin to look for a recent, authoritative article on the diagnosis or management of a particular malignancy? The few general oncology textbooks are generally out of date. Single papers in specialized journals are informative but seldom comprehensive; these are more often preliminary reports on a very limited number of patients. Certain general journals frequently publish good indepth reviews of cancer topics, and published symposium lectures are often the best overviews available. Unfortunately, these reviews and supplements appear sporadically, and the reader can never be sure when a topic of special interest will be covered.

Cancer Treatment and Research is a series of authoritative volumes which aims to meet this need. It is an attempt to establish a critical mass of oncology literature covering virtually all oncology topics, revised frequently to keep the coverage up to date, easily available on a single library shelf or by a single personal subscription.

We have approached the problem in the following fashion. First, by dividing the oncology literature into specific subdivisions such as lung cancer, genitourinary cancer, pediatric oncology, etc. Second, by asking eminent authorities in each of these areas to edit a volume on the specific topic on an annual or biannual basis. Each topic and tumor type is covered in a volume appearing frequently and predictably, discussing current diagnosis, staging markers, all forms of treatment modalities, basic biology, and more.

In *Cancer Treatment and Research*, we have an outstanding group of editors, each having made a major commitment to bring to this new series the very best literature in his or her field. Martinus Nijhoff Publishers has made an equally major commitment to the rapid publication of high quality books, and world-wide distribution.

Where can you go to find quickly a recent authoritative article on any major oncology problem? We hope that *Cancer Treatment and Research* provides an answer.

WILLIAM L. MCGUIRE
Series Editor

Preface

Malignant disease of the genitourinary tract continues to provide a major health hazard. The study of these disease processes has been hampered at the clinical level as there has been a serious lack of reasonably controlled treatment trials, and at the basic science level as many of the animal model systems do not compare favorably with the human tumor situation.

This volume defines current cancer treatment and research and its application to the control of human genitourinary malignancy. The authors have developed their chapters in such a way as to provide an up-to-date resource for the clinician who is involved in day-to-day patient care problems, for the clinician-investigator who is attempting to construct programs designed to evaluate the impact of current treatments, and for the clinician-scientist who is seeking to apply basic research technology and skills to understanding and control in this disease area.

This book does not attempt to cover the entire breadth of urinary malignant disease, but focuses in depth on specific problem areas. It provides the reader with sufficient background and understanding for him to be able to evaluate future studies in the areas addressed, or even to develop his own projects. A reasonable balance has been established between clinical and basic research problems, recognizing that the two disciplines truly are not separable. The book serves to define the state of the art and, as such, will provide a valuable resource for the student of urologic oncology.

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ROBERT A. BONAR

1. INTRODUCTION

Much has been learned about carcinogenesis in recent decades, although our ignorance still far exceeds our knowledge. The information already acquired is being used to reduce cancer risk, and further research offers substantial promise of additional understanding and, therefore, of additional ways of preventing some of our human cancer burden. This chapter will present a brief overview of what is known or suspected about carcinogenesis in general and, more specifically, deal with neoplasia in the urinary tract of both sexes and in the genital tissues of the male.

2. OVERVIEW OF CARCINOGENESIS

2.1. Carcinogenic Agents

A variety of kinds of agent is known to be carcinogenic in various tissues and species, including organic and inorganic chemicals, viruses, radiation, other physical factors, and elements of 'life-style' which probably consist, at least in part, of these other agents. Among those human tumors for which etiology is known or strongly suspected, organic chemicals are the most frequently implicated agents (Miller, 1978). Radiation is clearly important at certain sites, particularly in the induction of skin cancer by ultraviolet light. Viruses have been associated as causative agents with only a few kinds of human tumors (Rapp, 1980). It is important to note, however, that the specific causes of most human cancers remain unknown.

It appears likely that environmental factors play an important role (Miller, 1978) in the induction of a large proportion, perhaps 60–90%, of human cancer including urologic cancer. The term environment is used here in a very broad sense, meaning all those external factors which affect the organ-

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ism. The principal basis for this estimate of the importance of environmental factors is the marked geographic and temporal variation in the occurrence of most kinds of cancer (Doll, 1972; Wynder and Gori, 1977). Mortality from prostate cancer, for example, is low in Japan and much higher in the United States. This is true of colon cancer as well. Stomach cancer, on the other hand is more common in Japan. There are many other striking examples of variation in neoplastic disease among countries. It is unlikely that these are due to hereditary differences, since migrant populations tend to acquire the cancer incidence patterns of the country to which they move (Kmet, 1970).

Changes in incidence with time also suggest environmental rather than hereditary factors. Lung cancer, for example, was a relatively rare disease before about 1930 when its incidence began to increase considerably. This phenomenon followed, by about 20 years, the period when cigarette smoking had begun its rise in popularity among men. The lung cancer rate in women began to increase in a similar way about 1960, again following by about 20 years the rise in cigarette smoking among women.

While temporal and geographic variations strongly suggest the importance of environmental factors in human cancer, the relationship between a particular factor and a specific neoplasm is rarely so clear as in the case of lung cancer and cigarette smoking. We are exposed to an enormous array of environmental agents, natural and man-made, brought to our individual microenvironments by natural processes, by the activities of others, and by our own actions, and introduced into our bodies by a variety of routes. Moreover, these factors interact with each other and with the individual in complex ways.

One major group of agents of much concern as potential carcinogens is that of organic and inorganic chemicals. The mere number of such compounds is impressive (Maugh, 1978). As of November, 1977, the Chemical Abstract Service's registry of chemicals listed 4 039 907 distinct entities, and new ones were accruing at about 6 000 per week. Of these compounds about 96% contained carbon. About 3.4 million compounds were fully defined and about 3 million contained at least one ring system. Of course, many of these chemicals never leave the laboratory, but some 63 000 were in 'common use'. The Environmental Protection Agency (EPA) estimated that there were about 50 000 chemicals in common use, not including pesticides, pharmaceuticals and food additives, and that about 1 500 different ingredients were used in pesticides. The Food and Drug Administration estimated that drugs included about 4 000 active ingredients and 2 000 excipients, while food additives included 2 500 used for nutritional value and flavoring, and 3 000 to promote product life.

These figures are important in emphasizing the magnitude of the task of

testing and of toxicological evaluation, but it should be stressed that relatively few chemicals are known to be carcinogenic (Tomatis, 1979).

Much attention is being given to possible carcinogens in the workplace. The proportion of cancer incidence related to occupation varies greatly with site. Overall, the incidence ascribable to occupational exposure has been estimated to be about 5% of all cancer in the industrial countries (Higginson, 1979). The figure varies substantially with different populations and different tumors and cannot be determined precisely. For certain sites higher values are probable, and 20–30% of all bladder cancer in industrialized countries may be due to occupational exposure (Morrison & Cole, 1976).

Of the factors in the environment which may be involved in the induction or promotion of malignancy some are natural, such as sunlight, radiation from the decay of radioactive minerals, cosmic rays, and, possibly, certain food constituents. Other factors, such as the mycotoxins which can occur in a variety of grains and seeds in the field and in storage, are natural products whose occurrence depends in part on conditions of harvest and storage. Still others are formed as byproducts of our industrial society, reaching us through air, water or food. Elements which also appear to be important are a variety of customs and activities often called 'lifestyle'.

The effect of a potentially carcinogenic agent may be modulated by a number of factors. For example, the incidence of skin cancer as a result of ultraviolet exposure varies geographically, being higher in the middle latitudes where the amount of sunlight is greater. The incidence is also affected by inherited characteristics and is greater in light-skinned people than in those with more pigmentation. There is an occupational component, related to indoor vs. outdoor work and, also, an ingredient of 'life-style' such as the social desirability of a suntan, which encourages greater exposure.

While the emphasis in this chapter will be on carcinogenesis by extrinsic factors, it must be remembered that each individual may respond differently to a particular carcinogen. This individuality results both from genetic constitution and previous environmental influences. There is evidence of familial susceptibility to cancer in humans (Anderson, 1975, Knudson, 1979) and species and strain differences among experimental animals are well-known. A particularly striking example of genetic influence is provided by the platyfish-swordtail system (Anders and Anders, 1978). Inbreeding of wild-type populations produces normal offspring, but crossings produce progeny which spontaneously develops a variety of neoplasms.

2.2. The Carcinogenic Process

The development of urologic cancer, like that of cancer at other sites, appears to be a complex, multi-stage process. In an early demonstration that

at least two stages were involved, it was shown (Berenblum and Shubik, 1949) that tumors could be induced in mouse skin by a single 'initiating' dose of polycyclic aromatic hydrocarbon followed by repeated treatment with a 'promoter', croton oil. Tumors did not develop after the single dose of initiator alone, or after promoter alone, or if the order of application was reversed. Another interesting feature of the system was that the first application of promoter could be delayed many months after initiation, and still be effective in eliciting tumor formation. These observations suggested that one or more cells responded to the application of initiator with an irreversible change, but that no additional progression to tumor occured until the further stimulation by the promoter. Similar results, in principle, have been reported in other systems (Van Duuren, 1976) including rat bladder (Cohen *et al.*, 1979; Hicks, 1980). A sufficiently large or repeated dose of 'initiator' may obviate the need for treatment with a separate promoter.

Another important factor in carcinogenesis by organic chemicals is the role of the host in metabolizing the compound. Most chemical carcinogens appear to be inactive in the form encountered in the environment. They must be metabolized to more reactive ultimate carcinogens (Miller, 1978), sometimes by several steps, before they can react with constituents of the susceptible cell. The potential carcinogen may instead be excreted or metabolized to harmless products. The competition among these pathways, and the resulting development of a tumor or sparing of the host, may be influenced by many factors, including genetic constitution, diet, and previous exposure to the carcinogen, or to other chemicals which can affect the activity of the enzyme systems involved.

After an ultimate carcinogen is formed in, or transported to a susceptible cell, the reaction(s) with cell constituents which lead to neoplasia must take place. Most well-studied chemical carcinogens have been found to react with deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein. The fact that many carcinogens are also mutagens (Boyland, 1980) has suggested that a reaction with DNA leading to mispairing of bases, and thus to mutation, may be the key carcinogenic step. While the molecular mechanism of neoplastic change has not been established, the most widely held view seems to be that damage to DNA is the initiating event. Cells have means of repairing DNA damage (Roberts, 1980). If the repair is accurately carried out before cell division and the accompanying mutation, no harm is done to the cell. The effectiveness of DNA repair is thus another variable in the carcinogenic process, and it can be influenced by the genetic constitution of the host and by exogenous factors. It can also be influenced by the mitotic rate in the affected cell population and, thus, in turn influence the time available for repair.

It should be noted that while DNA modification and the resulting somat-

ic mutations are probably the most widely accepted mechanism of the initiation of carcinogenesis, this has not been proved to be the only, or even the usual, mechanism (Sivak, 1979). Analogy with tissue differentiation during which there is development of a great variety of cells with widely varying properties but with, apparently, the same genome, has suggested that changes in epigenetic regulatory mechanisms may explain neoplastic alteration. It is quite possible that both genetic and epigenetic mechanisms are involved in different tumors, and even in the same tumor. Even if the initiating event is a genetic change, many other factors play a role in determining whether a tumor forms and how it behaves. We know little about the actual mechanisms or steps in the development of most tumors. We are learning, however, and the picture which is emerging is one of many factors, both endogenous and exogenous, interacting in complex ways.

3. BLADDER AND LOWER URINARY TRACT

Tumors of the lower urinary tract will be considered first because more is known about carcinogenesis in this site than in other genitourinary sites and, indeed, more than almost any other site in the body. Most tumors of the lower urinary tract arise in the transitional epithelium, the urothelium, which lines the tract. The most frequent specific site is the bladder and the term bladder tumor is often used for brevity for all urothelial tumors. The discussion will deal almost exclusively with transitional cell tumors, about which we have the most information concerning etiology. Tumors of the renal pelvis will be considered in this section rather than with other kidney tumors because most renal pelvic tumors arise in the urothelial lining.

There is substantial international variation in bladder cancer mortality rates, the highest being in Great Britain and the lowest in the Asian Countries (Staszewski, 1980). The worldwide trend has been upward (Parkes, 1976). There is a dramatic difference in incidence between men and women (Mason *et al.*, 1975). The higher incidence in males may be partly explained by differences in occupational exposure to carcinogens and in smoking habits. Silverberg (1980) estimated that there would be about 35 000 new bladder cancer cases in the U.S. in 1980 (26 000 in men and 9500 in women) and 10 300 bladder cancer deaths (7000 men and 3300 women).

A feature of urothelial tumors which is of importance to an understanding of etiology, as well as to treatment and prognosis, is their frequent association with abnormal epithelium (Koss, 1975) elsewhere in the bladder. These abnormal epithelial cells may represent stages in developing neoplasia (Koss, 1975), and suggest multiple sites of tumor origin. Such multiplicity is consistent with a chemical or viral etiology. The possibility of intraepithelial migration of tumor cells has also been suggested (Weinstein, 1979).

It appears likely that the majority of human bladder cancers are induced by chemical agents and that radiation plays a relatively minor role (Hueper, 1969). There is some suggestive evidence of an association of herpes viruses with bladder tumor (Rapp, 1980). Cancer of the bilharzial bladder is a special case (Chevien *et al.*, 1979). The strong geographic coincidence of common infection with Schistosoma haematobium and a high incidence of bladder cancer leaves little doubt of a causative relation, although the mechanism is not established. In Egypt, the bladder is the most common site of cancer and, in contrast to industrial countries, most are squamous cell tumors.

3.1. Occupational Exposure

Much of the work on bladder carcinogenesis has focused on induction by exposure to organic chemicals, particularly in the workplace. An observant clinician, L. Rehn (1895), first reported an unusually high incidence of bladder tumors in workers engaged in the production of fuchsin (magenta) in an aniline-dye works. Rehn's study led him to the conclusion that aniline vapors inhaled by the workers over many years induced the bladder cancer, and the disease became known as aniline tumor of the bladder. Later studies showed that aniline was not itself at fault, but that other arylamines, particularly 2-naphthylamine, were associated with the increased risk of bladder cancer in dye workers.

The bladder carcinogenicity of commercial 2-naphthylamine was confirmed by the induction of bladder tumors in dogs fed the compound (Hueper *et al.*, 1938). These early studies have led to a large amount of work on bladder carcinogenesis in various animals (Clayson and Cooper, 1970; Friedell and Cohen, 1979), as well as to continuing epidemiologic investigations. More than in most other cancers, studies in bladder cancer have seen correlation of epidemiologic and laboratory studies, resulting in better progress in understanding the disease.

The extensive study of British dye-workers by Case *et al.* (1954) showed that the induction period, the time from first exposure to risk to the recognition of the bladder tumor, was both long and variable. The distribution of induction times was approximately Gaussian, with a mean of 17.8 years and a standard deviation of 7.2 years, and the range was from less than 2 to more than 45 years. An even longer mean latent period was found by Hoover and Cole (1973) in a different population. An exposure time of as little as one year was sufficient to induce the disease. The short effective exposure time and the long and variable latent period indicate some of the difficulties in determining possible etiologic factors from personal histories.

Workers in several other industries have an increased incidence of bladder cancer. In Great Britain (Somerville *et al.*, 1980) most occupational bladder cancers have occurred following work in the manufacture of dyes, in the rubber and electric cable industries, and in the retort houses of gasworks producing coal gas. Industries implicated less often were paint and pigment manufacture, chemistry laboratories, textile printing shops, and the production of rodent poisons. Other studies (reviewed by Morrison and Cole, 1976; Wynder and Goldmsith, 1977) have added other occupations to this list: Pitch and coal-tar workers, leather workers (especially leather finishing), hairdressers, tailors, printers, and cooks and kitchen workers. In many of these occupations the specific cancer-causing agent is unknown.

The excess bladder cancer in rubber workers was due, apparently, to the use of 2-naphthylamine in rubber compounding. Waterhouse (1979) reported that workers employed in the British rubber industry after 1949, the year in which 2-naphthylamine was banned, show no excess bladder cancer.

In the United States clusters of excess bladder cancer in males were found (Mason *et al.*, 1975) in New Jersey, in New York City, and in urban areas around the Great Lakes, probably associated with industrial exposure. Rates were also elevated in some rural areas. Hoover and Fraumeni (1975) found a significantly elevated risk for bladder (and lung and liver) cancer in men in the U.S. countries with the highest concentrations of chemical industries.

Under some conditions carcinogenic arylamines may be formed or liberated in the gastrointestinal tract from ingested compounds. Yoshida and Miyakawa (1973) reported that Yuzen dye painters show an eleveated risk of bladder cancer arising from azo dyes ingested when the dye brushes are touched to their lips. The carcinogenic benzidine moiety is liberated from some of these dyes by the action of intestinal bacteria.

The development of cancer in an individual depends on many factors (Bryan 1979, Sivak, 1979) interacting in complex ways. One important factor is variation in susceptibility which may be partly genetic. Families whose members have experienced an unssually high incidence of bladder cancer have been described (Lynch *et al.*, 1979; Purtilo *et al.*, 1979). One aspect of susceptibility may be the way in which the individual metabolizes environmental procarcinogens. Studies by Lower *et al.* (1979) showed that the capacity to acetylate N-hydroxyarylamines varies in human populations and suggested that this capacity is related to susceptibility to bladder cancer. This phenotypic variation could have both genetic and environmental components.

Increasing dose levels of carcinogen (Frith *et al.*, 1979) or longer time of feeding (Jacobs *et al.*, 1977) have both been shown to increase bladder tumor incidence in experimental animals, as might be expected. In humans

increased intensity or time of exposure can shorten the latent period of the disease (Case *et al.*, 1954; Hoover and Cole, 1973).

That a sufficient dose of a potent carcinogen can overwhelm individual differences in susceptibility was shown by the case studied by M. H. C. Williams (Parkes, 1976), of a group of 78 men who worked in a 2-naphthylamine distillation unit. All 18 of the men who worked there for more than 5 years developed bladder cancer.

3.2. Other Factors

In addition to the arylamines which have been particularly important in occupational bladder cancer, some N-nitroso compounds are potent bladder carcinogens in experimental animals and, therefore, suspect carcinogens in humans. They are of particular interest because they may be formed by the reaction of nitrite with certain amines. Their formation has been shown in the human achlorhydric stomach, infected urinary bladder, colon, and saliva (Hill, 1979). However, there was no relation of human bladder cancer incidence to estimated nitrate and nitrite consumption in cured meats (Howe *et al.*, 1980).

Following reports of the isolation of a RNA tumor virus from papillary transitional cell tumors of the human renal pelvis and bladder (Fraley *et al.*, 1974) we looked for evidence of such a virus in human bladder tumors (R. A. Bonar, Y. Sharief and C. F. Reich, unpublished observations). We examined fluids from cell cultures derived from 34 human bladder tumors for the presence of particulate RNA-dependent DNA polymerase activity, a property of the C-type RNA tumor viruses (oncornaviruses). Synthetic templates were used to increase the sensitivity of the assay. In no case did repeated testing reveal evidence of virus. In addition, RNA's were extracted from portions of 24 human bladder tumors and treated under hybridizing conditions with a DNA probe prepared from simian sarcoma virus (SSV-1) by the RNA-dependent DNA polymerase reaction. The hybridization products were fractionated on hydroxylapatite. There was no evidence of hybridization, which would have indicated the presence in the tumors of RNA's related to the primate oncornavirus. In summary, these experiments revealed no evidence for the association of oncornavirus or its RNA with human bladder tumors.

Several epidemiologic studies have implicated cigarette smoking as an important etiologic factor in bladder cancer. An elevated risk was found for cigarette smokers among both men and women (Cole *et al.*, 1971; Howe *et al.*, 1980; Morgan and Jain, 1974; Stevens and Moolgavkar, 1979; Wynder and Goldsmith, 1977). The relative risk (the ratio of the risk for users to that for non-users) was in the range of 2 to 6 and showed a dose-response effect. A smaller increased risk for pipe smokers was found by Howe *et al.* (1980),

but no association was seen in the other studies. The carcinogenic (or cocarcinogenic) effect of smoking is much less potent than the more severe occupational exposures, but the number of people exposed is far greater. A possible pathway for smoking-induced carcinogenesis is by way of carcinogenic agents in the smoke, including polycyclic hydrocarbons, arylamines (Wynder and Goldsmith, 1977), and nitrosamines (Hecht *et al.*, 1979). The smoking hazard is not limited to tobacco. Opium users have also been reported to be at elevated risk for bladder neoplasia (Sadighi *et al.*, 1979).

There has been a great deal of interest and very long controversy with respect to the possible role of saccharin (Hoover, 1980) in bladder cancer. An increased incidence of bladder tumors was found (Taylor *et al.*, 1980) in male rats which had been fed sodium saccharin chronically at a dietary level of 7.5%, from weaning. The parents of these rats had also been fed the same diet from weaning through mating, gestation and lactation. It appeared that the exposure in utero was the critical factor. Female rats on the same diet showed an increased incidence of urinary bladder hyperplasia but not of tumor. Other work has shown that dietary sodium saccharin can act as a promoter of bladder tumorigenesis in the rat (Cohen *et al.*, 1979; Hicks, 1980). Saccharin feeding led to an increased incidence of bladder tumors following low initiating doses of known carcinogens. The saccharin feeding experiments have been criticized by Meneely (1979) who argued that the sodium in the sodium saccharin, which is used for solubility, added to the sodium chloride present in rat chow, gives sodium levels which are themselves frankly toxic in the rat. The high sodium levels may lead to hypertension, renal lesions, and, in the pregnant female, to teratogenic effects in the pups.

Epidemiologic studies have generally not shown a significant relationship between consumption of artificial sweeteners and human bladder cancer. A case-control study in Canada (Howe *et al.*, 1980) showed an increased risk in males (risk ratio of 1.6 for ever-used vs. never-used). This has not, however, been found in several other studies (Hoover and Strasser, 1980; Kessler and Clark, 1978; Morrision and Buring, 1980; Wynder and Stellman, 1980). There was also no elevation of urinary bladder cancer in diabetics (Wynder and Stellman, 1980) even though they generally have a higher consumption of artificial sweeteners. The controversy has been reviewed by Hoover (1980) who concluded that the use of artificial sweeteners by the diabetic or the occasional user carries little or no risk of bladder cancer. In view of the evidence of toxicity and the lack of objective evidence of benefit, he suggested that any use by nondiabetic children or pregnant women, heavy use by young women of childbearing age, and excessive use by anyone were ill-advised and should be actively discouraged by the medical community. From the various experimental and epidemiologic studies it

seems clear that if saccharin is a carcinogenic agent in humans, it is a rather weak one, and an individual's judgement of the balance between risk and benefit will depend heavily on the perception of benefit.

Coffee drinking has attracted much attention for its possible association with bladder cancer. As Morrison and Cole (1976) note in their review, the results of epidemiologic studies on this association are mixed, but the exposure is so great that if a causal association is real it could account for about one-third of U.S. bladder cancer. Cole (1971) found a significantly increased risk of lower urinary tract cancer associated with coffee drinking among women (relative risk 2.58, $P<0.05$). Risk was not significantly elevated among men (r.r. = 1.24). No dose-response effect was seen. No association with coffee consumption was found by Morgan and Jain (1974) or Wynder and Goldsmith (1977), but Howe *et al.* (1980) reported a significantly elevated risk in males consuming all kinds of coffee, and in females drinking instant coffee. Again, no dose-response relationship was found. In a different approach to the question (Morrison, 1978), a weak correlation was found between the incidence of bladder cancer in ten countries and their *per capita* coffee imports. A comparison of the time trends of these variables in the U.S. and Denmark, however, gave mixed results. The question of the carcinogenic, or promoting, effect of coffee drinking must remain open, but warrants further study because of the great frequency of the custom.

Dunning *et al.* (1950) observed that added dietary tryptophan enhanced the induction of bladder tumors in rats by the carcinogen 2-acetylaminofluorene. Since some tryptophan metabolites are arylamines, as are some industrial bladder carcinogens, there was much interest in the possible role of this essential amino acid as a potential natural carcinogen (Bryan, 1971). Some bladder cancer patients showed an altered tryptophan metabolism, although this may be a consequence of the disease (Teulings *et al.*, 1978) rather than a cause. Tryptophan and its metabolites have not been shown to be carcinogenic. They could, however, be cocarcinogenic or promoting in humans, as they appear to be in dogs (Radomski *et al.*, 1977) and rats (Cohen *et al.*, 1979).

Several other dietary factors have been suggested as playing a role in urinary tract carcinogenesis. Consumption of bracken fern has been shown to induce bladder tumors in cattle and in laboratory animals (Evans, 1976; Pamukcu and Bryan, 1979). A carcinogenic factor was also found in the milk of the cows eating bracken fern. In addition to the potential human exposure via milk, fiddlehead greens, some of which are harvested from the bracken fern, are consumed directly by some human populations. There is no direct evidence, however, of induction of cancer in humans by bracken fern, and Howe *et al.* (1980) found no evidence of association with fiddlehead consumption.