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EDITORIAL

CAUSATION OF URINARY BLADDER CANCER

by

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Perhaps more knowledge has been accumulated about the causation of urinary bladder cancer in humans than has been found for any other cancer of man. Only chemicals have been conclusively shown to elicit urinary bladder cancer in workers involved in certain occupations, and only chemicals have clearly induced experimental bladder cancer in animals. There are almost no data available to substantiate a claim for viruses or diverse radiation sources as etiologic agents in the genesis of bladder cancer. During the past decade, much new information has been presented designed to identify additional sources of bladder carcinogens in the environment. This brief editorial will attempt to designate some of these sources.

Initial suggestions as to the types of chemicals related in the genesis of bladder cancer came from the observations of industrial physicians. A number of aromatic amino and nitro compounds such as 2-naphthylamine, benzidine, 4-aminobiphenyl, auramine, magenta, and 4-nitrobiphenyl were associated with an augmented incidence of bladder cancer occurring in workers exposed to them. Most of these compounds resulted in the formation of bladder cancers, histologically indistinguishable from those seen in man, in one or more species of animals when administered under controlled experimental conditions. Yet, most of the human population, even in highly industrialized societies, does not have a high level of intense exposure to these chemical agents. Thus, in order to ascertain the probable causal agents for the majority of patients with bladder cancers, other sources must be identified of a more ubiquitous nature. Some of these sources might be (1) the endogenous metabolism of essential nutrients; (2) the use of carcinogenic drugs or food additives; or (3) the ingestion of plant materials containing carcinogens.

The essential amino acid tryptophan has been investigated as playing a role in the genesis or development of urinary bladder cancer. Our working hypothesis is that bladder cancer might be a metabolic disease in which a disorder of tryptophan metabolism could cause an increased urinary concentration of certain tryptophan metabolites. Some of the urinary tryptophan metabolites bear a structural

resemblance to urinary metabolites of 2-naphthylamine. In addition, in the United States, England, and Italy, patients with spontaneous bladder cancer have been found with abnormally large quantities of urinary tryptophan metabolites, especially kynurenine, 3-hydroxykynurenine, acetylkynurenine, kynurenic acid, and 3-hydroxyanthranilic acid. These abnormalities were greatly accentuated by a loading dose of L-tryptophan. Additionally, five tryptophan metabolites, namely the 8-methyl ether of xanthurenic acid, xanthurenic acid, 8-hydroxyquinaldic acid, 3-hydroxykynurenine, and 3-hydroxyanthranilic acid were judged to be bladder carcinogens for the mouse when tested by the pellet implantation technique. Some of these metabolites have also been associated with an augmented incidence of experimental mouse leukemia. No evidence has been presented to refute the above-stated working hypothesis.

Not all patients with bladder cancer work with industrially hazardous chemicals or have abnormal tryptophan metabolism. More recently, drugs and food additives have been suggested as possible etiologic agents. Following the administration of N,N-bis(2-chloroethyl)-2-naphthylamine, bladder cancer was induced in patients with Hodgkin's disease or polycythemic rubra vera. Recent attention has been focused on 5-nitrofurantoin drugs and food additives as possible human bladder carcinogens. Drugs of this chemical type are widely used to treat urinary tract infections, and especially in Japan are utilized as food preservatives. One compound of this type, N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide, induced urinary bladder carcinomas in rats, mice, and dogs when studied in our laboratories. Other compounds of this chemical species have induced a wide variety of neoplasms in rats and mice, and some of these compounds that are carcinogenic are widely used by humans. We believe that this class of compounds represents a potentially serious hazard to man.

Finally, plant materials have been demonstrated to possess potent bladder carcinogens. Bracken fern (*Pteris aquilina*)* induced urinary bladder carcinomas in cows in Turkey, and in rats. Experimental intestinal carcinomas were also induced in rats fed this material. The urine of cows fed bracken fern contained carcinogenic substances, and more recently, the fern itself was found to harbor carcinogenic chemicals. This fern is consumed by people in many areas of the world and especially in Japan, as a salad green. Thus, this material, or other related plant materials may contain carcinogenic hazards for man. Studies of the carcinogenic potential of plants has been long neglected, but may represent a fertile area for inquiry.

Bladder carcinogens appear to be primarily chemicals, and are found in a number of sources, ie. industry, essential nutrients, drugs and food additives, and plants. This widespread diversity of sources of carcinogens suggests that no single chemical causes all human bladder cancer. Additionally, it appears that a most difficult task confronts scientists trying to identify and then restrict the exposure of people to these carcinogens.

* Bracken fern (*Pteris aquilina*): わらび (シダ植物). “わらび”を食するのは日本人に限らず、欧米においても同様であり、わらびのかんづめまである。日本で食べられる“ぜんまい”や“すぎな(孢子)”も同じくシダ植物に属している。(編集者・注)