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Multistage Carcinogenesis in the Urinary Bladder

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The induction of cancer of the urinary bladder is a multi-stage process involving multiple exogenous and endogenous factors. Based on the classical initiation-promotion model, we have used *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) as initiator and sodium saccharin (SAC) or tryptophan as promoters. These latter chemicals have the properties expected of promoters: induction of hyperplasia, reversibility and nonmutagenicity. Also, tumors were induced whether the promoter was administered immediately after FANFT or beginning 6 weeks after FANFT was discontinued, but no tumors resulted if either promoter was given without initiation with FANFT. Factor(s) present in normal urine also are involved in the promotion process, in addition to the role of urine as a carrier of carcinogens. However, administration of SAC to animals with a rapidly proliferating bladder mucosa, induced by ulceration, pellet insertion, or *in utero*, resulted in bladder tumor induction, even without prior initiation with FANFT. To better understand the complex interaction of the multiple variables in bladder carcinogenesis, a stochastic computer model has been formulated based on long-term carcinogenicity and tissue kinetic studies *in vivo*. This model indicates the importance of cell proliferation and the development of hyperplasia in carcinogenesis.

Urinary Bladder Cancer Induced by FANFT

Several chemicals have been identified which induce bladder cancer in humans and in experimental animals (*1,2*). Several of these, such as 2-acetylaminofluorene (AAF), induce tumors of other tissues in experimental animals, particularly the liver and breast. In the 1960's chemicals were identified which were bladder specific carcinogens, including *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN) administered in the drinking water (*3*), *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) administered in the diet (*4*) or *N*-methyl-*N*-nitrosourea (MNU) administered by intravesical instillation (*5*). We have utilized the FANFT bladder cancer model. It was originally described in female Sprague-Dawley rats (*6*), but our experiments have been performed in the model developed in inbred male Fischer rats by Tiltman and Friedell (*7*).
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The details of this model and its pathogenesis have been described (*7-10*). Briefly, the bladder epithelium progresses from the normal three cell layer urothelium to a simple hyperplasia, followed by focal nodular and papillary hyperplasia, papillomas and finally carcinomas. These carcinomas produce marked hematuria and frequently become invasive. Distant metastases occur but are relatively rare in this model, and hydronephrosis is also uncommon. A dose response is observed, and a 100% incidence of bladder tumors is induced if the FANFT is administered at a dose of 0.05% of the diet or higher (*11*).

For the remainder of the experiments to be described, FANFT was administered in the diet at a dose of 0.2%. To determine the reversibility or irreversibility of the early hyperplastic changes in bladder carcinogenesis, FANFT was fed in the diet for different periods of time followed by control diet until 1 (*8*), 1½ (*10*), or 2 years (*12-14*). It was shown that FANFT administered in the diet for 6 weeks or less induced a simple hyperplasia which regressed within 2 weeks after discontinuing the diet. The bladders remained normal through 1½ years, but a few animals fed FANFT for 6 weeks developed bladder tumors by the end of 2 years. Rats fed FANFT for 8 or 10 weeks showed partial regression of the nodular and papillary hyperplasia when FANFT was discontinued in the diet, but the bladders never returned to normal. By 1 year many of these animals had developed tumors, and by 2 years most of them had developed bladder cancer. Animals fed FANFT

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