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Letter to the Editor

Inhibition of Experimental Urinary Bladder Carcinogenesis by Partial Cystectomy*

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ANIMAL experiments regarding carcinogenesis in the lower urinary tract have so far been exclusively confined to normal, quiescent, physiologically slowly renewing urothelium [1, 2]. This prompted us to investigate carcinogenesis in the urothelium of the bladder following stimulation of its proliferative activity. The underlying concept was that tumor development would be enhanced by this experimental condition because tissues stimulated to proliferate are generally more susceptible to carcinogenic agents than quiescent cell populations [3, 4]. Furthermore, carcinogenic agents are known to be bound to DNA preferentially during the replicative phase and increased proliferative activity is an important prerequisite for tumor promotion. In the liver, for example, the incidence of tumors induced by several carcinogens can be considerably enhanced when proliferation of the hepatocytes has been increased by partial hepatectomy [3, 4]. In order to stimulate proliferative activity of the bladder urothelium we recently established partial cystectomy as a new experimental model [5].

A total of 151 adult female Wistar rats (effective number) underwent one-third resection of the urinary bladder, which induces an intensive reparative regeneration in the stump [5]. The animals of the first group received *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine (BBN) by gavage in three fractionated doses of 100 mg/kg (total dose: 300 mg/kg) at the time when proliferative activity was highest (30, 45 and 70 hr post-operatively). The rats of the second group received BBN by gavage in three fractionated doses of 300 mg/kg timed as in the first group. Additionally, the carcinogen was subsequently given in the drinking water for 40 days in a daily dose of 10 mg/kg (total dose 1300 mg/kg). One hundred and sixty-six non-operated rats served as controls and were administered BBN in an identical manner and dosage to the corresponding experimental animals with a partial cystectomy. The rats receiving the lower dose and their controls were killed after 6, 12 and 18 months, and the animals with the higher dose after 4, 6 and 12 months.

Following partial cystectomy and administration of a low total dose of BBN only 2 of 78 rats (2.6%) developed a small transitional cell papilloma of the bladder. In contrast, 11 of the 87 non-operated control animals (12.6%) showed non-invasive papillary urothelial tumors. Accordingly, only 20 of 73 rats (27.4%) with partial cystectomy and which had received BBN in a higher total dose developed urothelial neoplasms, whereas bladder tumors were found in 38 of 79 controls (48.1%) without resection. The differences in the tumor incidence of operated and non-operated animals are statistically significant. The observed reduction in tumor incidence is evidently not caused by a shortening of the latency period or induction time. Furthermore, after an experimental period of 1 yr the control animals frequently had several tumors in their bladder, a phenomenon which was not observed in the operated rats.

Contrary to our working hypthesis, the present experiments have shown that experimental bladder carcinogenesis is inhibited by partial cystectomy. At this time one can only speculate

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about the underlying mechanisms of the inhibition. It seems less probably that the reduced filling capacity of the resected bladder during the first days following the operation plays a role, since we also found an inhibition of tumor induction in the urinary bladder after stimulation of its proliferative activity by a single administration of cyclophosphamide [6]. Thus it may be argued that stimulation of de-novo DNA synthesis by partial cystectomy is accompanied by increased capacity for DNA repair by the rapidly proliferating urothelial cells, leading to elimination of BBN-damaged DNA and thus protecting against neoplastic cell transformation. This concept is supported by findings in peripheral human lymphocytes and human fibroblasts stimulated to proliferate after damage of their DNA: the activity of DNA-repair enzymes of lymphocytes increased up to 20 times simultaneously with stimulation of DNA replication by phytohemagglutinin or concanavalin [7–9]. Similarly, unscheduled DNA synthesis of fibroblasts were enhanced several times during or prior to induced cell proliferation [10]. Recently Rabes *et al.* [11] found an increased elimination of alkylated DNA bases in the liver after stimulation of its proliferative activity by a partial hepatectomy. Accordingly, Pegg *et al.* [12] observed an increase of enzyme activity catalyzing the loss of alkylated DNA and Gombar *et al.* [13] revealed an increase in the activity of uracil DNA glycosylase in regenerating liver. Thus there is evidence accumulating that stimulation of DNA synthesis induces the production of DNA-repair enzymes, which are at a low level or absent in quiescent cells. Further investigations are indicated to elucidate the significance of the stimulation of proliferative activity for the repair system and the neoplastic transformation of the urothelium.

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