The Induction of Sarcomas in the Colon of Rats by Intraluminal Application of Hydrocarbons*

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SUMMARY

The colons of 304 male Wistar rats were exposed to two known potent carcinogens by direct contact with impregnated strings and by oil enemas. In contrast to previous experiments in the same laboratory, only one invasive adenocarcinoma and two carcinomas in situ were observed. In addition, twelve lymphosarcomas and three spindle-cell sarcomas were observed. The experimental production of colon carcinomas by intraluminal agents still remains an unsolved problem.

It has been frequently postulated that carcinoma of the colon is due to some intraluminal carcinogen produced and carried in the fecal stream. The numerous breakdown products containing the phenanthrene nucleus have been particularly suspected. However, when chemical carcinogens have been introduced into the lumen of the intestines of rodents, few carcinomas have been produced. Only Horava and von Haam (2), in our laboratories, have produced a significant percentage of carcinomas in the large intestine of experimental animals. By inserting cotton strings impregnated with 20-methylcholanthrene into the lumen of the ceco-appendix of 62 male rats, they produced nineteen invasive and nine in situ adenocarcinomas. These results encouraged us to undertake more extensive experiments and to attempt to produce carcinomas in other portions of the colon by various methods of intraluminal application of 20-methylcholanthrene and 3,4-benzpyrene. The following report presents the results of these experiments.

MATERIALS AND METHODS

The experiments were divided into three principal groups: A, B, and C. Experiment A contained two subdivisions. Experiment A1 was conducted on 56 young adult male Wistar rats. A string impregnated with 3,4-benzpyrene, prepared according to the method published by Horava and von Haam, was surgically placed in the descending colon in such a manner that the string hung free in the lumen. Experiment A2 was conducted on 56 male Wistar rats of the same age as those used in Experiment A1. These animals were treated in a similar manner, except that the strings were impregnated with 20-methylcholanthrene.

Experiment B was also divided into subdivisions B1 and B2 composed of the same type and number of experimental animals as in Experiment A. The same method was followed except that the strings were placed in the transverse instead of the descending colon.

The animals of Experiments A and B were checked by laparotomy 6 months after the insertion of the strings, and new strings were inserted into those animals which had lost their strings. The animals were then observed for 18 months after the experiment was begun. Animals dying during this time were carefully examined, and histologic sections were prepared from any suspicious lesions of the large bowel. All surviving animals were sacrificed at the end of the observation period, and autopsies performed.

Experiment C was carried out for 1 year and was subdivided into four groups each consisting of twenty young, adult, male Wistar rats. Group C1 received twice-weekly oil enemas containing 0.5 per cent 3,4-benzpyrene; Group C2 received twice-weekly oil enemas containing 0.5 per cent 20-methylcholanthrene; Group C3 received twice-weekly oil enemas containing 0.5 per cent croton oil; Group C4 (control group) received twice-weekly enemas of pure olive oil. The enemas were given in doses of 3 cc. while the animal was under

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light ether anesthesia. After 1 year the animals were sacrificed and autopsies performed.

All animals were housed in groups of four in stainless steel cages and were fed Purina Laboratory Chow and tap water ad libitum.

RESULTS

Table 1 lists the results of these experiments. The remarkable and disappointing findings were the few colon carcinomas that were produced and the frequency of lymphosarcomas. The only invasive carcinoma was found in the descending colon of an animal with a 3,4-benzpyrene-impregnated string. Grossly, the mucosa was ulcerated, and the wall of the colon was thickened. Microscopically, we recognized a well differentiated adenocarcinoma invading the smooth muscle of the bowel but not extending through the serosa (Fig. 1). No enlarged nodes or distant metastases were present. Two carcinomas in situ, observed in the descending colon of animals bearing carcinogen-impregnated strings, showed glands composed of closely packed anaplastic columnar cells with large, dark, irregular nuclei (Fig. 2).

In attempting to explain the lack of carcinogenicity of both potent chemical carcinogens in these experiments, one may suggest that there was probably little absorption of the carcinogens, since these substances are fat-soluble and were dissolved in a nonintrinsic oil. Ernala, Sættä, and Ekwall (1) in fluorescence microscopy studies have pointed out that in the stomach and small intestine only little superficial absorption of this type of solution occurs and that one needs a hydrophilic agent to get adequate absorption. Carcinomas of the colon have been produced in a fairly high percentage of animals by the use of a systemic carcinogen (3). However, this is not in accord with the original postulate that an intraluminal carcinogen is the causal factor of these tumors. The failure of the carcinogen-impregnated strings to produce tumors in the ascending and descending colon is thought to be due to lack of adequate contact of the carcinogen with the epithelium, since many strings were coated with hard feces. Our previous success with strings placed in the ceco-appendix was probably owing to the semiliquid nature of the feces in this region, with a better chance for the string to remain in close contact with the wall.

The occurrence of the lymphosarcomas represents a new observation for which we have no explanation. They did not occur in our previous experiments and were never observed in our control animals. The tumors were dark red, soft, nodular masses measuring up to 3 cm. in diameter. They were always found near the ileocecal junction outside the bowel mucosa but intimately attached to the wall. The cut surface of these tumors showed a hemorrhagic, soft tissue with little gross architecture. Microscopically, these tumors were composed of medium-sized polygonal cells having a large, dark nucleus in a pink cytoplasm. The cells were single and were held together by a loose network of connective tissue (Fig. 3).

The spindle-cell sarcomas developed within the colon wall and were firm white tumors measuring up to 1 cm. in diameter. Microscopically, these tumors showed intertwining fascicles of long, slender cells with vesicular fusiform nuclei (Fig. 4). These tumors were probably due to deposition of carcinogenic material in the bowel wall at the time the strings were implanted.

REFERENCES

FIG. 1.—Invasive adenocarcinoma of descending colon. H. & E., X300.

FIG. 2.—Adenocarcinoma in situ of descending colon. H. & E., X300.

FIG. 3.—Lymphosarcoma of ascending colon. H. & E., X650.

FIG. 4.—Spindle-cell sarcoma of transverse colon. H. & E., X650.
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