Special lecture II

Experimental Tumors in Digestive Organs

Takashi Sugimura, M.D.

Director, National Cancer Center Research Institute, Tokyo, Japan

A review of experimental carcinogenesis in the esophagus, stomach, duodenum, colon and pancreas will be presented. Emphasis will be placed on the observations on experimentally produced cancer in digestive tract as a clinical model system of human cancer.

1) Esophagus carcinoma

The combined administration of N-methylbenzylamine and sodium nitrite to rat or dog produced specifically esophageal cancer. The chemical reaction of these two compounds yields and active nitroso-compound in the stomach. Autoradiographic study using [^{14}C-Me]-N-methylbenzylamine revealed an accumulation of radioactivity in the esophageal mucosa. Successive examinations with radiography and endoscopy gave information on the carcinogenic process.

2) Stomach cancers

Experimental gastric carcinogenesis had been considered a very difficult task until the administration of aqueous solution of N-methyl-N′-nitro-N-nitrosoguanidine (MNNG) to rats as drinking water proved to produce specifically gastric cancer. This method is simple. The rate of production of stomach cancer is high and reproducible.

Feeding of rats with 83 μg of MNNG/ml of drinking water for 7 months yielded stomach cancer, in over 80% of the rats, 15 months after the beginning of the treatment. Both differentiated type of adenocarcinoma with liver metastasis, and undifferentiated, signet ring cell type of adenocarcinoma with lymphnode metastasis were produced. This technique was applied to many interesting studies. For instance, pretreatment of stomach with iodoacetamide, which produces gastric ulcer, promotes the cancer yield by MNNG administration, and glass beads, which could not pass through the pylorus ring, also enhanced cancer production. The presence of high salt content in food also produced more malignant gastric tumors. Production of gastric carcinomas in many rats gave us a suitable autochthonous cancer system for chemotherapeutic study of gastric cancer.

Dog with stomach cancer is a good model for human gastric cancer. Ethyl derivative of MNNG, ENNG, has proved to produce gastric cancer. The process which produces gastric cancer in dogs was followed by radiographic and endoscopic examinations, without sacrificing the animals.

Knowledge of precancerous lesion of the stomach will also accumulate, and thus, provide us with the possibility for preventing cancer or blocking the carcinogenic process.

3) Intestinalization in the stomach

Intestinal metaplasia of gastric mucosa was suspected to be a precancerous legion. Intestinal metaplasia contains enzyme activities which are lacking in the normal stomach mucosa. Establishment of a method to produce intestinal metaplasia in animals was made possible by local X-ray irradiation or by administration of the propyl derivative of MNNG, PNNG, to rats.

4) Duodenal cancer

Oral administration of ENNG to mouse yielded duodenal adenocarcinomas with findings supporting a *one-step production* of malignant cells.

5) Colon cancer

Administration of azoxymethane or 1, 2 dimethylhydrazine to rats, mice, guinea pigs, rabbits and hamsters produced specifically colon cancers. Some nitroso-compounds produced colon tumors, by anal administration. Follow-up studies on the course of carcinogenesis by means of radiography and endoscopy were possible.

Spontaneous colon cancer was found in a colony of Wistar strain of rats. It mimics human familial polyposis.

6) Pancreas

Dimethylbenzanthracene, dihydroxypropylnitrosamine and dioxypropylnitrosamine, administered

by a suitable route, produced pancreas cancer in high incidence and fairly specifically.

Studies on experimental cancer of the digestive tract should give us not only new fundamental knowledge but also animal models for clinical investigations. For this purpose, the technique should be simple, the incubation time short, and the rate of incidence high and reproducible. Properties of the tumor in the animals should resemble those of human cancers. We have achieved most of these conditions.