Attempts To Produce Gastric Carcinoma Experimentally in a Gastric Ulcer*

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INTRODUCTION

The marked resistance of the glandular stomach of animals to spontaneously occurring cancer is well known. A similar resistance to the experimental production of cancer has been observed, since carcinogenic agents have been fed to mice and rats without producing cancer of the glandular stomach (6). However, when threads saturated with methylcholanthrene were imbedded in the mucosa of the stomach of mice, a cancer developed (6).

In view of these results it has been postulated that the gastric mucus or the superficial gastric mucous cells may serve as a barrier to carcinogens in the diet (4). In order to avoid this possibility, it was decided to produce a chronic ulcer of the glandular stomach of an animal so that the orally administered carcinogen might come into contact with the proliferating cells in the margin of the ulcer (5).

EXPERIMENTAL

Choice of an experimental animal.—The problem of the choice of an animal was first considered. It would have been desirable to have used the dog because of its size, but one of us had found that the pyloric mucosa of the dog has a very high grade resistance to methylcholanthrene, which may be imbedded in or rubbed into the mucosa without causing a tumor within 2 years (4). It was not desirable to use the mouse or rat, because a method for causing a chronic ulcer of the glandular mucosa is not available. The rabbit was not an ideal animal to use, because it is relatively resistant to the formation of neoplasms by the use of carcinogens (3). However, the rabbit was desirable because a chronic ulcer may be produced by excising a piece of pyloric mucosa and by feeding a rough diet (2), or by bilateral vagotomy and by feeding a rough diet. Since a relatively chronic ulcer was a basic necessity for the experiment, it was necessary to choose the rabbit despite its natural resistance to methylcholanthrene (MCA).

Controls (no operation).—Seven rabbits were given orally 15 mg. of methylcholanthrene (MCA) daily for the first 2 months, in the form of an emulsion in shale oil, each 15 mg. of MCA being dissolved in 0.1 cc. of benzene. After that period the following formula was used: 800 mg. MCA, 5 gm. cetyl alcohol, 1 gm. cholesterol, 6 gm. monoglyceride stearate dissolved in 80 cc. of shale oil (Texas Co., Altaire Oil, SAE #1), emulsified in 868 cc. of distilled water, with 50 cc. of 10 per cent Aerosol OT. Five cc. of this emulsion was given orally by tube daily until the end of the experiment.

Four animals were fed for slightly more than 9 months, one for 6 months, and two for slightly over 6 months. At the end of this time no lesions were found other than a very decided atrophic gastritis of the pyloric mucosa in the animal examined at 6 months.

Excision ulcers.—An operation was performed on fourteen rabbits, and an excision ulcer was produced after the method of Beazell and Ivy (1), after which they were given 15 mg. of MCA dissolved in 0.1 cc. benzene (placed in capsules) daily, except Sunday.

Nine rabbits were examined after 1 year and five after 18 months. No abnormality was found other than ulcer scars. One animal was fed MCA for 3.3 years (15 mg. in 0.1 cc. benzene in capsules). On examination, only papillomata were found at the site of a previous ulcer, as described by Beazell and Ivy (1) and Ivy and Cooke (5). Microscopic study showed no evidence of malignancy.

Bilateral vagotomy.—Fifteen rabbits were subjected to bilateral vagotomy (1). After the operation, 5–10 cc. of the following emulsion was administered daily, except Sunday: 800 mg. of MCA, 5 gm. cetyl alcohol, 1 gm. cholesterol, 1 gm. 4-dimethylaminoazobenzene, and 6 gm. of triglyceride stearate were dissolved in 80 cc. of warm shale oil; and 5 gm. of Aerosol O.T., dissolved in 50 cc. of distilled water and 2 cc. of 1.0 N NaOH, were added; this mixture was then emulsified in 868 cc. of distilled water.

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684
868 cc. of distilled water; then 1 gm. of 2-acetylamino-fluorene was added to the emulsion during vigorous shaking.

Three of the 15 rabbits survived 3 months, five for 4 months, four for 5 months, and three for 8 months. The animals were examined at autopsy, and a section of the liver was removed and examined microscopically. No evidence of malignancy was found, and the liver was normal—one animal dying of pyloric obstruction due to a penetrating pyloric ulcer.

DISCUSSION

The observations on the excision ulcer represent an extension of those reported by Ivy and Cooke (5). In their report, cystic changes were observed in three rabbits which had received MCA for 5—7 months, and epithelial “inclusions” were noted in the region of the papillomatous scar of a chronic ulcer in eight rabbits examined from 3 to 5.5 months after the ulcer was produced.

Unfortunately, the rabbits did not withstand bilateral vagotomy well, as only three survived up to 8 months.

Our failure to observe the development of a cancer in rabbits with a chronic gastric ulcer may be due to the fact that only one of our rabbits lived longer than 18 months. It may also be due to the possibility that, even when the “mucous barrier” is lacking, the MCA is not carcinogenic for the gastric epithelial cells of the rabbit. This latter point will have to be determined by implanting threads impregnated with MCA in the gastric mucosa of rabbits. It is of interest to indicate that neoplasms of the small intestine, which were obtained in mice by feeding MCA (6), were not seen in our rabbits.

The initial objective of this investigation was to obtain evidence concerning the origin, in man, of cancer in a chronic peptic ulcer of the stomach—which is a moot question and may not be answered with finality by clinical observation alone. The negative evidence obtained, to date, in the dog (4) and the rabbit is not conclusive. However, research should perhaps be directed to other species of laboratory animals or to the use of other carcinogens.

SUMMARY

A chronic gastric ulcer was produced in rabbits by excision or by bilateral vagotomy, and then methycholanthrene was fed for periods ranging from 3 to 18 months (one for 3.3 years and 30 for from 8 to 18 months) with the idea that a cancer might occur in the ulcer. A cancer was not observed, although cystic changes in and atrophic gastritis of the gastric mucosa and epithelial inclusions in papillomatous scars of healed ulcers were observed.

REFERENCES

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