An experimental study of gastric cancer in relation to gastric ulcer

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EDITORIAL SYNOPSIS This experimental study shows that carcinogens are relatively harmless on intact gastric mucosa but can induce lesions when the mucosa has been damaged, particularly when the injury is deep as in gastrostomy. Human gastric carcinogenesis is discussed in the light of these findings.

The question whether gastric ulcer is a precursor of gastric cancer has not yet been resolved with certainty. Various authors feel that on the grounds of clinical observation a definite correlation exists between these two entities (Pack *et al.*, 1950; Horn and Ravdin, 1953; Ivy, 1955; Monges, Payan, Bonneau, and Saint Pierre, 1960; Henschen, 1960; Ringertz, 1961) but observations on animals have failed to decide this question as spontaneous gastric ulcers and gastric tumours are rare in laboratory animals. There are, however, certain recent reports on spontaneous tumours of the stomach in mice (Wells, Slye, and Holmes, 1938; Miller and Pybus, 1956; Fischer and Kühl, 1958).

Several methods have been devised to induce experimental cancer of the stomach in laboratory animals, such as feeding carcinogenic hydrocarbons (Mulay and Firminger, 1952; Bock and King, 1959), adding certain solvents to peroral carcinogens (Peacock, Beck, and Chalmers, 1953; Setälä and Ekwall, 1950; Shemiakina, 1959), intramural injection of carcinogens (Stewart and Lorenz, 1942; Stewart and Hare, 1950; Hare, Stewart, Bennett, and Lorenz, 1952), or insertion of a carcinogen-impregnated thread into the stomach wall (Howes and de Oliveira, 1948; Ritchie, Webster, and Skoryna, 1959; Skoryna and Ritchie, 1960). Attempts to induce gastric cancer at the site of experimental gastric ulcer in rabbits have been unsuccessful (Ivy and Cooke, 1947; Denton, Sheldon, and Ivy, 1950).

The object of the present paper is to study once more the correlation between gastric ulcer and gastric cancer and to show that a carcinogen can induce local cancer when applied directly on the injured or ulcerated gastric mucosa in the rat, but not when it is applied to the intact mucous membrane of the stomach.

MATERIALS AND METHODS

Experiments were carried out on 272 white Wistar rats obtained commercially and weighing 150 to 180 g. They were housed in cages of six and fed on diet 41 rat cubes and water *ad lib*.

The carcinogens used were methylcholanthrene and dimethylbenzanthracene (Light & Co.) in powder form or dissolved in olive oil (75 mg. methylcholanthrene in 2 ml. olive oil).

Group A, consisting of 69 rats, was fed by stomach tube and each rat received one intragastric instillation of 75 mg. methylcholanthrene in olive oil, without further injury to the gastric mucosa.

Groups B, C, and D were all subjected to gastrostomies. Food hoppers were removed the night before operation. Anaesthesia was induced by intraperitoneal injection of nembutal Abbott. The stomach was incised and, after treatment, sutured with fine nylon thread. For the first two or three postoperative days the animals were fed on a diet of bread and milk. The carcinogen was delivered to the fore or glandular stomach using a probe topped with cotton wool which had been dipped in dimethylbenzanthracene powder. Approximately 1 mg. of carcinogen was delivered by this method. The surgical procedure varied in each group.

Group B consisted of 90 animals. Gastrostomy was performed on the squamo-glandular junction of the stomach and the squamous epithelium folded back. In the experimental animals ulcers were induced by scraping an area of about 2 mm. off the mucosa in the forestomach with a scalpel or painting it with concentrated caustic soda. The area so injured was then dusted with dimethylbenzanthracene powder. Twelve of the control animals were treated with caustic soda only and 28 with dimethylbenzanthracene only without prior ulceration.

In the course of the experiment it was observed that some cancers developed at the gastrostomy site and the technique was subsequently modified to avoid contact between carcinogen and gastrostomy site.

Group C consisted of 59 rats. The gastrostomy was

made in the prepyloric part of the stomach and an aural speculum passed through the incision; injury to the membrane and carcinogenic treatment to the forestomach were the same as in Group B, with the difference that all these procedures were carried out through the speculum.

Group D consisted of 54 rats. The procedure was identical with that in Group C, but the mode of application was reversed, *i.e.*, gastrostomy was performed on the forestomach and the glandular stomach subjected to the carcinogenic treatment.

The animals were killed whenever tumours were palpated in the abdomen or whenever they were found to be ill or suffering.

RESULTS

The rats survived for periods varying from five to 26 months, the average being 16 months. The most frequent causes of death were pneumonia or gastrointestinal abscesses.

From Table I it can be seen that no gastric lesion developed in animals receiving the carcinogen in a single gastric instillation but the carcinogen must have been absorbed into the gastrointestinal tract as five extragastric tumours were found in this series.

Table II shows the lesions in animals undergoing gastrostomy of the squamo-glandular junction. It is probable that the carcinogen was in intimate

TABLE I
LESIONS IN 69 ANIMALS RECEIVING ONE
INTRAGASTRIC DOSE OF METHYLCHOLANTHRENE

Gastric Lesions	Extragastric Lesions	Time (months)
None	Reticulo-sarcoma in the thorax	12
None	Reticulo-sarcoma in the thorax	12
None	Reticulo-sarcoma in the thorax	12
None	Mammary adenoma	12
None	Hypertrophy of the mammary gland secretion of milk	12

contact with the gastrostomy site as the stomach was seen to contract after handling. The incidence of local lesions was 22% in the experimental animals and 21% in the carcinogen-treated controls.

From Table III it can be seen that only two of 32 experimental animals developed any lesions in the forestomach and these were benign. In the control series there was one case of metastatic sarcoma of the glandular stomach. This was probably due to accidental implantation of the carcinogen in the gastrostomy site as the intention was to apply the carcinogen to the forestomach only.

Table IV gives the results in rats whose glandular stomach was subjected to carcinogenic treatment. These animals had to be sacrificed at eight months of the experiment when the laboratory was closed.

TABLE II
LESIONS IN 50 ANIMALS WITH GASTROSTOMY AT SQUAMO-GLANDULAR JUNCTION FOLLOWED
BY ULCERATION AND CARCINOGENIC TREATMENT OF FORESTOMACH

Gastric Lesions	Time (months)	Extragastric Lesions	Time (months)
Metastatic cancer (forestomach)	5	Intestinal sarcoma	15
Metastatic cancer (forestomach)	5	Sarcoma of abdominal wall	16
Metastatic cancer (forestomach)	8	Sarcoma of abdominal wall	16
Metastatic adenocarcinoma	8	Mammary fibroma	15
Cancer	8	Mammary fibroma	20
Sarcoma of glandular stomach (85 g.)	8	Fibroid of cervix uteri	22
Papilloma with malignant changes of forestomach	13	Wart of the lip	20
Papilloma of forestomach	13		
Papilloma of forestomach	17		
Papilloma of forestomach	20		
Papilloma of forestomach	20		

TABLE IIA
LESIONS IN 40 CONTROLS

Gastric Lesions	Time (months)	Extragastric Lesions	Time (months)
<i>Gastrostomy and dimethylbenzanthracene only (28 rats)</i>			
Carcinoma of forestomach	14	Sarcoma of abdominal wall	9
Carcinoma of forestomach	17	Sarcoma of abdominal wall	17
Sarcoma of glandular stomach (80 g.)	10	Mammary fibroma	18
Sarcoma of glandular stomach	12	Cervical fibroma	14
Papilloma of forestomach	13		
Papilloma of forestomach	20-5		
<i>Gastrostomy and NaOH only (12 rats)</i>			
No lesions		No lesions

FIG. 1. *Sarcoma of the glandular stomach weighing 80 g. (8 months).*

FIG. 2. *Metastatic sarcoma of the glandular stomach (8 months).*

FIG. 3. *Gastric submucosa in a case of metastatic adenocarcinoma. $\times 120$ (8 months).*

FIG. 4. *Keratinizing squamous carcinoma of forestomach. $\times 120$.*

TABLE III

LESIONS IN 32 EXPERIMENTAL ANIMALS WITH GASTROSTOMY OF PRE-PYLORIC STOMACH
AND ULCERATION AND DIMETHYLBENZANTHRACENE POWDER ON FORESTOMACH

Gastric Lesions	Time (months)	Extragastric Lesions	Time (months)
Ulcer of glandular stomach	16	Lymphoma of caecum	12
Papilloma of forestomach	12		

TABLE IIIA

LESIONS IN 27 CONTROLS

Gastric Lesions	Time (months)	Extragastric Lesions	Time (months)
Dimethylbenzanthracene only (18 rats)			
Metastatic sarcoma of glandular stomach	14	Reticulo-sarcoma in the thorax	9
NaOH only (9 rats)			
No lesions		No lesions	

Within that period two cases of metastatic sarcoma of the glandular stomach were observed in the experimental group. There were no lesions among the controls.

TABLE IV

LESIONS IN 34 EXPERIMENTAL ANIMALS WITH GASTROSTOMY OF FORESTOMACH AND ULCERATION AND DIMETHYLBENZANTHRACENE POWDER ON GLANDULAR STOMACH

Gastric Lesions	Time (months)	Extragastric Lesions	Time (months)
Metastatic sarcoma	6	None	
Metastatic sarcoma	6		

TABLE IVA

LESIONS IN 20 CONTROLS WITH GASTROSTOMY IN FORESTOMACH AND DIMETHYLBENZANTHRACENE POWDER ON GLANDULAR STOMACH

Gastric Lesions	Extragastric Lesions	Time (months)
None	Ovarian abscess	7

DISCUSSION

From the above data it appears that the animals in which the carcinogen was allowed to act on the gastrostomy site (group B) or on experimental gastric ulcers had a much higher incidence of gastric tumours than those where the carcinogen was applied to the intact gastric mucosa.

Trauma enhances the effects of chemical carcinogens on skin (Deelman, 1927; MacKenzie and Rous, 1941; Pullinger, 1943, 1945; Linell, 1947; Breedis, 1955; Gottfried, Molomut, and Patti, 1961) and it is probable that the same holds true for other epithelia, including stomach.

The decisive factor in malignant transformation

appears to be the intimate contact between the basal or stem cell, or young regenerating elements, and the carcinogen, such as is possible in areas of ulceration, abrasion, or wound repair.

The experimental gastric tumours obtained by various methods have probably been elicited by similar mechanisms. Simple feeding of carcinogens has not produced gastric adenocarcinoma (Peacock *et al.*, 1953) but the intramural introduction of such substances has caused tumours of the glandular stomach (Stewart and Lorenz, 1942; Howes and de Oliveira, 1948). Similarly, the addition of certain agents with lipophilic or hydrophylic properties to peroral carcinogens greatly increased the incidence of gastric tumours (Setälä and Ekwall, 1950; Berenblum and Haran, 1955; Shemiakina, 1959; Arffmann, 1960). Ivy (1955) offers the following explanation: 'For methylcholanthrene to cause cancer of the stomach it must act on the deeper cells of the gastric glands or the carcinogen must be sufficiently soluble to be absorbed into the deeper cells'.

The genesis of gastric cancer in man might be compared with what happens under experimental conditions, namely, exposure of basal or regenerating cells, such as is possible in atrophic gastritis or ulceration, to exogenous dietary carcinogens. Clinical gastric cancer may only emerge after a long latent quiescent period so that the primary episode of gastric ulceration might no longer be associated with it. On the other hand, the ulcer coexisting with the cancer will probably not be the one to have undergone malignant change. Pack *et al.* (1950) and Willis (1953) insist that cancer has rarely been found on the edges of gastric ulcer and that therefore no correlation exists between the two.

It is significant that similar observations have been made on the colon. As many as one-third of long-standing cases of ulcerative colitis eventually develop

malignant changes. Svartz and Gillnäs (1958), Rosenquist, Öhrling, Lagercrantz, and Edling (1959), and Reiferscheid (1960) stress the presence of a long period of apparent good health before the emergence of cancer of the colon. A similar course of events was reported in a case of ulceration of the rectum preceding rectal cancer (Simianovskii, 1959).

I wish to express my thanks to Mrs. P. David and Mr. Mass N'jie for skilful technical assistance and to Mr. Eric Saville for the photographs.

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