THE EXPERIMENTAL PRODUCTION OF PRECANCER AND CANCER
OF THE STOMACH

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Much work has been devoted to the experimental production of malignant growth of the glandular epithelium
of the stomach, but success has only rarely been achieved [15, 16]. The only carcinogen which has so far proved
capable of inducing malignant growth is methylcholanthrene. The use of 9,10-dimethyl-1,2-benzanthracene (DMBA)
for this purpose, irrespective of its mode of administration, led to the appearance of squamous-cell carcinoma of the
fores-tomach [3, 9]. Most of the work has been carried out on mice and rats, in which the stomach consists of a fore-
stomach, lined with stratified squamous epithelium, and a glandular stomach.

The numerous facts obtained by research workers point to the extraordinary degree of resistance of the glandu-
lar epithelium of the stomach of animals to the development of spontaneous and induced malignant neoplasms [10,
11, 12, 14, 16]. Analysis of the data in the literature also shows that the local action of the carcinogen alone is
clearly insufficient to disturb this resistance. We have examined the data on this subject more minutely in a survey
on experimental carcinoma of the stomach [1].

In the present investigation we set out from the assumption that in order to produce malignant growth in the
 glandular portion of the stomach the action of the carcinogen must be supplemented by other factors, disturbing
the general and local resistance of the organism and modifying the functional state of the organ. Of particular interest
is the disturbance of the gastric function which can be produced without any direct action being exerted on the stom-
ach wall.

For this purpose we ligated the pancreatico-duodenal vein. In small laboratory animals (mice, rats) this pro-
cedure leads to a disturbance of the liver function similar to that observed after the formation of an Eck’s fistula in
dogs [6]. According to S. I. Lebedinskaya [2], the formation of this fistula causes a prolonged increase in gastric
secretion besides disturbing the liver function.

DMBA was given as paraffin-wax pellets, in an attempt to create a depot of carcinogen and thereby to ensure
its prolonged administration to the surrounding tissues in small doses, and on the assumption that introduction of the
carcinogen in this way would lead to the appearance of heterotopic proliferation of the glandular epithelium as a
reaction to a foreign body. Moreover, the administration of a carcinogen in oily solutions and suspensions is accom-
panied, as a rule, by its penetration into the fore-stomach, which is particularly sensitive to the action of DMBA [3,
4, 5, 7, 8, 13].

EXPERIMENTAL METHOD

The experiment was conducted on 30 rats, 8 of which were controls. Under ether anesthesia the anterior ab-
dominal wall was incised in the midline. DMBA was implanted in the form of a 10% paraffin-wax pellet weighing
5 mg beneath the serosa of the anterior wall of the pyloric portion of the stomach. The pancreatico-duodenal vein
was ligated with silk thread and the wound was closed in layers. The stomach of sacrificed or dying rats was opened
up along the greater curvature and fixed in distended state in a 12% solution of neutral formalin. Celluloidin-paraffin
or frozen sections from strips of the stomach wall, cut to correspond to the position of the neoplasms along the long
axis of the stomach, were stained by the ordinary methods and also by special methods: the Dominici-Kodrovskii
method, Best’s carmine and Meyer’s mucicarmine, in order to reveal the secretory granules in the glandular cells of
the stomach.
EXPERIMENTAL RESULTS

As a result of the experiments conducted in the manner described above, neoplasms were produced in the gastric mucosa, always situated in the glandular portion on the anterior wall in the prepyloric region, where the main glands are still predominant in the mucous membrane. No changes were observed in the fore-stomach.

The neoplasms were of different sizes - from simple thickenings of the mucosa hardly visible with the naked eye to well defined nodules 2-5 mm in diameter. In one case (rat No. 5) a nodular growth occupied nearly the whole glandular part of the stomach, covering the passage into the duodenum.

Corresponding to the macroscopic appearances, in all the animals heterotopic proliferation of the glandular epithelium was found at the site of the growths, differing in depth and extent of spread. When the changes were hardly visible to the naked eye, the proliferating tissues occupied small areas of the mucous membrane, penetrating only into its muscular coat. Larger epithelial proliferations usually penetrated into the deeper layers of the stomach wall - into the submucosa and muscularis mucosae and as far as the serosa. The deeper it was found, the more extensive its area of spread.

Whereas in the normal mucosa the glandular tubes were arranged parallel to each other, in the heterotopic proliferations they differed in their shape and length and were oriented in different directions, sometimes lying close together, sometimes some distance apart. The lumina of these tubes varied in size, and they sometimes had the appearance of cystiform dilations.

In the course of the spread of the heterotopic proliferations, the morphological and functional characteristics of the glandular cells lining the epithelial tubes underwent modification.

In the first stages of the process, when the wax pellet implanted beneath the serosa, containing the carcinogen, was still present 24 days later in the subserous membrane and was penetrating into the muscularis mucosae, and when inflammatory infiltration and necrosis were observed in the stomach wall, changes also began to affect the main glands situated near the pellet. These changes took the form of dedifferentiation of the glandular cells. The first cells to disappear were the principal cells, in which the pepsinogen granules were replaced by a mucous secretion, then followed the parietal cells and, lastly, the typical accessory cells. New forms of cells appeared in the glandular tubes, proliferating deeply. They differed from the typical glandular cells in the shape and size of the cell body and in the position of the nucleus within the cytoplasm.

At the 4th and 6th months of the experiment, after elimination of the pellet containing the carcinogen (Fig. 1), signs of inflammation were no longer found. Although the foci of necrosis and inflammatory infiltration had disap-

Fig. 1. Focus, adenomatous in structure, situated in the submucosa (4 months after implantation of carcinogen). Objective 3, eye-piece 6.