MECHANISMS OF METAPLASIA OF THE DUCT EPITHELIUM OF ORGANS OF THE PANCREATICOBILIARY SYSTEM

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A steady increase in the number of cases of diseases of the organs of the pancreaticobiliary system is nowadays being observed in conjunction with a simultaneous increase in the relative contribution of malignant neoplasms to the morbidity and mortality structure. The pancreas and the extrahepatic bile ducts are most frequently affected; among patients of this category more than 10% have suffered for a long time from chronic pancreatitis and cholangiitis. The mortality from carcinoma of the pancreas, gall bladder, and extrahepatic bile ducts accounts for 5% of the total mortality from malignant neoplasms and it occupies 6th place among all tumors of the digestive organs [1, 6, 7].

In some cases malignant transformation is preceded by destabilization of processes of cell proliferation and differentiation, leading to the development of a pathological reaction, namely metaplasia [5]. It is accordingly interesting to attempt to explain some of the mechanisms of this metaplasia of the epithelium under the influence of endogenous or exogenous factors.

The object of this investigation was to study the kinetics of the cell population and the pathogenetic nature of metaplasia during increased pressure within the duct or under the influence of a foreign body while the patency of the ducts is preserved.

EXPERIMENTAL METHOD

Experiments were carried out on 87 noninbred albino rats weighing 150 g; the control consisted of 35 intact animals. In the experiments of series I, intracanalicular hypertension was induced in 39 rats by ligation of the efferent ducts. In series II the common bile duct was isolated and opened in the region where it receives the pancreatic ducts. A tube was formed from aluminum foil and introduced into the common bile duct toward the liver, after which it was shifted distally, so that the wall of the aluminum tube covered the hole into the duct. On the 4th day after the operation [2] an autoradiographic analysis was made of the kinetics of reproduction of the duct cells. For this purpose ^{3}H-thymidine was injected intraperitoneally into the rats in a dose of 5 μCi/g body weight. The animals were decapitated under anesthesia 1-38 h after the single injection of the isotope and preparations were made for autoradiography. The mean number of labeled duct cells with mitoses (in percent) was obtained by counting 50-100 cells in a field of vision of the ocular micrometer of the MBI-3 microscope. The duration of the cell cycle was determined graphically by Quastler's method. The results were subjected to statistical analysis by Montsevichyute-Éringene's method [3]. Rats for morphological investigation were killed 4-30 days after the operation and sections stained with hematoxylin and eosin were studied in the light-optical microscope.

EXPERIMENTAL RESULTS

The duct epithelium which, in intact animals, consisted of simple epithelium, 4-7 days after the operation was undergoing metaplasia with the formation of stratified foci of proliferation around the perimeter of the duct (Fig. 1). These foci of proliferation in the common bile and pancreatic ducts were similar in shape to intestinal crypts and villi, but differed from them in that in most cases their apices were joined together to form a continuous epithelial sheet (Fig. 2).

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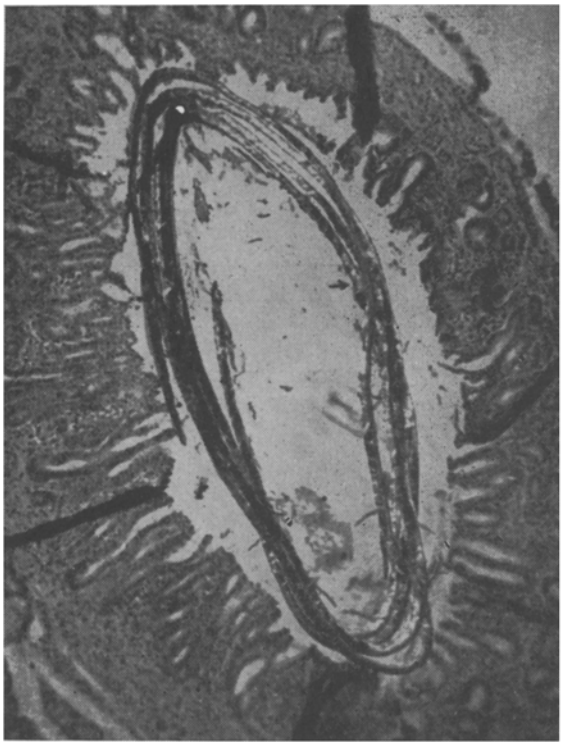

Fig. 1

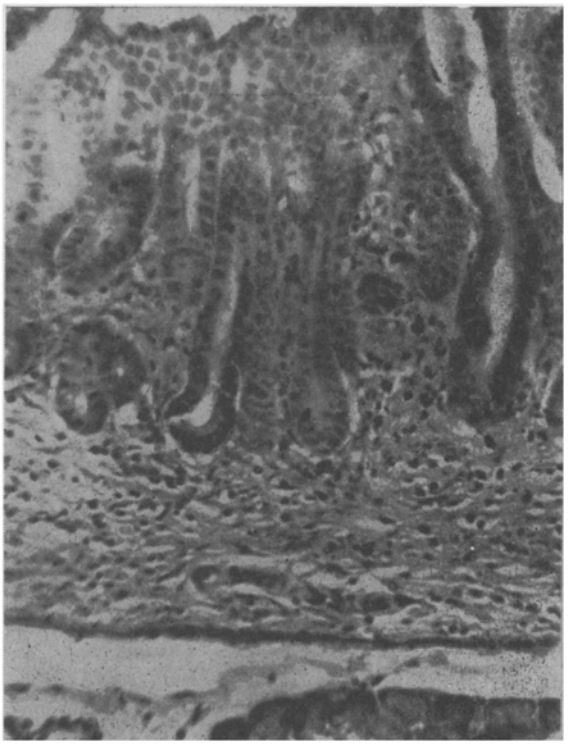

Fig. 2

Fig. 1. Metaplasia of epithelium of common bile duct on 7th day after introduction of aluminum foil tube (arrow) into lumen of duct. Magnification 85×.

Fig. 2. Metaplasia of epithelium of common bile duct of intestinal type. Formation of epithelial sheets, absence of any marked inflammatory manifestations (7th day after operation). Magnification 200×.

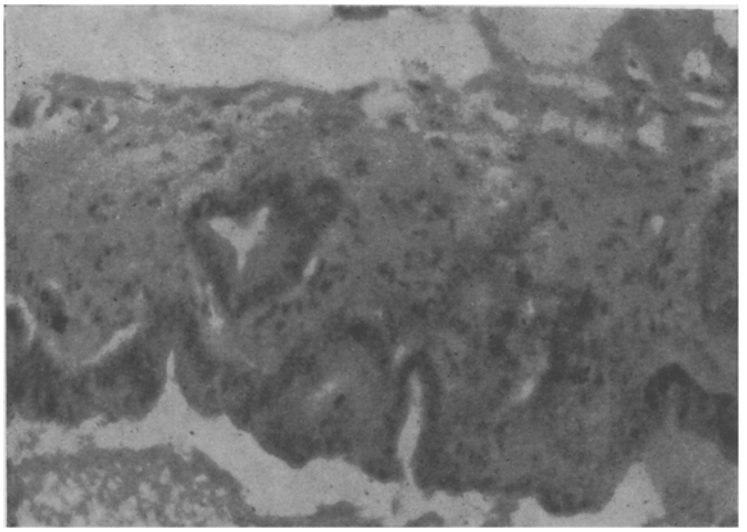

Fig. 3. Incorporation of ^{3}H-thymidine into cells of ductal crypts during metaplasia of epithelium of pancreatic efferent duct. Canalicular hypertension (4 days after operation). Magnification 150×.

A characteristic feature which, in the writers' opinion, confirms that the metaplasia obtained under these experimental conditions is true metaplasia, is the absence of any marked inflammatory changes, by contrast with the model of epithelial metaplasia obtained by other known methods [4]. With an increase in the period of observation the processes of metaplasia increased in intensity, cyst-like formations were formed, but there was no inflammatory component.

Comparative analysis of data on the kinetics of cell reproduction in the duct epithelial population obtained by autoradiography showed that the period between injection of the isotope and the appearance of the first labeled cells in a state of mitosis was 1 h in the control and experimental rats. The total duration of the presynthetic period and of mitosis in the control was 13 h, compared with 12 h for cells of the metaplastic epithelium.

Meanwhile the period of DNA synthesis in cells of the duct epithelium in intact animals was 8 h, whereas in the experimental rats it increased to 12 h. The total duration of the cycle of division of the duct cells in the control rats was 22 h, and in the experimental rats 25 h.

Consequently, during metaplasia of the epithelium under the experimental conditions described, one of the most stable phases of the cell cycle — the phase of DNA synthesis — was lengthened. This provided the necessary preconditions for an increase in the number of cells of the proliferating population. In this case the process of accumulation of cells took place through the development of special zones of growth in the ducts, which by analogy with the intestine, we called ductal crypts (Fig. 3). During the first few hours after injection of the isotope, the label was localized in the cells of the ductal crypts. After 10 h many labeled cells appeared at the base of the villi, but their number in the crypts decreased; in the writers' opinion this is evidence of possible displacement of the cells or of the focus of proliferation to the villus.

The appearance of proliferating foci of this sort would evidently be impossible without involvement of precursor cells that, under normal conditions, are at rest. Under the influence of harmful factors on generative ductal precursor cells, the single tissue system breaks up into a number of subpopulations of actively proliferating cells. Under these conditions the structure of the duct epithelium can no longer maintain equilibrium and metaplasia of intestinal type takes place. Through the formation of villi the system can be stabilized, but this stabilization is temporary in character, as a result of which the phenomena of metaplasia and cellular atypia increase in intensity.

With exhaustion of the compensatory powers of the cells of the duct epithelium its structure is destroyed, the ducts dilate and undergo sclerosis, with the formation of true and false cysts, and so on.

The development of metaplasia of the duct epithelium of organs of the pancreaticobiliary system, according to these observations, is thus associated with intensification of proliferation and lengthening of the phase of DNA synthesis in the proliferating (generative) cells. The dynamics of development of these processes obeys the laws of function of rapidly renewed cell systems. It may be that similar mechanisms lie at the basis of the development of precancerous states.

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