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Repair of Gastric Ulcer

A Cell Kinetic Study*

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Summary. By a cryosurgical method a mucosal defect was produced in the body of the rat stomach, and repair of the gastric ulcer was studied with ^{3}H-thymidine autoradiography. From 18 to 24 hours after cryoinjury, cell proliferation in the fundic mucosa was much increased, as indicated by an increase in the labeling index of the cells in the proliferating cell zone of the mucosa, or by reactive incorporation of ^{3}H-thymidine into the mucous neck, chief and parietal cells. Spatially, the increased cell proliferation was found in a region of the mucosa more than 600 μm distant from the injury, and lasted for more than 14 days. The mucous neck and chief cells around the ulcer which had incorporated ^{3}H-thymidine seemed to transform into flat cells after mitotic division and then continued to divide. After 3–5 days, so called regenerating epithelium or covering epithelium appeared around the ulcer. The upper part of this regenerating epithelium consists of tall columnar cells, the lower part is composed of cystic glandular structures, in which many ^{3}H-thymidine incorporating cells were seen. The formation of new glands in the mucosal defect appeared to take place by budding from these cystic glandular structures with subsequent differentiation of surface epithelial cells. After 3 weeks the mucosal defect was covered by mucinous glandular structures similar to the proper pyloric mucosa. The proliferating cells were confined to the middle level in the regenerated mucosa.

Key words: Gastric ulcer – Repair – Autoradiography – Cryosurgery

Introduction

The mechanism of healing of gastric ulcers has been studied intensively in human beings and in experimental animals (Myhre 1956; Hunt 1958; Myren

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and Torgersen 1960; Townsend 1961a, b; Williams 1961; Lawson 1970). There are only a few reports on the dynamics of repair of these ulcers, only Breining et al. (1974) have studied time dependent cell kinetics. In such investigations it is necessary to produce a gastric ulcer of a certain size at a certain site.

There are many methods of causing stomach ulceration. The simplest is surgical resection of the mucosa. An ulcer can be induced by chemical injury, using corrosive agents and it is also possible to make one by causing ischemia of the mucosa (see review Wanke 1971). With these methods, however, it is difficult to reproduce a gastric ulcer of given size at a given site.

By heat, or a cold coagulation method, it is possible to make reproducible ulcers (Frühmorgen et al. 1974; Bodic et al. 1979; Helpap 1980; Breining et al. 1974). Wound healing after thermo- and cryonecrosis has been studied in various organs and it has been shown that wound healing after cryonecrosis takes place rapidly and is free from severe complications (Helpap 1980). The cryosurgical method also has the advantage of reproducibility of the lesion in different tissues or organs. In the following study, gastric ulcer was produced in rats by cryosurgery and repair was studied with ^{3}H-thymidine autoradiography.

Material and Methods

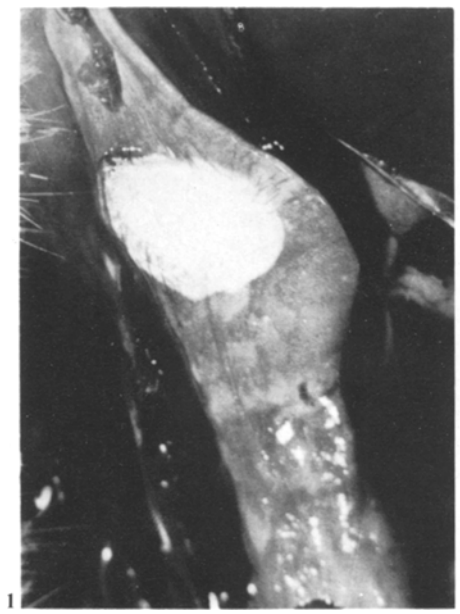
45 male Wistar rats (average body weight, 266 ± 33 g) were used in this experiment. 3 of them served as controls, and 42 rats received the following operation. After laparotomy, a small freezing injury was made on the anterior wall of the body of the stomach by applying a cryoprobe at $-196°$ C (diameter 6.5 mm, cryoprobe H 29, Cryocauter 190 Frigitronics) for 30 s. After thawing, the abdomen was closed with catgut and silk. The postoperative survival time was 12, 18, 24, 36 h and 2, 3, 5, 7, 10, 14, 21, 30, 50 and 74 days. 1 h before killing, each animal received a single intraperitoneal injection of ^{3}H-thymidine (2.5 μCi/gm of body weight; specific activity 20.0 Ci/mmol, NEN Chemicals, Boston, Mass., USA). After sacrifice of the animals, the resected stomach was cut along the greater curvature, pinned out flat on a cork block and fixed in 4% formalin for 24 h. After fixation, the stomach was cut into 5 mm wide rectangular pieces, embedded in paraplast and sectioned serially or semi-serially.

Morphological Study. Histological slides were stained with haematoxylin and eosin and PAS. In the normal fundic mucosa, mucous neck, chief and parietal cells were identifiable by these stains (Fig. 4b). In this study we used the following terms. The regenerating epithelium or covering epithelium refers to the newly formed, immature mucosal structures in the defect. The regenerated mucosa means the healed gastric mucosa. In the regenerated mucosa, we examined morphology, mucin content and stainability of the glandular cells.

Autoradiographic Study. The histological slides were covered with stripping film (AR 10, Kodak), and exposed for 21 days. After development and fixation, sections were stained with H.E.. The PAS staining of the autoradiographs preceded the film covering.

In the control rats, the labeling index of the proliferating cell zone was counted. The labeling index was expressed as the percentage of labeled cells in a total count of more than 1000 cells confined to the neck region. Occasionally, the border between the neck region and the superficial part of the fundic gland is indistinct. Under these circumstances, the zone of the glandular tubule from the uppermost labeled cells to the lowermost labeled cells was regarded as the proliferating cell zone. Without this frame of reference, an exact estimation of the labeling index was impossible. In a 600 μm wide zone of the fundic mucosa, the percentage of the labeled mucous neck, chief and parietal cells were also counted.

In the operated rats, the labeling index of the proliferating cell zone, and the percentage of the labeled mucous neck, chief and parietal cells were counted in a 600 μm wide region of



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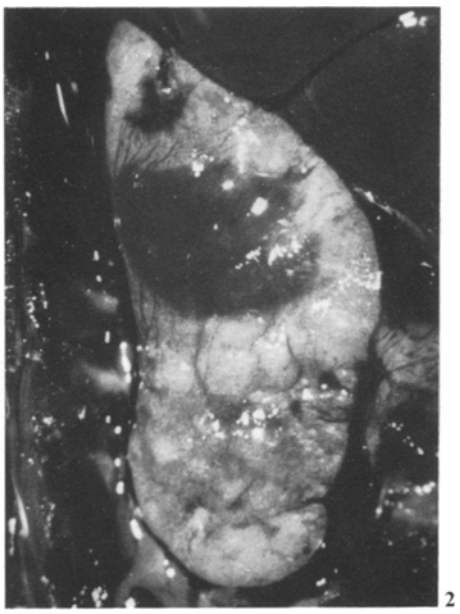

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Fig. 1. Immediately following contact with cryoprobe, a round frozen zone appeared on the anterior wall of the stomach

Fig. 2. After thawing a haemorrhagic zone appeared

the fundic mucosa, adjacent to the frozen injury. After the formation of the cryogenic ulcer, the labeling indices of the proliferating cells of the regenerating epithelium and of the fibroblasts in the granulation tissue around the ulcer were also determined. The mean and the standard deviation were expressed.

Results

Morphological Findings. After cryoprobe contact with the serosal surface of the stomach for 30 s a round frozen zone appeared. The frozen zone was fragile. 2 min after taking off the cryoprobe the zone became haemorrhagic (Figs. 1, 2). An ulcer was found in the resected stomach 24–36 h after the operation.

Microscopically, diffuse necrosis of the fundic mucosa was found 12 h after the in situ freezing (Fig. 3). The central part of the necrotic region was ulcerated, but mucosal structure was still visible at the margin of the frozen zone (Fig. 3). The submucosa showed marked oedema, and the muscle layer was partially destroyed (Fig. 3). At the serosal surface, fibrin precipitates were found and a small number of polymorphonuclear leukocytes infiltrated the submucosa. On the 2nd day after the operation, the necrotic region of the mucosa was sloughed off and a round ulcer appeared. The base of the ulcer and the connective tissue beneath the ulcer were infiltrated by polymorphonuclear leukocytes and monocytes. From the 2nd to the 3rd day after the operation, the remaining fundic mucosa bowed down towards the base of the ulcer. By this time, small

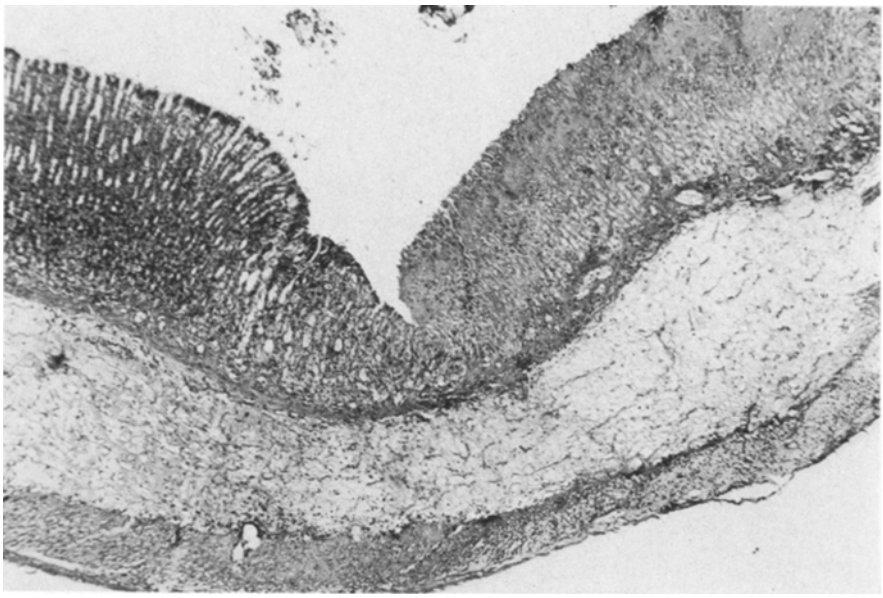
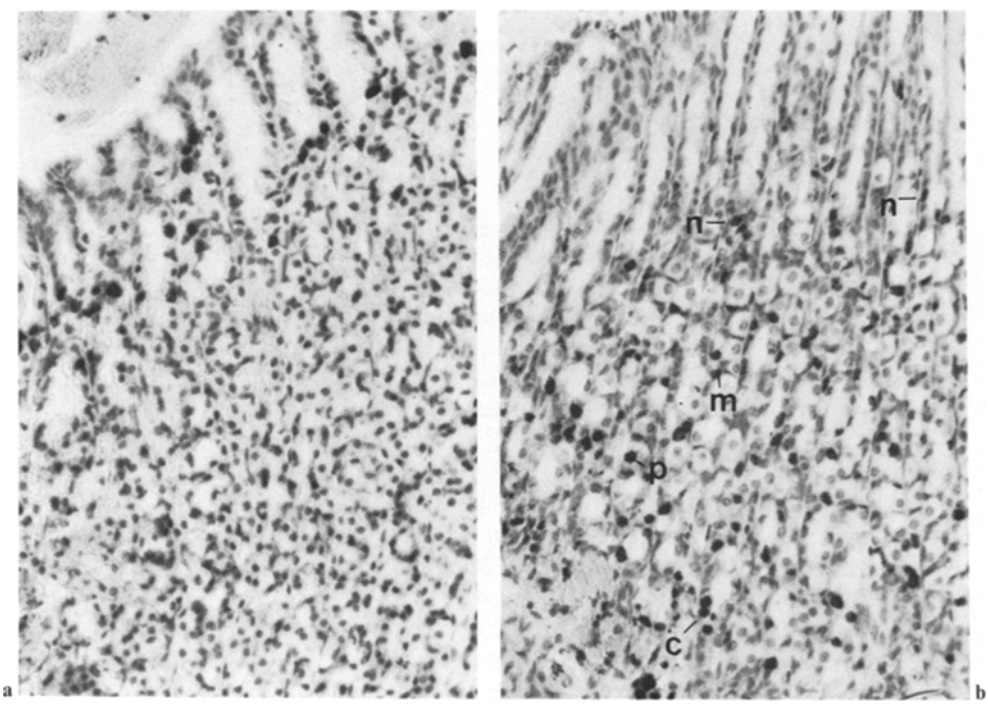


Fig. 3. Micrograph of the fundic mucosa 12 h after cryoprobe contact. Coagulation necrosis is seen in the zone of cryoprobe application (H.E. × 30)



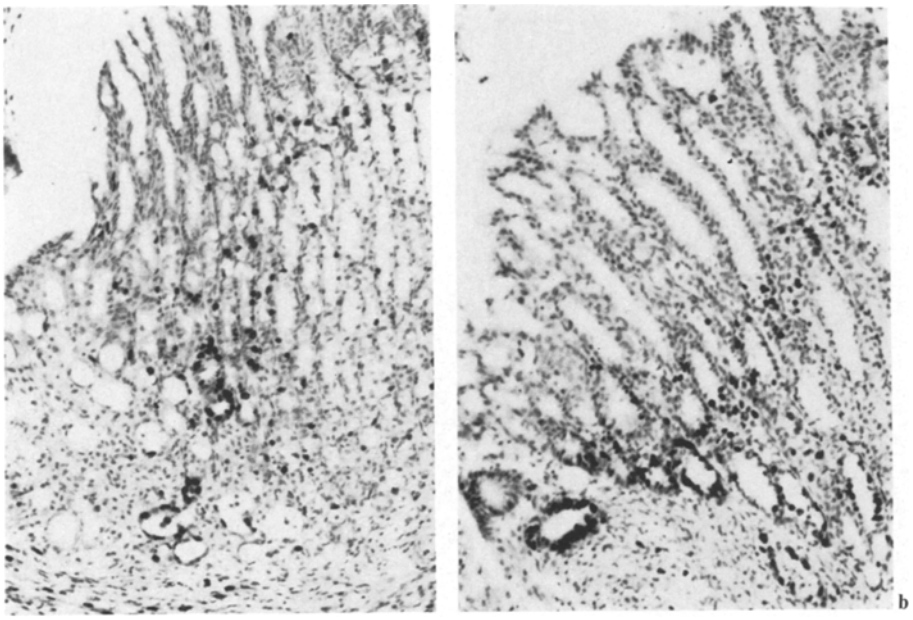


Fig. 5. a Autoradiograph of the fundic mucosa at the margin of the ulcer, taken 3 days after the operation. Note the small cystic structures at the margin of the ulcer. The label with ^{3}H-thymidine is seen on the cells forming the cyst (H.E. $\times 100$). **b** Autoradiograph of the fundic mucosa at the margin of the ulcer, taken 3 days after the operation. By this time, the regenerating epithelium has appeared. The labeled cells are confined to the lower part, and the surface epithelial and foveolar cells are not labeled (H.E. $\times 100$)

cystic structures appeared at the margin of the ulcer (Fig. 5a). Each cyst consisted of flat epithelial cells (Fig. 5a). After the 3rd day, the regenerating epithelium appeared at the margin of the ulcer (Fig. 5b). This epithelium consisted of irregular, cystic or tortuous glandular structures composed of relatively large, basophilic columnar cells, which sometimes accompanied surface epithelial cells at the luminal end (Fig. 5b). The leukocytic infiltration increased in the connective tissue around the ulcer until the 5th day. The frozen muscle layer was replaced by granulation tissue composed of many fibroblasts and capillaries, which was infiltrated by macrophages. The regenerating epithelium extended concentrically into the ulcer.

On the 10th day, more than half of the ulcerated region was covered by the regenerating epithelium. At the bottom of the regenerating epithelium, clear large glandular cells resembling the pyloric glandular cells or the Brunner's gland cells were found (Fig. 6a). At the center of the ulcer, a small tissue

Fig. 4. a Autoradiograph of the fundic mucosa at the margin of the cryolesion, taken 12 h after the operation. The labeled epithelial cells are confined to the neck region of the fundic mucosa not destroyed by the cryoinjury (H.E. $\times 10$). **b** Autoradiograph of the fundic mucosa at the margin of the cryoinjury, taken 24 h after the operation. Note that many cells in the fundic glands are labeled. Those labeled cells are mucous neck (*m*), chief(*c*) and parietal (*p*) cells. (*n*) indicates proliferating cells of the neck. (HE $\times 150$)

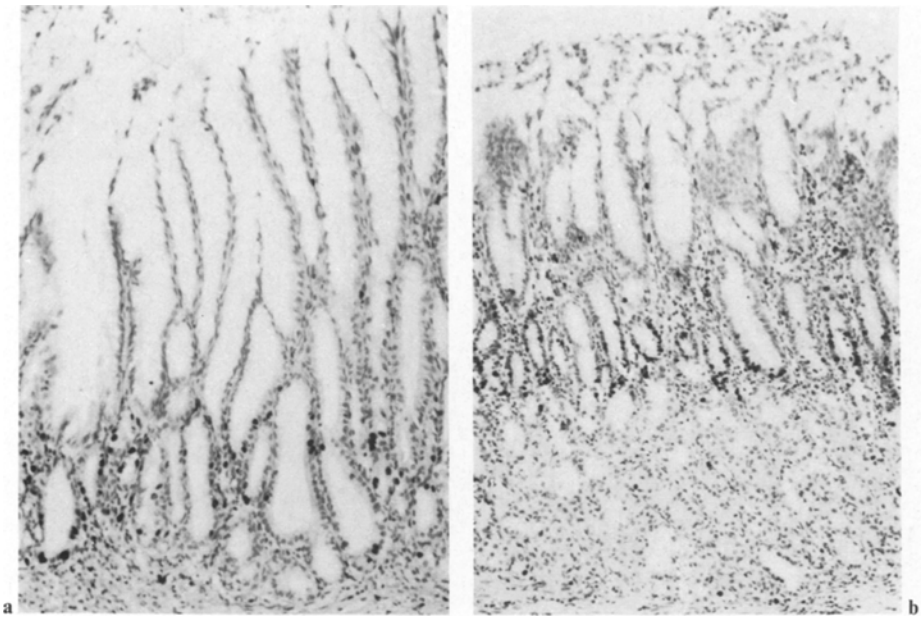


Fig. 6. a Autoradiograph of the regenerating epithelium, taken 14 days after the operation. The labeled cells are scattered in the lower level of the mucosa. A few glandular cells are found at the bottom of the mucosa (H.E. ×100). **b** Autoradiograph of the regenerating mucosa, taken 3 weeks after the operation. The labeled cell zone is located at the middle level of the mucosa. The mucinous glandular cells arise in the lower third of the mucosa (H.E. ×100)

defect was still found (Fig. 7), but a part of the ulcer base was occasionally covered by columnar cells or the surface epithelial cell type (Fig. 7).

After 2–3 weeks, the defect of the mucosa was almost completely covered by the regenerating epithelium, which became thicker. In the lower part of the regenerating epithelium, the mucinous glands appeared (Fig. 6b) and were composed of large clear cells which were similar to those of the normal pyloric gland (Fig. 6b). In the submucosa scar tissue appeared by this time. However, there was still resorptive granulation tissue at the center of the injury. After 50 days, the defect of the mucosa was completely covered by regenerated epithelium, which reached a thickness of the normal fundic mucosa. The lower part of the regenerated mucosa always consisted of mucinous glands. Almost all cells in these glands were clear cells, with cytoplasm filled with PAS-positive material. Neither distinct parietal cells nor cells with eosinophilic cytoplasm were found in the regenerated mucosa (Fig. 6b). The muscularis mucosae was split in a region of the regenerated mucosa, and in the submucosa a small amount of scar tissue was found.

Autoradiographic Findings. In control rats, the radioactively labeled cells were confined to the neck region of the fundic mucosa. The labeling index of the proliferating cell zone was 26.3% on average. Only a few mucous neck and

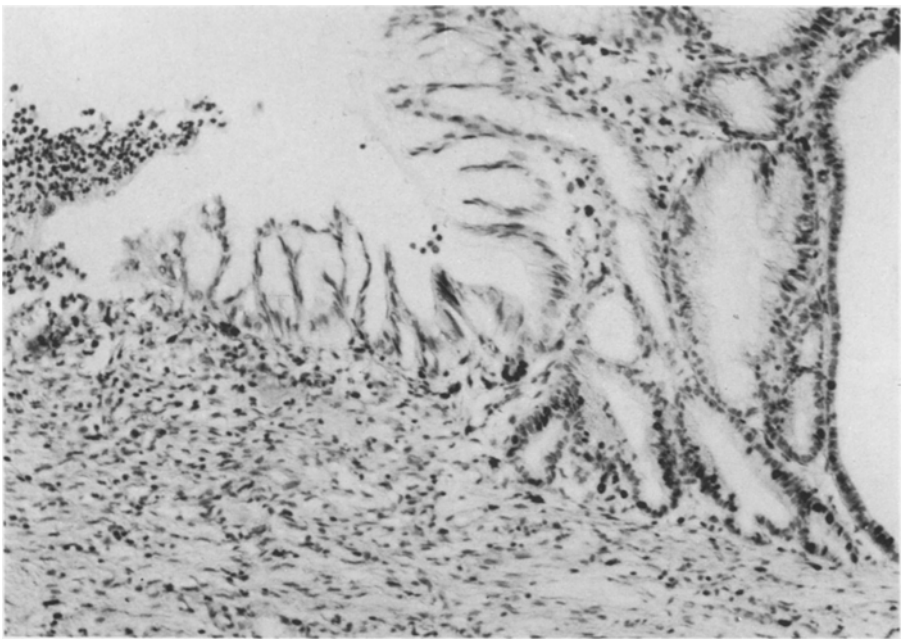


Fig. 7. Autoradiograph of the regenerating epithelium at the margin of the ulcer taken 10 days after the operation. The surface epithelial cells extend over the ulcerated region. These cells are not labeled with ^{3}H-thymidine, indicating that they are the progeny of the proliferating cells which form the cyst. (H.E. ×230)

chief cells were labeled (less than 0.1%) and no parietal cells were labeled, after a single injection of 3H-thymidine.

12 h after the cryosurgery, the labeled epithelial cells were confined to the neck region, and only a few glandular cells were labeled with 3H-thymidine (Figs. 4a, 8). 18–24 h after the operation, many labeled cells were found in a 600 μm wide zone of the fundic mucosa adjacent to the cryolesion (Fig. 4b). These labeled cells were either undifferentiated cells in the neck region, or mucous neck, chief and parietal cells (Figs. 4b, 8). The labeling index of these cell groups is shown in Fig. 8. The index for all cell types increased after 18 h and reached a maximum for the undifferentiated cells after 24 h, for the mucous neck cells after 36 h, for the chief cells after 36 h, and for the parietal cells between 36 and 48 h (Fig. 8).

After 3 days, the labeling index of all cell types showed a marked decrease, and the index of proliferating cell zone returned to normal values after 5 days. The increased cell proliferation of the mucous neck, chief and parietal cells lasted for more than 14 days, and subsided after 3 weeks. On the 3rd–5th day after the operation, the label with ^{3}H-thymidine was found on the flat cells which formed small cystic structures at the margin of the ulcer (Fig. 5a).

In the regenerating epithelium which appeared at the margin of the ulcer after 3–5 days, the labeled cells were scattered in the cystic or tortuous glandular structures, and no label was found on the surface epithelial or foveolar cells which extended over the mucosal defect (Fig. 5b). The labeling index of the proliferating cell zone in the regenerating epithelium ranged between 35 and

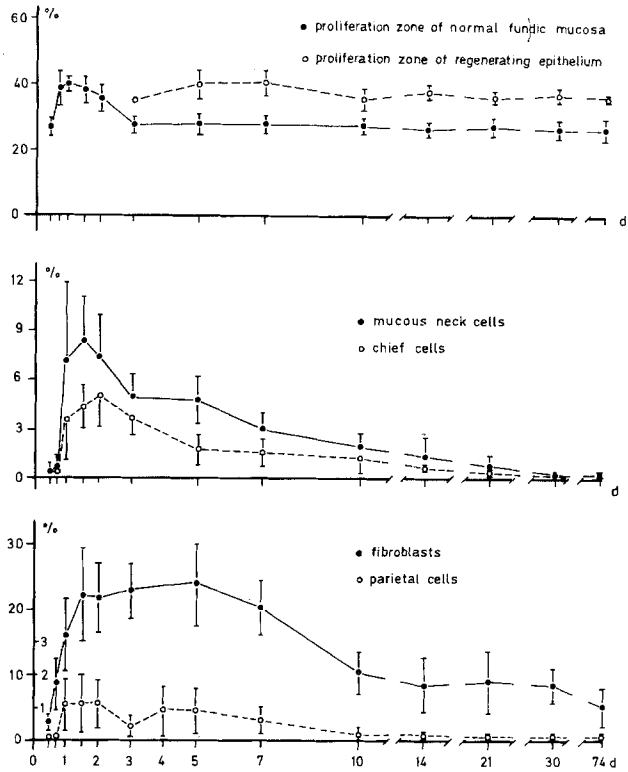


Fig. 8. The labeling indices of the proliferating cell zone of the fundic mucosa and the regenerating epithelium, and the percentages of the labeled fundic glandular cells and fibroblasts at various days after the operation

40% and it was always higher than the labeling index of the undifferentiated cells in the neck region (Fig. 8). The regenerating epithelium contained the proliferating cell zone initially (from 5 to 10 days after operation) at the base of the mucosa and later (from 2 to 3 weeks) at the middle level of the mucosa (Fig. 6a, b). The clear mucinous cells which were distributed in the deep layer of the regenerating epithelium were less often labeled with ^{3}H-thymidine (Fig. 6a, b).

The labeling index of fibroblasts in granulation tissue around the ulcer increased from 18 h and reached a maximum after 2–3 days following the operation. It showed an even higher value after 3 weeks. Following the formation of scar tissue the labeling index of the fibroblasts decreased. However, it remained high in cases in which the defect of the mucosa was not completely covered even after 3 weeks.

Discussion

Proliferative Pattern in the Normal Gastric Mucosa

In autoradiographs of control rats, labeled epithelial cells were confined to the neck region of the fundic mucosa, and a few mucous neck and chief cells but no parietal cells were labeled. These findings confirm previous reports showing

that cell proliferation in the neck area is directed towards replacement of surface epithelial and glandular cells (Messier and Leblond 1960; Lipkin 1965; Willems et al. 1972; Hattori and Fujita 1976a). The labeling index of the proliferating cell zone in the neck region was 26.4% on average. In the hamster stomach (Hattori and Fujita 1976b), the labeling index of the proliferating cell zone was reported to be 25% after a single injection of ^{3}H-thymidine and to be almost 100% after 4 repeated injections of ^{3}H-thymidine at 6 h intervals. From this, the generation time of the proliferative cells in the neck area was estimated to be about 30 h (Hattori and Fujita 1976b). By analogy with the labeling index after a single injection of ^{3}H-thymidine in the hamster, the proliferative cells in the neck region of the rat stomach appear to undergo cell division with a generation time of about 30 h under normal conditions.

Proliferative Pattern in Fundic Mucosa after the Cryolesion

Initial Phase. From 18 to 48 h after the cryolesion, cell proliferation was apparently increased in the neck region. The labeling index of the proliferating cell zone reached a maximum of 40% 36 h after the operation. This response is similar to that seen in wound healing of the skin after mechanical or thermal injuries (Helpap 1980; Yamada and Tsubouchi 1976).

Apart from the neck region, marked elevation of cell proliferation was encountered in the fundic mucosa in the vicinity of the cryolesion. The ^{3}H-thymidine incorporating cells were mucous neck, chief and parietal cells. Under normal conditions, these cells seldom divide by mitosis (Hattori and Fujita 1976a) and they are believed to be functioning mature cells. However, they can be stimulated to divide. These cells are in the G_0 phase of the cell cycle, like the hepatocytes.

Spatially, reactive cell proliferation of the glandular cells was found in a region of the fundic mucosa more than 600 μm distant from the injury. The increased cell proliferation lasted for more than 5 days after the operation, with a maximum on days 1–2, and subsided after 14 days. These modes of reactive cell proliferation of rat stomach after cryolesion are similar to those of liver, kidney, spleen and brain (Helpap et al. 1973, 1974a, b, 1976, 1979; Helpap 1980).

Reparative Phase. On the 2nd–3rd day after the operation, the remaining fundic mucosa bowed down towards the defect of the mucosa. At this time, small cystic structures appeared at the margin of the ulcer. Each cyst consisted of flat epithelial cells. In the autoradiographs, the cells forming the cysts were shown to incorporate ^{3}H-thymidine, indicating that these cells are not necrobiotic but retain their proliferative activity. As described above, many mucous neck and chief cells and a few parietal cells reacted by proliferation 18–24 h after the operation and the cystic structures were mostly located from the middle to the lower level of the mucosa. Therefore, the cells which formed the cystic structures at the margin of the ulcer on 2nd–3rd day post-operatively must be "postmitotic" cells coming from the reactively proliferating mucous neck and chief cells, since a time lag of more than 24 h would allow those cells to divide by mitosis and to transform into flattened cells. As shown in the autoradiographs, these cells continue to synthesize DNA.

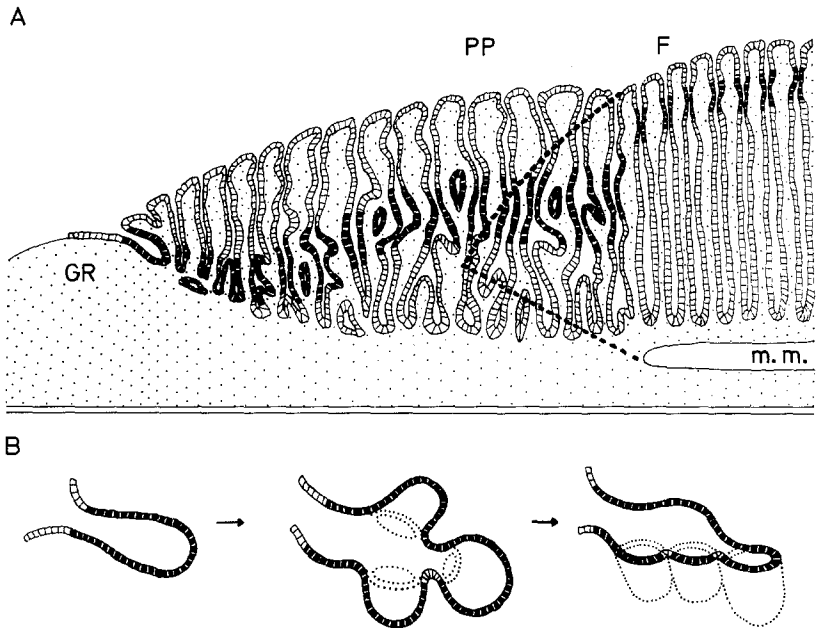


Fig. 9A, B. A schematic representation of repair of the gastric ulcer. As shown in dotted line of **A**, the remaining fundic mucosa (*F*) bowed down towards the defect in the mucosa. Cell proliferation is much activated at the margin of the ulcer, so that cystic structures composed of the proliferating cells appear. The formation of the new gland takes place by budding from this cystic glandular structure (as shown in **B**) and subsequent differentiation of the surface epithelial cells. The regenerated mucosa thus formed is at first immature; the proliferating cell zone is located at the bottom (left in **A**). In the course of time, the mucinous glandular cells arise at the bottom of the proliferating, cell zone, which allows the shift of this zone from the bottom to the middle level of the mucosa. The regenerated mucosa is similar to the normal pyloric mucosa, and is referred to as pseudopyloric mucosa (*PP*). The proliferative cells are drawn in black. *m.m.*, the muscularis mucosae. *GR*, Granulation tissue

On the 3rd–5th day after the operation, so called regenerating epithelium appeared at the margin of the ulcer. This consisted of irregular, cystic or tortuous glandular structures composed of relatively large basophilic cells, which sometimes accompanied the surface epithelial cells at the luminal end. In the autoradiographs, the proliferative cells were found widely distributed in the lower cystic or tortuous glandular structures. From observations on a series of the autoradiographs, it can be suggested that these cystic glands are formed partly as a result of the activated cell proliferation in the neck region of intact glands and partly as a result of growth of the small cysts found on the 2nd–3rd day at the margin of the ulcer. This implies that the mucous neck and chief cells at the margin of the ulcer transform into cells of the proliferative pool, and thus confirms the findings of Finchk and Milton (1960) and Townsend (1961a). The labeling index of the proliferative cell zone of the regenerating epithelium ranged between 35–40%, and was always higher than that of the normal fundic mucosa. This actively proliferating cell population must give rise to new glands in the ulcerated region.

With regard to the formation of new glands in the ulcerated region, there is general agreement that a single layer of epithelial cells which extends over

the ulcerated region invaginates to form foveolae in a sequence of events resembling an earlier stage of embryonic development (Myhre 1956; Hunt 1958; Townsend 1961b; Melnyk et al. 1967; Bloom and Fawcett 1968). However, our morphological and autoradiographic findings favor a modified conclusion, demonstrated in Fig. 9.

At the margin of the ulcer there first appeared an immature regenerating epithelium. This consisted of a large number of ^{3}H-thymidine incorporating cells and a small number of the surface epithelial cells. The ^{3}H-thymidine incorporating cells always formed the cystic structures which were surrounded by granulation tissue. The cells which covered the ulcerated region were the surface epithelial or foveolar cells. These cells were not labeled with ^{3}H-thymidine, indicating that these are the progeny of the proliferative cells which form the cystic structures at the margin of the ulcer. These cells cannot invaginate to form new glands. The formation of new glands appears to take place by budding from the cystic structure composed of the proliferating cells, and by subsequent differentiation of the surface epithelial cells (Fig. 9; Borchard et al. 1979). The situation might be analogous to the dichotomous gland division or intestinal crypt division, by which the gastric gland or the intestinal crypt increases in number in the later stage of ontogenic development (Bloom and Fawcett 1968; Hattori and Fujita 1974).

The new glands thus formed are immature. The lower half is composed of proliferative cells and the upper half is lined by foveolar and surface epithelial cells. Subsequently, differentiation of the glandular cells take place at the bottom of the newly formed glands. These glandular cells are mucin-containing cells, similar to the normal pyloric glandular cells or Brunner's gland cells. Following differentiation of the glandular cells, the proliferating cell zone of the regenerating epithelium appears to shift from the bottom to the middle level of the mucosa. The morphology of the regenerated mucosa and the localization of the proliferating cell zone in the regenerated mucosa were similar to those of the normal pyloric mucosa. Accordingly, the regenerated mucosa of the fundic area after the cryoinjury is referred to as "pseudopyloric" mucosa.

In previous studies there was controversy whether or not the parietal cells regenerate in ulcerated regions of the fundic mucosa. Myhre (1956), Hunt (1958), Williams (1961) and Lawson (1970) reported regeneration of the parietal cells, whereas Myren and Torgersen (1960) reported no regeneration. In the course of this experiment, the regenerated mucosa was always of the pseudopyloric type, and in this area no regeneration of the parietal cells was observed, In order to understand the biological significance of pseudopyloric gland formation following the injury of the fundic mucosa, it is necessary to define further morphological, histochemical and cell kinetic characteristics of the regenerated mucosa in the fundic region.

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