CCl_4 alone, either processes of cell division or an increase in volume of the nuclei predominate at different times. The action of γ-AHCS is phasic in character: alternation of periods of waxing and waning of regenerative processes.

LITERATURE CITED

1. I. N. Alekseeva, Byull. Éksp. Biol. Med., No. 7, 75 (1978).
2. A. G. Babaeva and N. I. Kuznetsova, Patol. Fiziol., No. 6, 62 (1968).
3. A. F. Blyuger and O. Ya. Kartashova, in: Advances in Hepatology [in Russian], No. 6, Riga (1977), pp. 120-132.
4. E. V. Gubler and A. A. Genkin, The Use of Nonparametric Statistical Criteria in Medical and Biological Research [in Russian], Leningrad (1973).
5. E. Kabat and M. Meyer, Experimental Immunochemistry, Thomas, Springfield, Ill. (1961).
6. D. S. Sarkisov, Essays on the Structural Basis of Homeostasis [in Russian], Moscow (1977).

CHANGES IN THE LIVER FOLLOWING PENETRATION BY A GASTRIC ULCER (EXPERIMENTAL INVESTIGATION)

L. I. Aruin, B. Z. Chikunova, and I. E. Trubitsyna

UDC 616.33-002.45-031:611.36]-07:616.36-091

Changes in the liver following penetration by a gastric ulcer were studied in 130 albino rats. Ulcers were produced by Okabe's method. During penetration the capsule of the liver is destroyed and four zones can be distinguished in the tissues of the organ: necrosis, demarcation inflammation, necrobiosis, and proliferation of hepatocytes. Together with destructive processes, in the early stages repair processes developed in the parenchyma and connective-tissue structures. Active proliferation of hepatocytes and of bile ducts leads to their penetration into the granulation tissue at the base of the ulcer. After healing of the ulcer complete restoration of the affected areas of the liver takes place but adhesions with the stomach remain.

KEY WORDS: penetration of the liver by an ulcer; regeneration of the liver; proliferation of bile ducts.

Penetration of the liver by a gastric ulcer is found in 2.1% of patients and accounts for about 6% of the complications [4, 5], but the state of the liver itself after penetration by an ulcer has not been studied.

The object of this investigation was to study the course of injury and regeneration of the liver after penetration by experimental gastric ulcers.

EXPERIMENTAL METHOD

Experiments were carried out on 130 albino rats in which chronic gastric ulcers were produced by Okabe's method; the method was described previously [1]. The animals were killed between 1 and 5 months after the procedure. Pieces of liver with adjacent stomach tissue were fixed in 10% buffered formalin and embedded in celloidin and paraffin wax. Sections were stained with hematoxylin-eosin and by Van Gieson's method and impregnated with silver by Foot's method; neutral mucopolysaccharides were detected by the PAS reaction and acid mucopolysaccharides with alcian blue and toluidine blue, RNA was detected by Brachet's method and fibrin by Shueninov's method.

Central Research Institute of Gastroenterology, Main Board for Health Care, Moscow City Executive Committee, Moscow.

(Presented by Adademician of the Academy of Medical Sciences of the USSR A. I. Strukov,) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 89, No. 3, pp. 370-372, March, 1980. Original article submitted June 12, 1979.

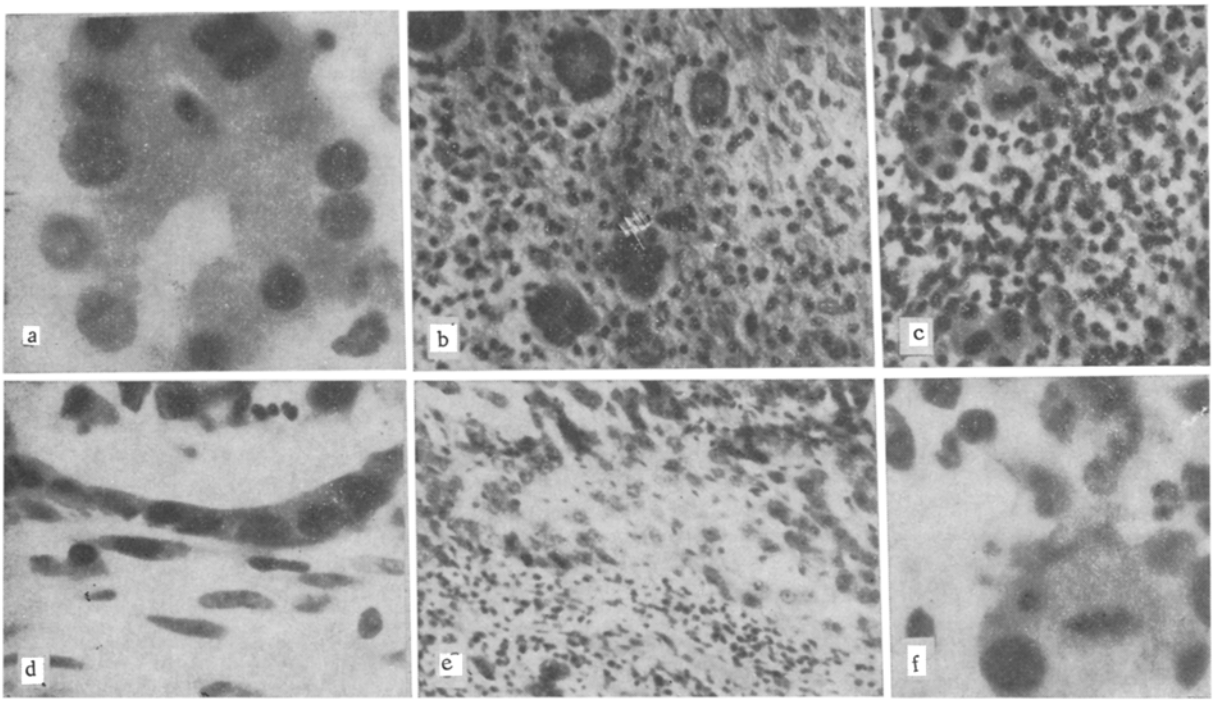

Fig. 1. Floor of ulcer penetrating into liver. a) Mitoses in proliferating bile ducts in granulation tissue; b) proliferation of bile ducts in ulcer floor; c) groups of hepatocytes in granulation tissue near liver; d) epithelium of bile duct lining part of ulcer floor; e) island of hepatocytes in granulation tissue; f) mitoses in hepatocytes in granulation tissue. Hematoxylin-eosin. Magnification: a, f) 720×; b, c, d) 280×; e) 112×.

EXPERIMENTAL RESULTS

On the first day, when necrobiotic and necrotic changes developed in the stomach wall, loose fibrin adhesions formed between the stomach and liver. The liver capsule appeared edematous and was moderately infiltrated by leukocytes. After 2 days all layers of the stomach wall were affected by necrosis, its integrity was disturbed in some areas, and an ulcer formed, with the liver as its base. Penetration led to destruction of the capsule and tissue of the liver. Four zones could be distinguished: a zone of necrosis, confluent with the necrotic masses of the base of the ulcer, and zones of demarcation inflammation, necrobiosis, and proliferation of hepatocytes. The presence of a marked demarcation barrier distinguished this picture from that described by Grigor'ev [2, 3] and others following mechanical injuries of the liver. These differences are connected both with the continued action of the harmful (peptic) factor and with infection of the affected areas from the lumen of the stomach, as shown by the constant discovery of colonies of microorganisms. After the 5th day, granulation tissue began to be formed and it replaced the necrotic regions of the parenchyma. After the 7th day, individual hepatocytes with mitotic figures and proliferating bile ducts could be seen in the granulation tissue (Fig. 1a, b). Their number increased toward the 10th and, in particular, toward the 20th day (Fig. 1c). They spread beyond the limits of the liver toward the surface of the floor of the ulcer, and examination of serial sections showed how the epithelium of the bile duct in some places lined areas of ulceration (Fig. 1d). Accordingly it is impossible to accept the view taken in the literature [2, 3] that epithelium of the bile ducts, unlike that of the gall bladder, is unable to form the lining of ulcers. Admittedly epithelization was observed only in the central parts of the ulcer and could not be enduring, for because of the absence of communication with the main layer of epithelium, the renewal essential for any epithelium could not take place, and this isolated epithelium could not regenerate after mechanical and peptic injury.

On the 30th-35th day wide adhesions between the liver capsule and the stomach and concentrations of lymphocytes and plasma cells, in the form of follicles, were found at the edge of the ulcer. Follicles and abundant cellular infiltration also were found in the depth of the liver tissue, around the portal tracts. Such changes have not been described after ther-

mal or mechanical injuries of the liver [2, 3]. It can be concluded that follicle formation is connected with the presence of a gastric ulcer penetrating into the liver and containing many colonies of microorganisms. Separate groups of hepatocytes were preserved in the granulation tissue and in the floor of the ulcer above the liver. In some places they resembled islands (Fig. 1e) with greatly dilated sinusoids. The discovery of single hepatocytes with mitotic figures (Fig. 1f), side by side with these nodules, suggests that they are formed in cicatrizing granulation tissue from proliferating liver cells "implanted" in the earlier stages. Unlike in the rest of the liver, in the nodules there were very few stellate endotheliocytes and a much higher DNA concentration. This shows that the appearance of nodules is connected with regeneration of hepatocytes and not with trapping of areas of parenchyma by the proliferating connective tissue, for endotheliocytes regenerate much more slowly than hepatocytes [6].

On the 45-55th day the boundary of the floor of the ulcer with the liver was rather more even. As before, proliferating bile ducts and isolated hepatocytes could be seen in the granulation tissue, but they were fewer in number and they lay closer to the liver surface. Large lymphatic follicles still remained, and in some cases they spread into the liver tissue along the portal tract.

After 90 days the boundary of the liver with the floor of the ulcer was still uneven and individual lymphatic follicles and proliferation of bile ducts could still be seen. Hepatocytes on the boundary with the floor of the ulcer contained much glycogen and RNA. Meanwhile islands of liver cells separated from the rest of the liver by fibrous connective tissue, abundantly infiltrated with lymphocytes and plasma cells, could be seen.

After 5 months, the liver capsule was partially restored in the animals with healing ulcers. Its surface in the region of previous penetration was only slightly undulating. The adjacent hepatocytes were larger than those located in deeper regions. No lymphoid follicles could be seen.

Penetration of a gastric ulcer thus leads to the development of a series of destructive, immunomorphological, and reparative changes which differ appreciably from the response of the liver to mechanical and thermal injury described in the literature. The difference is due to prolonged action of proteolytic enzymes and the microbial flora of the gastric juice on the liver. This model showed that epithelization of ulcers by the epithelium of bile ducts can take place. All changes in the liver were reversible, and after healing of the ulcer the structure of the tissue in the region of penetration was fully restored.

LITERATURE CITED

1. L. I. Aruin, B. Z. Chikunova, and I. E. Trubitsyna, in: Current Problems in Gastroenterology [in Russian], No. 9, Vol. 2, Moscow (1976), pp. 97-109.
2. N. I. Grigor'ev, "Reactivity of epithelium of the small intestine, gall bladder, and liver of vertebrates and man," Doctoral Dissertation, Leningrad (1955).
3. N. I. Grigor'ev, Structure and Regeneration of the Liver after Local Injury [in Russian], Leningrad (1975).
4. V. A. Samsonov, Complications of Gastric and Duodenal Ulcer [in Russian], Petrozavodsk (1959).
5. V. A. Samsonov, Peptic Ulcer. New Data on the Pathomorphology of Its Complicated Form [in Russian], Petrozavodsk (1975).
6. G. Fabris et al., Riv. Pat. Clin. Sper., 17, 85 (1977).