Role of Mast Cells in Reparative Processes in Inflammation

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Using the model of acute infectious peritonitis in rats, it is shown that inflammation induced in the absence of mast cells is characterized by marked inhibition of reparative processes. The most significant accumulation of functionally active fibroblasts and the development of granulations and young connective tissue in the mesentery occur 5-10 days after flogogen injection in the natural development of inflammation and after 10-20 days in the absence of mast cells. The data suggest that under natural conditions mast cells directly or indirectly stimulate reparative processes.

Key Words: *inflammation; mast cells; repair*

At present, mast cells (MC) are considered to be the source of the main transmitters of initial vascular and exudative processes, in particular the immediate phase of the increase of vascular permeability [8,9] underlying exudation. Recently, a modulatory effect of MC on infiltration processes during inflammation has been shown and mechanisms of this effect dependent on the main products of MC, histamine, serotonin, and heparin, have been studied [6,7].

The aim of the present study was to investigate the role of MC in reparative processes during inflammation.

MATERIALS AND METHODS

The experiments were performed on 396 male Wistar rats weighing 180-200 g. Acute infectious peritonitis was induced by intraperitoneal injection of 2×10^9 cells (0.5 LD_{50}) of a one-day-old *E. coli* culture, isolated from a patient with peritonitis, in 1 ml isotonic NaCl [5,7,8]. The animals were decapitated at different times of inflammation. The relative number of neutrophils, monocyte-macrophages, and mature and immature fibroblasts was calculated in mesenteric film preparations stained with hematoxylin and eosin and after Van Gieson [11]. The index of labeled nuclei of macrophages and immature and mature fibroblasts was also cal-

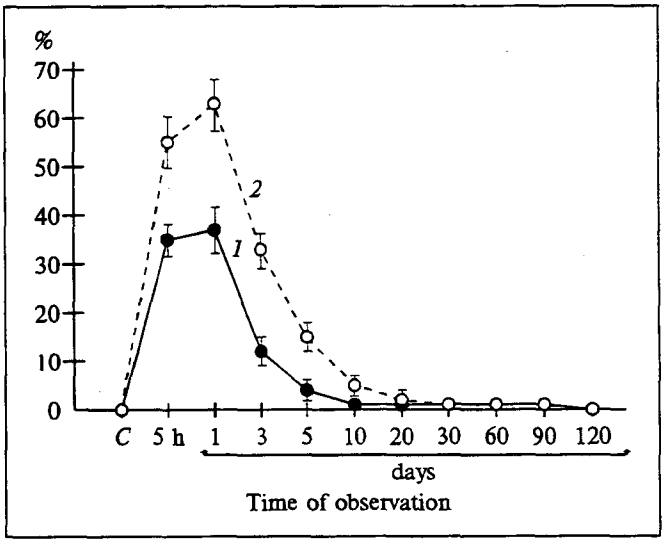

Fig. 1. Content of neutrophils in rat mesentery during the course of acute infectious peritonitis under natural conditions (*1*) and in the absence of MC (*2*). Here and on Figs. 2–4: *C* indicates control.

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culated [3,4]. The labels were methyl-$^3H_1$-thymidine and 5-^{3}H-uridine, and additionally D- and L-1-^{14}C-proline for fibroblasts. The isotopes were injected intramuscularly (37 MBq/kg body weight in 0.5 ml isotonic NaCl solution) in the hind paw 1, 2, and 3 hours before decapitation [3,4]. MC were removed from the peritoneal cavity by injecting 10 ml/100 g body weight distilled water 10 days before peritonitis was induced [5,8,9].

RESULTS

In the absence of MC inflammation was characterized by a markedly enhanced accumulation of neutrophils (Fig. 1). The content of neutrophils surpassed that under natural conditions during the entire neutrophil reaction (10 days), especially after 5 hours and 1 day (1.6- and 1.7-fold, respectively). At the same time, the accumulation of monocyte-macrophages was substantially decreased (Fig. 2). Their content was lower than that observed under natural conditions after 1 and 3 days of inflammation (2.5 and 1.9 times, respectively). The synthetic activity of macrophages determined using ^{3}H-thymidine and ^{3}H-uridine was also decreased after 1, 3, and 5 days, and its peak was less expressed and shifted from the 3rd-10th day under natural conditions to the 20th day.

The number of immature fibroblasts after 5 days of inflammation was also decreased (2-fold) and attained the maximum on day 10 *vs.* day 5 for the usual course of inflammation (Fig. 3). Their synthetic and secretory activity (evaluated by the incorporation of ^{3}H-thymidine, ^{3}H-uridine, and ^{14}C-proline) lagged behind that during the typical course of peritonitis, being lower after 1, 3, and 5 days and attaining the peak on day 10 *vs.* day 5 during the normal course of peritonitis.

The number of mature fibroblasts was also restored later: on day 20 instead of day 10 during the typical course of peritonitis (Fig. 4). Thus, the content of these cells on day 10 was 2.1-fold lower than is usually observed in inflamed mesentery. Judging from the inclusion of all three isotopes, the functional activity of mature fibroblasts attained its maximum on the 20th *vs.* the 10th day under natural conditions of inflammation, being lower after 3, 5, and 10 days.

These data are in conformity with the observation that in the natural course of inflammation granulation tissue is maximally developed on day 5 and then on day 10 completely replaced with young connective tissue, while in peritonitis in the absence of MC these phenomena were observed on days 10 and 20, respectively.

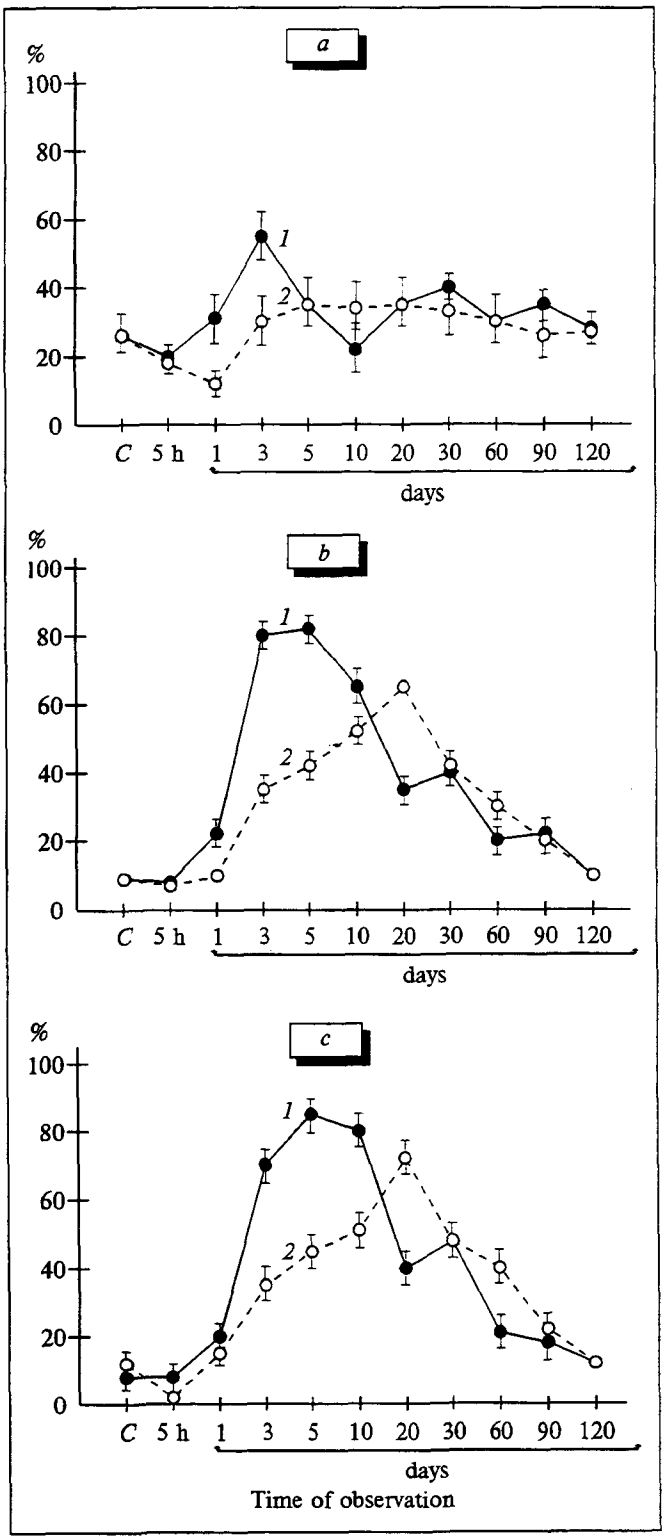

Fig. 2. Content (*a*) and index of ^{3}H–thymidine– (*b*) and ^{3}H–uridine– (*c*) labeled nuclei of macrophages in rat mesentery in the course of infectious peritonitis under natural conditions (*1*) and in the absence of MC (*2*).

Thus, inflammation in the absence of MC is characterized by a noticeable slowing of the repair phenomena. This suggests that MC markedly

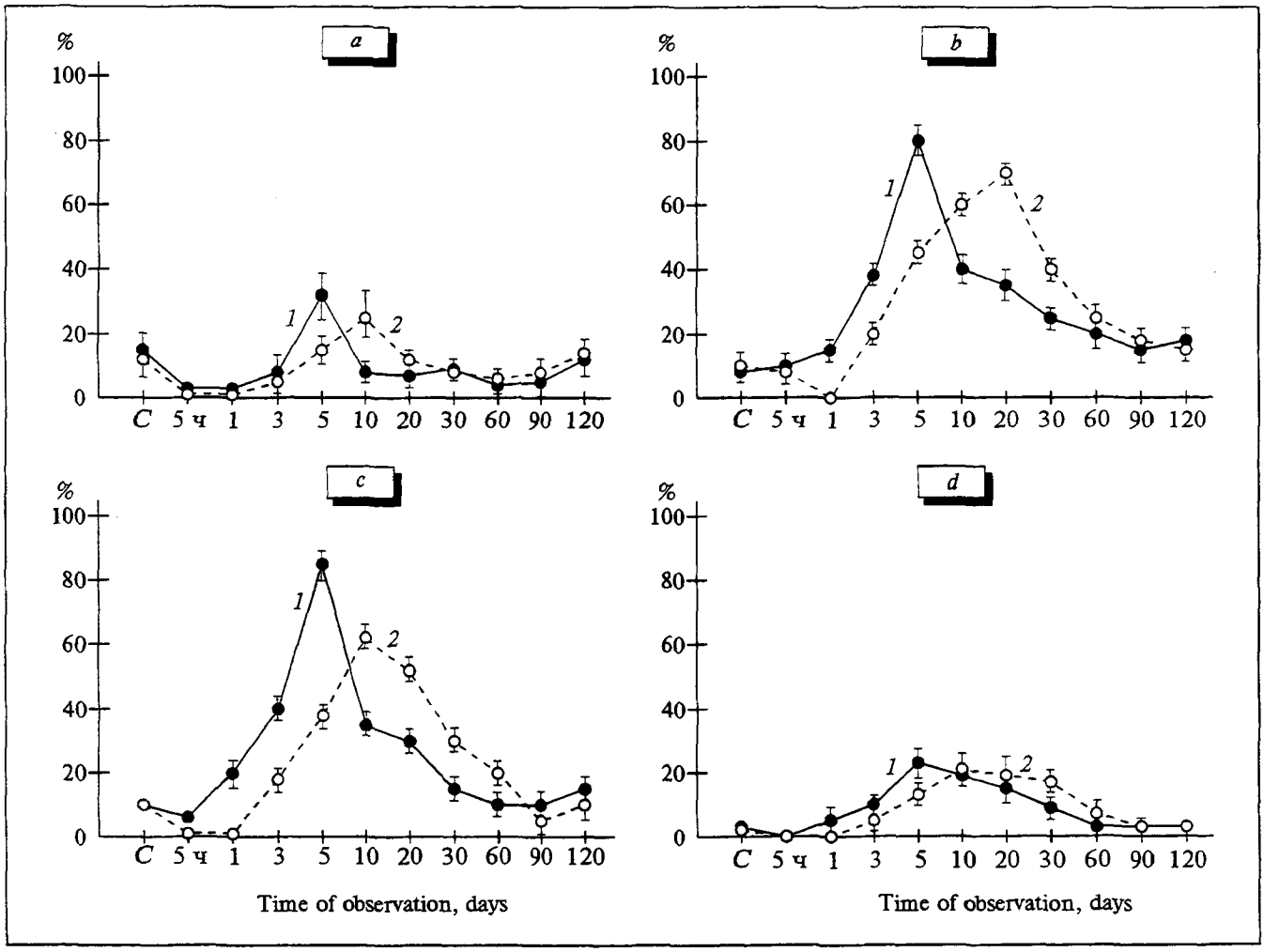

Fig. 3. Content (*a*) and index of ^{3}H–thymidine– (*b*), ^{3}H–uridine– (*c*), and ^{14}C–proline– (*d*) labeled nuclei of macrophages in rat mesentery in the course of infectious peritonitis under natural conditions (*1*) and in the absence of MC (*2*).

stimulate repair under natural conditions of inflammation. As follows from previous data [6,7] and the present study, the mechanism of the modulatory effect of MC on the reparative process may be related to inhibition of neutrophils and thereby to control of alternative phenomena and activation of monocyte-macrophages, which are primarily responsible for clearing the wound of the inflammatory focus, and for the attraction and activation of fibroblasts. Apart from the neutrophil- and monocyte-mediated effect of MC, the direct activation of fibroblasts by MC products is also important. For example, *in vitro* experiments have demonstrated the ability of histamine to stimulate collagen formation by fibroblasts mediated through H_2 receptors. This implies a substantial role of histamine in healing and even in the pathogenesis of postinflammation fibrosis [12,13]. As follows from the *in vitro* incorporation of ^{3}H-thymidine, serotonin directly activates the proliferation of fibroblasts [2]. Heparin presumably also directly stimulates the synthesis of structural glycoproteins and the formation of collagen and elastic fibers [1,10]. The modulating effect of MC on repair may also be related to other biologically active MC-produced substances and, apart from leukocyte factors, to non-MC-derived transmitters, in the production and activation of which MC act as one of the first steps in the cascade of the entire transmitter system.

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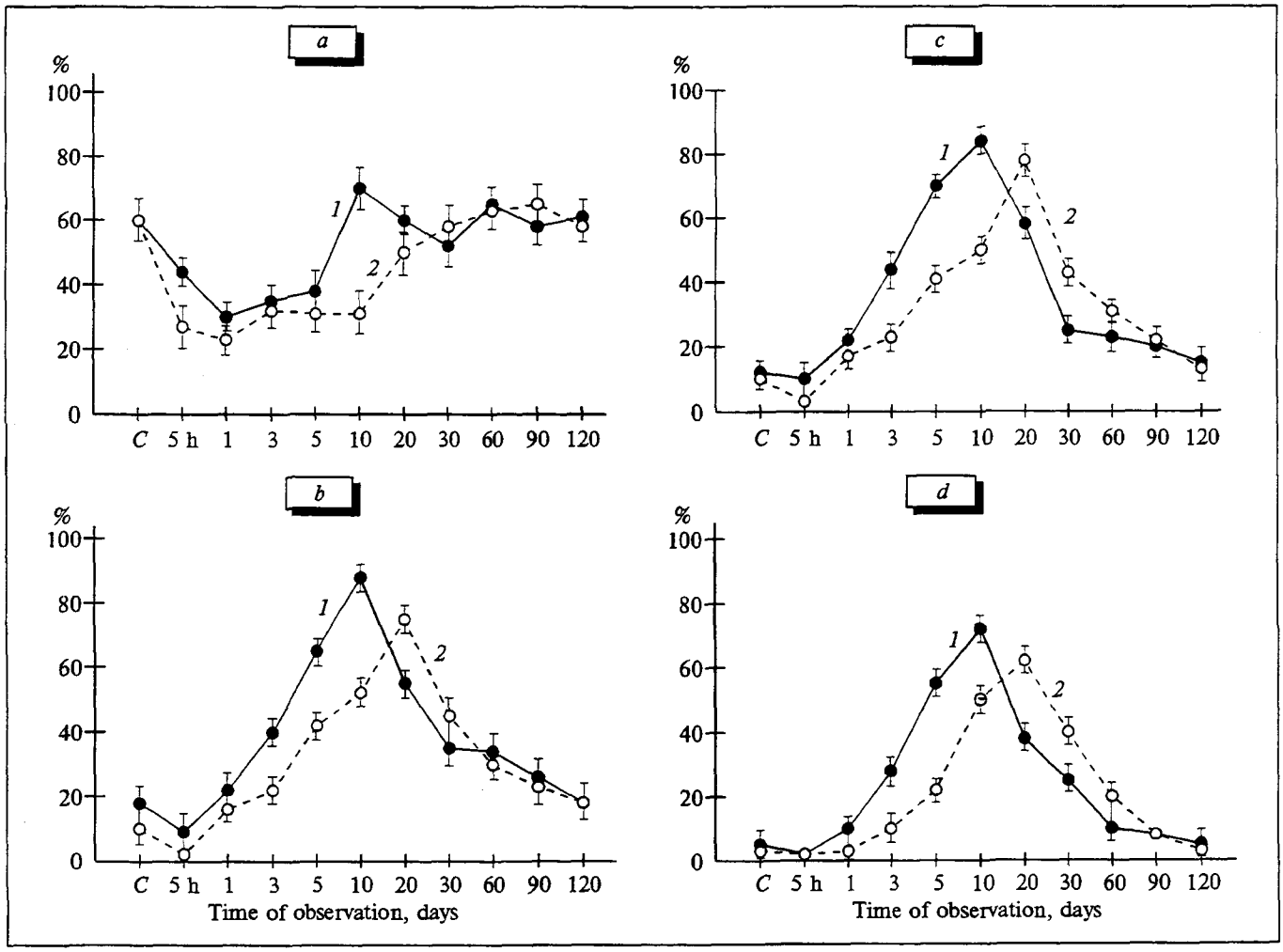

Fig. 4. Content (*a*) and index of ^{3}H–thymidine– (*b*), ^{3}H–uridine– (*c*), and ^{14}C–proline– (*d*) labeled nuclei of mature fibroblasts in rat mesentery in the course of infectious peritonitis under natural conditions (*1*) and in the absence of MC (*2*).

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