Chapter 8
Histamine-induced leukocytosis

1. Introduction
From the early years of the introduction of H₂ antagonists for clinical uses, many reports have been published that H₂ antagonists induce various kinds of cytopenia, such as neutropenia, agranulocytosis, thrombocytopenia, pancytopenia and lymphopenia. At the present time, it has become evident that histamine exerts a stimulative effect on the differentiation and proliferation of bone marrow stem cells, especially in neutrophil progenitors, via an H₂ receptor stimulation (Tasaka, 1991). However, as early as 8 years before the discovery of the H₂ receptor and histamine H₂ antagonist by Black et al. (1972), Tasaka and Code (1964) reported that chronic injection of histamine induces leukocytosis in various kinds of experimental animals. This was the first report which clearly pointed out the hematopoietic action of histamine in vivo. A growing body of evidence indicates that histamine is not only a physiological hematopoietic substance but also that it interacts with other hematopoietic cytokines, such as granulocytic colony stimulating factor (G-CSF) and interleukin-1α (IL-1), at physiological concentration range. The stimulative effect of histamine on several leukemia cells has also been reported (Nonaka et al., 1992). In this chapter, the mechanism of histamine-induced leukocytosis is reviewed.

2. Histamine-induced leukocytosis in experimental animals
It has been reported that after an intramuscular injection of histamine (1-6 mg/kg) in a beeswax-sesame oil mixture, to dogs, rabbits and guinea pigs, the number of leukocytes increased gradually, reached a peak in 6-8 hours, and then declined gradually, usually reaching the control levels within 24 hours after the injection (Tasaka and Code, 1964; Tasaka et al., 1992a) (Fig. 1). In this experiment, histamine was slowly released from the admixture with beeswax, maintaining a blood histamine concentration within 10-110 nM (3 mg/kg i.m. in dog) for prolonged periods. The mixture composed of beeswax and sesame oil alone did not affect leukocyte counts at all. When the plasma histamine concentration and leukocyte counts were measured simultaneously, it became apparent that a close relationship exists between peripheral leukocyte counts and blood histamine concentrations (Fig. 2).

In differential leukocyte counts, an increase in the number of neutrophils accounted for most of the leukocytosis in all species tested (Fig. 3). Erythrocyte counts and
Fig. 1. Sequential changes in the number of total leukocytes and plasma histamine concentration after single administration of histamine in beeswax (3 mg/kg, i.m.) in dogs (n = 5). On day 0, histamine-beeswax mixture was injected. Significant differences from the preinjection level at *p < 0.05 and **p < 0.01, respectively. Reproduced from Tasaka, K., Nakaya, N. and Code, C.F.: Meth. Find. Exp. Clin. Pharmacol., 14, 667-675 (1992a), with permission.

Fig. 2. Correlation between peripheral leukocyte counts and plasma histamine concentration after injection of histamine in beeswax (3 mg/kg, i.m.) in dogs (n = 5). Reproduced from Tasaka, K., Nakaya, N. and Code, C.F.: Meth. Find. Exp. Clin. Pharmacol., 14, 667-675 (1992a), with permission.

hematocrit values were not affected by histamine in any species. The absolute number of lymphocytes decreased somewhat; however, changes in the number of monocytes after histamine injection were small or nil. These findings are similar to the hematological