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Takagi K & Okabe S. The effects of drugs on the production and recovery processes of the stress ulcer. *Jpn. J. Pharmacol.* 18:9-18, 1968.

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This report is a description of a simple and reproducible method for producing stress ulcers in the rat stomach using a newly devised restraint cage. This method facilitates examination of the pathogenesis of stress ulcers and also the screening of antistress ulcer agents. [The SCI® indicates that this paper has been cited in more than 215 publications, making it the most-cited paper from this journal.]

A Simple Method for Producing Stress Ulcers in the Rat

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In a continuation of research on chemico-pharmacological properties of anticholinergic agents, we examined the antiulcer effects of drugs on Shay ulcers in rats. The agents tested significantly protected the gastric mucosa against the ulcers, and the effect was potentiated by antacids. As a researcher in pharmaceutical sciences, I wanted to research various antiulcer drugs and their combinations on gastric ulcers produced experimentally in rats. Central nervous system (CNS) depressants were without effect in animals with Shay ulcers. Therefore, I asked K. Watanabe (a graduate student) to design a method to produce stress ulcers in rats, one that would allow for detection of the antiulcer effects of various agents, including CNS depressants. He first used the restraint ulcer model,¹ and the incidence of ulceration was 66 percent. To increase the incidence, he fixed the animals on a board (about 30 x 40 cm) and ingeniously immersed them overnight in a water

bath (23-25° C) up to the xiphoid process. Accordingly, severe mucosal ulcers developed in the glandular stomachs at an incidence of 100 percent.² However, the method consisted of binding the rats' limbs strictly to the board with string, resulting in severe damage to the limbs. In addition, the use of such a board required too much space. Therefore, this restraint method was inappropriate to study the healing process of ulcers and to screen many compounds.

To circumvent this problem, S. Okabe (a graduate student) devised a sophisticated cage (10 x 20 x 20 cm) that had 10 compartments (one rat per compartment) separated by a diaphragm. This diaphragm alone would not hold each animal in the proper position. Since the animals readily changed posture in the compartment, their heads could be drawn down into the water. Therefore, it was necessary to put pressure on the animal with a spring-like material to prevent bending, without disturbing respiration. To obtain such a material, Okabe frequented hardware dealers at Akinhabra (an area specializing in electric and electronic equipment in Tokyo). However, he could not find the appropriate material. After a year's search, he found by chance that a flexible board, fixed to the upper end of the diaphragm with a stainless steel hinge, could serve as a spring. When the board was pressed toward the diaphragm, the head of each rat used to fix the hinge to the board and diaphragm became the lever. Using these cages, more than 50 rats could be stressed simultaneously in a water bath (40 x 70 x 50 cm), without damaging their limbs. The ulcers produced after 20 hours of stressing healed spontaneously within four weeks. We used this ulcer model for studies on the pathogenesis of stress ulceration and for screening antiulcer agents.³⁻⁵

The restraint cage is commercially available. This method of mass producing gastric stress ulcer has gained wide favor because it is simple and reproducible; and the animals recover rapidly.

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