

## This Week's Citation Classic®

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**Brodie D A & Hanson H M.** A study of the factors involved in the production of gastric ulcers by the restraint technique. *Gastroenterology* 38:353-60, 1960.  
[Merck Institute for Therapeutic Research, West Point, PA]

Factors important in the production of restraint ulcers in rats were duration of restraint, food deprivation, and age. Young, food-deprived rats restrained 24 hours had the highest incidence of gastric ulcers. This technique provides a simple, rapid, nonsurgical means of producing ulcers in the acid-secreting portion of the stomach. [The SCI® indicates that this paper has been cited in over 320 publications.]

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During the late 1950s, "The Golden Age of Drug Discovery," Harley Hanson and I, as very junior scientists, were doing research at the Merck Institute under the direction of Karl Beyer. In mid-1958, Harley came into my laboratory clutching a French article describing a new way to produce experimental ulcers.<sup>1</sup> Harley was, and is, a Skinnerian psychologist. I was a CNS pharmacologist, but since I knew where the stomach was, he asked me if we could collaborate in testing this "stress" method. We followed the somewhat cumbersome French protocol, and, to our delight, the next day all the rats had clear-cut ulcers in the fundi of their stomachs.

The next step was to simplify the method. We hit upon the idea of wrapping the rats in wire screen and stapling the screen together. The animals appeared to tolerate this well, and soon Harley and I were sitting across the table from each other stapling rats into wire one day and evaluating ulcers the next.

We saw great potential in the restraint technique for use in the study of CNS/GI

interaction and evaluating new antiulcer therapy. The standard test animal in ulcer research at the time was the pylorus-ligated (Shay) rat, a model that required surgery and a 24-hour period for ulcer development and that had the liability of producing the lesion in the non-acid-secreting portion of the rat stomach. The restraint procedure was a simple, rapid, nonsurgical method of producing a high incidence of ulcers in the acid-secreting area of the stomach. These advantages were probably the reasons that the test was used widely and the paper cited so frequently. Later, I modified the stressors to produce a 60-minute drug-sensitive ulcer test and even went "high-tech," switching from wire window screen to perforated metal tubes with a cork in each end to restrain the rats. A detailed review of restraint-induced ulcers has been made by Paré and Glavin.<sup>2</sup>

Several important events in my life resulted from this research. To begin with, I have a friendship with Harley that has lasted almost three decades. Secondly, I met and became friends with Serge Bonfils, one of the authors of the French paper and later director of GI Unit 10 at Bichat Hospital, Paris. And finally, this work started my career in experimental gastroenterology, which, through the good offices of Morton Grossman, led to my election to the American Gastroenterological Association.

Perhaps the most interesting incident produced by this paper happened a few years ago at a physiology meeting. The last paper in one of the afternoon sessions was a presentation on stress ulcers given by a young scientist. During the presentation, he was kind enough to refer to our method by name. After the talk, I congratulated him and thanked him for citing my paper. His eyes opened wide: he stepped back and queried, "You're Dr. Brodie?" "That's right," I assured him. "Oh," he said, "that paper is so old; I thought you must be dead by now." It was then I knew I belonged to the ages....

1. Rossi G, Bonfils S, Liefoght F & Lambling A. Technique nouvelle pour produire des ulcérations gastriques chez le rat blanc: l'ulcère de contrainte. *C. R. Soc. Biol.* 150:2124-6, 1956. (Cited 140 times.)

2. Paré W P & Glavin G B. Restraint stress in biomedical research: a review. *Neurosci. Biobehav. Rev.* 10:339-70, 1986.