

Geller I & Seifter J. The effects of meprobamate, barbiturates, d-amphetamine and promazine on experimentally induced conflict in the rat. *Psychopharmacologia* 1:482-92, 1960.

[Wyeth Institute for Medical Research, Philadelphia, PA]

The report describes a method for inducing and quantifying automated conflict behavior in laboratory rats and demonstrates its sensitivity to the effects of drugs. This technique reveals profound effects of meprobamate, a clinically useful drug that has not been reported to have important effects in other psychopharmacological tests. [The *SCI*® and *SSCI*® indicate that this paper has been cited in over 460 publications.]

An Experimental Model for the Study of Anxiolytic Drugs

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The experimentally induced conflict paradigm evolved from my attempts to apply operant behavioral techniques for the evaluation of clinically active drugs.

In 1957 I was hired by Wyeth Laboratories to establish a Department of Psychopharmacology. The late Dr. Joseph Seifter was the director of research at Wyeth at that time. This assignment required me to focus upon effects of psychopharmacological agents upon behavior, rather than the broader issues related to the experimental analysis of behavior. In my predoctoral training with Joe Brady, where I received invaluable experience in the behavior lab, I had conducted research on the effects of electroconvulsive shock on a conditioned emotional response (CER). At Wyeth I attempted similar CER studies with psychoactive

drugs. However, to my dismay, the administration of meprobamate or barbiturates to rats trained on a CER procedure produced minimal drug effects.

In my search for a procedure that would be more sensitive to drug effects, I became aware of reports in the literature describing approach-withdrawal responses as a screening test for tranquilizers.¹ Using this concept, I developed a procedure that established a conditioned suppression based on punishment, a situation that I regarded as being conflict-producing for the rat. Basically, the procedure required that a hungry rat balance the positive features of obtaining food rewards against the negative aspects of accepting punishment in order to obtain the food. These conflict experiments resulted in a behavioral baseline that proved to be sensitive and quite specific for anxiolytic drugs.

The development of the conflict technique and its subsequent application for preclinical evaluation of anxiolytics provides an example of a basic research endeavor that yielded a method for screening of psychoactive drugs. Our group at Wyeth used the conflict paradigm for many years; we determined the activity of oxazepam² and eventually provided the pharmaceutical industry with a validated drug screening procedure still used extensively today. I am pleased to acknowledge the contributions of Seifter, who provided me with invaluable pharmacological guidance, and of Larry Stein, whose critical input helped to make the development of the conflict technique a reality.

The conflict procedure and variations of it are still being used to determine anxiolytic activity of new drugs and to study possible mechanisms of action as well.³⁻⁵

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3. Branch M N. Behavioral pharmacology. (Iverson I H & Lattal K A, eds.) *Techniques in the behavioral and neural sciences: experimental analysis of behavior.* Amsterdam, The Netherlands: Elsevier. (In press.)
4. Gleeson S, Ahlers S T, Mansbach R S, Foust J M & Barrett J. Behavioral studies of anxiolytic drugs. VI. Effects on punished responding of drugs interacting with serotonin receptor subtypes. *J. Pharmacol. Exp. Ther.* 250:809-17, 1989.
5. Pollard G & Howard J. Effects of drugs on punished behavior: preclinical tests for anxiolytics. *Pharmacol. Ther.* (In press.)