

# This Week's Citation Classic

Randall L O, Heise G A, Schallek W, Bagdon R E, Banziger R, Boris A, Moe R A & Abrams W B. Pharmacological and clinical studies on Valium™ a new psychotherapeutic agent of the benzodiazepine class. *Curr. Ther. Res.* 3:405-25, 1961.  
[Depts. Pharmacology and Clinical Pharmacology, Hoffmann-La Roche, Inc., Nutley, NJ]

This monograph first described the pharmacological properties of Valium. It was qualitatively similar to Librium but more potent in many pharmacological tests for taming, muscle relaxant, anticonvulsant, and sedative effects. It was well tolerated in rats, dogs, monkeys, and man. [The SC® indicates that this paper has been cited over 260 times since 1961.]

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"This monograph summarized for the first time the pharmacological properties of Valium (diazepam) in comparison with Librium and tolerance testing in man. It reported the contributions of various members of the pharmacology and clinical pharmacology departments of Hoffmann-La Roche, Inc.

"The story of the chemical development of Librium and Valium was told by Sternbach.<sup>1</sup> The serendipity involved in the invention of this class of compounds was matched by the trials and errors of the pharmacologists in the discovery of the tranquilizing activity of the benzodiazepines. The discovery of Librium in 1957 was due largely to the dedicated work and observational ability of a gifted technician, Beryl Kappel. For some seven years she had been screening compounds by simple animal tests for muscle relaxant activity using myanesin as a standard and then meprobamate and chlorpromazine when they became available. All compounds submitted by the chemical staff for central nervous activity were screened. It was this battery of tests that picked out RO 5-0690 (Librium, chlordiazepoxide) as being similar but more potent than meprobamate. Within three months of receipt of the compound, we reported to management the muscle relaxant activity in mice and cats, blocking of spinal reflexes in cats, appetite stimulation

and antiinflammatory activity in rats, and only slight effects on blood pressure and autonomic responses in dogs and cats. By late fall sufficient pharmacological and toxicity data had been accumulated to recommend tolerance testing in man. This was authorized at a meeting of management in the Pocono mountains. It was perhaps coincidental that we rushed out of dinner one night to watch Sputnik cross the clear sky.

"In 1967, ten years after the discovery of Librium, a review by Zbinden and me<sup>2</sup> summarized the status of the benzodiazepines. Over 2,300 papers had been published on the clinical activity of these compounds. The laboratory and clinical work on 22 benzodiazepines that had been subjected to tolerance testing in man was summarized. It was reported that the best correlation of animal testing methods with clinical activity was observed with the early antimetrazol test in mice and the muscle relaxant test in cats. Ten animal screening tests reliably separated the highly active group from the intermediate and the low potency compounds. The excellent tolerance in man confirmed the high safety margins observed in animals between the effective pharmacological doses and the toxic dose. The selection of 22 new benzodiazepines from a long list of synthetic analogs, their tolerance testing in animals and man was done in those ten exciting years of drug development before the heavy hand of government bureaucracy throttled such work.

"This paper has been cited because (1) it was the first publication summarizing the pharmacological properties of Valium in comparison with Librium, (2) these compounds became the standard of reference for all work done in the Roche Laboratories and in other pharmaceutical companies on this class of compounds, (3) neuroscientists became interested in the mechanism of action of compounds having such a broad range of pharmacological and clinical activity, (4) samples of compounds were made freely available to all scientists who requested them for experimental work."

1. Sternbach L L. Pioneering in medical chemistry. *Chemist* 14:5-8, 1979.
2. Zbinden G & Randall L O. Pharmacology of benzodiazepines: laboratory and clinical correlations. *Advan. Pharmacol.* 5:213-91, 1967.