

# This Week's Citation Classic

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van Rossum J M. Cumulative dose-response curves. II. Technique for the making of dose-response curves in isolated organs and the evaluation of drug parameters.

*Arch. Int. Pharmacodyn.* 143:299-330, 1963.

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The importance of the study of dose-response curves for the analysis of the mechanism of action is stressed. A detailed description is given of the technique of making cumulative dose-response curves in various isolated organs. A brief review of the molecular theory of drug action is presented. Methods are derived to calculate relevant drug parameters. [The SC<sup>R</sup> indicates that this paper has been cited in over 700 publications since 1963. Based on an analysis of SCI data 1961-80, this paper is the most cited published in the journal.]

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"The study of dose-response curves of drugs in isolated organs has been the main topic of research during the first decades of the newly established department of pharmacology at the Catholic University of Nijmegen Medical School. Shortly after Ariëns was appointed chairman of the department, I moved with him in 1954 from the Rudolf Magnus Institute in Utrecht to Nijmegen.

"Nijmegen University, where the medical school had to find its course among the existing faculties of the humanities, was not used to the budgets necessary to do research in medical science, so the funds were meager. Dose-response curves and especially cumulative dose-response curves were made with relatively primitive means but nevertheless provided a wealth of information on the mechanism of action of drugs, receptor pharmacology, classification of drugs, and the relationships between chemical structure and pharmacological activity. Based on the tradition of quantitative pharmacology inherited from the Rudolf Magnus Institute it still took a good deal of pioneering and combined effort of an excellent team to reach our goals.

"The results, starting with the first series of papers by Ariëns and de Groot,<sup>1</sup> followed by studies by Ariëns, myself, and Simonis,<sup>2</sup> and by myself and Ariëns,<sup>3</sup> finally culminated in the monograph *Molecular Pharmacology*, edited by Ariëns in 1964.<sup>4</sup>

"Although we are not sure who first used the cumulative dose-response technique, it certainly was demonstrated in the paper by Ariëns and de Groot,<sup>1</sup> using the rectus abdominis muscle of the frog. The method, being practical and economical, was soon applied to other isolated organs in a number of PhD theses.

"From lectures presented at various departments and discussions with many colleagues, it became evident that there was a need for a paper covering the theory of drug receptor interaction combined with a detailed instruction on the technique of cumulative dose-response curves, of which we had years of experience. Frans van den Brink and I wrote an introduction,<sup>5</sup> while Coby Hurkmans used her expertise by carefully carrying out the many experiments used in the classical paper.

"I was surprised that this paper became a Citation Classic, although this type of research contributed to the S.E. de Jongh award, which I received in 1966. Probably the combination of presenting a theoretical basis underlying drug-receptor interaction and a clear experimental design greatly added to the impact of this paper. The continued interest in drug-receptor studies probably stimulates graduate students to use this paper as a starting point for their research.

"Receptor research should not merely rely on binding experiments, but should be in harmony with studies in intact tissues responding to drug receptor interaction. Pharmacology dealing with extremely complex systems such as the human body needs to study well-defined subsystems such as isolated tissues, but finally aims at understanding the interaction of drugs with the total system. It is this dynamic systems approach that is the topic of our current research. Recent work in the field has been published."<sup>6-8</sup>

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4. Ariëns E J, ed. *Molecular pharmacology: the mode of action of biologically active compounds*. New York: Academic Press, 1964. Vol. 1. 503 p.
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