

# This Week's Citation Classic®

Porsolt R D, Le Pichon M & Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. *Nature* 266:730-2. 1977. [Department of Neuropharmacology, LERS Synthelabo, Bagneux, France]

The original paper and two related papers<sup>2</sup> described a simple new behavioral model for testing antidepressant drugs. Rats or mice, forced to swim in a cylinder from which there is no exit, rapidly become immobile. Immobility is reduced by most known clinically effective antidepressants and thereby constitutes a useful screening test. [The SCI® indicates that this paper has been cited in more than 250 publications.]

## Behavioral Despair Revisited

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I moved to Synthelabo (Paris) at the beginning of 1975 to work as behavioral pharmacologist in Maurice Jalfre's neuropharmacology department. Maurice wanted me to set up as many new behavioral models as possible (learning, memory, depression, anxiety). He bombarded me with articles including a series by Marty Seligman describing "helpless behavior" in dogs exposed to inescapable shock. I did not feel very enthusiastic, as I love dogs (I have three) and did not see how a useful pharmacological test could be developed on the basis of this work. It so happened, however, that I was doing some learning experiments in a water maze at the same time with one of my technicians, Claudine Leonardon. I noticed that some rats, after exploring a bit, simply stopped swimming and remained motionless, making only those movements necessary to keep their heads above water. No doubt thinking of Seligman's experiments, it occurred to me that these rats may have "thought" that there was no exit, that they had given up "hope" and had resigned themselves to the apparently inescapable aversive situation ("despair"), I then asked another of my technicians, Michele Le Pichon, to see whether it was possible to induce the characteristic immobile behavior in a swim situation where there was really no escape. We provoked the mirth of

several of our colleagues by conducting these experiments in various kinds of containers, including a baby's bath in bright blue plastic! We invited further skepticism when we started testing drugs such as imipramine. But to the surprise of everyone including ourselves, these drugs clearly decreased the duration of immobility at doses which were otherwise markedly sedative. At Maurice's suggestion, we then tried some atypical compounds (mianserin, iprindole) and electroconvulsive shock, which were considered as false negatives in then available antidepressant tests (e.g., reserpine antagonism).

The positive findings encouraged us to prepare the first article. With this simple and purely behavioral procedure, we thought we now had the means to screen antidepressants with mechanisms of action different from those of currently available drugs. The paper was refused by *Science* ("not sufficiently interesting") but was accepted by *Nature*. We rapidly followed with two other papers, researched after Maurice and I had moved to Delalande, which presented a mouse version<sup>3</sup> and elaborated on the rat method.<sup>2</sup> Since then, the forced swim has become a standard antidepressant test in pharmaceutical laboratories worldwide. It is also used by academic laboratories as a simple animal model for investigating the neurobiology of depression and of antidepressant drug action. The reasons for its acceptance are probably its procedural simplicity and its high reproducibility. It also responded to a need for new methodology at a time when available methods were being criticized for missing potential new drugs (false negatives) and discovering only "me-too's." Although there has been considerable debate about its relevance to depression,<sup>3</sup> a recent paper<sup>4</sup> estimated that the method was sensitive to 87 percent and 94 percent of clinically known antidepressants in the rat and the mouse, respectively. It thus represents a useful drug screening tool.

Leonardon and Le Pichon still work for Synthelabo, Jalfre is professor of pharmacology in Marseille, and I direct a psychopharmacology contract research organization where, among other services, we offer the "behavioral despair" test and its dry version, the "tail suspension test"<sup>5</sup> on a commercial basis.

1. Porsolt R D, Bertin A & Jalfre M. Behavioural despair in mice: a primary screening test for antidepressants. *Arch. Int. Pharmacodyn. Ther.* 229:327-36. 1977. (Cited 245 times.)
2. Porsolt R D, Anton G, Blavet N & Jalfre M. Behavioural despair in rats: a new model sensitive to antidepressant treatments. *Eur. J. Pharmacol.* 47:379-91. 1978. (Cited 335 times.)
3. Porsolt R D. Behavioural despair: present status and future perspectives. (Leonard B E & Spencer P S J, eds.) *Antidepressants: thirty years on*. London: CNS. 1990. p. 85-94.
4. Borsini F & Meli A. Is the forced swimming test a suitable model for revealing antidepressant activity? *Psychopharmacology* 94:147-61. 1988.
5. Steru L, Chermat R, Thierry B, Mico J A, Lenegre A, Steru M, Simon P & Porsolt R D. The automated tail suspension test: a computerized device which differentiates psychotropic drugs. *Prog. Neuro-psych. Biol. Psych.* 11:659-71. 1987.

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