

This Week's Citation Classic™

Domino E F, Chodoff P & Corssen G. Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. *Clin. Pharmacol. Ther.* 6:279-91, 1965. [Depts. Pharmacology and Anesthesiology, Univ. Michigan Medical Center, Ann Arbor, MI]

The first clinical pharmacological effects of ketamine in human volunteers are described in this report. This drug has a unique spectrum of actions including analgesia, anesthesia, cardiovascular stimulation, and only minimal respiratory depression. Recovery from anesthesia is moderately rapid. Its use as an intravenous anesthetic is recommended. [The SO® indicates that this paper has been cited in over 290 publications since 1965]

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"It is interesting how during one's early professional career certain events shape subsequent research interests and endeavors. My involvement with the initial research on the clinical pharmacologic effects of CI-581 in man, now better known as ketamine, is certainly such an example for me. Twenty years ago a series of events culminated in a request by Alex Lane, then at Parke Davis, that I study the clinical pharmacology of a new chemical which had never been given to human beings. With my colleagues, Pete Chodoff and Gunther Corssen, and the collaboration of many colleagues at Parke Davis, including Graham Chen and Duncan McCarthy, we were able to study this unique new potential intravenous anesthetic. None of us shall ever forget the amazing spectrum of clinical pharmacological effects that this agent produced in the volunteers we studied. So unique were these effects that we had to invent a new set of words to describe its anesthetic properties. The drug produced 'zombies' who were totally disconnected from their environment, with their eyes open, and yet in a com-

plete anesthetic and analgesic state. The observation of being disconnected from the environment gave rise to the term 'dissociative anesthesia.'

"It is of interest that August 3, 1984, will be the twentieth anniversary of the administration of ketamine to human beings. It remains a unique and safe anesthetic agent. However, its major problem in humans is an emergence delirium which this first study clearly described. The reason our paper has been cited frequently over the years is because this study with ketamine was the first of its kind. Those early events in my research career have caused me to return again and again to study ketamine and other arylcyclohexylamines.^{1,2} Since ketamine has some actions clearly related to phencyclidine, we have tried to find ways to reduce the 'bad effects' of ketamine—or to 'tame the tiger' with diazepam premedication.³ I remain convinced that some day new ketamine analogues will be synthesized which will be much more useful than ketamine itself.

"Perhaps the most exciting new development in the 1980s has been definitive evidence that there are mammalian brain receptors for phencyclidine, ketamine, and other so-called *sigma* receptor opioid agonists.^{4,5} Even more exciting, there are now a number of endogenous peptides that have sigma receptor agonist actions.⁶ What are these endogenous peptides doing in the brain? Why should mammalian organisms have specific brain receptors for arylcyclohexylamines? Ketamine and phencyclidine have had an indelible influence on my professional life for they have stimulated many collaborative studies with medical chemists, anesthesiologists, psychiatrists, and psychologists. I even have a few friends in the pharmaceutical industry who, although not convinced to invest their company's research dollars in new ketamine analogues, still tolerate that 'dissociative' pharmacologist who just might have a good idea in attempting to find an even better ketamine, perhaps an endogenous one."

1. **Domino E F**, ed. (*PCP*) *phencyclidine: historical and current perspectives*. Ann Arbor, MI: NPP Books. 1981. 537 p.
2. **Kamenka J M, Domino E F & Geneste P**, eds. *Phencyclidine and related arylcyclohexylamines*. Ann Arbor, MI: NPP Books. 1983. 690 p.
3. **Zsigmond E & Domino E F**. Ketamine—clinical pharmacology, pharmacokinetics and current clinical uses. *Anesthesiol. Rev* 7:13-33. 1980.
4. **Vincent J P, Kartalovsky B, Geneste P, Kamenka J M & Lazdunski M**. Interaction of phencyclidine ('angel dust') with a specific receptor in rat brain membranes. *Proc. Nat Acad Sci US* 76:4678-82. 1979.
5. **Zukin S R & Zukin R S**. Specific [³H] phencyclidine binding in rat central nervous system. *Proc. Nat. Acad. Sci. US* 76:5372-6. 1979. (Cited 90 times.)
6. **Quirion R, O'Donohue T L, Everist H, Pert A & Pert C B**. Phencyclidine receptors and possible existence of an endogenous ligand. (Kamenka J M, Domino E F & Geneste P, eds.) *Phencyclidine and related arylcyclohexylamines*. Ann Arbor, MI: NPP Books. 1983 p. 667-83.