PCP (PHENCYCLIDINE): HISTORICAL AND CURRENT PERSPECTIVES

Edited by
E. F. Domino

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DEDICATION

This book is dedicated to the memory of Dr. Jacques S. Gottlieb, former Director of the Lafayette Clinic and Chairman, Department of Psychiatry, Wayne State University, Detroit, Michigan. Dr. Gottlieb felt strongly that phencyclidine was an excellent drug model of schizophrenia and encouraged research on this subject from the beginning. Perhaps some day his convictions about phencyclidine will be a key in unravelling the puzzle of schizophrenia. We all hope so.

PREFACE

The time has come to document the history of PCP (phencyclidine) - its synthesis, early pharmacology, clinical use and disappointment. No one associated with the early development of PCP would have, in their wildest imagination, predicted that this drug would be abused to the extent it has been in the United Sates in the past few years. Hence, a reexamination of the PCP problem and the need for a current perspective. This book provides both points of view. It is the outgrowth of a workshop held in San Juan, Puerto Rico, December 13, 1979 under the auspices of the American College of Neuropsychopharmacology. However, a number of additional investigators have submitted material that was not part of that meeting and this also is incorporated in this book. All chapters cover relatively new material which attempts to summarize the progress of a very rapidly changing field.

The Editor would like to acknowledge Mrs. Ellen Howard and Ms. Deborah Ashley for typing the manuscripts.

April 15, 1981
Edward F. Domino
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CHAPTER 1
THE HISTORICAL DEVELOPMENT OF PHENCYCLIDINE

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Two factors contributed to the discovery of phencyclidine. First was the interest that the author had in carrying out reactions of organomagnesium compounds with nitriles with the possibility that the ketones or stable imines synthesized would have analgesic activity. The second was the ready availability of a carbonitrile from prior work.

In the early part of the 1950s a seven-membered ring homolog of meperidine had been prepared and a small quantity remained of a 4-cyano intermediate for this compound. Rather than risk all of this material in one reaction with a Grignard reagent, it was decided to use a nitrile that was readily available from a previous development program. 1-Piperidinocyclohexanecarbonitrile (Kotz and Merkel, 1926) had been made available in significant amounts as a precursor to an amide shown to have analgesic properties.

The Discovery of Phencyclidine

The previously mentioned carbonitrile was reacted with ethylmagnesium bromide in diethyl ether. The Grignard complex was then hydrolyzed at low temperature with dilute mineral acid. A crystalline product which formed was not a ketone as shown by the infrared spectrum. Completion of the determination of the structure of this product was deferred because of the requirement to prepare other compounds for assigned research programs.

Sometime later, on March 26, 1956, the same substrate, 1-piperidinocyclohexanecarbonitrile, was treated with the organometallic reagent phenylmagnesium bromide in ether at reflux temperature. After cooling the reaction mixture, the Grignard complex that formed was hydrolyzed with dilute hydrochloric acid and a compound

separated at the liquid interface. This material was purified by recrystallization to give a colorless crystalline product, melting at 234-236°C. As in the case of the compound formed from ethylmagnesium bromide the infrared spectrum showed no absorption characteristic for a carbonyl group. When a rigorous acid hydrolysis was performed on a sample of the product, no chemical change occurred. Thus the possibility that a ketone or imine was produced was ruled out. Potentiometric titration showed that the original material was a hydrobromide. The microanalysis and molecular weight determination by the picrate method verified that the empirical formula corresponded to $C_{17}H_{26}BrN$ or 1-(1-phenylcyclohexyl)piperidine hydrobromide. The free base of this material, $C_{17}H_{25}N$, was crystalline and melted at 46-46.5°C from which the hydrochloride was formed.

The earlier prepared compound produced by the reaction of ethylmagnesium bromide with 1-piperidinocyclohexanecarbonitrile was shown to be a salt of 1-(1-ethylcyclohexyl)piperidine. Thus, under these reactiou conditions, an anomalous reaction had taken place, whereby the cyano group of the substrate, 1-piperidinocyclohexanecarbonitrile, had acted as a leaving group and the alkyl or aryl moiety of the organometallic reagent had functioned as an entering group facilitated by the neighboring nitrogen of the piperidine. It was earlier conjectured that this was due to the steric effect of the heterocyclic ring in the 1 position of cyclohexane. That a displacement reaction had occurred should not have been surprising if the author and his co-workers had been aware of the work performed many years earlier in Belgium by Bruylants (1925) and Velghe (1925) in which it was demonstrated that alpha-aminouitriles when reacted with organomagnesium reagents can yield displacement products. It may be considered that in the nitriles represented by $R_1R_2NC(R_3R_4)CN$ the carbon-CN bond has a high degree of ionic character which permits a second order nucleophilic substitution reaction to occur.

Pharmacology

A search of the literature confirmed that neither of the above-mentioned reaction products had been reported and because of their unique structure in the area of medicinal chemistry, both of them were submitted for general pharmacodynamic screening.

Dr. Graham Chen and his co-workers found that whereas

1-(1-ethylcyclohexyl)piperidine possessed minimal activity, 1-(1-phenylcyclohexyl)piperidine had unique properties. It acted mainly on the central nervous system with the effect varying with the animal species and dosage. Thus it elicited responses that ranged from ataxia, excitation, and catalepsy to a condition of surgical anesthesis. Most species investigated showed a taming or quieting effect at low dosage which was especially impressive in the rhesus monkey. The cat appeared not to undergo excitement; what was observed at 2 mg/kg intramuscularly was a state of catalepsy lasting for several hours with unimpaired corneal or pupillary reflexes and complete recovery with no apparent toxic effects.

The pharmacology of 1-(1-phenylcyclohexyl)piperidine, later referred to by its generic name of phencyclidine, was presented by Chen (1958) and published by Chen et al. (1959).

A detailed study of the analgesic and anesthetic effect of phencyclidine on the monkey (Macaca mulatta) was published by Chen and Weston (1960). The cataleptic state induced was considered practically indistinguishable from bulbocapnine hydrochloride. However, surgical intervention was not permissible in animals which received 10 to 40 mg/kg of body weight using bulbocapnine. This was compared with 5 to 10 mg/kg of phencyclidine administered intramuscularly which caused loss of consciousness permitting major surgery. Apparently the latter drug produced a depressant action on the central nervous system not manifested by bulbocapnine. The use of meprobamate at 200 mg/kg and phenobarbital at 100 mg/kg by intraperitoneal route led to general anesthesia in 30 min after injection, with respiratiou slowed and deepened. The depressant effect of these two agents were strikingly dissimilar to that of phencyclidine.

Medicinal Chemistry

In view of the unusual attributes of phencyclidine, it was decided that a medicinal chemistry program be launched with initially three major thrusts; variation in the aromatic group, modification of the cyclohexyl moiety, and alteration of the substituents on nitrogen. This program was carried out under the direction of Dr. R.W. Fleming and a portion of the synthetic work covering 1-arylcyclohexylamines with structure-activity correlations was published by Maddox et al. (1965). Reported were sixty analogs covering primary, secondary and

tertiary amines including cyclic variants plus phenyl, substituted phenyl, naphthyl and 9-fluorenyl modifications of the aryl portion.

Chen continued to coordinate the pharmacological studies of these compounds and in order to quantify the cataleptoid property, a screening method was developed utilizing the righting reflex of the pigeon, which he published in 1965.

Human Clinical Research

Since the early results of the activity of phencyclidine were promising, Dr. J.K. Weston and his associates carried out toxicological studies. The preliminary results along with the neuropharmacology were first presented by Chen et al. (1958). After adequate supportive toxicology data and the fate, distribution, and metabolism of phencyclidine had been obtained, permission was granted to perform human clinical research.

Phencyclidine was administered to over 3,000 patients according to Gorringe (1963). Catenacci (1958) used this drug as an anesthetic for local surgical procedures such as cystoscopy and as a preanesthetic for general surgery. The effects on seven patients by intravenous administration were reported by Greifenstein et al. (1958). Measurements of blood pressure response showed that systolic and diastolic pressure were consistently elevated and respiratory minute volume increased. Electrocardiography revealed no evidence of arrhythmia. Moderate changes were observed in the electroencephalographic pattern unlike those of natural sleep. At moderate doses reflex activity was unimpaired. Some sixty-four patients underwent various surgical procedures ranging from simple biopsy to partial gastric resection. It was demonstrated that phencyclidine possessed potent analgesic activity at 0.25 mg/kg of body weight. In many instances the surgeon was able to perform the entire procedure with the patient under phencyclidine alone. An outstanding feature was the amnesia experienced by all patients, there was no recollection by the patient of the operative procedure or of the the immediate postoperative phase. A disadvantage was the appearance in some patients of emergence phenomena.

Johnstone et al. (1959) investigated this drug for preoperative sedation, surgical anesthesia and postoperative analgesia in a total of 186 patients. In the conclusion of his publication it was stated that phencyclidine was undoubtedly the most potent general analgesic agent

which had yet been used in clinical medicine. Excitation reactions were most frequently encountered in young or middle-aged males. The advantage over the sedatives and analgesics was that it did not cause depression of the cardiovascular or respiratory function and thus could be used in elderly patients where agents such as opiates would be contraindicated.

Ultimately the use of phencyclidine in human clinical studies was terminated because of the extent of emergence phenomena.

Veterinary Medicine and Field Trials

A number of articles have been published which present the use of phencyclidine as an anesthetic or restraining agent in animals. For example, it has been successfully used in infrahuman primates such as the baboon (Collier, 1961; Florey et al., 1961; Kroll, 1962), chimpanzee (Joffe, 1964), Cynomolgus monkey (Spalding and Heymann, 1962), vervet monkey (Barany, 1963), spider monkey and Kikuyu Colobus monkey, gibbon and orangutan (Kroll, 1963). Other species in which this drug was used were: the goat (Wilkins, 1961, 1962); carnivora such as the wolf, fox, Cape hunting dog, coyote, California bobcat, black leopard, spotted hyena, American black bear, sun bear, and palm civet (Kroll, 1962); domestic cat (McCook et al., 1962); and rat (Abbott et al., 1964). Wright and Jordon (1963) showed it was clearly of no value in domestic fowl. Its utility in obstetric care in an Indian elephant was recorded by Lang (1963).

The utilization of phencyclidine alone or as an adjunctive agent for the immobilization of large animals and for transport such as in the case of the square lipped and black rhinoceros have been described in several publications (Carter, 1961; Prole, 1962; Harthoorn, 1962; Ditman, 1964). In the case of some ungulates, it was of little or no value (Talbot, 1960). For example, European cattle were only partially immobilized at 0.5 mg/pound. In Cape buffalo at 0.5 mg/pound and the eland at 0.68 mg/pound phencyclidine was lethal.

The above listing of animal species in which phencyclidine has been used alone or in combination with other agents is by no means complete.

Summary

Phencyclidine was first produced in the laboratory by

an anomalous reaction between an organometallic compound and an alpha-aminonitrile. This previously unknown material was submitted for general pharmacodynamic screening tests that showed it had quite unusual properties such as excitation, depression, catalepsy, and the ability to produce surgical anesthesia. Normally the first compound of a novel structure which has some pharmacological activity is later supplanted by other significantly more potent agents. Phencyclidine was rather unique in being the first member of the cataleptoid series and yet it continued to be one of the most interesting.

This drug was studied extensively in clinical research but trials terminated due to the extent of emergence phenomena. For several years veterinary study and use in a wide variety of wild and domestic animals were undertaken. Although unsuitable in some species such as ungulates, it was widely used for restraint and as an anesthetic agent in infrahuman primates. Domino et al. (1969) stated, "While phencyclidine does not meet all the criteria for an ideal immobilizing agent, it has distinct advantages with respect to reliability, favorable therapeutic index, rapid onset, lack of local irritation at the injection site, and low organ toxicity."

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CHAPTER 2
THE NEUROPHARMACOLOGY OF PHENCYCLIDINE

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The pharmacological study of phencyclidine began in the fall of 1956 when Dr. V.H. Maddox sent me a new compound he had just synthesized for pharmacological evaluation. The compound was 1-(1-phenyl cyclohexyl) piperidine (PCP). At that time I was with the Parke Davis Company in Detroit, Michigan. The compound was found to have marked pharmacological actions. The pharmacology of PCP involves actions on both the central and peripheral nervous systems. These effects are summarized below and in the publications cited at the end of this brief personal historical review.

Actions on the central nervous system

The chemical structure of PCP suggested that the compound would have a central excitatory action like phenylethylamines or diphenyl-2-piperidine methanol (pipradrol). The cyclohexyl and piperidinyl groups often act pharmacologically like alkyl and alkylamines, respectively. The central excitatory action of PCP was confirmed in mice and rats by an increase of locomotor activity. Our next step was to study the dose-effect relationship of PCP in rats, measuring their motor-activity in jiggle cages, and to examine its mode of action by antagonism with chlorpromazine. Parallel experiments were conducted with desoxyephedrine. The dose-effect curves were found to be similar for PCP and desoxyephedrine in doses of 1-4 mg/kg s.c. There was an important difference between the effect of PCP and that of desoxyephedrine in the antagonism experiments. Rats receiving a combination of PCP and chlorpromazine were more depressed than those receiving chlorpromazine alone. Such a difference in the extent of central nervous system depression was not observed with desoxyephedrine and chlorpromazine in appropriate doses.

This led us to investigate the central depressant action of PCP. It was observed in mice that the body movements of animals given PCP at moderate doses (4-8 mg/kg i.m.) were incoordinated in contrast to the coordinated movements of mice given desoxyephedrine at the same dose levels. Ataxia was clearly indicated in PCP-treated mice

by their inability to stay on a rotarod with an excitatory dose of 4 mg/kg. Desoxyephedrine-treated mice, on the other hand, would remain on the rotarod for two minutes at 8 mg/kg, four times the excitatory dose of PCP.

The central depressant action of PCP was then examined in the cat. Its body motor activity was not markedly influenced by excitants. The effects of PCP at 2 mg/kg i.m. in the cat included ataxia, catalepsy, analgesia and anesthesia. The limbs were not well relaxed. The eyes remained open with mydriasis. The corneal, pupillary and patellar reflexes were not impaired. Respiration, body temperature and muscle tone were not significantly altered. Some increase in salivation and urination occurred. Two cats receiving 20 mg/kg of PCP i.p. remained in a cataleptic state for 2 1/2 days and recovered without showing any toxic effect; in fact, they drank and ate immediately upon recovery.

The effect of PCP on the electroencephalogram of the cat, immobilized by cervical section and maintained in good condition with artificial respiration, was very different from what had been observed with known central excitants or depressants. The prominent feature was the appearance of high voltage spikes intermittently at low doses and consistently at anesthetic doses.

The cataleptic state, resembling that produced by bulbocapnine, was characterized by the abolition of the voluntary and reflex movements. This differed from the catalepsy induced by the so-called tranquilizers in that, with these drugs, voluntary and reflex movements were suppressed but not abolished. To study the cataleptic action of PCP further, a comparison was made with that of bulbocapnine in the monkey. The cataleptic symptomatology of monkeys receiving PCP (0.5-1.0 mg/kg) was indistinguishable from monkeys receiving bulbocapnine (5-10 mg/kg). The animals were immobilized without the loss of consciousness or muscle tension. Reflexes were not greatly impaired; the animal could hang on a bar with its hands for a long time. The muscles of the extremities were somewhat hypertonic and would resist passive motion. The eyes were open with the pupils dilated and reactive to light. Visual and auditory responses were somewhat impaired as were responses to nociceptive stimuli. The onset and extent of catalepsy proceeded in an ascending order (i.e., the lower parts of the body were affected before the upper). This order was reversed during recovery. With a suitable dose of PCP, the hind limbs would show reduced motor movement while the fore limbs remained active. Thus, the different parts of

the body appeared to be dissociated. PCP and bulbocapnine in large doses caused convulsions in the monkey.

PCP differed from bulbocapnine in producing analgesia and general anesthesia in doses below the convulsant level. Bulbocapnine did not have an anesthetic action. The signs and symptoms of monkeys anesthetized with PCP were similar to those described above for the cat. It is of interest that PCP anesthesia may be readily induced in decorticated monkeys, indicating the site of its anesthetic action is at regions of the brain below the neocortex.

Another distinct effect of PCP in low doses in the monkey is tameness. An otherwise vicious animal could be handled with ease. This was in marked contrast to its ferocious nature before receiving PCP. It would no longer bite when a finger or other object was placed in its mouth. A taming effect was not observed with bulbocapnine at low doses. The biting response was absent with bulbocapnine only in cataleptic dose levels (greater than 10 mg/kg). The tameness induced with PCP was somewhat similar to that induced by lysergic acid diethylamide (LSD) or bufotenin in low doses. Ataxic doses of the latter two drugs were not sufficient to produce loss of the biting response in monkeys. The biting response was absent in the monkey after the animal received a large dose of LSD or bufotenin and became stuporous and unable to grip the cage.

In view of the differences in response of mice, cats and monkeys to PCP in varying doses, its central action was also investigated in other animal species. The difference in the central effects of PCP was most marked in low versus high doses. In contrast to the excitatory effect of PCP in mice and rats, a quieting or taming effect was present in low doses of PCP in pigeons, rabbits, dogs, and cats, as well as monkeys. After PCP, they all became calm. Furthermore, hamsters and guinea pigs given PCP would no longer squeak upon being handled. With slightly higher doses of PCP, catalepsy was produced in all animal species. This was most striking in the pigeon, which would lie with an outstretched head, ventral flexion of the neck and shoulder, and wide-spread wings. It was thus chosen for testing PCP-like activity. With a further increase in dosage, the cataleptic stage passed into a stage of general anesthesia. General anesthesia in mice and rats was not sufficiently deep for surgery, probably due to the narrow range of doses producing anesthesia and those producing convulsions. Clonic convulsions occurred in pigeons, guinea pigs, cats, and dogs, as in the monkey, with doses larger than anesthetic levels. On the other hand, no

convulsions were observed in hamsters, rabbits, frogs, and fish. The expansion of melanophores (darkening of the skin) occurred under the influence of PCP in normal but not in hypophysectomized frogs. This indicates an effect of PCP on the hypothalamic-pituitary system. It is known that the expansion of skin melanophores is due to melanophore hormone released from the posterior pituitary whose activity is under the control of the hypothalamus.

In summary, the signs and symptoms of animals under the influence of PCP with low to high doses indicate the following central stimulating and depressant effects: tranquilization, excitation, catalepsy, analgesia, general anesthesia, and clonic convulsions. PCP did not produce any significant "hypnotic" effect. The antagonism of PCP induced excitation by chlorpromazine in mice and rats results in enhanced depression. PCP-induced clonic convulsions can be suppressed by the sedative-hypnotic drugs and by the minor tranquilizers such as the benzodiazepines like diazepam. No agent has been found to antagonize PCP induced catalepsy. The depressant action of PCP was ineffective in suppressing strychnine, caffeine, or pentylenetetrazol-induced convulsions. Whereas PCP was ineffective in antagonizing the initial clonic seizures induced by pentylenetetrazol, it would block the subsequent tonic-extensor seizures induced by this convulsant. This is consistent with the lack of a "hypnotic" property of PCP inasmuch as all conventional sedative-hypnotic drugs are efficacious in suppressing pentylenetetrazol-induced clonic seizures.

The anti-tonic extensor seizure effect of PCP was evaluated in mice given electroshock. Dose-wise, PCP was twice as active as phenytoin and six times more potent than phenobarbital in abolishing the electrically-induced tonic extensor seizures in mice.

PCP is very effective in suppressing audiogenic seizures in mice, nearly ten times more effective than phenobarbital and phenytoin. This suggests the possibility that PCP acts on both the afferent (sensory) and the efferent (motor) nervous systems while phenobarbital and diphenylhydantoin affect only the latter.

The duration of anti-tonic extensor seizure action of PCP is increased in mice pretreated with iproniazid (IPN), a monoamine oxidase inhibitor. The duration of the effect of PCP at 6 mg/kg i.p. was about two hours in mice without treatment with IPN. It was more than four hours in IPN-pretreated animals. Either a monoamine oxidase enzyme may be involved in the biologic disposition of PCP in the body

or IPN may interfere with the P450 drug biotransformation of PCP.

Actions on the peripheral nervous system

A 1% solution of PCP applied to the rabbit's cornea produces surface anesthesia in about one-half hour. This is about 2/3 the activity of a 1% solution of cocaine. In infiltration anesthesia, as tested intradermally in guinea pigs, PCP is twice as potent as procaine. Hence, PCP is a potent local anesthetic.

The effect of PCP on the peripheral autonomic nervous system was investigated by studying the blood pressure responses of dogs under pentobarbital anesthesia. PCP was found to be devoid of a cholinergic, anticholinergic, adrenergic blocking, ganglionic blocking, or antihistaminic action. The blood pressure was slightly increased by PCP initially at low doses; the hypertensive response became less upon repeated administration and was finally converted to hypotension. This appeared to indicate an indirectly acting sympathomimetic effect like cocaine and desoxyephedrine. Consequently, a comparative study was made of the three drugs on the blood pressure response of pentobarbitalized dogs given various autonomic drugs. The indirect sympathomimetic properties of the three compounds were studied as follows: potentiation of the hypertensive effect of norepinephrine, reduction of the hypertensive effect of phenethylamine, blockade of the adrenergic response to the ganglionic stimulant 4-(m-chlorphenylcarbamoyloxy)-2-butynyltrimethyl ammonium chloride (McN A343), and potentiation of the nicotine-like ganglion stimulant dimethylphenylpiperidine (DMPP).

In dogs pretreated with 3-phenoxypropyl guanidine, a catecholamine-releasing agent principally acting on the cardiovascular system without a demonstrable effect on the brain and adrenals, the initial cardiovascular effect of PCP, cocaine, or desoxyephedrine was hypotension which became more marked upon repeated injection of all three drugs. This indicated that the catecholamines of the peripheral vascular system might be involved in the hypertensive effect of these three indirectly acting sympathomimetic amines.

The sympathomimetic property of PCP was also tested on total urinary excretion. With low doses of PCP, just like with epinephrine, cocaine and desoxyephedrine, the output of urine volume increased in hydrated rats. This may account for the increase of urination in some animals

receiving PCP. Urinary excretion was diminished with large doses of PCP (10 mg/kg). The suppression of urination was not observed with epinephrine, cocaine, or desoxyephedrine at large tolerated doses. There is no general agreement at the present time regarding the mechanism of action of the sympathomimetic amines on urine excretion.

Discussion

The effects of PCP which we first described in animals have since been observed in man. A calming effect is present in some agitated individuals at very small dosage. At low doses, just sufficient to produce "tranquility" and amnesia but not analgesia or stupor, PCP will cause profound disturbance in perceptual and cognitive functions as the result of introceptive sensory deprivation. Like some animals, some patients are very excited by PCP.

The effect of PCP on sensory coordination mechanisms may account for the dissociation of voluntary motor function in the body. This dissociation is noticed subjectively. The dissociation generally occurs during the recovery period from the PCP induced anesthetic state. It resembles the condition of "sleeping paralysis." The cataleptoid state appears to result from sensory and motor deprivation as well. During the cataleptoid stage, light analgesia is present and marked analgesia prevails during the stage of surgical anesthesia.

It is to be noted that catalepsy occurs in rats given a large dose of morphine. A very potent synthetic narcotic analgesic agent structurally related to morphine is etorphine, first known by its code name M99. Like PCP, etorphine has been used for immobilization of animals in the wild. Whether or not PCP and the narcotic agents act on the same or on a different site of the central nervous system in producing catalepsy and analgesia is yet to be investigated.

The fact that PCP affects the hypothalamic-pituitary system is of interest in showing the possibility of "endorphin" secretion from the pituitary.

Due to its prolonged post-anesthetic effects, PCP is not used for general anesthesia in man. Had it a hypnotic action, the sensory and motor disturbances probably would not be perceived during emergence from anesthesia. Indeed, the post-anesthetic reactions in human subjects can be reduced by sedative agents like diazepam. In contrast to PCP itself the barbiturate anesthetics possess a hypnotic property that suppress such post-anesthetic effects.

The indirect sympathomimetic effect of PCP is seen in man as a slight increase of arterial blood pressure. A number of sympathomimetic agents introduced directly into the central nervous system will cause depression in animals and in man. Is it possible that PCP acts similarly centrally? On the basis of such a postulate, the term "sympathomimetic anesthetic" has been suggested for the PCP-like general anesthetics. The mydriasis and salivation produced by PCP may be due to its sympathomimetic effect on the higher autonomic nervous structures in the brain.

The anti-extensor electroshock seizure effect of anticonvulsants like phenytoin has been shown in man to be useful in the control of grand mal epilepsy. The therapeutic use of PCP for epilepsy is, however, not possible because of its undesirable side effects at therapeutic doses.

PCP is an outstanding example of centrally acting agents that affect the different parts of the central nervous system by stimulation and depression. One action, stimulation or depression, may be more prominent than the other. The different effects of centrally acting agents may be differentially observed by virtue of the evolutionary state of the cortical and subcortical nervous system of different animal species, from fish to primates.

PCP is a useful tool not only for the elucidation of the mechanism involved in sensory and motor deprivation, analgesia and anesthesia, but also for the discovery of agents which are antagonistic. A drug that would antagonize the cataleptic effect of PCP would be expected to be a useful drug for the management of some mental disorders. Such a drug has yet to be discovered.

Summary

PCP acts principally on the central nervous system, producing tranquilization, excitation, catalepsy, analgesia, anesthesia and convulsions in various animal species at different dosages. It has an indirect sympathomimetic action on the peripheral and the central autonomic nervous system. The mode and site of action of PCP are discussed and suggestions are offered for further investigation.

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CHAPTER 3
HISTORY OF THE DEVELOPMENT OF CATALEPTOID ANESTHETICS OF THE PHENCYCLIDINE TYPE*

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The compound, 1-(1-phenylcyclohexyl) piperidine hydrochloride (Sernyl, Parke Davis) was first synthesized in 1956 by Dr. Victor Maddox of the Product Development Department of Parke Davis and Company. It was synthesized by an unusual elimination reaction occurring in the treatment of α-aminonitriles with Grignard reagents.

The compound was submitted to Dr. Graham M. Chen for pharmacologic evaluation on September 11, 1956. This compound was recognized at once by Dr. Chen as having a unique set of pharmacologic properties. He was impressed with its mixed stimulant and depressant properties and the marked variation in species responsiveness. He observed that the drug produced a quieting or taming effect at low doses, and a cataleptoid or general anesthetic effect at higher doses in pigeons, guinea pigs, rabbits, cats, dogs and monkeys. In those species in which anesthesia was produced, respiration, heart rate, and blood pressure were not depressed. Higher doses led to convulsions rather than respiratory failure. His studies also demonstrated a potentiating effect upon drug-induced depression in all animal species, including rodents with nonselective central nervous system depressant drugs such as pentobarbital. He correctly predicted that the drug would produce acute effects in man that would constitute an acceptable alternative to those effects produced by the classical general anesthetic agents then in use. The first report on the pharmacology of the compound was given at the 1958 meeting of the Federation of American Societies for Experimental Biology (Chen et al., 1958). He and his associates, Charles R. Ensor, David Russell and

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**Deceased May 26, 1976.

Barbara Bohner, published the results of these first laboratory studies in 1959 (Chen et al., 1959).

Laboratory studies were promising enough to warrant human trials and the toxicological studies were initiated and directed by Dr. J.K. Weston. Fate, distribution, and metabolism studies were undertaken by Dr. A.J. Glazko. By May, 1957, sufficient information was acquired to support recommendation for cautious and judicious trials in man. The first of these were carried out under the direction of Dr. F.E. Greifenstein working in close collaboration with Dr. John Gajewski of the Clinical Investigation Department of Parke Davis and Company. These studies were carried out at Detroit Receiving Hospital in the late summer of 1957. While the very first trials went smoothly it soon became obvious that certain important limitations were associated with the use of the drug in man. Clinical experience by Dr. Greifenstein and by several other groups of anesthesiologists led to the conclusion that the drug could be expected to produce prolonged and stormy emergence phenomena in some fifteen to thirty percent of the patients. In spite of this serious handicap some of the investigators remained enthusiastic about the drug because it permitted them to produce desirable levels or states of anesthesia, or sensory deprivation, which were not achievable by other means. The emergence phenomena, including hallucinations and/or delirium attracted the attention of a number of persons interested in the psychotomimetic properties of the drug. A summary of conclusions drawn from these studies led to the consensus that the psychotomimetic action of the drug probably resulted from its capacity to produce a state of sensory deprivation. The delusional state and delirium produced by phencyclidine was obviously different from that produced by LSD and other potent hallucinogenic agents. Interest was sufficiently high among clinical investigators that a generic name (phencyclidine) and a trade name (Sernyl) were subsequently assigned to the drug. Further clinical studies continued to demonstrate the applicability of the drug under certain specific conditions and in certain areas of the world. But it became obvious that the drug would not be a useful general anesthetic in a modern clinical setting. Dr. Andrew C. Bratton, Jr., assumed the overall direction of all experimental therapeutic research associated with this class of drug. Dr. Bratton requested Dr. E. F. Domino at the University of Michigan to carry out independent neuropharmacological studies on phencyclidine. These were summarized years later in a review which

stressed the unusual nature of phencyclidine (Domino, 1964).

In the meantime, an intense chemical effort was mounted to prepare analogues which might either improve the quality of the anesthetic effect and/or minimize emergence phenomena. This chemical effort at Parke Davis was directed by Dr. Robert Fleming and included Drs. Robert Parcell, Eric Godefroi, and Victor Maddox. Scores of compounds were prepared and examined by Dr. Chen's group in pigeons for their cataleptic activity, and in mice for their antielectroshock activity. The more active compounds were referred to Dr. Jean K. Weston and later to Drs. Robert J. McAlpine, Kathryn Weston, and Thomas Reutner for study of the behavioral effects in monkeys as well as acute and chronic toxicity in monkeys, dogs, and rodents. During this period seven additional compounds were recommended for clinical trial. These were: N-ethyl-1-phenylcyclohexylamine HCl (CI-400); 1-phenylcyclohexylamine HCl (CI-401); 1-(1-(2-thienyl)cyclohexyl) piperidine HCl (CI-421); trans-decahydro-8a-phenylquinoline HCl (CI-426); N,N-dimethyl-1-phenylcyclohexylamine HCl (CI-459); 5a,6,7,8,9,9a-hexahydro-N-methyl-9a-dibenzofluoranamine HCl (CI-482); and 1,2,3,4,4a,9a-hexahydro-N-methyl-4a-fluorenamine HCl (CI-500). Dr. George Stevens was made responsible for the clinical trial of these potential general anesthetic agents. Slight differences were detected in the clinical responses to those compounds which were studied. However, none showed sufficient qualitative improvement over phencyclidine to warrant an extended clinical evaluation.

Extensive veterinary field trials with phencyclidine were undertaken in a wide variety of wild and domesticated animals. Dr. George Kurzon of Parke-Davis was assigned the responsibility for the control and the execution of this study. During this period of time, that is between 1960 and 1963, phencyclidine enjoyed prominence as an immobilizing agent for large wild mammals using the Palmer Cap-Chure Gun. Much of this work was carried out in Africa by Dr. A.M. Harthoorn and by Mr. Harold Palmer, the inventor of the Cap-Chure Gun. Because the drug was receiving considerable attention at this time it was marketed in Europe under the trade name Sernylan as a veterinary anesthetic and immobilizing agent. In 1964 studies of the veterinary application of phencyclidine were put under the direction of Dr. Harry Stoliker. Certain limitations, especially in ungulates, had become manifest after more extensive trials. These eventually

led to the removal of the drug from the veterinary market in Europe. Later, Sernylan was reintroduced in Europe and in the United States, restricted to use in infrahuman primates. In 1969, the status of Sernylan in relation to other general anesthetics in infrahuman primates was reviewed by Domino et al. (1969). They concluded it was a very useful anesthetic for such animals. For many years, Sernylan was considered the drug of choice for such purposes.

Expansion of the CNS program at Parke-Davis in the early 1960s included the addition of a small monkey colony. This enabled early studies on the analogues and chemical relatives of phencyclidine to be carried out by the CNS group under Dr. Chen's direction. The major objective of finding a compound with improved quality of anesthetic effect and having a briefer duration of action was defined at this time. The goal was to reduce the intensity and duration of the emergence phenomena and postanesthetic recovery phase. In 1960, Dr. Duncan A. McCarthy was assigned the responsibility for the evaluation of newly synthesized analogues for their potential use as cataleptoid-anesthetics. He designed a test procedure for use in Rhesus monkeys which enabled one to separate the anesthetic potency from duration of action of these compounds. About 100 of the older compounds were reevaluated in this test procedure along with those newly synthesized compounds which showed some promise in the pigeon test developed and standardized by Dr. Chen. The medicinal chemical group had prepared by this time approximately 300 closely related structures and the structure-activity relationships of this class of drugs was fairly well defined.

During this phase of chemical development, Dr. Calvin Stevens, a member of the Chemistry Department of Wayne State University, was a consultant to the chemical group of Parke-Davis Research. As such, he was kept informed of the Company's interest and progress in structural modifications and biological activity of the phenylcyclohexylamines. He and one of his graduate students, in the course of a new synthesis, ran a new alpha-hydroxyimine rearrangement that led to 2-(ethylamino)-2-phenylcyclohexanone HCl. This compound was tested in pigeons and monkeys and found to be active and to produce a quality of anesthesia in monkeys superior to that produced by phencyclidine. When this information was communicated to Dr. Stevens, he and his group at Wayne State University synthesized a series of close analogues which were submitted to the CNS group and tested by Dr. McCarthy. Minor

improvements with respect to duration, potency, and quality of effect encouraged Dr. Stevens to continue synthetic work in this area. In April, 1962, the 2-(o-chlorophenyl)-2-(methylamino)cyclohexanone was submitted for biological testing under test code #CL-369. It was immediately recognized as an outstanding candidate and additional material was requested. Chen et al. described its neuropharmacology in a publication in 1966. The chemical group at Parke Davis improved and upgraded the synthetic processes. Extensive behavioral and pharmacodynamic evaluations were initiated. Additional analogues were synthesized by a group of chemists under the direction of Dr. Parcell and which included Dr. Donald Butler and Mr. Yvon L'Italien. Testing continued in hopes of finding compounds of equal or greater promise. Of the numerous active compounds prepared, CL-399 (later designated CI-634) showed promise in the veterinary field.

By February, 1963, sufficient chemical and biological development had been completed on CL-369 so that a commitment was made to do the necessary acute and chronic toxicity studies and to initiate fate, distribution and metabolism studies preparatory for clinical evaluation. These studies were carried on at Parke Davis and Company under the direction of Drs. Donald H. Kaump and Anthony J. Glazko, respectively. The pre-clinical toxicological studies were completed and reported by Dr. Kaump and the pharmacological studies by Drs. Chen, McCarthy, and Mr. Ensor in December, 1963. Dr. A.C. Bratton, Jr. wrote the recommendation for clinical trial in January, 1964. The clinical code designation CI-581 was assigned. In preparation for human tolerance studies Dr. Alexander Z. Lane of the Clinical Investigation Department of Parke Davis contacted Dr. Edward F. Domino and Dr. Guenter Corssen of the University of Michigan. The Experimental Therapeutics Division provided them with a complete synopsis of the pharmacological and toxicological evidence of presumptive clinical utility and safety of the drug. The first human subject received the drug on August 3, 1964. The clinical pharmacological data of the first human study were summarized by Domiuo et al. (1965a,b) as well as the first clinical experiences by Corssen and Domino (1966). These investigators introduced the terms dissociative anesthetic and dissociative anesthesia. (Editor's note: Dr. McCarthy strongly objected to these terms which he viewed as inappropriate. He preferred the term cataleptoid anesthetic as evidenced by the title of this report.) The first publication dealing with the drug in animals was by

McCarthy et al. (1965). At the Spring meeting of the Federation of American Societies for Experimental Biology in 1965, McCarthy and Chen (1965) described the general anesthetic actions of CI-581 in Rhesus monkeys; Chang et al. (1965) described the metabolic disposition of CI-581 in laboratory animals and man; Domino et al. (1965a) of the University of Michigan presented the results of their early experience with the drug in man. CI-581 was given the generic name ketamine (Ketalar, Ketajet) and has been available as an intravenous anesthetic agent after its approval by the Food and Drug Administration.

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