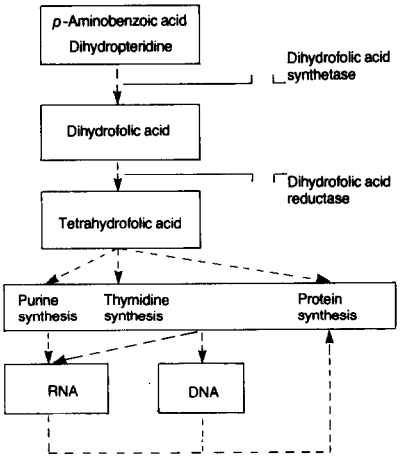

Fig. 5. Flow diagram of purine, thymidine and protein synthesis.

problems presented and the management of research show important differences, it is essential that industry continues to recruit its proper proportion of the available talent.

Medawar has commented that the ordinary processes of scientific discovery are slow, messy and uneconomic and cannot be premeditated. Industry is recognizing that 'creativity and ultimate rewards are supported by the greatest achievable sophistication and fostered by a very tolerant definition of relevance' (Hitchings).

JULIAN H. SHELLEY

Boehringer Ingelheim, Southern Industrial Estate, Bracknell, Berkshire, UK.

Reading list

1 Bindra, J. S. and Lednicer, D. (eds) (1982) *Chronicles of drug discovery*, Vol. 1, John Wiley, New York
2 Janssen, P. A. J. (1971) in *Discoveries in Biological Psychiatry* (Ayd, F. J. and Blackwell, B., eds), Lippincoot, Philadelphia
3 Hitchings, G. H. (1976) *Design and Achievements in Chemotherapy – A Symposium in honour of G. H. Hitchings, 31 October 1975*, Science and Medical Publishing Co. Inc.
4 Hitchings G. H. (1969) *The GHA Clowes Memorial Lecture, Cancer Research* 29, 1895

Mosaic

The joint French–US seminar on phencyclidine and related arylcyclohexylamines

A joint French–US seminar was held at La Grande Motte (Montpellier) France, 20–24 September 1982, to assess the current scientific status of phencyclidine (PCP) and related arylcyclohexylamines. The seminar was attended by 58 scientists interested in the chemistry, biochemistry, pharmacology, therapeutic applications and drug abuse aspects of arylcyclohexylamines. Thirty-four American, 19 French, 3 Japanese, 1 British and 1 Israeli investigator attended, representing each of the above major disciplines. The organizing committee consisted of E. F. Domino of the University of Michigan and P. Geneste and J. M. Kamenka of the Université de Montpellier, Ecole Nationale Supérieure de Chimie.

The medicinal chemical aspects were described first. It was shown that many different arylcyclohexylamines possess PCP-like properties which overlap with the opioid narcotics. The active conformation of PCP was described by Kamenka and Geneste (Montpellier). Its chameleon-like property of changing the aryl group from axial to equatorial to the cyclohexyl ring with protonated and non-protonated molecular species, suggests the complexity of determining its active form. This was accomplished by studying the effects of more thermodynamically stable compounds. It was suggested that the biologically active conformation of PCP requires an axial phenyl group in the complex ligand receptor. In addition, preferred solution conformations, similar to that of PCP hydrochloride, were found for a series of arylcyclohexylamine hydrochlorides by Brine and associates (Research Triangle Institute). Lednicer (Adria) and P. F. Von Voigtlander (Upjohn) described the chemistry and structure–activity relationships of a series of 4-amino-4-arylcyclohexanols. The presence of an oxygen function on the cyclohexane ring produces compounds that are narcotic opioids, both pure μ-agonists and mixed μ-agonists–antagonists, as well as pure μ-antagonists. The bromo, phenethyl derivative (U 48843) has 12 300 times the potency of morphine as an analgesic of the μ-type. This makes this compound, 4-(*p* bromophenyl)-4-(dimethylamino)-1-phenethylcyclohexanol (trans OH/N) one of the most potent opioid analgesics known. Removal of the oxygen group in this series produces compounds with PCP-like activity to varying degrees. Zimmerman and associates (Lilly) reported the discovery and characterization of a new series of benzo(f)isoquinoline derivatives that have stimulus discriminative properties similar to PCP. One of the most potent is the methylcyclopropyl bridged isoquinoline, LY 154045. PCP-like effects were maximized with a hydroxyl substituent in the aromatic ring.

One of the major questions in PCP research today is whether there is a PCP receptor. Lazdunski, Vincent and colleagues (Nice) reviewed the properties required for a PCP binding site to be called a PCP receptor. These include: (1) specific, reversible and saturable binding; (2) a specific correlation between affinity and biological activity such as PCP stimulus discrimination, mouse rotarod behavior etc.; (3) no displacement of binding by molecules with a different pharmacological action; (4) the K_D of binding must be in the concentration range for relevant pharmacological actions; (5) there must be stereospecificity; (6) tissue regional distribution of binding must be consistent with known pharmacological actions; (7) a specific antagonist of the pharmacological effects of PCP must prevent its binding.

In the case of PCP, most of these criteria, except that of a specific antagonist preventing binding, have been met. Lazdunski pointed out the maximum binding capacity of PCP of more than 2 pmol mg^{-1} protein. This is a very large amount of binding as compared with the binding capacities for most neurotransmitters. Pronase, trypsin and papain treatment destroys PCP binding, but phospholipases do not. This, and the stereospecificity of the binding, show that the receptor is a protein. High Na^+ concentration blocks PCP binding, as do local anesthetics and histrionicotoxin. PCP also acts on the muscarinic cholinergic receptor, but at high concentrations near 30 μM. In embryonic chick cardiac cells in culture, PCP produces a negative inotropic effect just like acetylcholine (ACh). In neuroblastoma cells in culture PCP blocks

the Na^+-channel and the K^+-channel. The K^+-channel is completely blocked when PCP reduces the Na^+-channel activity by 50%, causing a reduced, but prolonged action potential. The Ca^{2+}-dependent K^+-channel and the slow Ca^{2+}-channel are not affected. PCP also blocks dopamine (DA) uptake in concentrations which are the same as those found for the saturation of the PCP receptor with [^{3}H]PCP. From a structure–activity point of view, *meta* OH-PCP (a potential PCP metabolite) is the most potent of the compounds studied; it is also very potent in its affinity for opiate receptors.

S. R. Zukin (Albert Einstein College) reviewed recent progress in PCP receptor research. He further characterized its kinetic association and dissociation rate constants as $2.9 \times 10^6 M^{-1}$ and 4.8×10^{-1} min^{-1}, yielding a K_D of 1.6×10^{-7}M in agreement with previous data. The permissible separation time of 13 s was well above the 10 s of the rapid filtration assay. Precoating the filters with 0.01% poly-L-lysine or 0.05% polyethyleneimine eliminated any displaceable [^{3}H]PCP binding to GF/B filters. Stereospecificity for the PCP receptor was demonstrated in that (+)-ketamine was four times more potent than (−)-ketamine, and dexoxadrol was 100 times more potent than levoxadrol. Proteolytic enzymes, including trypsin, papain and thermolysin, inactivated stereospecific and overall specific PCP binding. The subicular cortex and hippocampus showed the greatest PCP binding, with intermediate levels in the frontal cortex, hypothalamus, cerebellum and striatum. Negligible levels of PCP binding were found in the white matter of the corpus callosum.

R. S. Zukin (Albert Einstein College) reviewed the biochemical evidence for a common PCP/σ opiate receptor. She stressed that it is not an opiate receptor, but rather a unique and distinctive receptor. According to this concept, Zajac, Roques and colleagues (Université René Descartes) showed that highly selective synthetic peptides with brain μ- and δ-opiate receptor agonist actions did not interact with PCP binding sites. Indeed, these agonists exhibited low inhibitory potency (IC_{50} 10 000 nM) on [^{3}H]PCP binding in rat brain. δ-Selective agonists increased [^{3}H]DA release *in vivo* after intracerebroventricular injection in caudate nucleus of cats and *in vitro* in rat striatal slices. This effect, which is not antagonized by naloxone, was obtained at low doses and may be related to the behavioral effects of opiates. Interestingly, PCP was also reported by Howard-Butcher (University of California, Los Angeles) and Johnson (University of Texas, Galveston), to increase dopamine release in similar assays but at higher doses.

M. E. and A. T. Eldefrawi (Maryland) pointed out that [^{3}H]PCP binds to allosteric sites on the ACh receptor of the torpedo electric organ and to proteins in crayfish abdominal muscle membranes. The latter binding is particularly sensitive to divalent cations, which inhibit Ca^{2+} channels. The rank-order of several PCP analogs in displacing [^{3}H]PCP binding to crayfish protein correlates better with their inhibition of [^{3}H]PCP binding to rat brain than to the torpedo ACh receptor. Although PCP actions on the Ca^{2+} channel are implicated, Albuquerque of the same University could find no direct effects of PCP on the Ca^{2+} channel of the frog neuromuscular junction.

Due to illness, neither Maayani nor Weinstein (Mount Sinai) was able to attend the seminar. The abstract of their paper covered the discriminant structure–activity relations of PCP and its derivatives, as well as the multiple pharmacological actions of PCP in which its actions on the muscarinic cholinergic receptor as well as on K^+ channels in cardiac muscle were studied. In spite of the absence of these investigators, the round table discussion chaired by Vincent brought out some heated discussion, in which the majority felt that the evidence for a distinct PCP receptor was considerable, and that the problem of the rapid filtration assay raised by the Weinstein group had now been resolved. All lamented the lack of a specific PCP antagonist and its need in further PCP receptor studies.

The biotransformation of the piperidine ring of PCP was described by Cho and Kammerer and colleagues (University of California, Los Angeles). They used rat and rabbit 9 000 × g liver supernatant to show the conversion of PCP to (1-phenylcyclohexyl)-1,2,3,4-tetrahydropyridine, a possible decomposition product of the corresponding carbinolamine. The *N*-oxide of PCP was not an important intermediate. Their data indicated that 5-[*N*-(1′-phenylcyclohexyl)amino] pentanoic acid and *N*-(5-hydroxypentyl)-1-phenylcyclohexylamine are formed from the carbinolamine of PCP or its open ring form, through oxidation or reduction by soluble liver enzymes. Kalir (Tel-Aviv) and Trevor (University of California, San Francisco) and colleagues reported on the formation of an iminium ion of PCP. The metabolically dependent covalent binding of [^{3}H]PCP to microsomal proteins was inhibited by cyanide ions, suggesting that the interaction of their iminium derivative of PCP could explain the long term, and irreversible binding of PCP to cellular proteins. Holsztynska and Domino (Michigan) described a new major route of phencyclidine biotransformation via hydroxylation at the 3 position of the cyclohexyl ring and subsequent formation of dihydroxylated derivatives, 3,4-dihydroxycyclo PCP and 3-hydroxycyclo-4-hydroxy-pip PCP in mouse, monkey and human. This pathway is deficient in certain inbred strains of mice and is completely undetectable in the rabbit. In general alicyclic hydroxylations occur preferentially over aromatic hydroxylations. The 3- and 4-positions on the cyclohexyl ring and the 4-position on the piperidine are preferred sites of PCP oxidation. Hydroxylation of the aromatic ring of PCP, if any, occurs only in trace amounts. Each hydroxylation of PCP on the alicyclic ring is probably mediated via a different form of cytochrome *P*450, as suggested by differential abundance and inducibility of each pathway in various mouse strains. On the basis of experiments with inbred strains of mice, it was concluded that the hydroxylations of PCP on alicyclic rings are mediated by cytochrome *P*450 forms different from those associated with aryl hydrocarbon hydroxylase activity. Trevor and his colleagues (University of California, San Francisco) reported on the remarkable stereoselective biotransformation of the enantiomers of ketamine by the liver of rats and human heart transplant donors. Marked stereoselectivity was observed in alicyclic ring hydroxylation in rat hepatic microsomes in contrast to that from humans. The major hydroxylated metabolites formed from both ketamine enantiomers by human liver microsomes were 4-hydroxyketamine and 6-hydroxynorketamine.

An overview of the human behavioral psychopharmacology of the arylcyclohexylamines was provided by Gallant (Tulane). PCP is a positive reinforcer in animals and, presumably, in man because it is abused extensively. A rather high incidence of PCP intoxication was observed in patients treated in the New Orleans Charity Hospital Emergency Room. Marked and confusing mental and neurologic symptomatology was observed in these patients. Gallant stressed the fact that the lipophilic nature of PCP and the prolonged clinical course of psychotic behavior in some patients may be associated with a slow rate of PCP excretion in the urine. For example, human urines can be positive for PCP as long as 30 days after the last exposure, with positive urines averaging 2 weeks after the last use of PCP. Aniline, Pitts and associates (University of Southern California) stressed the serious nature of PCP abuse in patients at Los Angeles County Hospital. They emphasized that epidemiological studies on the prevalence of PCP abuse

must be based upon highly sensitive and specific methods of PCP analyses in blood or urine, especially using modern gas chromatographic–mass spectrometric methods for detecting not only PCP but also its related congeners of abuse. Lack of suitable and sophisticated analytical methods to measure these substances may lead to false assumptions in surveys reporting, for instance, decreased use of PCP, while street use may involve smaller dosage of PCP and a shift to the use of its congeners.

While PCP is a major drug of abuse in the USA, Ingold (Centre Médical Marmottan) pointed out that PCP is not abused in France at this time. He suggested that its abuse in the USA is due to its general availability. Why do people use PCP? Ingold suggested its unique pharmacological properties of euphoria, amnesia and anesthesia; group pressure to accept a risk, and PCP negative, as well as positive reinforcing properties to induce a change of mental state, are all involved. PCP induces a unique state of distortion of body image, akin to a phantom limb syndrome.

Braude (US National Institute on Drug Abuse) provided an overview of the NIDA biomedical program on PCP and metabolites. Due to the epidemic of PCP abuse in the USA, beginning in 1979 NIDA funded about 40 projects and contracts on PCP in relation to other drugs of abuse, of which 17 projects were on PCP alone. Reduced availability of funds and reassessment of NIDA priorities will undoubtedly bring PCP research to a lower level in the future. In view of the scientific and public interest in PCP, the majority of participants felt this was most regrettable.

Balster and Wessinger (Virginia) reviewed their extensive research on the CNS depressant effects of PCP. Although PCP and other arylcyclohexylamines produce a unique type of general anesthesia, PCP has many pharmacological and behavioral effects similar to typical CNS depressants, such as the barbiturates. These include the phenomena of tolerance and dependence. PCP also markedly enhances the depressant effects of barbiturates. Mayersohn and associates (Arizona) reported on PCP disposition kinetics in dogs. They developed a radioimmunoassay for PCP, and a capillary column gas chromatographic method using nitrogen detection for a number of its metabolites.

In dogs, PCP has an extremely large volume of distribution indicating extensive distribution to tissues. Systemic clearance of PCP was large, and approached the value of hepatic blood flow. PCP is poorly bound to serum proteins with dependence on pH. Binding of PCP increases with pH. This raises an interesting question as to what are the consequences of extensive acidification techniques during PCP intoxication.

Only 80% of the total dose of [^{3}H]PCP could be accounted for, based on urinary (*c.* 60%) and fecal (*c.* 20%) excretion. About 1% of the dose of PCP is excreted in the dog as free PCP in the urine, with various metabolites, especially the aminopentanoic acid derivative (14.7%). Woods (Michigan) reported on drug modification of PCP discriminative performance in pigeons and rhesus monkeys. The data indicate a unique nature of PCP discriminative cues, which are shared by related arylcyclohexylamines as well as certain benzomorphans and homobenzomorphans. Haloperidol, diazepam and 1-phenylisopropyladenosine, in doses sufficient to alter performance, failed to alter the discriminative control of PCP. Important species differences to different drug classes were also noted.

Shannon (US National Institute on Drug Abuse) reported on the structure–activity relationships for producing arylcyclohexylamine-like behavioral effects in rats. In contrast with other investigators who use food reinforcement in discriminative stimulus studies, he used shock avoidance in rats. This facilitated the use of larger doses of these agents in determining their behavioral effects. Systematic structure–activity studies allowed Shannon and his colleagues to define the properties of the PCP receptor, including an anionic site which binds the protonated nitrogen, two opposing π aromatic sites and an intermediate lipophilic area.

Stiller and colleagues (Pittsburgh) reported on the developmental aspects of the human clinical pharmacokinetics of ketamine. Their data, using cardiac patients, were surprisingly consistent with other reports in the literature in which ketamine has a short $t_{1/2}$ α-phase of about 10 min and a much longer $t_{1/2}$ β-phase of about 120 min. Some unique data in infants, children and pregnant females during labor were also described. Ketamine $t_{1/2}$ β-phase was faster (55 min) in children (1–5 yr) and slower (185 min) in infants (2–10 m) than adults. The hemodilution effects of cardiac bypass (CBP) altered the β-phase in all patients, but resumed a log-linear concentration curve after CBP was concluded. Ketamine plasma protein binding levels were elevated in all patients except in the cord blood, where they were 1/3 to 1/2 those of the mother. These investigators also showed that increasing the blood pH increased ketamine binding, as is true for PCP. Emory University supplied some of the patient samples.

Albuquerque and associates reported on the ability to differentiate behaviorally active from inactive PCP analogues based on the interaction of the compounds with ionic channels of electrically excitable membranes and cholinergic receptors. An important correlation was made between the ability of PCP and its derivatives to block K^+- and Na^+-channel inactivation rather than affect the recognition sites of cholinergic receptors.

Palmer, Hoffer and associates (Colorado) described the remarkable properties of PCP and related derivatives on the release of norepinephrine (NE) from the rat cerebellum and hippocampus. These investigators used electrophysiological methods, together with micro-pressure ejection from multibarrelled micropipettes, to show that PCP mimicked the actions of NE on single unit activity, with ketamine being about 1/5 as potent. PCP no longer exerted its depressant actions on cerebellar Purkinje cells following lesions of the NE innervation to cerebellum with 6-OH dopamine, interruption of presynaptic NE release by local Mg_2^+ applications, or NE depletion by reserpine administration. These data suggest a presynaptic effect of PCP on NE release. The effect of PCP on hippocampal neurons was more complex, but consistent with a presynaptic mechanism of action at monoamine synapses. Higher doses caused local anesthetic effects in both brain areas. The expected stereospecific potency differences of PCP analogues were also described.

Lodge and associates (Royal Veterinary College, London) pointed out that the arylcyclohexylamines selectively reduce excitation of cat central neurons by aspartate-like amino acids. They used the technique of microiontophoresis and studied ketamine in particular. Ketamine reversibly reduced the excitation of spinal cord neurons by *N*-methylaspartate to a greater extent than that of either kainate or quisqualate. The (+)-enantiomer of ketamine was 3× as potent as its (−)-isomer as an *N*-methylaspartate antagonist, and only 1 to 1.5× as potent as an ACh antagonist. Ketamine had no effect on GABA-mediated transmission in contrast to barbiturates which potentiated it.

Howard-Butcher showed that there was an *in-vivo* release of dopamine (DA) in the cat caudate nucleus after PCP administration using the technique of cyclic voltametry. In addition she showed that PCP affected ACh turnover consistently with its effects on DA release in the striatum. Murray (Washington State University) and his colleagues (NIMH at St. Elizabeth's Hospital) compared the effects of PCP with those of other psychoactive drugs on cholinergic dynamics in the rat brain. Subanesthetic doses of PCP and ketamine

increased ACh turnover in the neocortex and diencephalon, but had no effect on striatal and hippocampal ACh. This regional brain pattern of ACh turnover induced by PCP was similar to that of cocaine, but was completely different from other classes of centrally acting drugs.

Johnson reported that PCP affects DA and ACh release from rat striatal slices *in vitro*. PCP increased the spontaneous release of DA but had no effect on K^+ stimulated [^{3}H]DA release. His results suggest that PCP releases [^{3}H]DA in a manner similar to non-amphetamine stimulants. PCP can release both stored and newly synthesized DA, which serves to down regulate DA synthesis. At similar concentrations (3–30 μM) PCP inhibited potassium stimulated release of [^{3}H]ACh, while atropine had no effect. Oxotremorine, a muscarinic cholinergic agonist, also inhibited [^{3}H]ACh release and in combination with PCP the effect was additive, suggesting that the atropine-like properties of PCP are unimportant in this paradigm. The (+)-enantiomer of SKF 10047 but not the (−)-enantiomer also inhibited [^{3}H]ACh release. This effect was blocked by haloperidol, just as with PCP. Hence, PCP and (+)-SKF 10047 may stimulate DA release via a PCP/σ-receptor action.

Castellani (Wichita) reported on the complex role of dopaminergic, cholinergic and opioid agonists and antagonists on various aspects of PCP induced behavior in rats. His data were consistent with PCP induced release of DA and its partial blockade by haloperidol in both rat and man. None of the transmitter agonists or antagonists alone reversed all of the complex behavioral effects of PCP, because all three brain transmitters seemed to be involved.

Browne and Welch (Pfizer) added adenosine to the list of putative neurotransmitters involved with PCP effects. They obtained data in rats showing that various adenosine agonists completely antagonized the discriminative stimulus effects of PCP *in vivo* and blocked the high, but not the low, affinity receptor of [^{3}H]N6-cyclohexyladenosine *in vitro*. Nabeshima and Kameyama (Meijo) studied the actions of acute and chronic PCP administration on Met-enkephalin in the mouse brain. A complex picture was produced by PCP, in which there was a lowering of Met-enkephalin in the medulla and midbrain but no change in the striatum, hippocampus and neocortex. After development of tolerance to PCP, an increase in Met-enkephalin levels was observed in the striatum. However, during morphine withdrawal in PCP tolerant mice, the increase in Met-enkephalin levels returned close to the control levels. These investigators also reported important sex differences of PCP in rats. Female rats were more sensitive to the diverse effects of PCP than males. The enhanced sensitivity of females compared with males was related to a higher brain content of PCP and more prolonged brain and plasma half-lives in the females. The content of hepatic microsomal cytochrome *P*450 was also found to be lower in the female rats.

Fukuda and Domino (Michigan) compared the EEG and gross behavioral effects of various dissociative, general and local anesthetics in *Macaca mulatta*. They concluded that PCP, ketamine, dexoxadrol and dextrorphan had similar EEG and gross behavioral effects in contrast to the other centrally active agents studied. Their findings are consistent with the data obtained from stimulus discrimination and PCP receptor binding studies.

Vaupel (US National Institute on Drug Abuse) reported on the effects of PCP in the chronic spinal dog. The pharmacology of PCP, its similarity to SKF 10047 and the profiles of eight PCP analogues abused by man were studied. He concluded that the chronic spinal dog was an excellent model in which to study PCP derivatives and obtain their behavioral, neurologic and physiologic profiles. The structure–activity relationships of various PCP derivatives were in the expected direction, with PCP and SKF 10047 showing very similar pharmacological profiles. Von Voigtlander and Tang (Upjohn) reported on an extensive search for PCP antagonists. Although no specific antagonists were found, prazosin and clonidine were noted to block a number of the effects of PCP in various behavioral studies. This suggests an important role for the α-adrenergic system in the mediation of some of the actions of PCP. Quirion and Pert (US National Institute of Mental Health) reported on the histochemical localization of PCP receptors in the rat brain. PCP binding was especially high in the hippocampus and neocortex. They also showed that DA_2-receptors, as measured by labelled spiperone, decreased with chronic PCP administration in a manner consistent with PCP induced DA release or blockade of DA uptake. Especially exciting was their report of the isolation of a peptide substance of small molecular weight which was a potent endogenous ligand of the PCP receptor. They named this peptide 'angeldustine'. The finding of endogenous peptides that displace PCP from its receptor was also reported by Vincent and associates and the Zukins.

Morre and associates (Sanofi) used guinea-pig brain membranes to show that PCP displaces [^{3}H]ethylketocyclazocine from its low affinity binding site. This site, which is insensitive to naloxone, may represent the σ-opioid receptor. Two other sites of high affinity for ethylketocyclazocine not affected by PCP may represent κ-opioid or benzomorphan sites. Kamenka, Geneste and coworkers demonstrated by ^{13}C-NMR spectroscopy that the stereoisomers in the 4-aryl-4-piperidino-1-phenethyl cyclohexanol series of hydrochloride salts are easily distinguishable by the chemical shifts of the methylene group α to the cyclohexane ring.

Rondoin, Baldy-Moulinier and associates (Montpellier) have recorded cortical and hippocampal EEG activity in chronic rats. PCP (2–5 mg kg^{-1}), or its active analogues, produced awake EEG activity associated with locomotor stimulation during the first hour following i.p. injection. Slow wave sleep and, finally, paradoxical sleep reappeared later. No changes in θ-activity were observed. Levine (University of California, Los Angeles) reported that chronic PCP treatment in doses of 1–2 mg kg^{-1} produced marked behavioral effects in developing kittens. He compared the effects of chronic low doses of PCP with single larger doses of PCP, two of its metabolites, 1-phenylcyclohexylamine, *N*-(5 - hydroxypentyl) - 1 - phenylcyclohexylamine, and the PCP analog *N,N*-diethyl-1-cyclohexylamine. The most intense PCP induced motor responses in kittens 30–50 days of age, consisted of waxy rigidity. The *N,N*-diethyl analog produced less intense effects. The two PCP metabolites were less active, with the alcohol derivative being the least potent.

Lozovsky, Kopin and associates (US National Institutes of Health) reported that PCP caused a rapid dose-dependent suppression of plasma prolactin in rats. Tolerance to this effect was observed following daily PCP for 28 days. They also showed that chronic PCP caused an 18% decrease in the B_{max} for [^{3}H]spiperone binding with no change in the K_D. Thus, a decrease in DA receptors might be responsible for the observed tolerance to the acute suppressive effect of PCP on plasma prolactin. However, there was no tolerance to the locomotor stimulant effects following 28 days of PCP administration in rats. The (+)-isomer of 1-(1-phenylcyclohexyl)-3-methylpiperidine was more potent in reducing plasma prolactin than its (−)-isomer. Their study suggested a PCP agonist action on the DA system to which tolerance can develop, but also a more complex effect on locomotor activity.

It was concluded after four days of intensive presentations and discussions that PCP and related arylcyclohexylamines are a very rich and fertile subject of research that can lead to a better understanding of neurobiology, and possibly new therapeu-

tic agents, particularly in the form of ultrashort acting anesthetics and analgesics with less respiratory depression. Such short acting agents would probably be less abused than longer acting compounds like PCP itself, with metabolites that irreversibly bind to proteins. The ultimate question still remaining unanswered after the meeting was why are there PCP receptors and related endogenous peptide ligands in the brain? For what purpose? Are they there to produce a dissociated mental state following severe trauma or stress?

EDWARD F. DOMINO
Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109, USA.

JEAN-MARC KAMENKA AND PATRICK GENESTE
Université de Montpellier, Ecolé Nationale, Supérieure de Chimie, Montpellier, France.

Current awareness series

Key developments in pharmacology

Conformation–activity study of 4-phenylpiperidine analgesics

In the light of the original hypothesis[1] that analgesic 4-phenylpiperidines should have their phenyl ring in an axial position on the piperidine ring, in analogy with the rigid polycyclic analgesics such as morphine, it is rather puzzling to note that over the years an impressive amount of experimental data has accumulated which shows, almost without exception, that the phenyl ring is in an equatorial position. In fact, X-ray crystallographic analysis, nuclear magnetic resonance data and quantum chemical calculations indicate that compounds structurally related to pethidine and prodines, have their phenyl rings in an equatorial position on the piperidine ring.

The fact that the various diastereoisomers of prodines and prodine-like analgesics show marked enantiomeric and diastereoisomeric potency differences, make these compounds extremely valuable for gaining a better understanding of receptor and receptor-induced events. As the question of axial v. equatorial phenyl has not yet been satisfactorily settled, Froimowitz[2] addressed the problem of the energy differences between phenyl equatorial and phenyl axial conformers in various 4-phenylpiperidine analgesics.

The conformational energy of pethidine **I**, ketobemidone **II**, α-prodine **III**, β-prodine **IV** and 1,3,4 - trimethyl - 4 - phenylpiperidines **V** was studied using the MM2 (Molecular Mechanics II) program developed by Allinger and co-workers[3]. The MM2 program is based on force-field calculations, and therefore offers the distinct advantage of speed of calculation over even the fastest semi-empirical quantum chemical calculation, such as PCILO (Perturbative Configuration Interaction using Localized Orbitals). Owing to its speed, this method of calculating empirical potential functions allows the user to minimize a structure with respect to all internal coordinates (bond lengths, bond angles and torsion angles).

Phenyl equatorial conformations were found to be preferred for **I** and **II** over the phenyl axial conformation by only 0.6 and 0.7 Kcal mole^{-1} respectively. The energy differences between the phenyl equatorial and axial conformers were calculated to be 1.9, 2.8 and 3.4 Kcal mole^{-1} in favour of the phenyl equatorial conformers for 3-demethylprodine, α- and β-prodine (**III, IV**) respectively. A phenyl axial conformer was calculated to be preferred by 0.7 Kcal mole^{-1} for the 3-demethyl derivative of **V** whereas the phenyl equatorial conformers were preferred by 1.3 and 3.3 Kcal mole^{-1} for the α- and β-compounds (**V**).

The results clearly show that the equilibrium distribution of phenyl equatorial:axial is quite variable, and depends on the nature of the substituent on the 4-position and the presence or absence of a substituent in the 3-position.

The relatively small energy difference between the axial and equatorial phenyl conformers of **I** and **II** suggests that in solution there should be an appreciable population of phenyl axial conformers present. This would make the structure–activity relationships of **I** and **II** more similar to the rigid 4-phenyl axial morphinomimetics, such as morphine, where the introduction of a *meta* hydroxy group is known to enhance potency. A similar effect of the *meta* hydroxy group is known for **I** and **II**. The fact that a *meta* hydroxy group has a detrimental effect on the analgesic activity of the prodines is in accord with the present calculations indicating that the phenyl axial conformation populations are virtually nonexistent. It is noted, however, that **I** and **II** are still different from the rigid 4-phenyl axial morphinomimetics, since *N*-allyl groups do not convert them into antagonists.

Whether the phenyl axial conformation is intimately connected with the presence of a *meta* hydroxy group is, however, still not settled, owing to the observation that phenylmorphans contain a *meta*-hydroxylated phenyl in a fixed equatorial position.

The present study of Froimowitz clearly suggests that a 3-methyl substituent on the piperidine ring strongly governs the prefer-