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'Signer Drugs' are substances intended for recreational use which are derivatives of approved drugs so as to circumvent existing legal restrictions. The term as popularised by the lay press lacks precision. Contrary to the popular belief that 'designer drugs' are original creations, the majority of these agents are 'borrowed' from legitimate pharmaceutical research. They merely represent the most recent developments in the evolution of mind-altering chemicals.

The most extensively studied class of psychoactive compounds is the phenylethylamines (mesoline analogues). This class includes catecholamines, therapeutic agents and numerous illicit derivatives. Subtle alterations of the phenylethylamine molecule give rise to a spectrum of pharmacological properties ranging from pure sympathomimetic stimula-
The term ‘designer drug’ was first coined by Dr Gary Henderson, a pharmacologist at the University of California at Davis, to describe chemical congeners of illicit drugs synthesised with the purpose of circumventing the law. The expression, as it is used today, lacks precision. The concept of developing chemical congeners of therapeutically useful molecules, in essence ‘designing’ drugs, is a traditional and fundamental activity of the pharmaceutical industry. The implication that the ‘street chemist’ can produce a made-to-order drug to place restricted ones by way of innovative research is generally incorrect. The majority of abused substances available for recreational use are ‘developed’ from legitimate pharmaceutical research. With a reasonable knowledge of chemistry, it is difficult for an interested individual to gather necessary information from various professional publications to synthesise any number of psychoactive compounds. Although media publications have dealt with the implications that the ‘street chemist’ can produce a made-to-order drug to place restricted ones by way of innovative research, the concept of not including new forms of drugs, such as cocaine, can have a base form (crack), does not refer to ‘Designer Drugs’ or ‘Blues’ (tadwil cocaine or amphetamine) and ‘research’ (coca at.

If the term ‘designer drugs’ is used, it is important to clarify the intended meaning, perhaps by adding the phrase ‘restricted drugs’ or ‘new psychoactive substances’. This would also help those who use recreational drugs. It is easy to see why this is so fine for substances that the determination of the user’s clinical presentation is similar to that of amphetamine overdose characterised by tachycardia, hypertension, hyperthermia, diaphoresis, mydriasis, agitation, muscle rigidity, and hyper-reflexia. Death usually results from arrhythmias, hyperthermia or intracerebral haemorrhage. Treatment is aggressive and supportive with careful attention to temperature, blood pressure and seizure control.

Synthetic opioid derivatives, which represent the second major class of ‘designer drugs’ are derivatives of fentanyl (e.g. 3-methylfentanyl, 3-ethylfentanyl) or pethidine (meperidine) and are extremely potent compounds responsible for numerous overdose deaths. Attempts to synthesise pethidine have resulted in the accidental production of MPTP and methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a compound which is metabolised in the brain by the monoamine oxidase system to a toxic intermediate (MPPP) which selectively stops the substantia nigra, resulting in the rapid onset of severe Parkinsonian symptoms. Naloxone will antagonise the opiate effects of this drug class, although high doses may be required.

Arylhexylamines constitute the third class of ‘designer drugs’. The predominant member of this class is phencyclidine (PCP), a derivative of the anaesthetic ketamine. This unique class of psychoactive agents exhibits broad and complex pharmacological effects. Overdose may result in extreme agitation, psychosis, sympathomimetic excess, hyperthermia and CNS and respiratory depression. Supportive care, benzodiazepines, haloperidol, and repeated doses of activated charcoal are the mainstay of treatment.

Methaqualone derivatives comprise the fourth class of ‘designer drugs’. Although commonly abused, especially in regional waves of popularity and availability, these primarily sedative agents rarely result in intoxication more serious than general central nervous system (CNS) depression.

The toxicology laboratory has a limited role in the evaluation of intoxication from designer drugs. Most laboratories do not have the capability to rapidly and accurately assay these synthetic analogues, nor are there sufficient data to aid in the interpretation of measured drug concentrations when available. Instead, the clinician must evaluate the intoxicated patient based on clinical presentation and routine laboratory measurements.

In the future, further derivatives of these classes may appear in recreational use and perhaps new classes will emerge. The line between legality and illegality is so fine for substances that the determination will need to be made in court. Potential therapeutic uses of these agents will be difficult to explore because of their automatic designation as controlled substances. The practicing clinician must approach ‘designer drug’-intoxicated patients symptomatically and continually be alert for new or unusual presentation substance abusers.

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would lead one to believe that there are legions of 'designer drugs' either already in use or waiting to be 'developed' and 'marketed', in reality there have only been a few that have caused clinical concern. The concept of 'designer drug' specifically does not include new forms or new dosing routes of old drugs, such as cocaine used in the crystalline freebase form (crack). Nor does it include legal, although abused, alternatives to controlled substances: phenylpropanolamine, ephedrine, caffeine and butyl nitrite, for example. 'Designer drugs' also does not refer to such drug combinations as 'T's and Blues' (talin and trippelenamine), 'speedballs' (cocaine or amphetamine and heroin) or 'star search' (cocaine and phencyclidine). 

If the term 'designer drug' is to have any useful meaning, perhaps it should include reference to the intent of the user to circumvent legal restrictions. Bearing this in mind, the ensuing discussion will review those drugs which, (a) are novel derivatives even greater potency. The prototype psychoactive phenylethylamine molecule is the basic sympathomimetic potential of these agents maybe expanded to even predominant hallucinogenic ketamine. The pharmacological effects include the central nervous system and peripheral effects. Although central nervous system effects are often described as hallucinogenic, the prototype for the class is mescaline which selectively produces mescaline syndrome, although few are truly hallucinogenic. 

The term 'hallucinogenic amphetamine', while commonly used, is in fact a misnomer. At nominal psychoactive doses these compounds exhibit neither true hallucinogenic activity (visualisation of unreal objects) nor amphetamine-like stimulation. What are often referred to as 'hallucinations' are actually alterations in colour, colour intensity, texture, or the elaboration of 'fantasy' states. At larger doses, in overdose, the hallucinogenic and/or sympathomimetic potential of these agents may be expressed, sometimes with serious consequences. 

The prototype psychoactive phenylethylamine is mescaline (3,4,5-trimethoxyphenylethylamine), an alkaloidal component of the peyote cactus. Although peyote has been recognised for its psychoactive properties for centuries, it was not until 1896 that the structure of mescaline was identified, and subsequently synthesised in 1918. Structural modifications of the mescaline molecule have resulted in a plethora of psychoactive compounds. 

In 1947 researchers produced the first psychoactive analogue of mescaline, TMA (3,4,5-trimethoxymphetamine), with twice the psychoactive potency of mescaline (Shulgin et al. 1973). Experimentation with ring substitution produced compounds with even greater potency. The α-methylation of mescaline to produce TMA yielded a compound structurally similar to amphetamine, yet without profound sympathomimetic properties. Further research has produced many such hallucinogenic amphetamine' analogues (phenylisopropylamines), although few are truly hallucinogenic. 

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which have appeared in some of the world's most popular press, and which at least minimally available.

1.1 Methamphetamine

Methamphetamine is a common recreational drug. It is usually used in the form of a 'crystal' or powder, and its effects can be felt within minutes.

Concern has been raised about the potential for clandestine synthesis of methamphetamine, and concern about its use and effects has led to calls for increased regulation and control. The production and distribution of methamphetamine is illegal in most countries, and its use is associated with serious health risks, including addiction, overdose, and death.

As a class, the phenylethylamines share a number of similar pharmacological effects. The psychoactive effects often involve a feeling of euphoria, mood intensification and empathy, and may include the visual changes noted above which are often misinterpreted as hallucinations. Some phenylethylamines do produce true hallucinations, especially in overdose. Despite the structural similarity to amphetamine, gross sympathetic stimulation is not typical of recreational intoxication but instead frequently accompanies serious intoxication or overdose.

The number of mescaline analogues which have been chemically synthesised in research laboratories is enormous. Only a fraction of these compounds have been tested in humans, and the studies have been limited. Thus, for the majority of these compounds, human pharmacological and toxicological data are sorely lacking. The compounds discussed below represent those material

![Chemical structures of phenylethylamines.](image)

Key: TMA-2 = 2,4,5-trimethoxyamphetamine; DOM/STP = 4-methyl-2,5-dimethoxyamphetamine; PMA = para-methoxyamphetamine; DOB = 4-bromo-2,5-dimethoxyamphetamine; 2-CB/MFT = 4-bromo-2,5-methoxyphenylethylamine; MDA = 3,4-methylenedioxyamphetamine; MDMA = 3,4-methylenedioxymethamphetamine; MDEA = 3,4-methylenedioxyethylamphetamine.
which have appeared in recreational use and for which at least minimal toxicological experience is available.

### 1.1 Methamphetamine

Methamphetamine is perhaps the most commonly used phenylethylamine compound. Among recreational users it is known as 'speed', 'crank', 'meth' or 'crystal meth'. In the late 1960s and early 1970s it was also called simply 'crystal'. However, as the use of phencyclidine increased, confusion developed because the term 'crystal' was used to refer to phencyclidine. A patient who admits to the use of 'crystal' must be evaluated for exposure to either an amphetamine product or an arylhexylamine, such as phencyclidine.

The introduction of a methyl-group on the terminal amine of amphetamine produces methamphetamine, a compound with improved CNS penetration and a more prolonged duration of action. The pharmacological profile of methamphetamine is qualitatively similar to that produced by amphetamine, but may persist for 6 to 24 hours or more. In addition to CNS stimulation, the increased sympathetic tone due to methamphetamine may result in tachycardia, hypertension, intracranial haemorrhage, seizures, arrhythmias, hyperthermia and death (Delaney & Estes 1980; Kalant & Kalant 1975; Kojima et al. 1984).

Concern has been expressed regarding the toxicity of potential contaminants produced during the clandestine synthesis of methamphetamine (Noggle et al. 1985). The use of phenylacetic acid to produce phenylacetone, a precursor to amphetamine and methamphetamine under US Federal control, may also result in the production of $\alpha$-benzylphenethylamine and $\alpha$-benzyl-N-methylphenethylamine. These contaminants have marked convulsant properties as evidenced by studies in mice. Depending on the sophistication of the clandestine production facilities, these contaminants may contribute substantially to the overall toxicity of recreational methamphetamine use.

Lead may be a further contaminant of methamphetamine, which has resulted in at least 2 cases of acute lead intoxication (Allcott et al. 1987). One synthesis procedure involves generating phenylacetone by reacting lead acetate with phenylacetic acid. The subsequent material, if not carefully purified, can leave significant amounts of lead in the final methamphetamine product. Patients with such lead intoxication may present with gastroenteritis, anaemia, encephalopathy, myalgias or hepatitis. Common laboratory tests (blood lead concentrations, free erythrocyte protoporphyrin, urinary coproporphyrin) are useful to assess the degree of intoxication and need for chelation therapy.

### 1.2 TMA-2

The chemical structure and pharmacology of TMA-2 ($2,4,5$-trimethoxyamphetamine) resembles both mescaline, with respect to the ring substituents, and amphetamine, due to the methylation of the basic phenylethylamine structure. It was first synthesised in 1933 but its psychoactive potential was not recognised until 1962. A more potent psychoactive drug than mescaline, TMA-2 shows qualitatively similar effects on mood alterations and sensory enhancement as mescaline. The difference in the amount of drug causing the desired psychoactive effects and that resulting in toxicity is small (Shulgin 1976).

### 1.3 DOM/STP

The next amphetamine-analogue to be investigated following TMA-2, and which became available recreationally in 1967, was DOM ($4$-methyl-2,5-dimethoxyamphetamine). Users of this drug gave it the name 'STP', representing 'serenity, tranquility and peace'. High initial doses (10 to 20mg) with attendant untoward responses gave the drug an unfavourable reputation on the street and limited its acceptance (Shulgin 1977; Snyder et al. 1967).

As was noted for TMA-2, the therapeutic index of DOM is narrow (Snyder et al. 1967). Low doses of 2 to 3mg produce mild sympathetic stimulation, euphoria and perceptual distortions. Amounts greater than 5mg consistently produce a halluci-
natory reaction and more significant sympathetic stimulation.

1.4 PMA

Para-methoxyamphetamine (PMA) appeared as a recreational drug in the early 1970s, and was quickly associated with several fatalities (Cimbura 1974). The drug exhibits potent hallucinatory and stimulatory properties. Overdoses with PMA have been characterised by marked adrenergic excess. It appears from the history of these exposures that PMA was a contaminant or substitute for what was often thought to be MDA. It is not generally a sought after drug, but rather an example of a misrepresented street drug.

1.5 DOB

Laboratory research found that replacing a methyl-ring substituent of DOM with a bromo-group dramatically increased the psychoactive potency of the compound, termed bromo-DOM or simply, DOB. One of the most potent phenylethylamine compounds yet synthesised, DOB exhibits at least 100 times the potency of Mescaline (Buhrich et al. 1983). It is one of the few drugs, like LSD, that are sold as drug-impregnated pieces of paper.

The course of intoxication is quite prolonged. Onset of effect following 2 to 3mg is about an hour; full intoxication requires about 3 to 4 hours (Shulgin 1981). A fantasy state and mood enhancement with minimal visual distortions persists for about 10 hours, followed by a gradual resolution of effects over 12 to 24 hours.

Bowen et al. (1983) described a patient who developed diffuse, peripheral vasospasm after a large oral ingestion of DOB. Intra-arterial administration of tolazoline, followed by an intravenous nitroprusside infusion, reversed the vasospasm and the associated tissue ischaemia. Buhrich and colleagues (1983) described 2 DOB-intoxicated patients who developed severe agitation, hallucinations and sympathetic excess. Two deaths from DOB intoxication have been reported (Bohn 1981; Winek et al. 1981).

1.6 2-CB/MFT

Removal of the methyl group at the α-carbon of DOB results in the phenylethylamine analoge 2-CB or MFT (4-bromo-2,5-methoxyphenylethylamine). 2-CB/MFT has one-tenth the potency of DOB and, at ‘therapeutic’ doses, produces a relaxed mood and sensory altering effect. However, at high doses it can cause agitation and hallucinations. Hallucinations were described in a group of students drinking spiked punch, but no clinical details were given (Ragan et al. 1985). In San Francisco, 2-CB is known by the name ‘afterburner’.

1.7 MDA

3,4-methylenedioxyamphetamine (MDA) appeared in recreational use in 1967 as the ‘love drug’. It held the reputation of being a mild intoxicant producing feelings of empathy and euphoria with out frank hallucinations. Subsequent experience demonstrated that large doses can cause agitation, delirium and hallucinations.

A number of fatalities have been attributed to intoxication with MDA and confirmed by laboratory analysis. Cimbura (1972) reported 5 deaths in Canada related to the ingestion of MDA. All patients developed agitation and hallucinations; patients had seizures. Other reports of MDA related deaths have involved obtundation (Reed et al. 1972; Simpson & Rumack 1981) and hyperthermia (Likasewski 1979; Simpson & Rumack 1981). The case described by Simpson and Rumack (1981) is worthy of note. The patient presented with coma, seizures, hypertension, tachycardia, hyperthermia and opisthotonic posturing. Despite temporary stabilisation, the patient went on to develop hypotension, acidosis, rhabdomyolysis, disseminated intravascular coagulation, repeated cardiac arrests, and eventually died.

Shulgin and Jacob (1982) presented a warning regarding the potential misrepresentation of MDA Piperonylacetone, one of the starting materials for synthesising MDA, is an ambiguous term referring to either methylenedioxyphenylacetone or methylenedioxybenzylacetone, depending on the source of the chemical. will produce the di-oxybenzylacetone compound HMD man pharmacology, it has been show (Davis & Borne adverse effects an may have been d indication. Shulgin a recognise the pole section 2.3).

1.8 MDMA/M

A close relative methamphetamine in street use in 1980s, first as an as a substance of a concentrated in Cal York (Siegel 1986: ‘Ecstasy’, but is a

Psychologists hance the psychoth & Cole 1987; Gr & 1987), and it was th was ‘rediscovered’. markable facilitat mal adverse effestimation. Patients claim mild intoxic increased self-esteem perception alteration. Because of increases MDMA was placed drugs (along with h the Comprehensive use has diminish Clinical studies c uncontrolled trials (1 1986) and descripti
One of the chemical. The use of the former chemical will produce the desired MDA, but methylene-dioxybenzylacetone will generate the unexpected compound HMDA. Little is known about the human pharmacology of HMDA; however, in mice it has been shown to be more toxic than MDA (Davis & Borne 1984). Conceivably, some of the adverse effects and fatalities associated with MDA may have been due to inadvertent HMDA intoxication. Shulgin and Jacob (1982) were the first to recognize the potential toxicity of synthetic errors, as was later confirmed in the case of MPTP (see section 2.3).

1.8 MDMA/MDEA

A close relative to MDA, 3,4-methylenedioxymethamphetamine (MDMA), was first identified in street use in 1972 (Gaston & Rasmussen 1972). Although first patented in 1914, MDMA did not become widely used until the late 1970s and early 1980s, first as an adjunct to psychotherapy, then as a substance of abuse. Its use has been primarily concentrated in California, Texas, Florida, and New York (Siegel 1986). MDMA is most often called Ecstasy, but is also known as Adam, XTC, MDM, and M & M. Psychologists have long sought a drug to enhance the psychotherapeutic experience (Chiarello & Neill 1987), and it was through these efforts that MDMA was ‘rediscovered’. Therapists have claimed remarkable facilitation of psychotherapy with minimal adverse effects beyond mild sympathetic stimulation. Patients receiving 50 to 125mg MDMA claim mild intoxication, with euphoria, empathy, increased self-esteem and occasionally mild visual perception alterations, but no true hallucinations. Because of increased recreational use, in 1985 MDMA was placed on the US list of Schedule I drugs (along with heroin, LSD, and others) under the Comprehensive Crime Control Act of 1984, and its use has diminished since then (Shulgin 1986).

Clinical studies of MDMA are limited to a few uncontrolled trials (Downing 1986; Greer & Tolber 1986) and descriptive reports (Siegel 1986) which mostly focus on psychoactive effects. MDMA consistently causes anorexia, bruxism, increased blood pressure and heart rate, diaphoresis, blurred vision, and ataxia. It may also cause nausea, anxiety, insomnia and, often as a delayed effect, lethargy.

There have been several reported deaths attributed to MDMA, though most have not had laboratory confirmation. Of the 5 deaths reported by Dowling et al. (1987), only 1 seemed to be the result of a direct drug effect (ventricular arrhythmia), while the other 4 had either significant underlying diseases which were exacerbated by the drug (asthma, coronary artery disease, cardiomyopathy) or died of trauma while intoxicated. The authors were involved in managing 1 patient who suffered hyperthermia, high output heart failure, disseminated intravascular coagulation and toxic hepatitis, but survived without residuum (Brown & Osterloh 1987; Hayner & McKinney 1986).

After MDMA became restricted, an N-ethyl congener, ‘Eve’ (3,4-methylenedioxymethamphetamine, MDEA), became popular. Experience with this drug is limited although 2 of the deaths reported by Dowling were associated with MDEA use. The use of both MDMA and MDEA has diminished since they became restricted, although the drugs still appear on the streets sporadically and some psychiatrists are still using them.

1.9 Clinical Toxicology of Phenylethylamines

The various types of phenylethylamines exhibit interesting qualitative differences in the psychoactive experience produced at nominal doses. However, in overdose the underlying potential of these drugs for hallucinogenic effects and, more importantly, sympathomimetic excess becomes evident. Adverse reactions to therapeutic doses and overdoses seem to follow a limited, fairly well described pattern typified by amphetamine, the most extensively studied and reported phenylethylamine.

In overdose, phenylethylamine derivatives act as sympathomimetic agents, stimulating α- and β-adrenergic receptors to various degrees, depending on the specific compound. The differences in their
psychoactive effects are blurred by the predominance of the sympathetic nervous system effects. Clinically, one sees anxiety, agitation, anorexia, nausea, bruxism, tremors, muscle rigidity, hyperreflexia, midriasis, diaphoresis, tachycardia, hypertension, and hyperthermia. In severe cases, a hyperdynamic cardiovascular collapse may occur.

Laboratory anomalies may include leucocytosis, hyperglycaemia and elevated concentrations of serum creatine phosphokinase (CPK). Increases in serum sodium, chloride and blood urea nitrogen (BUN) may occur, indicating dehydration, as well as lowered concentrations of bicarbonate due to hypermetabolism and impaired perfusion. Elevated levels of serum phosphate, uric acid and potassium can occur due to rhabdomyolysis.

Further complications of acute overdose include seizures (either single or multiple), arrhythmias (supraventricular or ventricular), intracerebral haemorrhage (secondary to a sudden increase in blood pressure with or without underlying cerebral vascular abnormalities such as a berry aneurysm or arteriovenous malformation), muscle rigidity with rhabdomyolysis (without localised muscle trauma), hyperthermia (usually associated with increased muscular activity or rigidity), which may lead to disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (ARDS), acute renal failure, hepatocellular necrosis and coma (Ginsberg et al. 1970; Simpson & Rumack 1981). Most severely intoxicated patients will present with a combination of the above complications, most commonly supraventricular tachycardia, hyperthermia, and seizures, a combination which can easily be fatal without immediate appropriate treatment.

Additional reported complications from short or long term use include cardiomyopathy (Ayers 1983, Call et al. 1982), diffuse vascular spasm, which may lead to mesenteric ischaemia or necrosis (Bowen et al. 1983), and pyrogenic reactions with chills, fever, shock, diarrhoea, DIC, and rhabdomyolysis (Kendrick et al. 1977).

Phenylethylamine derivative overdoses must be treated as medical emergencies. A rapid assessment of the psychological, neurological and haemodynamic status of the patient must be performed, including rectal temperature. Agitated patients may need to be restrained in order to be properly assessed. If the drug was ingested, gastric lavage (with appropriate airway protection) followed by the administration of activated charcoal is necessary.

Further therapy depends on which signs and symptoms predominate. β-Adrenergic blocking drugs, e.g. propranolol and esmolol, are effective agents in controlling tachycardia but should not be used to treat hypertension alone. Hypertension may be treated with α-receptor blockers (e.g. phentolamine), combined α- and β-blockers (e.g. labetalol) or vasodilators (e.g. nifedipine or nitroprusside), depending on the patient’s status. The presence of tachycardia and hypertension may be treated by a mixed α-, β-antagonist. In all situations, a rapidly acting, easily titratable drug, preferably intravenously administered, should be selected. Nifedipine is an oral calcium channel blocker with vasodilating properties, lowers blood pressure rapidly if the capsule is punctured and the liquid contents held sublingually.

Occasionally, blood pressure cannot be controlled without first controlling agitation with a benzodiazepine. This should be done cautiously, as mental status is an important parameter to follow in case of a CNS catastrophe; however, the availability of flumazenil, a new benzodiazepine anticonvulsant, may obviate this concern.

Hyperthermia is a frequent complication, especially in fatal overdoses. Temperatures above 40°C are not uncommon, and require urgent therapy. The most effective way to lower temperature is by application of tepid water and fanning. If this procedure is not effective then muscle paralysis with pancuronium, with proper airway protection, is recommended (Olson & Benowitz 1984). Dantrolene may be administered if the preceding measures are ineffective. Salicylates, paracetamol (acetaminophen) and cooling blankets are too slow and should probably be avoided.

Most amphetamine, MDMA, and other amphetamine derivative-associated deaths occur early and have been from arrhythmias, hyperthermia with seizures (which can be fatal), cerebrovascular damage, acute intracerebral haemorrhage, or resulted from exacerbation of pre-existing diseases such as cardiac disease, and asthma.

Hyperventilation induced by breathing into a weak base in the urine precipitating myoglobinuria, the rhabdomyolysis, sent to some degree. Administration (hepatic metabolism) lowers blood pressure rapidly if the capsule is punctured and the liquid contents held sublingually.

Patients who prese without significant affective therapy. Agitation activity respond well with lucubrations and para without significant agitative antipsychotic propulal. Adverse reactions represent either an (possible malignant h) the authors in one of in an drink underlying c coronary artery disease valve prolapse, berry malformation.

Chronic abuse may clinically indistinguishable though it is usually a drug-free state. Concerns regarding the possible use of these drugs.
Designer Drugs’

must be per. with seizures (which may lead to DIC, hepatocellular damage, acute renal failure, or ARDS), or intracerebral haemorrhage. Some deaths have resulted from exacerbation of underlying or occult diseases such as cardiomyopathy, coronary artery disease, and asthma, or from trauma related to behaviour induced by the intoxication. Delayed deaths are usually from complications of the acute intoxication or from inadequate gastrointestinal decontamination.

Enhancing elimination is difficult to do safely in severely intoxicated patients. Although the renal clearance of these drugs can be enhanced by acidifying the urine to trap the charged moiety of the weak base in the urine, this increases the risk of precipitating myoglobin in the renal tubules from the rhabdomyolysis, which is almost always present to some degree. While the routes of elimination (hepatic metabolism versus renal excretion) and the elimination half-life may vary with each compound from 4 to 36 hours, most patients will show marked improvement within the first 24 hours. Some may have residual effects such as sleep disturbances, tachycardia, anorexia, and tremor for several more days.

Patients who present primarily with CNS effects without significant autonomic effects require different therapy. Agitation and anxiety with hyperactivity respond well to benzodiazepines. If hallucinations and paranoid psychosis predominate without significant agitation or hyperactivity, traditional antipsychotics such as haloperidol are useful. Adverse reactions to ‘therapeutic doses’ may represent either an idopathic hypersensitivity (possible malignant hyperthermia, as observed by the authors in one instance) or an uncovering of an occult underlying disease such as hypertension, coronary artery disease, cardiomyopathy, mitral valve prolapse, berry aneurysm, or arteriovenous malformation.

Chronic abuse may lead to a paranoid psychosis clinically indistinguishable from schizophrenia, although it is usually reversible after a prolonged drug-free state. Concern has also been expressed regarding the possible neurotoxic effects of chronic use of these drugs. Ricaurte et al. (1985) first reported that MDA, likeamphetamine and methamphetamine, has neurotoxic potential. These workers demonstrated that high doses of MDA in rats destroyed serotonin nerve terminals. More recently, high doses of MDMA in rats produced a similar serotonergic neurotoxic effect (Schmidt et al. 1986). How these findings relate to the neurotoxic potential in humans remains to be seen.

2. Synthetic Opioids

Increased law enforcement activity in the US in the late 1970s reduced the amount of imported opium and heroin to the extent that shortages occurred. The response to the diminished availability of heroin was the search for synthetic alternatives which circumvented legal restrictions. Because of the difficult process of synthesising morphine-related compounds, effort was instead focussed on creating the more easily synthesised analogues of fentanyl and pethidine (meperidine).

2.1 Fentanyl Derivatives (fig. 2)

The summer of 1980 saw the introduction of the first ‘street-synthesised’ opioid material, a derivative of fentanyl, an analgesic used in anaesthesia, sold as ‘synthetic heroin’ or ‘China White’ (Ayres et al. 1981; Brittain 1982). The exceedingly high potency of the material led to several deaths in which no narcotic material could be detected in either the drug samples or the patients. The ultimate identification of the opiate as α-methylfentanyl proved to be a rigorous exercise in forensic toxicology (Kram et al. 1981).

A further homologue, 3-methyl-fentanyl (3MF), has recently appeared in illicit opiate samples (Cooper et al. 1986). 3MF is approximately 16 times as potent as fentanyl, which translates to a potency about 1600 times that of heroin. Other analogues of fentanyl which have appeared in recreational use include para-fluorofentanyl and α-methylacetylfentanyl. Since the late 1970s, 9 homologues have appeared in illicit use, with potencies probably between the extremes of fentanyl and 3MF.
2.2 Clinical Toxicology of Fentanyl Derivatives

Fentanyl is a specific µ-opiate receptor agonist with approximately 100 times the potency of morphine. The highly lipophilic nature of the drug results in rapid penetration of the CNS; the onset of subjective effects is within 90 seconds of intravenous administration. Plasma concentrations of fentanyl rapidly decline as the drug is both metabolised and distributed into tissues. Repeated doses of fentanyl lead to accumulation of the drug and its respiratory depressant effect. Prolonged or recurrent respiratory depression may occur due to fluctuating serum concentrations of the drug as it is eliminated. The receptor binding characteristics and pharmacokinetics of α- and 3-methylfentanyl are not known; however, they appear to be clinically similar to fentanyl.

Users of 'China White' (α-methylfentanyl) describe a qualitatively different psychoactive effect from that of heroin. 'China White' produces more analgesia than euphoria, yet the euphoria lasts 2 to 4 hours; a longer effect than for heroin. The classical symptoms of miosis and CNS and respiratory depression are observed in 'China White' intoxication as for heroin. Fatalities due to intoxication with fentanyl derivatives are due to respiratory arrest; patients are often found with the needle still in their arms. Naloxone is a specific antagonist for the CNS- and respiratory-depressant effects of fentanyl and its analogues, but high doses (2 to 10mg) may be required.

2.3 Meperidine Derivatives

One of the most fascinating and tragic episodes with 'designer drugs' resulted from a laboratory synthetic error in the San Jose, California area. In an attempt to synthesise MPPP (1-methyl-4-phenyl-4-propionoxypiperidine), a synthetic analogue of meperidine, an illicit chemist accidentally made a product contaminated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) which led to an 'epidemic' of parkinsonism among intravenous drug abusers.
Injection of MPTP-contaminated samples resulted in local burning and pain and an atypical, more dysphoric and 'spacey' high, occasionally with transient visual distortions and visual or auditory hallucinations. Within several days of repeated injections of what users thought was a new synthetic heroin, some patients developed the rapid onset of a severe form of parkinsonism with akinetic movements approaching catatonia, fixed facial expression and stare ("masked facies"), drooling, difficulty swallowing, hypophonia, 'lead pipe' rigidity with cogwheeling, and a shuffling gait with en bloc turning. Tremor was present to a variable degree. Other signs were normal, including cognition (Ballard et al. 1985).

Although only 7 known severe cases were studied during this epidemic, hundreds of other intravenous drug abusers were exposed and some have lesser forms of parkinsonism (Ballard et al. 1985; Langston et al. 1983, 1984).

In addition, other cases involving chemists have been seen (Burns et al. 1985). A probable eighth severe case was seen in May, 1987 in San Francisco by the authors, 2 years after the last MPTP confiscation by the Drug Enforcement Agency (DEA) in Florida (Frank, personal communication).

### 2.4 Clinical Toxicology of MPTP

MPTP-induced parkinsonism is more specific in its neuropathology than classic, idiopathic Parkinson's disease. The idiopathic form tends to have more widespread brain pathology, Lewy bodies, dementia, and decreased cerebrospinal fluid MHPG (3-methoxy-4-hydroxyphenylglycol, the major brain metabolite of noradrenaline) in contrast to the elevation seen in the MPTP-induced form. Both forms have similar clinical syndromes, loss of dopaminergic neurons in the substantia nigra, and decreased levels of HVA (homovanillic acid), the major dopamine metabolite in the brain (Fruncillo 1986).

All the patients studied have responded to some degree to standard anti-Parkinsonian medications; however, they have tended to develop the typical complications of levodopa therapy and have become increasingly severe management problems (Langston 1985). The long term prognosis of the exposed, but so far unaffected, patients is unknown. Additionally, intellectual changes have developed in MPTP-induced parkinson patients (Stern & Langston 1985).

While MPTP has been a catastrophe for the patients involved, its discovery has been a boon to neuroscientists. Research has shown that MPTP is metabolised in the brain by monoamine oxidase B (MAO-B) to MPP+ (1-methyl-4-phenylpyridinium ion) which selectively destroys the zona compacta of the substantia nigra (Langston 1985; Langston & Ballard 1984). However, pretreatments with the MAO-B inhibitor deprenyl (selegeline) protects against the neuronal damage of MPTP in certain models. MPTP is the first chemical substance known to cause a site-specific neurotoxic lesion and it is also the first example of a molecule metabolised in the brain to a toxic substance. MPTP now provides an ideal tool for Parkinson's disease research.

### 3. Arylhexylamines

The arylhexylamines, of which phencyclidine (PCP) is the most widely abused, represents a distinct class of psychoactive compounds. Phencyclidine and its related analogues, including the licit anaesthetic ketamine, exert effects on a variety of neurotransmitter systems: muscarinic receptor blockade, acetylcholinesterase inhibition and agonist actions at dopaminergic, adrenergic and opiate receptors. The complex pharmacological properties of the arylhexylamines produce a confusing array of symptoms in the intoxicated patient.

The ease with which arylhexylamines can be synthesised may lead to even more analogues appearing in the future. It is known that structural modifications can alter the potency (Shannon et al. 1983) and the affinity of the analogue for various receptors (Kamenka et al. 1982). A variety of ketamine analogues have been studied, including the thiophene analogue tiletamine, which conceivably may become available on the street. The physio-
logical effects these compounds will have upon humans remains to be determined.

3.1 Phencyclidine Analogues

A number of synthesis procedures are available to the 'street' chemist to produce phencyclidine and related arylhexylamine analogues (Shulgin & MacLean 1976). An intermediate product, PCC (pipеридиноксициклогексанкарбонitrile), as well as several end-product analogues, TCP (a thiophene analogue of PCP) and PCE (an N-ethyl analogue) have appeared in recreational use. Concern has been expressed that the labile cyano-group of PCC can be liberated upon heating (Soine et al. 1979). PCC may represent 10 to 70% of a phencyclidine sample, depending on the sophistication of production. Soine and colleagues (1979) have hypothesised that smoking large amounts of such material may release sufficient amounts of cyanide to produce toxic effects, but this remains to be proven. Little is known about the pharmacological properties of PCC itself.

PCE appeared in Los Angeles in 1969 as a substitute for PCP, though with greater potency. TCP, which first appeared in San Francisco in 1972, was found to be more potent than PCP itself, yet qualitatively similar in effect. It was included in the Controlled Substances Act in 1975. PHP (phenylcyclohexylpyrrolidine) has appeared as an abused substance in Los Angeles, with clinical effects similar to that of PCP (Budd 1980a; Giannini & Castellani 1982; Nakamura et al. 1979), although it has also been reported to cause an unacceptable degree of sedation (Shulgin & MacLean 1976). The use of pyrrolidine to manufacture PHP allows the 'street' chemist to circumvent the restriction on the sale of piperidine needed to make PCP. Further, PHP could not be detected by the methods originally used in Los Angeles county to assay for PCP.

Phenylcyclohexyl-4-methylpiperidine was identified from a street sample presumed to be PCP (Soine et al. 1982). This compound is synthesised using 4-methylpiperidine instead of the restricted piperidine. Human pharmacological data are lacking; however, in mice it was shown to have one-eighth the potency of PCP, yet was only 1.4 times less toxic. Doses required to produce phencyclidine-like behavioural effects could more easily produce toxic effects compared with PCP.

3.2 Clinical Toxicology of Arylhexylamines

The psychoactive and somatic effects of phencyclidine are dose related. Low doses produce sedation, euphoria and a feeling of depersonalisation accompanied by signs of sympathetic stimulation. Horizontal and/or vertical nystagmus is a common finding at this stage. The anaesthetic property of the drug dampens the perception of pain.

As the dose is increased the patient becomes more agitated, combative and paranoid. Violent behaviour is not uncommon in this setting. The sympathetic stimulation noted at lower doses is intensified. Hypertension is typically encountered accompanied by tachycardia, hyperthermia and hyperreflexia. The patient's course may be complicated by seizures, acidosis and rhabdomyolysis. Seizures are responsive to diazepam. Amines. Seizures are responsive to diazepam. Acidosis usually corrects spontaneously if seizures hyperthermia and excessive muscle activity are controlled. Hyperthermia is an important complication to detect and treat promptly, as it is a frequently overlooked sequela of moderate to severe intoxication.

Urinary acidification of phencyclidine has been shown to increase the risk of excretory myoglobinuria. Methaqualone has been reported to cause an unacceptable degree of sedation, euphoria and a feeling of depersonalisation accompanied by signs of sympathetic stimulation. Horizontal and/or vertical nystagmus is a common finding at this stage. The anaesthetic property of the drug dampens the perception of pain.

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Urinary acidification to enhance the elimination of phencyclidine is no longer recommended. The risk of exacerbating an existing acidaemia and precipitating myoglobin in the renal tubules outweighs the increased renal elimination of a drug that is predominantly hepatically metabolised. The severely intoxicated patient who would potentially benefit the most from enhanced drug elimination is also at greatest risk from acidification therapy. Instead, because significant quantities of phencyclidine undergo gastrointestinal recirculation, repeated doses of activated charcoal may be administered to adsorb the phencyclidine secreted in gastric juice. Continuous nasogastric suction is not recommended because of potential electrolyte imbalances. Haemodialysis is ineffective due to the large volume of distribution of phencyclidine.

4. Methaqualone Derivatives

Methaqualone has enjoyed a long-standing popularity as an intoxicating sedative, first as ‘quaalude’, then as illicitly produced tablets from diverted pharmaceutical methaqualone when legitimate prescription sources diminished. Subsequently, as the supply of diverted methaqualone has become more difficult to obtain, illicit suppliers have turned to synthetic production.

The synthesis of methaqualone and related quinazolinones is not difficult (Angelos & Meyers 1985; Soliman et al. 1978) and obviates the need for exogenous sources of methaqualone. Two homologues of methaqualone (mecloqualone, nitromethaqualone) which have been in clinical use in Europe are reported to be synthesised by clandestine laboratories in the United States (Daenens & Van Boven 1976).

Intoxication is typified by ataxia and lethargy, although initially a period of disinhibited stimulation may be noted. Overdose may result in coma and muscle hyperactivity. Marked respiratory depression is not commonly encountered. Nitromethaqualone has approximately 10 times the sedative potency of either mecloqualone or methaqualone. Treatment is supportive in nature.

5. Role of the Toxicology Laboratory

Efforts to identify ‘designer drugs’ by toxicological analysis are hampered by the inability of most laboratories to separate these drugs from the parent compounds they are modelled from. A further limitation is the lack of sufficient assay sensitivity to detect these drugs in the low concentrations in which they occur in human serum. Common procedures utilizing radioimmunoassay (RIA) or high-pressure liquid chromatography (HPLC) often lack both the sensitivity and specificity to conclusively identify these compounds. In general, the utility of ‘tox screens’ is sorely lacking, and specific assay capabilities, if they are available, are not of immediate use to the clinician faced with an intoxicated patient. Furthermore, no reliable serum concentration-response studies in humans have been performed by which serum measurements could be interpreted even if they were available. Autopsy data are equally difficult to interpret.

The limitations of toxicological analysis may be exploited by both the ‘street chemist’ and the recreational user. A consequence of the extreme potency of the fentanyl derivatives is that serum concentrations are too low to reliably measure even if one knew to look for a fentanyl product and not heroin. Users of phencyclidine who wish to avoid detection by the Roche RIA assay for PCP will tend toward products such as PHP with limited cross reactivity (Budd 1981). Similarly, nitromethaqualone is not strongly reactive using the Roche RIA assay for methaqualone, but can be analysed for when sufficiently large concentrations exist (Budd 1980b).

6. Legal Considerations

In the wake of the dramatic rise in the illicit manufacturing and recreational use of various psychoactive mescaline analogues in the late 1960s, the US Congress enacted the Controlled Substances Act. The provisions of this legislation attempted to halt the ‘street’ production of substances deemed to have no medicinal value and high abuse potential. The response to this by illicit
manufacturers was to search for other compounds which demonstrated similar pharmacological properties as the 'scheduled' drugs, yet which were not listed under the Controlled Substances Act. The Drug Enforcement Agency soon found itself in the difficult position of attempting to identify new substances of abuse and rapidly include them in the Act.

In response to this dilemma, the US Drug Enforcement Agency has restructured its approach to the control of illicit substances. In place of the reactive approach of placing new abused substances under restricted status as they appear, a more prospective method has been adopted in the form of an amendment to the Controlled Substances Act. This amendment, entitled the Controlled Substance Analogue Enforcement Act of 1986, places under Schedule I restriction those chemicals which: (a) have structures similar to those of existing Schedule I or II drugs, (b) are stimulants, depressants or hallucinogens, or (c) are represented as such. Human research with these compounds will be allowed by means of approved new drug applications or exemptions for investigational use.

During the development of legislation aimed at curbing the abuse of 'designer drugs', concern has been expressed that legitimate research with these compounds will be stifled. The outcry from the medical community claiming a medical use for MDMA took the Drug Enforcement Agency by surprise when it attempted to place MDMA under Schedule I status. While the present amendment to the Act allows for investigational uses, few pharmaceutical companies are likely to be interested in studying compounds unpatentable and easily manufactured by unsophisticated laboratories.

The present Controlled Substances Act amendment, by addressing the issues of both structural similarity and intent, renders the term 'designer drug', with its current meaning, obsolete. Whether illicit chemists will truly design novel compounds to circumvent these restrictions or find other means to evade the current constraints remains to be seen.

The current law has yet to be tested in the courts. Problems with interpretation can be anticipated as new compounds appear (see section 7).

7. Future Trends

Despite the Controlled Substance Analogue Enforcement Act, further analogues are expected to appear in recreational use. One direction in which interest has been generated is toward phenylethylamine materials in which the α-methyl group which gives the material an amphetamine-like structure, is removed. Specifically, the 2-carbomethoxy analogue of DOB and DOM, 2-CB and 2-CO, respectively, are potent agents which produce euphoria, increase sensory receptiveness and integrate sensory perception with the emotional state (Shulgin 1979). Cautious experimentation is warranted since other compounds in this series, notably 2-CI and 4-thiomescaline, have been associated with intense hallucinatory experiences and psychotic reactions.

Already in recreational use on the US West Coast is a substance called 'U-4-E-Uh', a methylated derivative of a European sympathomimetic, Aminorex, which was recently withdrawn due to instances of pulmonary hypertension. It is unclear how U-4-E-Uh will be treated under the new CSA regulations.

These new phenylethylamines, and perhaps other psychoactive agents, will likely continue to be investigated by psychotherapists. As happened with LSD and MDMA, their discoveries will eventually be found by recreational users.

One conceivable scenario of the future involves genetic engineering as a means of producing available substances.

Consider the use of bacteria into which has been added the gene to generate human endorphin. Clandestine bacterial laboratories may replace 'street chemists' of today.

As evidenced by the recent 'designer drug' of amphetamines, the public health risk of these compounds is considerable. The extreme potency of fentanyl derivatives, MPTP-induced parkinsonism and the potential neurotoxic effects of MDA and MDMA are a few examples of the recognised risks associated with 'designer drugs'. The medical community will be faced with other adverse effects.

8. Conclusion

'Designer drugs' intended either newly synthesised or by pharmaceutical companies or illicit chemists, will produce analogous effects and be alert to new substances intended to evade the current constraints. Further analogues are expected to appear in recreational use. The challenge is how to distinguish between these analogues and target their respective uses.

Fig. 3. Chemical structure of U-4-E-Uh.
further substances find their way into recreational use. The challenge will be to identify new syndromes as well as new abused substances and contaminant materials. Clinicians are encouraged to be alert to new complications of drug abuse.

8. Conclusion

‘Designer drug’ is a term which refers to substances intended for recreational use and which are either newly synthesised or ‘borrowed’ from legitimate pharmaceutical research in an attempt to circumvent legal restrictions. Although the subjective feelings of intoxication may vary significantly between these analogues, it is important for the clinician to understand that in overdose these substances produce qualitatively similar effects within their respective clinical classes. Serious intoxication with any of the phenylethylamine compounds will produce amphetamine-like effects. The symptoms resulting from an overdose with the fentanyl or phencyclidine analogues are similar to those seen with the parent compound. Some compounds will exhibit unexpected toxicity unique to that material, e.g. MPTP. Since there is no way to predict such novel toxic effects, the clinician may encounter adverse effects beyond that expected for the class. New drugs and new drug syndromes can be expected to present challenges to the clinician in the future.

The toxicology laboratory is unlikely to be able to firmly identify the ‘designer drug’ in an intoxicated patient, due to cross reactivity with the parent drug or because of inadequate sensitivity in the assay method. In treating the ‘designer drug’ intoxicated patient the clinician must rely on the clinical presentation and direct therapy toward these findings.

Despite the plethora of compounds described in this article, only a few appear to be currently in use. In the experience of the authors, those compounds currently in use in the San Francisco area include MDMA, MDEA, 2-CB and U-4-E-Uh. The recent case we observed of presumed MPTP exposure demonstrates that this contaminant may also be in circulation.

‘Designer drugs’ should not be assumed to be a new class of abused substances. Contrary to the impression gained from recent media attention, ‘designer drugs’ represent only the most recent developments in the evolution of mind-altering drugs.

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