"SOMETHING OLD...

SOMETHING NEW...

SOMETHING BORROWED...

SOMETHING BLEW!!

An American (Nose) Trilogy; Illicit Drug and Substance Abuse:

Cocaine

Phencyclidine

Amphetamine-Like Nasal Inhalers

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Medical Grand Rounds
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Dedications and Acknowledgements

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The History, Epidemiology and Medical Complications of Coca and Cocaine Abuse

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Introduction

The anesthetic alkaloid cocaine is a powerful CNS stimulant which is fast becoming "America's recreational drug of choice" (1). The use of cocaine by music and movie celebrities, professional atheletes, executives, professionals and the socially and politically affluent has hardly been concealed from the public (2).

The Drug Enforcement Agency (DEA), estimated that cocaine traffic accounted for $19 to $24 billion in criminal profits (more than heroin) in 1979 (3). While the primary CNS effect (euphoria) of cocaine is a strong positive reinforcement for repeated abuse, the drug's popularity has also been enhanced by the mistaken notion that it is "safe and nonaddicting". It is estimated that two million Americans have used cocaine and they purchased 68,000 pounds during 1979 (2).

In the last two months, local newspapers have carried the accounts of three large cocaine "busts" (826, 614, and 466 pounds respectively), each one of which was greater than the average year's seizure rate one decade ago. While drug seizures have markedly increased, so has drug traffic. As cocaine supplies have increased, the drug has become more accessible to those previously unable to afford it. As smugglers from South America strive to meet street market demands, the DEA predicts that the Texas Gulf Coast will become as active as Southern Florida in cocaine trafficking by the end of this decade. The illicit market for cocaine was stable for nearly sixty years; it was confined to the underground and a more affluent drug subculture. Cocaine abuse has become epidemic since 1970, making a review of cocaine toxicity timely. As we will see, this is not the first time such an epidemic has occurred with this drug.

Table I

The Many "Street Names" of Cocaine

Blow
Dama Blanca
Flake
Heaven-leaf, Her
Lady, Leaf
Nose Candy
Snow
The Pimp's Drug, The Rich Man's, The Star-Spangled Powder

The Source

Erythroxylum is a genus of 250 species of shrubs or small-to-medium trees, most of which inhabit the American tropics. This genus is the only natural source of the alkaloid cocaine. To date, 17 wild species have been shown to have minute quantities of cocaine, but only the leaves of two cultivated species contain sufficient alkaloid (0.65 to 1.2 % dry weight) to warrant mastication as a stimulant or extraction for pharmaceutical use (14). These latter species represent some of the oldest cultivated plants in recorded history and still are the most important cash crop for major portions of Peru, Bolivia and Columbia.

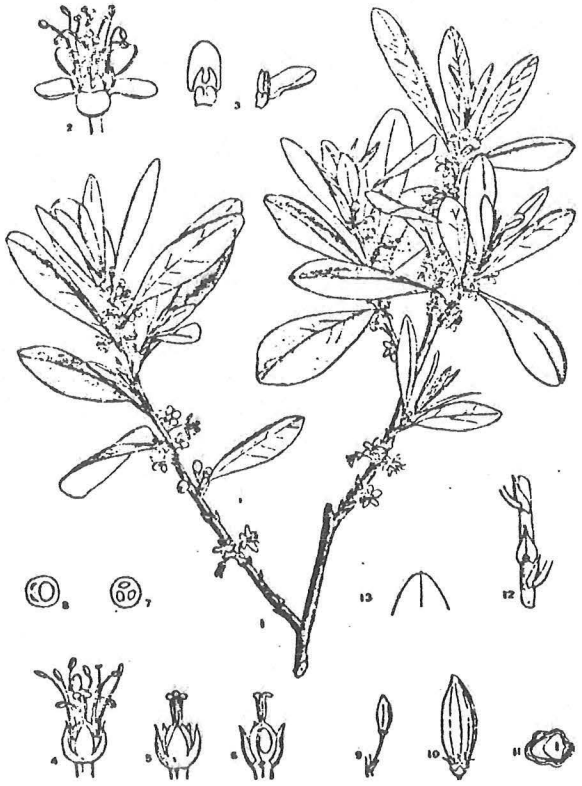

Figure 1: *Erythroxylon coca*. Black and white reproduction of hand-colored engraved plate from Robert Bentley and Henry Trimen's *Medicinal Plants*, Vol. 2(40):1880. Photo courtesy of National Library of Medicine.

Table II Cultivated Erythroxylon Species Yielding Cocaine (4)

I. E coca: (Huáuco or Bolivian coca) - Named by the botanist Lamarck in 1786, after the Peruvian common name for the plant.

Description: A 7 to 8 foot high shrub, usually grown on hillside plantation in rows. The leaves are large, thick, elliptic in shape and pointed at the apex. Two lines run parallel to the midrib on the underside of the green leaf. The plant produces alkaloid within 18 months of planting and has a productive life span of almost 40 years. The leaves are usually deciduous after the current season's growth. Very rarely, this species may be found in feral (wild) populations.

Habitat: This species is well adapted to wet, but not excessively hot climates; it does particularly well in the montana region of the Peruvian Andes where it is grown commercially. A few Indian tribes cultivate E coca for their own use (from cuttings in contrast to seed planting) in parts of the Amazon Basin of Brazil and Columbia. In historic times, this species was known from Ecuador, south to Bolivia.

Production Estimates: (unofficial)

Bolivia - 11 to 35 million kgs of dried leaves.
Peru - Approximately 30 million kgs of dried leaves (9 million of which are used in Peru alone).

Production is monitored by the respective governments.

II. E novagranatense: (Columbian coca) Identified by Hieronymus in 1895, and named after the old colonial name for Columbia, Nueva Grenada.

Description: The plant is similar to E coca except for smaller, thinner, narrower, bright yellowish green leaves that are usually rounded at the apex. This species characteristically holds its leaves on the branches year round. Unlike E coca, this species is essentially never found in semi-wild or feral populations.

Habitat: This species readily adapts to a diversity of environmental conditions. It grows both in lowland and mountain situations and is very resistant to prolonged periods of draught. The habitat are typically found in the upper Cauca and Magdelena river valleys of Columbia and all along the northern coast of South

America. In Columbia, plantations exists only in the Sierra Nevada de Santa Marta and the rugged mountainous areas of Cauca and Huila. In historic times, this species was extensively cultivated throughout Central America and the Caribbean coast of South America, as well as the Colombian mountains. For a brief time, Columbian Coca was grown commercially by the Dutch in Java. The plant can now be found as an ornamental in most tropical areas of the world which were touched by European colonization.

Production Estimates: Unlike the sanctioned Coca commerce found in Peru and Bolivia, the growing, marketing, or even chewing of Coca leaves in Columbia is illegal. Apparently, Coca prohibition is about as successful in Columbia as alcohol prohibition was in the USA. Since the early 1970's, a large illicit cocaine business has developed in Columbia, the magnitude of which is unknown.

III. E novagranatense var truxillense: (Trujillo coca) - First described as a separate variety by Rusby in 1900 who named the plant for the city of Trujillo, Peru.

Description: Morphologically similar to Columbian coca but has slightly different floral and vegetative characteristics, smaller, narrower, but slightly thicker leaves, which are a rich green in color. It is a large, many-branched shrub. It is never found growing outside of cultivation.

Habitat: Like its cousin, Trujillo coca is reputed to withstand prolonged droughts, perhaps better than any other cash crop on the Peruvian coast. In fact, the plant has adapted to semi-arid or desert conditions and plants transplanted to the Peruvian montaña or the Columbia mountains become weak, diseased and die. The plants do require human intervention for at least some irrigation and to protect the seeds from death by dessication. Trujillo coca is truly a "cultigen" and was favored even in historic times for its flavor and shipping qualities. Prior to the Spanish conquest, this plant was cultivated in nearly all of the coastal valleys of Peru.

Production Estimates: The Trujillo coca plantations in the Andean foothills ship several hundred tons of Coca leaves to New York each year. Their leaves are "decocainized" and used is the preparation of extracts which ultimately become flavorings used in the manufacture of Coca-Cola®. The cocaine extracted in this process is given to the U.S. government for legitimate medicinal uses or destroyed. There are numerous Trujillo coca plantations in the dry, upper Maranon Valley which runs parallel to the Peruvian coast. This area is largely inaccessible, even to the Peruvian government and estimates cannot be obtained as to the extent of cultivation there.

Historical and Epidemiological Perspectives on Cocaine

In Antiquity:

Limepots and figurines of Coca chewers (recognized by a bulge in one or both cheeks) have been found on the coast of Ecuador, dating the use and cultivation of Coca to approximately 3000 B.C. (5). The earliest specimens of archeological Coca leaves were recovered from northern Lima, Peru and date back to 1750 B.C. (6). A site (Asia, unit 1) 125 km south of Lima yielded similar specimens that carbon-date back to 1314 B.C. (± 100 years) (7). In pre-Columbian times, Coca was used in the Muisca and Qumbaya cultures as depicted in gold artifacts (Coca chewing paraphenalia, lime pots and figurines) on display at the Museo de Oro in Bogota, Columbia.

The Incas (1200-1553) recognized the two types of Coca, calling one "Mamox Coca" (also written Mamosh, Mamas, or Mumus) which was likely E coca, and the other plant was called "Tupa" (also written Ttupa or Thupa), which meant "noble", and most certainly referred to Trujillo coca. Coca leaves were dispersed as a reward for outstanding service or used in various religious ceremonies (8). According to legend, Coca was a gift from Manco Cepac, Royal Son of the Sun God, bestowed upon the founding of the Incan Empire. The Incan priests considered the plant divine, placed the Coca leaf on the royal emblem, and went so far as to name the first Incan Queen "Mama Cuca". Coca chewing, however, was primarily limited to the Incan royalty and clergy.

Today, it is estimated that over 90% of Andean Indian men and 20% of the women (20 million people) chew Coca leaves, the average daily dose being 2 to 4 oz; this equals 250 to 1000 mg of cocaine. Some habits are said to be 6 to 8 times higher than this amount (9). The Indians chew the Coca leaf much as they did in antiquity. The leaves are mixed with lime (the alkali helps extract the cocaine) and a binder (cornstarch or guano) to form a concoction called a "cocada". When placed in the cheek pouch the stimulatory effects of a modern day "quid" last about 40 minutes *(the term "cocada" came to be used as a measure of time (∿ 40 minutes) by the Incas and most certainly was based on cocaine's pharmacological half-life).*

There is good anthropologic evidence that cocaine-filled saliva was used as an anesthetic by the Incas and even earlier Indian civilizations. It is in fact likely that the early trephining procedures, done by these civilizations for a variety of ills (subdural hematomas, headaches, mental illness, frontal lobotomies, etc.), were carried out under cocaine-induced local anesthesia (10, 11).

In 1499, Amerigo Vespuccio provided the first European description of Coca chewing. He found natives from the Paria peninsula of Venezuela using a plant they called "bayo" (12). This term is still used to identify E. novagranatense by several primitive Indian tribes from the north coast of South America.

With Pizarro (1553) and the Spanish conquest came the destruction of the Incan civilization. The Spanish priests who came to Christainize the Indians tried to discourage Coca chewing ("an illusion of the devil"), however, the governing Spaniards promoted the practice realizing the value of a drug that could produce euphoria and alleviate hunger and fatigue in Indian gold miners and slaves. Coca leaves were dispensed as "partial pay" in order to increase productivity. It was in this way that Coca descended from royalty to the lower classes (9).

In 1580, Nicolas Monardes of Spain brought Coca leaves back to Europe, but again their stimulant qualities were suppressed by the church for the next three centuries. In 1859, the Italian physician, Paolo Mantegazza, rediscovered a great "new" medicinal on a trip to South America (13).

> *"Borne of the wings of two Coca leaves, I flew about in the spaces of 77,438 worlds, one more splendid than another. I prefer a life of 10 years with Coca to one of a hundred thousand without it."*
>
> *Paolo Mantegazza (1859)*

Modern Use of Cocaine:

American physicians picked up the banner and soon were using Coca as a cure for alcoholism, opiate addiction and even tuberculosis. In 1860, Niemann purified and identified the Coca alkaloid and named it "cocaine". He also described its numbing qualities. In 1865, "Vin Mariani" a red wine and Coca leaf preparation was introduced. Queen Victoria is said to have been particularly fond of this drink and Pope Leo XIII used Vin Mariani "through long periods of fasting and meditation" (2).

In 1873, Bennett demonstrated the local anesthetic properties of cocaine which lead to further investigation of this property by von Anrep (on himself). It was Carl Koller, an associate of Sigmund Freud,

who first introduced cocaine into medical practice in 1884 as an anesthetic agent for eye surgery. That same year the noted surgeon, Dr. William Halstead of Johns Hopkins University, injected cocaine into nerve trunks to obtain a "nerve block". Within a year, cocaine was used for spinal anesthesia by Dr. J. Leonard Corning of New York. The nearly simultaneous development of general anesthetic agents and local anesthetics heralded the beginning of a new era in surgery. These agents gave promise to surgery without pain, screaming patients, and the need for strong attendants.

The early self-experimentation with cocaine had its casualties including Dr. Halstead who became habituated and is reported to have used up to 2 Gms of cocaine per day (14). Most notably, it was Dr. Sigmund Freud that became virtually obsessed with the euphoriant properties of this drug. He began experimentation with the drug to combat the opiate addiction of a colleague, and later used it for his own depressive moods. Freud wrote five papers on Coca and cocaine between 1884 and 1887 (15). Like Halstead, Freud realized his own habituation and discontinued the use of cocaine and his research with it as a psychotropic drug. In his lifetime, Freud would become internationally known for two reasons; in one case he would be acclaimed for his work on the intrapsychic self and in another, denounced as the cause of the "Third Scourge of Mankind" (the first two being alcohol and morphine) (13).

During the 1890's and up to 1914, Coca or cocaine became widely available as a component of wine or brandy cordials, commercial cigarettes, and various nostrums, the most famous of which was Coca-Cola® (it really was the "Real Thing" until 1906) (16).

The very narrow role for cocaine in legitimate medicine became apparent as did the drug's abuse potential. In 1914, the Harrison Tax Act mislabeled cocaine a narcotic and all Coca or cocaine containing proprietary products (and prescription products by-and-large) were taken off the market. As a result of this important and timely legislation, the abuse of cocaine went "underground". During the 1920-30's, cocaine became the "drug-dealer's-drug", and the "pimp's-drug". In general, cocaine abuse was small scale and contained within the jazz and bohemian subcultures.

Table III

Take A Whiff On Me

CHORUS:

Take a whiff on me, take a whiff on me,
An' everybody take a whiff on me,
An' ho, ho, baby, take a whiff on me.

When I marry, gonna buy me a line,
Gonna whiff my baby, 'til she change her min',
An' ho, ho, baby, take a whiff on me.

When I marry gonna buy me a rope,
Gonna whiff my baby 'til she buzzard lope.
An' ho, ho, baby, take a whiff on me.

Chorus.

Blacker de berry, de sweeter de juice,
Takes a brown-skin woman for my partickeler use
An' ho, ho, baby, take a whiff on me.

Chew my 'baccer, spit my juice,
Gonna love my baby, 'till it ain't no use.
An' ho, ho, baby, take a whiff on me.

Chorus.

Walked up *Ellum an' I come down Main,
Tryin' to bum a nickle jes' to buy cocaine.
An' ho, ho, baby, take a whiff on me.

Tell you sumpin, gwine make you mighty tickle,
That's two bottles o' cocaine gwine for a nickle.
An' ho, ho, baby, take a whiff on me.

Chorus.

You take Sal an' I'll take Sue,
It's a mighty little difference in between dem two,
An' ho, ho, baby, take a whiff on me.

You take Sal an' I take Jane,
Dey both good-lookin' but dey ain't de same.
An' ho, ho, baby, take a whiff on me.

Whiffaree an' a whiffarye,
Gonna keep on a-whiffin' until I die.
An' ho, ho, baby, take a whiff on me.

Cocaine for horses an' not for men,
Doctors say it'll kill you but dey don't say when.
An' ho, ho, baby, take a whiff on me.

Two barrels o' pickle pork, two barrels o' meal,
An' oh, how glad de ol' lady feels.
An' ho, ho, baby, take a whiff on me.

Chorus.

-Huddie Ledbetter ("Leadbelly") (1933)
Electra Records EKL-301/2

Somewhat more American "mainstream" was the Cole Porter's lyric sung by Ethel Merman, *I get no thrill from cocaine....."* from the song, "I Get a Kick Out of You" (1934). This song was from the Broadway production "Anything Goes".

Likening cocaine abuse to a contagious disease, it was endemic during this period. In the late 1960's, cocaine was rediscovered by rock musicians and reintroduced into the drug culture. After more than a decade (called by some the "snorting seventies"), the abuse of cocaine has become epidemic once again. Some of the more recent cocaine ballads suggest that the drug's euphoria may have a high price.

"Come here mama...come here quick.
This old cocaine really got me sick.
Cocaine,.....cocaine running around
my brain".

Dave Von Ronk
from "Cocaine Blues"

Cocaine is an excellent local anesthetic, but unlike the synthetic "caines", it is a potent vasoconstrictor (17, 18). It is for this quality that cocaine continues to be available as a 1.5%, 5% or 10% solution or as a cocaine "mud" for ENT surgery.

The "Material"

Cocaine HCl, U.S.P. is a white crystalline compound, readily soluble in water. It is a naturally occurring ester of benzoic acid and the nitrogen-containing base ecgonine (19). The chemical structure ($C_{17}H_{21}NO_4$) is shown in Figure 3. Cocaine is legally classified in the United States as a Schedule II drug under the Dangerous Drug and Controlled Substance Act of 1970 and is limited to topical use in ophthalmology and E.N.T. It is a local anesthetic of high efficacy and relatively long duration of action, but also one which has significant toxicity.

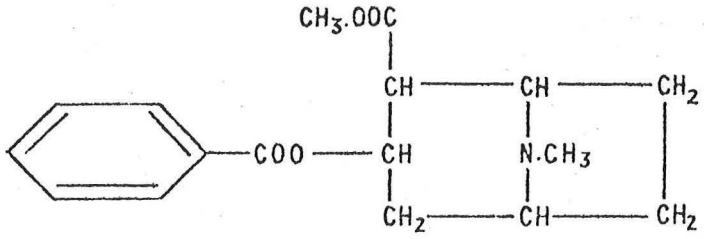

Figure 2: Structural formula of cocaine.

Cocaine has been described as "perhaps the most rapturously euphoric drug known to man" (19). The euphoria provided by cocaine is brief and can only be maintained by repeated dosing. The primary reinforcement is strong enough to encourage repeat usage; the high profitability is strong enough to encourage smuggling attempts by "freelancers" and organized crime. For example, a "key" (kg) of 90% pure cocaine can be brought for approximately $5,000 in Bogata. When sold to the dealer-middleman, it will bring over $50,000. It is then commonplace to dilute it to various percentages of purity (perhaps as low as 15-20%) to sell at a street price of $100 a gram or $100,000 per kg (a handsome mark-up of 2,000%).

Cocaine is one of the most extensively adulterated ("stepped on" or "cut") drugs on the present illicit market. Sugars such as lactose, or other white powders such as borax, talc, etc. may be used to cut cocaine. In an analysis of alleged cocaine samples analyzed at Pharm Chem (Palo Alto, Calif.), 73% contained cocaine as the only active drug, 21% contained cocaine in addition to a synthetic local anesthetic such as procaine, lidocaine, tetracaine or benzocaine. Six percent of the samples contained no cocaine at all (amphetamine, caffiene, phencyclidine, etc.) (20).

As adulterants go, procaine is the least toxic synthetic "caine", lidocaine being 2-3 times and tetracaine 7 times more toxic than procaine. Benzocaine is poorly soluble and particularly dangerous if injected because it will cause blood clotting (3% of the Pharm Chem samples contained benzocaine). The toxicity of each of these synthetic "caines" is additive to that of cocaine. High blood levels of local anesthetics can result in convulsions, respiratory collapse, and sudden death. In hypersensitive individuals, very low doses of any of the "caines" may cause serious systemic reactions, even death (as little as 20 mg of cocaine has been implicated) (21).

A "street assay" procedure is often used to avoid "beat merchandise" when large quantities of cocaine are being purchased (19).

Table IV Street Assay for Cocaine

1. The product should dissolve instantly in cold water.

2. A pinch of the product, dropped into a container of Clorox ® should immediately turn from white to a greenish blue halo as it sinks.

3. A "test line" snorted by the buyer should provide the desired effect and a numbing of the canine and incisors.

This assay procedure may tell the buyer that cocaine is present but it says little concerning adulterants that may also be present.

Law enforcement agencies have developed a field test to specifically identify cocaine from other common alkaloids. A three-solution system developed by Scott (22) provides a rapid, "sensitive and specific" color test for cocaine. Since these reagents are readily available, this technique may be used by dealers.

Table V

Scott's Field Test for Suspected Cocaine

A. Add five drops of Solution 1 (2% cobaltous thiocyanate dissolved in water and diluted 1:1 with 96% USP glycerine) to the suspected cocaine. If the pink solution turns blue, proceed to Step B; if it doesn't turn blue, it is not cocaine.

B. Add one drop of Solution 2 (concentrated hydrochloric acid) and shake. The blue color should disappear (if not, add one more drop of Solution B and shake). If a clear pink color develops, go to Step C.

C. Add 5 drops of Solution 3 (chloroform) and gently shake. If cocaine is present, the bottom layer of chloroform will turn blue.

Using Scott's three-solution method, Winek and Eastly (23) pointed out that only unadulterated cocaine gave positive results at all 3 steps compared to a series of (singular) common adulterants.

Table VI

Results of Scott's Method with Common Substitutes for Cocaine

Drug	Blue color with solution 1	Pink after adding solution 2	Blue chloroform layer from solution 3
Cocaine	Yes	Yes	Yes
Phencyclidine	Yes	Yes	No
Dibucaine	Yes	Yes	No
Methapyriline	Yes	Yes	No
Procaine	No change	No change	No
Benzocaine	No change	No change	No
Tetracaine	No change	No change	No
Chloroprocaine	No change	No change	No
Lidocaine	No change	Yes	Yes

These authors go on to point out that false positives can occur when these very same adulterants are mixed together (Table VII). In forensic investigations, it is therefore now recommended that field testing include confirmation by a thin-layer chromatography kit available from Eastman Kodak (test time approximately 10 minutes). In essence, "street assays" available to the common buyer cannot be totally relied upon.

Table VII

False Positive Results Using Scott's Procedure

Drug Combination	Solution 1	Solution 2	Solution 3
Lidocaine: cocaine (1:1)	+	+	+
Lidocaine: phencyclidine (1:1)	+	+	+
Lidocaine: dibucaine (1:1)	+	+	+
Lidocaine: methapyrilene (1:1)	+	+	+

The "Method"

Coca leaf chewing is primarily limited to the Indian populations of Peru, Bolivia, Columbia and a few areas of the Venuzuelan Amazon. Since the Harrison Tax Act of 1914, the oral ingestion of cocaine has become virtually negligible except as a component of smuggling attempts (condoms filled with drug are swallowed in an effort to avoid detection by custom agents) (24). "Snorting" or "snarfing" has been popular since the 1920's. A spoon or "a line" ($\sim$ 25 mg) of cocaine is sniffed at 20 to 40 minute intervals. There is a tendency to titrate dosage using this technique.

During the 19th century, cocaine was smoked in the form of Coca-leaf cigars and cigarettes (25). The relatively low level of alkaloid in the leaves probably prevented any serious problems. In a 1979 study of cocaine users reported by Siegel (26), 39% had engaged in the experimental smoking of cocaine preparations. To do this, the abuser must "free base" the alkaloid (via simple ether extraction kits available in your friendly, local "headshop") to obtain a substance that is

quite volatile, yet heat stable. Approximately 300 mg is distributed throughout a cigarette, joint, or in a water pipe. Unlike intranasal users, cocaine smokers do not appear to titrate dosage. The frequency and quantity of dosage tend to escalate at so-called "free-base parties" which may last one to four days until the participants literally fall asleep from exhaustion *(or until somebody catches on fire during the ether extraction process)*. This pattern of abuse is very similar to that seen when frequent (every few minutes) intravenous injections of cocaine (or cocaine mixed with heroin, i.e. a "speedball") are self-administered over several days (a "run") (27). These latter avenues are much more likely to result in dependency, overdose, psychiatric complications (paranoid psychosis) and sudden death.

On occasion, cocaine has been applied to the male genitalia (glans penis) to prevent premature ejaculation *(which it may do, but only at the expense of diminishing the sensory mucotaneous female input. Taken by more traditional avenues, cocaine was first described as an aphrodisiac by Freud (25) and later by his 20th century disciples (28), i.e., "Orgasms go better with Coke")*. A case of blindness has been reported in a drug abuser who developed bilateral corneal ulcerations and secondary angle-closure glaucoma from the illicit use of topical cocaine powder in the sclerae of the eye "to get high" (29).

Lest any portal of entry be left out, a case from Dallas (30) described a fatal overdose of cocaine, mixed with phenmetrazine (Preludin®) administered by enemization in a 28 year old man. The only other avenue I can think of is intrathecal; for now at least this route is limited to primate studies of drug reinforcement behavior. Who knows, maybe in a few years newer and more direct avenues will be tried (O'Maya reservoirs, ventriculoatrial shunts, Hickman catheters) by inventive addict personalities with iatrogenically acquired portals of entry.

The "Price"

The Psychiatric Complications of Cocaine Abuse:

Freud initially described the profound elation and sense of increased mental agility and physical endurance associated with the ingestion of cocaine for his own depressive moods.

"I take very small doses (50 to 100 mg) of it regularly against depression.....with the most brilliant success. The effects were exhilarating and lasting euphoria, which in no way differs from the normal euphoria of a healthy person..... You perceive increased self-control and possess more vitality and capacity for work....."

Sigmund Freud
(Reference 31)

In studies from the NIMH (32), 12 depressed patients were given incremental doses of cocaine intravenously and only one experienced a pure euphoria and a relief from perceived problems, this occurring at a relatively low dose of 5 mg. One patient became significantly more depressed, agitated and mute at somewhat higher doses and no one received any significant antidepressant effect. Increased anxiety, suspiciousness and dysphoria are often components of repeated intravenous injections of cocaine and may account for the frequent simultaneous abuse of heroin ("mellowing" the effect).

After chronic cocaine administration, the user may develop delusions of persecution, sometimes accompanied by auditory, visual or olfactory hallucinations. Unlike hallucinations from most toxic psychosis or delirium, the user has a clear sensorium, is not confused and is usually fully oriented. A peculiar delusion of parasitosis ("cocaine bugs") may rarely occur (33). A paranoid state may herald violent behavior. Its fullblown expression is almost indistinguishable from acute paranoid schizophrenia or manic-depressive psychosis and is similar to that induced by amphetamine abuse (34).

"Cocaine hallucinations" have been studied by Siegel (35) in 85 recreational cocaine users, 15 of whom reported hallucinatory experiences (37 or 44% reported perceptual phenomenon distinct from hallucinosis caused by chronic mydriasis). Thirteen subjects reported visual hallucinations, usually an object in a flash of light ("snow lights") in the peripheral field of vision. These subjects, after initial attempts at perceptual-motor validation of the sensations, realized these were "just tricks of the eye", i.e., pseudohallucinations. Subjects did not report "complex hallucinations" involving fully formed or recognizable objects or scenes, but other authors have reported this phenomenon (36). Some of the lights and visual phenomenon were described as similar to those associated with migraine. Eleven of these subjects reported tactile sensations (parasitosis), but again each affected subject knew that insects or objects were not really present in the skin. Just the same, they "scratch like mad" as they describe the situation in terms like "as if" or "it is as though". Finally, six subjects reported olfactory, three auditory, and three gustatory hallucinations (strong or offensive taste in food).

A classic description of cocaine induced psychosis has been provided by Sir Arthur Conan Doyle, who after creating Sherlock Holmes gave him "the needle" as a singular vice (13, 16). Just before Holmes disappeared at Reichenbach Falls in 1891, his appearance startled his comrade, Dr. Watson. He began to wear intricate disguises and he saw his arch enemy, Moriarity, in every shadow. Doyle may have also described another feature of chronic cocaine abuse, the repetitive pursuit of a task and the endless attention to minute detail.

Literature also provides us with possibly another description of psychic changes related to the chronic use of cocaine. In 1885, Robert Louis Stevenson wrote "Dr. Jekyll and Mr. Hyde" (in only three days) while being treated for tuberculosis with cocaine (37). *While it would be hard to blame the drug instead of the profit motives associated with its sale, over 40 cocaine related murders were committed in 1976 in Dade County, Florida alone (1). Cocaine related murder and kidnapping are common tools of the South American cocaine trade. Bogata, Columbia has the second highest murder rate in the world!*

In the aftermath of chronic abuse, the user often develops a depressive affect that results in a rapid return to drug usage to elevate mood. In a recent study, this aftermath depression was felt to contribute to 16 cocaine-related suicides (38).

It is known that repetitive subthreshold electrical stimulation of the limbic system results in a facilitation of neuronal transmission, which alters behavior, and eventually results in major motor convulsions with doses of electrical stimulation previously producing no effect (39). This process is called "kindling". Post, et al. (40) suggests that "kindling" is analagous to "reverse tolerance", i.e., a small dose of a drug given repetitively may eventually produce behavioral changes not elicited initially by the single small dose. It may be by such a mechanism that chronic cocaine (or amphetamine) abuse results in psychosis.

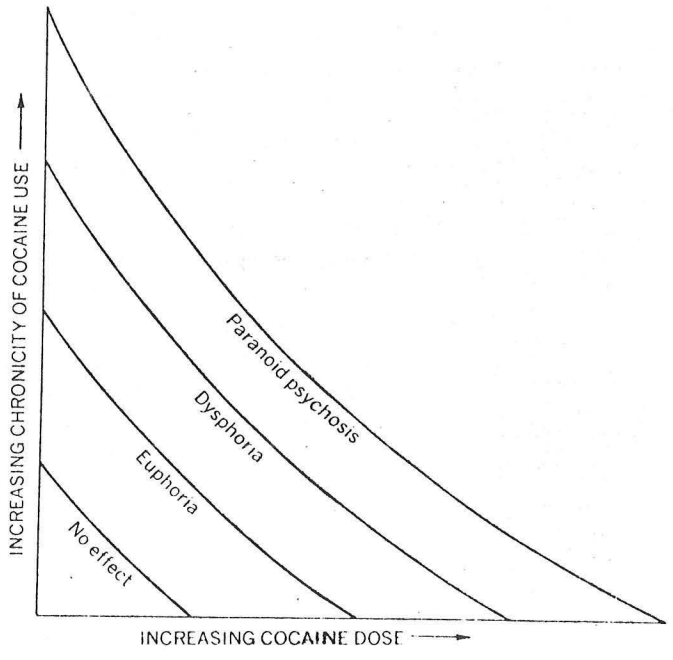

Figure 3:
Interaction of Dose and Chronicity in Cocaine-Induced Psychopathology

The Medical Complications of Cocaine:

To understand the toxicity of abused cocaine, one must first understand that "overdose" is not the only factor operative. In 1924, an AMA committee investigated 43 deaths resulting from local anesthetics (41). Twenty-six deaths were attributed to cocaine, six after nasal application and twenty after infiltration for tonsillectomy. In 1953, Pitkin (42) reported a 20 year survey that revealed 12 cocaine related deaths (route of administration was not mentioned). The actual incidence of toxic reactions to topical cocaine is unclear but most of the medically related deaths have occurred after cocaine infiltration or injection (18). One study offers some insight into the incidence of toxic cocaine reactions from a survey of plastic surgeons using the drug for submucous resections and rhinoplasties (43). During over 108,000 cases, there were 291 mild and 34 severe reactions, plus 5 fatalities.

Miller has shown that the local vasoconstrictive qualities of a 5% cocaine solution is adequate for surgery, and yields lower serum blood levels than a 10% solution (44). He recommends that "cocaine mud" be discontinued since excessive dosing may occur with this product. He also suggests that the topical dose of cocaine never exceed 200 mg. Because the respiratory mucous membranes and the trachea absorb cocaine much more rapidly than the nasal mucosa or pharynx, he recommends that cocaine be avoided during laryngoscopy or bronchoscopy.

The studies by Miller on cocaine blood levels were performed on patients with a surgical pre-op to minimize "caine" reactions: Pentobarbital (100 mg IM) and morphine sulfate (10-12 mg IM) 1 hour prior to surgery, followed by diazepam 5 mg IV just prior to cocainization of the mucous membranes. It is unlikely that such a cocktail protects the patient from cardiovascular complications, but it may reduce CNS excitation. Dysrhythmias are fairly common during cocaine anesthesia and may be significantly reduced by pre-op propranolol (45).

The first recognizable pharmacologic effect of cocaine is on the cortex ("stimulates the CNS from above downward") (19). Along with an increased capacity to do muscular work or avoid fatigue, the human subject develops euphoria, garulousness, restlessness and excitement. Headaches are not infrequent. At small doses, motor activity is coordinated, but with increasing dose levels, the lower motor centers are affected resulting in tremor and even tonic-clonic convulsions. This state is usually characterized by hyperreflexia and clonus.

The action of cocaine on the medulla results in an initial increase in respiratory rate, sweating and vomiting through stimulation of the respiratory center, vasomotor center and chemoreceptor trigger zone, respectively. At higher doses, Cheyne-Stokes respirations, or even apnea, develop through central depression of respiration. A respiratory

sudden death can also occur from loss of airway during unobserved seizure activity. Another central effect of cocaine is to decrease the heat-regulating center's ability to autoregulate heat dissipation and production. As a result, hyperthermia may occur during cocaine overdose. In reviewing such cases, clearly a major component of cocaine induced hyperthermia is the increased muscular activity (particularly if convulsions occur) coupled to an intense peripheral vasoconstriction.

It is possible that some of the toxicity of cocaine relates to its ability to potentiate the effects of epinephrine or norepinephrine on organs innervated by the sympathetic nervous system by blockade of neurotransmitter reuptake (46). Small doses of cocaine may decrease heart rate, but moderate to high doses cause tachycardia and an elevation of blood pressure (19). When cocaine was used simultaneously with injected epinephrine in ENT surgeries, ventricular fibrillation and sudden cardiac standstill were precipitated on occasion (41). Cocaine may sensitize the myocardium to endogenous or exogenous epinephrine. Kolhntop, et al. (47) demonstrated that cocaine enhanced the ability of epinephrine to induce cardiac arrhythmias during halothane/nitrous oxide anesthesia (an enhancement that was blocked by pre-op IV propranolol).

Figure 4 shows an EKG from a 37 year old man who had been repeatedly injecting cocaine over 48 hours (at least 5 "hits" per day or a total dose $\sim$ 140 mg). After complaining of palpitations, a rhythm strip was obtained which revealed a sinus rhythm with episodes of a wide QRS complex dysrhythmia (LBBB configuration) at a rate of 94 beats/minute. This rhythm was occasionally ushered in by fusion beats, suggesting an accelerated ventricular rhythm from cocaine overdose. After detoxification, the patient returned to his previously healthy status (48).

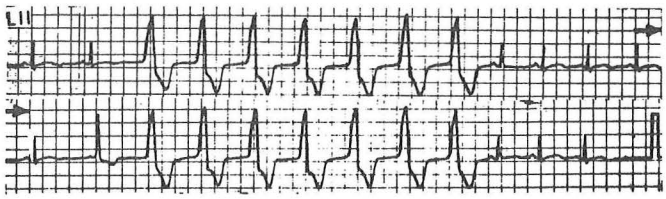

Figure 4: Lead II rhythm strip showing paroxysms of wide QRS complex dysrhythmia. A ventricular fusion beat (second QRS complex) can be seen in the lower portion.

The GI tract does not escape with just emesis; hypermotility and a curious gastro-colic reflex referred to by Freud as "cooling eructations" (49) may occur with an occasional explosive result.

Eye damage in the form of corneal abrasions, ulcerations and scarring may occur with repeated use of cocaine eye drops, or with abuse (29). Acute glaucoma may be precipitated by topical application of cocaine to the eye, presumably due to mydriasis induced mechanical block of drainage from the anterior chamber.

Nasal septal ulceration and perforation ("coke nose") are well known complications of "snorting" cocaine and results from mucosal necrosis due to vasoconstriction.

Treatment of Cocaine Overdose:

The local vasoconstriction caused by cocaine limits the rate of its absorption. With toxic reactions to topical cocaine in ENT surgery, efforts have to be made to remove the remaining drug from the mucous membranes. It is seldom possible to achieve this in "caine" reactions occurring outside the hospital. Intravenous cocaine is more likely to be implicated in overdoses and again the offending agent cannot be removed. Previously it was thought that cocaine was destroyed by gastric acidity. The "high" obtained by early nostrums should have dissuaded that belief. Frequently, oral overdose results during "free lancing" (smuggling attempts such as swallowing condoms filled with cocaine) (24). Should cocaine reach the small or large intestine, absorption will readily occur. The liver is capable of detoxifying relatively massive doses of cocaine *(one minimal lethal dose per hour - if you live that long!)*, but only if the doses are incremental (19). Ten to 20% of administered cocaine is excreted unchanged in the urine. Hydrolysis of cocaine also occurs in the plasma via cholinesterase (50). There is no way presently to enhance the elimination of cocaine except in the circumstance where cocaine-filled condoms have been ingested. It is currently recommended that such patients be subjected to surgery to remove the foreign bodies.

In 1977, Rappolt, et al. (51) described the use of intravenous propranolol in the treatment of the cardiovascular effects of cocaine abuse and overdose. They gave 1 mg IV, followed by 1 mg each minute for five minutes. They report a reduction in cardiac arrhythmias, a lyzing of tachycardia and a return of blood pressure to normal. They mention that the CNS effects of cocaine, such as euphoria, are also attenuated. More recently, these same authors go on to suggest propranolol as a "new therapeutic modality" for the emergency physician who encounters patients with signs and symptoms of: 1B advanced stimulation (sometimes called the "walking O.D.") from George Gay's Classification of "Caine" Reactions (52).

Table VIII

A Classification of "Caine" Reactions

Phase	Central nervous system	Circulatory system	Respiratory system
1a Early stimulation	Excitement, apprehension, other symptoms of emotional instability, headache, nausea, vomiting. "Twitchings" of voluntary muscles, particularly of face, fingers, arms, thighs.	Pulse varies, probably will slow. Elevation (usual) in blood pressure may occur. Fall in blood pressure may occur. Pallor of skin.	Increased respiratory rate and depth.
1b Advanced stimulation	Hyperkinesis, convulsions (tonic and clonic) resembles grand mal seizure.	Increases in both pulse and blood pressure.	Cyanosis, dyspnea, rapid (gasping), or irregular respiration.
2 Depression	Paralysis of muscles, loss of reflexes, unconsciousness, loss of functions, death.	Circulatory failure, no palpable pulse, death.	Respiratory failure, ashen gray cyanosis, death.

Cocaine Substitutes:

Cocaine is expensive; teenagers are curious, and often gullible. "Head shops" have a variety of products for sale that imply they are as good as "The Real Thing". Most are packaged as snuffs or incense. Many contain caffeine (e.g. Cocafine snuff, Coca Snow incense); others have a sugar base and a local anesthetic such as benzocaine or procaine (e.g. Iceberg, Rock Crystal and Snort). One snuff contains ground tobacco, menthol and fragrances (Cokesnuff) and delivers 20 to 60 mg of nicotine with an average dose. One incense contains ephedra (ephedrine) and is called the "new legal cocaine substitute (Ma-Huang Incense). Use of this compound may cause acute sympathomimetic poisoning. Another product capable of producing hypertension and palpitations, as well as GI distress, contains yohime hydrochloride and corzanthine (Yocaine). Whether or not these products provide a desired euphoria, or merely a placebo effect, it is not clear. It is clear, however, that these products are not innocuous; recently 61 cases of undesired effects requiring emergency room evaluation arising from the abuse of "head shop" cocaine substitutes were reported by Seigel (53).

Death Caused by Recreational Cocaine Use:

"He said he wanted Heaven,
But prayin' was too slow,
So he bought a one way ticket
On an airline made of snow,
Did you say you saw your good
friend flyin' low, dyin' slow,
blinded by snow?"

--Hoyt Axton

In 1972, Finkle (54) reported five fatalities associated with cocaine (one was a therapeutic misadventure with death from a "caine" reaction occurring 30 minutes after the larynx was sprayed with 12 cc of a 1% cocaine solution). Of the four remaining cases, one death was in a 7 year old child after oral overdose. Two drug abusers died after intravenous injection, and the final victim died after inhalation. No blood levels were available in this series.

In 1974, Price (55) described a case of fatal cocaine poisoning. The victim's death was witnessed while he was in police custody. Approximately two or so hours after a concealed oral ingestion of 2-3 Gms of pharmaceutical cocaine, the victim "collapsed suddenly and thrashed about", dying less than one hour later in the hospital.

In 1977, Suarez, et al (24) described severe cocaine overdose resulting from swallowing cocaine-filled condoms. In two cases (17 and 22 year old males) death occurred outside the hospital. One victim had 26 bags in the stomach, 3 in the duodenum, 1 in the jejunum, 15 in the ileum, and 8 in the colon. Only the bag in the jejunum had ruptured. The other victim had 75 bags of 75% pure cocaine in the GI tract at autopsy, of which 8 were ruptured. The surviving patient admitted to swallowing six bags of cocaine, each containing 5 Gms of drug. A flat plate of the abdomen showed foreign bodies in the stomach. The patient refused surgery so an attempt was made to remove the cocaine via fiber-optic gastroscopy which resulted in the rupture of one condom. Still refusing surgery, the patient went into shock (40 mm Hg systolic blood pressure), pulse rate jumped to 140 beats/minute, apnea ensued and massive tonic-clonic seizures occurred. The patient was treated supportively and once stable was taken directly to surgery. The remaining cocaine-filled condoms were removed and the patient made an uneventful recovery.

Lundberg and Garriott, et al. (30) reviewed nine cocaine-related deaths in 1977. In three, cocaine was the only drug involved; marked pulmonary edema characterized these cases. Cocaine was mixed with other drugs in five deaths (one by GSW suicide) and one patient died from rupture of a berry aneurysm. The toxicologic findings from this paper are summarized in Table IX.

Table IX

Toxicologic Findings

Case	Age	Sex	Weight, kg	Route of Administration	Cocaine, mg/100 ml or 100 g							Other Drugs
					Blood	Urine	Liver	Kidney	Brain	Lung	Vitreous	
1	16	f	54	injection	N/D	N/A	0.01	N/P	0.04	0.01	N/A	...
2	33	m	...	injection	0.82	N/A	0.15	2.70	N/A	N/A	N/A	...
3	28	f	56	injection	0.75	N/A	0.13	1.68	N/P	N/P	0.38	...
4	32	f	47	inhalation	2.1	21.5	2.0	N/P	N/P	N/P	N/P	morphine in bile and urine
5	21	f	59	inhalation	0.4	N/A	0.1	N/P	1.5	0.6	N/A	lidocaine in blood, liver, brain, and lung; blood ethanol 0.05%
6	24	m	68	injection	0.1	N/A	0.2	N/P	N/P	N/P	N/A	blood ethanol 0.12%
7	28	m	90	rectal	<0.01[a]	0.98[a]	N/D	N/P	N/P	N/P	N/D	phenmetrazine, phendimetrazine, amitriptyline, and nortriptyline in urine
8	28	m	85	uncertain	0.02	0.56	N/D	0.02	0.03	0.09	N/P	ruptured berry aneurysm with subarachnoid hemorrhage
9	33	m	70	injection	0.02	0.15	0.03	N/P	N/P	0.09	N/A	shotgun suicide; blood ethanol 0.22%

N/D = not detected.
N/P = not performed.
N/A = not available.
[a] Antemortem specimen.

The Local Forensic Experience:

In 1978, DiMaio and Garriott (56) from Dallas reported four deaths due to the intravenous injection of cocaine.

Case 1: A 19 year old white male college student, found by parents "trembling and shaking" probably five minutes after injecting IV cocaine. Convulsions and sudden death followed almost immediately. A fresh needle mark was found adjacent to older needle tracks. Only cocaine was present on post-mortem.

Case 2: A 19 year old white female was found in convulsions and transported by private auto to Parkland Memorial Hospital. On arrival to the ER, pupils were dilated and fixed and there was no detectable cardiac activity. The patient was resuscitated and placed on a respirator. Needle tracks were present in both antecubital fossa. ECG was consistent with irreversible hypoxic brain damage; the victim never regained consciousness and died on day nine of her hospitalization. Pulmonary narcotism was present on examination and admission toxicology revealed a low level of methaqualone (Quaalude®) as well as cocaine.

Case 3: A 28 year old white woman was found dead, face-up in a bathroom; a syringe and paraphenalia containing 74% cocaine powder was found 10 inches from the body. Old and new injection sites were found; pulmonary narcotism and marked pulmonary edema were also evident. Cocaine was the only drug detected.

Case 4: A 26 year old white female was found face-down in the bathtub, a needle and syringe containing cocaine residues were next to her on the commode. Pulmonary narcotism was present at post-mortem and cocaine was the only drug found.

In Ref. 30, Case 7 is also from Dallas: A 28 year old man with schizophrenia became extremely agitated and related to his father that he had inserted street drugs into his rectum. His father gave him an enema, but because he became even more wild and incoherent, he was transported to Parkland Memorial Hospital. Almost immediately upon arrival he suffered a respiratory arrest, followed by a seizure and a cardiac arrest. Cardiovascular vital signs were restored to normal, however, the patient suffered irreversible hypoxic brain damage and died 3 1/2 days later. Marked pulmonary congestion and pulmonary edema were present at post-mortem. Multiple drugs were present in this case.

A recent "cocaine" overdose death survived long enough to be resuscitated by DFD paramedics. Intravenous lidocaine, 100 mg bolus, was given for ventricular tachycardia and asystole resulted after a "sine wave" transiently appeared. Post-mortem revealed lidocaine overdose and confiscated paraphenalia contained crystalline lidocaine only. A previously unreported case from 1981 (Courtesy of Dan Hayes, M.D. and Bill McAnalley, Ph.D.) follows.

A 24 year old white woman, previously healthy except for a 1 to 2 year history of intranasal and intravenous cocaine abuse, injected cocaine in what is believed to be a suicidal gesture after an argument with her boyfriend. Approximately three hours after having last been seen by him, the boyfriend was awakened by the victim who complained of dizziness; soon thereafter, she collapsed. Her boyfriend started CPR (which was somewhat inadequate) and continued until paramedics arrived to take over. On their arrival, the patient had no pulse, blood pressure or respirations (CPR was continued and the patient was transported to Parkland Memorial Hospital. Despite a long period of asystole, a sinus rhythm and blood pressure (120/80 mm Hg) were achieved. The total CPR time in the ER was 45 minutes. The profound metabolic acidosis that developed during CPR was corrected expeditiously.

The patient was respirator dependent and remained in Stage IV coma with decerebrate posturing. The hospital course was punctuated with:

1. A right hemothorax secondary to CVP placement.
2. Disseminated intravascular coagulation.
3. Hyperamylasemia (vs pancreatitis)
4. ARDS
5. Rhabdomyolysis
6. Renal failure (oliguric)
7. Progressively refractory hypotension

The patient expired 5 days after admission. Post-mortem results are pending. This patient's cocaine blood levels were four times higher (6.7 mg/dL) than any previously reported in Dallas.

The National Forensic Experience:

Even though isolated case reports of sudden death related to cocaine surfaced, a controversy centered around the drug's toxicity in physician's circles outside of forensic medicine and toxicology. A very important contribution to the forensic literature was provided by Finkle and McClosky (57) in a retrospective review of 27 study sites (Figure 5), representing some of the best toxicology and forensic medicine departments in the U.S. and Canada. These study sites encompassed a jurisdictional population of 69.2 million people between the years 1971-76. A total of 111 cases involving cocaine were found, but only 26 involved cocaine alone indicating the trend toward polydrug abuse. The incidence does not appear to be predictable from general demographic considerations or the known drug abuse problems of the geographic area of participation. A segregation of the study cases (drug vs nondrug deaths) is represented in Figure 6.

COCAINE SURVEY SITES

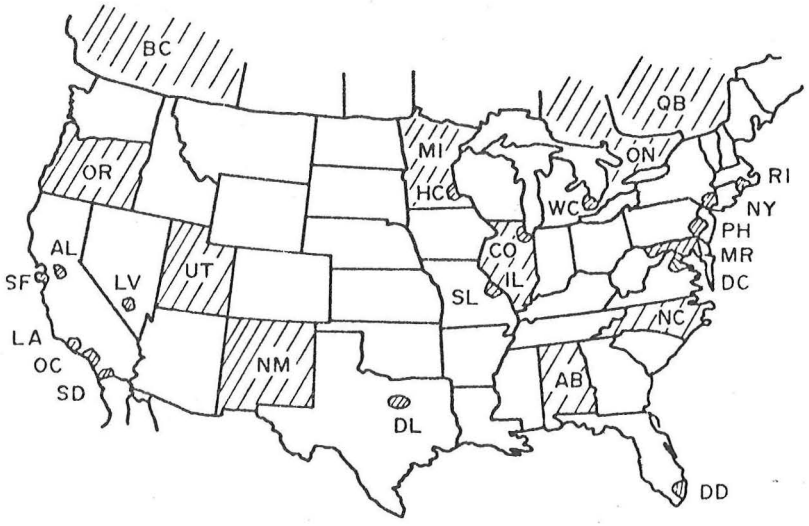

Figure 5: US Survey Population = 62.9 Million (29.8% of U.S. Population)

MAP OF SURVEY SITES

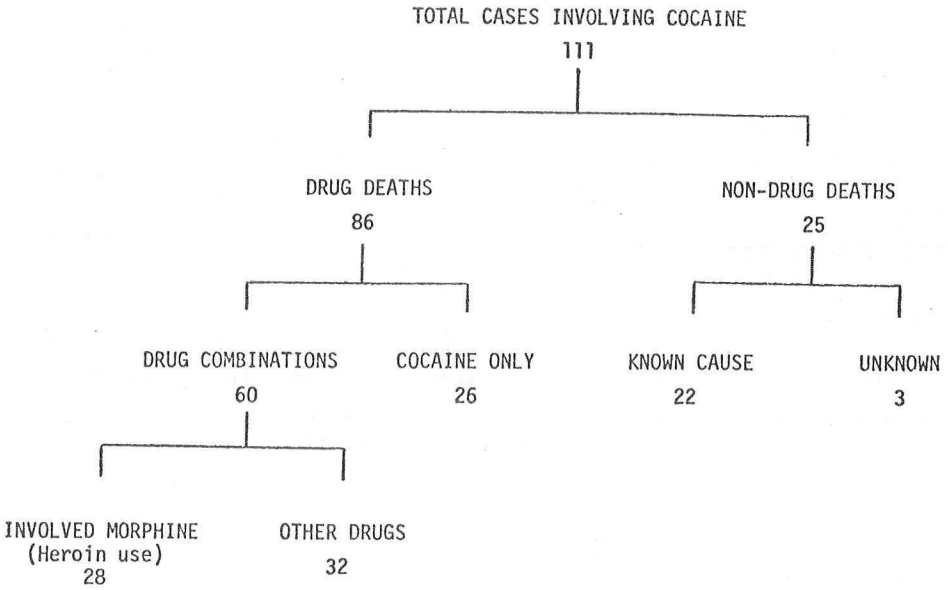

Figure 6: Segregation of study cases according to drug or nondrug deaths.

The number of reported cocaine-related deaths increased on a yearly basis from 1971 through 1975 and remained high until the final year of the study supporting previously cited epidemiologic data.

Table X: Occurrence of cocaine cases by year, including total cases from all study sites for the period 1971 through the first six months of 1976.*

Year	No. Cases
1971	2
1972	3
1973	11
1974	25
1975	37
1976	29

*Four cases prior to 1971 have not been included in the figures.

A general description of these survey cases reveal that the victims were principally young, white males under 30 years of age (2/3 were white, 3:1 bias in favor of males). The victims were generally medically healthy prior to demise, there being no definable history of recent acute or chronic illness for 85.6% of the cases. On the contrary, 61.3% of the deceased had emotional or behavioral problems almost exclusively centered around drug abuse. Despite this history, alcohol abuse was virtually nonexistent in this group. In general the victims did not represent a group with overt mental illness, nor did they appear to belong to that segment of society that thinks it requires tranquilizers as an adjunct to daily living *(life as a drug deficiency disease model)*. In fact, these victims were usually employed or students (77%) at the time of their death. Only 1.2% of the victims had a prior suicide attempt record. The classified manner of death for the total survey cases is summarized in Table XI; it indicates, as expected, a high incidence of accidental death in this recreational drug abuser population.

Table XI

Classified Manner of Death for Total Survey Cases

	Cases	
Manner	*n*	%
Suicide	16	14.4
Accident	48	43.2
Homicide	13	11.7
Natural	5	4.6
Undetermined	29	26.1
Total	111	100

In drug-death cases where the route of administration could be determined, intravenous self-administration was predominant. (See Table XII). One-third of these drug deaths resulted from the so-called "speedball" combination (cocaine plus heroin). The deaths by oral route were either suicides or smuggling attempts and large quantities of drug were involved.

Table XII

Route of Administration of Cocaine for Various Categories of the Survey Cases

Route of Administration	Total Survey Cases, %	Cocaine-Only Drug Deaths	Drug-Combination Deaths, %	Cases Deceased Had History of Cocaine Abuse, %
Undeterminable	54.1	15.4	56.8	17.4
Intravenous	31.5	61.5	30.0	56.5
Nasal	7.2	7.7	8.3	17.4
Oral	6.3	15.4	3.3	8.7
Rectal	0.9	...	1.6	...

The range of known survival times following cocaine ingestion is depicted in Figure 7. Only 11.8% (ten of the drug-death cases) actually reached the hospital alive. Roughly 32% died within one hour of cocaine ingestion, and roughly 2/3 died within 5 hours. In deaths occurring "overnight" or after greater than 10 hours, it is likely that the body just wasn't discovered earlier. If you break out the 26 cases of cocaine-only deaths, the results are fairly similar (over 50% died in the first hour and 3/4 of the total by the end of the second hour).

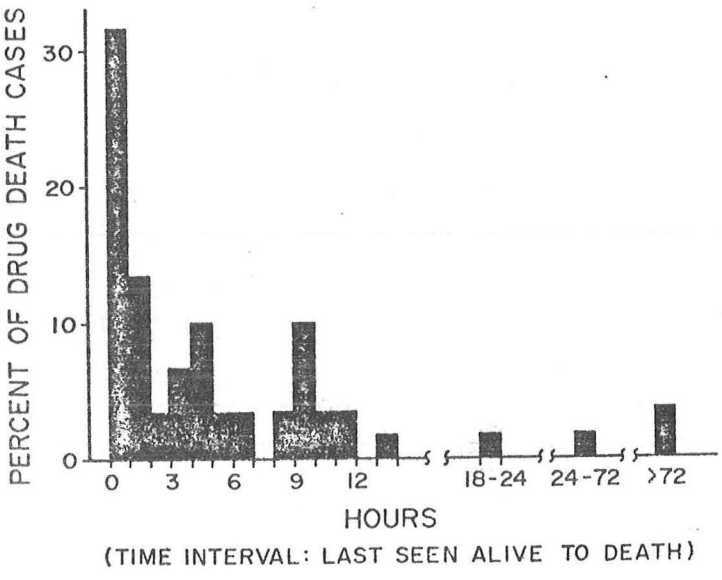

Figure 7: Distribution of survival times.

Terminal symptoms were reported in nearly one-half of the cocaine-only deaths. They were remarkably consistent and were primarily CNS-mediated events (seizures, followed by respiratory depression or arrest and coma). Cardiac arrest was reported on three occasions.

The gross observations by the pathologist at autopsy were generally nonspecific consisting of pulmonary edema, passive pulmonary, visceral and cerebral congestion, and pulmonary narcotism in those victims with a high incidence of intravenous drug abuse. Interestingly, not one of the deceased had a perforated nasal septum.

Fifty-three of the 86 cases of drug deaths had quantitative cocaine blood concentrations; 36% had 1.0 µg/ml or less, Figure 8. Seventy percent of the victim population died with cocaine blood levels below 4.0 µg/ml. In the cocaine-only deaths, 23 of 26 had quantitative cocaine levels which suggest a trend to higher blood concentrations in this group, for example, the blood level inclusive of 70% of the victim population was not reached until 9.0 µg/ml (Figure 9).

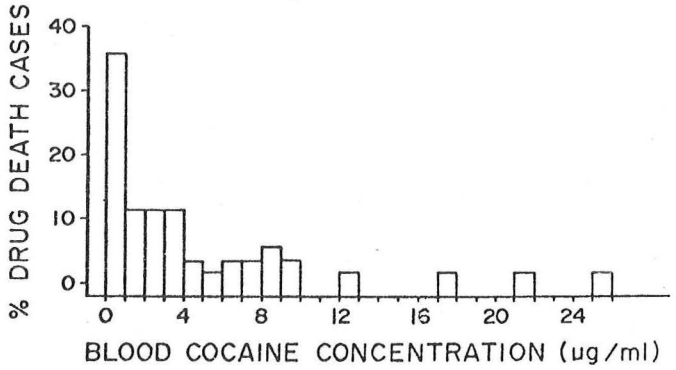

Figure 8: Distribution of blood cocaine concentrations for all drug deaths.

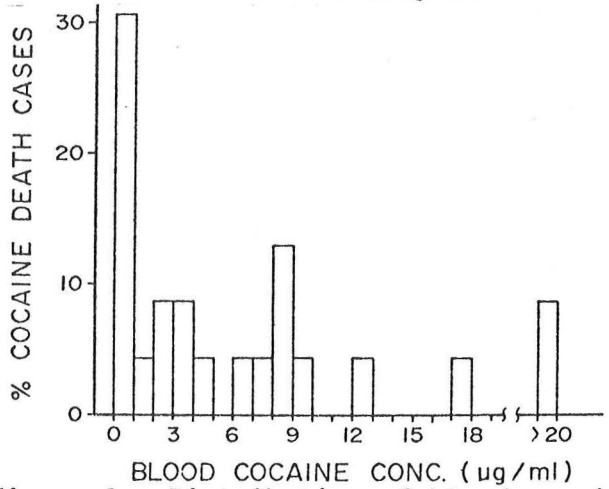

Figure 9: Distribution of blood cocaine concentrations for all cocaine-only deaths.

The last major series of cocaine-related deaths, 68 cases from recreational abuse, came from Dade County, Florida in 1979 (58). This series only overlaps with Finkle and McCloskey's national survey in three cases, since the majority of the cases occurred since 1975. Twenty-nine deaths involved the use of other drugs (particularly heroin), 24 died directly from the toxicity of cocaine alone and 15 died from trauma. Because cocaine is statutorily classified as a narcotic, deaths from Dade County are reported as a percentage of accidental narcotic overdose deaths (Figure 10).

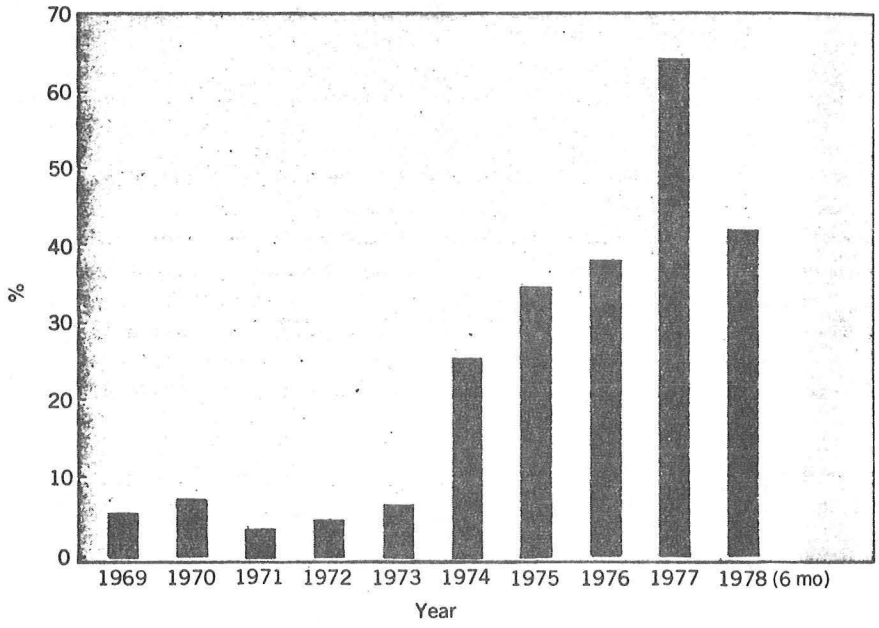

Figure 10: Cocaine-related deaths as percent of accidental narcotic-overdose deaths.

In the 24 deaths resulting from cocaine-only, 11 used the drug intravenously, seven took the drug orally (usually smugglers), and five died after snorting cocaine (at least twice during the preceding hour). Death occurred from a few minutes, up to an hour. Eight victims had witnessed deaths characterized by sudden, unexpected, grand mal type seizures. Most of the deaths in IV abusers likely resulted from loss of airway during Stage IV coma that occurred only minutes after injection (victims were usually found close to their paraphenalia "kits"). Three of the deaths after oral cocaine were in previously reported cases involving smuggling (24).

Again, the patients were predominantly white, male and young. Of the trauma victims, five died in motor vehicle accidents, seven died of homicidal and two of suicidal gunshots.

Table XIII

Cocaine-Related Deaths

	Street Cocaine Alone	Cocaine With Other Drugs	Trauma	Total No. of Cases
White men	12	14	11	37
White women	5	1	2	8
Black men	5	10	2	17
Black women	2	4	0	6
Total	**24**	**29**	**15**	**68**
Age range, yr	15-36	18-45	16-42	15-45
Average age, yr	26.0	26.5	25.8	26.2

Blood levels of cocaine and lidocaine were measured in 13 of the 24 cases of acute cocainism (Table XIV). The highest average blood cocaine occurred in those who took the drug orally (0.92 mg/dl), followed by those who snorted cocaine (0.44 mg/dl). Those who died after IV injection had the lowest average level (0.30 mg/dl).

Post-mortem examination in all cases disclosed pulmonary edema and generalized visceral congestion (no nasal septal perforations were noted in this review either).

A caveat: According to Smith and Wesson (59), knowledge derived primarily from clinical descriptions of adverse drug reactions or from descriptions of use patterns obtained by interviewing cocaine abusers is analagous to studying astronomy by sitting in a cave and asking visitors from the surface to describe the stars. Clinical reports are likely biased toward the bizarre or atypical cases and are subject to marked observer distortion. Human volunteers studies use substantially less cocaine than use patterns on the street where escalation in dosing is routine. The relative safety of a drug is further confused by such studies, if as in most cases, the probability for an adverse reaction is a function of increasing dosage. See Figure 11.

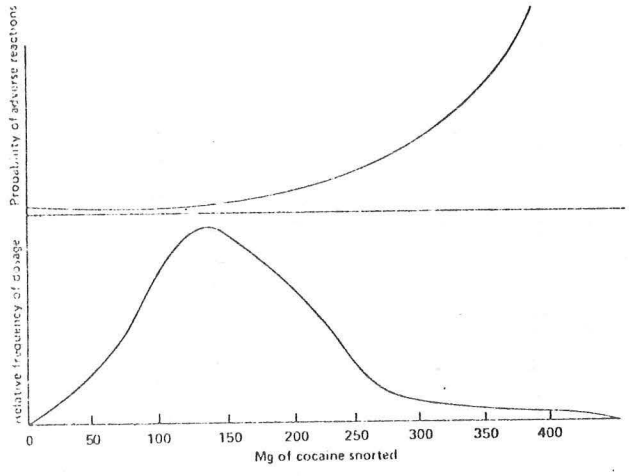

Figure 11: (Top) Relationship between dosage of cocaine used and probability of adverse reaction. (Bottom) Estimated distribution of cocaine dosage used per episode of cocaine use in noncontrolled setting.

Table XIV

Deaths Caused by Acute Cocainism

Table 2.—Deaths Caused by Acute Cocainism

Case No.	Route of Administration	Blood Cocaine Concentration, mg/dL	Blood Lidocaine Concentration, mg/dL	Comment
1	Oral	0.72	Not done	Terminal seizures
2	Oral	0.96	Not done	Found dead
3	Oral	1.28	0.96	Suicide, terminal seizures
4	Oral	0.70	Negative	Found dead (also snorted cocaine earlier)
5	Intravenous (IV)	0.14	Negative	Died after 3 hr of coma
6	IV	0.38	Not done	Collapsed and died
7	IV	1.10	0.20	Collapsed and died
8	IV	0.01	Positive*	Terminal seizures
9	IV	0.09	Not done	Collapsed and died
10	IV	0.05	Not done	Collapsed and died
11	Nasal	1.10	Negative	Terminal seizures
12	Nasal	0.03	Not done	Terminal seizures
13	Nasal	0.19	0.08	Terminal seizures
14	Undetermined	1.70	Positive*	Found dead at home

*Not quantified.

Important points concerning recreational cocaine-related deaths from the available literature can be summarized as follows:

1. The national picture of cocaine deaths is not uniform or predictable from known geographic drug abuse problems in various areas.

2. Analytical toxicology methods are now generally available with a sensitivity that allows rapid and reliable detection of cocaine in forensic cases. Further trend information should be available in similar epidemiological surveys.

3. Victims of cocaine-related death are predominantly young, white, employed and poly-drug abusers by history.

4. A significant number of heroin users were found among the victims.

5. The IV route was predominant.

6. The manner of classified death is usually accidental with death occurring prior to the victim's reaching the hospital.

7. Blood concentrations in the fatalities revealed a majority of deaths at relatively low blood concentrations.

8. Deaths do occur with intranasal cocaine abuse and the blood concentration is certainly in a range consistent with that seen with other routes of ingestion.

Conclusion

Cocaine has been used since antiquity as a component of the Coca leaf. The purification of cocaine by chemists has made available a much more lethal abuse preparation. The abuse of cocaine has waxed and waned much like an infectious disease that hides in an endemic state, only to surface when a new population is available for contagious spread. Sadly, there are no vaccines for illicit drug and substance abuse. A well-informed public and appropriate law enforcement efforts may be the preventive medicine needed for the control of a national illness. The real question, however, is why such a drive to illicit drug and substance abuse exists in man.

Finally, the toxicity of cocaine, in medical or illicit use, should preclude any support for the agent as a "safe and nonaddicting" recreational drug.

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The Hazards of Phencyclidine Abuse

Ron J. Anderson May 7, 1981

Historical

The desire to find a nonnarcotic, nonbarbiturate intravenous anesthetic lead to the investigation of a series of arylcyclohexamines in the late 1950's. Two drugs of high potency, phencyclidine and ketamine, appeared promising because they did not appreciably depress respirations (1-3). During the early clinical trials with phencyclidine (PCP), reports emerged of a psychologically distressing emergence reaction and a post-anesthetic syndrome characterized by dysphoria, depression and even psychotic behavior (4-6). Further human testing of PCP as an anesthetic was discontinued in 1965 due to the severity of these phenomena. Ketamine is still commercially available as Ketalar® for use as a human anesthetic agent. While not as common, or as severe in intensity, similar adverse post-anesthetic reactions do occur with this agent (7).

Animal experimentation with PCP revealed an ability to produce serenity in large primates and monkeys. In an effort to salvage the drug, Parke Davis & Co. introduced PCP (Sernylan®) as a veterinary anesthetic in 1967. Soon after, the drug emerged "on-the-street" with somewhat different results.

> *"It hit Haight-Ashbury in 1967 - PCP quickly acquired a reputation as a bummer drug. People named Strawberry were going around punching people named Wildflower....."*
>
> *(T. Cahill, Moonwalk Serenade, Rolling Stone, July 13, 1978)*

Widespread abuse of PCP lead to the discontinuation of the legal manufacture and sale of the drug in 1978. Currently, PCP falls under the Class II provisions of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (8).

The street supply of PCP was not curtailed in a major way by the withdrawal of veterinarian supplies. The main ingredients necessary for the illicit synthesis of PCP in so-called "kitchen laboratories" are extensively used in industry making it virtually impossible to monitor sales as a control device. The synthetic process is relatively simple and the ingredients are cheap (9); PCP has a high profitability which serves as a driving force in the street promotion of the drug by "pushers" who can either offer it at a lower price than other drugs, or sell it at higher prices, misrepresented as THC, cannabinol, mescaline, psilocybin, LSD, cocaine or amphetamines (10).

Epidemiology of PCP Abuse

The extent to which PCP is abused has been most likely underestimated by the traditional survey techniques employed by epidemiologists working in the field of drug abuse (10, 11, 12).

Table I DRUG ABUSE SURVEYS

Agency	Indicator Method	Year	% "Ever Used" PCP	Results	Ref.
National Institute on Drug Abuse (NIDA)	National Survey of Drug Abusers				
	Ages 12 to 17 yrs	1976	3.0	Doubling of reported users	
		1977	5.8		
	Ages 18 to 25 yrs	1976	9.5	50% increase of reported users	
		1977	13.9		(10)
Drug Abuse Warning Network (DAWN)	PCP related deaths emergencies	1974 to 1976		Deaths doubled (from 17 to 30) Emergencies doubled (from 54 to 111)	(11)
National Youth Polydrug Study NYPS)	Review of drug abuse in 2750 polydrug abusers, < 19 yrs of age (from 97 drug-abuse treatment centers)	1978	33	Use of PCP exceeded that of inhalants, sedatives, cocaine and opiates. Two-thirds of the users were "regular users" of PCP.	(11)
New York State	Survey of 1.8 million New York State secondary school students	1978	14	A quarter million children, from which 11,000 reported at least 10 uses in the previous 30 days	(12)

Unknowingly, a naive user may become intoxicated with PCP from smoking a "laced or dusted" marijuana joint, or purchase and use the drug misrepresented as another substance of abuse. Such data gathering efforts are further clouded by the myriad of "street names" for PCP, some of which may be used for other drugs in different geographic areas and used differently by various ethnic groups. (See Table II)

Table II

The Many Names of Phencyclidine*
(alphabetical order)

Common:

Angel Dust, Crystal, Hog, Kay Jay, K.J., Kristal, Kristal Joint, PCP

Less Common:

"Aurora Borealis"
Cadillac, Colombo, Cozmos, Cyclones
DOA, Dust
Elephant Tranquilizer, Embalming Fluid
Goon
Killerweed
Mintweed, Mist, Monkey Dust
"Niebla"
"Paz", Peace or Peace Pill, (the) Pits, "Polvo" or "Polvo de Angel" or "Polvo de Estrellas"
Rocket Fuel
Snuffle, Sheets, Shermans, Snorts, Soma, Supercools, Surfer
TAC, THC, Tic, Tranks, TTI-3

*In general, the wilder a street drug's name, the more likely it will contain PCP.

An automated analysis system (gas-liquid chromotography/mass spectrometry) to detect phencylidine in urine (and subsequently serum and tissue) was published in 1976 (15). While this system was not generally available, confirmation of suspected cases of PCP abuse became possible using this quantitative and qualitative analysis. More recently, a rapid radioimmunoassay screening test for the detection of phencyclidine has been described by Kaul and Davidow (16). In the most recent issues of the Annals of Emergency Medicine, the EMIT, one-minute assay for phencyclidine, is advertised as a diagnostic aid which purportedly allows for a rapid discrimination between PCP-induced psychosis and schizophrenia (17). Screening assays, rapidly available to the emergency room physician, will assist in a more definitive approach to the individual patient since PCP intoxication can mimick schizophrenia (18), mania (19) or even closed head injury (20). These assays can also be used to better determine the true incidence of PCP abuse in various study populations. If PCP abuse is suspected, but the urinary screen

is initially negative, a second screen should be obtained on urine obtained after the administration of 0.5 to 2.0 Gms of ascorbic acid. This step increases the sensitivity of the GC/MS assay (21), and most likely the radioimmunoassay, by increasing the urinary excretion of PCP.

Indirect indicators, that is PCP-related arrests or laboratory closures, suggest an increase in street availability (11).

Various street drug monitoring programs have been in existence in this country since the early 1970's. These programs depend upon the voluntary submission of samples for evaluation. Interpretation of data obtained from these sources must take into account several obvious shortcomings:

1. Naive users are usually impulsive and do not subscribe to such services.

2. Many drug abusers avoid such programs fearing prosecution or identity disclosure.

3. Users who do submit samples suspect a "rip-off", skewing results toward a higher percentage of misrepresentation.

4. Drugs of abuse commonly diverted from legitimate sources such as the pharmaceutical manufacturers are usually easily identified and therefore hardly ever brought in for analysis.

Still, such programs add a valuable dimension to the other epidemiologic efforts previously employed. In 1976, Brown and Malone (22) summarized the analytic results of three California and one Minnesota based programs. The programs were: a) University of the Pacific, b) Pharm Chem Laboratories of Palo Alto, c) LAC-USC Medical Center of Los Angeles and Metro Drug Awareness of Minneapolis, Minnesota. PCP alone, or in combination with LSD, was often sold as mescaline, as psilocybin, and as "THC". (See Table III) In fact, "THC" contained PCP in 151/160 samples. Since tetrahydrocannibol is unstable in crystal or powder form, virtually all street "THC" is PCP; less frequently, PCP was sold as LSD, amphetamine, cocaine, even heroin. Lysergic acid diethylamide (LSD) has been referred to as the "backbone of the trade" by drug pushers. It is commonly sold under the guise of another hallucinogen in much the same way PCP is misrepresented as "THC".

Table III

Summary of Analysis Results of Street-Drugs Containing PCP

Alleged Drug	Number of Samples	Actual Chemistry						
		As Claimed	LSD	LSD + PCP	PCP or Analog	Not Identified or Other	% LSD Mentioned	% PCP Mentioned
Mescaline	N=298	51	160	36	10	41	66 %	15 %
Psilocybin	N=323	47	162	14	1	99	55 %	∿ 5 %
"THC"	N=160	0	---	3	148	9	∿ 2 %	94 %

Reference No. 22

The User: "The Man"

The average first time PCP user is a 14 year old male and may be of any ethnic group or socioeconomic class (11). Reports depicting PCP abuse as a problem primarily of the black community (23), the Mexican-American community (14), or the white community (24) are merely descriptions of "telescoped" experiences. Phencyclidine is rarely the first drug with which experimentation starts and usually follows repetitive use of alcohol and marijuana, or possibly sedatives, stimulants and opiates. The chronic abuser of PCP is most usually a polydrug abuser who has abused twice as many drugs as the polydrug abuser who has managed to avoid PCP (12). Many chronic PCP users have pre-morbid features of depression, alienation, hopelessness and a self-destructive personality, or the wish to escape negative feelings (14, 24). The age range for chronic PCP abusers is wide but seems to peak between 18 to 21 years of age.

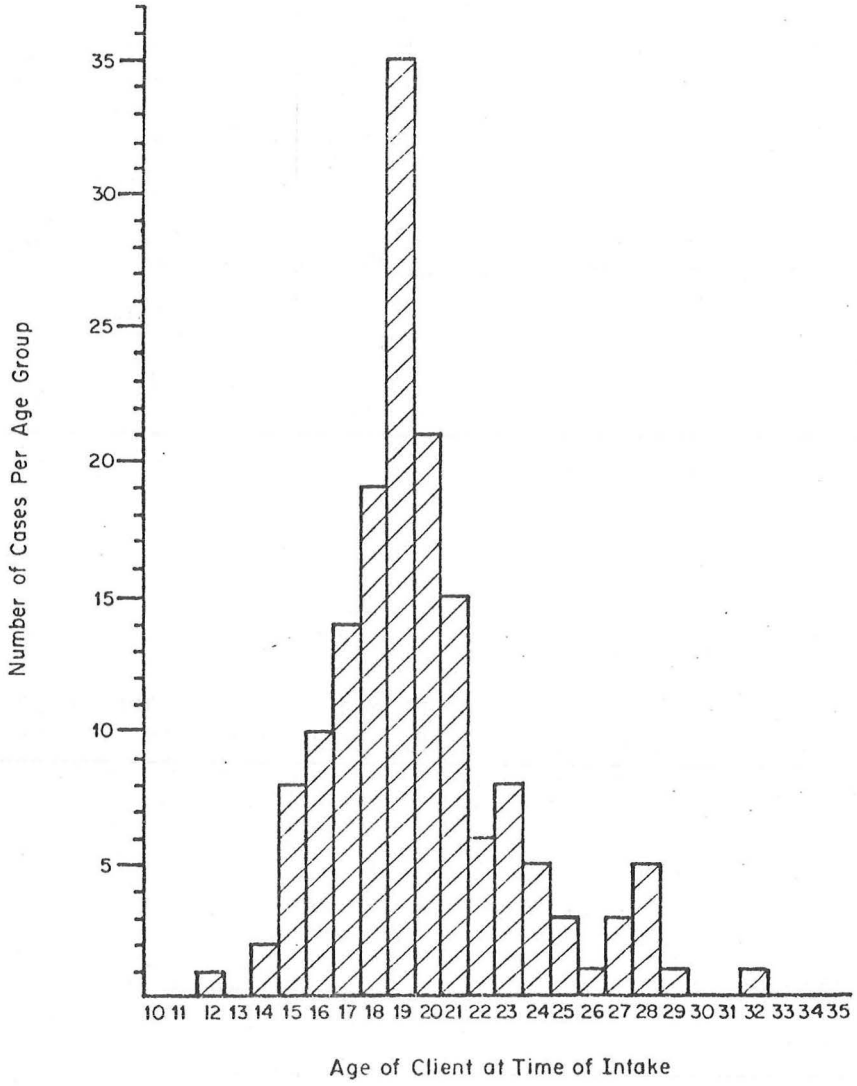


Figure 1: Age of client at time of intake for counseling concerning PCP abuse. Ref. No. 24

The "Method"

PCP may be self-administered by smoking a "laced or dusted" joint of marijuana, oregano or parsley, by snorting ("horning" or "snarfing"), by oral ingestion or by intravenous injection. Smoking and snorting are favored by most chronic PCP abusers since these avenues permit some degree of titration of the level of intoxication. The onset of action is slower, and the "coming down" longer after oral ingestion. The "high" begins within minutes when the drug is used by inhalation, intranasal or parenteral routes and lasts four to six hours (10). Adverse effects ("getting too high") and accidental overdose are more common after oral or intravenous PCP abuse. The sophisticated user ordinarily avoids the oral or intravenous routes except toward "the end of a run" (an attempt to stay intoxicated for several consecutive days), or as part of a suicide attempt. Oral ingestion of PCP by very young children of chronic abusers has been reported, but even passive inhalation may cause serious intoxication in this age group (25, 26).

The "Material"

PCP is classified as a potent sympathomimetic and hallucinogenic dissociative anesthetic, not a "psychedelic". In pure form, the hydrochloride salt of PCP is a white crystalline solid with a PKA of 8.5 and is readily soluble in both water and alcohol. The free base is not water soluble and is usually a granular powder. The "street form" of the drug, is usually a powder, tablet, or a leafy mixture, is often adulterated and is highly variable in appearance. Between 1971 and 1974, street samples of PCP analyzed in a west coast forensic laboratory had other drugs in 50% of the samples tested; since 1975, only 25% of the total samples contained additional drugs (27). Very few of these samples were sold as PCP. When PCP is sold as a granular powder identified to the buyer as "angel dust", purity may be as high as 50-100%, falling to 10-30% when sold under other names, or as another drug altogether (28). The percentage of PCP in leafy mixture is usually much lower, averaging 1 mg PCP to 150 mg leaves.

Presently, over 30 PCP analogs, some capable of producing psychic effects, have been synthesized and some of these are occasionally found in street samples (9). One intermediate of the synthetic process, 1-piperidinocyclohexanecarbonitrile (PCC), is a common contaminant of street samples of PCP. When smoked, PCC liberates hydrogen cyanide. Large doses of "presumed PCP" (20 to 100 mg) can cause cyanmethemoglobinemia and cyanosis (29). Intraperitoneal injection of PCC in mice is twice as lethal as PCP and their toxicities are additive (30).

The Desired Effect

It is hard for an emergency room physician, seeing only "the tip of the iceberg", to imagine how PCP has become a major drug of abuse. While many first time users say they would not knowingly take PCP again (that's probably how they took it the firt time!), a significant number of polydrug abusers repeatedly use this drug, alone or in combination. For some, it represents a "drug of choice" abused for either a perceived pleasurable effect or as a method of escaping perceived pain or negative feelings. The majority of PCP abusers are unknown to the medical community. The unpredictable nature of the street drug makes each of these individuals potential patients. Fauman and Fauman (31) reported that 76% of their sample chronic PCP users acknowledged having had "bad trips" and many reported a deterioration of intellectual capacity, memory, and personality. Still the "positive reinforcement" provided by the drug or the drug-taking milieu are strong enough to encourage repeated abuse. What are chronic PCP abusers looking for?

There is a great variability in PCP's effect from one user to the next. Usually PCP is taken as a social drug, but other times it is taken "solo" as an escape drug providing a euphoric state which permits the user to distance himself/herself from unpleasant feelings and other people. According to the user (24), PCP *"seems to heighten whatever you're feeling. It lets out whatever you've been holding back.... Being zoned is a stimulation of your emotions more than they really are."* Users try to avoid "bad trips" by regulating the dosage and by not using the drug when their mood or environment is inappropriate. When "getting too high" occurs, the users lose control of the intoxication. The reports of deep depression, suicides, paranoia and violence during PCP intoxication is interpreted by one user as: *"anything you do on dust is from you; you do what's in your mind"* (24). This may or may not be true, but the clinical translation of the drug's effect depends a lot on the premorbid emotional state of the user, the dose, the route of administration, and importantly, the presence of exteroceptive input.

During early trials with PCP as a human anesthetic, volunteer subjects in isolation chambers reported the feeling of "utter nothingness" attesting to the drug's ability to block sensory inputs such as pain and proprioreception (32). The difficulty in processing incoming sensory signals seems to be grossly impaired or distorted and leads to an intensification of feelings and possibly exaggerated behavior. A negative experience on PCP is primarily quantitatively, and not qualitatively, different than a positive one and the user cannot, with any certainty, be assured that the drug's effects will be as intended.

The pharmacological effects of PCP result in sensations described as "desirable" by some chronic PCP abusers. (See Table IV)

Table IV

"Desired" Effects During PCP Intoxication

1. A distortion of body image and distance.
2. Depersonalization or estrangement from surroundings
3. A sense of power, strength and/or invulnerability
4. Euphoria or a dream-like detached state

In the PCP intoxicated individual, time seems to expand as body movement slows and muscular coordination becomes impaired. A staggering gait, described as "moonwalking", or a state of near immobility may occur. Touch, pain and proprioceptive impulses are dulled. Speech is purposeless or blocked. Psychedelic kaleidoscopes of color have not been reported with PCP, however, visual and auditory hallucinations are common. Extreme anxiety, feelings of impending death, and dangerous protective behavior may be precipitated by hallucinatory signals.

Recently, Carrol and Meish (33) demonstrated that PCP serves as a "reinforcer" in food deprived Rhesus monkeys, over a wide range of concentrations. (See Figure 2). This work confirmed early animal studies by Balster and Chait (34) which highlighted PCP's ability to act as a discriminative stimulus and thereby lead to a pattern of self-administration consistent with the development of tolerance. PCP seems to create a strong psychological dependence in regular users who virtually must have the drug with them at all times. The sudden discontinuation of PCP does not cause withdrawal symptoms per se, however, a post-intoxication depression or a rapid return of negative feelings may serve as reinforcers of repetitive drug use.

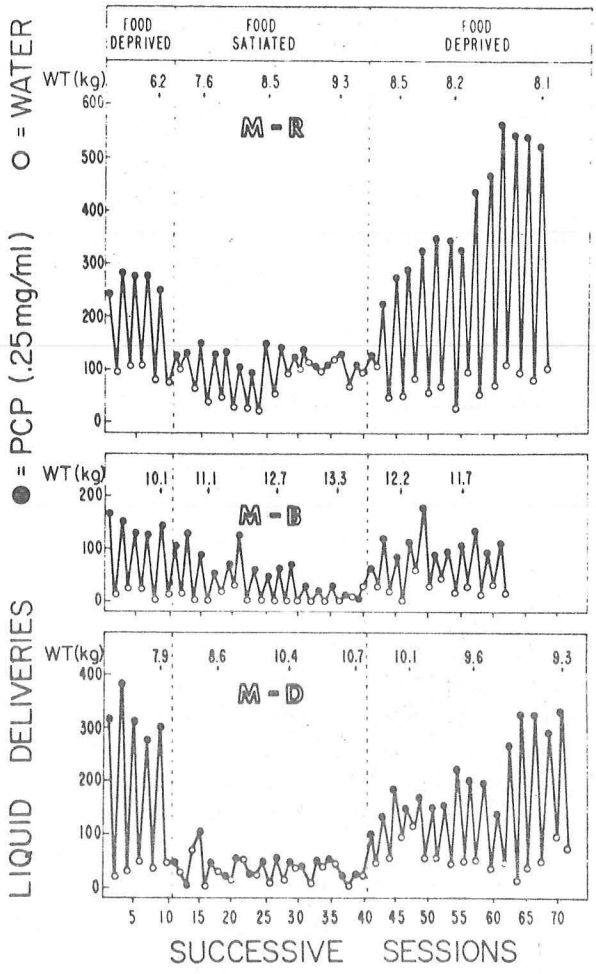


Figure 2: Self-administered, liquid deliveries with PCP were increased during "food-deprived" conditions (only 75 Gm of food between sessions) compared to periods where food supplies were unlimited between sessions in Rhesus monkeys. Numbers above data points refer to the body weights of the monkeys.

From Carroll and Meisch (33)

The "Price"

Clinically, the toxicity of PCP can be divided into four categories:

1. Chronic psychiatric complications of PCP abuse
2. Behavioral toxicity
3. Acute intoxication or overdose
4. Post-Ingestational syndromes

The Psychiatric Complications of Chronic PCP Abuse:

In normal persons intoxicated with PCP, assessment of attention span and quality, motor function, proprioception, symbolic and sequential thinking and response to sensory isolation yielded results similar to that expected in chronic schizophrenia (35). PCP is a drug which acutely produces schizophreniform activity in humans (and in animal models).

In 1959, Luby et al (6) reported the acute effects of PCP in nine normal volunteers, four chronic schizophrenics, one acute catatonic schizophrenic, two pseudoneurotic schizophrenics and two patients with character disorders. Each subject received 0.10 mg/kg PCP intravenously, and reported a clinical experience with a triphasic course. The first sensation was one of depersonalization, unanxious isolation, distortion of body image and blunting of sensory input. In the second phase, cognitive function became impaired and such schizophreniform thought disorders as blocking, echolia, use of neologisms and word salad were apparent. Proverb interpretations were fragmentary and serial sevens could not be done. Initially, lethargic and apathetic, these subjects later became hostile and displayed a negativistic affect. The normal volunteers had no lingering toxicity, however, the four relatively well compensated chronic schizophrenics became extremely disorganized, had a loosening of associations and an inappropriate affect for four to six weeks.

Burns and Lerner (36) reported persistent cognitive and memory deficits, speech disturbances and mood disorders in chronic PCP abusers. Weight loss, a lack of grooming and self-care, loss of employment or poor school performance occurred with prolonged abuse. Auditory hallucinations, paranoia and violent behavior were often present. Severe depression and a high rate of suicide occurred in chronic PCP abusers. The chronic PCP/polydrug abuser is often unable to cope with routine life circumstances because of a lack of a high school education, lack of job skills, a lack of meaningful personal relationships, and a sense of alienation, hopelessness, and disintegration of family. Whether a premorbid state, or a result of PCP abuse, these features are commonly mentioned by investigators.

PCP-induced psychosis may result from chronic PCP abuse, from the acute intoxication, or as a part of a post-ingestational syndrome. Table V summarizes the available literature concerning PCP induced psychosis.

Table V

Phencyclidine Induced Psychosis Persistent
Beyond the Drug's Half-Life
(case reports compiled from 1975-1980)

Reference No.	Cases	M:F Ratio	Age Range (yrs)	Time of Ingestion Prior to Admission	Duration of Hospitalization	Required Long Term Therapy > 1½ Month
37	3	3:0	18-19	1-4 days	13-17 Days	?
38	2	2:0	27-33	Hours	∿ 5 Days	?
39	3	1:2	2½-26	Hours	2- 8 Days	3
40	5	2:3	16-22	Hours to 4 Days	18-71 Days	2
41	3	2:1	22-44	Not Stated	4-15 Days	3
42	2	2:0	17-19	2 Wks-2 Months	∿ 2 Weeks	2
43	15	13:2	Mean Age 25.5	Not Stated	2-17 Days	Not Stated
18	9	8:1	18-24	a) Not Stated	7-90 Days	9
* 1 repeat PCP				b) 1 Week	1 Month	-
19	1	1:0	18	a) 1 Week	1 Month	-
* 1 repeat PCP				b) 4 Days	6 Weeks	1
40	2	0:2	20-26	2-3 Weeks	24-99 Days	2
Summary:	45 (47 episodes)	34:11	R = 2½-33	Variable	Variable	22/33 Patients

* Two patients repeated PCP use after discharge, resulting in a rapid return of psychosis.

These case reports represent individuals without a personal or family history of psychosis. As such, they represent PCP-induced psychosis and point out several salient features:

1. PCP induced psychosis may present temporally distant from the time of ingestion.

2. The clinical picture may mimick schizophrenia or more rarely, manic-depressive illness (19, 42).

3. Re-exposure to PCP may precipitate a rapid recurrence of psychosis (18, 19).

4. Prolonged hospitalization and chronic psychiatric therapy may be necessary.

5. Young males are over-represented in the case reports (but also more commonly abuse PCP).

In the report of Allen and Young (18), one individual developed a "schizoaffective disorder" after being free of any signs or symptoms of PCP-induced psychosis for over a month when he was incarcerated for legal problems. Apparently, this consequence is not uncommon. Psychiatric admissions from the catchment area served by Saint Elizabeth's Hospital (NIMH) in Washington, D.C., have been reviewed by Luisada and Brown (45). PCP induced psychosis is presently the leading cause of in-patient psychiatric admissions. A small fraction of their sample represents a second psychotic episode related to PCP or reactivation of schizophrenia in previously known patients through experimentation with PCP. Excluding these two categories of patients, one-fourth of the patients initially treated for PCP psychosis return within a year or so with a schizophrenic episode occurring in the absence of drug use. These latter episodes differ from the first by being less violent and more responsive to neuroleptic therapy.

Note: It will be important for investigators to follow such patients prospectively with PCP urinary screens to determine if such individuals actually do become "schizophrenic" in a drug-free environment.

The presence of vertical or horizontal nystagmus, a blank stare, ataxia, facial grimacing or jaw jerking, and unprovoked aggression suggest PCP induced psychosis and not schizophrenia. PCP-intoxicated individuals cannot estimate time intervals (30 second interval tests) (43); they tend to lack an organized symbolic process (14), and they do not benefit from attempts to help them interpret their delusional state ("talking down"). A past history of polydrug abuse, poor social adjustment, depression, etc. support the tentative diagnosis of PCP-induced psychosis which should be confirmed by toxicologic studies.

The immediate treatment goals for PCP-induced psychosis (not related to overdose or acute intoxication) include:

1. Prevention of injury to patient and others.

2. Assurance of continued treatment (non-voluntary admission if possible).

3. Reduction of stimuli, hence agitation.

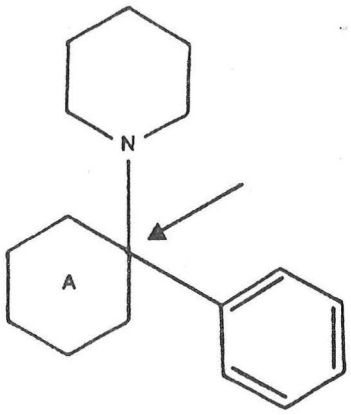
4. Amelioration of psychosis with neuroleptic therapy (halperidol or chlorpromazine).

Because of the intense paranoia, unpredictable aggression and protective behavior exhibited by such patients, they should always be admitted (from both the medical and legal viewpoints).

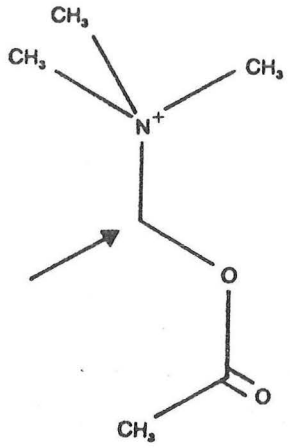
PCP-Induced Psychosis: A Model for Schizophrenia?

The dopamine hypothesis of schizophrenia is currently a widely accepted theory used to explain the biochemical basis for the malady (46, 47). This model postulates that psychosis arises from an imbalance of the cholinergic and dopaminergic systems of the brain which are intimately involved with control of emotions. The mesolimbic pathway contains dopamine containing neurons and is the area thought responsible for emotional expression. Amphetamine, which increases the release and blocks the reuptake of dopamine, can induce a psychosis resembling paranoid schizophrenia after prolonged administration (48). On the other hand, drugs which block dopamine, such as haloperidol, are potent antipsychotic (neuroleptic) agents and will also block PCP-induced stereotypic behavior in animals (49).

PCP is known to affect the catabolism, steady state levels and turnover rates of most of the punitive neurotransmitters in the brain (norepinephrine, serotonin, dopamine, etc) that are involved with emotion and locomotion. The drug has also been classified as an anticholinergic by Ban (50) and as a competitive inhibitor of acetylcholinesterase (cholinomimetic) by Maayani, et al (51). PCP's structural similarity to acetylcholine make this possibility attractive (Figure 3). PCP competively blocks the reuptake of dopamine into the presynaptic terminals, causes a spontaneous release of dopamine from nerve ending storage vessicles and stimulates dopamine sensitive adenylate cyclase activity, all of which increase dopaminergic activity (52, 53). This potent dopaminergic property, in addition to the anticholinergic and cholinomimetic properties, may be the reason that a schizophreniform psychosis can be precipitated by single doses of PCP. In time, the knowledge obtained from patients with PCP induced psychosis may provide the key to unlocking the biochemical abnormalities associated with functional psychosis.



Phencyclidine



Acetylcholine

Figure 3: The molecular structure of phencyclidine and acetylcholine: The electron densities surrounding the carbon competition for the same receptor occurs. The addition of the cyclohexyl ring (A) is PCP and its cogeners, however, results in antagonism and cholinergic blockade.

Another pathway, the nigrostriatal system, consists of dopamine-containing neurons and is primarily involved with motor activity and coordination (27). The abnormal movement disorders thought to arise from excessive dopaminergic activity in the nigrostriatal system (Huntington's Chorea, tardive dyskinesia, and drug-induced dyskinesia) (54), are somewhat akin to those associated with toxic PCP reactions.

A combination of dopaminergic hyperactivity and anticholinergic effects likely contribute to the development of hyperthermia during PCP intoxication. The dopamine containing neuronal distribution in the CNS is depicted in Figure 4 (47).

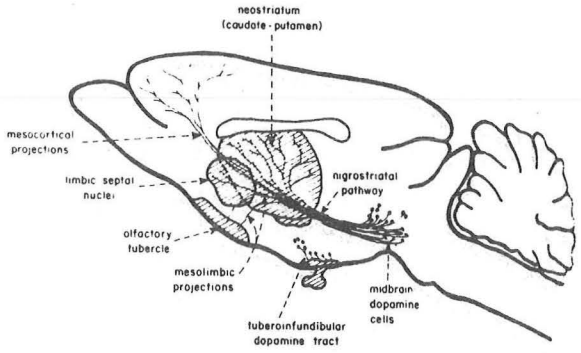


Figure 4: Dopamine-Containing Neurons in the Mammalian Brain.

Behavior Toxicity

The violent, aggressive and threatening behavior displayed by individuals intoxicated with PCP has lead to several murders (by the users) and a number of provoked homicides (committed by threatened bystanders or policemen). Bizarre acts of violence are often directed at close family members, but others appear to be fairly random. Self-mutilations (severed gentalia, severed limbs, eyes plucked out, etc) and suicide may result when hallucinatory directives are carried out. Figure 5 shows the arms of an individual who heard voices commanding him to "Eat your arms" (80). Often these directives are interpreted as "being from God".

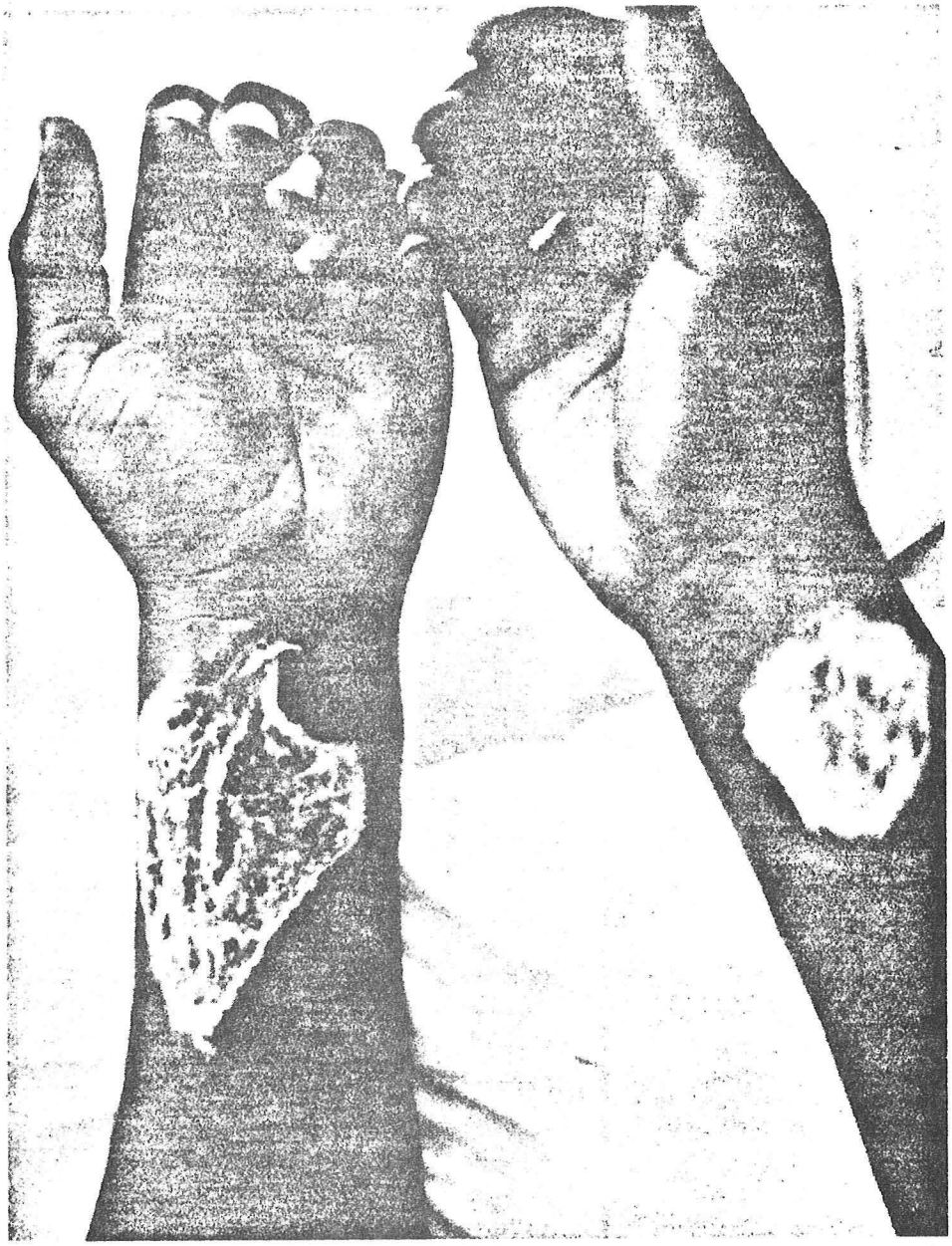


Figure 5: Self-inflicted injuries during PCP intoxication.

Swimming while intoxicated with PCP provides an unusual but pleasant sensation. The associated sensory disturbances, ataxia, muscular rigidity and incoordination, coupled to a sense of detachment, seriously impair swimming ability. The intoxicated individual may show no fear or respect for the water's depth or distance to shore, however, some drowning deaths have also occurred in shallow swimming pools, bathtubs, sauna's and even shower stalls. A similar disregard for heights, fire or other life-threatening events is common. It is this sense of invulnerability that often leads to attacks against armed policemen or multiple ER attendants.

The altered perception of time and distance, and the lack of motor skills, make driving an automobile extremely hazardous to the user and bystander alike.

Table VI summarizes several series of phencyclidine-related deaths. Realizing that forensic pathologists more than likely deal with victims dying outside the health care delivery system, it is the behavioral toxicity of PCP that accounts for the majority of deaths (72%) in these series.

Table VI

Phencyclidine Related Deaths

			Primarily PCP Overdose		Primarily Behavioral Toxicity		
Author	Location	Total No.	Suicides	Accidental	Suicides	Accidental	Homocides
Burns and Lerner (36)	Orange and Alameda Counties (1970-1976)	19:	2	4	3 (2 asphyxia/ drowning) (1 GSW/head)	8 (8 asphyxia/ drowning)	2 (1 asphyxia) (1 GSW/head)
Noguchi and Nakamura (55)	LA County (1976)	16	1	2	2 (1 GSW) (1 stabwound)	5 (3 asphyxia/ drowning) (1 multiple injuries from jump off balcony) (1 "massive intravascular sickling" during extreme exertion)	6 (5 GSW's) (1 strangulation)
Reynolds (56)	Oakland (1970-1976)	11	4 Intent Not Stated		2 (1 overdose with phenobarbital) (1 GSW)	5 (4 asphyxia/ drowning) (1 blunt trauma with multiple injuries)	--
		46	13 (28 %)			33 (72 %)	

Toxicologic examinations of victims of accidental or intentional PCP overdose reveal a higher blood level than that found in victims of behavioral toxicity (Figure 6). Often, the overdose deaths have a significant amount of PCP in their gastric contents.

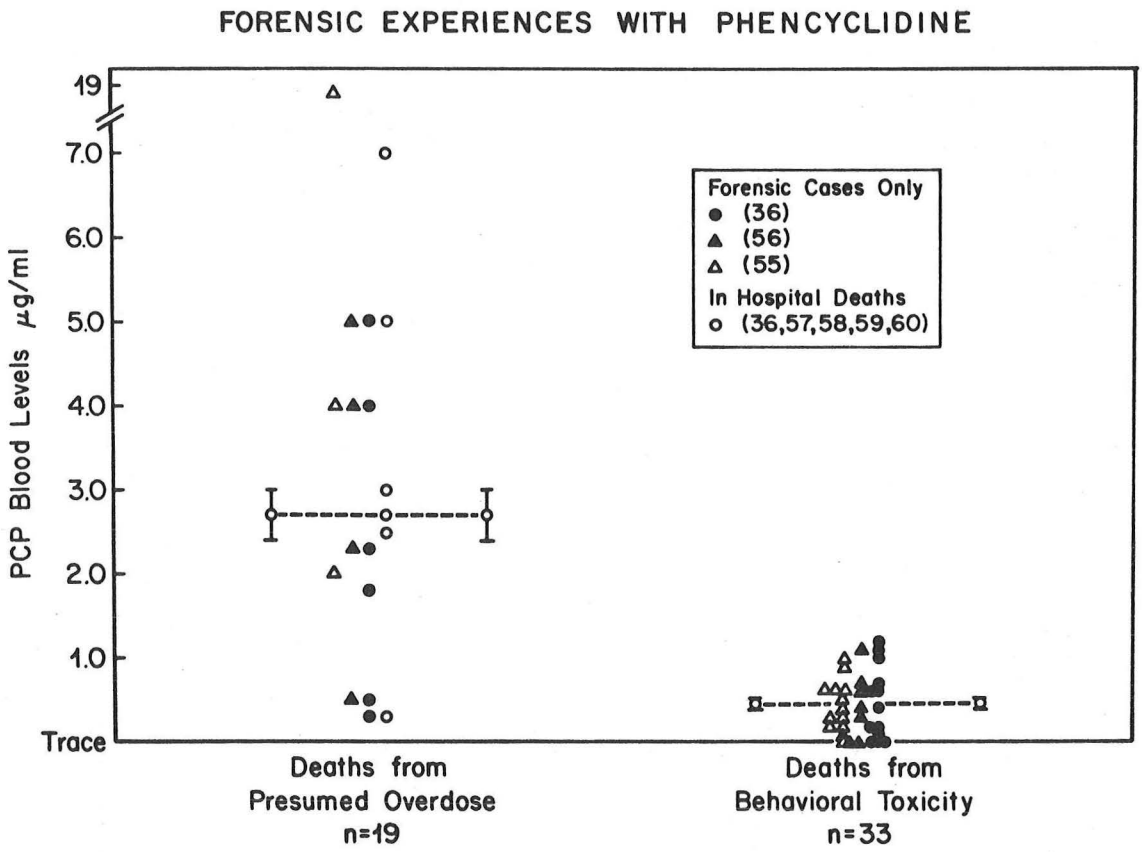


Figure 6. The mean PCP blood level in deaths from overdose, 2.7 µg/ml compares to a mean PCP blood level in deaths from behavioral toxicity of .45 µg/ml. Parkland has seen 26 Stage I PCP overdoses and their average PCP blood level was somewhat lower, .12 µg/ml (range 1.0 to trace or .001 µg/ml).

The deaths that result from PCP overdose are characterized by pulmonary congestion and aspiration of gastric contents consistent with an agonal loss of airway and an anesthetic death (36). Seizure activity and apnea are likely, given our knowledge of patients in Stage III intoxication.

Editorial Note

It is PCP's behavioral toxicity that poses the greatest threat to the public's health. Imagine a scenario where a large crowd, some members of which are intoxicated with various drugs and/or alcohol. Add in a few individuals "zoned on angel dust", a few commonly carried weapons (hand guns, knives, brass knuckles, etc.), an inciting event and subsequent crowd reaction, and you have all the ingredients for a mass casualty. During the last "Texxas Jam" music festival, our emergency room was placed on alert for such a possibility and it was considered likely considering our experience with PCP intoxicants during the first two festivals. Over a dozen PCP-like intoxications were treated that night and several required admission. Whether PCP or other drugs contributed to the multitudes of "aggravated assaults" treated by our surgical colleagues can only be speculated. It is also speculation as to the role drug intoxication may have played in the assault on the Cotton Bowl fence by 1,000 would-be attendees who had to be dispersed with tear gas by police. Crowd reaction, leading to a stampede at a recent rock concert, was responsible for a number of deaths, and one wonders what role drug intoxication may have played in this circumstance.

Sadly, an example of mass murder and assault has already occurred in conjunction with PCP intoxication. The sniper responsible for the massacre during the Battle of Roses Parade (San Antonio, 1978) was "laced with PCP" at autopsy (personal communication, Barry Wolcott MD, LTC MC, Chief, Section of Operational & Emergency Medicine, Brook Army Medical Center, Ft. Sam Houston, Texas).

The Medical Complications of Acute PCP Intoxication:

Patient Classification

The management of the patient intoxicated with PCP is dictated by the clinical presentation and subsequent course, not by PCP blood or urinary levels. Signs and symptoms wax and wane and may fluctuate rapidly and unpredictably. For convenience, PCP intoxication is divided into four stages:

Stage 1: A low level overdose, patient remains conscious and may display violent or self-destructive behavior.

Stage 2: A moderate level overdose, patient is unconscious, nonthreatening but does not have a compromised airway.

Stage 3: A high level overdose, patient is comatose and does not respond to deep pain. Airway may be in jeopardy, adrenergic crisis, seizures, etc. are possible.

Stage 4: The post-ingestional period, 72 to 96 hours after apparent recovery, may be characterized by hypertensive crisis or hyperthermia (so-called "dopaminergic storm").

Patients should be initially classified and treated according to the deepest level of anesthesia demonstrated since signs and symptoms in the individual patient often overlap several stages. As patients emerge from the deeper stages of anesthesia, they tend to go through the next lighter stage with all of its attendant risks.

Why the Waxing and Waning?

PCP is rapidly metabolized to relatively inactive metabolites principally by hydroxylation (61). Most of the mono-hydroxy metabolites exists as glucuronide conjugates when found in human urine (none have been found as yet in blood). Moderately high overdose situations result in some free drug excretion in the urine (8). The duration of poisoning symptoms is much longer than the drug's usual half-life at lower doses. This phenomenon can be partially explained. PCP has a pKa 8.5 (weak base). This property means that the drug exists in an ionized form in an acid medium where it is, in essence, trapped because of impenetrability of cell membranes to ions (62). PCP is secreted into the stomach via gastric juices, only to be reabsorbed later as the unionized drug after reaching the more alkaline intestine.

Using the reverse of this situation, pharmacological acidification of the urine and forced diuresis can enhance the elimination of PCP, unchanged in the urine, by 100-fold (13).

Another possible explanation for prolonged intoxication is the lipophilic character of the drug. James and Schnoel (63) administered phencyclidine to rats, and found that recovery of the drug was related to the nature of the tissue extracted and ranged between 65% to 90% of the administered dose. The lower range of recoveries was associated with adipose tissue and the highest with the blood and brain tissues. Extraction of PCP from a HCl acidified aqueous solution by extraction with chloroform allowed a recovery of 95-97% at a pH of 1.0 (see Figure 7). At one hour post-injection (50 mg/kg intraperitoneal PCP), adipose levels were 13 times higher than brain levels. See Figures 8 and 9. Adipose tissue levels then dropped by 50% in the second hour, but remained higher than blood and brain tissue throughout the study which ran for 48 hours.

At 48 hours post-injection, adipose tissue levels were still equivalent to the highest blood level which was seen at three hours. The highest level for brain tissue was also achieved by three hours and was slightly greater than the maximal blood level, however, blood levels were no longer detectable after 48 hours while low levels of drug persisted in the brain. The release of drug from adipose stores, long after blood levels are negative, may account for fluctuating levels of consciousness.

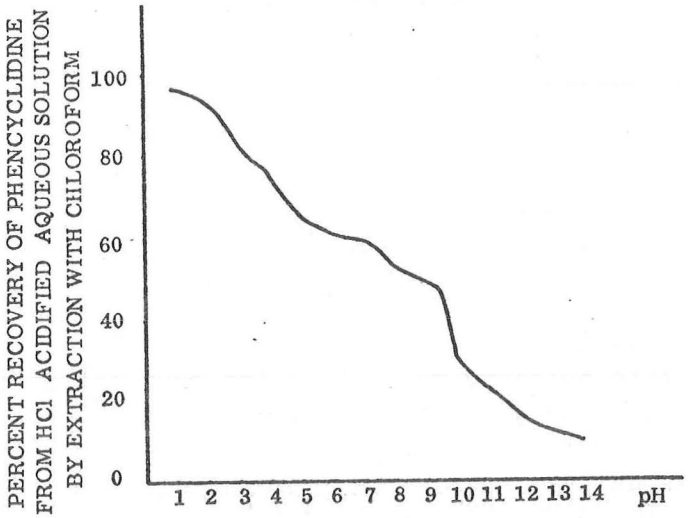


Figure 7: Percentage recovery of phencyclidine from HCl acidified aqueous solution by extraction with chloroform.

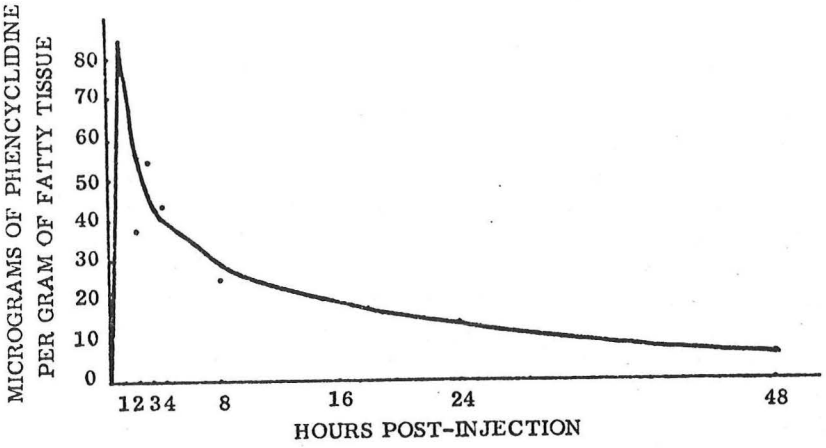


Figure 8: Adipose tissue levels of phencyclidine following injection of 50 mg/kg I.P.

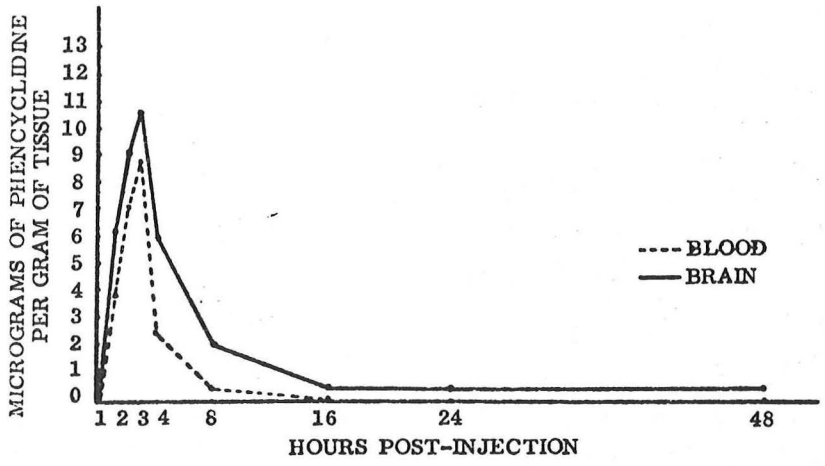


Figure 9: Blood brain tissue levels of phencyclidine following injection of 50 mg/kg I.P.

Stage 1 Intoxication

Clinical Features

Most PCP intoxications seen in emergency rooms will be in Stage 1. Usually, these patients have either smoked or snorted the equivalent of 2 to 5 mg of PCP (serum concentrations between 25 to 90 ng/ml) (13, 64). At this stage, PCP actually stimulates respiration, causes some rigidity of the strap muscles and virtually holds the airway open. With the degree of titration offered by smoking or snorting, the user is likely to become incapacitated before deeper levels of anesthesia are attained. The cardiovascular system is stable although blood pressure and heart rate are usually elevated. The clinical features of Stage 1 intoxication are outlined in Table VII.

Table VII

Clinical Features of Stage 1-PCP Intoxication

-Paranoid, agitated, volatile ⇌ catalepsy
-Blank stare with nystagmus, "Groucho eyes"
-Ataxia, gross muscular incoordination and rigidity, "moon-walking" or "zombie walk"
-Decreased sensory input for light touch, light pain and proprioception
-Blocked or purposeless speech.
-Hyperacousis
-Diaphoresis and facial flushing
-Hypersalivation, repetitive swallowing
-Bronchorrhea and noisy airways
-Repetitive vomiting (rarely)

Treatment: (Summarized by Algorithm in Table VIII)

The essence of treatment at Stage 1 is to reduce exteroceptive stimuli in order to protect the patient from self-inflicted injury and the ER personnel from assault. As a general rule, instrumentation should be avoided. In particular, because laryngeal and pharyngeal reflexes are accentuated, it is a mistake to attempt deep airway suctioning which can induce spasm necessitating endotracheal intubation.

Usually a "low sensory-input environment" (quiet room with restricted lighting) is adequate. If this is unavailable, some psychiatrists recommend covering the patient's head with a blanket (14). The patient must, none-the-less be carefully observed during this stage and hourly vital signs are necessary to establish the temporal sequence of the intoxication. Is the patient emerging from the intoxication or is the level of anesthesia deepening?

Chemical restraint with parenteral or p.o diazepam (Valium®) is quite helpful, usually quieting the agitated patient within 30 to 45 minutes (64). While our general ER policy discourages such therapy in favor of specific antidotes only, chemical restraint is far superior to, and safer than, physical restraint in these patients. Seriously threatening behavior, unresponsive to diazepam, can be treated with intramuscular haloperidol (Haldol®) or chlorpromazine (Thorazine®). The anticholinergic properties of cholorpromazine may be additive to those of PCP, which theoretically could result in an anticholinergic crisis. Hypotension seems to occur more frequently after chlorpromazine so we would recommend avoiding it in favor of haloperidol during the acute intoxication. Barbiturates potentiate the anesthetic qualities of PCP and should be avoided.

It is unlikely that Stage 1 patients have PCP in their stomachs, however, other drugs may have been ingested. Because of the excessive stimulation resulting from administration of syrup of ipecac in these convulsive-prone patients, induction of vomiting must be avoided. In more serious overdose (Stage II or III), the stomach should be emptied via lavage through a large bore Ewald tube, followed by administration of an activated charcoal slurry which has been showed to bind PCP (65).

Several authors recommend the routine administration of oral propranolol (Inderal®) 40 to 80 mg t.i.d., not only for its calmative effect, but to prophylax against adrenergic crisis should the intoxication deepen into Stage II or III (84, 66). Because acidification of the urine increases the urinary excretion of PCP, even in low level intoxications, it is valuable to have the patient slowly drink cranberry juice fortified with 0.5 to 2.0 Gms of ascorbic acid.

Table VIII

Algorithm for PCP Intoxication - Stage I

I. Reduce external stimuli.

   A. Avoid instrumentation.
   B. Protect patient from self-injury.
   C. Provide a low-sensory input room.

      1. "Talking-down" is of minimal value.
      2. Use physical restraints only as last resort.

II. Chemical restraint

   A. Diazepam - Options

      1. Intravenous-titration with 2.5 mg increments at 10 minute intervals to a total dose of 25 mg. Carefully monitor respirations.
      2. Intramuscular - 5 mg increments up to a total dose of 40 mg.
      3. P.O. - 10-30 mg p.o. in cooperative patients only - (check ability to swallow with sips of water).

   B. Haloperidol - intramuscular titration with 5 mg increments hourly until calm. We would avoid phenothiazines during the acute intoxication.

   C. Propranolol - 40 to 80 mg can be given t.i.d.

III. Enhance drug elimination.

   A. Do not induce vomiting.
   B. Charcoal does bind PCP but may be impossible to give now.
   C. Administer cranberry juice with 0.5 to 2.0 Gms ascorbic acid over 5-10 minutes.

IV. Psychiatry consultation after detoxification.

Adapted from Rappolt, Gay and Farris (64)
Aronow and Done (13)

Stage II PCP Intoxication

Clinical Features

The following set of signs and symptoms characterize this stage of intoxication which results from a moderate overdose, 5 to 10 mg by any route, and serum levels that overlap with both Stage I and Stage III (30-100 ng/ml) (64, 13).

Table IX

Clinical Features of Stage II PCP Intoxication

-Coma or semi-coma
-Blank stare with nystagmus - "Groucho eyes"
-Pupils mid-point and reactive
-Myoclonus or shivering
-Muscular rigidity with repetitive motor movements
-Markedly blunted pain, touch and proprioception
-Diaphoresis, facial flushing, hyperthermia-prone
-Hypersalivation, bronchorrhea
-Increased laryngeal and pharyngeal reflexes
-Vomiting
-Seizure-prone

Treatment: (Summarized by algorithm, Table XI)

The signs and symptoms of Stage II intoxication are very similar (but more intense) to Stage I. The precautions concerning instrumentation do not apply except for the admonition against deep oropharyngeal suctioning. A Foley catheter should be inserted to avoid bladder retention and support a forced diuresis utilizing "ion-trapping" as in Stage I. The urinary pH should be kept at 5.0 or below and the blood total carbon dioxide below 18 mEq/liter, which may require in addition to ascorbic acid, 2.75 mEq/kg/dose of ammonium chloride dissolved in 60 cc of saline given per NG tube. Usually, two or so doses of ammonium chloride achieve the initally desired results and a $\bar{q}$ 6 hour regimen will likely maintain an adequately acidified urine. After the achievement of a urinary pH of 5 to 5.5, and in conjunction with an expansion of the plasma volume, furosemide 40 mg IV should be administered and repeated as necessary. Intravenous fluids (normal saline) should be given to replace insensible and urinary losses. These are three contraindications to forced diuresis with an acidified urine.

1. aspirin overdose
2. phenobarbital overdose
3. rhabdomyolysis

The first two can be readily ruled out by the appropriate toxicological studies and the third by checking the urine for a nonheme benzidine reaction (myoglobinuria). If serum CPK activity and serum uric acid are readily available, they should be obtained. The combination of a concentrated acid urine with release of excessive amounts of uric acid and myoglobin causes crystallization of uric acid and obstruction by myoglobin in the renal tubule leading to acute renal failure (67). See Figure 10.

Rhabdomyolysis, severe enough to eventuate in myoglobinuric acute renal failure, can occur during Stage II or III PCP intoxication. The available literature concerning this complication is reviewed in Table X (68-72). Muscle death during PCP intoxication has resulted from a combination of crush injury, excessive isotonic muscular contractions, seizure activity and hyperthermia. In renal failure, gastric suctioning can be used in lieu of urinary acidification and diuresis to enhance the elimination of PCP up to 30-fold (13). With normal urinary function, the possible metabolic alkalosis resulting from gastric suctioning could compromise urinary acidification efforts.

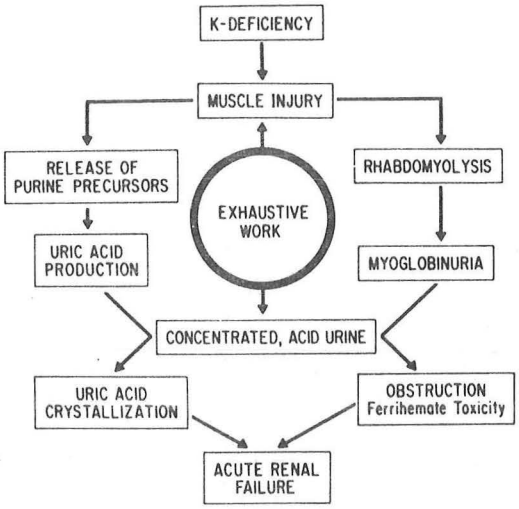


Figure 10: A hypothetical scheme to explain the role of exhaustive muscular work and K deficiency in the pathogenesis of "heat-stress" nephropathy.

Table X Phencyclidine-Associated Acute Rhabdomyolysis

Patient	Age	Sex	Oliguria* Present	Highest CPK (IU/L)	Highest Uric Acid (mg%)	Highest Serum Creatinine (mg%)	Lowest BUN/Creatinine Ratio (mg%)	Ref.	Comments
									All patients Stage II or III
1	23	M	No	2,000	13.0	4.0	7.0	71	Patients 1 thru 8: 4 had
2	25	M	Yes	54,000	20.0	14.0	8.8	"	Grand Mal seizures, all had
3	43	M	No	24,260	14.0	3.0	12.3	"	exaggerated locomotor
4	46	M	No	1,057	11.9	2.5	6.4	"	activity.
5	31	M	Yes	59,000	17.3	7.8	7.4	"	
6	25	M	No	1,766	14.7	7.5	10.0	"	
7	33	M	Yes	17,650	19.8	18.0	6.6	"	
8	35	F	Yes	20,000	18.0	11.7	8.5	"	
9	31	M	Yes	21,260	N.R.**	BUN = 131 mg% N.R.**	---	72	Hyperthermia 106° Seizures
10	27	M	No	97,600	24.4	12.0	---	70	Opisthotonic posturing
11	34	M	No	8,040	18.0	2.3	13.0	70	Physically restrained; Urine acidified
12	20	M	Yes	81,700	27.0	10.5	12.0	69	Fever 104°F; coma; Likely crush injury
13	21	M	No	210,000	7.4	1.5	14.0	68	Physically restrained; Opisthonic posturing
14	19	M	No	40,000	N.R.**	1.2	14.0	68	Opisthonic posturing; Repetitive movements; Coma; Fever 102°F

* Urine output less than 400 ml/day
** Not reported

Heat stroke has occurred as a complication of Stage II or III PCP intoxication both with, and without, seizure activity. In one case, core temperature of 106 °F was associated with rhabdomyolysis (72). In a second case, a core temperature of 109 °F proved fatal in a 16 year old male who had repetitive seizure activity (40). This death most likely resulted form hyperthermia, unlike the case of a 17 year old woman who had fatal status epilepticus which resulted in anoxic encephalopathy prior to ER arrival (58). She was said to have died 4 days after admission from progressive renal and hepatic failure and the case report failed to mention serum creatinine, serum uric acid, serum CPK activity or core temperature. It is prudent to monitor core temperature

with a rectal thermister during Stage II or III PCP intoxication and institute appropriate cooling modalities as indicated. Sponging with tepid water and loosening of clothing is usually enough intervention for temperatures of 100° to 103 °F. If the core temperature approaches 106 °F, aggressive cooling measures should be undertaken as for heat stroke (ice bath submersion, large fans, etc.).

Stage II may also be complicated by moderate to severe blood pressure elevation and tachycardia (73). Hypertensive crisis (BP 220/130 mm Hg) and a lethal intracerebral bleed occurred in a previously healthy 13 year old boy, 72 hours after apparent recovery from acute PCP intoxication (Stage II) (74). The rapid rise in blood pressure places such patients at extreme risk for CNS events (encephalopathy, bleed, etc.) and mandates an aggressive approach. Because of the repetitive muscular activity and uncooperative nature of these patients, infusion therapy with nitroprusside (Nipride®) or trimethaphan (Arfonad®) is not realistic. Intravenous diazoxide therapy and either intravenous or intramuscular hydralazine have been used in these patients with success. More appropriately the patient should be first treated with diazepam which may on occasion restore consciousness and orientation. This drug also decreases muscle spasm and rigidity, thereby protects muscles from further exercise injury and may "lower the blood pressure". This latter observation probably resulted from pseudohypertension causes by muscle rigidity. The most definitive antihypertensive therapy for these patients is propranolol administered intravenously (1 mg q 1 to 5 minutes to a maximum of 10 mg) (64).

Table XI

Algorithm for PCP Intoxication - Stage II

I. Instrumentation precautions can be lifted:

   A. Except for deep oropharyngeal suctioning.
   B. Insert large bore Ewald tube.
   C. Insert Foley catheter.

II. Chemical Restraint

   A. Give diazepam as in Stage I.

      1. Relieves muscular rigidity and spasm.
      2. Paradoxically, may awaken patient.

B. Give intravenous propranolol.

1. 1 mg q 30 min. as a prophylactic to avoid "adrenergic crisis" (total 10 mg).

2. 1 mg q̄ 1-5 minutes (up to a total of 10 mg) if patient becomes hypertensive, has dangerous tachyarrhythmias, or becomes hyperthermic.

3. For serious elevations of blood pressure, potent vasodilator therapy (IV or IM hydralazine or diazoxide) may be necessary; be aware of spurious blood pressure elevations secondary to muscular rigidity.

III. Enhanced excretion

A. Lavage stomach and give activated charcoal slurry (50-100 Gms).

B. After ruling out significant rhabdomyolysis, give intravenous ascorbic acid 0.5-2.0 Gms dissolved in 500 cc IV fluid q 6 hours.

C. May need to give ammonium chloride through NG tube, 2.75 mEq/kg/dose in 60 cc normal saline q 6 hrs until urinary pH < 5.0, then as necessary.

D. Give 40 mg IV furosemide to maintain high volume urine output (q 3-6 hours), replacing urinary and incipient losses with normal saline.

E. NG suction is optional, but should not be allowed to cause metabolic alkalosis or hypokalemia.

IV. Monitor for emergence to Stage I or progression to Stage III; change treatment protocol accordingly.

Adapted from Rappolt, Gay, Garris (64)
Aranow and Done (13)

Stage III PCP Intoxication

This stage usually occurs as a result of overdose with suicidal intent, or an accidental oral or intravenous dose (> 25 mg) and blood levels are very high (300 ng) (64, 13). The protective servomechanisms of Stage I and II are overwhelmed and the patient is at extreme risk for respiratory arrest, status epilepticus, hypertensive crisis, tachycardia, high out-put congestive heart failure, pulmonary edema and hyperthermia (so-called "adrenergic crisis" or "dopaminergic storm"). The clinical features of this stage are summarized in Table XII.

Table XII

Clinical Features of Stage III PCP Intoxication

-Prolonged coma (days); unresponsive to deep pain
-Absent gag and corneal reflexes.
-Loss of airway.
-Eyes are closed (pupils are usually wide, but still reactive).
-Opisthotonic positioning or decerebrate posturing
-Repetitive motor movements
-Seizures
-Hypersalivation, bronchorrhea, pulmonary aspiration
-Diaphoresis, facial flushing and hyperthermia
-Elevated blood pressure and heart rate

These patients require endotracheal intubation, preferably under controlled circumstances with expert supervision available. Respirator support is rarely necessary but endotracheal intubation needs to be performed anyway to protect the airway should seizure occur, to assist in tracheobronchial toilet, and to prevent aspiration pneumonitis.

A large bore Ewald tube should be used for gastric lavage, followed by installation of 100 Gm activated charcoal in a slurry. As with Stage II, the urine should be acidified, intravenous fluids (D_5NS) should be pushed to expand plasma volume and intravenous furosemide used to establish a high urinary output. Intravenous propranolol, in 1 mg increments may be given q 1 - 5 minutes (total dose 10 mg) for hypertensive crisis or other signs of "dopaminergic storm". Diazoxide or hydralazine can be used if necessary.

Even though PCP has anticholinergic properties, cholinergic drugs such as physostigmine salicylate, commonly used as a specific antidote for tricyclic antidepressant or phenothiazine overdose, should be avoided. This drug will further increase bronchial secretions.

Should repetitive seizures occur initially, intravenous diazepam should be given and followed by intravenous phenytoin (Dilantin®), 500 mg given slowly over 30 minutes. Core temperature should be monitored and appropriate steps taken to reverse hyperthermia if it presents.

Note: *As a patient emerges from deeper stages to "lighter levels" of intoxication, the signs and symptoms of that stage appear, possibly including violent and self-destructive behavior. The necessary precaution to protect the patient and ER personnel should be taken as "the patient is getting better".*

Table XIII

Algorithm for PCP Intoxication - Stage III

I. Instrumentation is necessary

A. Endotracheal intubation (prevent aspiration - protect airway during seizure, provide toilet)
B. Lavage stomach with a large bore Ewald NG tube
C. Instill 50 to 100 Gms activated charcoal slurry
D. Foley catheterization
E. IV fluids - push 1-2 liters of D_5NS

II. Enhance excretion by promoting "ion trapping".

A. Acidify the urine as in Stage II if rhabdomyolysis is not present.
B. Force diuresis with fluids and furosemide as in Stage II.

III. Supportive Care

A. Provide seizure precautions.
B. If seizures occur, treat initially with diazepam (10 mg IV slowly); follow with phenytoin, 500 mg IV slowly over 30 minutes.
C. Monitor core temperature, prevent rise > 102 ^{o}F.
D. Titrate intravenous propranolol, 1 mg increments $\bar{q}$ 1-5 minutes, up to 10 mg if adrenergic crisis develops.
E. If hypertensive crisis occurs, diazoxide or hydralazine can be utilized.
F. Avoid physostigmine salicylate.
G. Avoid digitalis (if "CHF" is present).

IV. Monitor for emergence or progression; apply appropriate therapy as Stage lightens.

Stage IV: "Post-ingestion Sequela"

There are three syndromes that occur in the emergency period even from Stage I. One is called the "anxiety/depression/confusional state". Symptoms range from moderate anxiety and slight depression to severe, even suicidal depression, withdrawal or catatonia and violent destructive behavior (64). Many patients are amnestic for the events of the acute intoxication. For the patients who do not require admission, the following protocol should be continued for one week to avoid this complication.

Table XIV

Treatment of PCP - Post-Ingestational Sequela

1. Continue diazepam 10 mg P.O., T.I.D. to Q.I.D.
   or
   Haloperidol 5 mg P.O., Q.I.D.

2. Continue urinary acidification with ascorbic acid 0.5 Gm P.O., Q.I.D. in cranberry juice - force fluids. Avoid citrus juices (they alkalinize the urine)

3. Continue furosemide 40 mg P.O., B.I.D. to Q.I.D.

4. Propranolol 40 mg P.O., Q.I.D. to prevent adrenergic-crisis.

5. Psychiatric consultation

TREAT FOR ONE WEEK

The second, and potentially life threatening, sequelae is the appearance of an "adrenergic crisis" or "dopaminergic storm". This complication occurs primarily after Stage II or III overdoses. These patients are usually admitted for 3-4 days, and this syndrome will likely declare by 96 hours post-ingestion. The presentation may be one of marked hypertension, complicated by encephalopathy or CNS bleed (74), or by hyperthermia. The prophylactic administration of oral propranolol 40 mg Q.I.D. for one week after PCP overdose apparently is effective in preventing this sequelae (66).

The third sequelae (previously discussed under Chronic Psychiatric Complications) ranges from "flashbacks" to prolonged psychotic episodes lasting weeks to months. It is also possible that schizophrenia will occur later in these patients even if they become drug free (45).

The Clinical Features of PCP Intoxication in Infants or Children (Less Than 6 Years of Age)

PCP should be suspected in young children and infants presenting with a rapid onset of lethargy or coma, strange behavior, staring spells, ataxia and nystagmus. Other findings such as opisthotonos, hypertension, hyperpnea, tachypnea, miosis, hyperreflexia, hypertonia, rigidity and seizures may be present (but the opposite finding

may also occur depending on dose) i.e. respiratory depression, flaccidity, etc. Urinary screens for PCP in the appropriate clinical circumstance may assist with the differential diagnosis that includes meningitis, seizure disorders, intracerebral lesion, metabolic abnormalities and head trauma. These intoxications usually result from accidental ingestion, but may occur by passive inhalation. In a recent review of the PCP experience at the Martin Luther King Jr., General Hospital (Los Angeles), 35% of 187 cases seen during 1978 involved children between 7 months and six years of age (75).

The features of 11 well-described cases of PCP intoxication in infants and children are compiled in Table XV to highlight the variability of the clinical presentation and the lack of an adequate history of drug exposure. A high index of suspicion is necessary to document such cases.

A recent report suggests that PCP may be teratogenic (77). As a neonate, this infant showed abnormal behavior, an unusual appearance (triangular face with a pointed chin and narrow mandibular angle, the eyes had an antimongoloid slant, and the anterior fontanelle was 4 cm wide), poor head control, nystagmus and inability to track visually. The infant had a confirmed grade 2 respiratory distress syndrome which resolved without treatment (it was felt this did not contribute to later sequelae). Within hours of birth, the infant became jittery, had increased muscle tone, and even slight auditory or tactile stimulation that resulted in a course of flapping of the extremities. When not stimulated, the infant was floppy and lethargic (blood glucose and calcium were normal). The child had persistent jaundice (bilirubin peak of 9.0 mg %), poor weight gain, poor feeding, and an abnormal neurological exam on discharge at 25 days. At the age of 2 months, the infant still had roving eye movements, coarse tremor exacerbated by stimulating and a spastic quadriparesis was evident.

Although the history was initially negative for drug abuse, the mother admitted after the first week of the infant's hospitalization to smoking an average of six joints of marijuana "dusted with PCP' per day throughout the entire pregnancy. A careful drug history from the mother may establish the diagnosis of neonatal distress and is a part of any such work-up.

Placental transport of PCP has not been studied in humans, but it has in the pig. Cooper, et al. (78) studied the placental transfer of PCP in the pig after a single IM injection prior to delivery. The concentration of PCP in the piglet plasma was almost 10 times higher than in the sow's plasma. The half-life of the drug in the piglet was 10-20 hours, compared to 2-4 hours in the sow.

Table XV

Pediatric Phencyclidine Intoxications

From Ref. No.	39	39	39	39	76	77	77	77	77	77	77
Age: Year/Sex	2/M	5-6/M	2 1/6/F	3 1/2/M	2 1/2/M	11 Day Old/M	1 1/6/M	1 1/2/F	1 1/12/M	5/F	2/3/M
History of Drug Exposure	Early (U.D.)*	Early (THC)	Early (LSD)	Early (U.D.)*	Early (PCP)	Late (PCP)	No	Late (PCP)	Late (PCP)	Late (PCP)	Late (PCP)
Onset of symptoms (hours)	1 1/2	1	1/2	1/2	1/2	~ 36	?	?	?	?	?
Duration of symptoms (hrs)	18	24	12	4	90	48	18	6	20	24	72
Pupils	Miotic	Normal	Normal	Normal	Miotic	Miotic	Miotic	Normal	Normal	Normal	Normal
Nystagmus	Vertical Horizontal	None	None	Vertical Horizontal	?	No	Yes	Yes	No	Yes	Yes
Coma	Yes	No	No	No	Yes	Yes	No	No	No	No	Yes
Deep Tendon Reflexes	↑↑	↑	Normal	↑	↑↑↑	↑ ↓	Normal	Normal	Normal	Normal	Normal
Muscle Tone	Normal	↓	Normal	↓	↓	↑ ↓	↑	Normal	Normal	Normal	Normal
Opisthotonos	Yes	No	No	No	Yes	Yes (h/o)	Yes	Yes (h/o)	No	No	No
Ataxia	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No
Respiration	Depressed Intubated	Normal	Rapid	Normal	Depressed Intubated	Rapid	↑	↑	↑	Normal	Depressed Intubated
Blood Pressure	↑ Early	Normal	↑ Early	↑ Early	↑ Early	Normal	Normal	Normal	Normal	↑ Early	Normal
Agitation on Recovery	Marked	Marked	Marked	None	None	Yes	None	None	Yes	None	None
Other			Violent Withdrawal from objects Long Term Self-Destructive Behavior	+ Babinski sign early	Seizures X 2 Bronchorrhea Reintubated x 48 hrs. Laryngeal Stridor	Pulse Varied 70-190/ min.	Seizures x 2				

* Unknown Drug

Addendum:

McCarron, et al (80) have recently reviewed the University of Southern California School of Medicine's ER experience (Los Angeles) with 1,000 cases of PCD intoxication. Unlike the case studies already reviewed in this Grand Rounds, this paper allows one to appreciate the true incidence of so-called "typical features" of PCP intoxication. The clinical findings are summarized in Table XVI. In 597 cases, only PCP was abused; in the remaining 403 cases, a second drug was taken, however, PCP was the most prominent component of the overdose, Table XVII.

This study also characterized the laboratory abnormalities in these patients, Table XVIII.

Table XVI

Assessing PCP Toxicity-Incidence of Findings in 1,000 Cases

Table 2
ASSESSING PCP TOXICITY — INCIDENCE OF FINDINGS IN 1,000 CASES

Finding	%
Hallmarks	
Nystagmus	57.4
Hypertension	57.0
Sensorium	
Alert and oriented	45.9
Acute brain syndrome	36.9
Unconscious	10.6
Lethargy/stupor	6.6
Behavior	
Violent	35.4
Agitated	34.0
Bizarre	28.8
Hallucinating/delusional	18.5
Mute and staring	11.7
Nudism	3.3
No behavioral effects	3.5
Motor Signs	
Generalized rigidity	5.2
Grand mal seizures	3.1
Localized dystonias	2.4
Facial grimacing	1.7
Athetosis	1.3
Cholinergic Signs	
Profuse diaphoresis	3.9
Bronchospasm	2.1
Pupils $\leq$ 1 mm	2.1
Hypersalivation	1.7
Bronchorrhea	0.6
Anticholinergic Signs	
Pupils > 4 mm	6.2
Urinary retention	2.4
Abnormal Vital Signs	
Tachycardia	30.0
Hypothermia	6.4
Apnea/respiratory arrest	2.8
Hyperthermia	2.6
Cardiac arrest	0.3

Table XVII

Drugs Taken with PCP (403 Cases)

Name of Drug	Cases No.	Cases %
Ethyl alcohol	223	55.3
Marijuana	151	37.5
Barbiturates	34	8.4
Amphetamines	17	4.2
Diazepam	12	3.0
Cocaine	11	2.7
Heroin	9	2.2
Glutethimide	4	1.0
Ethchlorvynol	3	0.7
Chlordiazepoxide	3	0.7
Methadone	2	0.5
Others (1 case each)	17	4.2

Table XVIII

Laboratory Findings in 1000 PCP Intoxications

Lab Finding	No. of Patients Tested	% of Those Tested
Hypoglycemia (<70 mg/dl) (avg. 59 mg/dl, lowest 10 mg/dl)	111	22%
Elevated Serum CPK (> 300 IU) (ranged up to 423,045 IU with clinical rhabdomyolysis in 22 cases).	506	70%
Elevated Serum SGOT (> 40 IU) (Ranged up to 9,760 IU and 93% had ↑ CPK)	508	50%
Hyperuricemia (> 7 mg/dl) (Ranged up to 35 mg/dl and 100% had ↑ CPK)	508	24%
WBC (5-11,000)	109	61%
12-15,000		27%
15-20,000		10%
Over 20,000		2%

This study described nystagmus and hypertension as "the hallmarks" of PCP toxicity, but the authors emphasized that only six patients required specific antihypertensive therapy. This study also reinforces our concerns about PCP induced violent and bizarre behavior. (Table XIX)

Table XIX

Violert and Bizarre Behavior in 1000 PCP Intoxications

	No. of Patients	% of Total
Violent Behavior	130	13 %
A. Used a gun or knife to threaten others	43	4.3 %
B. Self-inflicted wounds	30	3.0 %
C. Severe injuries received from others	19	1.9 %
Bizarre Behavior		
A. Wandering or wild in public	59	5.9 %
B. Nudity in public	33	3.3 %

Conclusion

Phencyclidine abuse among adolescents and young adults is reaching epidemic proportions. Increasingly, overdose in children and infants is being recognized. Oftentimes, this drug is sold, misrepresented as another drug of primary abuse; however, a number of polydrug abusers prefer PCP to other drugs, or with other drugs. The drug primarily displays behavioral toxicity in lower doses, but can kill in moderate to heavy overdose. The drug is a schizophreniform agent and may cause psychosis temporally distant from the intoxication. The medical complications of PCP abuse have been reviewed. Now, after a decade of street abuse, we can say unequivocably that PCP is indeed a bummer drug.

"While PCP was sometimes a good high, one that made you feel in tune with the music of the spheres, you had to watch those four ugly C's: combat, catatonia, convulsions and coma."

T. Cahill
Rolling Stone
July 13, 1978

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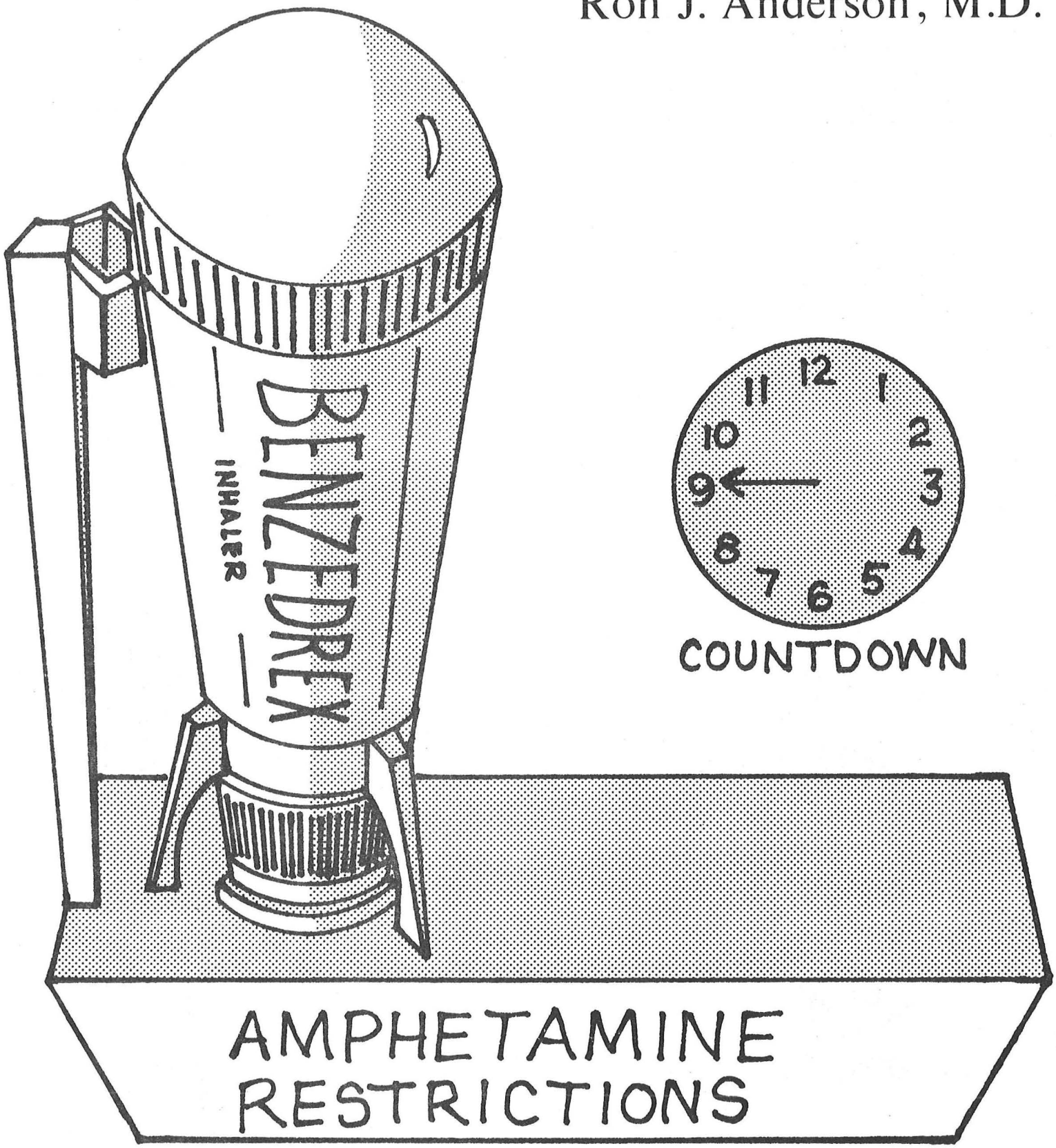
Abuse of Stimulants Obtained from Nasal Inhalers

Medical Grand Rounds May 7, 1981

Ron J. Anderson, M.D.



Abuse of Stimulants Obtained From Over-The-Counter Nasal Inhalers

The Amphetamine (Benzedrine®) Nasal Inhaler:

In mankind's age old battle against the all too obvious of human infirmities, the "runny nose" and nasal congestion, chemists from Smith, Kline & French Co., introduced the Benzedrine ® nasal inhaler in 1932. The inhaler contained 250 mg of synthetic racemic amphetamine base (beta-phenylisopropylanine), 12.5 mg of menthol, and various aromatics (1). When nasally inhaled, this volatile base provided a potent vasoconstrictor effect that produced shrinking of congested nasal mucosa. Early investigation noted that inhalation of amphetamine base was associated with a moderate rise of blood pressure and a tendency to cause sleeplessness. This latter side effect lead Printzmetal and Bloomberg (2) to investigate the utility of amphetamine sulfate in nine narcoleptic subjects. The success of this clinical trial lead to the suggestion that amphetamine might have a wider application in milder conditions of drowsiness or fatigue. The CNS stimulatory effects of amphetamine were soon applied to such varied conditions as obesity (exploiting the side-effect of anorexia), depression, alcoholism, and childhood behavioral problems (3).

The laypress and the market exaggerated the value, and understated the risks of amphetamine sulfate, which could be obtained readily without a prescription. Amphetamine tablets became known as "pep pills" and were generally popular as an aid to ward off sleep (students, truckers, etc.). The 1938 Food, Drug and Cosmetic Act empowered the FDA to impose "legend" or "prescription only" status on certain drugs felt to be of either high abuse potential or too powerful for self-medication. Amphetamine tablets fell into this category of drug that required a labeling change, warning against use except under medical supervision. *"Warning: Federal law prohibits dispensing without a prescription".* Reports of medical complications of amphetamine use were beginning to appear in the medical literature, i.e., convulsions (1), psychosis (4), hypertension (5), habituation (6), and death (7). Some states actually imposed more vigorous limitations on the prescription sale of amphetamines than that required by the FDA.

During World War II, the public's general awareness of amphetamine increased as they heard press accounts of "Nazi pep-pills" (8). In fact, both Axis and Allied troops were exposed to amphetamines on the front lines "as a weapon against sleep and fatigue during crucial periods" (9). The United States Armed Forces stated that "officially" our front line troops did not receive amphetamine tablets. Amphetamines, however, became routinely used by bomber crews who were asked to fly long missions too frequently. Amphetamine tablets were also issued

in survival kits (10). Whether this exposure in servicemen contributed to the postwar illicit demand for amphetamine is unclear, but likely. In defense of the military, the homefront had also become pretty fond of "dexies", "bennies", and "hearts" during the war (11).

The federal regulation restricting the sale of amphetamine was a first step, but a very short one. The illicit manufacture of amphetamine tablets flourished and they could be bought in many truck stops, filling stations and bars. The quantities of amphetamines manufactured by the "ethical pharmaceutical houses" were (as they still are) massively in excess of any legitimate medical need. So-called "script-doctors", strictly for monetary gain, diverted large quantities of amphetamine tablets into illicit channels or to individual users. These individuals still account for a large component of the street traffic in amphetamines (12). Although still available with effort, the acquisition of amphetamine tablets for nonmedical use became more expensive.

The Benzedrine® nasal inhaler was exempted from legend controls by the FDA because the product was felt to be safe when used according to the manufacturer's directions which were explicit and easy to understand. The FDA may have felt it legally impossible to impose regulatory controls on a product that was dangerous only through deliberate misapplication by the user.

In 1946, when the song "Who Put the Benzedrine in Mrs. Murphy's Ovaltine" was still popular, an article appeared in Everybody's Digest entitled "On a Bender with Benzedrine" (13). The author (anonymous) described the oral use of the volatile amphetamine base from a nasal inhaler by entertainers and musicians. These inhalers were inexpensive (less than a dollar) and were available in every corner drug store (14). Contained in a plastic case, the inhaler could be easily dismantled to get to an impregnated paper folded into eight sections (each containing approximately 31 mg of amphetamine base). The contents of one inhaler were roughly equivalent to 25 -10 mg Benzedrine® sulfate tablets. On the paper was written, *"Warning: For Inhalation Only± Unfit for Internal Use. Dangerous if Swallowed"*. This admonition did little to discourage the oral use of this product. The usual method was to chew and then swallow the paper strip (or mix the paper with chewing gum to decrease the irritant properties of the amphetamine base). Sometimes the paper strips were soaked in coffee, Coca-Cola®, or various alcoholic beverages. Other times, the moistened strips were wrapped in a cigarette paper and swallowed whole. Monroe and Drell (15) reported that 25% of an inmate population in a United States disciplinary barracks (military prison) at Fort Benjamin Harrison, Indiana, used inhaler material for intoxicating purposes and as a corollary, this abuse resulted in increased disciplinary problems (inmate violence). Fourteen percent of

the inmate population of that same prison admitted abuse of the inhaler material prior to incarceration. Inhalers were easy to smuggle into inmates or the paper strips could be concealed in a letter. One guard in the prison was discovered with over 300 empty inhalers in his quarters. In fact, it was common practice for profit-minded guards to sell the paper strips to inmates. Other prisons experienced similar problems with the inhaler material.

Monroe and Drell (15) investigated the solubility of the benzedrine base from the paper strips in 200 cc of gastric juice compared to either beer, coffee or tapwater. One strip yielded 19.45 mg amphetamine in gastric juices, and approximately 6 mg in the other liquids. Previously, Beyer (16) had shown that amphetamine sulfate is totally absorbed from the GI tract but only 43% is later excreted in the urine. It was presumed that "approximately half the drug" disappeared due to deamination in the body. The absorption, distribution and elimination of amphetamine base from the inhaler material was quite similar. Amphetamine from the inhaler material was found in the urine within 1 hour and 45 minutes from oral ingestion and was still present in the 120 hour specimen (15). Nearly 11 mg (from the 31 mg in one strip) was excreted in the first 24 hours and approximately 9 mg in the second.

Smith, Kline and French unsuccessfully tried to deter the misemployment of the inhaler by first changing from plastic to an unbreakable iron container. In states where large-scale abuse had been reported, a special Benzedrine® inhaler, adulterated with denatured picric acid was marketed to halt internal ingestion. While some abusers may have been deterred, most were willing to endure the nausea to get the euphoria (17). In 1949, with legislation pending in the House of Representatives to make amphetamines (including inhalers this time) subject to the same federal controls as narcotics, Smith, Kline and French, voluntarily withdrew the Benzedrine® nasal inhaler from the market, notifying the FDA that they were field-testing a new, nonamphetamine nasal inhaler with minimal CNS effects, to be called Benzedrex® (propylhexedrine). The FDA saw this move as a positive step toward the resolution of a problem arising from an "inability to apply existing federal regulations" to the inhaler. This situation had become an embarrassment to the agency.

Unfortunately, victory was elusive; with Smith, Kline and French's patent expiration, multiple manufacturers entered the amphetamine inhaler market. Valo® (S. Pfeiffer & Co.), Wyamine® (Wyeth) and Nasal-Ator® (Rexall) nasal inhalers enjoyed extensive misapplication. The FDA warned the individual manufacturers that these products were commonly abused. Their attempts to obtain voluntary recall were unsuccessful so the agency began to lobby for more restrictive legislation regarding

nasal inhalers. Meanwhile, the new manufacturers, following the footsteps of Smith, Kline and French, attempted to denature the inhaler material to discourage oral abuse. Quickly, abusers found that boiling the inhaler material got rid of the adulterant. At about this time, the hypodermic needle and intravenous injection of the inhaler contents were added to the equation (18).

The reports of inhaler material abuse accumulated once again. Localized epidemics of intravenous abuse were reported to the FDA. One such epidemic in Kansas City, Missouri, lead Senator Thomas Hennings (Mo) to introduce legislation aimed at restricting the sale of amphetamine nasal inhalers to a "prescription only" status (14). This episode began after a handful of Missouri teenagers were initiated in the technique of amphetamine extraction and injection of the contents of the Valo® nasal inhaler by Oklahoma City youths during the fall of 1957 (at a ball game). The teenagers returned home and enthusiastically shared their method of "getting high". By 1959, Kansas City had an estimated 400 chronic Valo® abusers. Valo® sales were sky-rocketing, the police talked to an average of 10 abusers per week, and officials claimed a positive connection between inhaler abuse, crime and violence.

Like their predecessor, the S. Pfeiffer Company withdrew Valo® and Wyeth removed Wyamine®. The amphetamine was taken out of each product and they were reintroduced much in the same fashion as Benzedrex®.

Not wishing to cycle this problem through a new set of manufacturers at some later date, in February 1959 the FDA took a decisive step. They invoked Section 503(b) of the Durham-Humphrey amendment (of 1951) to the Food, Drug and Cosmetic Act to cover the amphetamine inhaler because "recurring reports of abuse and misuse indicate the potentiality for harmful effect" (19). This amendment states *"because of toxicity or other potentiality for harmful effect or the method of its use, or the collateral measures necessary to its use"* a drug may be considered safe for use only under the supervision of a physician. So ended the legal, over-the-counter sale of amphetamines in nasal inhalers. It was assumed that the misapplication of nasal inhalers was over.

The Propylhexedrine (Benzedrex®) Nasal Inhaler:

Propylhexedrine, a member of the family of alicyclic aliphatic sympathomimetic amines, is structurally similar to amphetamine (Figure 1). Monroe and Drell (15) were the first to suggest that a solution to the problem of nasal inhaler abuse might be found if a local vasoconstrictor with minimal CNS effects could be substituted for amphetamine. In this regard, Smith, Kline and French reported that propylhexedrine was an effective local vasoconstrictor possessing only 1/12th the CNS stimulatory effect of amphetamine. In 1949, they introduced the Benzedrex® nasal inhaler which contained 250 mg of propylhexedrine, 12.5 Gms of menthol and various aromatics. As a journalist of the time put it, *"it won't wake you up, cheer you up, or pep you up. All it will do if you swallow it is make your mouth dry and puckered"* (17). He was wrong, but the problems associated with the misapplication of the Benzedrex® nasal inhaler were not to surface until the more attractive amphetamine nasal inhalers were pulled from the market.

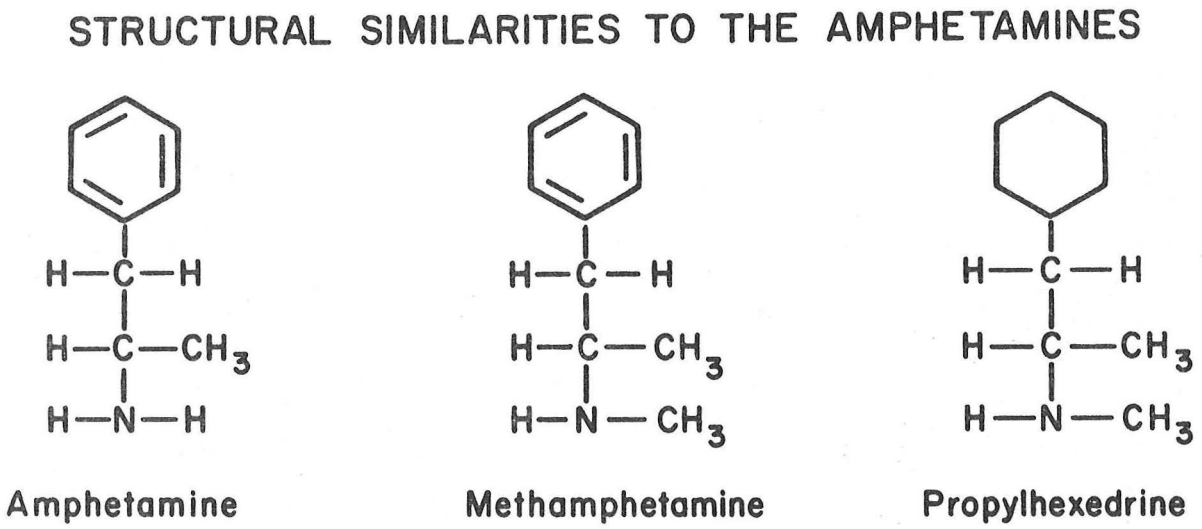


Figure 1: Propylhexedrine's structural similarities to the amphetamines.

Early Reports of Oral Propylhexedrine Toxicity:

In 1972, Marsden and Sheldon (20) reported a case of propylhexedrine poisoning with a nearly fatal outcome.

Case: A previously healthy 22 year old man swallowed the contents of one Benzedrex® inhaler. Several hours later he experienced "violent palpitations, headache, and severe central chest pain". His first vital signs on arrival to the hospital, a blood pressure of 110/70 mm Hg and a pulse rate of 120/minute, rapidly deteriorated and shock ensued (blood pressure of 50/0 mm Hg). The electrocardiogram (EKG) revealed multifocal ventricular ectopy and a chest x-ray showed bilateral pulmonary edema. The arterial pO_2 was 18 mm Hg. The patient was supported with fluid resuscitation, mechanical ventilatory support, digoxin, lignocaine, steroids and practalol. On the second hospital day, blood pressure was normal but the EKG had evolved a pattern consistent with an anterior myocardial infarction complicated by AV dissociation and an accelerated junctional tachycardia. The patient improved enough to allow discontinuation of the respirator support by the third day. The next day the patient developed a pericardial effusion without tamponade, one melenic stool, and an abrupt drop in the platelet count to 26,000/mm^3, suggesting disseminated intravascular coagulation (DIC). The chest x-ray, consistent with adult respiratory distress syndrome (ARDS), cleared over the next 1½ weeks in parallel with improvements in arterial oxygenation and pulmonary function.

In the same time period, three reports (21, 22, 23) appeared which described four patients with propylhexedrine induced psychosis, similar to the schizophreniform psychosis induced by amphetamines (24). Three of these patients had previously been habituated to methamphetamine and during heavy use had been admitted to psychiatric hospitals for paranoid schizophrenia. Their daily habit ranged from 2 to 11 inhalers, chewed or swallowed daily. The other patient had chronic schizophrenia but several exacerbations were precipitated by chewing the contents of multiple Benzedrex® inhalers.

A Forensic Experience with Intravenous Propylhexedrine Toxicity:

Between 1973 and 1979, 15 propylhexedrine-related deaths were reported from Dallas County (Texas) (25, 26, 27, 28). Twelve deaths resulted directly from acute propylhexedrine intoxication (superimposed on chronic abuse). Two deaths represent homicides and one a suicide which occurred as part of an acute drug-induced psychosis. The method of administration was intravenous in each situation, but at least one victim also "skin popped". These deaths were sudden, often precipitated by a "flight or fight" provocation. Unlike sudden death with intravenous heroin or cocaine, the victims often died temporally distant from injection. The post-mortem findings of these victims are summarized in Table I. Pulmonary granulomas were present in 9, intimal and medial

proliferation of pulmonary arterioles were present in 8, and right ventricular hypertrophy was present in 9 of the victims. In all 12 victims dying from propylhexedrine intoxication, pulmonary edema was evident at post-mortem. The range of serum values for propylhexedrine was 0.03 to 0.27 mg/dl (mean 0.16 mg/dl), but this is somewhat skewed with lower values from victims surviving 8 to 12 hours before toxicology studies were obtained.

TABLE I Intravenous Propylhexedrine-Related Fatalities

Case No.	Age (yr), Race and Sex	Clinical History	Blood Level (mg/dl)	Pulmonary Granulomas	Pulmonary Vascular Changes	Pulmonary Edema	RVH	Other
		Unreported Cases						
1	34,B,F	Sudden collapse; ER resuscitation unsuccessful	0.23	+	+	+	+	LVH
2	27,B,M	Found unresponsive; patient died 3 hr after initial ER resuscitation	0.22	−	+	+	+	LVH
3	22,B,M	Sudden collapse after vigorous exertion; DOA (resisting arrest)	0.12	−	+	+	+	70% occlusion LAD coronary artery
4	29,B,M	Found unresponsive; cardiopulmonary arrest followed seizure activity; patient died 12 hr after initial ER resuscitation	0.07	+	+	+	+	Focal myocardial fibrosis
5	22,B,M	Found dead; last seen alive 3 hr prior to discovery	0.12	−	+	+	+	Interstitial pulmonary fibrosis
6	26,B,M	Sudden collapse after exertion; DOA	0.14	+	−	+	+	. . .
		Reported Cases						
7	19,B,F	Sudden collapse; DOA	0.27	+	−	+	−	Focal sarcoid
8	29,B,M	Sudden collapse; unsuccessful ER resuscitation	0.18	+	−	+	+	SC Hbg; emphysema
9	19,B,M	Sudden collapse after physical exertion	0.20	−	−	+	−	. . .
10	17,B,F	Found dead; last seen alive 8 hr prior to discovery	0.03	+	+	+	+	. . .
11	24,B,M	Found unresponsive; pulmonary edema, shock, and recurrent cardiopulmonary arrest characterized 3 hr unsuccessful resuscitation	0.16	+	+	+	+	. . .
12	28,B,M	Sudden collapse and death after physical exertion and a superficial gun shot wound (fleeing burglary suspect)	0.16	−	+	+	−	. . .
		Traumatic Deaths During Propylhexedrine Intoxication						
13	27,B,M	Homicide; multiple gun shot wounds to chest and abdomen	0.08	+	−	−	−	. . .
14	23,B,M	Suicide by hanging; decedent acutely psychotic in jail	0.25	+	−	−	−	. . .
15	25,B,M	Homicide; multiple gun shot wounds to head and hand	0.11	−	−	−	−	. . .

NOTE: RVH = right ventricular hypertrophy; LVH = left ventricular hypertrophy; DOA = dead on arrival; LAD = left anterior descending artery; SC Hbg = sickle cell hemoglobin.

Thirteen of the victims were young black men, and two were young black women (age range 17 to 34), several were homosexual males (in some cases, male prostitutes) who were dressed in women's clothing at the time of death. The duration of Benzedrex® abuse ranged from several months to many years. Pulmonary vascular changes were profound in the chronic users, Figure 2.

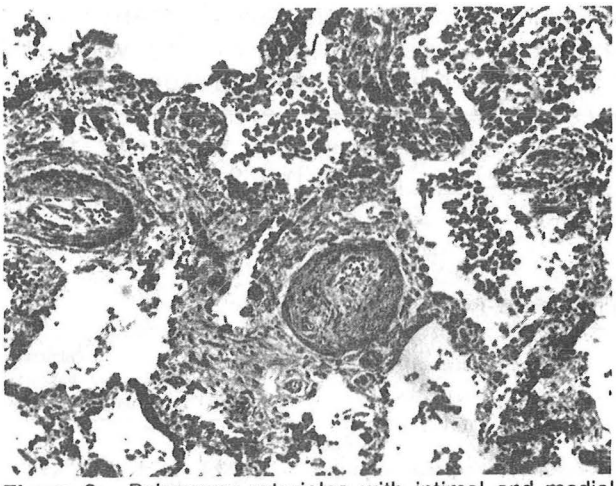


Figure 2. Pulmonary arterioles with intimal and medial proliferation and obstruction of the lumens.

The mechanism or mechanisms responsible for sudden death in these victims were not clear from post-mortem studies. Several hypotheses were attractive, i.e., cardiac arrhythmias induced by the drug, cardiac arrhythmias resulting from drug-induced sensitization of the myocardium to endogenous catecholamines (particularly during stress), or a sequel to syncope in the setting of pulmonary hypertension. Whatever the etiology, it is painfully evident from the clinical picture of those victims surviving to reach medical care that intravenous abuse of propylhexedrine can result in sudden collapse, refractory shock, cardiac arrhythmias and sudden death. On the average, several deaths due to propylhexedrine abuse occur yearly in Dallas. Propylhexedrine can be detected and quantitated in blood and tissue by gas chromatography after extraction by n-butyl-chloride, using the procedure described by Foerster, et al (29). Forensic reports from other laboratories concerning propylhexedrine have not appeared to our knowledge, but several cases have been related to us by personal communication.

The Epidemiology and Pathophysiology of Intravenous Propylhexedrine Abuse . A Clinical Study:

In an effort to clarify the epidemiology and pathophysiology of intravenous propylhexedrine abuse, we have subsequently identified (over a six month period) and studied nine patients who were chronic "Benzedrex® shooters". As in the post-mortem study, all patients were young, black, and 8 of 9 were male. Two of the males were homosexual

prostitutes and many of the patients knew each other "from the street". One patient previously had used heroin and several more had used phenmetrazine (Preludin®) tablet material for intravenous injection. Their reasons for using Benzedrex® were simple. The drug is not illegal, it is readily accessible and it is cheap ($1.09 to $1.50 currently in Dallas-Fort Worth pharmacies). The patients with previous intravenous amphetamine experiences compared the euphoria obtained by injecting the contents of a cotton wick from the Benzedrex® inhaler (Figure 3), to that obtained from either 15 mg of methamphetamine (Desoxyn®) or the "CORE" from a Preludin® Enduret, 75 mg phenmetrazine. The going street price for Preludin® in the Dallas-Ft. Worth Metroplex is never below $15 a tablet. Discussions with the users suggests that forensic pathologists and emergency room physicians see only the tip of an iceberg concerning the misapplication of the Benzedrex® inhaler. Police seizures of paraphenalia containing Benzedrex® inhaler material have markedly increased. A recent police communique described the seizure of a formula by which propylhexedrine from the inhaler can be converted to methamphetamine. The by-product from this simple reaction using hydrochloric acid is known locally to abusers as "Peanut Butter Meth". Police intelligence learned that the formula has been sold to street dealers throughout Texas for $800 to $1,000 each.

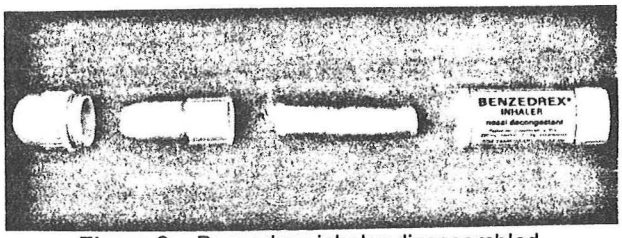


Figure 3. Benzedrex inhaler disassembled.

Discussions with our patients lead to the description of "Benzer" parties. Usually one of the older male users would buy (or send someone else in to buy) multiple inhalers from local pharmacies. Several pharmacies would be visited until "enough stuff" was available for perhaps a dozen users (high school age usually). The older users would then initiate novice users. In a number of instances, the ritual use of propylhexedrine was a prelude to homosexual activities. In our nine patients, Benzedrex® had become their drug of choice, after a history in every case of polydrug abuse. One patient had been introduced to the method of abuse while in the military, another while in prison, and the others by peers or older users "on the street". Studies performed at the Southwestern Institute of Forensic Pathology on volunteer subjects inhaling fifteen times from a Benzedrex® inhaler revealed that only minimal blood levels of propylhexedrine can be achieved by this technique (21). (Table II). Accordingly, symptoms of hyperventilation

would probably occur before euphoria could be experienced. However, the desired euphoria apparently can be obtained without using the intravenous route. A few users report soaking the cotton wick in coffee or an alcoholic beverage (much as Benzedrine® was used previously) and drinking the solution, or actually swallowing the entire cotton wick. These users like the intravenous route better and our interviews would suggest that oral abuse occurs primarily in novice users and in the older abusers who have "run out of veins". One of the sudden death victims turned to "skin popping" after obliteration of easy venous access.

TABLE II

Propylhexedrine Concentrations After Inhalation

	Propylhexedrine Concentration (mg/100 ml)		
Specimen	10 Minutes	30 Minutes	135 Minutes
Blood	0.001	0.001	-----
Urine	0.004	-----	0.060

Invasive and/or noninvasive cardiopulmonary studies were performed in each subject. On presentation, five patients had complained of dyspnea, one of chest pain. Physical examination revealed an increased pulmonic component of the second heart sound in seven, and a right ventricular heave in three. Chest x-ray showed prominent pulmonary arteries in five, cardiomegaly in seven, and diffuse pulmonary infiltrates in two. Spirometry was normal but pulmonary diffusing capacity for carbon monoxide (DL_{CO}) was markedly reduced (mean of 39% of predicted) even when corrected for lung volumes ($DLCO_{VA}$). (Figure 4) Arterial blood gases revealed mild hypoxemia and respiratory alkalosis.

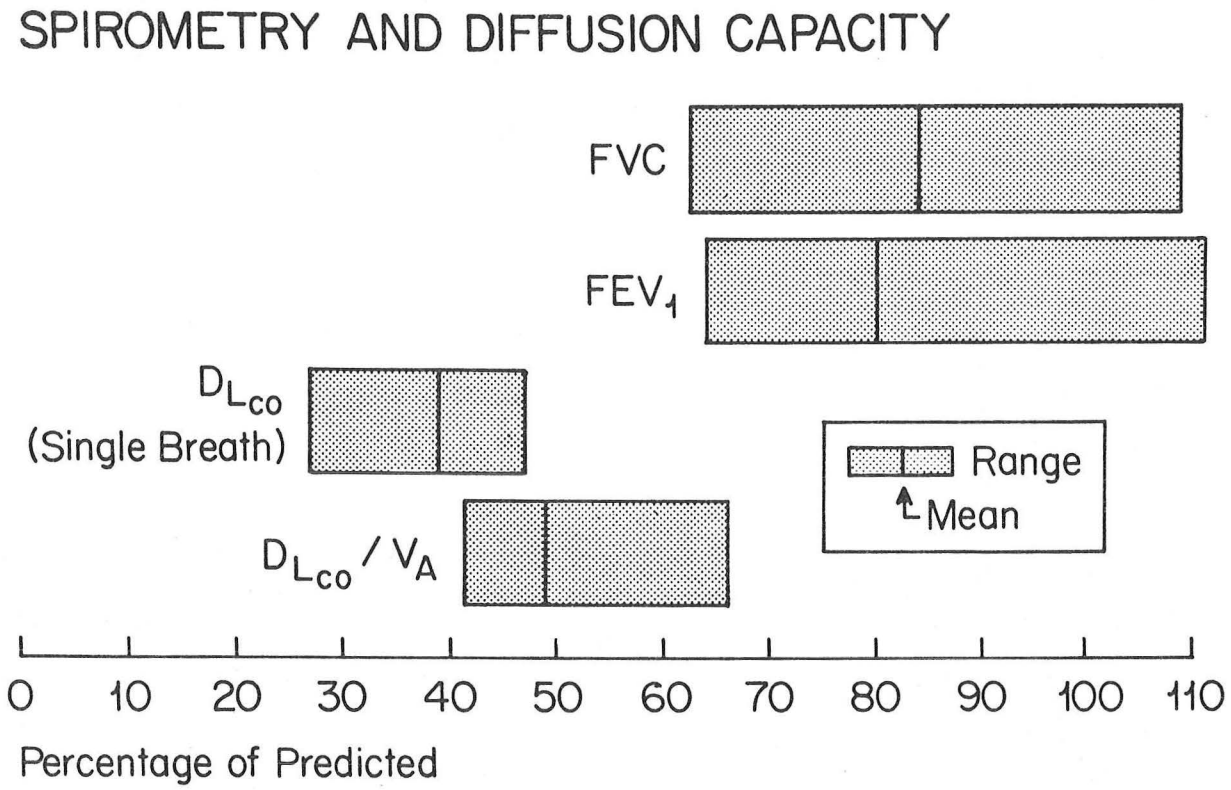


Figure 4: Pulmonary function in nine Benzedrex® shooters.

M-mode echocardiograms revealed right ventricular dilation in seven of eight subjects studied (average supine right ventricular diameter RVD = 3.4 cm). Only two patients consented to a right and left cardiac catheterization. Pulmonary hypertension was present in each, PA = 50/32 and 42/24 mm Hg respectively. Surprisingly, left ventricular dysfunction was pronounced in one patient and moderate in the second, left ventricular ejection fractions of 12 and 45% respectively. Of the remaining patients, 4 consented to gated radionuclide blood pool scans (so-called MUGA scans) performed by the method of Dehmer, et al (31). Mean right and left ejection fractions were 34 and 38% respectively. (Figure 5).

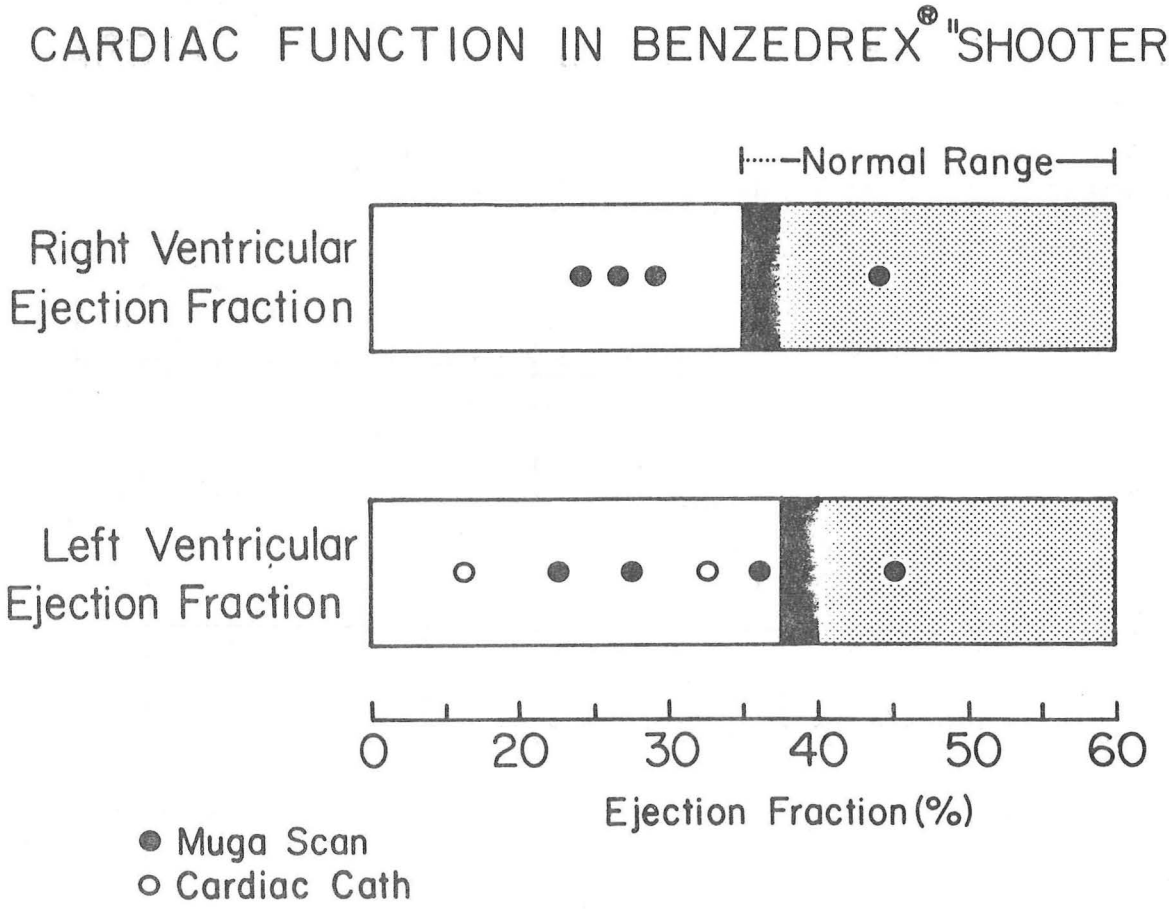


Figure 5: Invasive and noninvasive ventricular function in six Benzedrex® shooters.

Despite abstinence of intravenous propylhexedrine abuse, two of these severely affected individuals subsequently suffered a syncopal sudden death. The only woman patient abused Benzedrex® throughout a pregnancy. She was delivered at term by Caesarean section as a special precaution for pulmonary hypertension. The infant was small-for-date, suffered respiratory distress syndrome and required prolonged neonatal intensive care. The mother left the hospital AMA, but returned in two weeks with florid right and left congestive heart failure. She was treated with digoxin, furosemide, nitrites, and a direct acting arterial vasodilator (hydralazine) to reduce left ventricular afterload and right ventricular preload. She became much less symptomatic, diuresed approximately 20 lbs., and left again AMA.

This preliminary study confirms the earlier observations by Robertson, et al (32) from this center. The intravenous injection of propylhexedrine results in pulmonary hypertension most likely as a consequence of the pulmonary vascular changes previously demonstrated by post-mortem examinations (marked intimal and medial proliferation with partial or complete obliteration of small arteriolar lumen) and not from pulmonary fibrosis and granulomatosis. The earlier investigation suggested that reductions in DL_{CO} in abusers of nasal inhaler sympathomimetics correlate with pulmonary artery pressures measured directly (Figure 6) and should be used as a noninvasive screen to rule out pulmonary hypertension. From our studies, it would seem that DL_{CO} is a sensitive guide to pulmonary damage in these patients.

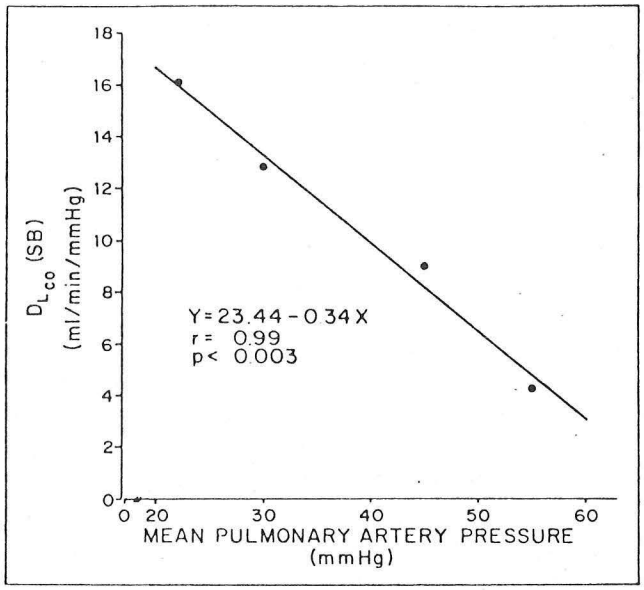


Figure 6: Relationship between single breath diffusing capacity of carbon monoxide (DL_{CO}) and mean pulmonary artery pressure at rest.

Cor pulmonale can occur secondary to talc granulomata in narcotic addicts, particularly those who inject drugs intended for oral use (33-36). A well described reaction also occurs in the pulmonary arteries after cotton fiber embolization (37). The intravenous injection of an alpha-sympathomimetic which may induce pulmonary arteriolar vasoconstriction, in addition to the local reactions arising from simultaneously injected foreign bodies, likely accounts for the intense pulmonary vascular changes identified in victims of sudden death from Benzedrex® "shooting".

Among the many idiosyncrasies of drug abuse, perhaps the most unique is the continual search by the abuser for previously undiscovered sources of gratification. In some ways, it was inevitable that the Benzedrex® nasal inhaler would be misapplied like its predecessor, Benzedrine®. The irony of the situation is the intravenous toxicity of propylhexedrine, a compound selected as a safe substitute for amphetamine. Perhaps the same toxicity would have become more evident with Benzedrine® nasal inhalers if the intravenous route of self-medication had become more prevalent. Perhaps propylhexedrine is simply more toxic to the pulmonary vasculature and the myocardium than its cousin.

The successful efforts to restrict the sale of amphetamines in Wisconsin has been recently published by Treffer and Joranson (38). The program they describe was capable of identifying the major prescribers and dispensers of the amphetamine product, Biphetamine-20®. The Wisconsin Controlled Substances Board (CBS) was able to identify the "script doctors" and problem pharmacies as well as to take the appropriate punitive actions necessary to stop the diversion of legally prescribed amphetamines to nonmedical usage. Working with 1975 data, they discovered that 26 practioners (20 M.D.'s, 3 D.O's, 2 dentists and 1 podiatrist) out of 9,500 licensed practitioners in the state, accounted for prescriptions totaling 118,300 doses of Biphetamine-20® ("black cadillacs"). Five of these 26 practitioners accounted fully for 71% of the doses. There were 16 pharmacies that purchased more than 10,000 doses apiece (less than 5% of all pharmacies accounted for nearly one-half of all Biphetamine-20® sold in the state). The Medical Examining Board then promulgated a policy which defined the term "unprofessional conduct" to mean "the prescribing or dispensing of amphetamines for any purpose other than five limited clinical indications and one research use". Penalties were imposed by the Board on practitioners in violation of this policy. Subsequently, this information assisted the DEA in the arrest of several practitioners, who were convicted in federal court for unlawful distribution of a controlled substance without a legitimate medical purpose.

The results of the combined efforts of the CSB, the Wisconsin Board of Medical Examiners, and the DEA can be seen in Figures 7, 8 and 9.

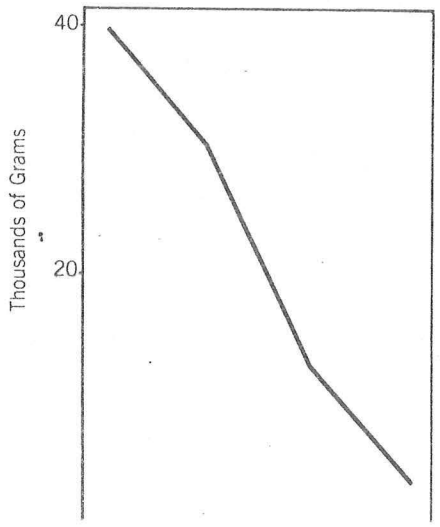


Figure 7: Wisconsin retail amphetamine purchases.

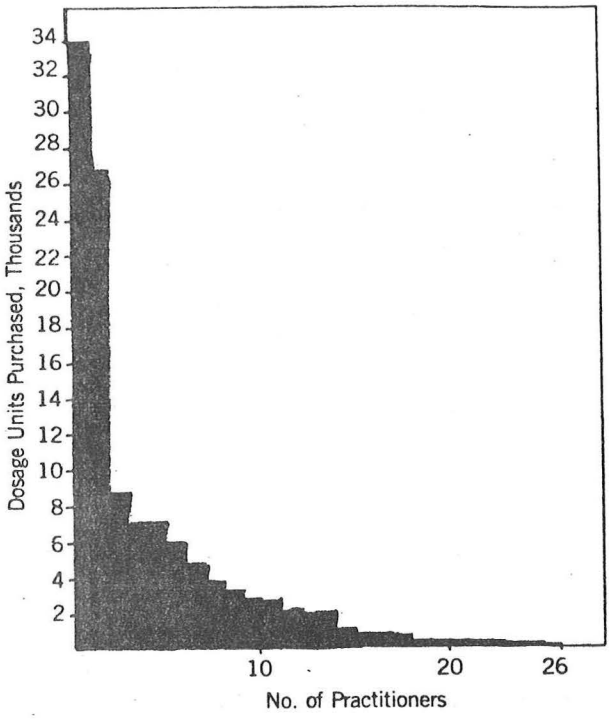


Figure 8: Calendar year 1975 purchases of the combination drug containing dextroamphetamine and amphetamine (Biphetamine-20®) by 26 Wisconsin practitioners.

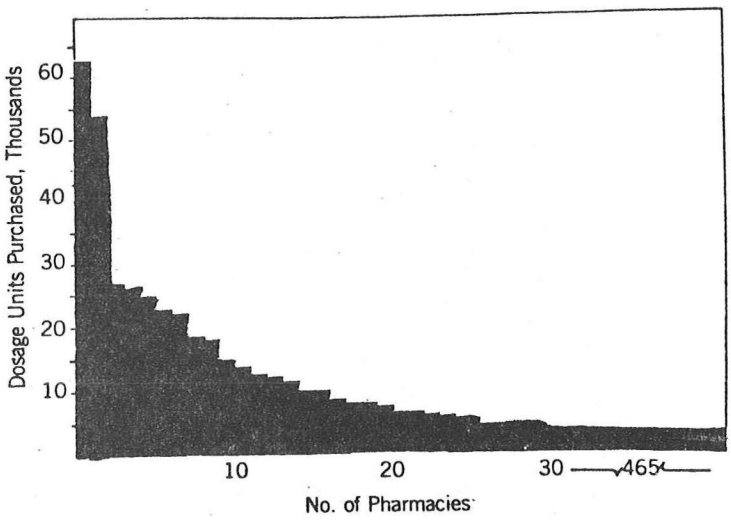


Figure 9: Calendar year 1975 purchase data of the combination drug containing dextro-amphetamine and amphetamine (Biphetamine-20®) by 465 Wisconsin pharmacies.

Hopefully, other states, or the federal government, will follow the Wisconsin lead. Should this occur, the attractiveness of the Benzedrex® nasal inhaler as an amphetamine substitute may increase. The legal accessibility and the inexpensive nature of the instrument make the growth potential for abuse unlimited. In anticipation of this event, it would be prudent to once again invoke section 503(b) of the Durham-Humphrey amendment to eliminate over-the-counter sales of the Benzedrex® nasal inhaler in order to avoid widespread abuse and the potentially devastating consequences for the individual abuser.

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