Medical Staff Conference

Neurologic Aspects of Cocaine Abuse

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

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In addition to his research on the psychopharmacology of cocaine in humans, Dr Rowbotham is part of the very active group in the UCSF Department of Neurology investigating the neurologic complications of cocaine use.

MICHAEL C. ROWBOTHAM, MD†: In the five years since the well-publicized death of a popular comedian and the serious injury of another, cocaine has dominated the news like few other issues. Despite a torrent of negative press on all aspects of cocaine use, the "cocaine epidemic" is far from over. In the medical literature, with every passing month come new reports of toxicity associated with its use. Fortunately, it is now widely recognized among physicians that even an occasional use of cocaine by the intranasal route can produce fatal complications. Unfortunately, despite the large volume of published medical literature on cocaine, relatively little is known about the pathophysiology of medical complications associated with its use. Even less is known about the effective prevention and treatment of cocaine-associated medical illness.

The First Wave of Cocaine Use

In the past two decades, we have seen the cyclic romance with cocaine repeated. In an identical replay of the 1880-1920 wave of cocaine use, we are now in what has been described as the third stage in the cycle of drug use in a society. First, a small elite experiments with the drug and reports few negative effects. Second, a middle period of the dispersion of drug use to a wide population and a recognition of ill effects takes place. Finally, a period of rejection ensues as the popular image of the drug becomes negative.

In 1880 an Italian neurologist, Paolo Mantegazza, waxed lyrical about the effects of cocaine on his favorite subject—himself. After describing the physiologic effects of the coca leaf in detail, he wrote: "God is unjust because He made man incapable of sustaining the effect of coca all life long."[1] A few years later Sigmund Freud began to experiment with cocaine after reading of its use in the treatment of morphine withdrawal and of battlefield exhaustion. In his famous 1884 paper, "On Coca," Freud listed many therapeutic uses for cocaine, including its local anesthetic effects. Fame for this discovery went not to Freud but rather to his two ophthalmologist friends, Carl Koller and Leopold Konigstein, who demonstrated the usefulness of cocaine as an anesthetic in eye surgery. Also in the 1880s, William Halsted began injecting cocaine into peripheral nerves to produce regional anesthesia for surgery.

Cocaine use was costly to these early researchers. Freud's career was nearly destroyed when his colleague Fleischl became cocaine-dependent in an effort to overcome morphine addiction and when one of Freud's patients died of a cocaine overdose. Halsted also became cocaine-dependent, "curing" himself by becoming morphine-dependent. By 1891, more than 200 reports of systemic cocaine intoxication had appeared, with 13 deaths attributed to the drug. Despite this, cocaine-containing patent medicines and tonics became popular, none more so than Coca-Cola and Vin Mariani.[2,3] Angelo Mariani's cocaine wine advertisements included testimonials from two popes and a host of reigning monarchs. Eventually the hazards of cocaine use were appreciated and its widespread use in the United States gradually ended following passage of the Harrison Narcotics Act in 1914.

During this same period, an understanding of the physiologic effects of cocaine progressed rapidly. Sollman's *A Manual of Pharmacology,* published in 1922, described in detail the cardiovascular, respiratory, thermoregulatory, mydriatic, and local anesthetic actions of the drug. The stimulant effects on the central nervous system and abuse liability are explained, as is the convulsive toxicity of the drug. The central nervous system effects were noted to follow a path from elation and vigor to mania and delusions, with depression following drug withdrawal.[4] In a special article in the *Journal of the American Medical Association* in 1924, Mayer reported an analysis of 43 deaths from local anesthetics, primarily cocaine.[5] Although the effect of cocaine in blocking the neuronal reuptake of norepinephrine was not to be described for another 35 years, he astutely pointed out the hazards of using cocaine and adrenaline together in anesthesia.

The Current Wave of Cocaine Use

From the latter half of the 1920s through much of the 1960s, cocaine was expensive and favored mostly by jazz musicians, members of the cultural avant-garde, and affluent drug dealers. The introduction of inexpensive synthetic am-

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
EEG = electroencephalogram
ICSS = intracranial self-stimulation
SFGH = San Francisco General Hospital and Medical Center
UCSF = University of California, San Francisco

phetamines in the 1930s reduced the popularity of cocaine to the point where only 2.8 kg (6 lb) of the drug was seized by the Federal Bureau of Narcotics in 1960. During this long period of obscurity, cocaine gained a reputation as the nonaddicting "champagne" of drugs. As recently as 1980, cocaine was claimed in major textbooks to be a relatively safe, nonaddicting euphoriant drug. The stage was set for the next wave of popularity of cocaine. By 1986, the National Institute on Drug Abuse estimated that almost 15% of the United States population had tried cocaine and that 3 million people abused cocaine regularly.[6] Although cocaine had been injected since the turn of the century, the introduction of low-priced "crack" made cocaine smoking a widespread practice. By the smoked route, extremely high blood levels can be achieved within seconds and the latency between first use and addiction shortened from years to weeks. It was estimated in 1984 that 18% of cocaine users smoked cocaine, a percentage that is likely to be higher now. With such a large number of people abusing cocaine, previously unrecognized complications began to emerge in the medical literature. The full impact of widespread cocaine smoking in the form of "crack" is not yet known, but the introduction of "crack" into the Bahamas in 1983 dramatically increased the number of persons seeking treatment for cocaine addiction and medical problems related to cocaine abuse.[7] The medical complications of cocaine have been the subject of several comprehensive reviews, but relatively little attention has been paid to the incidence, pathogenesis, or treatment of cocaine-related neurologic complications.[6,8-10]

Physiologic Effects of Cocaine Use

Although some of the medical complications of cocaine use represent a sudden expression of previously silent anatomic abnormalities that put even a first-time user at risk, most are related to compulsive high-dose cocaine abuse. Why is cocaine so addicting? To understand this, a brief review of the pharmacology and neural effects of cocaine is necessary. Cocaine is an alkaloid prepared from the leaves of the plant *Erythroxylon coca*. Cocaine hydrochloride is the water-soluble salt used medicinally. It decomposes on heating and melts at 195°C. The cocaine alkaloid, or "free base," is not soluble in water. It melts at 98°C and vaporizes at higher temperatures without decomposing, allowing it to be smoked.[8] The plasma half-life of cocaine is approximately 60 to 80 minutes, much shorter than that of methylphenidate and amphetamines.

The time course of the physiologic and subjective effects of a single dose of cocaine is closely correlated with the route of administration and blood concentrations achieved. An oral dose of 2 mg per kg body weight produces peak effects in about 45 minutes, with a rise in the heart rate of 27 beats per minute, a rise in the systolic blood pressure of 26 mm of mercury, a decrease in the skin temperature of 7°C, and a 1-mm increase in pupil size.[11] Administered intravenously, intense effects can be achieved with doses one-fifth those administered orally. When smoked, an intense and relatively brief mental and physiologic state follows just one or two inhalations of cocaine, reflecting a concentrated bolus delivered efficiently to the brain with only eight seconds of transit time.[12] An intravenous infusion of lethal doses of cocaine in dogs produces a predictable sequence of events culminating in generalized convulsions and death. The heart rate, blood pressure, cardiac output, and body temperature all rise, with the blood pH falling to nearly 7.0 as convulsions begin.[13] Rapid administration of a lethal dose can produce apnea and cardiac arrest without generalized convulsions. The experience of cocaine "body packers"—persons who smuggle cocaine by ingesting large numbers of cocaine-filled balloons or condoms—who had one or more packets rupture while in hospital has confirmed this same sequence of events in humans.[14-16] Before the onset of generalized seizures, a toxic delirium was observed.

The effects of the repetitive administration of cocaine are more complex. Tolerance to both the subjective and the cardiovascular effects of cocaine occurs quickly. Fischman and Schuster gave a group of experienced human cocaine users the opportunity to self-administer repeated bolus doses of cocaine as often as every ten minutes in a tightly controlled experimental situation.[17] Even though blood levels continued to rise throughout the experiment, the subjects could not discern any additional increase in effects after the first few doses. The same effect was observed for doses administered 60 minutes apart. Post described an orderly progression of clinical syndromes of euphoria, dysphoria, and paranoid psychosis related to the dose and chronicity of use.[18] High-dose cocaine abuse in humans produces disinhibition, impulsiveness, hypervigilance, compulsively repeated actions, and extreme psychomotor activation.

Access to the drug is a critically important factor in understanding the complications of cocaine abuse. Under proper conditions, monkeys will self-administer the same drugs taken illicitly by humans, a laboratory model used extensively in research on psychoactive drugs. Animals will self-administer cocaine under a broad range of conditions and by all routes, which may be an indication of the substantial size of the human population at risk for abuse. Cocaine has been a potent reinforcer in all animal species tested so far, evidence that a preexisting psychopathologic disorder is not a prerequisite for cocaine addiction in humans. Once self-administration has begun, the organism becomes totally preoccupied with acquiring the drug to the exclusion of food and socialization.[19] Given unlimited access, animals self-administer the drug in erratic bursts, similar to the cocaine binging seen in humans, with seizures or exhaustion terminating each binge.[20,21] In contrast, when access to cocaine is limited, animals self-administer cocaine in a relatively regular manner with greatly reduced morbidity and mortality. The economic parallel to human use patterns is unmistakable. Users report that, once started, binge use continues until no more drug is available. In the past, the high price of cocaine, difficulties in converting the hydrochloride to the free base, and the natural reluctance of most people to inject themselves provided limits on cocaine use that allowed most users to maintain health and continue to work. Longitudinal observations of cocaine users in the 1970s and early 1980s indicated about a two-year period between first use and addiction. With the introduction of cheap cocaine in the smokable base form, extremely high blood levels can be achieved almost instantaneously and maintained for longer periods,

increasing the likelihood of behavioral and medical toxicity and establishing an addictive pattern of use much more rapidly, sometimes within weeks.

Neurologic Effects

Knowledge of the neurochemical actions of cocaine has continued to advance in recent years. The local anesthetic actions of cocaine were described by Freud more than 100 years ago. As do lidocaine, procaine, and related drugs, cocaine blocks the sodium channel and inhibits the depolarizing inward sodium current necessary for impulse propagation along axons. Unlike all other local anesthetic drugs, cocaine has potent sympathomimetic actions.[22] In 1959 Trendelenburg found that cocaine inhibited the neuronal reuptake of administered catecholamines like norepinephrine and epinephrine.[23] Later, serotonin and dopamine were added to the list of transmitters whose inactivation by reuptake was blocked by cocaine. In 1978 Chiueh and Kopin showed that increased blood levels of epinephrine and norepinephrine after systemic cocaine administration were due in large part to a centrally mediated release of the transmitters from the sympathoadrenal medullary system.[24] Later work has indicated that cocaine also stimulates release of both serotonin and dopamine. Cocaine binding sites have been identified in the brain, but their density and distribution in relation to the dopamine, norepinephrine, and serotonin systems are not yet known.

Much of our knowledge about the effects of cocaine comes from comparing cocaine with other stimulant drugs and studying brain "reward" systems. Although the neurochemical basis of the euphoriant effect of any of the stimulant drugs is still not clear, it does not depend on any one neurotransmitter system.[6] This is based on a large body of research using drugs with specific neurochemical effects to try and modulate the euphoriant effects of stimulants and the observation that these more specific drugs are not euphoriants. Cross-tolerance occurs between cocaine, amphetamine, and methylphenidate in self-stimulation studies.[25] These three drugs have some neurochemical actions in common, especially dopamine release and catecholamine re-uptake blockade. Since Olds and Milner's discovery in 1954 that rats would work to earn electrical stimulation of some but not all portions of their brains,[26] intracranial self-stimulation (ICSS) had proved a powerful tool in research on stimulants. Cross-tolerance occurs between ICSS and stimulants, and procedures that alter ICSS also affect stimulant self-administration. Several lines of evidence indicate that dopamine, but not norepinephrine, is critical in maintaining the self-administration of cocaine. The mesolimbic and mesocortical dopaminergic pathways must be intact. 6-Hydroxydopamine lesions in the nucleus accumbens, medial prefrontal cortex, or the dopamine neurons of the ventral tegmental area in the brain stem disrupt cocaine self-administration. Dopamine-receptor blockers, but not noradrenergic blockers, also disrupt cocaine self-administration.[27] It has recently been shown that the self-administration of cocaine is related to its binding of neuronal dopamine transporters but not to its binding of the transporters for norepinephrine and serotonin.[28]

The long-term administration of cocaine produces supersensitivity of central dopaminergic, α-adrenergic, and β-adrenergic receptors. Brain dopamine levels and striatal tyrosine hydroxylase levels are persistently decreased in rats, and a variety of neuroendocrine changes have been noted in human cocaine abusers.[29-31] Responses to ICSS are persistently decreased, indicating a long-lasting subsensitivity of brain "reward" areas. These effects are thought to underlie the cocaine withdrawal syndrome and the persistent anhedonia seen in habitual stimulant abusers. Conditioned cues from the environment in addition to these physiologic changes may explain why relapse rates after abstinence in cocaine abusers are so high.

TABLE 1.—*Neurologic Complications of Cocaine Abuse in Adults*

Seizures	Single
	Multiple
	Status epilepticus
Stroke	Subarachnoid hemorrhage due to rupture of arteriovenous malformation or aneurysm
	Intracranial hemorrhage
	Nonhemorrhagic infarction
Headache	
Transient focal symptoms and signs	
Toxic encephalopathy	

Cocaine can produce a variety of neurologic problems, a finding that is not surprising when one keeps in mind that it is both a potent sympathomimetic and a local anesthetic agent. A short list of reported neurologic complications in adults is presented in Table 1. Of these, seizures are correlated with the route and the amount of drug used. Others, such as stroke, may be idiosyncratic reactions to the drug of unknown pathogenesis that can affect both first-time and experienced users. Preexisting anatomic abnormalities, such as coronary artery disease and cerebrovascular anomalies, may render some persons particularly likely to suffer medical catastrophes after using modest doses. The use of cocaine does not need to be active; the fetus and newborn are at special risk as well.

Cocaine-Induced Seizures

Seizures induced by cocaine were well recognized before the 1920s. The convulsant effects of cocaine are most likely related to its local anesthetic effects. Lidocaine is an anticonvulsant at low doses but is a potent convulsant at doses similar to those required to produce convulsions with cocaine. Likewise, multiple seizures following the rupture of cocaine-filled condoms in "body packers" have been associated with high blood levels of 2.0 to 5.2 μg per ml.[14,15] Comparison studies of amphetamine, cocaine, and lidocaine in seizure-kindled paradigms have shown that cocaine's effects on brain electrical activity are similar to those of lidocaine.[32] Studies by Matsuzaki and others have shown that seizure activity induced by cocaine begins in the temporal lobe and then generalizes.[33] The daily administration of a convulsive dose of cocaine produces bizarre behavior and abnormal interictal electroencephalographic activity recorded using depth electrodes, but the mean convulsive dose rises instead of falls over time. The role of catecholamines in cocaine-induced seizures is not yet clear. A nearly total selective depletion of either brain dopamine or norepinephrine has no effect on cocaine-induced seizures.[34] Pretreatment, however, with drugs that antagonize all cocaine effects and have a more general effect on catecholamines, such as chlorpromazine and reserpine, prevent cocaine-induced seizures. Of the traditional anticonvulsants, only diazepam and barbi-

TABLE 2.—*Evaluation of Suspected Cocaine-Induced Seizures**

Toxicology: urine specimen for cocaine, cocaine metabolites, and other drugs
CBC, sedimentation rate, chemistry panel, thyroid function tests, FTA test
Brain imaging: computed tomography or magnetic resonance
Lumbar puncture
Electroencephalogram

CBC=complete blood count, FTA=fluorescent treponemal antibody

*Patients with multiple observed seizures or status epilepticus require monitoring of core body temperature, cardiorespiratory function, and an electroencephalogram. See text for details.

turates have any protective effect. Phenytoin has been found to be ineffective in animals, and carbamazepine has not been adequately studied. Two factors greatly reduce the blood level of local anesthetic required for seizure production: an elevated body temperature and a decreased blood pH. In their study of cocaine poisoning in dogs, Catravas and Waters found that merely placing the animals in a cold room prevented the hyperthermia, seizures, and death produced by cocaine.[13]

The management of a patient with cocaine-induced seizures is empiric at this time and should be based on the presentation. All patients should have a thorough evaluation to rule out other causes of seizures. A schema for evaluation is shown in Table 2. If no cause for a seizure other than drug use is found, no long-term treatment other than drug abstinence is required because of both the lack of effect of traditional anticonvulsants in preventing cocaine-induced seizures and the lack of evidence that cocaine-induced seizures will later produce seizures independent of usage of the drug. A patient who presents with a history of a single, unobserved seizure related to cocaine use and is not cocaine intoxicated at the time of presentation should be evaluated for a nondrug cause of the seizure but will not require immediate anticonvulsant therapy. The electroencephalogram (EEG) should be normal soon after the seizure. A patient who presents with a history of cocaine-induced seizures and is intoxicated with the drug or who has an observed seizure in the emergency department requires a rapid and thorough assessment. Attention to the basics—blood pH, core body temperature, and electrocardiogram—is the first step. A urine specimen should be sent for a toxicologic analysis. Once the patient is stable, brain imaging with computed tomography (CT) or magnetic resonance imaging followed by lumbar puncture should be carried out to exclude stroke, subarachnoid hemorrhage, and infection. An EEG and other studies will be necessary to rule out other causes of seizures. If only a single seizure occurs and the patient recovers rapidly, no anticonvulsants are needed. If a second seizure is observed, diazepam can be administered to stop the seizure, but phenytoin loading should be carried out without delay. Although the use of phenytoin may not be effective in patients with cocaine-induced seizures, a reliable history and toxicologic confirmation are not available in the emergency situation, and a standard treatment protocol should be followed.

If status epilepticus develops, phenobarbital loading and the protocol for pentobarbital anesthesia in use at the San Francisco General Hospital and Medical Center (SFGH) should be followed.[35] This will require admission to an intensive care unit, intubation, and continuous EEG monitoring. It is absolutely essential to keep the body temperature as near normal as possible. Not only is hyperthermia directly damaging to the brain, but there is evidence that anticonvulsants administered in this situation will be more effective if the body temperature is kept normal.[36] It is difficult to give recommendations regarding blood pH during cocaine-induced status epilepticus. The degree of arterial blood pH depression due to the lactic acidosis of seizures is not correlated with mortality or central nervous system injury.[37] Acidosis may, however, exacerbate local anesthetic-induced seizures, and cocaine may cause acidosis even before seizure activity begins. Even profound degrees of lactic acidosis are reversed by the metabolism of lactate in about an hour, and cocaine itself has a short half-life of 60 to 80 minutes. Until further research clarifies this aspect of the management of cocaine-induced seizures, attempts to correct the blood pH should not divert attention from more critical aspects of seizure control. Because cocaine-induced seizures, especially status epilepticus, are associated with high blood concentrations of the drug, arrhythmias and hypotension may coexist. I recommend avoiding using lidocaine in this situation because its similarities to cocaine may aggravate the seizures.

Drug-induced seizures are difficult to manage. When combined with hypotension and hyperthermia, morbidity and mortality are high. An illustrative case is presented in Figure 1. Assuming the patient survives, long-term anticonvulsant therapy is probably not necessary unless focal brain injury or a persistently abnormal EEG is present.

Cocaine-Induced Stroke

Stroke associated with cocaine use is a recently recognized phenomenon. There has been little research into this problem, and the literature consists almost entirely of case reports. Since the first well-described case in 1977, there have appeared 15 more articles describing a wide variety of stroke types in a total of 41 patients.[38-49] Subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic stroke located in all vascular territories including the anterior spinal artery have now been described. Nearly all were in patients younger than 50 years and many younger than 30. Cocaine was used by the intranasal, intravenous, intramuscular, and smoked routes. The quality of the evaluations has varied widely. The first case reported by Brust and Richter was based on a clinical examination without CT confirmation.[38] Many subsequent cases reported have been limited by a lack of toxicologic confirmation of cocaine use and evaluations lacking angiography and lumbar puncture. In nine of the reported cases, angiography has documented either an arteriovenous malformation or an aneurysm. In only five cases has angiography been carried out and found to be normal. Several cases of documented middle cerebral artery branch occlusions have been associated with "crack" smoking. It is tempting to speculate about a cause-and-effect relationship between the high cocaine blood concentrations achieved nearly instantaneously by cocaine smoking and stroke of this type, but so far no evidence has emerged of a relationship between the route of administration of cocaine and the stroke type.[42] One case of "vasculitis" associated with the use of cocaine, analogous to the cerebral "speed arteritis" associated with amphetamine use, has been reported.[46] In this case, however, the spinal fluid was bloody, which alone could account for the angiographic findings.[47] Stroke may follow cocaine use within a period of seconds to as long as 12 hours. There is no ready explanation for a modest delay in the start

of the symptoms, but it indicates that stroke following cocaine use may be only indirectly related to the route, dose, and peak blood levels achieved in some cases.

Stroke in young adults is uncommon. In persons younger than 30 years, atherosclerosis is unlikely to play a role, and an underlying cause is present in most cases. In Bogousslavsky and Regli's recent series, the most important etiologic factors were mitral valve prolapse, arterial dissection, vasculitis, migraine, hypercholesterolemia, and oral contraceptive use.[50] The mechanism by which cocaine causes stroke is unknown, but it is most likely related to its sympathomimetic effects. Large doses of local anesthetic drugs like lidocaine have been used for various problems for more than 50 years without an observed relationship to stroke. In contrast, amphetamines, methylphenidate, phencyclidine, LSD, and phenylpropanolamine all share with cocaine the ability to alter vascular tone and all have been associated with stroke.[49] LSD and phencyclidine produce a potent contractile response when applied to isolated canine basilar and middle cerebral arteries that may be mediated by serotonin. The others have prominent catecholaminergic effects or directly stimulate α-adrenergic receptors. Edvinsson and co-workers showed in the middle cerebral artery of cats that cocaine produced a prejunctional type of sensitivity to norepinephrine that was similar to that produced by surgical sympathectomy.[51] The role of platelets in cocaine-associated stroke is unclear but potentially important. Catecholamines and sympathetic stimulation enhance platelet aggregation, and platelet thrombi have been found in some cases of cocaine-associated myocardial infarction. As the cerebral vasculature has not been studied pathologically in any reported case of cocaine-associated stroke, a discussion of the pathogenesis must remain speculative.

A patient with a suspected cocaine-associated stroke should have a thorough evaluation to exclude all possible treatable causes of stroke. An evaluation scheme is shown in Table 3. In addition to a toxicologic confirmation of cocaine use, brain imaging using magnetic resonance or CT, lumbar puncture, echocardiography, angiography, and hematologic studies are indicated. In the absence of an identified cause other than cocaine use, conservative treatment is advised. There is no literature to support the long-term use of prednisone, heparin, or aspirin in these cases.

Both headache and a variety of transient neurologic signs and symptoms have been observed in association with cocaine abuse.[43] Although cocaine-related headache is an uncommon reason for patients to present to an emergency department for treatment, it is a symptom commonly reported in community treatment facilities and in users calling a toll-free telephone help line. A large number of drugs have been reported to cause headaches, and headache is a common symptom in drug-withdrawal syndromes. Because of the association between cocaine and stroke and the hypertensive effects of the drug, headache is a symptom that should be taken seriously. Deciding which patients require evaluation is difficult, but a complete evaluation should include brain imaging, lumbar puncture, and, in many cases, angiography.

Sympathomimetic drugs and local anesthetics can produce transient neurologic signs and symptoms related to the amount used. The enhancement of physiologic tremor, vertigo, nonspecific dizziness, blurred vision, ataxia, and tinnitus have all been reported. Cocaine "hallucinations" drawn by users bear a notable resemblance to the visual auras of migraine. Although some symptoms may reflect an increased awareness of bodily sensations or a misinterpretation of the cardiovascular effects of the drug, focal abnormalities such as a transient hemiparesis have been seen and are of unknown origin. In animals, high doses of cocaine produce abnormal motor activity and stereotypic behavior. In humans, tics and choreiform movements due to amphetamine abuse have been noted but have not been reported in association with cocaine use. In all cases of neurologic signs and symptoms due to cocaine abuse, toxicologic confirmation of

TABLE 3.—*Evaluation of Suspected Cocaine-Associated Stroke*

Toxicology: urine specimen for cocaine, cocaine metabolites, and other drugs
CBC, sedimentation rate, ANA, chemistry panel, FTA test, coagulation studies
Electrocardiogram
Brain imaging: computed tomography or magnetic resonance
Lumbar puncture—including VDRL
4-Vessel cerebral angiography
2-Dimensional echocardiography

ANA=antinuclear antibody, CBC=complete blood count, FTA=fluorescent treponemal antibody

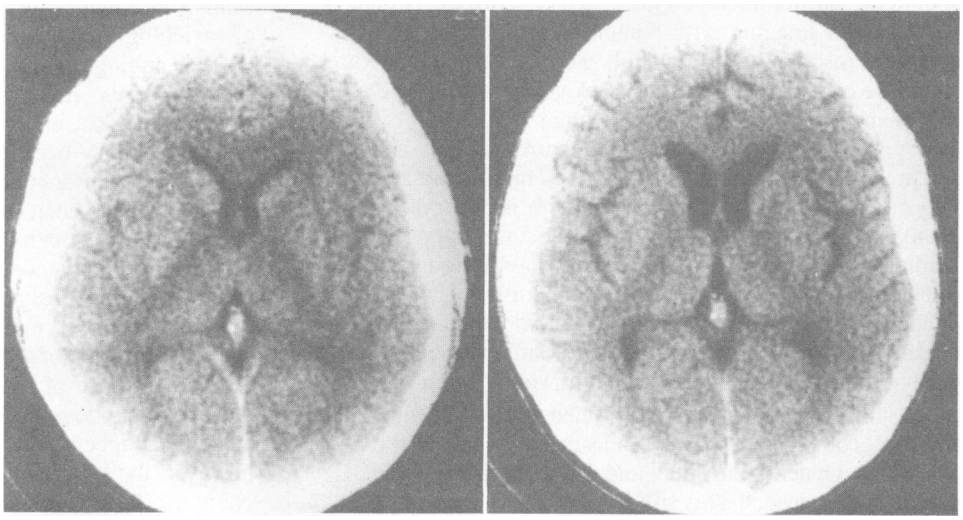

Figure 1.—The scans show cerebral atrophy following oral cocaine-induced status epilepticus. A 24-year-old man was brought to an emergency department in a confused and hypervigilant state. When generalized seizures began, his blood pressure dropped from 210/138 mm of mercury to 68/24 mm of mercury with a wide QRS complex tachycardia on an electrocardiogram. A blood pH of 6.77 and a temperature of 40.5°C (105°F) were noted during the ictus. Seizures continued despite intubation and the intravenous administration of diazepam, phenytoin, and phenobarbital. The blood cocaine value was 4.0 μg per ml. A noncontrast computed tomographic (CT) scan on the day of admission **(left panel)** was normal. A CT scan at 30 days **(right panel)** and thereafter showed widespread cerebral atrophy. Severe neurologic impairment was permanent.

cocaine use and the exclusion of the use of other drugs are essential. There is not yet enough information available to know which patients require a complete evaluation, but, at a minimum, all patients with abnormalities on a neurologic examination require a neurologic consultation and further study as indicated. Any patient who presents with a stroke-like syndrome following cocaine use should be promptly studied using the schema in Table 3.

Cocaine-associated behavioral abnormalities, especially a drug-induced psychosis, are commonly seen. An uncommon event is a true toxic encephalopathy following cocaine use that may present as coma of an unknown cause. This is a major medical emergency and when due to cocaine probably indicates the intake of a lethal or near-lethal dose. In addition to other evaluations and treatment indicated in managing such patients, a urine specimen for toxicology and a blood specimen for a plasma cocaine level (where available), an emergency portable EEG to exclude status epilepticus, and attention to the core body temperature are particularly important. A search of the oropharynx and x-ray films of the abdomen are needed to exclude retained cocaine-containing packets. β-Blockers such as propranolol hydrochloride are not useful in this situation. Preliminary studies in animals indicate that neuroleptics and calcium channel blockers each enhance survival in cocaine poisoning.[13,52] In humans, calcium channel blockers antagonize some effects of cocaine.[53] It must be pointed out that in these studies, the drugs were either given concurrently or as a pretreatment. Their usefulness in reversing signs of cocaine poisoning in humans remains to be proved.

Perinatal Effects of Cocaine Use

In the past three years there has been a tremendous surge of interest in complications of pregnancy and childbirth due to maternal cocaine abuse. Long-term follow-up studies are underway, but preliminary data indicate that some cognitive-behavioral abnormalities persist in the children for at least six months to two years. Even when compared with pregnant women who abuse heroin or are on methadone maintenance therapy, cocaine-using women have worse pregnancy outcomes. Increased incidences of spontaneous abortion, abruptio placentae, fetal death, and premature and precipitous labor have all been documented in these women compared with methadone-maintained and non-drug-using women.[54,55] Infants born to cocaine-using mothers are more likely to be small for gestational age and have smaller head circumferences. There have been several reports—including one prospective study—of an increased incidence of sudden infant death syndrome in infants of cocaine-using mothers, but whether the increased incidence is greater than that associated with the abuse of opiates is not established.[56,57] Perinatal cerebral infarction and hemorrhage, sometimes presenting as seizures, has occurred in full-term infants. An illustrative case is presented in Figure 2.

A variety of lesions have been seen, including diffuse atrophy, deep brain cysts, periventricular leukomalacia, and hemorrhages in many locations.[58,59] The pathophysiology of these complications received little study until recently. Woods and associates showed in pregnant ewes that the maternal administration of cocaine produced a substantial dose-dependent increase in uterine vascular resistance, an increased maternal blood pressure, and decreased uterine blood flow.[60] Associated with this were fetal hypoxemia, hypertension, and tachycardia. Directly administering cocaine to the fetus did not cause fetal hypoxemia and produced a lesser degree of hypertension and tachycardia. Of importance is that the doses used overlapped with those used experimentally in nonpregnant human volunteers and are probably similar to those used by cocaine abusers. In addition, pregnant women and infants do not metabolize cocaine as rapidly because of lower levels of plasma cholinesterases. An alternative pathway that generates the biologically active metabolite, norcocaine, may assume more importance. Urine specimens from newborns of cocaine-using mothers may test positive for cocaine metabolites for as long as five days, and cocaine exposure of the infant may continue after birth through breast milk. These findings raise the possibility that some signs, especially seizures, of the "cocaine withdrawal" syndrome seen immediately postpartum may actually represent prolonged intoxication with the drug.

The magnitude of the problem of cocaine-related neurologic illness is unknown. No population-based studies are available to estimate how frequently any of the reported medical complications of cocaine occur. A seven-year retrospective study of patients presenting for treatment for cocaine-related neurologic and psychiatric problems at SFGH was recently reported.[43] Of 989 cases attributed to cocaine use alone, 150 patients had primarily neurologic complaints. The two largest categories were seizures and focal neurologic symptoms and signs—including stroke—with headache, a transient loss of consciousness, tremor, and toxic encephalopathy occurring less frequently. The neurologic complications observed were not benign. Of the patients presenting with seizures, status epilepticus developed in two requiring pentobarbital anesthesia for control, with one patient dying and the other left with permanent neurologic sequelae. Of the patients with stroke, all had significant per-

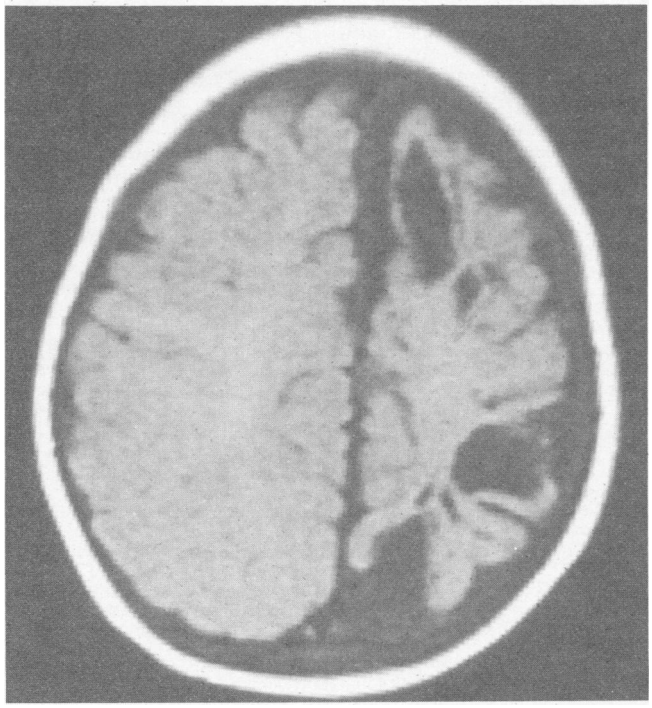

Figure 2.—Magnetic resonance imaging (MRI) of the brain of a 4-month old male infant shows multiple areas of left (viewer's right) hemispheric infarction. The mother had used cocaine but no other drugs throughout pregnancy. Seizures developed after delivery and MRI on day 4 of life showed left hemispheric edema.

manent residual effects. One of three patients admitted for toxic encephalopathy died shortly after admission with hyperthermia, rhabdomyolosis, disseminated intravascular coagulation, and renal and cardiac failure.

Consistent with nationwide trends, the number of cocaine-associated neurologic complications rose steadily each year throughout the seven-year study period. Although the number of patients seems small compared with the total number of patients seen each year at a large urban hospital like SFGH—80,000 emergency department visits and 18,000 hospital admissions annually—the problems encountered are sufficiently rare and the evidence in favor of an association with cocaine use too strong to dismiss the findings as coincidental. Population-based figures cannot be calculated, but at the present time stimulant abuse is a significant cause of stroke in patients younger than 40 years at SFGH. Cocaine abuse among pregnant women has risen considerably in recent years, and neurologic complications in newborns are frequently seen. In 1987 at SFGH, 119 mother-infant pairs tested positive for cocaine only, making up 12% of all newborns at that center.

Perhaps because of the current negative image of cocaine, the number of first-time users of cocaine has begun to decline. It will be some time before the end of the "cocaine epidemic." Another cycle of abuse of stimulant drugs will undoubtedly begin in the not-so-distant future. Next time, let us hope we more critically evaluate abuse liability and toxicity before public use spins out of control.

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