THE CARDIOVASCULAR COMPLICATIONS OF COCAINE USE

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I. INTRODUCTION

As cocaine abuse has increased dramatically over the past 15 years, the number of cocaine-related emergency room visits, hospital admissions, and deaths has also increased dramatically. In 1973 the Strategy Council on Drug Abuse reported little morbidity and no confirmed deaths attributable to cocaine overdose [1]. However, recent reviews and anecdotal reports have heightened awareness of the many medical complications associated with cocaine use. Cardiac, pulmonary, central nervous system, psychiatric, obstetrical, gastrointestinal, and endocrine complications have all been associated with cocaine use [2].

Currently, cocaine is the illicit drug of abuse most often involved in emergency rooms visits and one of the leading causes of drug-related deaths [3-5]. According to the Drug Enforcement Administration, cocaine-related emergency room visits rose 200 percent between 1985 and 1989, and more than 5 of every 1000 emergency department deaths are related to cocaine [6]. While many of these are caused by cocaine's toxic effect on the central nervous system, numerous reports have linked cocaine-induced death with its cardiovascular effects. Accordingly, my purpose today is to review our current understanding of the clinical characteristics, pathophysiology, and treatment of the various cardiovascular complications of cocaine use.

II. HISTORICAL PERSPECTIVE

Cocaine use has been traced back to 600 A.D. with the finding of coca leaves in the tombs of South American mummies. Believed to be a gift of the Royal Son of the Sun God, the plant was declared divine by the Inca Indians, its leaf placed on the royal emblem, and the first Inca Queen dubbed "Mama Cuca" [7]. In the thirteenth to sixteenth centuries coca leaves were used as a local anesthetic for trephination and other skull surgery [2].

Although the first reported medicinal use of coca leaves is attributed to a Spanish physician in 1596 [2], it was not until 1855 that the active agent - cocaine - was isolated. At that time it was touted by physicians as a cure for everything from fatigue, alcoholism, and opiate addiction to tuberculosis and dyspepsia. In 1884 Sigmund Freud obtained the drug from Eli Merck in hopes of curing his friend and colleague Dr. Ernst von Fleischel of an opiate addiction. Following several months of experimentation on himself and von Fleischel, Freud wrote the first major report extolling its medicinal value and describing the physiologic effects of the drug [8].

That same year, William Halsted, the Johns Hopkins surgeon, became the first American to use it as a local anesthetic and, as a result of self-experimentation, became addicted to it. In 1885 he wrote extensively of its anesthetic use then ominously wrote nothing in 1886 as he battled his own addiction of up to 2 gm a day. In 1885, the Journal of the American Medical Association reported the case of Dr.

Robert Louis Stevenson, who had received cocaine for treatment of tuberculosis (and who incidentally wrote the first draft of Dr. Jekyll and Mr. Hyde in 3 days) [7]. Even Sir Arthur Conan Doyle (vicariously through his character Sherlock Holmes) experienced problems with cocaine addiction [8].

In the early 20th century, cocaine was used in over-the-counter drugs, home remedies, and soft drinks (i.e., Coca Cola) until 1914 when it was classified as a narcotic in the United States and its use restricted to valid medical purposes. Although used routinely as a local anesthetic since then, its recreational use waned until approximately 20 years ago. A number of factors have contributed to the recent, sharp rise in illicit use of cocaine. First, it can be administered via a variety of routes: intranasally, subcutaneously, intravenously, orally, or smoked. Second, the high cost of cocaine, which previously limited its use, dropped as supplies - primarily from Columbia and Peru - became more available. Third, in addition to becoming cheaper and more plentiful, the purity of street cocaine increased. Finally, the widespread -- but incorrect -- belief that cocaine was a "safe", nonaddicting drug popularized its use.

III. PATTERNS OF USE

In 1987 the National Institute of Drug abuse estimated that 30 million Americans had used cocaine at least once, 5 million used it regularly, 5000 used it for the first time each day, and 1 million were addicted to the drug [2]. Its increasing illicit use and the administration of higher doses of drug has led to the increased number of cocaine-related cardiovascular deaths and complications.

Although recent statistics suggest that cocaine-related emergency room visits have decreased over the last year, they remain a serious problem in Dallas and Parkland Memorial Hospital. According to Drug Abuse Warning Network reports, 896 cocaine overdoses presented to Parkland Memorial Hospital in 1988 and 733 presented in 1989. Whether this represents a real decline in use of the drug or more care on the part of the users is not known. Sixty to 65% of the cocaine emergencies in a six county area are treated at Parkland Memorial Hospital [9].

Unlike other illicit drugs, cocaine abuse has not been confined to population subgroups of certain socioeconomic or education status. Of pertinence to the medical community, at least eight separate studies [10-17] over the last decade have documented high rates of cocaine use among medical students both before and during medical school (Table 1, below). Among medical students, cocaine is the second most frequently used illicit drug (behind marijuana) and once used is the least likely to be discontinued during medical school [10].

Table 1: Cocaine Use By Medical Students: Review of Eight Studies

Region	Year of Study	No. of Student	Cocaine Use (Life)
Boston, MA	1979	364	76 (21%)
Florida	1980	165	51 (31%)
Chicago, Ill	1982-83	116	32 (28%)
Nationwide	1983	476	157 (33%)
San Antonio, TX	1984	133	27 (20%)
New England	1984	381	149 (39%)
Nationwide	1986	589	212 (36%)
Washington DC	1987	263	44 (17%)
	TOTALS	2487	748 (30%)

Taken together, the studies reveal that approximately one of every three medical students used cocaine before medical school. Fifty to 80% of medical students who used cocaine before medical school continued to use it during medical school (Table 2, below) [10,13,15]. In a survey of five New England medical schools conducted in 1979 and repeated in 1984, the number of students who had used cocaine before or during medical school almost doubled (from 21% to 39%) during the five year period [19].

Table 2: Cocaine Use Before and During Medical School (n = 236, George Washington Health Sci Ctr) [10]

Frequency of Use	Before Medical School No. (%)	During Medical School No. (%)
No use	219 (83%)	220 (84%)
1-10 times	5 (2%)	31 (12%)
> 10 times	11 (4%)	5 (2%)
Each month	5 (2%)	5 (2%)
Each week	11 (4%)	2 (1%)
Daily	10 (4%)	-----
Unknown amount	2 (1%)	-----

IV. PHARMACOLOGY

Cocaine (benzoylmethylecgnonine; Figure 1, below) is an alkaloid extracted from the leaves of the *Erythroxylon coca* plant (not to be confused with the cocoa plant: while the latter might provide a soothing nightcap, the former would impart an entirely different experience). It is prepared by dissolving the alkaloid in hydrochloric acid to form a water-soluble salt (cocaine hydrochloride). This melts at 195°C, decomposes when heated, and is available in a crystalline, powder, or granular form.

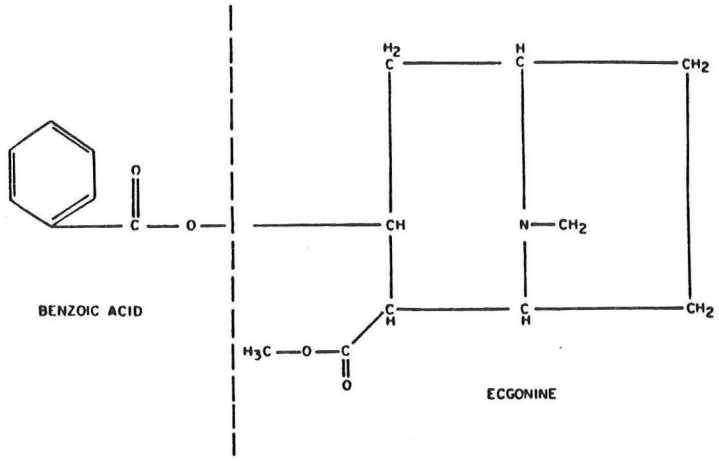

Figure 1. Chemical Structure of Cocaine, Benzoylmethylecgonine (from ref 6)

"Freebase" is the alkaloid cocaine which is heat stable and melts at 98°C, thus allowing it to be smoked. The freebase form is insoluble in water and soluble in ether, acetone, or alcohol. It is prepared by extracting cocaine with an alkaline solution, adding a solvent (such as ether), separating the layers, and evaporating the solvent, leaving behind relatively pure cocaine crystals. It is more potent and addicting than cocaine. Crack (named so because of the popping sound made when heated) is prepared by precipitating cocaine from an aqueous alkaline solution. This relatively simple street technique avoids the use of organic solvents with their attendant explosive risks.

Cocaine is well absorbed by all body mucous membranes accounting for its intranasal (snorting), oral, sublingual, intravaginal, and rectal administration. Mucosal administration results in a slower onset of action, later peak effect, and longer duration than intramuscular, subcutaneous or intravenous administration (Table 3, below). However,

high serum levels of cocaine can occur with any route of administration. When the free base form is smoked, the effects are obvious in seconds, peak quickly (within 1-3 minutes), and last only 15-30 minutes.

Table 3. Pharmacokinetics of Cocaine By Route of Administration

Route	Onset of Action	Peak effect	Duration
Inhalation (smoking)	3-5 sec	1-3 min	5-15 min
Intravenous	10-60 sec	3-5 min	20-60 min
Intranasal	1-5 min	15-20 min	60-90 min

Cocaine is detoxified by plasma and liver cholinesterases to benzoylecgonine and methylecgonine (Figure 2) which are water soluble and excreted in the urine [20]. Approximately 85-90 percent of a cocaine dose is recovered in the urine: 1% as the unchanged parent compound, and 75-90% as the above mentioned inactive metabolites [21].

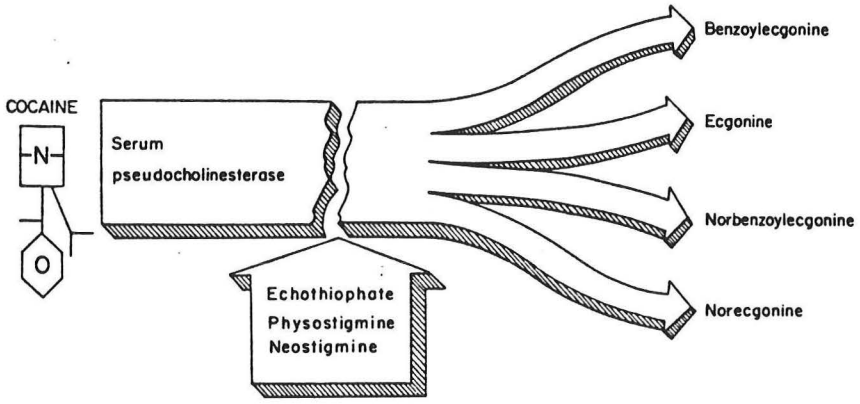

Figure 2. Cocaine Metabolism of (from ref 22)

The biologic half-life of cocaine is about one hour. Detoxification can be blocked by the serum cholinesterase inhibitors physostigmine or neostigmine [21]. As would be expected, patients deficient in cholinesterase activity are highly sensitive to even small doses of cocaine [23]. Depending on the route of administration and endogenous cholinesterase activity, metabolites may be found in the

urine up to 24 to 36 hours after cocaine use. This provides a useful screening test to evaluate for possible cocaine use.

When applied locally, cocaine acts as an anesthetic via its ability to block the initiation and transmission of electrical signals by interfering with membrane sodium permeability during depolarization. When administered systemically, its effects are mediated through alterations in synaptic transmission (Figure 3). Cocaine blocks the presynaptic reuptake of norepinephrine and dopamine, producing an excess of these neurotransmitters at the postsynaptic receptor site [24]. There is also experimental evidence suggesting that it may induce release of norepinephrine stored in sympathetic nerves in peripheral tissue through alpha-adrenergic stimulation [21]. It thus acts as a powerful sympathomimetic agent potentiating the effects of direct sympathetic stimulation (and infused catecholamines).

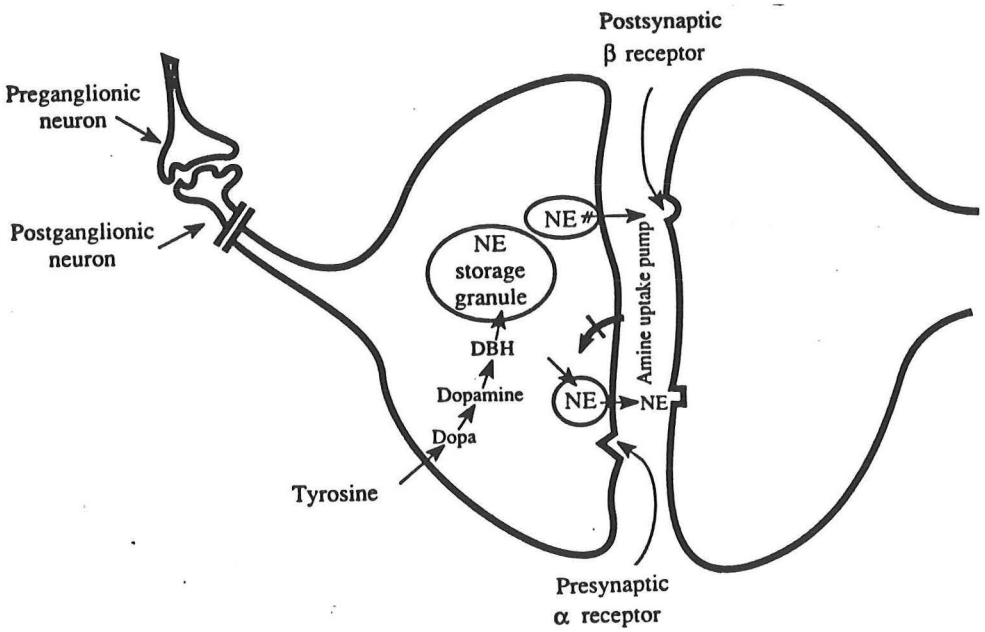

Figure 3: Effects of Cocaine on the Presynaptic Uptake of Catecholamines

IV. COCAINE-RELATED CARDIOVASCULAR COMPLICATIONS

The cardiovascular complications related to cocaine use include: acute myocardial infarction, myocarditis, dilated cardiomyopathy, cardiac arrhythmias, aortic dissection, and endocarditis. The clinical charcteristics, mechanism and treatment of each will be presented.

A. MYOCARDIAL INFARCTION

1. Incidence

An association between cocaine use and myocardial ischemia was first noted in 1982 when Coleman and colleagues described a 38 year old male with angina and subsequent myocardial infarction after drug use [25]. Since then, at least 65 cases of myocardial infarction temporally related to cocaine use have been reported in the literature [26-57].

The incidence of myocardial infarction following cocaine use is not known. No studies have directly addressed this, and since it is now a well recognized association, new cases are rarely reported in the literature. In addition, many patients with cocaine-induced myocardial ischemia go unrecognized. Although only a fraction of cocaine users develop myocardial infarction with drug use, the majority of urban (and many rural) hospitals care for patients with cocaine-related chest pain and infarction.

A recently published study confirms that cardiopulmonary complaints are common among patients seeking medical care for acute and chronic cocaine-associated medical problems.

Table 4. Symptoms Associated with Cocaine Use Among 233 Consecutive Emergency Room Patients

Symptoms	No.	(%)
ENT	19	(8%)
Gastrointestinal	31	(13%)
Constitutional	55	(23%)
Psychiatric	83	(36%)
Neurologic	91	(39%)
Cardiopulmonary	131	(56%)
Chest pain	93	(40%)
Short of breath	51	(22%)
Palpitations	48	(21%)
Diaphoresis	15	(6%)
Cough	16	(7%)
Cardiac arrest	2	(1%)

From Ref 58

Hospital visits for cocaine-related medical problems at Grady Memorial Hospital were examined retrospectively over a 6 month period between August 1986 and February 1987. The majority of complaints among 233 cocaine users were cardiopulmonary (Table 4, above). While chest pain was the most common symptom, only 1 patient had angina and 2 experienced cardiac arrest. Thus while cardiac symptoms were common, myocardial infarction occurred infrequently among their population of cocaine users.

A recent study by Nademanee et al suggests that myocardial ischemia occurs in a significant number of cocaine abusers, and many of the episodes are silent [59]. Of 21 male chronic cocaine users undergoing continuous electrocardiographic ambulatory (Holter) monitoring during a substance abuse treatment program, 8 (38%) had frequent episodes of ST segment elevation during the first two weeks of withdrawal. Of note 87% of the episodes were silent. Hence, even in the absence of symptoms, ischemia may occur frequently in those who use cocaine.

2. Clinical Characteristics

Subjects with cocaine-induced myocardial ischemia usually present with typical retrosternal chest pain and characteristic electrocardiographic changes. Ventricular tachycardia and fibrillation are common. Despite their typical presentation, clinical characteristics distinguish them from patients with ischemia from other causes. These characteristics are summarized in Table 5.

Table 5: Clinical Characteristics of Patients With Cocaine-Induced Myocardial Infarction

Young age (mean age, 31 years)
Male gender
No or minimal risk factors for coronary artery disease
Habitual, recreational, or first time cocaine users
Symptoms occur minutes to hours after cocaine use
Associated with all routes of cocaine administration
May occur with large or small doses of cocaine

The average age of subjects with cocaine-induced infarction is 31 years, with the youngest being 19 years of age and the oldest 47. Thus, the possibility of cocaine use must be considered whenever infarction occurs in the young patient. Of the individuals reported to have cocaine-related myocardial infarction, 93% have been male. Whether sex is a risk factor or this reflects gender-associated cocaine abuse patterns is not known.

Most patients develop evidence of ischemia within minutes of cocaine use [25,31,32,40,42,44,47,51]. However, myocardial infarction has been reported as late as 11-15 hours after drug use [33,45]. As mentioned previously, Nademanee and colleagues [59], using 24 hour Holter ,monitoring, demonstrated ST segment elevation consistent with ischemia in 8 of 21 (38%) subjects admitted to a substance abuse program. In 45% of patients this occurred during the first week of abstinence from drug, and in over 25% this persisted into the second and third weeks. Thus, chronic cocaine users continue to be at risk for myocardial ischemia even weeks after withdrawal from the drug.

Although most reported cases of cocaine-related infarctions have occurred following its intranasal administration, all routes of administration have been associated with ischemia and infarction. Likewise, habitual [32,34,35,42], recreational [25,29,36,42], and first time users [48,38] of the drug have been afflicted. Continued drug use after infarction has resulted in recurrent episodes of angina and infarction - even in individuals with angiographically normal coronary arteries [31,39,42,43].

Twenty five percent of individuals have none of the risk factors associated with atherosclerotic coronary artery disease. In the remainder, cigarette use is common (in 67% of subjects), and hypertension, hyperlipidemia, or a positive family rare (< 5% of subjects for each).

Two thirds of the infarctions associated with cocaine use are transmural (Q-wave). Of the reported infarctions, 62% have been anterior in location, 34% inferior, and 5% could not be localized. Short-term mortality for these patients is 10%.

Although, ingested doses and serum levels of cocaine have been reported for patients who died (from all causes) following its recreational use, few data are available for those with myocardial infarction. In cocaine abusers with infarction, ingested doses have ranged from 5-6 "lines" (approximately 150 mg) to 2 grams [35,48]. Doses as little as those required for nasal anesthesia have been associated with infarction [27]. Serum cocaine concentrations have been reported in only four patients with myocardial infarction [29,33,51,52]. Postmortem samples obtained 7 and 12 hours after drug ingestion demonstrated 0.4 and 0.02 mg/L of cocaine, respectively and serum samples obtained from two patients at autopsy (at an unspecified known of time from death) had concentrations of 0.02 and 1.02 mg/L. Since cholinesterases continue to metabolize the drug in the post-mortem period, these levels probably underestimate the serum concentration of

cocaine at the time of death

3. Mechanism(s)

Three pathophysiologic mechanisms may be operative in patients with cocaine-induced myocardial ischemia. Cocaine may provoke ischemia by (1)increasing myocardial oxygen demands in the setting of fixed coronary blood flow (demand/supply mismatch), (2)inducing coronary vasospasm, or (3)enhancing thrombotic potential.

Increased myocardial demand: In man, single-dose administration of cocaine induces a dose dependent increase in heart rate and blood pressure (Figure 4, below) [60]. The pattern of response to intravenous, intranasal, or inhaled (freebase) cocaine is similar with hemodynamic changes peaking within 30 minutes and dissipating within approximately one hour.

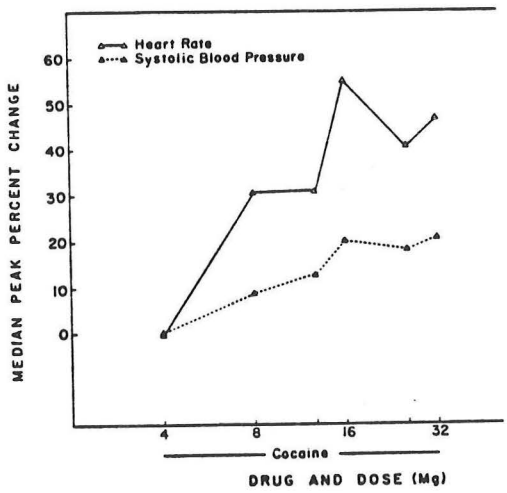

Figure 4: Median Peak Change in Heart Rate and Systolic Pressure in Response to Increasing Doses of Intravenous Cocaine (from ref 60)

Although it has been suggested that acute tolerance to the cardiovascular effects develops when cocaine is administered repeatedly in humans [61], tolerance has not been observed when cocaine was administered to chronic drug users or volunteers receiving continuous intravenous infusions [63,64].

Cocaine-induced increases in heart rate and systemic arterial pressure serve to increase myocardial oxygen demand. In patients with fixed atherosclerotic coronary artery disease this process may alter the tenuous balance between myocardial oxygen supply and demand, leading to ischemia or even infarction.

Vasospasm: Several observations provide the basis that cocaine-induced changes in coronary vascular tone may be the primary pathophysiologic mechanism responsible for ischemia and infarction. Pooling all reports, arteriography has been performed in 36 patients with myocardial infarction temporally related to cocaine use and has demonstrated no evidence of fixed coronary artery disease in approximately one-half (17 patients). In the most dramatic case reported by Zimmerman et al in 1987 [43], a 29 year old male presented with an inferolateral MI after intranasal cocaine use, and cardiac catheterization revealed normal coronary arteries. Two months later, he presented with recurrent infarction following repeated intranasal cocaine use, and emergent catheterization demonstrated complete occlusion of the left anterior descending coronary artery that partially resolved with nitroglycerin.

Additionally, noninvasive testing has frequently been negative in those with documented ischemia after cocaine use. In the study of chronic cocaine users by Nademanee and colleagues [59], only 1 of 8 patients with ST segment elevation on ambulatory electrocardiographic monitoring after cocaine use had a positive maximal exercise stress test. Thus, angiography and noninvasive testing fail to demonstrate evidence of fixed coronary artery disease in many subjects with documented cocaine-induced ischemia.

The vasoconstrictor effects of cocaine on the small intranasal vessels are well known. Recently, in-vitro studies have also provided evidence of enhanced vascular reactivity of larger vessels following cocaine use. In isolated rings of aorta from rabbits, Isner and colleagues have provoked reversible vasoconstriction with cocaine in concentrations of 10^{-8} to 10^{-3} M [64]. Furthermore, the same investigators have observed cocaine-induced vasoconstriction in isolated segments of human umbilical arteries and human coronary arteries from explanted hearts at the time of cardiac transplantation [64,65]. Thus the vasoconstrictor effects of cocaine extend to both small and large arteries.

Until recently, in-vivo evidence for cocaine-induced vasoconstriction was available only in canine models. In response to incremental doses of intravenous cocaine in mongrel dogs, Hayes et al [66] observed dose-dependant vasoconstriction of the left descending coronary artery by angiography. Similarly, Pierre et al [67], using an electromagnetic flow probe placed around the left anterior descending coronary artery of dogs, observed a reduction in coronary blood flow and increase in coronary vascular resistance following intravenous cocaine.

The most direct evidence for cocaine-induced coronary artery vasoconstriction has come from recent in vivo studies in man from our laboratory [68]. We studied the effects of intranasal cocaine (2 mg/kg, approximately 1/2 to 2/3 the dose used for standard intranasal anesthesia) in 29 subjects undergoing cardiac catheterization for the evaluation of chest pain. Systemic hemodynamics, coronary sinus blood flow, and coronary arterial dimensions were assessed before and after the administration of a 10% cocaine solution.

In response to cocaine, heart rate and arterial pressure rose modestly increasing myocardial oxygen demand (Table 6, below). Normally, in response to increased oxygen demand, the coronary arteries dilate, and coronary blood flow increases as a result of a reduction in coronary vascular resistance. In response to cocaine, however, coronary sinus blood flow *decreased* by almost 20% and coronary vascular resistance *increased* by 33%. By computer assisted quantitative arteriography, coronary arterial diameters decreased by 8 to 12%

Table 6: Hemodynamic and Arteriographic Measurements of the Response to Intranasal Saline (Group 1) or Cocaine (Group 2)

Variable	Group 1 (N = 16)		Group 2 (N = 29)	
	Base line	After intranasal saline	Base line	After intranasal cocaine
Heart rate (beats/min)	71±10	70±10	76±12	78±13†
Systolic arterial pressure (mm Hg)	134±22	133±17	141±24	152±27†
Heart rate–arterial pressure product ($\times 10^3$)	9.5±2.2	9.3±1.8	10.6±2.4	11.9±2.8†
Mean arterial pressure (mm Hg)	94±11	94±10	101±15	110±16†
Coronary-sinus blood flow (ml/min)	131±51	131±51	149±59	124±53†
Coronary vascular resistance (mm Hg/ml/min)	0.81±0.29	0.83±0.34	0.79±0.36	1.05±0.49†
Transcardiac oxygen-content difference (ml/dl)	10.6±1.7	10.6±1.9	10.2±1.8	11.1±1.6†
Coronary-artery diameter (mm)				
Left anterior descending				
Proximal	3.01±0.95	3.02±1.07	2.96±0.67	2.67±0.66†
Middle	1.96±0.26	1.97±0.24	2.11±0.47	1.90±0.41†
Distal	1.58±0.31	1.61±0.33	1.59±0.41	1.40±0.38†
Left circumflex				
Proximal	3.23±0.70	3.26±0.71	2.86±0.81	2.63±0.78†
Middle	2.46±0.53	2.45±0.52	2.23±0.43	2.02±0.42†
Distal	1.64±0.49	1.67±0.49	1.69±0.29	1.49±0.27†

*Plus–minus values are means ±SD.

†P<0.01 for the comparison with the corresponding base-line value.

Although the direction of change in coronary sinus blood flow and coronary vascular resistance was the same for all patients, there was substantial variation among them with regard to the magnitude of cocaine-induced coronary vasoconstriction. Some patients had marked vasoconstriction in response to this modest dose of cocaine: coronary vascular resistance rose by >50% and coronary diameter decreased by >25%. Similar patients, in response to the much higher serum concentrations associated with recreational use, probably develop intense and sustained vasoconstriction and subsequent myocardial infarction.

There is controversy surrounding the mechanism of cocaine-induced coronary vasoconstriction. Ergonovine provocation testing has been performed in 40 patients with cocaine-induced ischemia and infarction by a number of different investigators and, with only one exception [69], has uniformly been unsuccessful in eliciting vasospasm [32-34,42,43, 70,71]. Hence, these patients differ pathophysiologically from those

with Prinzmetal's angina.

In our patients, the administration of the alpha-adrenergic blocking agent phentolamine reversed the systemic hemodynamic and coronary vasoconstrictor effects of cocaine: coronary sinus blood flow, coronary vascular resistance, and coronary arterial dimensions returned to normal (Table 7, below). Thus, cocaine's effects in man appear to be mediated via alpha-adrenergic stimulation. Similar observations have been made in laboratory animals.

Table 7: Hemodynamic and Arteriographic Responses to Intranasal Cocaine Followed by Intracoronary Phentolamine

VARIABLE	(N = 13)		
	BASE LINE	AFTER INTRANASAL COCAINE	AFTER INTRACORONARY PHENTOLAMINE
Heart rate (beats/min)	74±12†	77±12†	88±14†
Systolic arterial pressure (mm Hg)	145±25	153±31†	138±27
Heart rate–arterial pressure product ($\times 10^3$)	10.6±2.3†	11.8±3.0	12.1±3.0
Mean arterial pressure (mm Hg)	103±16	110±20†	103±19
Coronary-sinus blood flow (ml/min)	157±60	129±62†	173±83
Coronary vascular resistance (mm Hg/ml/min)	0.74±0.31	1.03±0.53†	0.74±0.46
Transcardiac oxygen-content difference (ml/dl)	9.9±1.8	10.6±1.8†	9.4±1.5
Coronary-artery diameter (mm)			
Left anterior descending			
Proximal	2.63±0.39	2.38±0.40†	2.63±0.44
Middle	2.14±0.47	1.86±0.36†	2.04±0.35
Distal	1.50±0.46	1.28±0.30	1.49±0.30
Left circumflex			
Proximal	2.63±0.96	2.44±0.90†	2.68±0.96
Middle	2.24±0.47†	1.99±0.42†	2.33±0.43†
Distal	1.70±0.32	1.58±0.27†	1.76±0.25

*Plus–minus values are means ±SD. †P<0.05 for the comparison with the other values in the same patients.

Based upon data obtained in isolated arterial segments in rabbits and man, others have suggested that cocaine acts directly on vascular smooth muscle to cause vasoconstriction [64]. Presumably, enhanced calcium flux across membranes is involved as calcium channel blockers inhibit the vasoconstrictor effect of cocaine [65].

Whatever the mechanism, substantial evidence implicates coronary vasospasm as causative or contributory to cocaine-induced ischemia. It is clear that individuals vary markedly in their response to cocaine, with some experiencing marked coronary vasoconstriction to even small doses of the drug. Recent studies from the Dallas VAMC cardiac catheterization laboratory have demonstrated acetylcholine-induced coronary vasoconstriction -- an indication of endothelial dysfunction -- in cocaine-abusers with angiographically normal coronary arteries [74]. Data from our lab demonstrate enhanced vasoconstriction with cocaine at

sites of atherosclerotic narrowing implying that subjects with endothelial damage may be more susceptible to the untoward vasoconstrictor effects of cocaine [75]. Thus, endothelial dysfunction in cocaine users may set the stage for enhanced vasoconstriction in response to cocaine.

Enhanced thrombotic potential: In 1986, Simpson and Edwards described severe coronary obstructive lesions, as a result of chronic, nonatherosclerotic intimal proliferation and acute platelet thrombosis in a 21 year old man with a myocardial infarction after cocaine use [29]. They hypothesized that coronary spasm occurred, producing focal endothelial injury and platelet aggregation and that organization of previous platelet thrombi with secretion of growth factors resulted in intimal smooth muscle proliferation.

Since then, several angiographic studies have demonstrated occlusive coronary thrombi in patients with cocaine-induced infarction, and post-mortem examinations have revealed platelet-rich thrombi and chronic intimal hyperplasia of large and small coronary vessels [51,71,74,76]. Enhanced platelet aggregability due to a direct effect of cocaine on platelets or alpha-adrenergically mediated platelet adhesion may lead to chronic intimal inflammation and hyperplasia.

These speculations are based on an in vitro study in animals where platelets were found to be more aggregable, release more thromboxane, and inhibit endothelial prostacyclin release after incubation with cocaine [77]. Little data, however, are available concerning platelet function in man after cocaine use in the setting of normal coronaries. Additional research is needed before the etiologic role of thrombotic occlusion in cocaine-related myocardial infarction is elucidated.

4. Treatment

Strategies for treatment of cocaine-related myocardial ischemia and infarction have evolved from data obtained from animal studies, in-vitro observations, and anecdotal reports in patients. To date, no large trials have evaluated the various treatments strategies to determine which is most efficacious.

Experimental evidence suggests that coronary vasodilators - in particular, calcium channel blockers - may be especially useful in the treatment of cocaine-related ischemia. In isolated aortic segments from rabbits, diltiazem has been shown to inhibit cocaine-induced vasoconstriction [65]. Likewise, in the rat model, investigators have shown that nitrendipine, a long acting calcium blocker and potent coronary vasodilator, is an antidote to the cardiac and lethal toxicity of cocaine [78]. Moreover, both nitrendipine and verapamil have been shown to suppress cocaine-induced ventricular arrhythmias [78,79].

No studies have reported on the use of nitrates or aspirin in patients with myocardial infarction after cocaine use. Even, in the absence of published data, the vasodilatory action of nitrates and the antithrombotic and antiplatelet effects of aspirin would appear to be beneficial in these patients and therapy with these agents is advised.

Beta-adrenergic blockers, by virtue of their antihypertensive and negative chronotropic actions, result in decreased myocardial oxygen demand and have been advocated as a therapy for cocaine-related ischemia. However, data from our laboratory [80] show that beta-adrenergic blockade may result in unopposed alpha-adrenergic stimulation and actually worsen myocardial ischemia. In our study of 10 patients who received an infusion (2 mg over 5 minutes) of intracoronary propranolol following intranasal cocaine administration, beta-adrenergic blockade intensified the cocaine-induced vasoconstriction. In one patient, this propranolol administration resulted in total obstruction of a large epicardial coronary artery (that was quickly relieved by nitroglycerin). Further studies are needed to establish whether systemically administered beta-adrenergic blockers would exhibit similar deleterious effects.

Thrombolytic agents have been administered to some cocaine abusers presenting with infarction: 6 patients have received streptokinase [37,42,45,47,48,56] and 3 have received tissue plasminogen activator [42,50]. Follow-up coronary arteriography demonstrated "normal" coronary arteries in 6 of these patients and significant residual stenosis in the remaining two (unavailable in one). While, some advocate thrombolytic therapy for patients with evidence of transmural ischemia in spite of vasodilator therapy with vasodilator agents, others have suggested that intravenous drug abuse may be a relative contraindication to the administration of a thrombolytic agent. In a recent case report, a patient developed a large intracranial hemorrhage three hours after administration of tissue plasminogen activator and, at autopsy, was found to have a ruptured mycotic aneurysm [50]. While the safety of thrombolytic agents in drug abusers is not known, these agents should clearly not be used in individuals with pericarditis, endocarditis, or known intracerebral aneurysms.

5. Summary

The recent increase in cocaine abuse has resulted in an increase in the number of cocaine-related cardiovascular complications, including myocardial ischemia and infarction. The possibility of cocaine use should be entertained in any young person who presents with evidence of myocardial ischemia or infarction. Cocaine may cause myocardial ischemia through (a)coronary vasospasm, (b)increased thrombosis, (c)increased myocardial oxygen demands, or (d)a combination of these mechanisms. Treatment should include prompt recognition of the cause of ischemia, administration of vasodilating agents, and efforts to prevent recurrent drug abuse which may lead to repeated episodes of ischemia and infarction.

B. CARDIAC ARRHYTHMIAS

1. Clinical and Experimental Data

Although the list of arrhythmias (Table 8, below) attributed to cocaine use is extensive [24,28,30,38,55,81,82], the actual

arrhythmogenic potential of cocaine remains uncertain. Electrophysiologic studies assessing its effects in man have not yet been published. In many instances, the cardiac arrhythmias ascribed to cocaine, have occurred in the setting of profound metabolic abnormalities, hypotension, hypoxemia, seizures, or myocardial ischemia. Nevertheless, because of its pharmacologic properties and ability to induce an enhanced sympathetic state, it is likely that cocaine produces, or exacerbates, cardiac arrhythmias under certain conditions.

Table 8: Arrhythmias Associated With Cocaine Use

Sinus tachycardia
Sinus bradycardia
Supraventricular tachycardia
Bundle branch block
Complete heart block
Accelerated idioventricular rhythm
Ventricular tachycardia
Ventricular fibrillation
Asystole
Torsades des pointes

Dose dependent increases in PR, QRS, and QT intervals have been described when isolated rabbit hearts are perfused with cocaine [83]. In vivo canine experiments have shown that intravenous cocaine administration may cause sinus tachycardia and prolong cardiac conduction causing sinoatrial and atrioventricular block [84-86]. Moreover, in the intact sedated dog, cocaine potentiates (a)the chronotropic responses of the sinus node, (b)AV nodal conduction, and (c)shortening of ventricular effective refractory period in response to infused norepinephrine [87].

During anesthesia with halothane and nitrous oxide, cocaine renders dog hearts sensitive to epinephrine-induced ventricular arrhythmias [88]. It also potentiates the development of ventricular arrhythmias during norepinephrine infusion in dogs with myocardial infarction -- but not in those *without* infarction [87]. It appears that the development of lethal arrhythmias in the setting of cocaine use may require "abnormal myocardium" as a substrate. In support of this, Billman and Hoskins have shown that cocaine precipitates ventricular arrhythmias and fibrillation in exercising dogs when ischemia is induced, but not when ischemia is absent [79].

Clinically, cocaine in large doses in man may prolong PR, QRS, and QT intervals via its inhibition of sodium channels at the membrane level [89]. In essence, it acts as a Type I antiarrhythmic. One study of active crack users demonstrated significant QTc prolongation associated with crack use [90], and another has noted shortening of the QT interval

as the acute effects of cocaine waned [91]. When cocaine is used as a local anesthetic during laryngoscopy the frequency of premature ventricular complexes increases [92]. Ventricular fibrillation, ventricular tachycardia, and asystole have been reported in man following cocaine use in the absence of myocardial ischemia [28,33,55,81]. In addition, heart block, bundle branch block, and torsades des pointes [38,51] have been reported in the setting of cocaine-induced myocardial ischemia.

2. Mechanism(s)

Several mechanisms for cocaine-mediated cardiac arrhythmias have been proposed. Cocaine may precipitate arrhythmias by a)altering automaticity via direct effects on myocardial tissue, b)altering autonomic balance, c)causing electrical inhomogeneity by inducing ischemia, or d)creating anatomic substrate for reentrant arrhythmias.

Cocaine, through its direct membrane effects on sodium channels, is known to alter depolarization and may affect automaticity in normal myocardium (Type I antiarrhythmic effects). In addition, catecholamines have been shown to increase calcium flux in myocardial cells allowing increased calcium entry, which in turn results in action potential after-depolarizations [93]. If the after-depolarizations reach threshold, spontaneous and sustained extrasystoles occur.

Circulating levels of epinephrine and norepinephrine in acutely intoxicated cocaine users are elevated as much as fivefold [91]. This may be sufficient to initiate autonomic imbalance and repolarization abnormalities comparable to that observed with torsades des pointes from congenitally prolonged QT syndrome.

As reviewed earlier, animal studies suggest that the development of lethal arrhythmias following cocaine use is facilitated when "abnormal myocardium" is a substrate. To this end, life threatening arrhythmias and arrhythmogenic sudden death related to cocaine use occur most often in patients with myocardial ischemia and infarction, or those with myocellular damage. Pathologic examination of 30 patients who experienced sudden cardiac death related to cocaine use demonstrated contraction bands in 93% [94]. These may act to provide the substrate for the arrhythmias associated with cocaine use [95].

3. Treatment

In dogs that are administered cocaine, ventricular tachycardia and fibrillation during myocardial ischemia can be prevented by pretreatment with a calcium channel antagonist [79]. Although an interesting observation, clinical studies examining the role of calcium channel blockers are not available. It would not, however, be surprising to find that interventions that decrease myocardial calcium entry prove to be effective in treating cocaine-induced arrhythmias (perhaps it should be suggested that the Medellin cartel "cut" cocaine with calcium channel blockers prior to shipment).

Beta-adrenergic blocking agents (i.e., propranolol) have been

useful in treating sinus and supraventricular tachycardia [96-99]. Use of a combined alpha-adrenergic and beta-adrenergic blocking agent (i.e., labetalol) has been described [100]. It offers the advantage of avoiding the unopposed alpha stimulation caused by other beta-adrenergic agents which may result in worsened coronary [80] or systemic vasoconstriction [101].

Ventricular arrhythmias and heart block resulting from cocaine use should receive standard therapy including (a)treatment of underlying ischemia (if present), (a)correction of underlying metabolic disturbances (i.e., electrolyte abnormalities, hypoxemia, acid-base disorders), (a)administration of antiarrhythmic agents, and (c)temporary pacing when appropriate. Unless myocardial infarction occurs, the rhythm disturbances associated with cocaine intoxication are transient and resolve when the drug is metabolized.

C. MYOCARDITIS AND CARDIOMYOPATHY

1. Experimental Evidence

Animal experiments suggest that cocaine may be a direct cardiodepressant. In isolated myocardial strips from ferrets [102] and rabbits [103], cocaine has been shown to exert a negative inotropic effect and decouple excitation-contraction. These acute toxic effects are reversible and attributed to changes in intracellular calcium handling [102].

Deleterious effects of cocaine on myocardium have also been demonstrated in whole animal preparations. Intravenous administration of large doses of drug (5-10 mg/kg, bolus) in anesthetized dogs results in (a)decreased cardiac output, stroke volume, and left ventricular systolic function (+dP/dt) [57,104-106]; (b)diminished left ventricular compliance [104,105]; and, (c)dilatation of the left ventricle [105]. These effects may be due to a direct effect of the drug on cardiac muscle or to reduction in regional myocardial blood flow.

2. Clinical Experience

The data supporting an association between cocaine and cardiomyopathy in man are not voluminous. In 1986, Wiener and colleagues [107] reported two cases of dilated cardiomyopathy in man associated with cocaine abuse. Two other reports [108,109] linking cocaine use to left ventricular dysfunction have subsequently been published. The clinical data for these 4 patients is summarized in Table 9.

Table 9: Reported Cases of Cardiomyopathy Associated With Cocaine Abuse

Pt. No.	Age (yrs)	LVEF	Cocaine use & duration	Comments, Possible etiology
1	42	20%	heavy, IN x 3yr, IV x 1 yr	Recurrent MI (Nl cardiac cath)
2	28	41%	7 g/wk x 2 yr	
3	31	25%	6 g/wk x .5 yr	
4	35	10%	NA	Seizure, hypoxemia, hypotension; LVEF 45% at 1 wk

Abbreviations: IN, intranasal; IV, intravenous; LVEF, left ventricular ejection fraction; Nl, normal.

In two of the cases, myocardial dysfunction can be attributed to causes other than a direct cardiodepressant effect of cocaine (patient 1 had two well documented myocardial infarctions despite normal coronary arteries at cardiac catheterization, and patient 4 had severe, reversible myocardial dysfunction in the setting of seizures, hypoxemia, and hypotension). Nevertheless, there are several similarities in these cases. Other than cigarette use, no cardiac risk factors were present. All patients were relatively young and, with the exception of case 4, known to use large doses of drug chronically. Hence, prolonged and repeated exposure to cocaine may be necessary to induce chronic cardiac dysfunction.

In a recent study by Bertolet and colleagues [110] to determine the incidence of myocardial dysfunction associated with cocaine use, 84 asymptomatic cocaine abusers underwent cardiac evaluation, including radionuclide angiography, after a two week abstinence from drug. Left ventricular dysfunction was discovered in 6 (7%); 4 with global depression (ejection fraction < 50%) and two with regional wall motion abnormalities. The clinical characteristics of these subjects is shown in Table 10.

In all cases, cardiac dysfunction was clinically unrecognized and unsuspected after routine evaluation. As in the cocaine users with symptomatic cardiac dysfunction, these patients were relatively young, had used large doses of cocaine chronically, and had no evidence of coronary artery disease or cardiac risk factors other than cigarette use.

Table 10: Asymptomatic Cardiac Dysfunction in Cocaine Users: Summary of Cases

Pt. No.	Age (yrs)	LVEF (%)	Cocaine use & duration	RWMA	Cardiac Cath
1	37	58	"Every chance" x 22yr	Ant	No CAD
2	37	58	14 g/wk x 2 yr	Ant, Inf & Post	NA
3	25	41	6 g/wk x 6 yr	Global	NA
4	38	49	2 g/wk x 16 yr	Global	NA
5	44	49	"Experimental"	Global	No CAD
6	33	47	14 g/wk x 14 yr	Global	No CAD

Abbreviations: Ant, anterior; CAD, coronary artery disease; NA, not available; RWMA, regional wall motion abnormality.

Myocarditis has been reported to be a frequent finding in cocaine abusers dying of a drug-related death. Histologic examination of myocardial tissue from 40 patients who died of natural or homicidal mechanisms and had cocaine detected in body fluids at the time of death revealed active myocarditis in 20% [76].

3. Mechanism(s) and Pathologic Findings

Several mechanisms exist whereby cocaine may deleteriously effect cardiac function (Table 11).

Table 11: Possible Etiologies for the Cardiotoxic Effects of Cocaine

1. Myocardial ischemia and infarction
2. Chronic catecholamine stimulation
3. Hypersensitivity myocarditis
   a. to cocaine
   b. to "adulterants"
4. Heavy metal exposure (i.e., manganese)
5. Infection (viral or bacterial)

Cocaine may induce myocardial ischemia and infarction causing a dilated cardiomyopathy. While occlusion of large epicardial vessels causes clinically apparent infarction, occlusion of small vessels may cause focal ischemia and infarction that is clinically unrecognized. If small, clinically inapparent infarctions occur repetitively, left ventricular dysfunction may result. Indeed, autopsy studies of cocaine abusers [76,94,95] have demonstrated patchy areas of myocardial fibrosis consistent with focal ischemia in the absence of myocarditis or significant epicardial coronary artery obstruction.

The association between pheochromocytoma, a state of chronic sympathetic stimulation, and cardiomyopathy is well known [111-113]. Profound sympathetic stimulation produces areas of subendocardial necrosis and myocarditis characterized by contraction band necrosis, often with lymphocytic or neutrophil infiltrates. Taleazer et al [94] reported a 93% incidence of contraction band necrosis in the myocardium of cocaine-associated deaths. Furthermore, the extent of myocardial injury correlated with urinary and blood levels of cocaine.

Eosinophilic myocarditis has also been observed [33,76] in some cocaine abusers, suggesting a hypersensitivity reaction. Cocaine is often mixed with other drugs and adulterants and rarely ingested in its pure form. Thus, hypersensitivity may develop to cocaine or any of the diluents with which it is mixed.

Ensen [114] has reported manganese carbonate concentrations between 5 and 15% in "bazooka", a cocaine base product. Manganese is known to have acute cardiotoxic effects and reduce cardiac contractility by uncoupling excitation and contraction [115]. Although there are no published data concerning serum or tissue concentrations of manganese or heavy metals in cocaine addicts, they have been postulated to be relevant factors in the cause of cocaine-related cardiomyopathy [108].

Finally, cardiomyopathy may be caused by infectious agents in the subjects who abuse cocaine parenterally. This may occur directly through infection of myocardial tissue (i.e., viral myocarditis) or indirectly via a hypersensitivity reaction.

4. Treatment

Although little is known about the treatment of cocaine-induced cardiac dysfunction, it goes without saying that abstinence from the drug is the most important aspect of treatment. In some patients with pheochromocytoma, the catecholamine cardiomyopathy may be reversed when sympathetic stimulation ceases [116,117]. Whether similar benefits may be observed after cocaine abstinence is unknown. Immunosuppressive therapy for endomyocardial biopsy documented eosinophilic myocarditis has been reported in a 25 year-old man [33]. Six months after initiation of prednisone and azathioprine, repeat biopsy was normal. Whether the favorable result was attributable to immunosuppressive therapy or the patient's subsequent abstinence from cocaine is speculative.

D. ENDOCARDITIS

One study has reported an association between cocaine use and endocarditis [118]. In the study of 102 intravenous drug abusers hospitalized at San Francisco Hospital for evaluation of fever, endocarditis was detected in 20%. Analysis of the patient's history by logistic regression analysis revealed that cocaine was the variable most strongly predictive for endocarditis -- more so than the presence of valvular murmurs or signs of septic emboli. Why cocaine would more likely be associated with endocarditis than would other injected drugs is not clear.

E. AORTIC DISSECTION

Aortic dissection in a man with longstanding hypertension [119] and aortic rupture in a previously healthy man [120] have been temporally linked to cocaine use. These complications were most likely the result of the acute and substantial increase in systemic arterial pressure induced by cocaine. A blood pressure of 280/170 was recorded in the former patient.

V. CONCLUSION

Cocaine use in the United States has reached epidemic proportions and has not spared the medical profession. The increase in cocaine abuse has resulted in an increase in the number of cocaine-related emergency room visits, hospital admissions, cardiovascular complications, and death. Recognition and an understanding of cocaine-related cardiovascular complications is essential to proper treatment. The possibility of cocaine use should be entertained in any young person who presents with evidence of myocardial ischemia or infarction, arrhythmias, myocarditis, or dilated cardiomyopathy.

REFERENCES

1. Kozel NJ, Adams EH. Epidemiology of drug abuse: An overview. Science 1986; 234:970-974.

2. Cregler LL, Mark H. Medical complications of cocaine abuse. N Engl J Med 1986; 315:1495-1500.

3. MacDonald DI. Cocaine leads ED drug visits. JAMA 1987; 258:2029.

4. Mittleman RE, Wetli CV. Death caused by recreational cocaine use: An update. JAMA 1984; 252:1889-1893.

5. Litovitz TL, Schmitz BF, Matyunas N, Martin TG. 1987 annual report of the American Association of Poison Control Centers national data collection systems. Am J Emerg Med 1988; 6:479-515.

6. House MA. Cocaine. Am J Nursing 1990; 90:41-45.

7. Gay GR, Inaba DS, Sheppard CW, Newmeyer JA. Cocaine: History, epidemiology, human pharmacology, and treatment. A perspective on a new debut for an old girl. Clin Toxicology 1975; 8:149-178.

8. Musto DF. A study in cocaine: Sherlock Holmes and Sigmund Freud. JAMA 1968; 204:27-32.

9. Taylor J. Cocaine overdoses decrease: Drop may mean use in Dallas declining. Dallas Times Herald, June, 10,1990:pp 1,16.

10. Schwartz RH, Lewis DC, Hoffmann NG, Kyriazi N. Cocaine and marijuana use by medical students before and during medical school. Arch Intern Med 1990; 150:883-886).

11. Kory WP, Crandall LA. Nonmedical drug use patterns among medical students. Int J Addict 1984; 19:871-884.

12. McAuliffe WE, Wechsler H, Rohman M, et al. Psychoactive drug use by young and future physicians. J Health Soc Behav 1984; 25:34-54.

13. Maddux JF, Hoppe SK, Costello RM. Psychaoctive substance abuse among medical students. Am J Psychiatry 1986; 143:187-191.

14. Conrad C, Hughes P, Baldwin DC. Substance use by fourth-year students at 13 medical schools. J Med Educ 1988; 63:747-758.

15. Epstein R, Eubanks EE. Drug use among medical students. Kansas City, Mo: University of Missouri-Kansas City; 1986 (dissertation).

16. Clark DC, Fawcett J. Drug involvement of medical students during the school year. In: Program and abstracts of the National Meeting of the American Medical Society on Alcoholism and other Drug Dependencies; April 18-22, 1986; San Francisco, Calif. Abstract 17P.

17. Conrad S, Hughes P, Baldwin DC, et al. Cocaine use by senior medical students. Am J Psychiatry 1989; 146:382-383.

18. DATAGRAM: Substance abuse policies and programs at U.S. medical schools. J Med Educ 1988; 63:759-761.

19. McAuliffe WE, Rohman M, Santangelo S, et al. Psychoactive drug abuse among practicing physicians and medical students. N Engl J Med 1986; 315:805-810.

20. Fish F, Wilson WDC. Excretion of cocaine and its metabolites in man. J Pharm Pharmacol 1969; 21:1355-1385.

21. Gradman AH. Cardiac effects of cocaine: A review. Yale J Biol Med 1988; 61:137-147.

22. Verlander JM Jr, Johns ME. The clinical use of cocaine. Otolaryngol Clin No Amer 1981; 14:521-531.

23. Jatlow P, Barash PG, VanDyke C, et al. Cocaine and succinylcholine sensitivity: A new caution. Anesth Analg 1979; 58:235-238.

24. Ritchie JM, Greene NM. Local anesthetics. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. The Pharmacologic Basis of Therapeutics. 7th ed. New York: Macmillan, 1985:309-10.

25. Coleman DL, Ross TF, Naughton JL. Myocardial ischemia and infarction related to recreational cocaine use. West J Med. 1982; 136:444-446.

26. Jonsson S, O'Meara M, Young JB. Acute cocaine poisoning: Importance of treating seizures and acidosis. Am J Med. 1983; 75:1061-1064.

27. Chiu YC, Brecht K, DasGupta DS, Mhoon E. Myocardial infarction with topical cocaine anesthesia for nasal surgery. Arch Otolaryngol Head Neck Surg. 1986; 112:988-990.

28. Nanji AA, Filipenko JD. Asystole and ventricular fibrillation associated with cocaine intoxication. Chest. 1984; 85:132-133.

29. Simpson RW, Edwards WD. Pathogenesis of cocaine-induced ischemic heart disease. Arch Pathol Lab Med. 1986; 110:479-484.

30. Boag F, Havard CW. Cardiac arrhythmia and myocardial ischaemia related to cocaine and alcohol consumption. Postgrad Med J 1985; 61:997-999.

31. Pasternack PF, Colvin SB, Baumann FG. Cocaine-induced angina pectoris and acute myocardial infarction in patients younger than 40 years. Am J Cardiol 1985; 55:847.

32. Howard RE, Hueter DC, Davis GJ. Acute myocardial infarction following cocaine abuse in a young woman with normal coronary arteries. JAMA. 1985; 254:95-96.

33. Isner JM, Estes NAM, Thompson PD, et al. Acute cardiac events temporally related to cocaine abuse. N Engl J Med. 1986; 315:1438-1443.

34. Cregler LL, Mark H. Relation of acute myocardial infarction to cocaine abuse. Am J Cardiol. 1985; 56:794.

35. Wilkins CE, Mathur VS, Ty RC, Hall RJ. Myocardial infarction associated with cocaine abuse. Texas Heart Inst J 1986; 12:385-387.

36. Schachne JS, Roberts BH, Thompson PD. Coronary-artery spasm and myocardial infarction associated with cocaine use. N Engl J Med 1984; 310:1665-1666 (letter).

37. Rod JL, Zucker RP. Acute myocardial infarction shortly after cocaine inhalation. Am J Cardiol 1987; 59:161.

38. Rollingher IM, Belzberg AS, Macdonald IL. Cocaine-induced myocardial infarction. Can Med Asoc J 1986; 135:45-46.

39. Weiss RJ. Recurrent myocardial infarction caused by cocaine abuse. Am Heart J 1986; 111:793.

40. Kossowsky WA, Lyon AF. Cocaine and acute myocardial infarction: A probable connection. Chest 1984; 86:729-731.

41. Gould L, Gopalaswamy C, Patel C, Betzu R. Cocaine-induced myocardial infarction. NY State J Med 1985; 85:660-661.

42. Smith HWB, Liberman HA, Brody SL, et al. Acute myocardial infarction temporally related to cocaine use. Ann Intern Med 1987; 107:13-18.

43. Zimmerman FH, Gustafson GM, Kemp HG. Recurrent myocardial infarction associated with cocaine abuse in a young man with normal coronary arteries: Evidence for coronary artery spasm culminating in thrombosis. J Am Coll Cardiol 1987; 9:964-968.

44. Hadjimiltiades S, Covalesky V, Manno BV, et al. Coronary arteriographic findings in cocaine abuse-induced myocardial infarction. Cath Cardiovasc Diagn 1988; 14:33-36.

45. Ascher EK, Stauffer JCE, Gaasch WH. Coronary artery spasm, cardiac arrest, transient electrocardiographic Q waves and stunned myocardium in cocaine-associated acute myocardial infarction. Am J Cardiol 1988; 61:939-941.

46. Lam D, Goldschlager N. Myocardial injury associated with polysubstance abuse. Am J Med 1988; 115:675-680.

47. Ring ME, Butman SM. Cocaine and premature myocardial infarction. Drug Therapy 1986; 16:117-125.

48. Wehbie CS, Vidaillet HJ JR, Navetta FI, Peter RH. Acute myocardial infarction associated with initial cocaine use. South Med J 1987; 80:933-934.

49. Haines JD Jr, Sexter S. Acute myocardial infarction associated with cocaine abuse. South Med J 1987; 80: 1326-1327.

50. Bush HS. Cocaine-associated myocardial infarction: A word of caution about thrombolytic therapy. Chest 1988; 94:878.

51. Stenberg RG, Winniford MD, Hillis LD, et al. Simultaneous acute thrombosis of two major coronary arteries following intravenous cocaine use. Arch Pathol Lab Med 1989; 113:521-524.

52. Cooke CT, Dowling GP. Cocaine-associated coronary thrombosis and myocardial ischemia. Pathology 1988; 20:305-6.

53. Zimmerman FH, Lipton B. Cocaine and MI. Chest 1987; 92:767 (letter).

54. Amin M, Gabelman G, Karpel J, Buttrick P. Clinical characteristics of myocardial infarction after cocaine use. J Am Coll Card 1990; 15:146A (abstract).

55. Benchimol A, Bartall H, Desser KB. Accelerated ventricular rhythm and cocaine abuse. Ann Intern Med. 1978; 88:519-520.

56. Wang T, Hadidi F, Triana F, Bargout M. Morning report at Charity Hospital: Myocardial infarction associated with the use of cocaine. Am J Med Sci 1988; 295:569-571.

57. Mathias DW. Cocaine-associated myocardial ischemia: Review of clinical and angiographic findings. Am J Med 81; 1986:675-678.

58. Brody SL, Wrenn KD. Cocaine-related medical problems: Consecutive series of 233 patients. Am J Med 1990; 88:325-331.

59. Nademanee K, Gorelick DA, Josephson MA, et al. Myocardial ischemia during cocaine withdrawal. Ann Int Med 1989; 111:876-880.

60. Fischman MW, Schuster CR, Resnekov L, et al. Cardiovascular and subjective effects of intravenous cocaine administration in humans. Arch Gen Psychiatry 1976; 33:983-989.

61. Fischman MW, Schuster CR, Javaid J, et al. Acute tolerance development to the cardiovascular and subjective effects of cocaine. J Pharm Exper Ther 1985; 235:677-682.

62. Kumor K, Sherer M, Thompson L, et al. Lack of cardiovascular tolerance during intravenous cocaine infusions in human volunteers. Life Sci 1988; 42:2063-2071.

63. Majid PA, Cheirif J, Rokey R, et al. Acute hemodynamic effects of intravenous cocaine in chronic cocaine abusers. J Am Coll Cardiol 1990; 15:146A (abstract).

64. Isner JM, Chokshi SK. Cocaine and vasospasm. N Engl J Med 1989; 321:1604-1606 (editorial).

65. Chokshi SK, Gal D, Whelton JA, Isner JM. Evidence that fetal distress in newborns of cocaine users is due to vascular spasm and may be attenuated by pre-treatment with diltiazem. Circulation 1989; 80: II-185 (abstract).

66. Hayes SN, Moyer TP, Bove AA. Intravenous cocaine causes epicardial coronary vasoconstriction in the intact dog. J Am Coll Cardiol 1988; 11:49A (abstract).

67. Pierre A, Kossowsky W, Chou ST, Abadir AR. Coronary and systemic hemodynamics after intravenous injection of cocaine. Anesthesiology 1985; 63:A28 (abstract).

68. Lange RA, Cigarroa RG, Yancy Cw, et al. Cocaine-induced coronary artery vasoconstriction. N Engl J Med 1989; 321:1557-1562.

69. Patel R, Haider B, Ahmed S, Regan TJ. Cocaine-related myocardial infarction: High prevalence of occlusive coronary thrombi without significant obstructive atherosclerosis. Circulation 1988; 78:II-436 (abstract).

70. Halle AA, Insel J, McDonald MB, Ramanathan KB. Ergonovine testing in cocaine induced myocardial ischemia. J Am Coll Cardiol 1989; 13:79A (abstract).

71. Majid PA, Patel B, Kim HS, et al. An angiographic and histologic study of cocaine-induced chest pain. Am J Cardio 1990; 65:812-814.

72. Vargas R. Zukowska-Grojec Z, Gillis RA, Ramwell PW. Cocaine and coronary artery reactivity. Circulation 1988; 78:II-223 (abstract).

73. Kuhn FE, Gillis RA, Wahlstrom SK, et al. Cocaine induced deleterious effects on the canine coronary circulation. J Am Coll Cardiol 1989; 13:79A (abstract).

74. Eichhorn EJ, Grayburn PA, Bedotto JB, Willard JE, et al. Abnormal endothelium-dependent coronary vasoreactivity and intimal proliferation in patients with chronic cocaine abuse. (in review).

75. Flores ED, Lange RA, Cigarroa RG, Hillis LD. Effect of cocaine on coronary arterial dimensions in atherosclerotic coronary artery disease: Enhanced vasoconstriction at sites of significant stenoses. J Am Coll Cardiol 1990 (in press).

76. Virmani R, Robinowitz M, Smialek JE, Smyth DF. Cardiovascular effects of cocaine: An autopsy study of 40 patients. Am Heart J 1988; 115:1068-1076.

77. Togna G, Tempesta E, Togna AR, et al. Platelet reactivity and biosynthesis of thromboxane and prostacyclin in response to in vitro cocaine treatment. Haemostasis 1985; 15:100-107.

78. Trouve R, Nahas G. Nitrendipine: An antidote to cardiac and lethal toxicity of cocaine. Proc Soc Exper Biol Med 1986; 183:392-397.

79. Billman GE, Hoskins RS. Cocaine-induced ventricular fibrillation: Protection afforded by the calcium antagonist verapamil. FASEB J 1988; 2:2990-2995.

80. Lange RA, Cigarroa RG, Flores ED, et al. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. Ann Int Med 1990; 112:897-903.

81. Young D, Glauber JJ. Electrocardiographic changes resulting from acute cocaine intoxication. Am Heart J 1947; 34:272-279.

82. Chokshi SK, Rongione AJ, Miller G, Isner JM. Cocaine and cardiovascular disease. The Leading Edge: Cardiology 1989; 3:1-10.

83. Costard-Jackle A, Jackle SE, Kates RE, Fowler MB. Electrophysiological and biochemical effect of chronic cocaine administration. Circulation 1989; 80:II-15 (abstract).

84. Kanter RJ, Devane CL, Epstein MI. Electrophysiologic effects of high dose intravenous cocaine in dogs. J Am Coll Cardiol 1988; 11:60A (abstract).

85. Kabas DS, Blanchard SM, Matsuyama Y, et al. Cocaine mediated impairment of cardiac conduction in the conscious dog. J Am Coll Cardiol 1989; 13:79A (abstract).

86. Tracy C, Bachenheimer L, Solomon A, et al. Evidence that cocaine slows cardiac conduction by an action on both AV nodal and His-purkinje tissue in the dog. J Am Coll Cardiol 1989; 13:79A (abstract).

87. Inoue H, Zipes D. Cocaine-induced supersensitivity and arrhythmogenesis. J Am Coll Cardiol 1988; 11:867-874.

88. Koentop DE, Liao JC, Van Bergen FH. Effects of pharmacologic alterations of adrenergic mechanisms by cocaine, tropolone, aminophylline, and ketamine on epinephrine-induced arrhythmias during halothane-nitrous oxide anesthesia. Anesthesia 1977; 46:83-93.

89. Frishman WH, Karpenos A, Molloy TJ. Cocaine-induced coronary artery disease: Recognititon and treatment. Med Clin No Amer 1989; 73:475-486.

90. Rezkalla S, Reddy R, Bhasin S, et al. Electrocardiographic abnormalities in cocaine users: A prospective study. J Am Coll Cardiol 1990; 15:190A (abstract).

91. Karch SB. Serum catecholamine levels in cocaine-intoxicated patients with cardiac symptoms. Ann Emerg Med 1987; 15:481 (abstract).

92. Orr D, Jones I. Anesthesia for laryngoscopy: A comparison of the cardiovascular effects of cocaine and lignocaine. Anaesthesia 1968; 23:194-202.

93. Witt AL, Rosen MR. Afterdepolarization and triggered activity. Fozzard HA, Haber E, Jennings RB, Katz AM, eds. The Heart and Cardiovascular System. New York: Raven; 1986:1449-1490.

94. Tazelaar HD, Karch SB, Stephens BG, Billingham ME. Cocaine and the heart. Hum Pathol 1987; 18:195-199.

95. Karch SB, Billlingham ME. The pathology and etiology of cocaine-induced heart disease. Arch Pathol Lab Med 1988: 112:225-230.

96. Gay GR. Clinical management of acute and chronic cocaine poisoning. Ann Emer Med 1982; 11:562-572.

97. Anderton JM, Nassar WY. Topical cocaine and general anaesthesia: An investigation of the efficacy and side effects of cocaine on the nasal mucosa. Anaesthesia 1975; 30:908-917.

98. Rappolt RT, Gay GR, Inaba DS. Propranolol: A specific antagonist to cocaine. Clin Toxicol 1977; 10:265-271.

99. Rappolt RT, Gay GR, Soman M, Kobernick M. Treatment plan for acute and chronic adrenergic poisoning crisis utilizing sympatholytic effects of the B1-B2 receptor site blocker propranolol (inderal) in concert with diazepam and urine acidification. Clin Toxicol 1979; 14:55-69.

100. Gay GR, Loper KA. The use of labetalol in the management of cocaine crisis. Ann Emer Med 1988; 17:282-283.

101. Ramoska E, Sacchetti AD. Propranolol-induced hypertension in treatment of cocaine intoxication. Ann Emerg Med 1985; 14:1112-1113.

102 Hague N, Perreault C, Morgan JP. Effects of cocaine on intracellular Ca++ handling in mammalian myocardium. Circulation 1988; 78:II-359 (abstract).

103. Morcos NC, Fairhurst AS, Henry WL. Direct but reversible effects of cocaine on the myocardium. J Am Coll Cardiol 1988; 11:71A (abstract).

104. Bedotto JB, Lee RW, Lancaster LD, et al. Cocaine and cardiovascular function in dogs: Effects on heart and peripheral circulation. J Am Coll Cardiol 1988; 11:1337-1342.

105. Hale SL, Alker KJ, Rezkalla S, et al. Adverse effects of cocaine on cardiovascular dynamics, myocardial blood flow, and coronary artery diameter in an experimental model. Am Heart J 1989; 118:927-933.

106. Koerker RL, Moran N. An evaluation of the inability of cocaine to potentiate the responses to cardiac sympathetic nerve stimulation in the dog. J Pharmacol Exp Ther 1971; 178:482-496.

107. Wiener RS, Lockhart JT, Schwartz RG. Dilated cardiomyopathy and cocaine abuse: Report of two cases. Am J Med 1986; 81:699-710.

108. Duell PB. Chronic cocaine abuse and dilated cardiomyopathy. Am J Med 1987; 83:601 (letter).

109. Chokshi SK, Moore R, Pandian, Isner JM. Reversible cardiomyopathy associated with cocaine intoxication. Ann Int Med 1989; 111: 1039-1040.

110. Bertolet BD, Freund G, Martin CA, et al. Unrecognized left ventricular dysfunction in an apparent healthy cocaine abuse population. Clin Cardiol 1990; 13:323-328.

111. Garcia R, Jennings JM. Pheochromocytoma masquerading as a cardiomyopathy. Am J Cardiol 1972; 29:568-571.

112. Gilsanz FJ, Luengo C, Conejero P, et al. Cardiomyopathy and phaeochromocytoma. Anesthesia 1983; 38:888-891.

113. Velasquez G, D'Souza VJ, Hacksaw BT, et al. Phaeochromocytoma and cardiomyopathy. Br J Radiol 1984; 57, 89-92.

114. Enseng JG. Bazooka: Cocaine-base and manganese carbonate. J Anal Toxicol 1985; 9:45-46.

115. Wolf GL, Blum L. Cardiovascular toxicity and tissue proton T_1 response to manganese injectiooon in the dog and rabbit. AJR 1983; 141:193-197.

116. Imperato-McGinley J, Ehlers K, Zullo MA, et al. Reversibility of catecholamine-induced dilated cardiomyopathy in a child with a pheochromocytoma. N Engl J Med 1987; 316:793-797.

117. Lam JB, Shub C, Sheps SG. Reversible dilatation of hypertrophied left ventricle in pheochromocytoma: Serial two-dimensional echocardiographic observations. Am Heart J 1985; 109:613-615.

118. Chambers HF, Morris L, Tauber MG. Cocaine use and the risk for endocarditis in intravenous drug abusers. Ann Int Med 1987; 106:833-836.

119. Edwards J, Rubin RN. Aortic dissection and cocaine abuse. Ann Int Med 1987; 107:779-780.

120. Barth CW, Bray M, Roberts WC. Rupture of the ascending aorta during cocaine intoxication. Am J Cardiol 1986; 57:496.