Prevalence and Patterns of Cocaine Use In Premature Coronary Atherosclerosis

By

Teri Beasley

A Master's Research Project

Presented to

Oregon Health Sciences University

School of Nursing

in partial fulfillment of

the requirements for the degree of

Master of Science

April 21, 1998

APPROVED:

[redacted]

Linda Felver, Ph.D., R.N., Research Advisor

[redacted]

Marie Napolitano, Ph.D., R.N., F.N.P., Committee Member

[redacted]

Linda Meyer, M.S.N., R.N., C.C.R.N., Committee Member

[redacted]

Beverly Hoeffer, R.N., DNSc, F.A.A.N., Associate Dean for Academic Affairs

Acknowledgments

First and foremost I would like to thank my research advisor, Linda Felver for her enthusiasm, encouragement and support of this research project. This project would have been impossible had it not been for her immense wisdom as an advisor, researcher, and colleague. I would also like to thank Marie Napolitano for her perspective, encouragement, and unyielding support of this research project. Thanks also to Linda Meyer for her insight and wisdom with regards to the cardiology specialty. I would also like to thank the following people for their contributions to the success of this project: Johnathan Fields for the many hours of help he gave me with the statistical tests, the SPSS software package, and in the interpretation of the tests, indeed I might still be sifting through data without his help; Linda Cioffi, Gary Gelardo, Carol Ford, Chris Tanner, Pat Archbold, Barbara Stewart, Roberta Erikson, George Pantely, Vincent Reyes, and John Rudoff.

Lastly, I would like to thank all those who never told me "you can't do it" and those who understood that this project was more to me than an exercise in academics.

This project was funded in part by a research award from Sigma Theta Tau, Beta Psi chapter.

Abstract

Background. The use of cocaine has been shown to be a significant risk factor for the development of atherosclerotic coronary artery disease (CAD). Cocaine users have been found to an increased incidence of CAD at an unusually young age (<45; premature CAD). Despite this relationship, the prevalence and prior patterns of lifetime cocaine use and other CAD risk factors in persons with premature CAD have not been identified in previous studies.

Purpose. To describe the prevalence and patterns of past cocaine use among those diagnosed with CAD between 18 to 44 years of age and to test the significance of difference in CAD risk factors between those who self-report the past use of cocaine and those who do not. A secondary purpose was to explore the relationship between the patterns of past cocaine use, and CAD risk factors and the degree and extent of coronary artery stenosis.

Methods. The final sample was 113 (48% response rate) subjects (mean age 39.8 $\pm$ 3.6 years) who had been diagnosed with CAD via hospital ICD-9 codes, had undergone a coronary angiogram, and who were under the care of a participating cardiologist in the Portland, Oregon area. Data were collected via a mailed questionnaire and a review of the medical records.

Results. The prevalence of self-reported past cocaine use was significant ($p<0.001$) at 35% ($n=39$) (95% C.I., 26-44%). Most cocaine users were white (85%) males (95%; $p<0.001$), who began using cocaine at an average age of 20 ($\pm$5), and continued to use approximately 1 gram ($\pm$ 0.59) of cocaine mostly via nasal insufflation (89%) on a weekly

(41%) to monthly (38%) basis for an average of 8 (± 4.9) years. Gender was significant within the entire sample ($p<0.001$) and within the two groups ($p<0.001$), in that there were significantly fewer women included (n=32) in the sample and significantly fewer (n=2) who reported the past use of cocaine. Cocaine users were significantly younger (39.8 ± 3.6, $p<0.001$) and had a significantly lower prevalence of hypercholesterolemia ($p<0.001$), hypertension ($p=0.001$), diabetes ($p=0.03$), and positive family history of CAD ($p<0.02$) when compared to the cocaine non-users. The cocaine users also had significantly fewer cumulative CAD risk factors than did the cocaine non-users ($p<0.001$). The groups did not vary with regards to cigarette smoking, obesity, or sedentary lifestyle. Hypercholesterolemia ($p<0.001$) was found to be significantly associated with degree of stenosis in the right coronary artery among the cocaine users. Hypertension ($p=0.02$) and positive family history ($p=0.03$) were found to be significantly associated with degree of stenosis in the left anterior descending coronary artery among the cocaine non-users.

Conclusions. This is the first study to address the prevalence and patterns of past cocaine use among those diagnosed with CAD and to compare the CAD risk factors between persons with a history of cocaine use and those without a history of cocaine use. This study demonstrated a significant prevalence of past cocaine use among those diagnosed with premature CAD. The cocaine users had significantly fewer CAD risk factors than did the cocaine non-users. These findings suggest that past use of cocaine may be a significant risk factor for the premature development of CAD. The modification of other risk factors might reduce the risk of premature CAD among those with a significant history of cocaine

use. Primary care providers should question their patients about the past use of cocaine, particularly those patients who may have at least one modifiable CAD risk factor.

[redacted]

Approved: Linda Felver, Ph.D., RN, Research Advisor

TABLE OF CONTENTS

LIST OF TABLES

TABLE PAGE

LIST OF FIGURES

FIGURE PAGE

LIST OF APPENDICES

APPENDIX PAGE

Prevalence and Patterns of Cocaine Use in Premature Coronary Atherosclerosis

Chapter I

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in the United States (McGinnis & Foege, 1993). Cocaine is a dangerous illicit drug that has been found to be a factor in the development of a wide-variety of chronic and acute cardiovascular conditions such as cardiomyopathy, left ventricular hypertrophy, myocarditis, endocarditis, premature atherosclerosis, coronary artery spasm, lethal arrhythmias, myocardial ischemia, and myocardial infarction (Om, Warner, Sabri, Cecich, & Vetrovec, 1992). The primary purpose of this research study is to examine the relationship between self-reported cocaine use and the development of premature coronary atherosclerosis. This research study will sample a group of persons between the ages of 18 to 44 years old, and will examine the following variables: past use of cocaine, past patterns of cocaine use, and established coronary artery disease risk factors.

In the U.S., cocaine use sharply increased from 1976 through 1985, reaching a peak of 7.1 million users in 1985, and thereby surpassing all other drugs of abuse. Currently approximately 1.4 to 3.6 million persons report using cocaine on a regular basis (National Household Survey on Drug Abuse, 1996).

Cocaine-associated myocardial infarction (MI) was first reported in the literature in 1982 (Coleman, 1991). Kossowsky & Lyon (1984) first reported significant coronary artery stenosis (>75%) in 4 patients who presented for treatment of acute myocardial infarction as a result of cocaine use. In this young group of patients (age 36 SD ± 6.7) the only previously known cardiovascular risk factor was cigarette smoking. To date,

approximately 1,083 cases of cocaine-associated cardiovascular events (primarily chest pain) have been reported in the research literature. Of these 1,083 cases of cocaine-associated cardiovascular incidents, approximately 37 percent were examined for the presence of coronary artery stenosis through either angiography or autopsy. Of the 37 percent of individuals examined, approximately 64 percent were found to have significant coronary artery stenosis of more than 50 percent, and 39 percent were found to have coronary artery stenosis of >70 percent. The majority of these individuals were in their late 20's to mid 30's, and their primary coronary artery disease risk factor was cigarette smoking. These findings are significant when compared to the prevalence of severe coronary artery stenosis (>75%) among those individuals without a history of cocaine use. For example, Roberts (1989) studied at autopsy the coronary arteries of a much older group of 40 leukemia patients (mean age 52, SD not reported) and found that only 25 percent exhibited a cross-sectional area narrowing of >51 percent--and only 3 percent demonstrated severe (>75% cross-sectional area luminal narrowing) coronary artery stenosis. Similarly, in a personal communication from Cornhill, Kolodgie (1991) reported post-mortem coronary analysis findings from a group of a 162 youths who died as a result of trauma (age range 21 to 34 years) in which no severe (>75% cross-sectional area luminal narrowing) coronary artery stenosis was identified. However, Kolodgie did not report if any of these 162 youths exhibited cross-sectional area luminal narrowing of less than 75 percent.

Higher rates of coronary artery stenosis have been reported through cross-sectional analysis of coronary arteries during post-mortem exams of cocaine users, in comparison to the examination of coronary arteries through the use of angiography

(Karch, Green, & Young, 1995; Mittleman & Wetli, 1987; Virmani, Robinowitz, Smialek, & Smyth, 1988). One likely explanation for this finding is that angiography is an indirect, subjective measure of coronary artery stenosis that frequently underestimates the degree of luminal narrowing (Dietz, Tobis, & Isner, 1992); however despite this limitation, angiography remains the gold standard for the identification of the degree and extent (number of coronary arteries) of coronary artery stenosis and for the definitive diagnosis of coronary artery disease (CAD) in live persons (Bashore, 1990; Yang, Bentivoglio, Maranhao, & Goldberg, 1988).

Most researchers have focused on the acute cardiovascular effects of cocaine use, such as cocaine-induced myocardial infarction, cocaine-induced arrhythmias, or sudden death. Little research has focused on the long-term cardiovascular effects of chronic cocaine use. No research has been found which focuses on those persons who have not used cocaine for a number of years, but have a positive history of cocaine use and who have subsequently developed premature coronary atherosclerosis at an (abnormally) early age, when compared to the general population.

A paucity of research related to the patterns of cocaine use among those who have developed cocaine-associated cardiovascular problems exists--particularly research focused upon the duration, frequency, and amount of cocaine used among those who have developed premature CAD. Of the 1083 cocaine-associated cardiovascular events reported in the literature, the average quantifiable duration or frequency (measured in days or years) of cocaine use was reported in only 292 (26%) of the cases--and a quantifiable amount (measured in grams or rocks) of cocaine use was reported in only 107 (9%) of the cases. Regardless, among those who did report anything at all pertaining to the frequency,

duration, or amount of cocaine use, many important details of such were found to be lacking by this researcher (see Appendices A, B, and C).

The further evaluation of cocaine as a possible risk factor for the development of CAD among young persons who may lack traditional risk factors, such as hypertension or diabetes, is essential. This researcher became interested in this topic because of personal clinical experience in caring for a disproportionately high number of persons with CAD who lacked any significant CAD risk factors. However, when questioned, these persons consistently self-reported the past use of cocaine. If primary care providers, including nurse practitioners are to diagnose accurately and treat those at the greatest risk for the premature development of CAD, they must first come to understand the past patterns of cocaine use among those who have already developed CAD at a young age (before age 44). Then they will be able to identify those who may be at an increased risk for the premature development of CAD.

In general, substance abuse is perhaps the most ignored or underdiagnosed disease in the United States. Primary care providers, including nurse practitioners, recognize only 10 percent of those who are actively abusing substances (Caulker-Burnett, 1994; Kamerow, Pincus, & Macdonald, 1986). Research regarding the assessment of <u>past</u> drug use among the ambulatory care population is lacking; however, if the rate of current drug use recognition by primary care providers is only 10 percent, it seems highly likely that primary care providers recognize even fewer <u>prior</u> substance users. Perhaps many primary care providers feel they are adept at recognizing those persons who are under the acute effects of sympathomimetic drugs such as cocaine, but fail to assess for past use in part

because they do not understand the grave physiological consequences of past drug use upon future health.

The primary purpose of this study is to determine the prevalence of self-reported cocaine use among a group of individuals 18 to 44 years of age who have been diagnosed with coronary atherosclerosis by angiogram. In addition, this study will also describe the self-reported past patterns of cocaine use and other established CAD risk factors within this group. Thus far, with regards to the use of cocaine, nursing research has focused upon the acute cardiovascular effects of cocaine. Nursing has failed to describe, report, or even formally recognize that chronic cocaine use may be a possible risk factor for the development CAD. As the number of nurse practitioners providing primary health care in the United States increases, and as they become increasingly responsibile for the primary health care management for a wide variety of people, it is imperative that they seek answers to these questions which impact the future cardiovascular health of those who may have a past history of cocaine use.

Chapter II

Review of The Literature and Conceptual Framework

The review of the literature will focus on the following areas relevant to this study: Demographics of cocaine use; patterns of use; pharmacokinetics; acute and chronic effects of cocaine on the cardiovascular system; research regarding the development of premature coronary atherosclerosis among cocaine users; poly-substance use; established CAD risk factors; diagnosis of CAD; and self-report of cocaine use.

Demographics of Cocaine Use

Cocaine use in the United States peaked in the mid 1980's and has decreased over the past decade from 7.1 million users in 1985 to 1.4 to 3.6 million users in 1995 (National Household Survey on Drug Abuse, 1996). The high incidence of cocaine use in the mid-1980's is a potential public health concern in the 1990's because cocaine has been associated with the premature development of coronary atherosclerosis. Young people who used cocaine regularly in the 1980's may now, a decade later in their 30's or 40's, be at a higher risk for the development of cardiovascular problems associated with past cocaine use--10 to 20 years sooner than would normally be expected whether they continue to use cocaine or not.

While there was a reported decrease in cocaine-related medical incidents in the early 1990's, recent statistics (1995) from the Substance Abuse and Mental Health Services Administration (SAMHSA) indicate that emergency medical treatment for cocaine related problems increased 15 percent in 1994 compared to the prior year. Among individuals between 35 to 44 years of age, cocaine-related emergency department visits have more than doubled since 1988. Overall, according to information from SAMHSA

(1995), cocaine has remained the primary substance implicated in drug-related emergency department incidents since the 1980's.

Pharmacokinetics of Cocaine

Depending upon the route of administration, peak serum cocaine concentrations occur within 15 to 120 minutes after use (Schindler, Tella, Erzouki, & Goldberg, 1995). Cocaine is most rapidly absorbed into the systemic circulatory system via the intravenous and smoking routes, with peak levels occurring within as few as 15 minutes (Warner, 1993). Slower absorption rates occur via the intranasal and oral routes, with peak blood levels occurring within 30 to 120 minutes (Benowitz, 1993). The half-life of cocaine is 45 to 90 minutes. Therefore, serum cocaine levels are of a limited value in that they are not reflective of toxicity (Warner, 1993). The metabolites of cocaine may be present in the urine for up to 6 days after use. However, the detection of these compounds in the urine is not reflective of acute intoxication (Kolodgie, Farb, & Virmani, 1995).

Cocaine is metabolized via several pathways. The majority of the drug is metabolized by plasma cholinesterases and to a lesser extent through the spontaneous hydrolysis of cocaine and by other hepatic esterases (Kolodgie, Farb, & Virmani, 1995). The liver esterase enzymes are largely responsible for the hydrolysis of cocaine into two major metabolites, benzoyl ecgonine and ecgonine methyl ester (Jatlow, 1988; Stewart, Inaba, Lucassen, & Kalow, 1979). Other metabolites of cocaine, such as norcocaine and other hydroxylated compounds, are also detectable in the urine of cocaine users. Some studies suggest that persons with low plasma cholinesterase activity may be more predisposed to suffer from the cardiotoxic effects of cocaine (Whitkin & Katz, 1993).

Despite a short half-life, the persistent effects of the cocaine metabolites appear to be largely responsible for the cardiotoxic actions of cocaine. Whether or not all of the metabolites are biologically active or inactive is unclear. A recent study suggests that the metabolites of cocaine, whether active or inactive, exert prolonged toxic cardiovascular effects long after the use of cocaine. Schindler et al. (1995) compared the cardiovascular effects of four cocaine metabolites (benzoyl ecgonine, ecgonine methyl ester, cocaethylene and norcocaine) to the effects of cocaine alone. Schindler and associates concluded that the metabolites of cocaine exert prolonged toxic cardiovascular effects that appear to play a significant role in both the acute and chronic cardiovascular effects of cocaine. Schindler et al. also suggested that the subsequent use of cocaine prior to complete elimination of the metabolites may have a cumulative toxic effect upon the cardiovascular system, which may last for as long as 48 hours. Whitkin and Katz (1993) reported that the metabolite benzoylecgonine has been shown in cat cerebral arteries to be a more potent vasoconstrictive compound than cocaine.

Acute Cardiovascular Effects of Cocaine

The cardiovascular effects of cocaine are complex in that there are a variety of mechanisms through which it acutely alters overall cardiac function. Two major acute actions of cocaine include 1) a local anesthetic effect, and 2) a sympathomimetic effect. Cocaine also has been shown to have direct toxic effects upon the cardiovascular system through 1) platelet activation causing thrombus formation, and 2) vasoconstriction which may result in acute myocardial ischemia or infarction.

Local Anesthetic Effect.

The local anesthetic effect of cocaine occurs as a result of its ability to alter the nerve cell by stabilizing the cell membrane and inhibiting the nerve

impulse. Cocaine molecules are absorbed into the lipid matrix of the cell membrane and bind to sodium channel receptors. This inhibits the influx of sodium into the cardiac cells and impairs impulse conduction, creating a pro-arrhythmic environment within the myocardium. The local anesthetic or membrane-stabilizing effect is also thought to be largely responsible for the negative inotropic effects of cocaine (Kloner & Hale, 1993; Das, 1993). Electrocardiograph manifestations of this effect are a prolongation of the PR, QRS, and QT intervals. Depression of the pacemaker cells may lead to severe bradycardia and asystole (Olshaker, 1994).

Sympathomimetic Effects. Cocaine initially causes stimulation of the vagus nerve, resulting in transient bradycardia. This is rapidly followed by increased sympathetic stimulation resulting in increased blood pressure and heart rate as a result of increased alpha-adrenergic and beta-adrenergic stimulation (Kloner, Hale, Alker, & Rezkalla, 1992). Cocaine blocks the action of the catecholamine reuptake pump at the presynaptic membrane, thus causing a concentration and buildup of neurotransmitters (dopamine, epinephrine, norepinephrine, and serotonin) to remain in the synaptic cleft. The neurotransmitters continue to excite the succeeding postsynaptic membrane receptor cells (Om, 1992; Hollander, 1995). Alpha-adrenergic and beta-adrenergic stimulation of the heart increases free calcium within the myocytes, resulting in increased inotropic and chronotropic effects. Cocaine is also thought to stimulate the release of catecholamines from the adrenals (Om, 1992). As a result of increased sympathetic tone and circulating catecholamines, coronary and peripheral vasoconstriction occurs at the same time when myocardial workload and oxygen demand are greatly increased. Prolongation of this sympathomimetic cycle may result in cardiovascular complications including ischemia,

infarction, fatal arrhythmias, and pulmonary edema (Kloner, Hale, Alker, & Rezkalla, 1992; Das, 1993; Zimmerman et al., 1991).

Rate-pressure product has been shown to be an accurate predictor of myocardial oxygen consumption in healthy individuals as well as those with CAD. The rate-pressure product produced by cocaine has been shown to increase significantly more in response to exercise among subjects who are under the acute effects of cocaine, as compared to those who are not (Foltin, Fishman, & Levin, 1995). This is most likely due to the effects of cocaine on the peripheral vascular system. In persons not under the acute effects of cocaine, the peripheral vascular system would normally react to an increase in oxygen demand by causing peripheral vasodilation. Cocaine appears to impair this reflex mechanism (Foltin, et al., 1995; Das, 1993).

Platelet Aggregation and Thrombus Formation. The exact mechanism responsible for the cocaine-related aggregation of platelets is unknown. Cocaine has been shown to affect platelet aggregation both directly and indirectly. Jones and Tackett (1991) found that cocaine directly enhanced platelet activation in canine arteries. Cocaine in vitro has also been shown to cause increased platelet aggregation and thromboxane production, and decreased prostacyclin production (Kolodgie et al., 1991). Epinephrine, norepinephrine and serotonin have also been suggested to cause platelet aggregation and to increase platelet adhesiveness; aggregating platelets have also been noted to release serotonin, and thromboxane A2, which may contribute to vasoconstriction and vasospasm (Goldfrank & Hoffman, 1993; Minor, Brook, Scott, & Winniford, 1991; Haverneck et al., 1996).

Several studies have shown that cocaine causes an increase in platelet aggregation and thrombus formation (Dressler, Malekzadeh, & Roberts, 1990; Kossowsky, Lyon, &

Chou, 1989; Kolodgie et al., 1991; Smith et al., 1987). Kolodgie et al. (1991), in a description regarding findings from a post-mortem exam of the coronary arteries of cocaine users, noted that the atherosclerotic plaques of cocaine users were "rich in smooth muscle and foam cells, with the media frequently infiltrated by chronic inflammatory cells" (p. 1557), and that none exhibited atherosclerotic plaque hemorrhage, rupture or calcification--despite the fact that 3 of these subjects had prior evidence of MI. In comparison, Kolodgie et al., in the same study, found that the coronary arteries of the cocaine non-users demonstrated hemorrhage into a plaque. This would seem to suggest that the mechanism of platelet activation and subsequent thrombus formation among cocaine users is different from that of cocaine non-users in that the main cause in 95 percent of coronary artery thrombosis in cocaine non-users is "atheromatous plaques undergoing fissure or rupture" (Kolodgie et al., 1991, p. 1557).

Vasoconstriction, Vasospasm, Myocardial Ischemia, and Infarction. The literature discusses 5 mechanisms by which cocaine may cause vasoconstriction and /or vasospasm: 1) a direct calcium-channel and endothelium-dependent effect; 2) a indirect vasoconstrictive effect, mediated by an overall increase in sympathetic tone; 3) a vasoconstrictive or vasospasm effect that is the result of mediators released from platelets, white blood cells, or the endothelium; 4) a dysfunctional endothelial effect leading to vasoconstriction and vasospasm; and 5) a cocaine metabolite mechanism.

The direct calcium-channel and endothelium-dependent vasoconstrictive effect has been suggested as a possible mechanism because cocaine appears to have an independent effect upon the endothelium, causing alpha-adrenergic stimulation and a calcium-dependent vasoconstriction (Isner, & Chokshi, 1989). An experimental study in humans

demonstrated that administration of a calcium channel blocker prior to the administration of cocaine inhibited the cocaine-induced vasoconstriction (Flores, Lange, Cigarroa, & Hillis, 1990). Cocaine may also increase calcium flux across the cell membrane, augmenting vascular smooth muscle tone which, when coupled with alpha-adrenergic stimulation, may result in vasospasm (Nadamanne, 1992).

The indirect vasoconstrictive effect, mediated by an overall increase in sympathetic tone which may lead to myocardial ischemia or infarction, is thought to occur primarily because cocaine activates alpha-adrenoceptor-mediated systems in the heart and blood vessels indirectly through an overall increase in sympathetic tone, and because cocaine stimulates the release of catecholamines from the adrenals (Benowitz, 1992). Phentolamine (an alpha-adrenergic blocker) has been shown to block the vasoconstrictive action of cocaine in some studies (Lange et al., 1990; Romoska & Sacchetti, 1985) but not all. Flores et al. (1990) found that the pre-treatment with alpha-blockers produced no significant inhibition of cocaine-induced vasoconstriction. Non-selective beta-adrenergic blocking agents, such as propranolol, have been found to worsen the systemic and coronary vasoconstriction caused by cocaine by blocking beta-2-mediated vasodilation and thus allowing unopposed alpha-adrenergic action (Lange et al., 1990).

The vasoconstrictive effect that is believed to be the result of platelets, white blood cells, mast cells, or endothelium-derived mediators is suggested as a possible mechanism for three reasons: 1) Aggregating platelets have been shown to release serotonin, which is thought to be a potent vasoconstrictor (Goldfrank & Hoffman, 1993; Minor, Brook, Scott, & Winniford, 1991). 2) White blood cells and mast cells are known to release vasoactive substances such as histamine, prostaglandin D2, and leukotrienes C4 and D4.

Histamine has been shown in human and animal models to induce focal vasospasm in areas of atherosclerotic plaque (Kolodgie et al., 1991). Prostaglandin D2 has been shown to be important in the regulation of smooth muscle tone; leukotrienes C4 and D4 have been found to constrict human and canine arteries from 500% to 800% more than the maximal effects obtainable from the use of norepinephrine alone (Toda, 1982; Burke, Levi, Guo, & Corey, 1982; Isner, & Saurabh, 1989; Kolodgie et al., 1991). 3) In atherosclerotic arteries, there may be an impairment in the release, or synthesis, of endothelium-derived relaxing factor, which has been shown in animal models to induce arterial spasm and vasoconstriction (Kolodgie et al., 1991).

The dysfunctional endothelial mechanism may occur as a result of several factors. Haverneck et al. (1996) postulate that in a damaged, or dysfunctional endothelium the release of nitric oxide is impaired. Nitric oxide is known to inhibit the aggregation of platelets. Cocaine is also thought to interfere with prostaglandin metabolism thereby potentiating vasoconstriction and thrombosis. According to Haverneck et al., a relative deficiency of vasodilating substances such as nitric oxide, and an increase of vasoconstrictive substances such as thromboxane A2, serotonin and endothelin may result in vasoconstriction and vasospasm.

Recurrent coronary vasoconstriction has been shown to occur in response to the cocaine metabolites benzoylecgonine and ethyl methyl ecgonine (Brogan, Lange, Glamann, & Hillis, 1992). Brogan et al. demonstrated, in a controlled study of 18 self-reported cocaine non-users, that the metabolites of cocaine have a profound ability to constrict the coronary arteries. Peak contractions of the coronary arteries occurred 90 minutes after the administration of cocaine--which is temporally related to decreasing

serum concentrations of cocaine and to rising serum elevations of the metabolites studied. The subjects studied by Brogan et al. received only 2mg/kg of intranasal cocaine.

Acute myocardial infarction is the most frequently reported cardiac complication as a result of cocaine use (Nademanee, 1992). Myocardial ischemia and infarction have been reported in patients with and without underlying atherosclerotic disease (Om, 1992). Flores and associates (1990) demonstrated coronary artery vasoconstriction after cocaine administration in individuals with and without underlying coronary artery atherosclerosis. Nademanee (1992) reported that chronic cocaine use is a factor in coronary artery vasospasm and/or myocardial ischemia, suggesting the cardiovascular effects of cocaine may occur in the absence of acute cocaine use, although the exact mechanism is unknown. The fact that the majority of myocardial ischemia has been shown to develop beyond the initial acute use of cocaine (Havranek, Nademanee, Grayburn, & Eichhorn, 1996) suggests that in some way the metabolites of cocaine must play a significant role (Brogan et al., 1992). The concomitant use of other vasoconstrictive drugs--illicit or not--has also been found to increase the risk for cardiovascular complications of cocaine use (Om et al., 1992).

Chronic Cardiovascular Effects of Cocaine

The primary chronic cardiovascular effects of cocaine are cardiomyopathy and atherosclerosis.

Cardiomyopathy. Cardiomyopathy and left ventricular failure have been associated with the chronic use of cocaine (Om, Warner, Sabri, Cecich, & Vetrovec, 1992; Virmani, Robinowitz, Smialek, & Smyth, 1988). The main mechanism for the development of cardiomyopathy is believed to be the result of chronic catecholamine stimulation of

cardiovascular system which may result in myocarditis and the development of contraction band necrosis. Contraction band necrosis is defined by Goldfrank and Hoffman (1993) as, "the hypercontracted sarcomere and myofibrillar disruption commonly occurring in patients in the presence of high catecholamine levels, such as pheochromocytomas, or in the presence of cocaine" (p. 77). As a result of myocyte necrosis, the once healthy tissue is replaced with fibrous tissue, resulting in a self-perpetuating area of inflammation and perhaps the eventual development of dilated cardiomyopathy (Kloner et al., 1992; Goldfrank & Hoffman, 1993).

Premature Coronary Atherosclerosis. The exact mechanism that causes the development of atherosclerosis among cocaine users is not well understood. Haverneck et al.(1996) believes that if the marker of repetitive endothelial damage in cocaine users is the impairment of endothelium-dependent relaxation, then the first step in the atherosclerotic process has been identified. Disruption of the vascular endothelium often occurs as a precursor to coronary atherosclerosis and may be present despite the absence of atherosclerotic evidence via coronary angiogram (Quillen et al., 1993). A dysfunctional endothelium, increased platelet aggregation, impaired nitric oxide release, and altered prostaglandin metabolism, as well as the many complex acute effects of cocaine, all either directly or indirectly appear to contribute to the development of atherosclerosis in chronic cocaine use (Havranek et al., 1996; Jones & Tackett, 1990; Kolodgie et al., 1991).

Kolodgie et al. (1991) found, in a post-mortem comparison of the coronary arteries of cocaine users to the coronary arteries of cocaine non-users, that the numbers of adventitial mast cells were significantly greater in the coronary arteries of the cocaine users than the cocaine non-users. The role of mast cells in the development of

atherosclerosis may involve the release of vasoactive substances, primarily histamine, which alters endothelial permeability and subsequently increase lipoprotein intake and atherogenesis. The exact cause of mast cell recruitment and degranulation is unknown. Kolodgie et al. postulate that the recruitment may be related to a delayed allergic reaction, stimulation of the mast cells by helper T-lymphocytes, or a result of cocaine alone. Kolodgie et al. further suggest that mast cell degranulation in the coronary arteries may occur as a result of an endothelial antigen, which may increase the adhesiveness of the leukocytes, or may be in part related to the complement system, low density lipoproteins, or other types of chemicals or chemical impurities associated with cocaine (Kolodgie et al., 1991).

Research on Premature Atherosclerosis Among Cocaine Users

Through a review of the literature using MEDLINE, the author of this proposal identified forty-three published articles which described 1083 patients who presented to a hospital emergency department in the United States between 1982 through 1996, with cardiovascular events (primarily chest pain) related to cocaine use, who tested positive for cocaine, or who died with the presence of cocaine or cocaine metabolites in their body (see Table 1 and Appendix A).

Evaluation of Coronary Artery Stenosis. Of these 1083 patients, 407 were studied by either coronary angiography or post-mortem cross-sectional analysis of their coronary arteries. Of the 407 patients who had further examination of their coronary arteries, 252 (62%) were found to have mild (≥ 25%) to severe (≥ 70%) coronary artery stenosis. Of the 252 patients with coronary artery stenosis, 162 (64%) were found to have coronary

artery stenosis of 70% or greater, despite the fact that the majority of these patients were in their late twenties to mid-thirties.

CAD Risk Factors in Cocaine Users With Cardiovascular Events. In the literature to date, coronary artery disease risk factors have not been well described among cocaine users who subsequently suffer an adverse cardiovascular event (see Table 2 and Appendix B). Overall, from the published literature reports, only 39 percent of these cocaine users were identified as cigarette smokers, which appears to be the predominant risk factor in this young group of patients. However, it is very likely that the overall incidence of cigarette smoking is much higher among these patients. It is difficult to determine the actual prevalence of tobacco use among this entire group because approximately 50 percent of the researchers failed to address or include data in their published research reports concerning this risk factor.

In previous studies that have examined coronary artery disease risk factors of cocaine non-using young persons who have had an MI, the incidence of cigarette smoking has been found to be particularly high--50 to 80 percent were current

Table 1.

Summary of Evaluation of Coronary Artery Stenosis in Published Literature of Cocaine-Related Cardiovascular Events.

Total Number of Cases	1083	Degree of Coronary Artery Stenosis	
Total Number Evaluated	407 (37%)	25% to 70%	n=90 (22%)
		>70%	n=162 (39%)
Evaluation Methods:			
Angiogram	150		
Autopsy	257		

Note: For more detailed information see Appendix A.

Table 2

Summary of Known CAD Risk Factors Among Cocaine Users With CAD in Published Research Reports.

		Total Sample	Reported Sample
Total Number of Cases Evaluated	n=1083		
Times Risk Factors Not Addressed	n=444	41%	0%
Number of Cases With Reported Risk Factors	n=639	59%	100%
Specific Risk Factors:			
Diabetes	n= 40	3%	6%
Hypertension	n=182	16%	28%
Hypercholesterolemia	n= 51	4%	7%
Positive Family History	n=155	14%	24%

Note: For more detailed information see Appendix B.

smokers;40 to 70 percent were former smokers (Kanitz, Giovannucci, Jones, & Mott, 1996; Zimmerman, Cameron, Fisher, & Ng, 1995). However, cigarette smoking is only one risk factor in the development of coronary artery disease and would not appear to explain fully the development of significant coronary atherosclerosis among young persons who lack other established coronary artery disease risk factors.

Incidence of CAD in Cocaine-Associated Cardiovascular Events in Comparison to the General Population. Overall, the incidence of coronary artery disease in the general population less than 40 years of age is low, generally less than 4 percent (Zimmerman, 1995). Roberts (1989) found during the autopsy of a group of 40 cocaine non-using leukemia subjects (mean age 52, SD not reported) who had no history of CAD, that only 25 percent of those examined exhibited cross-sectional area narrowing of >51%--and of that 51%, only 3% exhibited cross-sectional narrowing of >75%. In a younger group of 162 patients, ages 21 to 34 years, Kolodgie (1991) reported, in a personal communication from Cornhill, that none of these patients exhibited severe (>75% cross-sectional area luminal narrowing) coronary artery stenosis on post-mortem examination. Karch, Green, and Young (1994) in a post-mortem study that compared the amount of coronary artery stenosis in males who tested positive for cocaine at the time of death with a control group that tested negative for cocaine at the time of death, found that both groups showed some evidence of atherosclerotic lesions. However, atherosclerotic lesions were found to be more severe and to involve a greater number of coronary arteries in the cocaine positive group when compared to the control group, and additionally when compared to another historical control group of persons who died during the Vietnam War.

A certain degree of arterial sudanophilia (fatty streaking) has been found to be present among many populations studied, regardless of the occurrence of CAD. CAD risk factors have been found to be predictive of the amount of aortic and coronary artery sudanophilia. Coronary atherosclerosis has been found to occur as soon as ten years after the presence of aortic sudanophilia (Solberg & Strong, 1983; Newman et al., 1986). Kolodgie et al. (1992) compared the degree of post-mortem aortic sudanophilia present in a group 16 subjects (mean age 25 ± 1 years) who tested positive for cocaine or cocaine metabolites at the time of death to that of a group of 10 subjects (mean age 24 ± 2 years) who had no history of cocaine use. Kolodgie et al. found that "although the cardiovascular disease risk factors were the similar in both groups, sudanophilic lesions (fatty streaks) in the lower thoracic and abdominal aorta were significantly increased in habitual cocaine abusers" (p. 57).

Most of the research literature to date has focused on the acute effects of cocaine in the form of isolated case studies, retrospective medical record reviews, and findings obtained through prospective and retrospective postmortem evaluation. The true incidence of cocaine-related medical complications is most likely underreported for a variety of reasons. Many persons under the acute effects of cocaine may be reluctant to seek medical attention, and those who do seek medical attention may not appear to be acutely intoxicated. Furthermore, many persons may never be identified as current or past cocaine users depending upon the treatment provider's level of suspicion, past experience, and personal biases (Chen & Kandel, 1995).

The prevalence of cocaine-associated cardiovascular events among those who use cocaine is unknown. Regardless of cocaine use, not all persons who have experienced an

acute MI have underlying coronary artery atherosclerosis (Alpert, 1994). Based upon the information present in the scientific literature to date, this may or may not be true of cocaine users who experience a cocaine-associated MI or other adverse cardiovascular events (Gitter, Goldsmith, Dunbar, & Sharkey, 1991; Hollander et al., 1994). However, the high incidence of cocaine-associated medical complications in young persons, specifically cardiovascular events, and the implication of cocaine as a factor in the development of premature coronary atherosclerosis supports further evaluation of cocaine as a coronary artery disease risk factor (Dressler, Malekzadeh, & Roberts, 1990; Eichhorn et al., 1992; Kolodgie et al., 1992; Kolodgie, Virmani, Cornhill, Herderick, & Smialek, 1991).

Patterns of Cocaine Use Among Those With Cocaine-Associated Cardiovascular Events. The patterns of cocaine use in general tend to be irregular, consisting of binging with multiple, repeated doses of cocaine, followed by absence of use for several days (Foltin, Fischman, & Levin, 1995). Foltin et al (1995) reported on repeated cocaine dosing using various routes, and concluded that patterns of repeat binging may result in cardiovascular tolerance to the acute effects of cocaine. However, this study was limited in that it controlled for the intervals between repeated cocaine use and may not reflect true patterns of cocaine use in the general population or among those who have developed CAD.

Little is known about this entire (1,083) group of patients regarding the total length of cocaine use, the average amount of cocaine used on a daily basis, other drugs used in combination with cocaine, or even how many may have had a positive history of tobacco use (see Table 3 and Appendix C). In a retrospective study by Zimmerman and

associates (1991) of 48 cocaine users, the mean duration of cocaine use reported for 28 patients was 5 (±) 4.8 years. All of Zimmerman et al.'s subjects tested positive for cocaine; in addition five subjects tested positive for amphetamines; three for opiates, and 16 other subjects had positive urinalysis for other non-specified drugs or alcohol. However, the researchers did not report on the use of tobacco among this group. In this same study, three patients were confirmed to have had an MI, and one 32-year-old patient was found to have <50% stenosis of the right coronary artery, diagnosed via coronary angiogram. The exact details of this patient's patterns of cocaine use, poly-substance use, or other cardiac risk factors were not specifically reported (Zimmerman, Dellinger, & Majid, 1991).

In a prospective study conducted by Hollander and associates (1994), 246 current cocaine users who presented to a hospital emergency department with chest pain were questioned about current patterns of cocaine use including duration, frequency, route, last time used, and amount used in the past 24 hours. Past cocaine use patterns were not studied. Hollander et al. reported the median length of cocaine use among 245 patients to be 5 years (IQ 25-75, 2-7 years), and a median frequency of ten episodes of cocaine use per month (IQ 25-75, 4-30 times per month). Although the question was reportedly asked, the amount of cocaine used per occasion was not reported in the published research report. The majority, 205 of these patients, admitted to smoking cigarettes for a median of 12 pack years (IQ 25-75, 5-20 pack years). In this same study fourteen patients

Table 3

Summary of Research Reports of Patterns of Cocaine Use and Poly-Substance Use Among Cocaine Users With CAD

Total Number of Cases	n=1083
Known Route of Use	n=738 (68%)
IV	n=135 (12%)
Smoked	n=388 (36%)
Nasal	n=181 (17%)
Combination	n=34 (3%)
Route of Use Not Reported	n=345 (32%)
Total Cases Reporting Duration	n=283 (26%)
Total Cases Reporting Amount	n=109 (10%)
Total Cases Reporting Other Drugs	n=112 (10%)
Total Cases Reporting Tobacco Use	n=536 (50%)

Note: For more detailed information see Appendix C.

had a confirmed MI, yet none underwent a cardiac catheterization (Hollander et al., 1994).

Poly-Substance Use and Confounding Substances Associated With Cocaine

Many substances of abuse have been associated with the use of cocaine. The following substances will be discussed: heroin, amphetamines, anabolic steroids, and alcohol. The use of marijuana has frequently been associated with the use of cocaine; however, no evidence exists that it has any adverse cardiovascular effects. In addition to substances of abuse, the possible role of cocaine impurities and oral contraceptives will be discussed.

Heroin. A single case report of heroin-associated MI has been reported in the literature (Sztajzel, Karpuz, & Rutishauser, 1994). Glauser, Downe & Smith (1977), in a retrospective chart review of 25 heroin addicts (mean age 25.4, ±6.3 years) who presented with an acute overdose to a hospital emergency department, found that 17 had non-specific ST-T wave changes. They did not report any other cardiac risk factors, cocaine use, or the occurrence of an acute MI. Sztajzel, Karpuz, and Rutishauser (1994) reported on a 25-year-old female with a 4-year history of intravenous heroin abuse, who denied past cocaine use, but who also smoked cigarettes and marijuana and subsequently experienced an acute MI after the intravenous use of an unreported amount of heroin.

Amphetamines. Amphetamine use has also been associated with MI; however, there have only been 5 such individual cases reported in the literature, and there are no reports of amphetamine-associated atherosclerosis (Appleby, Fisher, & Martin, 1994; Bashour, 1994; Carson, Oldroyd, & Phadke, 1987; Packe, Garton, & Jennings, 1990; Ragland, Ismail, & Arsura, 1993). The mechanism by which amphetamines may cause an acute MI may be similar to that of cocaine, in that amphetamines are sympathomimetic

drugs that may cause a catecholamine-induced cardiovascular event (Bashour, 1994). Packe, Garton, and Jennings reported on a 27-year-old male who had an acute MI after the intravenous use of two 1.5 gm doses of amphetamine, 1/2 hour apart. He also was a cigarette smoker and abused an unknown variety of "other drugs"; he subsequently had a normal coronary angiogram. Appleby, Fisher & Martin (1994) reported a single case of a 31-year-old male, cigarette smoker and body-builder who had an acute MI shortly after the use of anabolic steroids and amphetamines, of which he had a 10-year history of use. It is not known if he also used any other drugs in combination with amphetamines and steroids. Bashour (1994) reported a single case of a 29-year-old woman who had an acute MI after the oral use of amphetamines. She was also a cigarette smoker, and had a positive family history of coronary heart disease; she subsequently had a normal coronary angiogram.

Anabolic Steroids. Those who use anabolic steroids are primarily young (late teens to late twenties) athletes and body-builders wishing to improve their athletic performance. Welder and Melchert (1993) reported that as many as 1 million persons may currently use high doses of anabolic steroids to improve their athletic performance--historically, one-half are high-school children. The cardiovascular effects of anabolic steroids have not been well studied in humans, primarily because of the reluctance of those using them to admit using these drugs. To date, fewer than 20 published case reports supporting the adverse cardiovascular effects of anabolic steroids in humans exist in the literature (Melchert & Welder, 1995; Nieminen, Viitasalo, Heikkila, Karjalainen, Mantysaari, & Heikkila, 1996). Adolescents who report using anabolic steroids have been found to be more likely to use cocaine, marijuana, and smokeless tobacco when compared to those who do not report

use (Durant, Rickert, Ashworth, Newman, & Slavens, 1993). Those who use anabolic steroids in combination with cocaine may be at an increased risk for the adverse cardiovascular effects of both of these drugs (Tseng, Rockhold, Hoskins, & Ho, 1994; Welder, Grammas, & Melchert, 1993).

The anabolic steroids are a class of over 30 sex steroids that exhibit anabolic as well as adrenergic activity. They are composed primarily of natural and synthetic derivatives of testosterone. The use of large doses of anabolic steroids has been associated with many of the same adverse cardiovascular effects as cocaine, such as myocardial hypertrophy and cardiomyopathy, atrial and ventricular arrhythmias, MI, coronary thrombosis, and possibly coronary atherosclerosis. Through hepatic mechanisms, anabolic steroids have been found to affect serum lipids adversely, by decreasing high-density lipoproteins (HDL) and increasing low-density lipoproteins (LDL). However, most researchers have reported little or no increase in the total cholesterol levels of those under the acute effects of anabolic steroids. Currently, there is no direct evidence that anabolic steroids are atherogenic; however, changes in lipoprotein concentrations like those induced by the use of anabolic steroids have long been associated with atherosclerosis (Nieminen et. al., 1996; Mewis, Spyridopoulos, Kuhlkam, & Seipel, 1996; Melchert, & Welder, 1995).

The long-term cardiovascular effects of anabolic steroids have not been well studied. Published case reports have documented the acute effects of anabolic steroids, but none have reported on the long-term cardiovascular effects of the chronic use of these drugs. It seems highly likely that those who have a history of using these drugs are at an increased risk for the development of cardiovascular complications.

Alcohol. In addition to cigarette smoking, alcohol has been cited as one of the most common drugs associated with the use of cocaine (Kolodgie, Farb, & Virmani, 1995; Mittleman & Wetli, 1987); other drugs commonly associated with cocaine use include marijuana and heroin (Foltin, Fischman, Nestadt, & Stromberge, 1990). Brody and associates (1990) cited alcohol as the most commonly used drug in combination with cocaine in their population studied. Cocaine used in concomitantly with alcohol produces the metabolite of cocaethylene. Cocaethylene blocks the fast sodium channels, which further alters cardiac conduction, and greatly increases the likelihood of cardiac arrhythmias, particularly, ventricular tachycardia and ventricular fibrillation; thereby placing cocaine users at a greater risk of sudden cardiac death (Kolodgie et al., 1995). Cocaethylene also exerts a chronotropic effect on heart rate and increases cardiovascular reactivity in response to stimuli (Foltin et al., 1995).

Cocaine Impurities. Impurities in cocaine have also been suggested to play a role in its cardiovascular effects. However, while additives such as local anesthetics, stimulants, sugars, toxins, and inert compounds (Schrank, 1993; Hannan & Alder, 1990) may be commonly found in cocaine and have some influence on the action of cocaine, the overall purity of cocaine is considered to be high, especially in comparison to other illicit drugs, and therefore the impact of possible adulterants is generally considered negligible (Schrank, 1993).

Oral Contraceptives. The use of oral contraceptives has been found to have an additive effect in increasing a woman's cardiac risk (Pandey, & Vlajinac, 1989; Burkman, 1996; Iversen, Tverdal, & Stensvold, 1996). Women who use oral contraceptives and smoke cigarettes seem to be at the greatest risk of having a MI. Studies have shown that a

woman's risk greatly decreases almost immediately after cigarette smoking is stopped, suggesting that the cardiovascular effects are more thrombolic as opposed to atherosclerotic. In general, studies have found that women who have at least one CAD risk factor and who also use oral contraceptives may have a four times greater likelihood of sustaining a MI, although women who are now in their late-fifties have not been found to be at an increased risk for CAD as a result of prior oral contraceptive use (Pandey, & Vlajinac, 1989; Burkman, 1996; Iversen, Tverdal, & Stensvold, 1996).

The primary reason for this increased risk appears to be related to the effects of progesterone, specifically the 19-nortestosterone derivatives, (which are also known to be active metabolites of some anabolic steroids) and their effects on the serum lipids. Since the 1960s, the amount of estrogen and progesterone contained in oral contraceptives has greatly decreased; however, it is only recently that a generation of non-19-nortestosterone progestins (desogestrel, gestodene, and norgestimate) have been in use. These newer progestins have been shown to have neutral or favorable effects on serum lipids (Burkman, 1996). In a similar manner to that of the anabolic steroids, the use of oral contraceptives may theoretically place women at an increased risk if changes in the lipoprotein concentrations are adverse enough to induce atherosclerosis.

Established CAD Risk Factors

The development of coronary artery disease is a complex, multifactorial problem, and while many persons may have CAD risk factors, not all will develop CAD--regardless of the severity, or the number of risk factors. According to epidemiological research from the Framingham study (Kannel & Larson, 1993), five major categories of risk factors promote the development of coronary artery disease. Each is considered to be an

independent risk factor: 1) lifestyle, inactivity, and cigarette smoking; 2) personal biological factors which promote atherogenesis, including hypertension, hyperglycemia, obesity, and dyslipidemia; 3) signs of coronary artery degeneration, including elevated fibrinogen and leukocyte levels; 4) impaired circulation, including any ECG abnormalities, and echocardiographic abnormalities; and 5) host susceptibility, including gender, inherent genetic factors, and positive family history of CAD before the age of 50 (Kanitz, et.al., 1995) to 55 (Kannel & Larsen, 1993). Each of these risk factors has been found to contribute independently to the development of coronary artery disease in large epidemiological studies (Castelli et al., 1986; Kannel & Larson, 1993; Kannel, McGee, & Gordon, 1976; Kannel, Wolf, Castelli, & D'Agostino, 1987).

Cigarette Smoking. Cigarette smoking seems to be the most prevalent risk factor for the development of CAD in the young population, compared to CAD risk factors associated with the general population over age 40 (Kanitz et al., 1996; Uhl & Farrell, 1983). Kanitz et al (1995) studied the incidence of risk factors among a population of individuals with a median age of 34.8 years (range 17-39 years of age). Cigarette smoking was identified as the most common risk factor for development of an acute MI in this age group. Sympathomimetic drug use was briefly evaluated, and 7 percent of the patients studied had documented drug use, specifically of cocaine in 6.2 percent of these individuals. However, Kanitz noted that underreporting of sympathomimetic drug use most likely occurred in this study based on known prevalence of the drug use and the lack of testing for drug presence.

The role of cigarette smoking in the development of atherosclerosis and subsequent cardiovascular effects is well documented in the literature (Folts & Bonebrake,

1982; Quillen, Rossen, Oskarsson, Minor, Lopez & Winniford, 1993). Mechanisms by which cigarette smoking affects the coronary vasculature include 1) stimulation of the adrenal medulla and activation of the sympathetic nervous system (SNS), hence causing vasoconstriction in a similar manner to that of cocaine; 2) platelet aggregation and activation as a direct result of nicotine or as an indirect result by stimulating the release of epinephrine from the adrenal medulla; and 3) endothelial damage as a result of chronic SNS stimulation and circulating catecholamines, and as a result of increased vasopressin, and the impaired release of vasodilating substances from vascular endothelium (Benowitz, 1993; Folts & Bonebrake, 1982; Quillen et al., 1993)

Moliterno et al. (1994) reported on the deleterious vasoconstrictive effects of cocaine and nicotine in subjects who used intranasal cocaine and simultaneously smoked cigarettes. Myocardial oxygen demand increased to a much greater extent when these two substances were used together than when either was used alone. In this same study, Moliterno et al. also examined the vasoconstrictive effects of cocaine and cigarette smoking separately and in combination. In each instance, cigarette smoking and cocaine use were found to cause a greater degree of vasoconstriction in diseased coronary artery segments, when compared to non-diseased segments, and that the combination of both of these substances increased the vasoconstrictive effect to a much greater extent than either substance alone.

Diagnosis of Coronary Atherosclerosis

The purpose of coronary angiography is to define the presence or absence of significant narrowings in the coronary arteries. Coronary angiography is considered the gold standard for diagnosis of CAD, despite limitations in its ability to define accurately

the extent of atherosclerotic vessel lesions (Bashore, 1990). Coronary angiography may underestimate or overestimate the degree of vessel obstruction or narrowing. Yang and associates noted that the interpretation of degree of luminal narrowing is subjective and often has considerable interobserver and intraobserver variability--sometimes varying by as much as 20 to 50 percent among 2 or more reviewers (Reiber & Serruys, 1991; Yang et al., 1988). The largest interobserver and intraobserver variations have been noted during review of the right coronary artery. Observer variability has also been found to be the greatest in instances when the degree of stenosis is between 20 to 80 percent (Reiber & Serruys, 1991). Reviewers most often tend to underestimate the severity of lesions because angiography compares a narrowed segment of the coronary vasculature to an adjacent, less narrowed segment based on the assumption that the narrowing is focal and relative to the remainder of a normal (nondiseased) vessel (Roberts, 1989). Therefore, determination of the lumen diameter is dependent on the extent of atherosclerosis, the length of plaque within the vessel, the angle of the vessel, and the skill of the angiographer (Bashour, 1994). The minimal degree of coronary artery stenosis that has been demonstrated in experimental studies to affect coronary flow reserve and coronary vasodilator response is 30 to 45 percent (Reiber & Serruys, 1991).

Several studies (Dietz et al., 1992; Roberts, 1989; Arnett et al., 1979) have reported from autopsy that atherosclerosis is not a focal process, but rather diffuse and extensive. Angiography measures the specific lumen diameter, rather than the cross-sectional area. Research has shown that diameter narrowing is less when compared to cross-sectional narrowing on autopsy. Roberts (1989) reported that a 50 percent luminal diameter narrowing is equivalent to a 75 percent cross-sectional narrowing.

Glagov et al. (1987) reported the occurrence of arterial dilation in response to coronary atherosclerosis as a mechanism for adapting to increasing plaque deposits in the artery lumen. Therefore, the differences in cross-sectional findings on autopsy may be significant in terms of the extent of atherosclerosis, while cross-sectional lumen narrowing may not reflect similar disease. The extent to which luminal narrowing is significant is dependent on the amount of arterial dilation and the extent of plaque development (Glagov, Weisenberg, Zarins, Stankunavicius, & Kolettis, 1987).

Historically, the exact definitions regarding the degree of atherosclerosis, as measured by the degree of coronary artery diameter narrowing via coronary angiogram, have not been well defined. Fallovollita (1996) defined early coronary atherosclerosis as the presence of less than 50 percent lumen narrowing on angiogram. Tomatis and associates (1972) defined moderately severe coronary artery disease as 50 to 75 percent luminal narrowing and severe CAD as 75 to 100 percent luminal narrowing (Kazmers, 1994). In general, researchers have reported that angiographic findings of luminal diameter narrowing of 50 to 70 percent are indicative of severe atherosclerotic disease. In general, coronary artery narrowing is considered to be non-critical, with regards to coronary flow reserve and coronary vasodilator response, until a 50 to 70 percent narrowing occurs (Bashour, 1994).

The severity of coronary angiographic narrowing in myocardial ischemia or infarction made be misleading in that ischemic occurrences have been shown to occur at sites of minor atherosclerotic plaque (Nakagomi, Celermajer, Lumley, & Freedman, 1996). Nakagomi reported that the number of major epicardial arteries with significant narrowing is a significant factor in the morbidity and mortality associated with ischemic

cardiac events. The progression of plaque is often a silent factor in myocardial ischemia. Roberts (1990) suggests that in individuals with symptomatic myocardial ischemia, coronary angiography will usually reveal significant narrowing in one or more of the major epicardial vessels. Lastly, the finding of significant luminal narrowing in one vessel is usually indicative of atherosclerotic narrowing to a lesser extent in the remaining vessels (Roberts, 1990).

Self-Report of Cocaine Use

There is no gold standard against which to measure the validity of self-reported drug use; however, self-report remains the primary source of estimating the prevalence of drug use (Hser, 1993), for predicting future drug use trends (National Household Survey on Drug Abuse, 1996), or for describing the current or past patterns of individual drug use (Sobell, Sobell, & Nirenberg, 1988; Sobell, Toneatto, & Sobell, 1994). Most research findings suggest that the information provided through self-report is truthful and accurate and that most people are more willing to admit to past drug use than to current drug use; therefore, if there is a self-report bias it tends to be in the direction of under-reporting among those who are currently using illicit substances (Harrison, Haaga, & Richards, 1993). Many factors, such as questionnaire construction (Sobell, Kwan, & Sobell, 1995), normal distortions of memory recall (Hammersley, 1994), and social desirability (Gibson & Young, 1994) may affect the validity of self-reported drug use.

Hammersley (1994) reports that many drugs such as alcohol, cannabis, and hallucinogens may impair memory function when the individual is under the acute effects of the drug and therefore recall of events during the period of acute intoxication may be distorted or impaired. The acute effects of cocaine cause an impairment of cognition and

performance, but do not appear to affect memory recall of events during the period of acute intoxication. Therefore, Hammersley suggests that the recall of the quantity of cocaine use per episode would not be distorted as a direct result of the acute effects of cocaine.

In general, the self-report of past drug use has been found to be very reliable when the person being questioned is 1) assured of confidentiality, 2) no longer abusing drugs, and 3) being interviewed for research or clinical purposes (Sobell et al., 1995; Sobell et al., 1988; Sobell et al., 1994). Shillington et al. (1995), in a 10 year follow-up evaluation study which investigated the stability of self-reported drug use, found that current and prior cocaine users self-reported information about patterns of use significantly more consistently than did users of amphetamines, cannabis, sedatives, or opiates. Shillington and associates also found that those who had used cocaine on a regular basis were more likely to provide consistent answers about patterns of use than were sporadic users.

Only a few instruments are available to assess past drug use history. Those that are available require the use of an interview format and are primarily focused on recent (within the past year) usage history, as opposed to lifetime drug use history (Sheila LaCroix, Addiction Research Foundation, personal communication, May 6, 1997). According to Sobell et al. (1994), the interview format that most researchers typically follow includes asking the subject the following questions for each category of drugs they report ever having used 1) age first used; 2) total years used; 3) year last used; 4) frequency of use (using coded categories, such as daily, once a month, 2 to 3 times a day); and 4) route of administration.

Conceptual Framework

A variety of mechanisms are known to cause coronary atherosclerosis, and each factor may result in the premature morbidity and/or mortality of an individual. A number of well-established risk CAD risk factors are widely recognized to be contributory to the development of CAD. These factors include dyslipidemia, hypertension, diabetes, cigarette smoking, family history, males over age 50, post-menopausal women, the concomitant use of oral contraceptives and cigarette smoking in women, obesity, and physical activity. In addition to the established CAD risk factors, possible CAD risk factors may exist that have yet to be identified as such.

Cocaine use has been associated with the development of coronary atherosclerosis and is supported as a likely risk factor by a wide-variety of researchers and research studies. Self-report is the primary method of obtaining information about current and past patterns of cocaine use regardless of the purpose of obtaining information. The main purpose of determining self-reported cocaine use in this study is to identify persons who are at increased risk for the development of premature CAD. Identification of this high-risk population will aid the primary care provider in assisting these individuals in the modification of these behaviors if they currently exist and in modifying other established CAD risk factors to reduce the incidence of premature morbidity and mortality (see Figure 1).

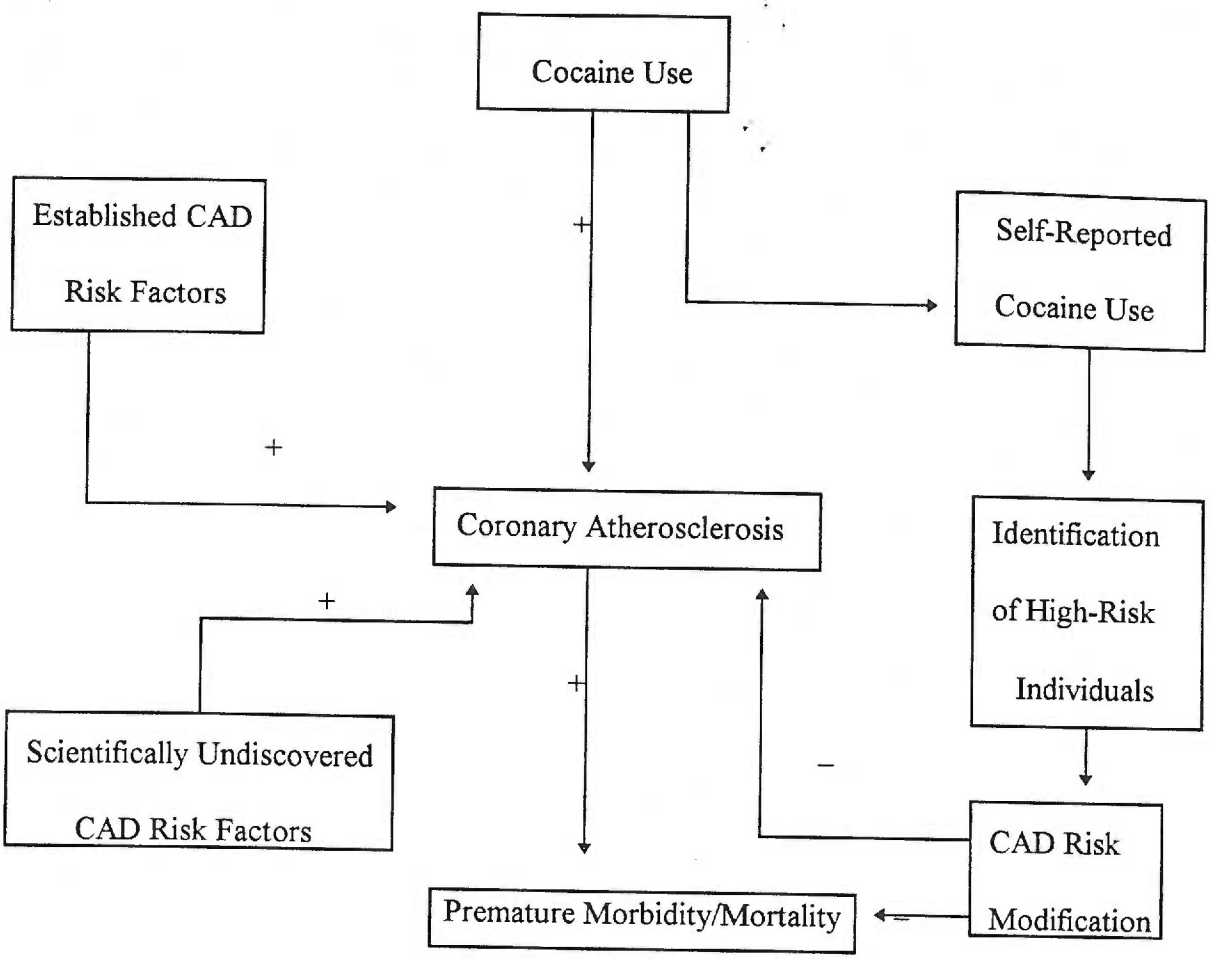

Figure 1. Conceptual Framework.

Research Questions

The primary purpose of this study is to answer the following questions:

1. What is the percent of self-reported past cocaine use among persons 18 to 44 years old who have been diagnosed with coronary artery disease?
2. What are the self-reported patterns of past cocaine use and CAD risk factors (diabetes, hypertension, hypercholesterolemia, cigarette smoking, positive family history, obesity, prior MI, oral contraceptive use among women, and sedentary lifestyle) within this group?

Secondary questions to be explored include the following:

S1. Are the CAD risk factors (see above) different between the group that self-reports cocaine use and the group that self-reports no cocaine use (see Figure 2)?

S2. Is there a relationship between the degree (percent narrowing) and extent (number of major coronary arteries involved) of coronary artery stenosis and the patterns of past cocaine use (duration, frequency, and amount)?

S3 Is there an association between the degree (see above) and extent (see above) of coronary artery stenosis and established CAD risk factors (see above)?

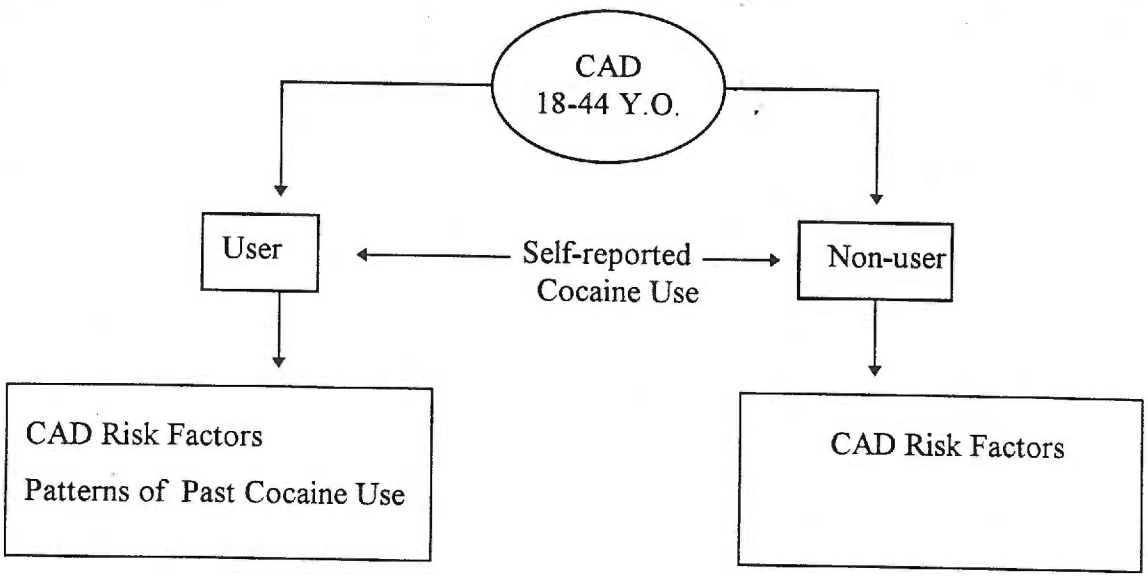

Figure 2. Comparison of CAD risk factors between self-reported cocaine users and self-reported non-users (Research Question S1).

Chapter III

Methods

Overview of Study Design

In order to answer the research questions, 246 persons 18 to 44 years of age who were diagnosed with coronary atherosclerosis and who had a coronary angiogram were contacted via mail for inclusion in the study. The investigator gained the assistance of cardiologists at the selected hospitals in order to identify and contact the potential subjects (see Figure 3). The study included a mailed questionnaire survey (see Appendix D) and a review of the medical records using a data collection instrument (see Appendix E). The mailed survey followed procedures recommended by Dillman (1978). Subjects were contacted through the mail by their treating cardiologist (see Appendix F) and the Principal Investigator (P.I.) (see Appendix G). Those subjects who agreed to participate in the research study completed the survey questionnaire (see Appendix D) and returned it to the P.I. in a self-addressed, coded, stamped envelope. All subjects were mailed a letter from the P.I. one week after the initial mailing which thanked those who had already responded and re-invited the entire sample (Appendix H). Approximately 3 weeks after the initial mailing those who had not yet returned the questionnaire were sent the same information that was included in the initial mailing as well as an additional letter from the P.I. (Appendix I). Approximately 6 weeks after the initial mailing those subjects who had not returned questionnaires were sent a final letter (Appendix J) as well as the information contained in the original mailing. After each subject returned the survey questionnaire, the investigator reviewed the medical records for pertinent

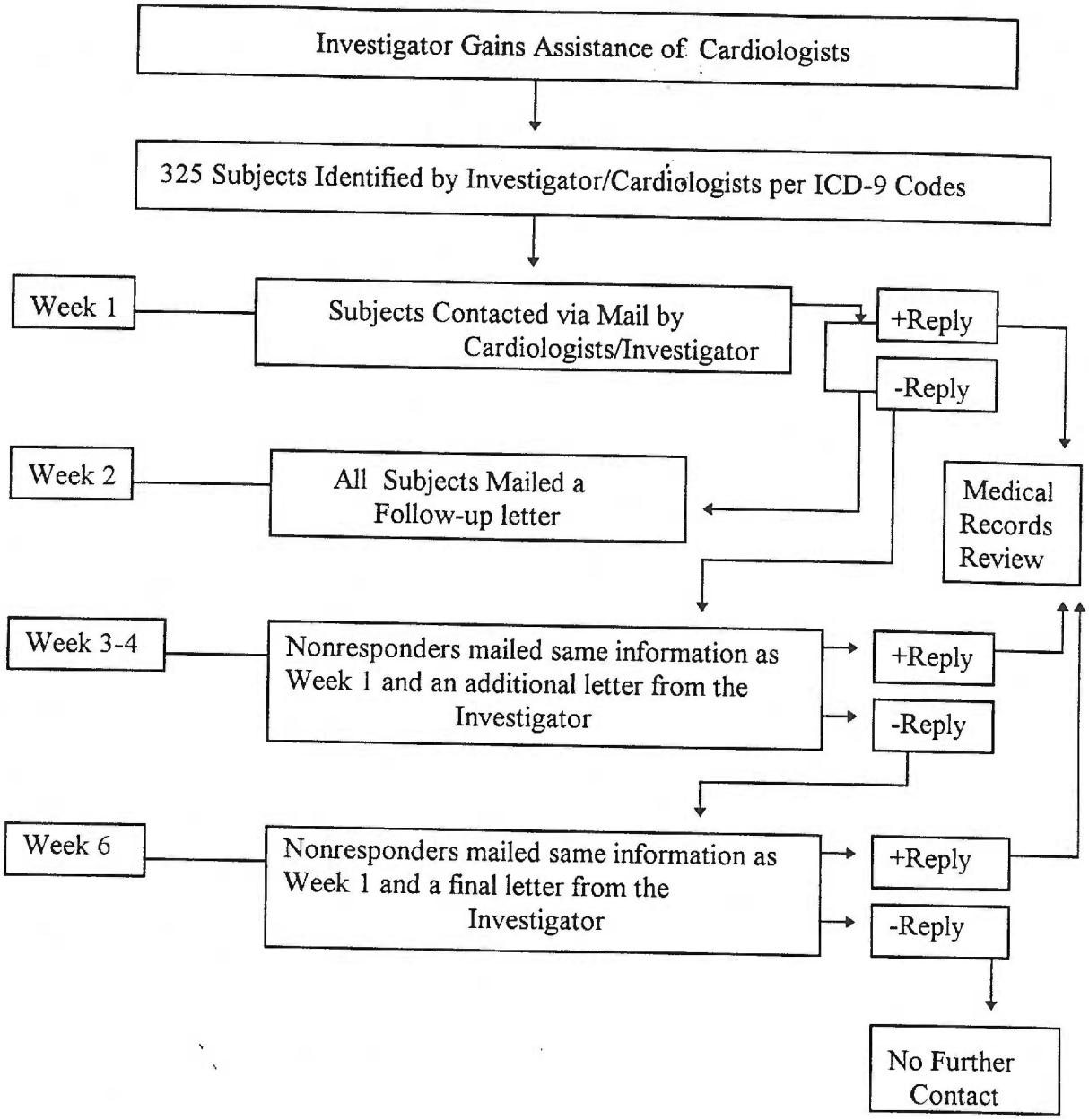

Figure 3. Procedure For Identifying Subjects and Data Collection.

cardiovascular disease risk factors and pertinent information contained in the cardiac catheterization report (see Appendix E).

Criteria for Subjects

Inclusion Criteria

- Persons whose cardiologist granted the investigator access to contact.
- Persons who were 18 to 44 years of age at the time of their diagnosis of coronary atherosclerosis.
- Persons who were treated at Oregon Health Sciences University Hospital/Clinics, Providence Portland Hospital, Providence St. Vincent's Medical Center, Emanuel Hospital and Health Center, or Good Samaritan Hospital and Medical Center between January 1, 1995 through September 1, 1997 to the extent that the medical records were available to the researcher.
- Persons who were diagnosed with coronary atherosclerosis as identified through ICD-9 codes 414.00, 414.80, 411.80, 411.81, 411.89 and 414.90.
- Persons who had coronary angiography as identified by ICD-9 procedural codes 36.00 through 36.05, and 37.20 through 37.23.
- Persons who had a current address included in the medical record of the hospital or physician.
- Persons who agreed to participate by returning the survey questionnaire.

Exclusion Criteria

- Persons with an inability to read and understand English.
- Persons with no mail access.

Justification for Sample Size

In 1992, 79,000 persons between the ages of 15 to 44 were discharged from short-stay, non-Federal hospitals in the United States with a diagnosis of coronary atherosclerosis (Centers for Disease Prevention, 1996). Preliminary information gathered from Portland, Oregon area hospitals indicated that over 700 persons between the ages of 18 to 44 underwent a coronary angiogram and were discharged with the diagnosis of coronary atherosclerosis from January 1, 1995 through May 1, 1997.

A sample of 246 subjects was contacted, and 114 subjects returned the survey questionnaire. One subject was not included in the final sample because all of the questions were marked as "no comment." The sample of 113 subjects provided a 95% confidence interval with a standard error of 9% which was used to address the first primary research question regarding the percent of self-reported past cocaine use among persons 18 to 44 years old who had been diagnosed with coronary artery disease. This sample size calculation was based on a normal approximation from binomial distribution (see Appendix K) (Johnathan Fields, Oregon Health Sciences University Office of Research and Development, personal communication, July 1, 1997).

Method of Selecting Sample

In the interest of protecting the confidentiality of access to medical records, prior to the identification of any potential subjects, the investigator met with and gained the assistance of various cardiologists who treated patients at the Oregon Health Sciences University, Legacy Hospital System, Providence Portland and Providence St. Vincent's Medical Centers. Each cardiologist at the above named hospitals was given the opportunity to have his or her patients enrolled in this study. The investigator explained

the goals, the potential risks, and the overall plan of the study (see Appendix L and M) to each cardiologist in person, through the mail, or via the telephone. The investigator provided a copy of the research proposal to any cardiologist who desired one.

The investigator, acting as an agent of the cardiologists, offered full assistance to the participating physicians in the identification and contacting of the subjects who were found to meet the inclusion criteria of the study. Potential subjects of the participating physicians were identified by a medical records run of the ICD-9 procedural and diagnostic codes for coronary angiography and coronary atherosclerosis with the assistance of the medical records department. Some potential subjects who met the inclusion criteria of the study may have been excluded from the possible final sample selection at the cardiologist's discretion.

A convenience sampling procedure was used. As potential subjects were identified by ICD-9 codes, the first 246 were selected. The source of the subject's addresses was the hospital's and physician's medical records. The investigator attempted to obtain accurate addresses from the cardiologists' offices for all questionnaires which were returned as undeliverable.

Variables and Their Measurement

The primary research questions (1-2) were descriptive and did not involve a dependent variable. The independent variables of the primary research questions were the self-report of past cocaine use, the patterns of past cocaine use, and CAD risk factors. The presence of CAD was an inclusion criterion; since all subjects were diagnosed with CAD, it was not a variable. Question S1was a comparison of the CAD risk factors between the cocaine users and cocaine non-users.

Secondary research questions S2 and S3 had both independent and dependent variables. The independent variables were the patterns of past cocaine use (duration, frequency, and amount) of cocaine use and the CAD risk factors. The dependent variables were the degree and extent of coronary artery stenosis.

All variables were collected through self-report (questionnaire) and through a review of the medical records (see Table 4). Additionally, demographic variables were collected to describe the overall characteristics of the sample population.

Self-Reported Independent Variables. The past use of cocaine was self-reported. Subjects were classified as never having used cocaine only if they reported 3 or fewer episodes of use in their lifetime. Subjects who self-reported past cocaine use had their cocaine consumption quantified in a fashion similar to that of pack-years for smoking (see Figure 4). Objective diagnostic criteria for the definition of frequency of use of all illicit drugs are not currently defined (Chen & Kandel, 1995).

A family history of coronary artery disease was defined as any first-degree relative younger than 55 years who had angina pectoris or MI (Kannel & Larsen, 1993). Family history was self-reported. Oral contraceptive use was self-reported among women, and included age of onset of use and total years of use. Physical activity was self-reported by asking the subjects if they exercised for at least 20 minutes at a time, 3 or more times per week prior to being diagnosed with CAD. Those who answered yes to this question were asked to approximate the total number of months or years in which

Table 4.

Summary of Variables and Their Measurement

Variable	Measurement
I. Independent Variables:	
Self-Reported	
Cocaine use	Self-reported past use.
Oral contraceptive use	Self-reported past and present use.
Sedentary Lifestyle	Self-reported prior exercise.
Cigarette smoking	Self-reported past and present use.
Family history	Any first-degree relative diagnosed with CAD before age 55.
From the Medical Record	
Obesity	BMI >26
Hypertension	Current use of anti-hypertensive agent or medical diagnosis of hypertension.
Hypercholesterolemia	Current use of cholesterol-lowering agent or total cholesterol >300 mg/dL, or triglycerides >500 or medical diagnosis.
Diabetes	Current use of oral or injectable anti-diabetic agent, or medical diagnosis.
Prior M.I.	As recorded in the medical records
II. Dependent Variables for Research Questions S2-S3:	
Degree and extent of coronary artery stenosis.	As diagnosed by the cardiologist Data obtained from cardiac catheterization report.

gram-years = (years of use) (grams per year)

years of use = (age at last use) - (years of abstinent use) - (age at first use)

grams per year = (grams per 24 hrs) (number of days used per year)

Self-Reported Frequency of Cocaine Use	Number of Days Used Per Year
Daily	365
Weekly	
1 day per week	52
2-6 days per week	208
Monthly	
1 times per month	12
2-3 times per month	30
4 or more times per month	52
<1 Time per Month	6

Figure 4. Formulas For Calculating Gram-Years of Cocaine Use

they were engaged in this type of exercise in order to assure that they had engaged in this type of exercise for at least one year prior to the diagnosis of CAD (Blair & Connelly, 1996). Sedentary lifestyle was defined as those who did not exercise for at least 20 minutes for 3 times per week prior to the diagnosis of CAD. Cigarette smoking was self-reported. Subjects were classified as nonsmokers only if they had never smoked. Subjects who self-reported past smoking or who self-reported current cigarette smoking had their tobacco consumption quantified by multiplying the number of packs (20 cigarettes per pack) of cigarettes smoked per day by the number of years smoked (Siedel, Ball, Dains, & Benedict, 1995).

Independent Variables From the Medical Record. Obesity was defined using admission height and weight. Persons were considered obese if they had a calculated BMI >26% (Keller, Oveland, & Hudson, 1997; Kanitz, et. al., 1995) (see Appendix N). Hypertension was considered to be present if the subject was on antihypertensive medication for the treatment of hypertension (as opposed to strictly for the treatment of CAD) at the time of the medical records review or if the past medical history reflected a prior diagnosis of hypertension. Hypercholesterolemia was considered to be present if the subject had a medical diagnosis of hypercholesterolemia or was on a cholesterol-lowering agent, or if the cholesterol was noted to be greater than 300 mg/dL, or total triglycerides were greater than 500 mg/dL (NIH Consensus Development Panel, 1993; Kanitz, et.al., 1995). Diabetes was considered to be present if the subject was currently on an oral or injectable anti-diabetic agent, or if the past medical history reflected a prior diagnosis of Type I or Type II diabetes.

Dependent Variable. Only secondary research questions S2 and S3 involved dependent variables. The dependent variable for secondary research question S1 was the CAD risk factors, which were discussed above. The dependent variables for S2 and S3 were the degree and extent of stenosis.Degree of stenosis was measured as the percent (1% to 100%) of coronary artery stenosis. The extent of coronary artery stenosis was measured as the number of major coronary arteries that were stenosed in one or more arterial sections. Only the greatest amount of coronary artery stenosis in each of the major coronary arteries was recorded. The major coronary arteries were defined as left main (LM), left anterior descending (LAD), diagonal (DIAG), right coronary artery (RCA), posterior descending artery (PDA), circumflex (CIRC), and obtuse marginals 1 through 4 (OM 1-4). Coronary atherosclerosis was operationally defined as any irregularity or abnormality in the coronary artery vasculature definitively diagnosed via coronary angiogram. The degree and extent of coronary artery stenosis were obtained from the medical records cardiac catheterization report, which was reported by the physician who performed the coronary angiogram.

Procedures

The investigator gained the assistance of individual cardiologists at each of the selected hospitals to identify and contact the potential subjects who met the inclusion criteria of the study. Once the cardiologists agreeded to grant the investigator access to the potential subjects, the physician or the investigator (acting as the physician's agent) identified potential subjects through a medical records run of the ICD-9 diagnostic and procedural codes with the assistance of the medical records department of the selected hospitals.

In order to ensure the highest possible response rate, the design and timing of the mailings to the potential subjects were based upon mail survey research conducted by Dillman (1978). Dillman is considered by many researchers to be the most reliable and authoritative source of information by which to design mail surveys. Dillman's methods are well-established and are consistently considered as standard procedures by many researchers (Christine Tanner, Ph.D., R.N., Oregon Health Sciences University, personal communication April 16, 1997).

Once subjects were identified with the assistance of the cardiologists, they were contacted via mail with information from the cardiologist and the investigator contained in one envelope. This envelope contained a letter from their cardiologist (see Appendix F), an informational sheet about the study from the investigator (see Appendix G), a survey questionnaire (see Appendix D), and a self-addressed, coded, stamped reply envelope.

One week after all subjects were initially contacted, all subjects were mailed a follow-up letter from the investigator. This letter thanked those who had already responded and asked those who had not yet completed the questionnaire please to do so (see Appendix H). The envelope code numbers on the stamped return envelopes enabled the investigator to identify which subjects had returned the questionnaire. At that point those subjects who had returned the questionnaire received no further contact from the investigator.

As recommended by Dillman (1978), approximately 3 weeks after the initial mailing, the investigator mailed the same information contained in the initial mailing to all nonresponders, as well as an additional letter from the investigator (see Appendix I).

Approximately 6 weeks after the initial mailing the investigator sent a final mailing to all nonresponders as well as an additional letter from the investigator (see Appendix J).

The investigator reviewed the medical records of the subjects who returned the questionnaire for the following CAD risk factors: height and weight, cholesterol and triglycerides, hypertension, diabetes. The investigator also reviewed the cardiac catheterization report from the medical records for information regarding the degree and extent of coronary artery stenosis (see Appendix E).

The survey questionnaire contained questions regarding demographic characteristics, CAD risk factors and the past use of cocaine (see Appendix D). Completion time was estimated to be 20 to 30 minutes. The questionnaire was developed by the investigator and was reviewed by doctorally prepared nursing researchers, local drug treatment center personnel, and four anonymous recovering cocaine users (not employed as health care professionals) for content and face validity, clarity, and relevance of the questions.

Protection of Human Subjects

Review process. The proposal was submitted and subsequently approved by the Institutional Review Boards at Oregon Health Sciences University, Legacy Hospitals (Good Samaritan and Emanuel) and Providence Hospitals (St. Vincent's and Portland).

Consent. The major risk to subjects who participated in this study was a breach of confidentiality. Since cocaine is an illicit substance the potential for harm as a result of breech of confidentiality would have been great.

This study met the requirements for waiver of written consent in 45 CRF paragraph 46.117, subsection (c) (1) in that the only record linking the subject and the

research would be the consent document and the principal risk would be potential harm resulting from a breech of confidentiality. Therefore, a waiver of written consent was requested and subsequently granted from each of the Institutional Review Boards.

Subjects were provided with a written statement regarding the research (see Appendix G). Subjects indicated their willingness to participate by returning the survey questionnaire.

Benefits and Risks of Participation. The subjects who participated in this research project may or may not have benefited from their participation. Subjects may have benefited in that the information they provided may be helpful to similar groups of people in the future. The primary risks to subjects who participated in this research project would have been a breech of confidentiality and that the investigator was unable to ensure the privacy of the environment in which the subjects chose to complete the survey questionnaire.

Assurance of Confidentiality

A double coding system was employed to ensure that there was no written record linking the subject's identity with the research data. The two codes consisted of an envelope code number and a subject number. A master list was maintained that contained the subject's hospital medical record number, envelope code number, name, address, and whether or not the questionnaire had been returned yet. The master list did not contain the subject number.

The self-addressed, stamped, reply envelope contained an envelope code number in the return address of the P.I. As the questionnaires were returned in the mail to the P.I., subject numbers were written on the questionnaires in sequential order as they were

received. This procedure ensured that there was no correlation between the envelope code number and the subject numbers. By means of the master list, the P.I. used the envelope code number to find the subject's name and hospital medical records number. The P.I. wrote the subject's name and hospital medical records number on a post-it note and temporarily attached it to a blank medical records data collection form. At this point the returned envelope was destroyed. The medical records data collection form contained the subject number but not the envelope code number, name, hospital medical records number, or other identifiers. The P.I. collected the information from the medical records and immediately destroyed the post-it note. By this procedure, the subject's name and medical records number were unable to be linked to the medical records data. Additionally, the subject's name and address were deleted from the master list once the information was collected from the medical records. By the procedures described above, no one, not even the investigators, was able to link the subject's number or name with the research data. (See Figure 5).

The master list contained envelope code numbers. The computer research data file contained the subject numbers. No list contained both the envelope code number and the subject numbers. Returned questionnaires and the medical records data collection forms contained only a subject number which was assigned as the questionnaires were returned. The investigator opened the returned questionnaires in a private closed room with no one else present. The master list was kept in a separate locked file that contained no research data. Access to this file was restricted to the P.I. and the Research Advisor.

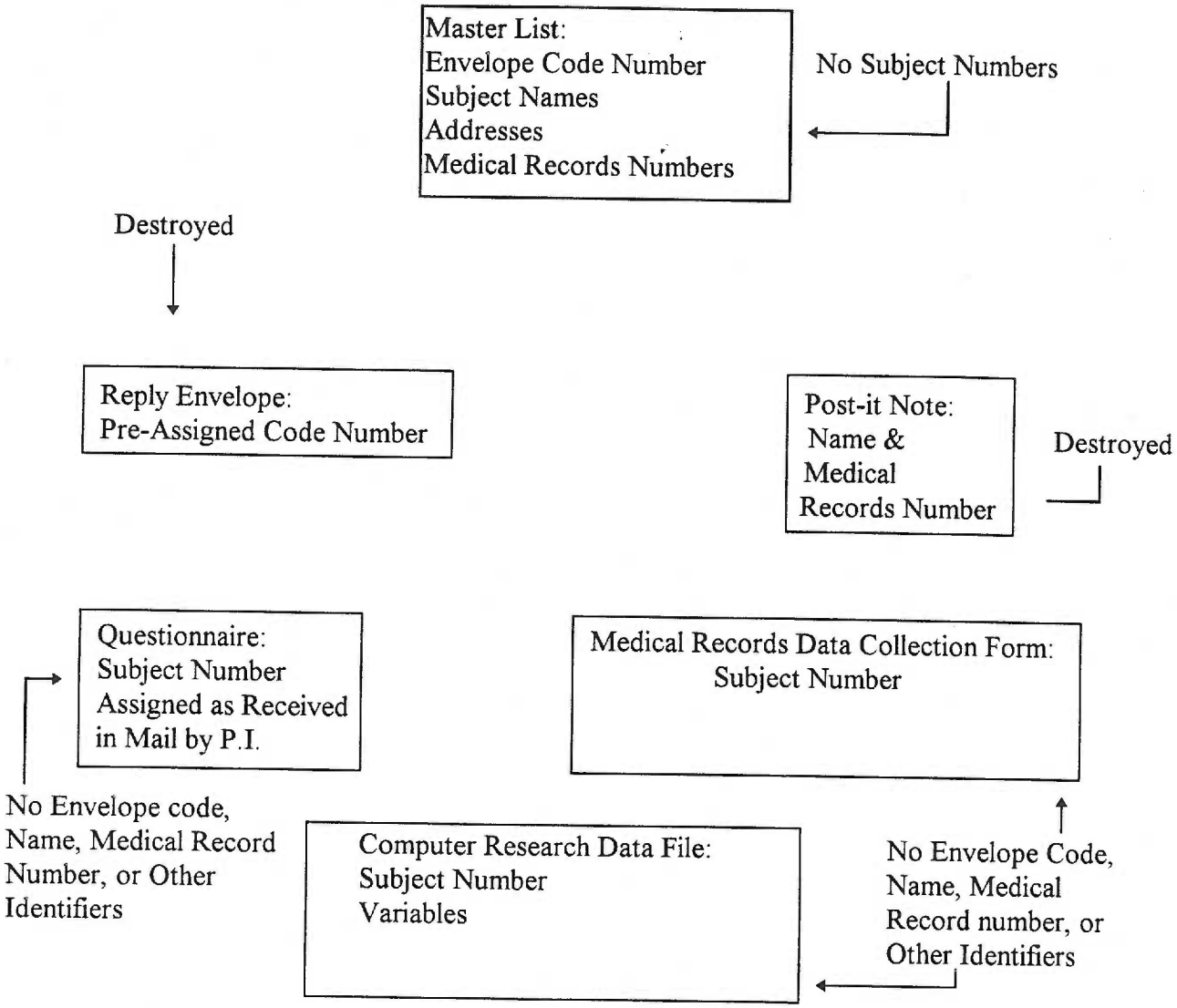

Figure 5. Double Coding System

The master list was destroyed at the end of the research study.

Data Analysis

The data were analyzed on a 586 Compaq personal computer using the SPSS statistical software package.

Demographic Characteristics. The demographic characteristics (age, exercise, BMI, gender, race, marital status, education, and income) of the study sample were reported through the use of descriptive statistics, including percentages, frequency distributions, contingency tables, and measures of central tendency (Polit & Hungler, 1995).

Primary Questions. The two primary research questions were addressed through the use of descriptive statistics, including percentages, frequency distributions, contingency tables, and measures of central tendency (see Table 5). The use of descriptive statistics allowed reduction, summarization and description of the quantitative data obtained from the interview and the medical records review (Polit & Hungler, 1995).

Secondary Questions. Secondary question number one (S1) was addressed through the use of contingency tables which permited the cross-tabulation of the variables of CAD risk factors. Chi-square was used to test the significance of the difference in the proportion of CAD risk factors in the group that self-reported using cocaine versus the group that did not self-report using cocaine. T-tests were used for the continuos variables of pack-years of cigarette smoking and age (see Table 6) (Polit &

Table 5

Primary Research Questions With Corresponding Questionnaire and Medical Records Data Collection Tool Items, Levels of Measurement, and Statistical Tests.

Research Question	Questionnaire Item	Level of Measurement
1. What is the percent of self-reported past cocaine use among persons 18 to 44 years old who have been diagnosed with CAD?	12	Nominal
	MR Tool	
	None	
Statistical Tests. Percentages, frequency distributions, contingency tables, measures of central tendency (mean, median, mode, range, standard deviation).		
Research Question	Questionnaire Items	Level of Measurement
2. What are the self-reported patterns of cocaine use and CAD risk factors within this group?	8 a-d, 9a-b, 13, 15, and 16a.	Interval
	14, 14a-c, and 18 a-b.	Ordinal
	8, 9, 10, 10a-b, 11, 16, and 17.	Nominal
	MR Tool Items	
	6, 10, 11, 12, and 13.	Nominal
	7 and 8.	Interval
	12 and 13.	Ordinal
Statistical Tests. Percentages, frequency distributions, contingency tables, measures of central tendency (mean, median, mode, range, standard deviation), chi-square, t-tests, Pearson's correlations.		

Note: MR=Medical Records Data Collection Tool. See Appendix D and E for Items.

Hungler, 1995). Secondary question number two (S2) was addressed through the use of Pearson's correlation. Pearson's correlation was used to determine if a relationship existed between the degree and extent of coronary artery stenosis and the patterns of past cocaine use (see Table 6) (Polit & Hungler, 1995).

Secondary question number three (S3) were addressed through the use of contingency tables, cross-tabulation of the CAD risk factors with the degree and extent of coronary artery stenosis, chi-square, Pearson's correlation and t-tests (see Table 6). Chi-square was used to test the significance of association between the degree and extent of coronary artery stenosis and established CAD risk factors which were dichotomous. T-tests and Pearson's correlations were also used for the continuos variables (see Table 6) (Polit & Hungler, 1995).

Table 6

Secondary Research Questions With Corresponding Questionnaire and Medical Records Data Collection Tool Items, Levels of Measurement, and Statistical Tests.

Research Question	Questionnaire Items	Level of Measurement
S1. Are the established CAD risk factors different between the group that self-reports cocaine use and the group that self-reports no cocaine use?	8, 8a, 9, 10, 10 a-b, and 11a.	Nominal
	8b-d, 9a-b.	Interval
	MR Tool	
	6, 10, 11, 12, and 13.	Nominal
	7, 8, and 9.	Interval
Statistical Tests. Cross-tabulation. Chi-square. T-tests		
Research Question	Questionnaire Items	Level of Measurement
S2. Is there a relationship between the degree and extent of coronary artery stenosis and the patterns of past cocaine use?	13, 15, and 16a.	Interval
	14, 14a-c, 18a-b.	Ordinal
	MR Tool	
	15, 16a-g (DV)	Ordinal
Statistical Tests. Pearson's Correlations, t-tests.		
Research Question	Questionnaire Items	Level of Measurement
S3. Is there an association between the degree and extent of coronary artery stenosis and established CAD risk factors?	8, 8a, 9, 10, 10a-b, and 11	Nominal
	8b-d, 9a-b.	Interval
	MR Tool	
	15, 16a-g (DV)	Ordinal
	6, 10, 11, 12, and 13.	Nominal
	7, 8, and 9.	Interval
Statistical Tests. Cross-tabulation, Chi-square, t-tests, Pearson's correlations.		

Note: MR=Medical Records Data Collection Tool. DV=Dependent Variable. See Appendix D and E for items.

Chapter IV

Results

Description of the Sample

The potential sample size was 246 subjects. Twelve questionnaires were returned as undeliverable; 114 completed questionnaires were returned in the mail to the investigator. One subject was not included in the final sample because all questions were answered as "no comment." The investigator reviewed the pertinent portions of the medical records for all 113 subjects.

Many questionnaires were incomplete with regards to the patterns of cocaine use. Thus gram-years of cocaine use were calculated only for 23 (58%) of the prior cocaine users. The medical records inconsistently contained information necessary for the calculation of the BMI (n=71). The final sample size was 113 (48% response rate).

Sample Characteristics. The subjects had a mean age of 39.8 (± 3.6) years (see Table 7). They were predominately white (95%). There were two (2%) African-Americans, and four (4%) Native Americans. There were no other ethnic or racial groups included in the final sample. The majority of the subjects were males (72%; $p<0.001$) of middle income (60%). Sixty-eight percent of the sample had either a graduate degree (7%), an undergraduate degree (20%) or had some college (40%). Most were married or living with a partner (77%).

The cocaine users and cocaine non-users did not vary significantly with regards to marital status, education, income, BMI, or exercise. The cocaine users were significantly

Table 7

Demographic Characteristics of Subjects

	Total Sample n=113	Cocaine Users n=39	Cocaine Non-Users n=74
Age ($\bar{x}$ ± SD)	39.8 ± 3.6	39.83 ± 3.6*	42.1 ± 2.7*
(min - max)	(33 - 46)	(33 - 45)	(36 - 46)
Exercise ≥ 3 X/Week			
Prior to Diagnosis	34 (31%)	10 (26%)	24 (32%)
(n=111)			
BMI ($\bar{x}$ ± SD) (n=71)	29.9 ± 6.8	28.0 ± 4.2	30.8 ± 7.6
(min - max)	(19 - 53.7)	(19.8 - 37.4)	(20.8 - 53.7)
Gender			
Male	81 (72%)**	37 (95%)***	44 (59%)***
Female	32 (28%)**	2 (5%)***	30 (40%)***
Race			
White	107 (95%)	33 (85%)	74 (65%)
African-American	2 (2%)	2 (2%)	0
Native American	4 (4%)	4 (4%)	0

* t-test -3.51 df 60.3 p=0.001 **Chi-square 85.6 df 2 p<0.001 ***Chi-square 15.7 df 1 p <0.001

Table 7 (continued)

Demographic Characteristics of Subjects

	Total Sample	Cocaine Users	Cocaine Non-Users
Marital Status			
Never Married	8 (7%)	2 (5%)	6 (8%)
Married or Living			
With Partner	87 (77%)	29 (74%)	58 (78%)
Divorced	16 (14%)	8 (21%)	8 (11%)
Education			
Some High School	10 (9%)	0	10 (9%)
High School			
Graduate	28 (25%)	10 (26%)	18 (46%)
Some College	44 (39%)	16 (41%)	28 (38%)
College Graduate	23 (20%)	2 (5%)	12 (16%)
Graduate Degree	8 (7%)	2 (5%)	6 (8%)
Income			
Low	24 (21%)	6 (15%)	18 (24%)
Middle	68 (60%)	24 (62%)	44 (59%)
High	19 (17%)	9 (23%)	10 (14%)

younger ($p=0.001$) than the cocaine non-users. Gender was distributed unequally between the cocaine users and cocaine non-users ($p<0.001$). Significantly fewer women ($p<0.001$) reported the past use of cocaine than did men. Both of the African-Americans and all four of the Native Americans reported the past use of cocaine (see Table 7).

Major Findings

The main purposes of this research study were as follows:

a) to identify the percent of self-reported past cocaine use among persons 18 to 44 years of age who had been diagnosed with CAD; and,

b) to describe the self-reported patterns of past cocaine use and CAD risk factors within this group.

A secondary purpose was to determine if the CAD risk factors were different between the cocaine users and the cocaine non-users.

Prevalence and Patterns of Past Cocaine Use. The past use of cocaine was self-reported by 35% (39) of the respondents (95% C.I., 26 - 43), which is highly significant (chi-square 70.32, df 1, $p<0.001$) when compared to the 10.3% (95% C.I., 9.4 - 11.2) prevalence of cocaine use in the total population of the United States. No subjects indicated that they were currently using cocaine (see Table 8).

Most cocaine users were white (85%) males (95%; $p<0.001$), who began using cocaine at an average age of 20 ($\pm$ 5), and continued to use approximately 1 gram ($\pm$ 0.59) of cocaine on a weekly (41%) to monthly (38%) basis for an average total period of 8 ($\pm$ 4.9) years. The most common route of cocaine use was nasal insufflation (89%).

Table 8

Self-Reported Patterns of Cocaine Use in Subjects (n=39) with Premature Coronary Atherosclerosis

Age at First Use ($\bar{x} \pm$ SD) (n=39)	20.2 ± 5.0
(min - max)	(14 - 35)
Age at Last Use ($\bar{x} \pm$ SD) (n=37)	30.1 ± 5.6
(min - max)	(22 - 42)
Abstinent Period >1 year	12
Years of Abstinent Period ($\bar{x} \pm$ SD)	3.5 ± 1.9
(min - max)	(1 - 7)
Total Years of Use ($\bar{x} \pm$ SD) (n=37)	8.3 ± 4.9
(min - max)	(2 - 19)
Frequency of Cocaine Use (n=37)	
Daily	4 (11%)
Weekly	15 (41%)
Monthly	14 (38%)
< 1 Time per Month	4 (11%)
Grams of Cocaine Used in 24 Hours ($x \pm$ SD)	1.0 ± 0.59
(n=26) (min - max)	(0.25 - 2.00)
Total Gram-Years ($\bar{x} \pm$ SD) (n=23)	1436.30 ± 2073.05
(min - max)	(12 - 6935)
(median)	312

Table 8 (continued)

Self-Reported Patterns of Cocaine Use in Subjects (n=39) with Premature Coronary Atherosclerosis

Route of Cocaine Use (n=39)	
Smoked	11 (28%)
Intravenous	4 (10%)
Nasal Insufflation	35 (89%)
Ingested by Mouth	2 (5%)

Gram-years of cocaine use was calculated for 23 subjects who reported age of first use, age of last use, and usual amount of use (see Figure 6). The mean gram-years of cocaine use was 1436.30 ± 2073.05 with a median of 312 gram-years.

The most frequent route of past cocaine use was via nasal insufflation (89%). Many subjects (n=13) reported using cocaine via multiple routes (see Table 8).

CAD Risk Factors Among Cocaine Users and Cocaine Non-Users. The CAD risk factor data are presented in Table 9. The major CAD risk factors are cigarette smoking, diabetes, hypertension, and hypercholesterolemia. With respect to the CAD risk factors, 69% of the entire sample had a history of cigarette smoking, with 43% currently smoking; 12% had diabetes; 27% had hypertension; and 38% had hypercholesterolemia.

The cocaine users and cocaine non-users did not vary significantly with respect to the CAD risk factors of cigarette smoking, prior MI, obesity, or sedentary lifestyle. The cocaine non-users had a significantly ($p<0.001$) increased incidence of hypertension, hypercholesterolemia, diabetes, and personal family history of CAD prior to age 55 than did the cocaine users (see Table 9). None of the women who used oral contraceptives reported the past use of cocaine. When the number of major CAD risk factors was considered, the cocaine users had significantly ($p<0.001$) fewer major CAD risk factors than did the cocaine users (see Table 10).

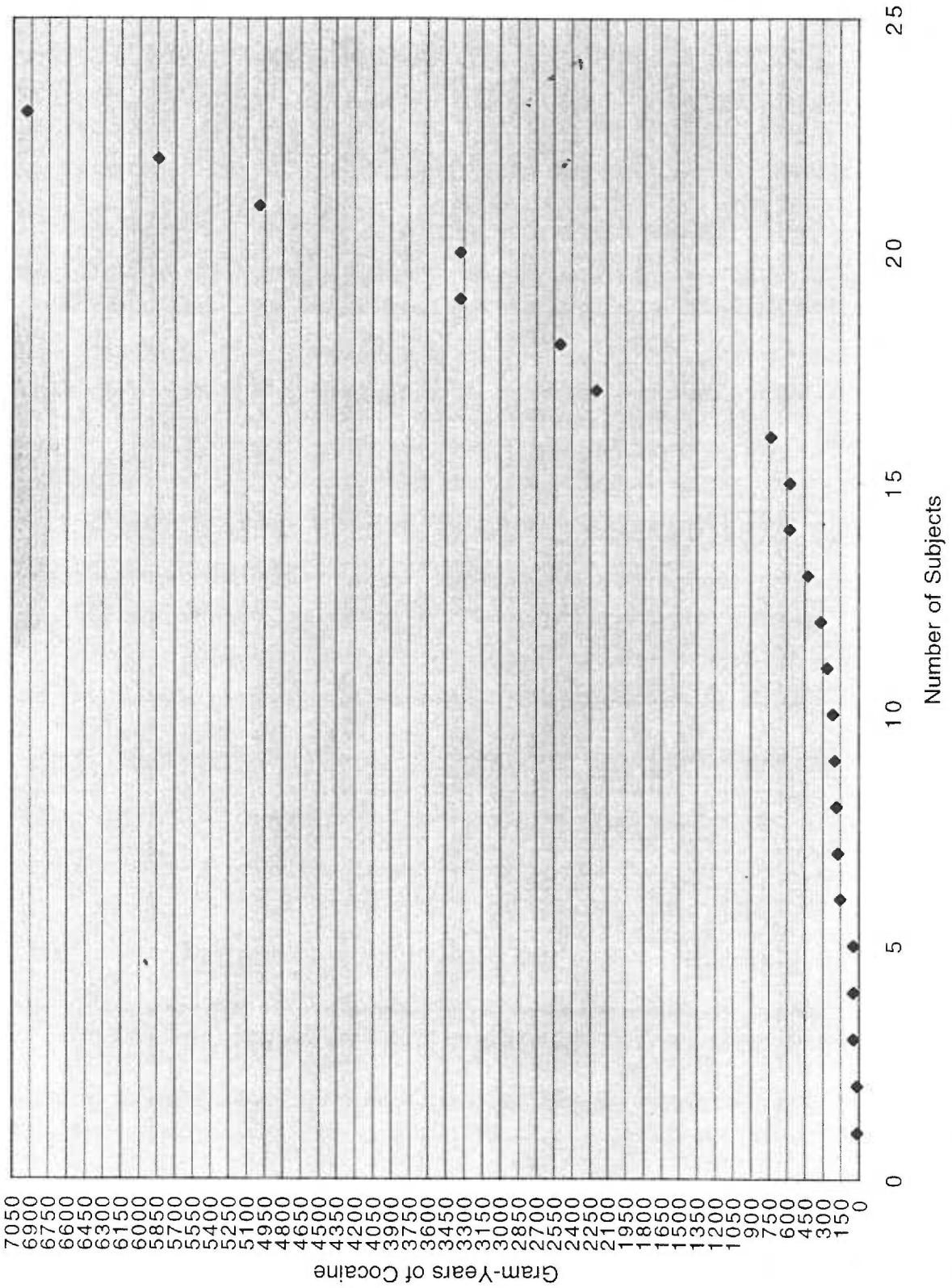

Figure 6. Gram-Years of Cocaine Use.

Table 9

CAD Risk Factors Among Cocaine Users and Cocaine Non-Users

CAD Risk Factors	Total Sample	Cocaine Users	Cocaine Non-Users
Cigarettes			
Ever Smoked	78 (69%)	30 (76%)	48 (64%)
Current Smokers	32 (43%)	10 (25%)	27 (36%)
Age First Smoked	15.5 ± 3.1	15.7 ± 3.1	15.6 ± 3.6
($\bar{x}$ ± SD)			
(min - max)	(9 - 23)	(9 - 21)	(9 - 23)
Pack-Years	26.0 ± 18.7	26.9 ± 19	25.5 ± 18.7
($\bar{x}$ ± SD)			
(min - max)	(0.6 - 66)	(1.25 - 66)	(0.5 - 66)
Oral Contraceptives			
Ever Used	16	0	16
	(50% of Women)		
Total Years Used			
($\bar{x}$ ± SD)	4.29 ± 2.9	0	4.29 ± 2.9
(min - max)	(1- 10)		(1- 10)
Family History of	43 (38%)	11 (28%)*	32 (43%)*
CAD			
Sedentary Lifestyle	75 (66%)	29 (74%)	42 (62%)

* Chi-square 8.32 df 2 $p < 0.02$

Table 9 (continued)

CAD Risk Factors Among Cocaine Users and Cocaine Non-Users

CAD Risk Factors	Total Sample	Cocaine Users	Cocaine Non-Users
Obesity	44 (39%)	12 (30%)	32 (43%)
BMI > 26 ($\bar{x} \pm$ SD)	33.32 ± 6.6	31.1 ± 3.5	34.1 ± 7.4
(min - max)	(26.2 - 53.7)	(26.9 - 37.4)	(26.2 - 53.7)
Hypercholesterolemia	43 (38%)	5 (12%)**	38 (51%)**
Hypertension	20 (27%)	2 (5%)***	18 (24%)***
Diabetes	9 (12%)	0***	9 (12%)****
Prior M.I.	3	2	1

** Chi-Square 16.08 df 1 p<0.001 *** Chi-square 6.46 df 1 p=0.01

****Fisher's Exact p=0.03

Table 10

Number of Major CAD Risk Factors (cigarette smoking, diabetes, hypertension, and hypercholesterolemia) Among Cocaine Users and Cocaine Non-Users.

Number of Major CAD Risk Factors	Cocaine Users	Cocaine Non Users
0	7 (18%)*	13 (18%)*
1	28 (72%)*	20 (27%)*
2	3 (7%)*	30 (40%)*
3	1 (3%)*	12 (16%)*
4	0	0

* Chi-square 25.17 df 3 $p<0.001$; t-test -3.928 df 107 $p<0.001$

Exploratory Findings

Secondary questions were explored:

a) Is there a relationship between the degree and extent of coronary artery stenosis (CAS) and the patterns of past cocaine use?

b) Is there an association between the degree and extent of CAS and established CAD risk factors?

Among the sample as a whole, the most frequently stenosed coronary arteries were the Left Anterior Descending (LAD) (65%), the Right Coronary Artery (RCA) (45%), and the Circumflex artery (CIRC) (19%) (see Table 11). Subjects who reported the past use of cocaine more frequently had two vessel stenosis, whereas those who reported being cocaine non-users more frequently had single vessel stenosis (see Figure 7 and Table 12). Five cocaine users and two cocaine non-users did not have any degree of CAS reported by their cardiologist on the coronary angiogram record. However, these seven persons did not obviously vary from the remaining sample with regards to demographic characteristics, CAD risk factors, or patterns of past cocaine use. These seven subjects were included in the analysis because they met the inclusion criteria of the study as defined in the methods section, in that they had an ICD-9 code assigned that identified them as having a diagnosis of CAD and that they had a coronary angiogram.

Degree and Extent of CAS and Patterns of Past Cocaine Use. The degree of CAS, using three categories of percent stenosis (see Table 11) in each artery, was tested against patterns of past cocaine use by using a t-test for the variable of ever used cocaine, and Pearson's correlation for the variables of frequency of use, total years of use, and gram-

Table 11

Degree and Extent of Coronary Artery Stenosis

Stenosis	Cocaine Users	Cocaine Non-Users
LAD		
1 - 49%	4	4
50 - 74%	6	8
75 - 100%	17	34
Total	27	46
Right		
1 - 49%	3	7
50 - 74%	6	6
75 - 100 %	11	18
Total	20	31
Circumflex		
1 - 49%	2	2
50 - 74%	1	4
75 - 100%	6	7
Total	9	13

Table 11 (continued)

Degree and Extent of Coronary Artery Stenosis

Stenosis	Cocaine Users	Cocaine Non-Users
Posterior Descending		
1 - 49%	0	0
50 - 74%	0	2
75 - 100%	1	6
Total	1	8
Diagonal		
1 - 49%	0	1
50 - 74%	1	3
75 - 100%	1	2
Total	2	6
Obtuse Marginal		
1 - 49%	0	0
50 - 74%	0	0
75 - 100%	1	1
Total	1	1

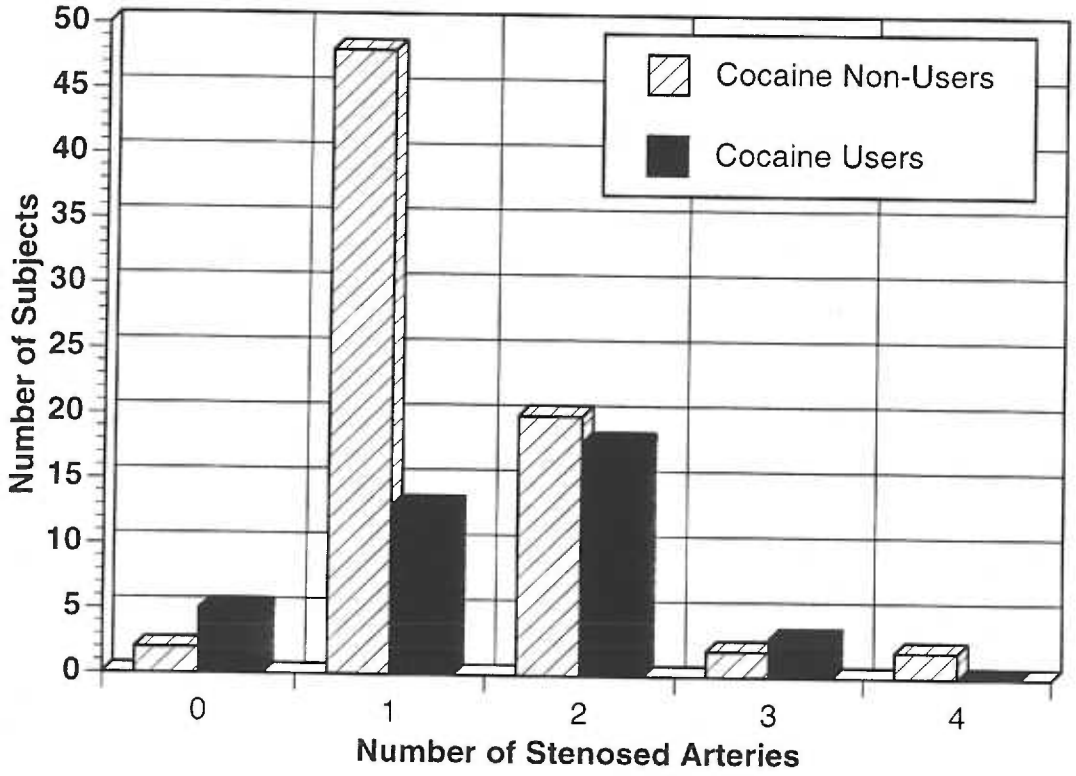

Figure 7. Comparison of Extent of Coronary Artery Stenosis Among Cocaine Users and Cocaine Non-Users.

Table 12

Extent of Stenosis of Major Coronary Arteries

Number of Stenosed Arteries	Total Sample n=113	Cocaine Users n=39	Cocaine Non-Users n=74
0	7 (6%)	5 (13%)	2 (3%)
1	61 (54%)	13 (33%)	48 (65%)
2	38 (34%)	18 (46%)	20 (27%)
3	5 (4%)	3 (8%)	2 (3%)
4	2 (2%)	0	2 (2%)
5	0	0	0
6	0	0	0

years of use. Degree of CAS using the categories <75% stenosis and ≥75% for the LAD, RCA and CIRC were tested against the same cocaine variables and no significant relationships were found using a t-test for the variable of gram-years of cocaine use and chi-square for the remaining dichotomous variables. The extent of CAS (number of stenosed arteries) was tested against the variables ever used cocaine (t-test), and frequency of use, total years of use, and gram-years of use (Pearson's correlation). None of the other patterns of cocaine use were found to be related significantly to the degree or extent of CAS (see Tables 11 and 12).

Degree and extent of CAS and established CAD risk factors.

The degree of stenosis, using three categories of percent stenosis in each artery (see Table 11), was tested against CAD risk factors by using t-tests for the variables of gender, positive family history, diabetes, hypertension, hypercholesterolemia, sedentary lifestyle, oral contraceptive use and obesity. Pearson's correlation was used to test the CAD risk factor variables of pack-years of cigarette smoking, and age against the degree of stenosis in each artery. The extent of CAS (number of stenosed arteries) was tested against the same CAD variables by using t-tests and Pearson's correlations. When the variables were tested in this manner, there was a significant association between the degree of stenosis in the RCA and the CAD risk factor of hypercholesterolemia (t-test 10.7 df 17 $p<0.001$) among the cocaine users only. Among the cocaine non-users, there were significant associations between the CAD risk factors of hypertension (t-test 2.43 df 42.8 $p=0.02$) and positive family history (t-test -2.24 df 25.9 $p=0.03$) with regards to the degree of stenosis in LAD artery only.

When the data regarding the percent stenosis for the three most frequently stenosed coronary arteries (LAD, RCA, CIRC) were collapsed into two categories of <75% stenosis or ≥75% stenosis, the CAD risk factor of hypercholesterolemia remained significantly associated with degree of stenosis of the RCA among the cocaine users. No other significant relationships were found between the degree of stenosis and any of the remaining CAD risk factors for the cocaine users or cocaine non-users using chi-square for the variables of gender, positive family history, diabetes, hypertension, sedentary lifestyle, oral contraceptive use and obesity. A t-test was used for the CAD risk factor variables of pack-years of cigarette smoking and age for both groups against <75% or ≥75% stenosis, no significant relationships were noted. Neither the cocaine users or cocaine non-users showed any significant relationships between any CAD risk factor variable and extent of CAS.

Summary of Major Findings

The cocaine users and cocaine non-users did not vary significantly with regards to cigarette smoking, sedentary lifestyle, obesity, or prior MI. The cocaine users were significantly younger than the cocaine non-users and had significantly fewer individual and cumulative CAD risk factors (diabetes, hypertension, hypercholesterolemia, and positive family history) than did the cocaine non-users. The prevalence of self-reported cocaine use was 35% which is highly significant when compared to the prevalence of life-time cocaine use in the general U.S. population of 10.3% (U.S. Department of Health and Human Services, 1996).

The only CAD risk factors significantly associated with the degree of stenosis was hypercholesterolemia among the cocaine users in the RCA and hypertension and positive family history among the cocaine non-users in the LAD. When the data was collapsed into two categories of stenosis <75% or stenosis ≥75% for the LAD, RCA and circumflex coronary arteries, hypercholesterolemia was found to be significantly associated with degree of stenosis ≥75% in the RCA for the cocaine users. However, among the cocaine non-users the CAD risk factors of hypertension and positive family history were not statistically significant for degree of stenosis in the LAD when the data was collapsed and tested in the fashion described above.

When the major CAD risk factors were grouped together in a cumulative fashion there were no significant findings for degree and extent of CAS among either the cocaine users or cocaine non-users. No significant relationships were found between the patterns of past cocaine use and the degree and extent of CAD among the cocaine users.

Chapter V

Discussion

Percent of Self-Reported Cocaine Use

This is the first study to examine the prevalence of self-reported cocaine use among persons diagnosed with CAD. The percent of self-reported cocaine use among subjects in this study was 35% (95% C.I. 26 - 44%). This is highly statistically significant ($p<0.001$) when compared to the prevalence of cocaine use in the total population of the U.S. According to population estimates from the 1995 National Household Survey on Drug Abuse, only 10.3% of the entire population (all ages) of the U.S. has reported ever (1 or more life-time uses) using cocaine (U.S. Department of Health and Human Services, 1996). Because persons in this research study were classified as prior cocaine users if they had three or more life-time uses of cocaine, the prevalence of ever use of cocaine among the subjects in this study may be greater than 35%.

As noted previously, there have been no published research studies conducted on the prevalence of cocaine use among those with CAD. In addition, there are no published studies regarding the prevalence of CAD among cocaine users. The fact that a significantly higher percentage of subjects in this study reported the past use of cocaine than is reported by the population at large, suggests that the past use of cocaine may be an independent risk factor for the development of CAD.

Self-Reported Patterns of Cocaine Use

Cocaine is distinguished from other drugs of abuse in that the age of first use tends to be higher than it is for other drugs of abuse. Cocaine is more frequently used by

those who are in their twenties and early thirties (U.S. Department of Health and Human Services, 1996; Chen & Kandel, 1995). Consistent with these findings, the majority of the prior cocaine users in the present study were younger than 40 years of age, reported their first cocaine use at approximately age 20, and continued using cocaine for an average period of 8 years. Thus, the majority of cocaine users in this study would have began using cocaine around 1978 and continued to use until the mid 1980s, which is when cocaine use in the U.S. peaked at 7.1 million users (U.S. Department of Health and Human Services, 1996).

Most cocaine users in the present study reported the use of cocaine on a weekly basis (median use 2 to 6 times per week). The U.S. Department of Health and Human Services (1996) reports similar findings among the cocaine users of 15 to 20 years ago; specifically, the typical cocaine user consumed cocaine on a weekly basis, beginning in the early to mid-twenties and had ceased using cocaine by the age of 35. The similarity of age of first cocaine use and duration of use between the present study and the Monitoring the Future Study, 1975-1994, suggests that the cocaine users in the present study did honestly and accurately self-report these data.

The average amount of cocaine used in a 24-hour period by subjects in this study was 1 gram. To this researcher's knowledge, there is no published data available on the average amount of cocaine consumed by most cocaine users in a 24 hour period, and it is even less likely that any data exist, published or not about the average amount of cocaine used among persons 10 to 20 years ago. Thus there are no national averages with which to compare the data collected in the present study. However, it seems reasonable that

cocaine users would be able to report approximately how much cocaine they consumed since cocaine is purchased in grams, or rocks. No subject in this study reported the use of cocaine rocks. Rocks are also known as crack cocaine. Rocks typically weigh a quarter gram and are most frequently smoked. Crack (cocaine rocks) cocaine did not emerge as a drug of abuse until the mid to late 1980's (U.S. Department of Health and Human Services, 1996), which is after the majority of the subjects in this ceased the use of cocaine.

Most of the subjects in the present study reported using cocaine via multiple routes; the most common route of use was nasal insufflation. Again, as with the average amount of cocaine consumed in a 24-hour period, there are no national statistics with which to compare the route of use. However, since cocaine is sold in a powdered form, nasal insufflation is likely the most convenient way to obtain the desired effects of this drug. Therefore, it does not seem surprising to this researcher that the subjects in this study reported using cocaine most frequently via this route.

The calculation of total gram-years of cocaine use is important in that those with a history of little or rare cocaine use may theoretically be at a lower risk for the development of CAD as a result. Information regarding the relationship between total amount of life-time cocaine use and degree CAD risk has been non-existent to date. The quantification of the total amount of life-time cocaine grams, to this researcher's knowledge, has not been previously attempted by other researchers. In this study, gram-years was calculated in a similar fashion to that of pack-years for cigarette smoking. To calculate the pack-years of cigarette smoking, the total number of packs of cigarettes smoked per day is multiplied by

the total number of years smoked. For example, a person who smoked 1 pack of cigarettes per day for 25 years would be said to have a 25 pack-year history of cigarette smoking. The patterns of cocaine use are not as predictable as they are for cigarette smoking and often consist of binge use followed by periods of abstinent use (Chen & Kandel, 1995). Thus gram-years, which take abstinent periods into account as reported in this study, are an estimate of the total life-time consumption of cocaine in grams.

CAD Risk Factors Among Cocaine Users and Cocaine Non-Users

Each of the risk factors that were explored in this study has been found to contribute either directly or indirectly to the development of CAD in large epidemiological studies (Castelli et al., 1986; Kannel & Larson, 1993; Kannel, McGee & Gordon, 1976; Kannel, Wolf, Castelli, & D'Agostino, 1987).

Age. Age is a known risk factor for the development of CAD. As a person ages the risk of developing CAD increases. It is plausible to speculate that if one lives long enough, one will eventually develop CAD--it remains the leading cause of death in males over the age of 35 and of all persons over the age of 45 in the United States (McGinnis & Foege, 1993). The cocaine users were significantly younger than were the cocaine non-users. The fact that the cocaine users were significantly younger than were the non-users suggests that perhaps there were other factors that would explain the development of CAD among the cocaine users. This finding is consistent with the idea that the past use of cocaine may be a significant risk factor for the premature development of CAD.

Gender. Gender is a known risk factor for the development of CAD. Women have a much lower prevalence of CAD at an early age and traditionally do not develop CAD

until 10 to 15 years after men. Gender was a significant finding in this study. Significantly more women reported the non-use of cocaine than reported the use of cocaine and significantly fewer women were included in the sample as a whole. Perhaps this is because when only the risk factor of gender is considered, women do not equal males in CAD risk until at least an average of 8 years later in life (Kannel & Larson, 1993).

Family History. A positive history of heart disease among a first-degree relative prior to the age of 55 has been shown to be a significant independent risk factor for the development of CAD (Kannel & Larsen, 1993). The cocaine non-users reported a positive family history of CAD prior to the age of 55 significantly more frequently than did the cocaine users. Therefore the majority of the cocaine users in the present study did not have a positive family history of heart disease and thus again one must conclude that there were other factors responsible for their development of CAD.

Cigarette Smoking. Cigarette smoking has been cited as the most common CAD risk factor in the young population when compared to the general population over age 40, and its prevalence is estimated to range from 50 to 80% (Kanitz et al., 1996; Zimmerman et al., 1995). Previous studies of atherosclerosis in young persons (<40 years of age) have noted that the primary CAD risk factor was cigarette smoking, and that the prevalence of other CAD risk factors was much lower when compared to those over the age of 40 (PDAY research group, 1993). Consistent with these findings, 76% of the cocaine users and 64% of the cocaine non-users reported a past history of smoking. Each group reported smoking for approximately 15 pack-years. The cocaine users and cocaine non-users did not vary significantly with regards to the CAD risk factor of cigarette smoking.

Cigarette smoking among cocaine users is slightly lower in this sample than the prevalence which has been reported in the general population of cocaine users (U.S. Department of Health and Human Services, 1996). As previously discussed, an analysis of the literature to date by the investigator (Appendix B) revealed that overall 39% of the persons who sustained a cocaine-associated cardiovascular event were reported to be cigarette smokers. However, the prevalence of cigarette smoking was likely to have been much greater among this population, since it was not reported 50% of the time by these researchers.

Cocaine users who also smoke cigarettes may be an even greater risk for the development of an acute MI or for the development of CAD because studies have demonstrated that the concomitant use of both of these substances causes an even greater degree of coronary vasoconstriction than either substance used in isolation (Moliterno et al., 1994). Furthermore, cigarette smoking has been found to accelerate the atherosclerotic process by 50% among current smokers, by 25% among former smokers, and by 20% among those who are exposed to second-hand smoke for 20 hours or more a week (Howard, Manolio, Burke, Wolfson & O'Leary, 1997). The concomitant use of cocaine and cigarettes may perhaps accelerate the atherosclerotic process to an even greater extent.

Diabetes, Hypertension, and Hypercholesterolemia. Each of these conditions has been found to be a major independent risk factor for the development of CAD (Kannel & Larsen, 1993). None of the cocaine users in this study had diabetes. The prevalence of hypertension and hypercholesterolemia was significantly lower among the cocaine users

than it was in the cocaine non-users. Furthermore, the cocaine non-users had significantly more cumulative risk factors when compared to the cocaine users. The accumulation of multiple CAD risk factors has been found to increase significantly the risk of developing CAD at any age (Kannel & Larsen, 1993).

Obesity. Obesity has been found to be a risk factor for the development of CAD, particularly abdominal obesity. It is often associated with other more significant CAD risk factors such as hypertension, diabetes, and hypercholesterolemia (Poothullil, 1993). The cocaine users and cocaine non-users did not vary in average BMI or on the risk factor of obesity.

Sedentary Lifestyle. Sedentary lifestyle, or physical inactivity, has not been linked directly to the development of CAD in large epidemiological studies. This is because there are multiple variables involved. Beyond the obvious caloric expenditure and amelioration of hyperlipidemia, how physical activity may work to decrease the risk of CAD is not well understood (Vos, de Feyter, Simoons, Tijssen, & Deckers, 1993). The cocaine users and cocaine non-users in this study did not vary significantly with regards to sedentary lifestyle.

Oral Contraceptive Use. The use of oral contraceptives, particularly in women over the age of 35 who also smoke, has been found to have an additive effect in increasing a woman's chance of having an MI and may induce atherosclerosis to the extent that it alters the lipid profile (Pandey & Vlajinac, 1989; Burkman, 1996). Fifty percent of the female cocaine non-users in the present study reported the past use of oral contraceptives.

None of the women cocaine users in this study reported the past use of oral contraceptives.

Grouping of Major CAD Risk Factors. CAD risk factors are believed to cumulative in that they have an additive effect in increasing one's risk of developing CAD. The major CAD risk factors are cigarette smoking, hypertension, hypercholesterolemia, and diabetes (Kannel & Larson, 1993). When the major CAD risk factors were grouped together in this study, the cocaine non-users were found have significantly more major independent risk factors than did the cocaine users. This finding is consistent with the idea that past use of cocaine may be a significant risk factor for the premature development of CAD.

Summary of CAD Risk Factors Among Cocaine Users and Cocaine Non-Users. The cocaine users in this study were younger and had fewer CAD risk factors than did the cocaine non-users. The cocaine non-users had a significantly higher prevalence of hypertension, hypercholesterolemia, and a positive family history of heart disease than did the cocaine non-users. None of the cocaine users were diabetics. The two groups did not vary significantly with regards to cigarette smoking, BMI, or sedentary lifestyle. Again, these findings are consistent with the idea that the past use of cocaine may be a significant risk factor for the development of premature CAD.

Degree and Extent of CAS and Patterns of Cocaine Use

Some previous studies (Eichhorn et al., 1992; Kolodgie et al., 1992) have demonstrated a greater degree and extent of coronary atherosclerosis among cocaine users when compared to cocaine non-users. These subjects were studied at autopsy and not

angiographically. In the present study the cocaine users were not found to have a greater degree or extent of CAS when compared to the cocaine non-users. One explanation for why the two groups of subjects in the present study did not demonstrate any significant differences with regards to the degree and extent of CAS is that angiographic measurement of CAS is not as sensitive as is post-mortem measurement (Reiber & Serruys, 1991; Yang et al., 1988; Roberts, 1989; Bashour, 1994; Dietz et al., 1992). Another possible explanation for the discrepancy between the degree and extent of CAS the findings of this research and the research of others, is that other researchers have used a much larger sample size. Sample size is known to increase the power of the research design and thus the ability to detect a relationship among variables (Polit & Hungler, 1995).

Only 23 subjects reported enough information in this study to calculate gram-years of cocaine use. A power analysis was performed with the following assumptions: alpha .05, one-tailed t-test, equal sample sizes, and an effect size of approximately .4. Using these assumptions, 30 cases in each group would provide a 47% of rejecting the null hypothesis, 50 cases would provide a 66% chance of rejecting the null hypothesis, and 70 cases in each group would provide a 78% chance of rejecting the null hypothesis. In the present study, a larger sample size might have produced findings more similar to that which has been reported by others

The most frequently stenosed arteries among the cocaine users and the cocaine non-users were the LAD, RCA, and circumflex. The predilection for the involvement of the LAD, RCA, and circumflex arteries, regardless of CAD risk factors, has been noted by

other researchers who have studied angiographically the coronary arteries of young persons (Zimmerman et al., 1995).

To the investigator's knowledge, the relationships between the degree and extent of CAS and past patterns of cocaine use have not previously been examined by other researchers. Based upon what is known about CAD risk factors (i.e., that they are cumulative and the longer the condition exists in an individual, the greater the risk becomes for developing more serious disease) then one would expect that those with a longer history of use and those who have used more cocaine would most likely have a greater degree and extent of CAS. There was no correlation or association with the patterns of past cocaine use among subjects in this study with the degree and/or extent of CAS. Again, as discussed earlier, angiography is less sensitive than post-mortem techniques and a larger sample size might have produced significant results because it would have given the statistical tests more power and thus a greater ability to detect a significant relationship among these variables and thus to reject the null hypothesis.

Degree and Extent of CAS and Individual CAD Risk Factors

Among the cocaine users there was an association between the degree of CAS and the CAD risk factor of hypercholesterolemia in the RCA artery only. Hypercholesterolemia is a known independent risk factor for the development of CAD (Kannel & Larson, 1993. This investigator can offer no explanation for the association between hypercholesterolemia and the degree of stenosis in the RCA only among cocaine users. It seems logical that if hypercholesterolemia were to be predictive of the degree of CAS, then one would expect to find that this risk factor is consistently associated with the

degree of CAS among all three (LAD, RCA, and circumflex) of the major coronary arteries. In addition, no single CAD risk factors were found to be significant among the cocaine users with regards to the extent of CAS. Again this may be as a result of the sample size and the power of the statistical tests, the lesser sensitivity of angiography as compared to post-mortem study, or it may be perhaps that these variables are not related significantly.

Among the cocaine non-users there was an association between the CAD risk factors of hypertension and positive family history in the LAD artery only. Hypertension, and to a lesser extent, positive family history are significant risk factors for the development of CAD (Kannel & Larson, 1993). Again this researcher can offer no explanation for the association of these risk factors with the degree of stenosis in only the LAD and among only the cocaine non-users. However, the cocaine non-users did have a significantly increased prevalence of hypertension and positive family history compared to the cocaine users, and the LAD artery is one of the most commonly occluded arteries among young persons with CAD (Zimmerman et al., 1995). So the fact that these two risk factors were associated with the degree of stenosis in the most commonly occluded coronary artery is not surprising.

The data in this study were collapsed for the LAD, RCA, and circumflex arteries two times. First from a continuous (1-100% stenosis) variable to a categorical (1-49%, 50-74%, 75-100%) variable, and second to a dichotomous variable of <75% stenosis and ≥75% stenosis. This was done in order to ascertain fully if a relationship existed among these variables. Each time the data were reduced to a lower level of measurement, the

categories became less powerful and less sensitive. The ability to detect a significant relationship became more difficult and the likelihood of making a type II error increased significantly as a result. Lower levels of measurement in combination with a small sample size decreased the probability of detecting a significant relationship among these variables and greatly increased the probability of making a type II error in the present study.

It is somewhat surprising to this researcher that neither the cocaine users nor the cocaine non-users who had a history of cigarette smoking were found to have a greater degree or extent of CAS. In previous studies, cigarette smokers who died of causes other than CAD have been found to have a greater degree and extent of CAS on autopsy exam than were non-smokers--regardless of their other CAD risk factors (Zimmerman, 1995; Leone, 1993). In addition, in a large epidemiological study of 19,000 persons of a broad age range, smokers were found to have greater CAS than were non-smokers when examined by means other than autopsy exam (Howard et. al., 1997). Again, among those studies which have examined the coronary arteries of cocaine users, the method of estimating the degree and extent of CAS was direct and highly objective, whereas coronary angiography is an indirect and somewhat subjective measure of CAS when compared to direct cross-sectional analysis (Reiber & Serruys, 1991; Yang et al., 1988; Roberts, 1989; Bashour, 1994; Dietz et al., 1992). The large epidemiological study had many more participants (19,000) of a wider age range than were included in the present study. Each of these factors, in addition to the sample size, level of measurement, and power of the research design discussed earlier, may explain the discrepancies of the findings of the present study when compared to findings of other studies.

Grouping of the Major CAD Risk Factors. To this researcher's knowledge no researchers have reported findings on the grouping of the major CAD risk factors in order to determine if a relationship exists between the number of individual CAD risk factors and the degree and/or extent of CAS. Again, since risk factors are cumulative and have an additive effect (Kannel & Larson, 1993), it would seem likely that those with more single risk factors may have a greater degree and extent of CAS. When the major CAD risk factors of cigarette smoking, hypertension, hypercholesterolemia, and diabetes were grouped together in this study neither the cocaine users or cocaine non-users were found to have a greater degree or extent of CAS. Again, perhaps these findings are explained by the method used to evaluate CAS among the subjects in this study, and by lack of power of the statistical tests as was discussed earlier.

Limitations

One of the main limitations of this study is that it relied heavily upon the self-report of past cocaine use. Many may question the validity of the data collected in this study because cocaine is an illicit substance. While there is no direct, totally objective manner by which to validate the subjects' responses, a considerable amount of evidence exists that the data obtained from the self-report of prior cocaine are largely valid (U.S. Department of Health and Human Services, 1996; Shillington et al., 1995). In addition, the research methods of this study ensured complete confidentiality of the subjects' responses, the subjects were told that the information would be used strictly for research purposes, and none of the subjects reported the current use of cocaine. Each of these factors is known to increase the validity with regards to self-reported sensitive information (Sobell et al.,

1995; Sobell et al., 1988; Sobell et al., 1994). Therefore if there exists a self-report bias, the investigator believes it would have been in the direction of underreporting. Thus the prevalence of prior cocaine use among these subjects may be significantly higher than the values reported.

In some instances the questionnaires were incomplete with regards to patterns of past cocaine use and the medical records were incomplete with regards to the height and/or weight of the subjects. The height and weight were required in order to calculate the BMI; therefore it was calculated for only 63% (n=71) of the subjects. Complete data regarding the patterns of past cocaine use and the gram-years of cocaine use were available for only 23 (58%) of the subjects who reported prior cocaine use.

This was a small sample size with low power and thus the likelihood of making a type II error was significant. In addition, when the data regarding degree of stenosis were collapsed into a dichotomous variable the ability to detect a significant relationship among the variables diminished greatly, thus further increasing the likelihood of making a type II error.

A possible sampling bias may exist in that this was a convenience sample of 246 subjects. The under-representation of minority groups and groups of a lower socio-economic class may be a result of a sampling bias. A sampling bias may also exist in that subjects were included or excluded from the sample at the cardiologists' discretion. Furthermore, while all cardiologists at the participating hospitals were asked to participate, not all cardiologists agreed to allow their patients the opportunity to participate in this research study.

A response rate bias may exist in that only 48% of the sample returned the questionnaire. Traditionally, response rates of 60% or more are needed in order to consider the sample non-biased and to consider the findings entirely generalizable (Polit & Hungler, 1995). Issues of confidentiality prevented the investigator from gathering information about the non-responders; therefore little is known about the non-responders other than they met the inclusion criteria defined earlier in this study. While the response rate was nearly 50% in this study, the findings may not be entirely generalizable because of a less than traditionally desired response rate.

Further Research Implications

While the prevalence of CAD among persons less than 40 years of age is estimated to be approximately 4% (Zimmerman, 1995), the prevalence of CAD among cocaine users remains unknown. Perhaps the greatest support of cocaine as a independent risk factor for the development of CAD would come from information gleaned from a study of known cocaine users and known cocaine non-users comparing the prevalence of CAD in each group, as well as the CAD risk factors of each group

Further research in this area should include a sample population that is more diverse with regards to socio-economic status, gender and race. Since women do not develop CAD until 8 years later in life on average when compared to men (Kannel & Larson, 1993), future studies of women may be indicated in order to generalize to this population. Furthermore, because women do not usually develop CAD until an average of at least 8 years later in life than do men, the definition of premature coronary

atherosclerosis should be increased for pre-menopausal women by at least 8 years.

Practice Implications

Among the subjects included in this research study, those who self-reported the past use of cocaine were mostly younger than age 40 and had few CAD risk factors. Many primary care providers believe that substance abusers are of a low socio-economic status or that they are not college educated. As the findings of this research demonstrate, prior cocaine users share the same demographic characteristics as do those who have never used cocaine. There was no difference in economic status, marital status, education or race between the cocaine users and cocaine non-users in this study. Primary care providers will not be able to identify those with a positive history of cocaine use if they do not specifically ask their patients these questions. In addition, primary care providers should also assess for the current use of cocaine among all patients in order to reduce the risk of premature CAD and other related cardiovascular diseases. Currently there is no treatment of atherosclerosis, only of its complications; thus prevention is the only treatment. As the number of CAD risk factors increase, so does the likelihood of developing CAD. Removal or, when possible, the reversal of single or multiple risk factors may delay or arrest the atherosclerotic process. Those with a prior history of habitual cocaine use should be strongly encouraged to stop cigarette smoking, and maintain their weight at recommended levels though diet and exercise. In addition, primary care providers should aggressively treat hypertension, diabetes and hypercholesterolemia in persons with a positive history of cocaine use.

Conclusions

This is the first study to report the prevalence and patterns of past cocaine use among those with CAD. Furthermore, it is the first study to describe the CAD risk factors among those with a history of cocaine use and those without a history of cocaine use. It showed a substantial prevalence (35%) of prior cocaine use in persons with premature CAD. The fact that the cocaine users were younger and had significantly fewer CAD risk factors, than the non-users, yet still developed CAD, is highly suggestive that the past use of cocaine may be a significant risk factor for the premature development of CAD.

Most health care providers likely believe they are adept at recognizing current substance abusers. It is likely that most providers are unaware of the importance of assessing for past substance abuse. As this study demonstrates, those with a history of cocaine use are of the same socio-economic level as those who have never used cocaine. Therefore, primary care providers will have no clues as to who has and who has not used cocaine in the past if they never specifically ask their patients to be forthright with this information. Primary care providers should include an assessment for the past history of cocaine use among all of their patients, but most importantly among those patients who have at least one other CAD risk factor which may be modifiable. The modification of other risk factors may be beneficial to the overall reduction of risk among those with a significant history of cocaine use.

References

Alpert, J. S. (1994). Myocardial infarction with angiographically normal coronary arteries. Archives of Internal Medicine, 154, 265-290.

Amin, M., Gabelman, G., Karpel, J., & Buttrick, P. (1990). Acute myocardial infarction and chest pain syndromes after cocaine use. American Journal of Cardiology, 66, 1434-1437.

Appleby, M., Fisher, M., & Martin, M. (1994). Myocardial infarction, hyperkalemia and ventricular tachycardia in a young male body-builder. International Journal of Cardiology, 44, 171-174.

Ascher, E. K., Stauffer, J. C., & Gaasch, W. H. (1988). Coronary artery spasm, cardiac arrest, transient electrocardiographic Q waves and stunned myocardium in cocaine-associated acute myocardial infarction. American Journal of Cardiology, 61, 939-941.

Bashore, T. M. E. (1990). Invasive cardiology. Principles and techniques: Philadelphia, PA: B.C. Decker Inc.

Bashour, T. T. (1994). Acute myocardial infarction resulting from amphetamine abuse: a spasm-thrombus interplay? American Heart Journal, 128(6 Pt 1), 1237-1239.

Benowitz, N. L. (1993). Clinical pharmacology and toxicology of cocaine. Pharmacology & Toxicology, 72, 3-12.

Billman, G. E. (1995). Cocaine: a review of its toxic actions on cardiac function. Critical Reviews in Toxicology, 25, 113-132.

Blair, S.N., & Connelly, J.C. (1996). How much physical activity should we do? The case for moderate amounts and intensities of physical activity. Research Quarterly for Exercise and Sport, 67, 193-205.

Brody, S. L., Slovis, C. M., & Wrenn, K. D. (1990). Cocaine-related medical problems: consecutive series of 233 patients. American Journal of Medicine, 88, 325-331.

Brogan, W., Lange, R.A., Glamann, D.B., & Hillis, L.D. (1992). Recurrent coronary vasoconstriction caused by intranasal cocaine: possible role for metabolites. Annals of Internal Medicine, 7, 556-561.

Burke, J.A., Levi, R., Guo, Z.G., & Corey, E.J. (1982). Leukotrienes C4, D4, and E4: Effects on human and guinea-pig cardiac preparations in vitro. Journal of Pharmacology & Experimental Therapy, 221, 235-241.

Burkman, R.T. (1996). Oral contraceptive use and coronary and cardiovascular risk. Medicine & Science in Sports & Exercise, 28, 11-20.

Carson, P., Oldroyd, K., & Phadke, K. (1987). Myocardial infarction due to amphetamine. British Medical Journal Clinical Research Education, 294, 1525-1526.

Castelli, W. P., Garrison, R. J., Wilson, P. W., Abbott, R. D., Kalousdian, S., & Kannel, W. B. (1986). Incidence of coronary heart disease and lipoprotein cholesterol levels. The framingham study. Journal of the American Medical Association, 256, 2835-2838.

Caulker-Burnett, I. (1994). Primary care screening for substance abuse. Nurse Practitioner, 19 (6), 42-48.

Centers for Disease Control and Prevention. (1996). Advanced Data From Vital and Health Statistics: Numbers 261-270. Vital and Health Statistics.

Chen, K., & Kandel, D.B. (1995). The natural history of drug use from adolescence to the mid-thirties in a general population sample. American Journal of Public Health, 85, 12-30.

Coleman, D. L., Ross, T. F., & Naughton, J. L. (1982). Myocardial ischemia and infarction related to recreational cocaine use. Western Journal of Medicine, 136, 444-446.

Cooke, C. T., & Dowling, G. P. (1988). Cocaine-associated coronary thrombosis and myocardial infarction. Pathology, 305-306.

Cregler, L. L., & Mark, H. (1985). Relation of acute myocardial infarction to cocaine abuse. American Journal of Cardiology, 56, 794.

Das, G. (1993). Cardiovascular effects of cocaine abuse. International Journal of Clinical Pharmacology, Therapy, & Toxicology, 31, 521-528.

Derlet, R. W., & Albertson, T. E. (1989). Emergency department presentation of cocaine intoxication. Annals of Emergency Medicine, 18, 182-186.

Dietz, W. A., Tobis, J. M., & Isner, J. M. (1992). Failure of angiography to accurately depict the extent of coronary artery narrowing in three fatal cases of percutaneous transluminal coronary angioplasty. Journal of the American College of Cardiology, 19, 1261-1270.

Dillman, D. A. (1978). Mail and Telephone Surveys: The Total Design Method. New York: John Wiley & Sons.

Dressler, F. A., Malekzadeh, S., & Roberts, W. C. (1990). Quantitative analysis of amounts of coronary arterial narrowing in cocaine addicts. American Journal of Cardiology, 65, 303-308.

Durant, R.H., Rickert, V.I., Ashworth, C.S., Newman, C., & Slavens, G. (1993). Use of multiple drugs among adolescents who use anabolic steroids. The New England Journal of Medicine, 328, 922-926.

Eichhorn, E. J., Peacock, E., Grayburn, P., Bedotto, J. B., Willard, J. E., Willerson, J. T., & Demian, S. E. (1992). Chronic cocaine abuse is associated with accelerated atherosclerosis in human coronary arteries. Journal of the American College of Cardiology, 105A, 1271.

Fallovollita, J., Kumar, K., Brody, A., Bunnell, I., & Canty, J. (1996). Detection of coronary artery calcium to differentiate patients with early coronary atherosclerosis from luminally normal arteries. American Journal of Cardiology, 78, 1281-1284.

Flores, E. D., Lange, R. A., Cigarroa, R. G., & Hillis, L. D. (1990). Effect of cocaine on coronary artery dimensions in atherosclerotic coronary artery disease: enhanced vasoconstriction at sites of significant stenoses. Journal of the American College of Cardiology, 16, 74-79.

Foltin, R. W., Fischman, M. W., & Levin, F. R. (1995). Cardiovascular effects of cocaine in humans: laboratory studies. Drug & Alcohol Dependence, 37, 193-210.

Foltin, R.W., Fischman, M.W., Nestadt, G., & Stromberge, R.H. (1990). Demonstration of naturalistic methods for cocaine smoking by human volunteers. Drug & Alcohol Dependence, 26, 145-154.

Folts, J. D., & Bonebrake, F. C. (1982). The effects of cigarette smoke and nicotine on platelet thrombus formation in stenosed dog coronary arteries: inhibition with phentolamine. Circulation, 65, 465-470.

Gibson, D. R., & Young, M. (1994). Assessing the reliability and validity of self-reported risk behavior. National Institutes of Drug Abuse Research Monograph, 143, 218-236.

Gitter, M. J., Goldsmith, S. R., Dunbar, D. N., & Sharkey, S. W. (1991). Cocaine and chest pain: clinical features and outcome of patients hospitalized to rule out myocardial infarction. Annals of Internal Medicine, 115, 277-282.

Glagov, S., Weisenberg, E., Zarins, C. K., Stankunavicius, R., & Kolettis, G. J. (1987). Compensatory enlargement of human atherosclerotic coronary arteries. New England Journal of Medicine, 316, 1371-1375.

Hadjimiltiades, S., Covalesky, V., Manno, B. V., Haaz, W. S., & Mintz, G. S. (1988). Coronary arteriographic findings in cocaine abuse-induced myocardial infarction. Catheterization & Cardiovascular Diagnosis, 14, 33-36.

Hammersley, R. (1994). A digest of memory phenomena for addiction research. Addiction, 89, 283-293.

Hannan, D.J., & Adler, A.G. (1990). Crack abuse do you know enough about it? Postgraduate Medicine, 88, 141-147.

Harrison, E. R., Haaga, J., & Richards, T. (1993). Self-reported drug use data: What do they reveal? American Journal of Drug and Alcohol Abuse, 19, 423-441.

Havranek, E. P., Nademanee, K., Grayburn, P. A., & Eichhorn, E. J. (1996). Endothelium-dependent vasorelaxation is impaired in cocaine arteriopathy. Journal of the American College of Cardiology, 28, 1168-1174.

Hollander, J.E. (1995). The management of cocaine-associated myocardial ischemia. The New England Journal of Medicine, 333, 1267-1272.

Hollander, J. E., Hoffman, R. S., Burstein, J. L., Shih, R. D., & Thode, H. C., Jr. (1995). Cocaine-associated myocardial infarction. Mortality and complications. Cocaine-Associated Myocardial Infarction Study Group. Archives of Internal Medicine, 155, 1081-1086.

Hollander, J. E., Hoffman, R. S., Gennis, P., Fairweather, P., DiSano, M. J., Schumb, D. A., Feldman, J. A., Fish, S. S., Dyer, S., Wax, P., & et al. (1994). Prospective multicenter evaluation of cocaine-associated chest pain. Cocaine Associated Chest Pain (COCHPA) Study Group. Academic Emergency Medicine, 1, 330-339.

Howard, G., Manolio, T.A., Burke, G.L., Wolfson, S.K., & O'Leary, D.H. (1997). Does the association of risk factors and atherosclerosis change with age? An analysis of the combined ARIC and CHS cohorts. The Atherosclerosis risk communities (ARIC) and cardiovascular health study (CHS) investigators. Stroke, 28, 1693-701.

Howard, R. E., Hueter, D. C., & Davis, G. J. (1985). Acute myocardial infarction following cocaine abuse in a young woman with normal coronary arteries. Journal of the American Medical Association, 254, 95-96.

Hser, Y.(1993). Data sources: Problems and issues. Special Issue: Prevalence estimation techniques for drug-using populations. Journal of Drug Issues, 23, 217-228.

Isner, J.M., & Chokshi, S.K. (1989). Cocaine and vasospasm. The New England Journal of Medicine, 11, 562-572.

Isner, J. M., Estes, N. A., Thompson, P. D., Costanzo-Nordin, M. R., Subramanian, R., Miller, G., Katsas, G., Sweeney, K., & Sturner, W. Q. (1986). Acute cardiac events temporally related to cocaine abuse. New England Journal of Medicine, 315, 1438-1443.

Isner, J.M., & Saurabh, C.K. (1989). Cocaine and vasospasm. The New England Journal of Medicine, 321, 1604-1606.

Iversen, S.G., Tverdal, A., & Stensvold, I. (1996). Cardiovascular risk factors in norwegian women using oral contraceptives: Results from a cardiovascular health screening 1985-88. Contraception, 53, 337-344.

Jatlow, P. (1988). Cocaine: analysis, pharmacokinetics, and metabolic disposition. Yale Journal of Biology & Medicine, 61, 105-113.

Jennings, L. K., White, M. M., Sauer, C. M., Mauer, A. M., & Robertson, J. T. (1993). Cocaine-induced platelet defects. Stroke, 24, 1352-1359.

Jones, L. F., & Tackett, R. L. (1990). Chronic cocaine treatment enhances the responsiveness of the left anterior descending coronary artery and the femoral artery to vasoactive substances. Journal of Pharmacology & Experimental Therapeutics, 255, 1366-1370.

Kanitz, M. G., Giovannucci, S. J., Jones, J. S., & Mott, M. (1996). Myocardial infarction in young adults: risk factors and clinical features. Journal of Emergency Medicine, 14, 139-145.

Kannel, W. B., & Larson, M. (1993). Long-term epidemiologic prediction of coronary disease. The Framingham experience. Cardiology, 82, 137-152.

Kannel, W. B., McGee, D., & Gordon, T. (1976). A general cardiovascular risk profile: the framingham study. American Journal of Cardiology, 38, 51-56.

Kannel, W. B., Wolf, P. A., Castelli, W. P., & D'Agostino, R. B. (1987). Fibrinogen and risk of cardiovascular disease. The framingham study. Journal of the American Medical Association, 1183-1186.

Karch, S. B., Green, G. S., & Young, S. (1995). Myocardial hypertrophy and coronary artery disease in male cocaine users. Journal of Forensic Sciences, 40, 591-595.

Kazmers, A. E. (Ed.). (1994). Cardiac risk assessment before vascular surgery. Armonk, NY: Futura Publishing Company, Inc.

Keller, K. B., & Lemberg, L. (1991). Myocardial infarction in the young adult. Heart & Lung, 20, 95-97.

Keller, C., Oveland, D., & Hudson, S. (1997). Strategies for weight control success in adults. The Nurse Practitioner, 22 (3), 33-54.

Kloner, R. A., & Hale, S. (1993). Unraveling the complex effects of cocaine on the heart. Circulation, 87, 1046-1047.

Kloner, R. A., Hale, S., Alker, K., & Rezkalla, S. (1992). The effects of acute and chronic cocaine use on the heart. Circulation, 85, 407-419.

Kolodgie, F. D., Farb, A., & Virmani, R. (1995). Pathobiological determinants of cocaine-associated cardiovascular syndromes. Human Pathology, 26, 583-586.

Kolodgie, F. D., Virmani, R., Cornhill, J. F., Herderick, E. E., Malcom, G. T., & Mergner, W. J. (1992). Cocaine: an independent risk factor for aortic sudanophilia. A preliminary report. Atherosclerosis, 97, 53-62.

Kolodgie, F. D., Virmani, R., Cornhill, J. F., Herderick, E. E., & Smialek, J. (1991). Increase in atherosclerosis and adventitial mast cells in cocaine abusers: an alternative mechanism of cocaine-associated coronary vasospasm and thrombosis. Journal of the American College of Cardiology, 17, 1553-1560.

Kossowsky, W. A., & Lyon, A. F. (1984). Cocaine and acute myocardial infarction: A probable connection. Chest, 86, 729-731.

Kossowsky, W. A., Lyon, A. F., & Chou, S. Y. (1989). Acute non-Q wave cocaine-related myocardial infarction. Chest, 96, 617-621.

Lam, D., & Goldschlager, N. (1988). Myocardial injury associated with polysubstance abuse. American Heart Journal, 115, 675-680.

Langner, R. O., Bement, C. L., & Perry, L. E. (1988). Arteriosclerotic toxicity of cocaine. National Institutes of Drug Abuse Research Monograph, 88, 325-336.

Majid, P. A., Patel, B., Kim, H., J.L., Z., & Dellinger, R. P. (1990). An angiographic and histologic study of cocaine-induced chest pain. The American Journal of Cardiology, 65, 812-814.

Max, B. (1991). This and that: the ethnopharmacology of simple phenethylamines, and the question of cocaine and the human heart. Trends in Pharmacological Sciences, 12, 329-333.

McGinnis, J. M., & Foege, W. H. (1993). Actual causes of death in the United States. Journal of the American Medical Association, 270, 2207-2212.

Melchert, R.B., & Welder, A.A. (1995). Cardiovascular effects of androgenic-anabolic steroids. Medicine & Science in Sports and Exercise, 27, 1252-1262.

Mewis, C., Spyridopoulos, I., Kuhlkamp, V., & Seipel, L. (1996). Manifestation of severe coronary heart disease after anabolic drug abuse. Clinical Cardiology, 19, 153-155.

Mittleman, R. E., & Wetli, C. V. (1987). Cocaine and sudden "natural" death. Journal of Forensic Sciences, 32, 11-19.

Minor, R.L., Scott, B.D., Brown, D.D., & Winniford, M.D. (1991). Cocaine-induced myocardial infarction in patients with normal coronary arteries. Annals of Internal Medicine, 115, 797-806.

Moliterno, D. J., Willard, J. E., Lange, R. A., Negus, B. H., Boehrer, J. D., Glamann, D. B., Landau, C., Rossen, J. D., Winniford, M. D., & Hillis, L. D. (1994). Coronary-artery vasoconstriction induced by cocaine, cigarette smoking, or both. New England Journal of Medicine, 330, 454-459.

Moreyra, A. E., Lacy, C. R., Wilson, A. C., Kumar, A., & Kostis, J. B. (1992). Arterial blood nicotine concentration and coronary vasoconstrictive effect of low-nicotine cigarette smoking. American Heart Journal, 124, 392-397.

Nademanee, K. (1992). Cardiovascular effects and toxicities of cocaine. Journal of Addictive Diseases, 11, 71-82.

Nakagomi, A., Celermajer, D. S., Lumley, T., & Freedman, S. B. (1996). Angiographic severity of coronary narrowing is a surrogate marker for the extent of coronary atherosclerosis. American Journal of Cardiology, 78, 516-519.

National Household Survey on Drug Abuse: Population Estimates 1995.US Department of Health and Human Services (DHHS Publication No. (SMA) 96-3095.) (1996).

Newman, W.P., Freedman, D.S., Voors, A.W., Gard, P.D., Srinivasan, S.R., Cresanta, J.L., Williamson, G.D., Webber, L.S., & Berenson, G.S. (1986). Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis: The bogalusa heart study. The New England Journal of Medicine, 314, 138.

Nieminen, M.S., Ramo, M.P., Viitasalo, M., Heikkila, P., Karjalainen, J., Mantysaari, M., & Heikkila, J. (1996). Serious cardiovascular side effects of large doses of anabolic steroids in weight lifters. European Heart Journal, 17, 1576-1583.

NIH Consensus Development Panel. Triglyceride, high-density lipoprotein, and coronary heart disease. Journal of the American Medical Association, 269, 505-510.

Olshaker, J.S. (1994). Cocaine chest pain. Concepts and Controversies in Toxicology, 12, 391-396.

Om, A. (1992). Cardiovascular complications of cocaine. American Journal of the Medical Sciences, 303, 333-339.

Om, A., Warner, M., Sabri, N., Cecich, L., & Vetrovec, G. (1992). Frequency of coronary artery disease and left ventricle dysfunction in cocaine users. American Journal of Cardiology, 69, 1549-1552.

Oster, Z. H., Som, P., Wang, G. J., & Weber, D. A. (1991). Imaging of cocaine-induced global and regional myocardial ischemia. Journal of Nuclear Medicine, 32, 1569-1572.

Packe, G. E., Garton, M. J., & Jennings, K. (1990). Acute myocardial infarction after inhalation of amphetamine. New England Journal of Medicine, 64, 23-24.

Pandey, J.A., & Vlajina, H. (1989). Myocardial infarction in young women with reference to oral contraceptive use. International Journal of Epidemiology, 18, 585-588.

Pasternack, P., Colvin, S., & Baumann, F. (1985). Cocaine-induced angina pectoris and acute myocardial infarction in patients younger than 40 years. American Journal of Cardiology, 55, 847.

PDAY Research Group (1993). The natural history of aortic and coronary atherosclerotic lesions in youth. Findings from the PDAY study. Pathobiological determinants of atherosclerosis in youth (PDAY) research group. Arteriosclerosis & Thrombosis, 13, 1291-1298.

Polit, D.F., & Hungler, B.P. (1995). Nursing research principles and methods (5th ed.). Philadelphia: J.B. Lippincott Company.

Poothullil, J. M. (1993). Obesity, hyperlipidemia and non-insulin-dependent diabetes: a unified theory. Neuroscience & Biobehavioral Reviews, 17(1), 85-9.

Quillen, J. E., Rossen, J. D., Oskarsson, H. J., Minor, R. L., Jr., Lopez, A. G., & Winniford, M. D. (1993). Acute effect of cigarette smoking on the coronary circulation: constriction of epicardial and resistance vessels. Journal of the American College of Cardiology, 22, 642-647.

Ragland, A. S., Ismail, Y., & Arsura, E. L. (1993). Myocardial infarction after amphetamine use. American Heart Journal, 125, 247-249.

Reiber, J. H., & Serruys, P. W. (1991). Quantitative Coronary Angiography. In M. L. Marcus, H. R. Schelbert, D. J. Skorton, G. L. Wolf, & E. Bruanwald (Eds.), Cardiac Imaging. A Companion to Braunwald's Heart Disease . Philadelphia: W.B. Saunders Company.

Roberts, W. C. (1989). Qualitative and quantitative comparison of amounts of narrowing by atherosclerotic plaques in the major epicardial coronary arteries at necropsy in sudden coronary death, transmural acute myocardial infarction, transmural healed myocardial infarction and unstable angina pectoris. American Journal of Cardiology, 64, 324-328.

Roberts, W. C. (1990a). Coronary "lesion," coronary "disease," "single vessel disease, "two-vessel disease": word and phrase misnomers providing false impressions of the extent of coronary atherosclerosis in symptomatic myocardial ischemia. American Journal of Cardiology, 66, 121-123.

Roberts, W. C. (1990b). Sudden cardiac death: a diversity of causes with focus on atherosclerotic coronary artery disease. American Journal of Cardiology, 65, 13-19.

Rod, J. L., & Zucker, R. P. (1986). Acute myocardial infarction shortly after cocaine inhalation. American Journal of Cardiology, 59, 161.

Rollingher, I. M., Belzberg, A. S., & Macdonald, I. L. (1986). Cocaine-induced myocardial infarction. Canadian Medical Association Journal, 135, 45-46.

Romoska, E., & Sacchetti, A.D. (1985). Propranolol-induced hypertension in treatment of cocaine intoxication. Annals of Emergency Medicine, 14, 1112-1113.

Rouse, B. A., Kozel, N. J., & Richards, L. G. (Eds.). (1985). Self-report methods of estimating drug use: Meeting current challenges to validity. Rockville, MD: NIDA (DHHS publication no. (ADM) 85-1402).

Schachne, J. S., Roberts, B. H., & Thompson, P. D. (1984). Coronary artery spasm and myocardial infarction associated with cocaine use. The New England Journal of Medicine, 310, 1665-1666.

Schindler, C. W., Tella, S. R., Erzouki, H. K., & Goldberg, S. R. (1995). Pharmacological mechanisms in cocaine's cardiovascular effects. Drug & Alcohol Dependence, 37, 183-191.

Schrank, K.S. (1993). Cocaine-related emergency department presentations. National Institutes on Drug Abuse Research Monograph, 123, 110-127.

Shen, W. K., Edwards, W. D., Hammill, S. C., Bailey, K. R., Ballard, D. J., & Gersh, B. J. (1995). Sudden unexpected nontraumatic death in 54 young adults: a 30-year population-based study. American Journal of Cardiology, 76, 148-152.

Simpson, R. W., & Edwards, W. D. (1986). Pathogenesis of cocaine-induced ischemic heart disease. Autopsy findings in a 21-year-old man. Archives of Pathology & Laboratory Medicine, 110, 479-484.

Sloan, M. A., & Mattioni, T. A. (1992). Concurrent myocardial and cerebral infarctions after intranasal cocaine use. Stroke, 23, 427-430.

Smith, H. W., Liberman, H. A., Brody, S. L., Battey, L. L., Donohue, B. C., & Morris, D. C. (1987). Acute myocardial infarction temporally related to cocaine use. Annals of Internal Medicine, 107, 13-18.

Sobell, L. C., Kwan, E., & Sobell, M. B. (1995). Reliability of a drug history questionnaire (DHQ). Addictive Behaviors, 20, 233-241.

Sobell, L. C., Sobell, M., & Nirenberg, T. (1988). Behavioral assessment and treatment planning with alcohol and drug abusers: A review with an emphasis on clinical application. Clinical Psychology Review, 8, 19-54.

Sobell, L. C., Toneatto, T., & Sobell, M. B. (1994). Behavioral assessment and treatment planning for alcohol, tobacco, and other drug problems: Current status with an emphasis on clinical applications. Behavior Therapy, 25, 533-580.

Solberg, L.A., & Strong, J.P. (1983). Risk factors and atherosclerotic lesions. A review of autopsy studies. Arteriosclerosis, 3, 187.

Stenberg, R. G., Winniford, M. D., Hillis, L. D., Dowling, G. P., & Buja, L. M. (1989). Simultaneous acute thrombosis of two major coronary arteries following intravenous cocaine use. Archives of Pathology & Laboratory Medicine, 113, 521-524.

Stewart, D. J., Inaba, T., Lucassen, M., & Kalow, W. (1979). Cocaine metabolism: cocaine and norcocaine hydrolysis by liver and serum esterases. Clinical Pharmacology & Therapeutics, 25, 464-468.

Substance Abuse and Mental Health Services Administration. (1995). Drug-related emergency room visits up nationally. [on-line], Available: www.SAMHSA.GOV/OASFTP.HTM.

Sztajzel, J., Karpuz, H., & Rutishauser, W. (1994). Heroin abuse and myocardial infarction. International Journal of Cardiology, 47, 180-182.

Tardiff, K., Gross, E., Wu, J., Stajic, M., & Millman, R. (1989). Analysis of cocaine-positive fatalities. Journal of Forensic Sciences, 34, 53-63.

Toda, N. (1982). Different responsiveness of a variety of isolated dog arteries to prostaglandin D2. Prostaglandins, 23, 99-112.

Tseng, Y.T., Rockhold, R.W., Hoskins, B., & Ho, I.K. (1994). Cardiovascular toxicities of nandrolone and cocaine in spontaneously hypertensive rats. Fundamentals of Applied Toxicology, 22, 113-121.

Uhl, G. S., & Farrell, P. W. (1983). Myocardial infarction in young adults: risk factors and natural history. American Heart Journal, 105, 548-553.

Valladares, B. K., & Lemberg, L. (1987). The Miami Vices in the CCU. Part I. Cardiac manifestations of cocaine use. Heart & Lung, 16, 456-458.

Virmani, R., Robinowitz, M., Smialek, J. E., & Smyth, D. F. (1988). Cardiovascular effects of cocaine: an autopsy study of 40 patients. American Heart Journal, 115, 1068-1076.

Vos, J., de Feyter, P. J., Simoons, M. L., Tijssen, J. G., & Deckers, J. W. (1993). Retardation and arrest of progression or regression of coronary artery disease: a review. Progress in Cardiovascular Diseases, 35(6), 435-54

Warner, E. A. (1993). Cocaine abuse. Annals of Internal Medicine, 119, 226-235.

Weiss, R. J. (1986). Recurrent myocardial infarction caused by cocaine abuse. American Heart Journal, 111, 793.

Welder, A.A., Grammas, P., & Melchert, R.B. (1993). Cellular mechanisms of cocaine cardiotoxicity. Toxicology Letter, 69, 227-238.

Whebie, C. S., Vidaillet, H. J., & Navetta, F. I. (1987). Acute myocardial infarction associated with initial cocaine use. Southern Medical Journal, 80, 933-934.

Wiener, R. S., Lockhart, J. T., & Schwartz, R. G. (1986). Dilated cardiomyopathy and cocaine abuse. The American Journal of Medicine, 81, 699-701.

Whitkin, J.M., & Katz, J.L. (1993). Preclinical assessment of cocaine toxicity: Mechanisms and pharmacotherapy. National Institutes on Drug Abuse Research Monograph, 123, 44-69.

Yang, S. S., Bentivoglio, L. G., Maranhao, V., & Goldberg, H. (1988). From cardiac catheterization data to hemodynamic parameters. (3rd ed.). Philadelphia, PA: F.A. Davis Company.

Zimmerman, F. H., Cameron, A., Fisher, L. D., & Ng, G. (1995). Myocardial infarction in young adults: angiographic characterization, risk factors and prognosis (Coronary Artery Surgery Study Registry). Journal of the American College of Cardiology, 26, 654-661.

Zimmerman, F. H., Gustafson, G. M., & Kemp, H. G. (1987). Recurrent myocardial infarction associated with cocaine abuse in a young man with normal coronary arteries: evidence for coronary artery spasm culminating in thrombosis. Journal of the American College of Cardiology, 9, 964-968.

Zimmerman, J. L., Dellinger, R. P., & Majid, P. A. (1991). Cocaine-associated chest pain. Annals of Emergency Medicine, 20, 611-615.

Appendix A

Evaluation of Coronary Artery Stenosis in Cocaine-Related Cardiovascular Events in Published Research Reports

Evaluation of Coronary Artery Stenosis in Cocaine-Related Cardiovascular Events in Published Research Reports

Authors	# of PTS.	Age	#Examined	Methods	25%-70%S.	>70% S.
Kossowsky & Lyon, 1984	6	35.8(±6.7)	4	angiogram	0	4
Karch et.al, 1995	32[1]	34 (±9)	32	autopsy	not reported	9[2]
	26[3]	36 (±7)	26	autopsy	not reported	11[4]
Coleman et.al., 1982	1	38	0	not reported	0	0
Zimmerman et al., 1991	48	29.3 (±2.3)	1	angiogram	1	0
Sloan & Mattioni, 1992	1	37	0	N/A	0	0
Wiener et al., 1986	2	35 (±9.8)	1	angiogram	0	0
Cooke & Dowling 1988	1	27	1	autopsy	0	1
Amin et al., 1990	70	34 (±9)	9	angiogram	0	4
Gitter et al., 1991	101	31.5[5]	1	angiogram	0	0
Rollingher et al., 1988	1	24	1	angiogram	0	0
Schachne et al., 1984	1	21	1	angiogram	0	0
Cregler & Mark, 1985	1	32	1	angiogram	0	0
Howard et al., 1985	1	28	1	angiogram	0	0
Pasternack et al, 1985	3	36.6 (±1.5)	3	angiogram	0	3

[1] Cocaine + trauma deaths.
[2] Did not report actual amount of coronary stenosis.
[3] Cocaine overdose deaths.
[4] Did not report actual amount of coronary stenosis.
[5] SD or individual ages not reported, only age range.

Evaluation of Coronary Artery Stenosis in Cocaine-Related Cardiovascular Events in Published Research Reports (continued).

Authors	#of Pts	Age	#Examined	Methods	25%-70%S.	>70%S.
Isner et al., 1986	7	28.4 (±6.5)	3	angiogram	0	0
			2	autopsy	0	1
Rod & Zucker, 1986	4	26.2 (±4.3)	4	angiogram	0	3
Barth et al., 1986	1	45	1	autopsy	0	1
Lam & Goldschlager, 1988	11	34.6 (±6.3)	5	angiogram	1	0
Ascher et al., 1987	1	47	1	angiogram	1	
Zimmerman et al., 1987	1	29	1	angiogram	0	0
Wehbie et al., 1987	1	33	1	angiogram	0	1
Smith et al., 1987	9	32 (±4.6)	9	angiogram	1	3
Weiss, 1986	1	19	0	not reported	not reported	not reported
Simpson & Edwards, 1986	1	21	1	autopsy	0	1
Stenberg et al., 1989	1	38	1	autopsy	0	1
Kossowsky et al., 1989	19	31 (±2)	5	angiogram	0	1
Virmani et al., 1988	40	29 (±6)	40	autopsy	[6]	2
Hadjimiltiades et al., 1988	1	31	1	angiogram	0	0
Kolodgie et al., 1991	12	28 (±5.2)	12	autopsy	6	6
Dressler et al., 1990	22	32.2 (±7.9)	22	autopsy	6	7

[6] Did not report any coronary stenosis less than "severe."

Evaluation of Coronary Artery Stenosis in Cocaine-Related Cardiovascular Events in Published Research Reports (continued).

Authors S.	#of Pts.	Age	#Examined	Methods	25%-70%S.	>70%
Hollander et al., 1994	246	33[7]	0	not reported	not reported	not reported
Hollander et al., 1995	130	38 (±10)	52	angiogram	35[8]	not reported
Om et al., 1992	33	37[9]	33	angiogram	7	13
Majid et al., 1989	11	27[10]	11	angiogram	0	0
Shen et al., 1995	10	31.5 (±7.1)	10	autopsy	[11]	10[12]
Mittleman & Wetli, 1986	19	46 (±13.1)	19	autopsy	1	15
Valladares & Lemberg, 1987	2	32 (±14.8)	1	autopsy	0	0
			1	angiogram	0	0
Keller & Lemberg, 1991	2	31.5 (±3.5)	0	not reported	not reported	not reported
Kolodgie et al., 1992	20	25 (±4)	20	autopsy	[13]	20[14]
Derlet & Albertson, 1989	21	not reported	not reported	not reported	not reported	not reported
Eichhorn et al., 1992	24	27 (±6)	24	autopsy	24	not reported
Tardiff et al., 1989	45	[15]	45	autopsy	0	45
Brody et al., 1990	93	29.5[16]	NR	NR	NR	NR
			150	angiogram	90 +	162
Totals=	1083		407 257	autopsy	Total	stenosis=252

[7] SD or individual ages not reported, only age range.
[8] Reported in amounts >50% coronary stenosis
[9] SD or individual ages not reported, only age range.
[10] SD or individual ages not reported, only age range.
[11] Did not report actual amount of coronary stenosis.
[12] Did not report actual amount of coronary stenosis.
[13] Did not report actual amount of coronary stenosis.
[14] Did not report actual amount of coronary stenosis.
[15] SD or individual ages not reported. From a group of 935 persons who died with cocaine or cocaine metabolites in their body. Ages ranged from 0 to 65+ years. Majority (70%) of the group age was 25 to 44 years. Death from occlusive CAD was defined as >75% coronary artery stenosis.
[16] SD or individual ages not reported, only age range of entire group of cocaine + persons evaluated.

Appendix B

Summary of Traditional Cardiac Disease Risk Factors

Among Cocaine Users With CAD in Published Research Reports.

Summary of Traditional Cardiac Disease Risk Factors Among Cocaine Users With CAD in Published Research Reports.

AUTHOR	# PTS	Diabetes	Hypertension	↑ cholesterol	+family hx	Other
Kossowsky & Lyon, 1984	6	0	0	0	0	0
Karch et al., 1995	58	NR	NR	NR	NR	NR
Coleman et.al., 1982	1	0	0	0	0	1="mildly overweight"
Zimmerman et al., 1991	48	0	3	0	0	1=W.P.W.
Sloan & Mattioni, 1992	1	0	0	0	0	0
Wiener et al., 1986	2	0	0	0	0	0
Cooke & Dowling 1988	1	NR	NR	NR	NR	NR
Amin et al., 1990	70	2	10	0	1	0
Gitter et al., 1991	101	NR see note	NR see note	NR see note	NR see note	NR see note[17]
Rollingher et al., 1988	1	0	0	0	0	0
Schachne et al., 1984	1	0	0	0	0	0
Cregler & Mark, 1985	1	0	0	0	0	0
Howard et al., 1985	1	0	0	0	0	0
Pasternack et al, 1985	3	0	0	0	0	0
Isner et al., 1986	7	1	0	1	1	1=obese
Rod & Zucker, 1986	4	0	0	0	0	0

Note: NR=not reported

[17] Report that 74% of this group had two or more cardiac risk factors for atherosclerosis. Did not specifically list risk factors, or describe further.

Summary of Traditional Cardiac Disease Risk Factors Among Cocaine Users With CAD in Published Research Reports (continued).

AUTHOR	# PTS	Diabetes	Hypertension	↑ cholesterol	+family hx	Other
Barth et al., 1986	1	0	0	0	0	0
Lam & Goldschlager, 1988	11	0	2	0	2	0
Ascher et al., 1987	1	0	0	0	0	0
Zimmerman et al., 1987	1	0	0	0	0	0
Wehbie et al., 1987	1	0	0	0	0	0
Smith et al., 1987	9	0	1	0	1	0
Weiss, 1986	1	0	0	0	1[18]	0
Simpson & Edwards, 1986	1	0	0	0	0	0
Stenberg et al., 1989	1	0	0	0	0	0
Kossowsky et al., 1989	19	0	0	0	0	0
Virmaini et al., 1988	40	NR	NR	NR	NR	NR
Hadjimiltiades et al., 1988	1	0	0	0	0	0
Kolodgie et al., 1991	12	NR	NR	NR	NR	NR
Dressler et al., 1990	22	0	5	0	0	0
Hollander et al., 1994	246	27	114	29	89	0
Om et al., 1992	33	1	5	0	9	2=obese

[18] Mother was a "heavy" cigarette smoker who had an MI in her "early" 40's

Summary of Traditional Cardiac Disease Risk Factors Among Cocaine Users With CAD in Published Research Reports (continued).

AUTHOR	# PTS	Diabetes	Hypertension	↑ cholesterol	+family hx	Other
Majid et al., 1989	11	0	0	0	0	0
Shen et al., 1995	10	NR	NR	NR	NR	NR
Mittleman & Wetli, 1986	19	NR	NR	NR	NR	NR
Valladares & Lemberg, 1991	2	0	0	0	0	0
Keller & Lemberg, 1991	2	0	0	0	0	0
Kolodgie et al., 1992	20	NR	NR	NR	NR	NR
Derlet & Albertson, 1989	21	NR	NR	NR	NR	NR
Eichorn et al., 1992	24	NR	NR	NR	NR	NR
Tardiff et al., 1989	45	NR	NR	NR	NR	NR
Brody et al., 1990	93	NR	NR	NR	NR	NR
Hollander et al., 1995	130	9	45	21	52	47=prior chest pain. 18=prior M.I.
Totals n=	1083	40 (3%)	182 (16%)	51 (4%)	155 (14%)	

Appendix C

Summary of Patterns of Cocaine Use and Poly-Substance Use Among Cocaine Users With CAD in Published Reports.

Summary of Patterns of Cocaine Use and Poly-Substance Use Among Cocaine Users With CAD in Published Research Reports.

Authors	# of pts.	Route	Years of Use	Amount	Other drugs	Tobacco use
Kossowsky & Lyon, 1984	6	4 IV 2 N	NR[19]	NR	4=heroin 2=ETOH	6=1pp/day years NR
Karch et.al, 1995	58	NR	NR	NR	NR	NR
Coleman et.al., 1982	1	1 N	NR	.5 gm[20]	NR	yes. 40 pack year
Zimmerman et al., 1991	48	29 S 16 IV 3 S & IV 1 UNK	28=5 (±) 4.8yr	NR	16[21] 5 amphetamine 3 opiates	NR
Sloan & Mattioni, 1992	1	1 N	3 years	NR	+hx heroin and amphetamines . Occasional ETOH	NR
Wiener et al., 1986	2	1 N 1 IV	1=3yrs 1=2 yrs daily use	1=1gm per occasion 1=1gm per occasion	1=ETOH & heroin. 1=marijuana	1=20 pack year hx. 1=1 pp/day X 10 yrs.
Cooke & Dowling 1988	1	NR	NR	NR	NR	NR
Amin et al., 1990	70	25 S 24 N 8 IV	NR	NR	NR	=18. pp/day or years NR
Gitter et al., 1991	101	60 S 10 N 30 IV	NR	13 pts= <1gm 63 pts= 1-2gm 24 pts.= >2gm	11=opiates 4=benzodia-zapenes	NR
Rollingher et al., 1988	1	1 IV	first time	NR	0	yes. 10 cigarettes/ day/ years NR
Schachne et al., 1984	1	1 N	sporadic	1=.25 gm	0	0
Cregler & Mark, 1985	1	NR	sporadic	NR	1 heroin	NR

Note: NR=not reported

[19] Two pts. reported as chronic users.
[20] Acute use.
[21] Only report that other drugs or alcohol were detected.

Summary of Patterns of Cocaine Use and Poly-Substance Use Among Cocaine Users With CAD in Published Research Reports (continued).

Authors	# of pts.	Route	Years of Use	Amount	Other drugs	Tobacco use
Howard et al., 1985	1	1 N[22]	8[23]	1=1 gm/day	0	0
Pasternack et al, 1985	3	NR	sporadic	NR	NR	3=2 packs/day for at least 15 years
Isner et al., 1986	7	6 N 1 S	NR[24]	1=.5gm[25] 1=1 gm	[26]	1=1.5 pp/day years NR
Rod & Zucker, 1986	4	4 N	NR	NR	NR	NR
Barth et al., 1986	1	NR	NR	NR	NR	NR
Lam & Goldschlager, 1988	11	4 IV 4 S 3 combination	NR[27]	NR	1=Ritalin 4=IV heroin 1=marijuana 2=ampheta-mines.	NR
Ascher et al., 1987	1	1 N	NR	NR	1=ETOH, marijuana	yes pp/day/year NR
Zimmerman et al., 1987	1	NR	NR	NR	NR	NR
Wehbie et al., 1987	1	1 N	NR	NR[28]	1=Marijuana & amphetamines	yes. pp/day or years NR
Smith et al., 1987	9	5 N 3 IV 1 S	NR	NR[29]	NR	8 pp/day or years NR
Weiss, 1986	1	NR	NR[30]	NR	NR	yes. pp/day or years NR

Note: NR=Not reported. IV=Intravenous. S=Smoked. N=Nasal

[22] Reported as "inhalation"
[23] Report that patient began using in early 20's.
[24] Two pts. described as frequent users
[25] Acute use
[26] 1 pt tested positive for propoxyphene and norpropoxyphene amide.
[27] Reported to be long-standing, habitual users. Abuse ranged from 1 to >9 years.
[28] Reported expermintational use of 5-6 "lines".
[29] Reported 4 as habitual users, 5 as not being habitual users
[30] Reported to be a "frequent" user.

Summary of Patterns of Cocaine Use and Poly-Substance Use Among Cocaine Users With CAD in Published Research Reports (continued).

Authors	# of pts.	Route	Years of Use	Amount	Other drugs	Tobacco use
Simpson & Edwards, 1986	1	1 IV	1 to 2 times per month	NR	1=ETOH & marijuana	yes. pp/day or years NR
Stenberg et al., 1989	1	1 IV	NR	NR	NR	NR
Kossowsky et al., 1989	19	4 combination 8 S 3 IV 4 N	NR	NR	2=marijuana 1=ETOH 3=heroin	18 pp/day or years NR
Virmaini et al., 1988	40	NR	NR	NR	NR	NR
Hadjimiltiades et al., 1988	1	NR	NR	NR	NR	yes. pp/d & years NR
Kolodgie et al., 1991	12	2 IV 4 N 2 S	NR[31]	NR	NR	NR
Dressler et al., 1990	22	4 N 2 IV 3 S	NR	NR	NR	NR
Hollander et al., 1994	246	179 S 67 N 26 IV 23 multiple	mean years 5[32] 10 times/mo[33]	NR	NR	205 yes. Median of 12 pack/years[34]
Om et al., 1992	33	15 IV. 9 S. 6 N 3 UKN	NR	NR	33 ETOH	24 smokers pp/d & years NR
Majid et al., 1989	11	NR	3 years[35]	NR	NR	NR
Shen et al., 1995	10	NR	NR	NR	NR	NR

Note: NR=Not reported. IV=Intravenous. S=Smoked. N=Nasal

[31] 10 persons reported as "long term" abusers, not further defined.
[32] IQ25–75, 2-7 years.
[33] IQ25–75, 4-30 times/month.
[34] IQ25–75, 5-20 pack years.
[35] Reported as "average" length of use.

Summary of Patterns of Cocaine Use and Poly-Substance Use Among Cocaine Users With CAD in Published Research Reports (continued).

Authors	# of pts.	Route	Years of Use	Amount	Other drugs	Tobacco use
Mittleman & Wetli, 1986	19	NR	NR	NR	5 ETOH 1 diazepam 1 methadone 2 lidocaine 1 morphine 1 qualudes	NR
Valladares & Lemberg, 1991	2	1 N	NR	1 gram[36]	1 amphetamine	0
Keller & Lemberg, 1991	2	1 N	NR	1 gram[37]	NR	2 pp/day. Years NR.
Kolodgie et al., 1992	20	NR	NR	NR	NR	NR
Derlet & Albertson, 1989	21[38]	NR	NR	NR	NR	NR
Eichorn et al., 1992	24	NR	NR	NR	NR	NR
Tardiff et al., 1989	45	NR	NR	NR	NR	NR
Brody et al., 1990	93	NR	NR	NR	NR[39]	NR
Hollander et al., 1995	130	67 S 18 IV 36 N	NR	NR	NR	124 pp/day & total years NR
		IV=135 (12%) N=181 (17%) S=388 (36%) mixed=34 (3%)				smokers=417 (39%) non-sm.=119 (11%)
Total n=	1083	known=738 (68%) unknown=345 (32%)	known=283 (26%) unknown=800 (74%)	known=109 (10%) unknown=974 (90%)	known=112 (10%) unknown=968 (90%)	known=536 (50%) unknown=547 (50%)

Note: NR=Not reported. IV=Intravenous. S=Smoked. N=Nasal

[36] Actue use, history not reported.
[37] Acute use, history not reported.
[38] Unable to determine actual demographics of this cohort of 21 of 137 pts who sought care secondarily to complaints of chest pain. Of the entire cohort 47% used multiple drugs of abuse, including ETOH.
[39] Unable to determine actual demographics of this cohort of 93 of 233 pts who sought care secondarily to complaints of chest pain. Of the entire cohort 48.5% used multiple drugs of abuse, including ETOH.

Appendix D

Survey Questionnaire

Survey Questionnaire

Thank you for completing this questionnaire about your heart disease risk factors. I want to assure you that any information you share with me will be kept confidential. Please do not write your name down on this paper. I will record only your answers to these questions. Neither your name nor your identity will be used for publication or publicity purposes. No one else will be able to find out who you are or what your answers to these questions are, including your doctor or any law enforcement personnel.

This questionnaire should take about 20 to 30 minutes to complete. It contains questions about your personal background, your heart disease risk factors and asks if you have used cocaine in the past. You can refuse to answer a question if you wish by simply marking no comment.

1. What is your gender? (circle answer)
    1. Male
    2. Female
    3. No comment
2. What is your present age? (fill in blank)
    1._____
    2. No comment
3. Which of the following best describes your racial or ethnic identification? (circle answer)
    1. White (non-Hispanic)
    2. Black (African-American)
    3. Native American or Indian
    4. Asian, Pacific Islander
    5. Hispanic
    6. Other race_____
    7. No comment

4. What is your present marital status? (circle answer)
    1. Never married
    2. Married or living with a partner
    3. Divorced
    4. Widowed
    5. No comment

5. Which best describes your education level? (circle answer)
    1. Some high school
    2. Completed high school or obtained GED
    3. Some college
    4. College graduate
    5. Graduate degree
    6. No comment

7. In general, what do you consider your income level to be? (circle answer)
    1. Low
    2. Middle
    3. High
    4. No comment

There are many known risk factors for the development of coronary heart disease. The following questions are related to these known risk factors.

8. Have you ever been a cigarette smoker? (circle answer)
    1. yes (please go to 8a)
    2. no (please go to question 9)
    3. No comment

8a. Do you currently smoke cigarettes? (circle answer)

1. yes (please go to 8c)

2. no (please go to 8b)

3. No comment

8b. At what age did you quit? (fill in blank)

1._____ (please go to 8c)

2. No comment

8c. How old were you when you first started smoking? (fill in blank)

1._____(please go to 8d)

2. No comment

8d. About how many cigarettes do you, or did you in the past, smoke every

day? (fill in blank)

1._____

2. No comment

9. For women only: Have you ever used, or do you currently use oral contraceptives (birth control pills)?

1. yes (please go to 9a)

2. no

3. No comment

9a. How old were you when you started using them? (fill in blank)

1._____(please go to 9b)

2. No comment

9b. For how many total years have you been using, (or did you use) them? (fill in blank)

1._____

2. No comment

10. Has your mother, father or any of your brothers or sisters ever had a heart attack, or ever been told they have a heart problem known as angina, or angina pectoris? (circle answer)

1. yes (please go to 10a)
2. no (please go to question 11)
3. don't know (please go to question 11)
4. No comment

10a. What was their relationship to you? (circle answer and go to 10b and 10c)

1. Birth father
2. Birth mother
3. Sister
4. Brother
5. None of the above
6. No comment

10b. How old were they when they were first told they had a heart attack, or heart problems? (circle answer)

1. 55 years of age or younger
2. Older than 55 years of age
3. Don't know age
4. No comment

10c. Did your relative have any of the following medical problems? (Circle all that apply)

1. Diabetes
2. High blood pressure
3. High cholesterol
4. Smoked cigarettes
5. Don't know
6. No comment

11. Before you were diagnosed with heart disease, did you exercise 3 times a week for at least 20 minutes at a time? (circle answer)

1. yes (please go to 11b)
2. no (please go to question 12)
3. No comment

11b. If yes: For how many total months or years did you exercise before you were diagnosed with heart disease?

(fill in months or years)

_____Months

_____Years

Many people have experimented with illegal drugs, including cocaine, at least once in their lifetime. Some of these questions may seem sensitive to you, but your honest answers are important to me in order to study the possible relationship between cocaine use and the development of early heart disease.

12. Have you every used cocaine, including crack cocaine, more than 3 times in your lifetime? (circle answer)

1. yes
2. no
3. No comment

(If no or no comment , thank you and please proceed to closing statement)

13. At what age did you first use cocaine? (fill in blank)

1._____

2. No comment

The following questions are related to your past cocaine use. Please take your time and try to answer these questions as accurately as you can.

14. How often did you use cocaine? (circle answer or fill in blank)

1. Daily (please go to 14a)
2. Weekly (please go to 14b)
3. Monthly (please go to 14c)
4. Less than 1 time per month; please fill in frequency_____
5. No comment

14a. If daily, how many times per day? (circle answer)

1. About once a day
2. About 2 to 3 times a day
3. About 4 or more times a day
4. No comment

14b. If weekly, how many times per week?

1. About once a week
2. About 2 to 6 times per week
3. No comment

14c. If monthly, how many times per month?

1. About 1 time per month
2. About 2 to 3 times per month
3. About 4 or more times per month
4. No comment

15. How old were you when you last used cocaine? (fill in blank)

1._____
2. No comment

16. Has there ever been a period of time greater than 1 year when you stopped using cocaine and then started using cocaine again? (circle answer)

    1. yes (please go to 16a)
    2. no
    3. No comment

    16a. About how long did you <u>not use</u> cocaine for? (fill in blank)

        1._____
        2. No comment

17. What was the usual way in which you used cocaine?

    (Circle all that apply):

    1. Smoked (including free-base)
    2. Injected into a vein (shot-up)
    3. Inhaled through nose (snorted)
    4. Swallowed
    5. Other (please specify)_____
    6. No comment

18. About how much cocaine did you usually use in a 24 hour period? (fill in blank or blanks)

    18a. _____Grams

    18b_____Rocks

    18c. No comment

Thank you for your participation in this study. Your answers to these questions will help others, like yourself, who have developed heart disease at an early age. Please return this in the mail in the enclosed envelope. If you have any questions, please call Teri Beasley at (503) 604-6322. Thank you again.

Appendix E

Medical Records Data Collection Tool

Medical Records Data Collection Tool

Subject number_____

DOB_____

Height_____

Weight_____

Total cholesterol >300, triglycerides >500/medical diagnosis/meds? A. yes B. no

Previous MI A. yes B. no

HTN/diagnosis present on chart if on meds? A. yes B. no

Diabetes diagnosis or meds? A. yes B. no

Coronary angiogram. Date_____

Total number of stenosed main coronary arteries_____

Percent stenosis. Record only greatest amount noted in each of the following:

LM_____B. LAD_____C. DIAG_____

RCA_____E. PDA_____F. CIRC_____

OM 1-4_____

Appendix F

Letter From Cardiologist to Subjects.

Dear (00) ,

I am aware of a research study in which you may be interested in participating. As you may know, there are many risk factors that appear to increase the chances of developing heart disease. You may be aware of some of the more common heart disease risk factors such as high blood pressure, diabetes, high cholesterol, cigarette smoking, family history, physical inactivity, and being very overweight. Sometimes people develop heart disease even though they do not have any of these common risk factors. In recent years many researchers have discovered that the past use of cocaine may be a risk factor for the development of heart disease.

One of the main purposes of this study is to determine how many people between the ages of 18 to 44 who currently have heart disease may have, or may not have used cocaine at some point in their life. This study will also look at other common heart disease risk factors as well.

You may or may not have used cocaine at some point in your life. **You are being invited to participate in this study by the investigators because you are 18 to 44 years of age and have heart disease. You are <u>not</u> being invited to participate in this study because of any possible past use or non-use of cocaine at some point in your life.** Teri Beasley, the Principal Investigator of the study, is interested in your answers to these questions regardless of any possible past cocaine use.

Participation in this study is voluntary and confidential. I will never know whether or not you have decided to participate in this study. I will not be made aware of your individual answers to any questions.

This study is being conducted by Teri Beasley, a Registered Nurse who is completing a Masters Degree at the Oregon Health Sciences University. Enclosed is more information about the study. If you are interested in participating please return the enclosed questionnaire in the self-addressed, stamped envelope. If you have any questions about the study please contact Teri Beasley at (503) 604-6322. Thank you.

Sincerely,

MD (00)

Appendix G

Research Subject Information Letter

Study Title: Prevalence and Patterns of Cocaine Use in Premature Coronary Atherosclerosis

Investigator: Teri Beasley, BSN, RN, CCRN

Oregon Health Sciences University, School of Nursing

3181 S.W. Sam Jackson Park Road

Portland, Oregon 97201-3098

(503) 604-6322

What is the study about? The purpose of this study is to examine factors associated with heart disease in people ages 18 to 44 who may, or may not have used cocaine at some point in their life.

Who is conducting the study? Teri Beasley is a Registered Nurse completing a Master of Science degree to become a Family Nurse Practitioner at Oregon Health Sciences University.

Why am I being asked to participate? You are being invited to participate in this research study because you are between the ages of 18 to 44 years and have developed heart disease. You may or may not have used cocaine at some time in your life. There are many reasons why people develop heart disease. Cocaine use, for some people, may be one possible reason.

How do I participate? Just complete and return the enclosed questionnaire in the self addressed, stamped envelope. If you have any questions please call Teri Beasley at the number listed above.

May I participate if I have never used cocaine? Yes. **If you have never used cocaine your answers to these questions will still be very important**. Teri is interested in gathering information both from people who have, and those who have never used cocaine. Completion of the questionnaire should take you less than one-half hour.

Can I get into trouble with the law if I tell you that I have used cocaine? No. Your answers to the questions on the questionnaire will be kept absolutely confidential! No one will contact any law enforcement personnel, or anyone else for that matter, about any past or present drug use you may reveal.

Will anyone ever be able to find out my answers to these questions? No. Your answers to these questions will be kept confidential. Your name will not appear in any publication or be used for any publicity purposes. Your name will not be recorded on the questionnaire. Your answers will be identified by a code number rather than by your name. No record will link your name to your answers on the questionnaire. No one, not even your doctor, will know that you participated in this study.

Are you going to look at my medical record? If you participate, by returning your questionnaire, Teri will collect only the following information related to your heart disease from your medical record: Height, weight, cholesterol, blood pressure, diabetes status, and a description of which coronary arteries in your heart were narrowed. No record will link your name to the information collected from your medical records.

How will the information I provide be of help? The information you give will help to answer some very puzzling questions about the development of heart disease in young persons.

Appendix H

First Follow-up Letter to all Subjects

Teri Beasley, BSN, RN, CCRN

Oregon Health Sciences University

School of Nursing

3181 S.W. Sam Jackson Park Road

Portland, Oregon 97201-3098

Dear (00) ,

About one week ago you were sent information inviting you to participate in a research study about the risk factors associated with heart disease in people ages 18 to 44 who may, or may not have used cocaine at some point in their life.

If you have already returned the questionnaire to participate in this research study please accept my sincere thanks. If you would like to participate, but have not yet responded, please take a moment now to complete the questionnaire and return it in the mail to me. If you have misplaced your questionnaire, or have any questions about the study, please contact me at (503) 604-6322.

Sincerely,

Teri Beasley, BSN, RN, CCRN

Principal Investigator

Appendix I

Second Follow-up Letter to All Nonresponders

Teri Beasley, BSN, RN, CCRN
Oregon Health Sciences University
3181 S.W. Sam Jackson Park Road
School of Nursing
Portland, Oregon 97201

Dear (00)

About three weeks ago you received information about a research project I am conducting titled "Prevalence and Patterns of Cocaine Use in Premature Coronary Atherosclerosis." As of today I have not received your completed questionnaire.

I have undertaken this research project as part of the requirements for completing my Masters of Science degree as a Family Nurse Practitioner because I am very interested in the risk factors associated with the development of coronary heart disease in people ages 18 to 44. One possible risk factor for the premature development of coronary heart disease may be the past use of cocaine.

In order for the results of this study to be truly representative of the heart disease risk factors among persons 18 to 44 years of age, it is important that I receive your answers to these questions. If you have never used cocaine your answers to these questions are essential to the success of this study. Your answers to these questions will remain strictly confidential.

In the event that you have misplaced your questionnaire, I have enclosed a replacement. If you have any questions about the study, please do not hesitate to contact me at (503) 604-6322.

Your participation in this research study is greatly appreciated. Thank you.

Sincerely,

Teri Beasley, BSN, RN, CCRN

Appendix J

Final Follow-up to all

Nonresponders

Teri Beasley, BSN, RN, CCRN
Oregon Health Sciences University
School of Nursing
3181 S.W. Sam Jackson Park Road
Portland, Oregon 97201

Dear (00)

I am writing to you about the research study I am conducting titled "Prevalence and Patterns of Cocaine Use in Premature Coronary Atherosclerosis." I have not yet received your completed questionnaire.

The large number of questionnaires I have received is very encouraging. But, whether or not I will be able to accurately describe the heart disease risk factors among persons ages 18 to 44 depends very much upon you and others who have not yet responded.

This research study is important in that it may point to why young persons develop coronary heart disease at a young age. Your answers to these questions are essential to the success of this research study, regardless if you have ever used cocaine or not.

In case you have misplaced your questionnaire, I have enclosed a replacement. I remind you again, that your answers to these questions will remain confidential. No record will be kept that will link your name with your answers. Not even your doctor will know that you have participated in this research project.

If I can answer any questions or concerns you may have about this study, please call me at (503) 604-6322.

Your participation in this study will be appreciated greatly.

Sincerely,

Teri Beasley, BSN, RN, CCRN

Appendix K

Formula of the Normal Approximation

From Binomial Distribution.

Normal Approximation From Binomial Distribution

p = proportion

$\Rightarrow$ varience = p (1-p)

standard error = $\sqrt{\frac{p\,(1-p)}{n}}$

90% confidence interval: $p \pm (z.90)\ (1.645)\sqrt{\frac{(s.e.)\ p(1-p)}{n}}$

Note: From Johnathan Fields, Oregon Health Sciences University, Office of Research, Development and Utilization, personal communication, July 1, 1997.

Appendix L

Physician Letter and Agreement to Assist

Dear Dr. (00),

I am writing to request your assistance in contacting some of your patients for possible inclusion in a research study that I will be conducting. I am a graduate nursing student at the Oregon Health Sciences University completing a Master of Science degree as a Family Nurse Practitioner.

Some of the factors that contribute to premature coronary atherosclerosis are not well understood. Cocaine use has been associated with the development of premature coronary atherosclerosis by many researchers. The title of my study is Prevalence and Patterns of Cocaine Use in Premature Coronary Atherosclerosis. I plan to determine the prevalence of past cocaine use, the past patterns of cocaine use, and other CAD risk factors among a group 325 persons 18 to 44 years of age who have developed atherosclerotic coronary artery disease. I have enclosed a one-page summary of the study for your consideration. The specific information I would be asking of your patients is listed under Data Collection.

This research project has been approved by the Institutional Review Boards (IRB) of (00). I will be sending potential research subjects information about the study in the mail as well as a letter from you to your patients that has been approved by the IRB. Enclosed is a copy of what I would be sending your patients, as well as the IRB approved subject letter from you to sign if you agree to allow your patients to participate in this study. I will be responsible for the letter preparation and the mailing of information to all potential research subjects

I shall telephone your office within the next week to see what questions you may have and to hear your decision. If it would be more convenient, you could leave me a message with a contact person at your office regarding your decision.

Please feel free to contact me at (503) 297-9496 or 604-6322 with any additional questions or concerns you may have regarding this research project, or if you would like

to have a copy of the research proposal. At your convenience, I am available to discuss this study with you in person or on the telephone if you would prefer. Thank you.

Sincerely,
Teri Beasley, BSN, RN, CCRN
Principal Investigator

I Dr (00) agree that Teri Beasley may contact the patients I have identified and who were treated by me who at (00) Hospital from January 1, 1995 to (00) for the possible inclusion in the research study titled Prevalence and Patterns of Cocaine Use in Premature Coronary Atherosclerosis.

Signature_____Date_____

If you agree, please sign and return in the enclosed envelope or fax to: (503) 494-7783, Attention Linda Felver/Teri Beasley

Appendix M
Physician Information Sheet

Teri Beasley, BSN, RN, CCRN
Oregon Health Sciences University, School of Nursing
3181 S.W. Sam Jackson Park Road
Portland, Oregon 97201-3098
(503) 297-9496 or 604-6322

Title of Study: Prevalence and Patterns of Cocaine Use in Premature Coronary Atherosclerosis

Primary Purpose: To determine the prevalence and patterns of self-reported past cocaine use among a group of individuals 18 to 44 years of age who have been diagnosed with coronary atherosclerosis by angiogram. In addition, this study will also report the presence or absence of the following CAD risk factors: diabetes, HTN, hypercholesterolemia, cigarette smoking, family history, obesity, prior MI, oral contraceptive use among women, and physical inactivity.

Subjects: Persons 18 to 44 years old who have been diagnosed with CAD, who have had a coronary angiogram and who have been treated at OHSU, Providence Portland Hospital, Providence St. Vincent's, Good Samaritan, or Emanuel Hospital.

Data Collection: The data will be collected through a review of the medical records and a survey questionnaire. The following data will be collected from the medical record: Medical record number, name, address, telephone number, cardiovascular ICD-9 codes, gender, date of birth, height, weight, HTN (yes, no), diabetes (yes, no), hypercholesterolemia (yes, no), previous MI (yes, no), and the amount of coronary artery stenosis reported in each of the main coronary arteries. The following data will be collected from a mailed survey questionnaire: Demographics

(gender, race, age, marital status, economic status, and education level); CAD risk factors (cigarette smoking, exercise, family history, and oral contraceptive use among women); prior cocaine use (age of first use, age of last use, frequency of use, and average amount [grams]used).

Prior Research: The use of cocaine has been found to be a factor in the development of a wide variety of chronic and acute cardiovascular conditions such as cardiomyopathy, myocarditis, arrhythmias, myocardial ischemia and infarction, and atherosclerosis. Cocaine use appears to be a significant risk factor for the development of atherosclerotic CAD. Research has shown that cocaine users have a higher rate of significant coronary atherosclerotic lesions when examined post-mortem and through angiography in comparison to the general population. With regards to risk factor assessment, the main question that remains unanswered is this: What are the prior patterns of lifetime use (frequency, duration, and amount) that appear to place an individual at an increased risk for the development of CAD?

References: Karch, S.B., Green, G.S., Young, S. (1995). Myocardial hypertrophy and coronary artery disease in male cocaine users. Journal of Forensic Sciences, 40, 591-595.

Kloner, R.A., Hale, S., Alker, K., & Rezkalla, S. (1992). Unraveling the complex effects of cocaine on the heart. Circulation, 85, 407-419.

Appendix N

Body Mass Index Calculation

The body mass index (BMI) was calculated by dividing the weight in kilograms by height in meters squared.

$$BMI = \frac{\text{weight}}{(\text{height})^2}$$

Appendix O

Institutional Review Boards Approval Forms

Providence | Health System

Institutional Review Board

5050 N.E. Hoyt
Plaza, B-Level
Portland, Oregon
97213-2967

Tel 503.215.6512

October 1, 1997

Teri Beasley, BSN, RN, CCRN
1838 SW Broadway Drive
Portland, OR 97201

re: **Prevalence and Patterns of Cocaine Use in Premature Coronary Atherosclerosis** (97-120).

Dear Ms. Beasley,

The study listed above has been approved by expedited review on October 1, 1997.

A Continuing Review Report form must be submitted to the IRB within one year. **PLEASE NOTE THAT YOU CANNOT ENROLL RESEARCH SUBJECTS IF THE REPORT FORM IS DELINQUENT/NOT CURRENT.**

The IRB must also be notified of any protocol form changes as well as adverse events that are related to this study. These reporting forms are enclosed for your convenience.

Members of the IRB will be informed of this study approval at their October 28, 1997 meeting.

Sincerely,

[redacted]

Craig S. Fausel, MD
Chairperson
Institutional Review Board

Enclosures

97120.apv

Legacy Emanuel Hospital & Health Center
Legacy Good Samaritan Hospital & Medical Center
Legacy Meridian Park Hospital
Legacy Mount Hood Medical Center
Legacy Holladay Park Medical Center

LEGACY
Health System
Legacy Research

Legacy IRB: M-1517-02

September 25, 1997

Theresa Beasley, BSN
Oregon Health Sciences University
3181 SW Sam Jackson Park Rd.
Mail Code SN-GER
Portland, OR 97201-3098

Dear Ms. Beasley:

At its meeting of September 23, 1997, the Legacy IRB reviewed and approved your protocol **"Prevalence and Patterns of Cocaine Use in Premature Coronary Atherosclerosis".**

You are reminded that you should inform the IRB of any changes in your protocol or if any problems emerge or serious or unexpected adverse patient experiences have been observed.

Sincerely,

[redacted]

Casey Bush
Executive Secretary
Legacy IRB

OREGON HEALTH SCIENCES UNIVERSITY
Research Support Office (RSO), L106 (503) 494-7887

MEMO

Date: August 12, 1997

To: *Theresa Beasley, BSN, RN, CCRN, SN-GER,* c/o Linda Felver

From: Richard T. Jones, MD, PhD Chair Institutional Review Board, L
Leslie Bevan, PhD, Director Research Support Office, L106

Subject: *4563*
Prevalence and Patterns of Cocaine Use in Premature Coronary Atherosclerosis

Protocol/Consent Form Approval

We received your response to the IRB recommendation(s) on 9/7/97.

Your protocol/consent form is approved for One Year **effective** 9/12/97.

The IRB# and the date of this approval should be placed at the top right corner of the first page of the consent form.

Investigators must provide subjects with a copy of the consent form, keep a copy of the signed consent form with the research records, and place a signed copy in the patient's hospital/clinical medical record (if applicable).

If this project involves the use of an Investigational New Drug, a copy of the approved protocol must be forwarded to the Pharmacy and Therapeutics Committee (Pharmacy Services - Investigational Drugs, OP-16A).

If this is a cancer study, we will notify the Oregon Cancer Center (OCC) of the IRB approval. As the PI, you are responsible for providing the OCC with copies of the final approved protocol/consent form.

If other levels of review and approval are required, the project should not be started until all required approvals have been obtained. In addition, studies funded by external sources must be covered by an agreement signed by the sponsor and the Oregon Health Sciences University. Principal Investigators are not authorized to sign on behalf of the University.

Thank you.

Appendix P

Letters of Support

SCHOOL OF MEDICINE OHSU

OREGON HEALTH
SCIENCES UNIVERSITY
DEPARTMENT OF MEDICINE

3181 S.W. SAM JACKSON PARK RD
MAIL CODE L462
PORTLAND, OR 97201-3098
TEL 503-494-8750
FAX 503-494-8550
VAMC TEL 503-220-8262, EXT. 5632
FAX 503-273-5366

DIVISION OF CARDIOLOGY

JOHN H. McANULTY, M.D.
PROFESSOR AND HEAD

PETER BLOCK, M.D.
PROFESSOR

J. DAVID BRISTOW, M.D.
PROFESSOR EMERITUS

KATHY CRISPELL, M.D.
ASSISTANT PROFESSOR

HENRY DEMOTS, M.D.
PROFESSOR

GEORGE D. GIRAUD, M.D., Ph.D.
ASSOCIATE PROFESSOR, (VAMC)

SUSAN GRAUER, M.D.
ASSISTANT PROFESSOR, (VAMC)

KENTON W. GREGORY, M.D.
ASSISTANT PROFESSOR

ALAIR D. HALPERIN, M.D.
ASSOCIATE PROFESSOR

RAY E. HERSHBERGER, M.D.
ASSOCIATE PROFESSOR

SHERRI JOHNSON
DEPARTMENT ADMINISTRATOR

JACK KRON, M.D.
PROFESSOR

GREG C. LARSEN, M.D.
ASSOCIATE PROFESSOR, (VAMC)

CYNTHIA D. MORRIS, Ph.D., M.P.H.
ASSOCIATE PROFESSOR

MARK J. MORTON, M.D.
PROFESSOR

EDWARD S. MURPHY, M.D.
PROFESSOR, (VAMC)

GEORGE A. PANTELY, M.D.
PROFESSOR

MERRITT RAITT, M.D.
ASSISTANT PROFESSOR, (VAMC)

RANAE M. RATKOVEC, M.D.
ASSISTANT PROFESSOR

KENT L. THORNBURG, Ph.D.
PROFESSOR

RICHARD A. WILSON, M.D.
PROFESSOR

July 17, 1997

To whom it may concern,

I am writing this letter to you in support of a proposed research project by Teri Beasley, BSN, RN, CCRN, titled "Prevalence and Patterns of Cocaine Use in Premature coronary Atherosclerosis".

I first learned of this research project last fall when Teri sought my consultation during the planning phase of this project. The use of cocaine is known to have many deleterious cardiovascular effects, including coronary atherosclerosis. However, what has not been identified is the prevalence and prior patterns of cocaine use among those who have developed premature coronary atherosclerosis. The results of this study may provide important insight about the relationship of prior cocaine use and the development of coronary artery disease in persons younger than 45 years of age.

I have given Teri Beasley permission to contact any of my patients at the Oregon health Sciences university for possible inclusion in this study.

Sincerely yours,

[redacted]

George Pantely, M.D.
Professor of Medicine
Division of Cardiology

Oregon Cardiology Clinic, P.C.
501 N. Graham, Suite 415
Portland, Oregon 97227

Cardiovascular Diseases

John Antonovic, M.D., F.A.C.C.
Leonard M. Goldberg, M.D., F.A.C.C.
John Rudoff, M.D., F.A.C.C.

Telephone 288-8385
Fax 288-2120

8/7/97

Legacy Health Systems
Institutional Review Board
2801 N Gantenbien Avenue
Portland OR 97227

Dear Committee on Human Research:

I am writing this letter to you in support of a research study being conducted by Teri Beasley, BSN, RN, CCRN titled "Prevalence and Patterns of Cocaine Use in Premature Coronary Atherosclerosis." Teri and I have discussed this research project and I have agreed to be the physician sponsor of the research study.

The acute cardiovascular effects of cocaine have been well documented in the research literature. The results of this research study may provide important insight regarding the long-term deleterious cardiovascular effects of prior cocaine use, and may additionally provide important data regarding the coronary artery disease factor assessment of young persons who have a history of cocaine use.

If I may be of further assistance during the review process of this research study, please contact me at (503) 288-8385. Thank you.

Sincerely,

John Rudoff, MD, FACC