Acute Activation of Circulating Polymorphonuclear Neutrophils Following \textit{In Vivo} Administration of Cocaine*

A Potential Etiology for Pulmonary Injury

Gayle Cocita Baldwin, PhD; Dawn M. Buckley, BS; Michael D. Roth, MD, FCCP; Eric C. Kleerup, MD, FCCP; and Donald P. Tashkin, MD, FCCP

Crack cocaine has become a major drug of abuse in the United States and its use is associated with a broad spectrum of pulmonary complications. The present study was conducted to determine whether controlled \textit{in vivo} administration of cocaine (inhaled or IV) alters the function of circulating inflammatory cells in a manner capable of contributing to acute lung injury. Subjects who regularly smoked crack cocaine were asked to abstain from illicit drug use for at least 8 h, and were then administered one of the following treatments on each of 4 study days: inhaled cocaine base (45 mg), inhaled placebo (4.5 mg cocaine base, a subphysiologic dose), IV cocaine HCl (0.35 to 0.50 mg/kg), or IV placebo (saline solution). Samples of blood were obtained from a peripheral venous catheter and blood cells were isolated before and 10 to 45 min after treatment. The administration of either cocaine base or cocaine HCl, but not their corresponding placebos, resulted in the activation of circulating polymorphonuclear neutrophils (PMNs). Exposure to cocaine \textit{in vivo} enhanced the antibacterial activity of PMNs, as measured by their ability to kill \textit{Staphylococcus aureus}. Antitumor activity, as measured in an antibody-dependent cell-mediated cytotoxicity assay, also increased following short-term administration of cocaine. Finally, short-term exposure to cocaine enhanced production of interleukin 8, a potent PMN chemotactant and neutrophil-activating factor associated with both acute and chronic lung injury. These studies demonstrate that short-term \textit{in vivo} exposure to cocaine activates the effector function and cytokine production of circulating PMNs. Therefore, it is possible that bursts of acute inflammatory activity resulting from crack use could contribute to lung injury.

(CHEST 1997; 111:698-705)

Key words: antibacterial; cocaine; crack; crack lung; interleukin 8; polymorphonuclear neutrophils

Abbreviations: ADCC=antibody-dependent cell-mediated cytotoxicity; BE=benzoylcegonin; CPM=counts per minute; GM-CSF=granulocyte-macrophage colony-stimulating factor; IL=interleukin; PMN=polymorphonuclear neutrophils

*From the Divisions of Hematology-Oncology and Pulmonary and Critical Care, Department of Medicine, UCLA School of Medicine, Los Angeles. Supported by NIH/NIDA grants DA08254 and NS33432 (Dr. Baldwin). Manuscript received July 11, 1996; revision accepted October 2.

The dramatic increase in cocaine use over the past decade is due largely to the increased availability and popularity of smoked freebase or crack cocaine. Freebase or crack is an alkaloidal form of cocaine that is heat stable and evaporates at a high temperature, allowing it to be smoked. Different methods exist for smoking, but the most common involve use of a heated pipe or mixing cocaine with tobacco or marijuana in a cigarette form. When smoked, cocaine is readily absorbed through the pulmonary circulation and reaches the CNS within seconds. Thus, the euphoric effect is nearly instantaneous and easily attained, rendering crack cocaine a frequently desired and abused substance. Although toxicity is often attributed to CNS or cardiovascular side effects, cocaine in crack form is also associated with a number of pulmonary complications, as recently reviewed by Haim et al. These complications are associated with a variety of pulmonary pathologic changes, including noncardiogenic pulmonary edema, acute and chronic alveolar hemorrhage, diffuse alveolar damage, interstitial pneumonitis, and pulmonary fibrosis. The potential of crack cocaine to cause chronic lung injury is also supported by...
findings of diffusion impairment and evidence of increased alveolar epithelial permeability among habitual users of crack cocaine.9,10

The causes underlying these pulmonary complications are probably multifactorial. However, we considered the possibility that crack cocaine might acutely activate inflammatory cells known to be involved in lung injury. To evaluate this possibility, we examined the short-term effect of in vitro administration of inhaled or IV cocaine on the activity of polymorphonuclear neutrophils (PMNs) derived from the peripheral blood of habitual crack users. PMN activation was assessed using assays that measure cell-mediated antimicrobial and tumoricidal activities, as well as the production of interleukin 8 (IL-8). IL-8 is one of the few cytokines produced by activated PMNs, and it acts both as an attractant and activator for these inflammatory cells.11 Our results indicate that short-term exposure to cocaine in vivo induces an inflammatory state by activating the effector function of PMNs and their ability to produce IL-8. These short-term effects may therefore prove to be relevant to the pulmonary complications that develop in long-term cocaine users.

**MATERIALS AND METHODS**

**Subjects**

Twenty-four current crack-smoking subjects, including 17 men and 7 women, were recruited from a cohort of crack smokers participating in ongoing studies9,12 of the pulmonary effects of habitual use of cocaine, as well as from chemical dependency treatment programs in the local community. All subjects were between the ages of 21 and 50 years, and were regular smokers of alkaloidal cocaine, with only limited use of IV cocaine (≤12 times per lifetime). Exclusionary criteria, described in detail previously,13 included but were not limited to the following: IV drug abuse (including IV administered cocaine) >12 times per lifetime or within the previous year; history of smoking (>20 times per lifetime) other illicit substances except cannabis (eg, phencyclidine, heroin, opium, methamphetamine); and history of chronic lung disease (eg, asthma, interstitial lung disease). All subjects tested negative for HIV. Eligible volunteers were studied after signing informed consent forms approved by the UCLA School of Medicine Human Subject Protection Committee and the West Los Angeles Veterans Affairs Medical Center Human Studies Committee.

**Procedures**

Preliminary examination procedures included a detailed respiratory and drug use questionnaire (modified from the American Thoracic Society/National Heart, Lung, and Blood Institute respiratory questionnaire11 and National Institute on Drug Abuse National Survey on Drug Abuse11), medical history and physical examination, urine drug screen, 12-lead ECG, spirometry and single-breath diffusing capacity for carbon monoxide measurement, blood test for pseudocholinesterase deficiency, and a urine pregnancy test in female subjects. Following completion of these procedures, eligible volunteers were studied on 2 to 4 separate days 1 to 2 weeks apart, beginning at approximately 8 AM. Subjects were to have refrained from smoking cocaine or marijuana, taking any prescription or over-the-counter medication, or consuming any caffeine-containing beverage for at least 8 h. In addition, subjects were admonished not to smoke tobacco for at least 2 h before testing or to use any antihistamine preparation for at least 48 h. Studies were performed with a physician in attendance and an emergency crash cart nearby.

On each study day, the amount of daily drug use (crack cocaine, marijuana, tobacco) during the preceding week and the time of last use were ascertained by questionnaire, and a urine sample was obtained for determination of cocaine metabolite (benzoylcegonine [BE]). Venous blood sampling occurred before and after (1) IV administration over 30 s of cocaine HCl (0.35 to 0.5 mg/kg) or an equivalent volume of saline solution, or (2) smoking of cocaine base (45 mg) or placebo (cocaine base in a subphysiologic dose, 4.5 mg), using a previously described smoking device.12 The peripheral IV catheter for injection of cocaine HCl or saline solution was inserted in the arm opposite to that used for repeated blood sampling. Ten-milliliter samples of blood were obtained from the venous catheter before and 10 to 45 min after injection or inhalation of cocaine or placebo; the blood samples were withdrawn into evacuated specimen tubes (Vacutainer; Becton Dickinson; Franklin Lakes, NJ) with sodium heparin and held at room temperature until completion of the study and eventual isolation of PMNs and monocytes. Immediately following blood collection for functional assays, an additional blood sample was collected in another evacuated tube containing ethylenediaminetetraacetic acid, for determination of blood cocaine and metabolite levels.

**Purification of Primary Cells From Peripheral Blood**

PMNs were isolated from peripheral blood by Ficoll-Hypaque (Pharmacia Biotech AB; Uppsala, Sweden) gradient centrifugation, followed by dextrin sedimentation as previously described.16 Cells were used immediately in cytotoxicity assays and the IL-8 supernatant collection assays. Pretreatment and post-treatment samples were assayed simultaneously to reduce inter-assay variability.

**PMN Phagocytosis Assay**

PMNs were purified for use in both phagocytosis and intracellular killing assays according to the previously described methods.16 Briefly, at appropriate times (T=5, 15, and 30 min), 0.2 mL of the PMNs (10⁸ cells/mL) and Staphylococcus aureus (10⁸ bacteria/mL) suspension was removed and combined with 0.2 mL 0.25% N-ethyl maleimide (Sigma; St. Louis) in Hanks’ balanced salt solution, which inhibited additional phagocytosis. Samples (0.05 mL) were removed and cytocentrifuge slides were prepared, fixed, stained, and examined by light microscopy. Individual PMNs were evaluated as having either 0, 1 to 10, 11 to 20, 21 to 30, or >30 bacteria associated with them. A weighted phagocytic index was calculated by multiplying the number of PMNs in each category by 0, 1, 2, 3, or 4, respectively, and dividing the total score by the number of PMNs examined (≥100).

**PMN Intracellular Killing**

PMNs were resuspended in 0.9 mL Hanks’ balanced salt solution containing 10% human AB serum and allowed to warm to 37°C for 5 min, following which, 0.1 mL of S aureus was added at a 1:1 ratio (10⁶ organisms). Reaction tubes were
incubated with rocking at 37°C, and at the appropriate time-points (T=0, 30, 60, and 90 min), 0.1 mL of the cell/bacteria suspensions was removed, serially diluted in water, and plated in duplicate on trypticase soy agar. Plates were incubated at 37°C overnight, and bacterial colonies were counted. Results were either expressed as a direct ratio \(N_0/N_0\), where \(N_0=\)number of colonies counted at initial combination of cells and bacteria and \(N_0=\)number of colonies at each time interval, or as percent killing \(\left(\frac{N_0-N}{N_0}\times100\right)\).

**PMN Antibody-Dependent Cell-Mediated Cytotoxicity Assay**

PMN cytotoxicity was assayed as previously described. Briefly, following isolation from peripheral blood, PMNs were washed and stimulated in the presence of 100 picomolar granulocyte-macrophage colony-stimulating factor (GM-CSF; Genetic Institute; Boston). M14 melanoma tumor target cells were radiologically labeled by incubating 1.8 to 2.0×10⁷ cells in 1.5 mL of cytotrophic medium containing 0.3 mL Na₅¹CrO₄ (1 μCi=37 GBq; New England Nuclear) for 90 min at 37°C. Following incubation, target cells were washed and incubated in the presence of monoclonal antibody 14G2A⁷ (0.5 μg per well), and plated at a concentration of 3×10⁴ cells per well in a 96-well polystyrene flat-bottom plate. An equal volume of prepared PMNs (3×10⁶) was added to the wells, resulting in an effector/target cell ratio of 100:1 and a final well volume of 0.3 mL. The plates were centrifuged at 200g for 7 min and incubated for 3 h at 37°C in a humidified atmosphere (5% CO₂ in air). After incubation, 0.15 mL of supernatant was removed and counted in a gamma counter.

Percent lysis was calculated as \((A-B)/C\times100\), in which A represents the mean counts per minute (cpm) in the supernatant from wells containing target and effector cells, B is the mean cpm from wells containing target cells alone (representing spontaneous release of Na₅¹CrO₄), and C is the total cpm added to each well. Assays were run in triplicate.

**PMN Supernatant Collection and Quantitation of IL-8 Production**

Peripheral blood-derived PMNs were isolated from study subjects and normal donors as previously described, washed and resuspended in iscoves modified dulbecco medium (IMDM; Gibco; Grand Island, NY) supplemented with 2 mmol/L glutamine/penicillin (100 mg/mL)/streptomycin (100 mg/mL) and plated (4×10⁸ cells per well) in 48-well plastic plates (Corning Costar Corp; Cambridge, Mass). Recombinant human IL-2 (10,000 U/mL, Boehringer Mannheim; Indianapolis) was added to wells at a final concentration of 1,000 U/mL. PMNs were incubated for 3 h at 37°C in a humidified atmosphere of 5% CO₂ in air. At T=0, 1, and 3 h, 0.250 mL of the supernatant was harvested to sterile tubes and centrifuged (1,000g) for 5 min. The supernatant was then stored at −80°C for time periods that did not exceed 1 month, and subsequently utilized in an IL-8 enzyme-linked immunosorbent assay (ELISA). Commercially available enzyme-linked immunosorbent assay (R & D Systems; Minneapolis) was used to determine IL-8 levels in supernatants collected from PMNs incubated in the presence or absence of IL-2. Procedures described by the manufacturer were strictly followed without alteration.

**RESULTS**

**Subject Characteristics**

Demographic and smoking characteristics of the 24 study subjects are shown in Table 1. Subjects were in their fourth to fifth decade of life, and reported current smoking of at least 0.2 g (mean=1.3 g) of crack cocaine per week, with a duration of smoking of at least 3 years. Approximately two thirds of the subjects also currently smoked tobacco and/or marijuana.

**Functional Analysis of Effector Cells**

PMNs were assayed for their ability to kill *S aureus* before and after administration of cocaine or placebo. As shown in Figure 1, the number of remaining bacteria capable of forming colonies following PMN-mediated killing diminishes over time. This is evident whether the PMNs were exposed *in vitro* to cocaine (top panel) or placebo (bottom panel). However, PMNs isolated following short-term *in vitro* exposure to cocaine are significantly more efficient at killing bacteria than PMNs isolated before cocaine exposure. In contrast, PMNs isolated before and after placebo retain similar patterns of intracellular killing, and ultimately kill the same percentage of bacteria over time. Thus, exposure to cocaine *in vitro* enhanced the antibacterial activity of PMNs, as measured by their ability to kill *S aureus*.

Figure 2 shows the percent change from baseline in PMN-mediated bacterial killing in all subjects following *in vitro* administration of cocaine (n=7) or placebo (n=5), either IV or by smoking. Antibacterial activity was significantly increased (p<0.02) from baseline by an average of 12.6% following cocaine administration. In comparison, antibacterial activity, as measured by percent killing, generally decreased following placebo administration, but the mean decrease of 9.5% was not statistically significantly different from baseline. The percent change in antibacterial activity following cocaine administration was also significantly differ-

![Table 1—Age and Smoking History of Subjects (n=24, 17 Male and 7 Female)](image-url)
Cocaine-mediated cellular activation was also evident when PMN-ADCC (antibody-dependent cell-mediated cytotoxicity) was compared precocaine and postcocaine administration vs preplacebo and postplacebo administration (Fig 3). PMNs were assayed in the absence of GM-CSF (top panel) and in the presence of this stimulatory cytokine (bottom panel), since we have previously shown that GM-CSF specifically enhances PMN-ADCC. As PMN-ADCC is antibody dependent, experiments shown in Figure 3 utilized cultured melanoma cells (cell line M14) as tumor targets and a monoclonal antibody specific for the sialoganglioside overexpressed on these tumor cells. Regardless of whether the PMNs were GM-CSF stimulated, the trend was toward cellular activation following short-term exposure to cocaine. In the top panel, the mean change in cytotoxic capability (before vs after) following placebo was 1.8%, while the mean change following cocaine was 6.7%. In five of seven subjects shown in the top panel, cocaine administration resulted in a substantial increase in tumor cell killing (before vs after) (mean percent increase = 10%), while placebo controls (before vs after) consistently changed very little (largest increase was only 2%). The inherent variability in before vs after changes in cytotoxicity seen following cocaine administration confounds the statistical significance of the results presented in both panels. However, GM-CSF-stimulated PMNs (bottom panel), while exhibiting a considerable range in before vs after changes (−6.4 to 25), are also characterized by a trend toward activation following cocaine administration. This was especially evident in four of six subjects following cocaine administration. Moreover, there was no significant change in cytotoxic activity (before vs after) following placebo.

Figure 1. Intracellular killing of \textit{S. aureus} by PMNs before (open circles) and after (closed circles) short-term exposure to cocaine (top) and placebo (bottom). The viability of \textit{S. aureus} throughout the time course is also indicated (squares). Assays were performed in triplicate, and triplicates varied <5%.

Figure 2. Change in percent of \textit{S. aureus} killed at T=90 min before and after placebo or cocaine administration. Open circles=IV administration; closed circles=inhaled administration.
average of 27.0±12.6 min after infusion or inhalation of active cocaine. However, 50% (7/14) of subjects showed no detectable change (both measurements below threshold of detection) in blood cocaine levels at the time of measurement. This was likely due to unavoidable delays in blood sampling in these subjects. Despite the delays, a modest correlation was noted between change in cocaine level and change in percent killing ($r^2=0.43$) from baseline.

**Analysis of IL-8 Protein Synthesis by IL-2-Activated PMN**

IL-8 is a potent granulocyte attractant/activation factor and a designated inflammatory cytokine. Unstimulated PMNs from normal donors release low or undetectable levels of IL-8 protein, which remain relatively constant throughout a 6-h culture period. Following stimulation with IL-2, PMNs secrete increased amounts of IL-8, which reach a maximum at 3 to 6 h poststimulation and remain stable thereafter (Fig 4). In *vivo* administration of cocaine enhanced production of IL-8 from IL-2-stimulated PMNs to levels that were significantly greater than levels produced by stimulated PMNs recovered from normal donors, cocaine subjects at baseline, or cocaine subjects following placebo administration (Fig 4). There is a suggestion that the inducibility of PMN-derived IL-8 is elevated in cocaine subjects when

**Blood Levels**

At baseline, all subjects had evidence of recent cocaine use, as indicated by detectable levels of cocaine or cocaine metabolite in the urine and/or blood. Levels of urinary BE (76,433±57,751 ng/mL, mean±SD), blood BE (616±648 ng/mL), and blood cocaine (37.4±18.3 ng/mL) were above the detectable limit of 30 ng/mL in 100%, 96%, and 22% of subjects, respectively. No differences in these levels were noted between placebo and cocaine groups at baseline. A modest correlation was found between baseline measures of cocaine exposure (urinary BE [$r^2=0.16$], plasma BE [$r^2=0.68$], and plasma cocaine [$r^2=0.62$]) and predose percent PMN intracellular killing of *S. aureus*. Blood cocaine levels increased by a mean of 35.9±58.5 ng/mL, which was measured an

**Figure 3.** PMN-mediated ADCC activity in the absence (top) and presence (bottom) of GM-CSF stimulation, as measured in percent cytotoxicity before (pre) and after (post) administration of placebo or cocaine. Open circles=IV administration; closed circles=inhaled administration.

**Figure 4.** PMN production of IL-8 with (shaded bars) and without (unshaded bars) IL-2 stimulation in normal donors (A; n=7), in all crack-using test subjects at baseline (B; n=5), postplacebo (C; n=4), and postcocaine (D; n=5).
compared with normal control subjects (Fig 4, categories A and B). However, given the small sample size and variability in values, these differences did not achieve statistical significance.

**Discussion**

The mechanisms by which crack cocaine injures the lung are not well defined. However, the frequent autopsy findings of diffuse alveolar damage, interstitial pneumonitis, and pulmonary fibrosis in crack users suggest that both acute and chronic inflammatory reactions are involved.\(^6\)\(^-\)\(^8\) The present study was designed to assess the effects of short-term cocaine exposure on circulating inflammatory cells. Our findings suggest that short-term exposure to cocaine, either by inhalation or the IV route, activates circulating PMNs. In measuring PMN function, we first evaluated the intracellular killing of ingested *S. aureus*. In this assay, antibacterial killing is a cumulative measure of phagocytosis, phagolysosomal fusion, and the production of both oxidative and nonoxidative metabolites.\(^1\) PMNs collected 10 to 45 min after the administration of cocaine demonstrated significantly enhanced antibacterial activity compared with PMNs collected from the same subjects before the exposure. The validity of these results is supported by the fact that antibacterial activity did not significantly change from baseline in the same subjects when they were administered placebo instead of cocaine. Likewise, we observed the same trend toward cellular activation when we measured PMN-mediated tumor cell killing in an ADCC assay. This assay measures a nonoxidative mode of killing mediated through Fc receptor binding and release of inflammatory cytokines.\(^1\) Finally, as an additional correlate of PMN activation, we measured release of IL-8, a potent inflammatory mediator involved in neutrophil chemotaxis and activation.\(^1\) We found that short-term exposure to cocaine primed stimulated PMNs to release enhanced levels of IL-8. Although we failed to find a significant correlation between the observed changes in plasma cocaine levels and changes in functional assays, this may likely be explained by delays in blood sampling. Venous plasma levels of cocaine reach a peak within 2 min after administration, and its clearance is quite variable, depending primarily on the subject’s circulating pseudocholinesterase activity.\(^20\) This generally occurs within a few minutes, due to tissue uptake and metabolism. In our study, plasma cocaine sampling was delayed an average of 27.0±12.6 min postadministration, because physiologic experiments performed during the period immediately following cocaine administration prevented earlier sampling.

Results presented herein support the conclusion that in *vivo* exposure to cocaine induces an acute inflammatory response. Although the systemic activation we observed was relatively modest, it is realistic to hypothesize that effects within the pulmonary microenvironment of crack abusers are more pronounced. First, the amounts of cocaine administered in our study, 20 to 45 mg, were small compared with the usual 1 to 4 g/wk consumption of our subjects. This was confirmed by the relatively low levels of cocaine that could be measured in the blood an average of 27 min after experimental administration. In addition, pulmonary parenchymal concentrations are likely to be substantially greater than that in the systemic circulation, due to direct exposure of the lung to the inhaled drug. For example, studies in tobacco smokers have demonstrated significantly higher acute concentrations of nicotine in arterial blood compared with simultaneous venous sampling (D.P.L. Sachs, personal communication, 1996). This is presumably due to dilution and peripheral consumption/metabolism of inhaled substances. The same phenomenon likely exists for cocaine, due to its rapid metabolism by plasma pseudocholinesterase.\(^1\)

Information documenting the pulmonary effects of cocaine comes primarily from autopsy studies performed on individuals dying of a variety of causes, whose toxicology studies were positive for cocaine. The most frequent findings at autopsy were pulmonary edema (in 77%), acute and/or chronic hemorrhage (in 71%), and interstitial pneumonitis and/or fibrosis (in 38%).\(^7\) Injury included variable infiltration by both PMNs and mononuclear cells, as well as evidence of diffuse alveolar damage, fibrosis, and hyperplasia of type II pneumocytes.\(^7\)\(^-\)\(^8\) Similar findings have also been reported in patients hospitalized with an acute crack lung syndrome.\(^2\)\(^-\)\(^5\) Patients usually present with diffuse pulmonary infiltrates and hypoxemia that respond to corticosteroids and supportive care. Cucco et al\(^24\) performed BAL on one such patient and documented a fourfold increase in protein content, consistent with the presence of noncardiogenic pulmonary edema. Forrester et al\(^25\) reported that transbronchial and/or open lung biopsy specimens also show diffuse alveolar damage and alveolar hemorrhage, as well as interstitial and intra-alveolar inflammatory cell infiltration.

The clinical and pathologic characteristics associated with crack abuse are in many ways similar to those observed both in ARDS and in idiopathic pulmonary fibrosis. Similarity to ARDS strongly suggests a role for PMN activation in the pathogenesis of crack-associated lung injury. PMNs collected from patients with ARDS demonstrate similar signs of activation, including enhanced effector cell function, superoxide production, and release of extracellular
elastases and proteases. A role for these activated PMNs in lung injury is also supported by studies in mice, in which experimental ARDS can be induced in normal animals but not in animals that have been rendered neutropenic.

Our observation that cocaine primes PMNs for IL-8 release is also relevant to lung injury. Both acute injury, as in ARDS, and chronic lung injury, as in idiopathic pulmonary fibrosis, are correlated with elevated circulating intrapulmonary levels of IL-8. Chollet-Martin et al measured IL-8 levels in the plasma and BAL fluid of 18 patients with pneumonia and ARDS, and found elevated levels of IL-8 in the alveolar spaces of all such patients in comparison to IL-8 levels of control subjects without acute lung injury. Other reports also show a direct correlation between plasma levels of IL-8 and PMN infiltration in ARDS patients and in patients with idiopathic pulmonary fibrosis. Lynch et al observed that the intrapulmonary expression of IL-8 messenger RNA correlated directly with the degree of PMN infiltration, as measured in the BAL fluid. Finally, other support for PMNs and IL-8 as acute mediators of lung injury comes from patients treated with systemic IL-2. In these subjects, activated PMNs induced to secrete IL-8 are believed to play a role in the pulmonary endothelial injury and cytokine-associated noncardiogenic edema that complicates this form of immunotherapy.

Given the known roles of PMNs and IL-8 in acute lung injury, our observations suggest a potential mechanism for cocaine-associated lung injury. However, to further understand why some crack users develop crack lung while others do not, it may be necessary to relate this syndrome to the following: intensity, frequency, and recency of exposure; and frequency, route of administration, and possible contributions by other coincident exposures, such as other drugs or viral infections. Herein we have described a short-term exposure study that is limited by the amount of cocaine that can be safely administered, as well as by the lack of direct access to the pulmonary microenvironment at the time of exposure. Therefore, it may be useful to perform bronchoscopy with BAL in subjects following short-term experimental exposure or in patients admitted to hospital with acute manifestations of crack lung. Interestingly, in contrast to PMN activation following short-term exposure, we find that long-term exposure suppresses the immune function of BAL-derived alveolar macrophages (Baldwin et al; unpublished data in manuscript preparation). This suggests that repeated short-term exposure to cocaine may culminate in long-term chronic lung damage. The pathogenesis of pulmonary complications associated with cocaine is undoubtedly multifactorial; our findings, however, support the involvement of PMNs as activated acute inflammatory mediators of lung injury.

ACKNOWLEDGMENTS: The authors thank Michael Simmons for statistical analysis and figure preparation, and Wendy Aft for preparation of the manuscript.

REFERENCES
1 Smart RG. Crack cocaine use: a review of prevalence and adverse effects. Am J Drug Alcohol Abuse 1991; 17:13-26