The incidence of this previously rare disorder, cocaine-associated agitated delirium, appears to have increased drastically within the last 18 months. The underlying neurochemical abnormalities have recently been characterized, but most clinicians have had little experience with management of agitated delirium. The basic clinical and pathological features of this disorder are reviewed, and common pitfalls in diagnosis and management that frequently lead to needless but very expensive litigation are discussed. (Am J Emerg Med 1996;14:425-428. Copyright © 1996 by W.B. Saunders Company)

The first modern mention of cocaine-associated agitated delirium was in 1985. Reports of patients with similar symptoms had appeared in the early 1900s, but because these reports were deeply interwoven with elements of racist hysteria they were never taken seriously. The syndrome is comprised of four components which appear in sequence: hyperthermia, delirium with agitation, respiratory arrest, and death. Individuals succumbing to this disorder uniformly have low to modest cocaine blood levels and do not behave like patients with massive overdose (continuous seizures, respiratory depression, and death). Recent data also show that these victims have high blood levels of benzoylecgonine, the principal cocaine metabolite. The incidence of this disorder is not known with any certainty. There is, however, little doubt that the number of cases has increased markedly since the late 1980s, and it seems likely that the increase is related to the widespread popularity of crack cocaine.

In the early stages of the disorder, victims are hyperthermic and grossly psychotic, with marked physical agitation. They often perform amazing feats of strength, particularly after citizens or police attempt to restrain them. Shortly after being restrained, agitation ceases and the victim is frequently found dead, or near death, just moments later. Not uncommonly, victims have been "hogtied"; their wrists and ankles are bound together behind their back while they lie prone. Victims who do not come to police attention are often found dead in their bathrooms. Because of their hyperthermia they will often be found surrounded by wet towels and clothing, sometimes even with empty ice trays scattered about. Since the victims frequently die in police custody, there are often allegations that death resulted from asphyxia related to hogtying, or other police procedures such as restraining neck hold, pepper sprays, or electrical stun devices. However, it is important to note that many victims of this disorder die suddenly and without the application of any law enforcement restraining techniques.

In their original report, Wetli and Fishbain described the syndrome in seven cases. All had fairly stereotypical histories. Typical was the case of a 33-year-old man who started pounding on the door of a house he had moved out of some time previously. He was shouting that he wanted to see his wife and daughter. The occupants informed him that nobody by that name resided there, yet he pursued his actions. Four bystanders finally restrained him and assisted police units upon their arrival. The subject was handcuffed and put into a police car, whereupon he began to kick out the windows of the vehicle. The police subsequently restrained his ankles and attached the ankle restraints and handcuffs together. He was then transported to a local hospital. While en route, the police officers noted that he became tranquil (about 45 minutes after the onset of the disturbance). On arrival at the hospital a few minutes later, the subject was discovered to be in a respiratory arrest. Resuscitative attempts were futile. A postmortem examination was performed 1 hour and 45 minutes later (about 3 hours after the onset of the disturbance), and a rectal temperature of 41°C (106°F) was recorded. He had needle marks typical of intravenous drug abuse, as well as pulmonary and cerebral edema. Abrasions and contusions of the ankles and wrist were also evident from his struggling against the restraints. Toxicologic analysis of postmortem blood disclosed 52.3 mg/L of lidocaine and 0.8 mg/L of cocaine. No lidocaine was administered to the victim during resuscitative attempts.

The clinical presentation of agitated psychotic cocaine abusers is quite different from that of nonpsychotic cocaine abusers with sudden death or massive drug overdose. The psychotic cocaine users are almost always men, they are more likely to die in custody, and they are more likely to live for 1 hour after onset of symptoms. In Miami, men with agitated delirium account for 10% of cocaine deaths. Approximately 39% of the victims of excited delirium deaths in Miami occurred in police custody (Mash, Ruttenber, et al, personal communication, August 1995). Their deaths tend to occur in summer, especially when the weather is warm and humid. Two thirds of the victims die on the scene or while being transported by paramedics to the hospital. The few who live long enough to be hospitalized succumb to disseminated intravascular coagulation, rhabdomyolysis, and renal failure. In the Miami patients, the average temperature at the time of first medical encounter was nearly 105°F. The demographics appear to be similar in other locals.
The mean cocaine concentration in 45 cases seen by the Dade County Medical Examiner was 1.32 mg/L (range .05 to 11.8 mg/L, n = 34), while the benzoylcegonine level was 3.78 mg/L (range .08 to 14.75 mg/L, n = 38). In these same patients, the mean brain cocaine concentration was 1.90 mg/kg (range .05 to 4 mg/kg, n = 10), while the mean benzoylcegonine concentration was 2.69 mg/kg (range .85 to 3.5 mg/kg, n = 6). A consistent finding at autopsy was cardiomegaly. The median heart weight in 44 men was over 420 grams.

The cellular and neurochemical changes associated with this disorder are starting to become clearer. Using ligand binding and autoradiographic methods, researchers have identified three different neurochemical abnormalities in the brains of cocaine abusers dying of agitated delirium. One factor that is clearly implicated in the effects of cocaine is the neurotransmitter dopamine. Some of the abnormalities in the dopamine system involve alterations in certain types of dopamine receptors and in the cocaine's ability to block the reuptake pump or "transporter" by which dopamine is recycled back to the nerve terminal. The net effect is that cocaine prevents dopamine from being taken back up by the sending neuron, promoting its actions on dopamine receptors. Cocaine users often go on binges, consuming a large amount of the drug over a few days. The neurochemical changes over the "binge" and crash periods involve adaptive alterations of the dopamine receptors on receiving cells.

Dopamine receptors were initially classified into two main groups. With advances in molecular biology, these two main subtypes are now known to be comprised of five different receptors, but they are still considered as two receptor families: the "D1-like receptors" (dopamine receptors D1 and D5), and the "D2-like receptors" (dopamine receptors D2, D3, and D4)..

The situation is somewhat confusing and difficult to understand, largely because of the nomenclature used to describe dopamine receptors. Most antipsychotic drugs block the D2 receptors with affinities that correlate with their clinical potency. The atypical antipsychotic clozapine has been shown to prefer the putative D4 receptor subtype. D1 and D2 receptors interact with each other and enhance each other's actions within the neuron, possibly by causing subunits of G proteins to alter the cascade of second messenger signaling. In schizophrenia, D2 and D3 receptor density is elevated by 10%, while the D4 receptors are elevated even more. It has been suggested that cocaine "craving" may result in part because of alterations in D3 receptor signaling within limbic sectors of the striatum (Staley, Mash, et al, unpublished observations).

The occurrence of agitated delirium probably has something to do with the fact that both D1 and D2 receptors and dopamine transporters are altered by chronic cocaine use. In comparison with drug-free controls, the brains of nonpsychotic cocaine abusers contain an elevated number of cocaine recognition sites on the striatal dopamine transporter. No such increase is seen in the agitated delirium victims. The fact that the psychotic cocaine users fail to demonstrate this compensatory increase means that they cannot clear excess dopamine from their synapses. Pathologically high dopamine levels may occur after a "binge" and that, in turn, may lead to psychosis.

Psychotic and nonpsychotic cocaine users can also be distinguished by the number of dopamine binding sites. In most people, chronic cocaine abuse leads to striking decreases in the density of the D1 receptor subtype throughout the striatal reward centers, probably as a result of receptor down-regulation. The fact that cocaine users quickly become tolerant to the drug's euphoriant effects is probably explained by the change in the number of dopamine receptor sites. Striatal D2 receptors in nonpsychotic cocaine abusers are unchanged. However, in the psychotic subgroup, marked reductions in the number of D2 receptors were found within temperature regulatory centers of the hypothalamus. Since these receptors are known to decrease core body temperature, decreased numbers of D2 receptors may explain the occurrence of malignant hyperthermia in the psychotic patients. With fewer D2 receptors available, D1-mediated temperature increases would be unopposed.

Agitated delirium can be the result of other medical disorders, not just cocaine toxicity. In fact, the syndrome is said to have first been described in the 1800s, years before cocaine was isolated from the coca leaf. According to Wendkos, Bell first described patients with agitated delirium in 1849. Episodes occurring in patients with non–drug-related psychosis were further characterized by Shulack in 1938. Recently it has been suggested that this constellation of symptoms is actually a variant of neuroleptic malignant syndrome (NMS) is a highly lethal disorder seen in patients taking dopamine antagonists and in individuals who have been withdrawn from dopaminergic agents such as bromocriptine and levodopa. NMS is usually associated with muscle rigidity, although variants of the syndrome without rigidity are also recognized.

Alterations in the number of dopamine receptors and cocaine recognition sites on the dopamine transporter may not be the sole explanation for the death of these individuals. There is mounting evidence that the stress of restraint makes fatal outcomes more likely. Rats injected daily with moderate doses of cocaine (30 mg/kg) and then restrained are three times more likely to die from seizures than rats injected with the same amount of drug and allowed free access to their cages. Since so many of the agitated delirium patients die while restrained, it has been suggested that the mechanism of death may involve a surge of catecholamines released by the stress response, superimposed on a myocardium already sensitized by cocaine. This notion is further supported by the observation of myocardial enlargement, presumably catecholamine related, in most victims.

Autopsy findings are generally minimal and nonspecific, and associated injuries are generally minor. However, because blood concentrations of cocaine tend to be fairly low, and because there is confusion about the interpretation of cocaine blood levels anyway, it is often tempting to attribute the cause of death to one of the minor injuries, such as minor head injury. Needless litigation is often the result. When cocaine users with agitated delirium die, cocaine should be considered the cause of death, unless there is clear physical evidence that death is due to some mechanism other than
FIGURE 1. In vitro autoradiographic maps of [3H]WIN 35,428 labeling of the dopamine transporter in coronal sections of the human brain from a representative (A) age-matched and drug free subject, (B) a cocaine overdose victim, and (C) a cocaine-related agitated delirium victim. The brain maps illustrate the adaptive increase in dopamine transporter density over the striatum in the cocaine overdose victims and the lack of any apparent elevation in the victim presenting with agitated delirium. Since the dopamine transporter regulates the synaptic concentration of neurotransmitter, the lack of compensatory upregulation may result in a dopamine overflow following a cocaine “binge.” Elevated synaptic dopamine with repeated exposures may kindle the emergence of agitated delirium syndrome. Gray scale codes are presented at the right and are matched for the range of density values across the groups (black = high densities; gray = intermediate; light gray to white = low to background densities). Abbreviations: Cd, caudate; NA, nucleus accumbens, Pt, putamen.

cocaine toxicity, such as positional or mechanical asphyxia. It is well to remember that in most cases of agitated delirium death occurs without significant police restraint, and frivolous speculation about the cause or mechanisms of death will only invited needless litigation.

Emergency physicians rendering care to victims of this disorder are also at risk for needless litigation. However, some of the risks can be minimized. Allegations that positional asphyxia occurred in transit are difficult to prove when the victim is monitored and observed during transport. Emergency medical services (EMS) boards need to establish protocols for the field management of such patients, not only to improve chances for patient survival but also to limit paramedic and physician liability. It is also worthwhile remembering that the diagnosis of agitated delirium can be made by postmortem measurement of dopamine synaptic markers in the striatum and hypothalamus. The pattern in agitated delirium is very different from that in cases of simple cocaine overdose (Figure 1) and is totally different from the pattern that would be anticipated with mechanical or positional asphyxia. Of course, it is possible for someone with agitated delirium to be strangled, but establishing that the deceased suffered from a highly fatal disease may dampen some litigants’ enthusiasm. If postmortem neurochemical measurements are to be made, the brain must be removed and processed within 12 to 18 hours. Neurochemistry laboratories located at several referral hospitals are capable of such measurements and should be contacted immediately for instructions (1-800-UM-BRAIN).

REFERENCES
2. Williams E: Negro cocaine “fiends” are a new southern menace. New York 1914:1