ELEVATED BLOOD CYANIDE CONCENTRATIONS IN VICTIMS OF SMOKE INHALATION

FRÉDÉRIC J. BAUD, M.D., PATRICK BARRIOT, M.D., VÉRONIQUE TOFFIS, PHARM.D., BRUNO RIOU, M.D., ERIC VICAUT, M.D., PH.D., YVES LECARPENTIER, M.D., PH.D., RAYMOND BOURDON, PH.D., ALAIN ASTIER, PH.D., AND CHANTAL BISMUTH, M.D.

Abstract *Background.* The nature of the toxic gases that cause death from smoke inhalation is not known. In addition to carbon monoxide, hydrogen cyanide may be responsible, but its role is uncertain, because blood cyanide concentrations are often measured only long after exposure.

Methods. We measured cyanide concentrations in blood samples obtained at the scene of residential fires from 109 fire victims before they received any treatment. We compared the results with those in 114 persons with drug intoxication (40 subjects), carbon monoxide intoxication (29 subjects), or trauma (45 subjects). The metabolic effect of smoke inhalation was assessed by measuring plasma lactate at the time of admission to the hospital in 39 patients who did not have severe burns.

Results. The mean (±SD) blood cyanide concentrations in the 66 surviving fire victims (21.6±36.4 μmol per liter, $P<0.001$) and the 43 victims who died (116.4±89.6 μmol per liter, $P<0.001$) were significantly higher than those in the 114 control subjects (5.0±5.5 μmol per liter). Among the 43 victims who died, the blood cyanide concentrations were above 40 μmol per liter in 32 (74 percent), and above 100 μmol per liter in 20 of these (46 percent). There was a significant correlation between blood cyanide and carbon monoxide concentrations in the fire victims ($P<0.001$). Plasma lactate concentrations at the time of hospital admission correlated more closely with blood cyanide concentrations than with blood carbon monoxide concentrations. Plasma lactate concentrations above 10 mmol per liter were a sensitive indicator of cyanide intoxication, as defined by the presence of a blood cyanide concentration above 40 μmol per liter.

Conclusions. Residential fires may cause cyanide poisoning. At the time of a patient's hospital admission, an elevated plasma lactate concentration is a useful indicator of cyanide toxicity in fire victims who do not have severe burns. (N Engl J Med 1991;325:1761-6.)

SMOKE inhalation has been well established as a cause of death in fire victims.[1-3] The identity of the toxic gases leading to death is uncertain, however. In addition to carbon monoxide, hydrogen cyanide is a major source of concern. The thermal decomposition of various nitrogen-containing materials, either natural (such as wool and silk) or synthetic (such as polyurethane and polyacrylonitrile), can produce toxic levels of hydrogen cyanide.[3-8] For example, the thermal degradation of 1 g of polyacrylonitrile in a 15.6-liter combustion chamber produces a hydrogen cyanide concentration of 1500 ppm.[6] Bertol et al. estimated that a lethal concentration of hydrogen cyanide could be achieved by burning 2 kg of polyacrylonitrile in an average-sized living room.[6] The effect of the hydrogen cyanide content of smoke has been well studied experimentally.[3,4] The exposure of animals to combustion products containing hydrogen cyanide rapidly produced severe incapacitation, and the animals who died had toxic cyanide concentrations in the blood.[4,6,8,9]

Many injuries caused by fire result from an inability to escape from the fire.[5] Obscuration of vision and toxic effects produced by smoke, such as irritation and asphyxia, may impede the victims' escape.[7] So may incapacitation due to cyanide exposure. Delay in escape prolongs the exposure to toxic gases and to flames and increases the probability of death or injury.[4] Forensic and clinical reports on the clinical and biologic importance of blood cyanide concentrations in fire victims are conflicting, because cyanide disappears rapidly from blood and blood specimens have often been obtained from fire victims only several hours after exposure.[4,10-15]

Accordingly, we sought to determine the clinical and biologic importance of blood cyanide concentrations in fire victims who died and those who survived by measuring blood samples obtained at the scene of the fire.

From Réanimation Toxicologique (F.J.B., C.B.), the Département de Biophysique (E.V.), and the Laboratoire de Toxicologie (R.B.), Hôpital Fernand Widal, Université Paris 7, Paris; the Service Médical de la Brigade des Sapeurs-Pompiers de Paris, Paris (P.B.); the Laboratoire de Toxicologie, Hôpital Henri Mondor, Créteil (V.T., A.A.); the Département d'Anesthésie-Réanimation, Hôpital Pitié-Salpétrière, Université Paris 6, Paris (B.R.); Institut National de la Santé et de la Recherche Médicale Unité 275, LOAENSTA-Ecole Polytechnique, Palaiseau (Y.L.), and the Service de Physiologie, Hôpital de Bicêtre, Le Kremlin-Bicêtre (Y.L.); all in France. Address reprint requests to Dr. Baud at Réanimation Toxicologique, Hôpital Fernand Widal, Université Paris 7, 200, rue du Faubourg Saint-Denis, 75010 Paris, France.

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METHODS

This study was approved by the Ethics Committee of the Assistance Publique–Hôpitaux de Paris. Because the patients required immediate emergency care, informed consent was not obtained.

Study Subjects

We studied 109 victims of residential fires in the Paris area who were examined by ambulance physicians at the scene of the fire from April 1988 through April 1989. There were 50 women and 59 men, ranging in age from 2 to 87 years (mean, 33). Blood specimens were collected in dry heparin by the first medical squad to reach the scene after the start of isobaric oxygen therapy in all patients who were still alive and the start of mechanical ventilation in some, but before the administration of hydroxocobalamin (an antidote to cyanide) and any hyperbaric oxygen therapy. Thirty-six of these patients had already died at the scene of the fire when the blood sample was collected. Two or three blood samples were collected from six patients to estimate the half-life of cyanide in blood before any antidote to cyanide or any hyperbaric oxygen therapy was administered. These six patients were among those in whom measurements were made early in the course of the study, before we recognized that fire victims had elevated blood cyanide concentrations and before we began to use hydroxocobalamin as an antidote to

cyanide poisoning. Even so, it was not used routinely, but only when serious cardiovascular compromise was evident.

Control Groups

We also measured blood cyanide concentrations in three groups of control subjects. Since we did not know whether the fire victims who died and those who lived were smokers or nonsmokers, blood samples were obtained from both smokers and nonsmokers among the control subjects.

The first group of controls included hospital inpatients with drug intoxication. For each fire involving one or more victims, a corresponding blood sample was obtained from each of one or more randomly chosen patients who were admitted to the intensive care unit on the same day for treatment of acute drug intoxication. Twenty-one of the patients were women and 19 were men, ranging in age from 15 to 93 years (mean, 35).

The second group of controls included patients with carbon monoxide poisoning caused by the malfunction of a heating appliance. Blood specimens were collected in the homes of patients with carbon monoxide poisoning resulting from the malfunction of a gas water heater or a coal stove. Fifteen of these patients were women and 14 were men, ranging in age from 7 to 80 years (mean, 45). Three were dead at the time the blood sample was collected.

The third group of controls included patients with major trauma from whom blood specimens were collected at the scene of the accident. Five were women and 40 were men, ranging in age from 10 to 91 years (mean, 37).

After collection and during transport, the blood specimens were stored for up to 90 minutes at ambient temperature, then stored at 4°C until the measurements were made[16] — normally on the day after the blood collection, and always within three days. The laboratory personnel who performed the analyses did not know the source of the samples.

Metabolic Study

Plasma lactate concentrations were measured as described elsewhere[17] (normal range, 1 to 2 mmol per liter) on arrival at the hospital in 39 of the fire victims thought to suffer from smoke inhalation. These patients were examined by a physician at the scene of the fire, where blood samples were obtained for the determination of the cyanide and carbon monoxide concentrations. The blood samples used for the plasma lactate measurements were obtained from 32 to 152 minutes (mean [±SD], 80±28) after the samples used for the blood cyanide measurements. Patients with burns over more than 15 percent of their body surface were excluded from this part of the study. The plasma lactate concentrations were correlated with the concentrations of cyanide and carbon monoxide in the blood samples obtained at the scene of the fire. The addition of a high concentration of hydroxocobalamin (300 μmol per liter) in vitro raised the measured plasma lactate concentration by 7 percent.

Analysis of Cyanide and Carbon Monoxide

Blood cyanide concentrations were measured with a colorimetric assay using microdiffusion.[18] The detection threshold was 2.2 μmol per liter, and the interassay coefficient of variation was 8 percent. We assigned a value of zero to blood samples that had cyanide concentrations below the threshold of detection. To determine the extent of artifactual loss of cyanide from blood specimens between collection and analysis, an in vitro study was performed. The blood samples from normal subjects were supplemented with 40 μmol of cyanide per liter, placed in rubber-sealed glass tubes containing lithium heparinate, and stored for three days at 4°C or at room temperature (22±2°C) (one tube per day at each storage temperature, in triplicate). Each day, the tubes designated for that day were opened and their cyanide concentrations immediately measured. The mean (±SD) decrease in the cyanide concentration after storage at 4°C was 10.3±2.2 percent after one day, and the decrease remained constant after three days (11.2±2.1 percent). After storage at room temperature, the mean decrease in the cyanide concentration was 15.3±2.3 percent; after three days the decrease remained constant (16.2±2.7 percent).

Blood carbon monoxide concentrations were measured by infrared analysis[19] in the 109 fire victims and the 29 patients with carbon monoxide poisoning due to the malfunction of a heating appliance.

On the basis of previous reports,[11-13,20,21] nontoxic blood concentrations of cyanide and carbon monoxide were defined as those less than 40 μmol per liter and 1.0 mmol per liter, respectively. Potentially toxic concentrations were defined as those ranging from ≥40 to <100 μmol per liter for cyanide and from 1.0 to 5.8 mmol per liter for carbon monoxide. Potentially lethal concentrations were defined as those ≥100 μmol per liter for cyanide and ≥5.8 mmol per liter for carbon monoxide.

Statistical Analysis

Nonparametric tests were used because of the nongaussian distribution of the variables studied.[22] The results in the three control groups were analyzed with Kruskal–Wallis nonparametric analysis of variance. Since no differences were found between the control groups, the results in the three groups were combined to form a single control group. An overall comparison between the combined control group and the fire victims was made by Kruskal–Wallis analysis of variance. Multiple comparisons were made with Dunn's nonparametric method.[22] Correlations between the carbon monoxide and the cyanide concentrations in blood were assessed with Kendall's rank-correlation coefficients. Correlations between plasma lactate levels and the blood concentrations of carbon monoxide and cyanide were assessed with Kendall's rank-correlation and partial-rank-correlation coefficients. Kendall's rank-correlation coefficients were calculated to determine the correlations between the extent of burns and the blood concentrations of carbon monoxide and cyanide.[22] All the tests were two-tailed, and P values of 0.05 or less were considered significant. The results are expressed as means ±SD.

Results

Blood Cyanide Concentrations in the Control Group

The mean blood cyanide concentration in the 40 inpatients with drug intoxication was 6.0±6.3 μmol per liter. In the 29 patients with carbon monoxide poisoning due to the malfunction of a heating appliance, the mean blood cyanide concentration was 4.3±5.7 μmol per liter, and the mean carbon monoxide concentration 2.9±1.5 mmol per liter. The carbon monoxide poisoning in 23 patients resulted from the malfunction of a gas water heater and in 6 patients from the malfunction of a defective coal stove. Twenty-eight patients had at least temporary loss of consciousness. Three patients were found dead at the scene, two died in the hospital, and another was discharged with severe neurologic impairment.

In the 45 patients with trauma, the mean blood cyanide concentration was 4.6±4.5 μmol per liter. The trauma resulted from a fall in 7 patients, motor vehicle accidents in 30, and penetrating wounds in 8. Eight patients in this group died at the accident scene despite intensive supportive treatment.

Since there were no significant differences in blood cyanide concentrations among these three groups, they were considered as a combined group of 114 patients in the following analysis.

Blood Cyanide Concentrations in the Fire Victims

Of the 109 fire victims from whom we obtained blood specimens, 43 died (39 percent). The mean blood cyanide concentration in these 109 patients was

59.0±77.9 μmol per liter. In those who died, it was 116.4±89.6 μmol per liter, and in those who survived it was 21.6±36.4 μmol per liter. All these values were significantly higher than those for the control group (Fig. 1). The corresponding mean blood carbon monoxide concentration in the 109 fire victims was 1.5±1.7 mmol per liter. In those who died it was 2.8±2.0 mmol per liter, and in those who survived it was 0.7±0.7 mmol per liter.

Of the 43 victims who died, 36 were found dead at the scene of the fire, and 7 died after admission to the hospital. The blood cyanide concentrations were above 40 μmol per liter in 32 of these 43 persons (74 percent), and above 100 μmol per liter in 20 (46 percent).

Thirty patients were less than 14 years old, and 13 of them died. In these 30 patients, the mean blood cyanide concentrations were 27.4±53.0 μmol per liter in those who survived and 87.0±76.1 μmol per liter in those who died ($P<0.01$). The corresponding mean blood carbon monoxide concentrations were 0.6±0.8 mmol per liter and 1.9±2.0 mmol per liter.

Seventy-nine patients were 14 years old or older, and 30 of them died. In these 79 patients, the mean blood cyanide concentrations were 19.6±28.9 μmol per liter in those who survived and 129.0±93.1 μmol per liter in those who died ($P<0.001$). The corresponding mean blood carbon monoxide concentrations were 0.8±0.7 and 3.1±2.0 mmol per liter.

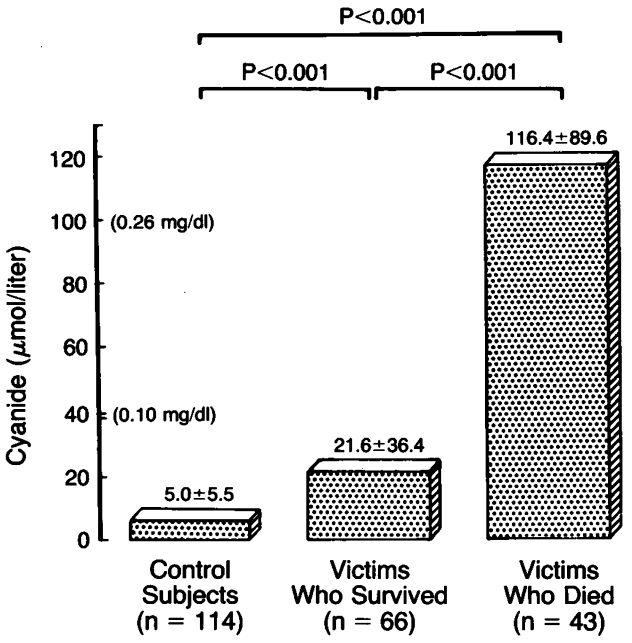

Figure 1. Mean (±SD) Blood Cyanide Concentrations in the Control Subjects, the Fire Victims Who Died, and the Victims Who Survived.

Blood cyanide concentrations below 40 μmol per liter were defined as nontoxic, those from ≥40 to <100 μmol per liter as potentially toxic, and those ≥100 μmol per liter as potentially lethal. Conventional units for cyanide measurements are shown in parentheses.

Twenty-seven of the 109 fire victims had burns. Thirteen of them had burns over more than 80 percent of their body surface that were considered to be life-threatening. There were no significant correlations between the extent of burns and the blood concentrations of either cyanide or carbon monoxide.

There was a significant correlation between the blood concentrations of cyanide and those of carbon monoxide in the 109 patients ($r = 0.50$, $P<0.001$), the 66 survivors of fire ($r = 0.26$, $P<0.001$), and the 43 fire victims who died ($r = 0.26$, $P<0.05$). Fifty-five patients had nontoxic blood concentrations of cyanide and carbon monoxide (Fig. 2); five of them died (9 percent), including four with life-threatening burns. Potentially toxic blood concentrations of cyanide, carbon monoxide, or both were found in 29 patients (Fig. 2), of whom 16 died (55 percent), including 8 with life-threatening burns. Potentially lethal blood concentrations of cyanide, carbon monoxide, or both were found in 25 patients (Fig. 2), of whom 22 died (88 percent), including 1 with life-threatening burns.

The half-life of cyanide in blood was approximately one hour in the six patients in whom it was serially measured (Table 1). One patient had no neurologic symptoms, two were agitated and confused, and three were comatose. All these patients had increased plasma lactate concentrations (range, 3.0 to 20.6 mmol per liter). None of them received hyperbaric oxygen therapy or any antidote to cyanide before the blood samples were collected.

Metabolic Consequences

Blood specimens were obtained from 39 fire victims thought to have had smoke inhalation on arrival at the hospital. The mean interval from the blood collection for the measurement of cyanide to the blood collection for the measurement of plasma lactate was 80±28 minutes.

Of these 39 patients, 10 had minor burns, 25 had transient or prolonged impairment of consciousness, 8 were agitated, confused, or both, and 29 had rhonchi or wheezing. Only three patients had no neurologic or respiratory symptoms. Nine of the 39 patients eventually died. At the time of admission to the hospital, however, only one fire victim, a two-year-old baby, was in refractory cardiac arrest, and the arterial origin of the blood sample could not be ascertained. The mean systolic arterial blood pressure recorded when the 38 remaining fire victims were admitted to the hospital was 129±25 mm Hg. The mean pH was 7.31±0.10, the mean partial pressure of oxygen in arterial blood was 33.0±23.3 kPa, and the mean plasma bicarbonate concentration was 19.1±4.5 mmol per liter.

Six fire victims had plasma lactate concentrations ≥29 mmol per liter. These six were discovered in cardiac arrest and required mechanical ventilation and infusions of epinephrine and sodium bicarbonate; five had already received hydroxocobalamin. One of these fire victims was the two-year-old child. In the five

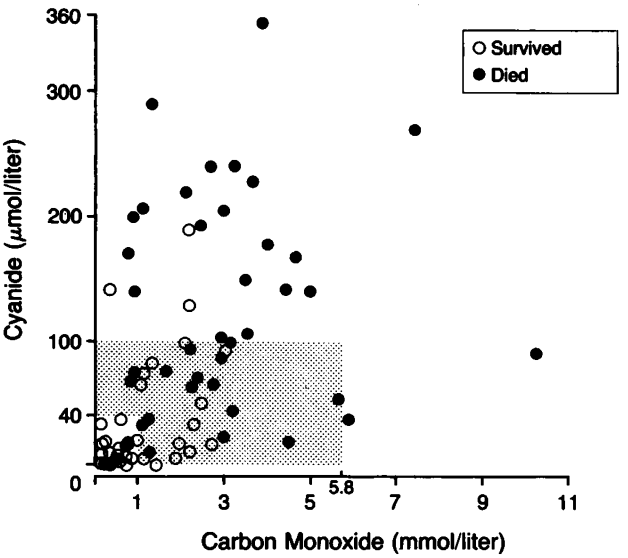

Figure 2. Correlation between Blood Concentrations of Carbon Monoxide and Those of Cyanide in Fire Victims Who Died and Victims Who Survived.

Blood concentrations of cyanide and carbon monoxide below 40 μmol per liter and 1 mmol per liter, respectively, were considered to be nontoxic (open square at lower left); those ranging from ≥40 to <100 μmol per liter for cyanide and from 1 to 5.8 mmol per liter for carbon monoxide were considered to be potentially toxic (stippled area); and those ≥100 μmol per liter for cyanide and ≥5.8 mmol per liter for carbon monoxide were considered to be potentially lethal.

others, the mean systolic arterial blood pressure at the time of admission to the hospital was 130±27 mm Hg, the mean pH 7.22±0.14, the mean partial pressure of oxygen in arterial blood 57.5±19.2 kPa, and the mean plasma bicarbonate concentration 13.1±2.5 mmol per liter. Despite the use of hyperbaric oxygen therapy and the administration of high doses of hydroxocobalamin, these five fire victims died. The deaths occurred two to seven days after admission to the hospital, and all were related to brain death.

The mean plasma lactate concentration in the 39 patients thought to have had smoke inhalation (11 of whom had received hydroxocobalamin) was 14.0± 12.3 mmol per liter. The mean blood carbon monoxide and cyanide concentrations measured at the scene of the fire were 2.1±1.5 mmol per liter and 76.2±75.1 μmol per liter, respectively. There was a significant correlation between the plasma lactate concentration and both the blood cyanide ($r = 0.55$, $P<0.001$) and the blood carbon monoxide ($r = 0.38$, $P<0.001$) concentrations. There was also a significant correlation between the blood concentration of carbon monoxide and that of cyanide ($r = 0.43$, $P<0.001$). The correlation between the blood carbon monoxide concentration and the plasma lactate concentration, with the effect of blood cyanide held constant, was 0.18, as expressed by the partial correlation coefficient. The partial correlation coefficient between the blood cyanide concentration and the plasma lactate concentration, with the effect of carbon monoxide held constant, was 0.47. We concluded that the plasma lactate concentrations measured at the time of admission in patients suffering from smoke inhalation who did not have severe burns correlated more closely with the blood concentrations of cyanide than with those of carbon monoxide.

Among these 39 patients, 23 had blood cyanide concentrations at the scene of the fire that were higher than 40 μmol per liter. Only 3 of these 23 patients had plasma lactate concentrations below 10 mmol per liter (Fig. 3). Sixteen patients had blood cyanide concentrations below 40 μmol per liter, and only 1 of the 16 had a plasma lactate concentration above 10 mmol per liter. Hence, in the context of smoke inhalation without severe burns, the sensitivity of a plasma lactate concentration above 10 mmol per liter for cyanide poisoning, defined by a blood cyanide concentration above 40 μmol per liter, was 87 percent; the specificity was 94 percent, and the positive predictive value 95 percent.

Table 1. Estimated Half-Life of Blood Cyanide Concentrations in Six Fire Victims before the Administration of Any Hydroxocobalamin or the Initiation of Hyperbaric Oxygen Therapy.

Patient No.	Blood Cyanide Concentration		Estimated Half-Life*
	Initial Sample	Follow-up Samples	
	μmol/liter	μmol/liter (hr elapsed†)	hr
1	128.6	36.6 (2)	1.1
2	11.5	4.2 (1)	0.7
3	98.9	52.3 (1)	1.1
4	80.9	11.6 (2.5), 6.9 (3.5)	0.9
5	50.0	21.2 (2), 7.7 (4)	1.5
6	73.1	33.5 (5), 4.6 (7.5)	2.1
Mean ±SD			1.2±0.5

*Calculated for each patient by linear regression analysis.
†Since the time the initial sample was taken.

Discussion

Several potential pitfalls have been noted in the measurement of blood cyanide concentrations in patients with either fatal or nonfatal poisoning. Cyanide may disappear rapidly from body tissue after death from acute cyanide poisoning,[21] and its half-life in blood is short in cases of nonfatal cyanide poisoning in dogs and humans.[15,23,24] Our finding that the half-life of cyanide is approximately one hour agrees with the results of previous studies. Such rapid disappearance precludes accurate evaluation of cyanide poisoning by delayed blood sampling in surviving fire victims. Furthermore, the production of cyanide has been described in various tissues, including blood. The potential for postmortem cyanogenesis is uncertain, however, since some have failed to demonstrate it.[16,21]

The conditions of blood sampling, storage, and analysis in our study were those known to influence blood cyanide concentrations the least.[21] The blood samples were collected by the first medical team to

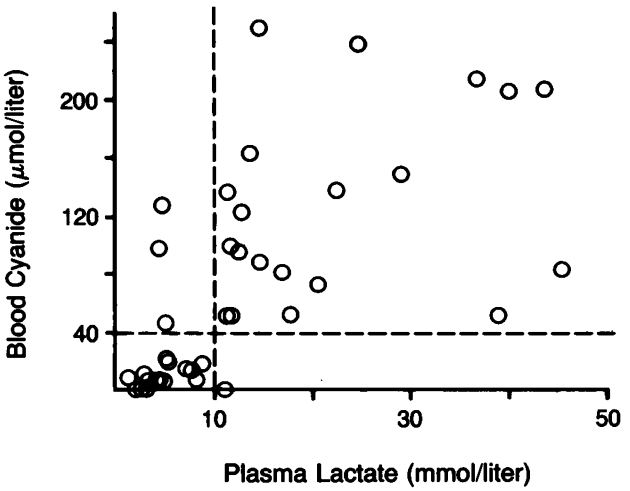

Figure 3. Correlation between Plasma Lactate and Blood Cyanide Concentrations in 39 Fire Victims with No Severe Burns.

arrive at the scene of the fire, even when there were fatalities. Furthermore, the samples were collected from the victims of carbon monoxide poisoning or major trauma under the same conditions as those used for the collection of blood from fire victims.

In the fire victims who survived, the mean blood cyanide concentration was significantly higher than that in the control subjects. Nine patients had blood cyanide concentrations above 40 μmol per liter, and three had values above 100 μmol per liter. Survival despite a blood cyanide concentration in the potentially lethal range has been reported previously.[12,14] These results indicate that there is no blood cyanide concentration above which the outcome is invariably fatal.[16,21] Among the 43 fire victims who died, the blood cyanide concentrations were above 40 μmol per liter in 74 percent and above 100 μmol per liter in 46 percent. These results suggest that it is reasonable to suspect cyanide poisoning whenever fire victims have smoke inhalation.

As reported elsewhere,[11-14] the blood carbon monoxide and cyanide concentrations were significantly correlated. Blood carbon monoxide concentrations may be considered an index of cyanide poisoning in fire victims. However, the low value of the Kendall's rank-correlation coefficient indicated a wide spread in blood cyanide concentrations for a given blood concentration of carbon monoxide. This finding precludes the possibility of predicting the blood cyanide concentration accurately on the basis of the blood carbon monoxide concentration. Furthermore, a few of the fire victims who died in our study had potentially lethal blood cyanide concentrations despite having blood carbon monoxide concentrations in the range generally considered nontoxic. Thus, in contrast to those of previous studies,[11,12] our results suggest that cyanide poisoning may prevail over carbon monoxide poisoning as the cause of death in some fire victims.

In accordance with the results of an earlier study,[25] 36 of the 43 victims we studied who died (84 percent) were found dead at the scene of the fire. The major lethal factors in fires are toxic gases, heat, and oxygen deprivation.[5] By far the most commonly reported cause of smoke inhalation–related death is carbon monoxide, which is a systemic toxin with no irritant properties. However, respiratory irritants alone produce a chemical tracheobronchitis that contributes to thermal injury of the upper respiratory tract and to chemically mediated alveolar injury in the lower respiratory tract. The exact contribution of each toxic gas to the rapid deaths of fire victims is difficult to quantitate in the setting of a fire.[26] One of the most striking results was the fact that 55 percent of the 29 patients who died had blood concentrations of either carbon monoxide or cyanide that were within the potentially toxic but not the potentially lethal range. In addition to severe burns that might have occurred after death,[27] these patients may also have suffered from low inspired-oxygen content and smoke-induced damage to the respiratory tract. However, studies in animals have shown that there may be physiologic potentiation of toxicity from carbon monoxide and cyanide combined.[4,28] Our data suggest that both gases may have an additive toxic effect in humans.

The high lactate concentrations in the fire victims' plasma were probably related to cyanide poisoning, for several reasons. First, the values for partial pressure of oxygen in arterial blood excluded hypoxia as a cause of lactic acidosis. Second, despite initial cardiac arrest in a few fire victims, the values obtained for systolic arterial blood pressure at the time of admission to the hospital could not easily explain the very high plasma lactate concentrations. Third, in the 39 fire victims thought to have had smoke inhalation, a significant correlation was found between the plasma lactate and the blood cyanide concentrations. Lactic acidosis is known to be an important consequence of cyanide poisoning.[29] Metabolic acidosis occurs frequently in fire victims, and cyanide poisoning may be an unrecognized cause of lactic acidosis.[12,14] Carbon monoxide poisoning is also a cause of lactic acidosis, which depends not only on blood carboxyhemoglobin levels but also on the duration of exposure.[30,31] However, the exposure of fire victims to toxic gases is usually short. Our results indicate that in victims with no burns or only minor ones, high plasma lactate concentrations are strongly suggestive of cyanide poisoning in addition to carbon monoxide poisoning.

The basic treatment for severe cyanide inhalation includes mechanical ventilation with pure oxygen and the administration of an antidote to cyanide. Although a variety of agents have proved effective in experimental studies, the choice of an antidote in the clinical setting remains a matter of debate.[32] Only a kit containing nitrites and thiosulfate is approved for use in the United States. However, the potential hazards of nitrite therapy in cases of combined poisoning with cyanide and carbon monoxide have recently been outlined.[33] Because of the strong affinity of cyanide for

cobalt, cobalt compounds (such as cobalt edetate and hydroxocobalamin) are rapid and powerful cyanide antidotes. However, cobalt edetate induces side effects that may be deleterious in patients with suspected but not confirmed cyanide poisoning.[32] Hydroxocobalamin combines with cyanide to form cyanocobalamin (vitamin B_{12}).[34] We began to use it during this study because of its promise as an antidote whose action appears to be rapid and efficient and because, in comparison with nitrites and cobalt edetate, it appears to have low toxicity.[34-37]

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