CASE REPORT

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Acute Dimethylnitrosamine Poisoning Outbreak

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ABSTRACT: In an 8-h period, five members of two kindred families suddenly became ill with nausea, vomiting, and malaise. This was followed by acute liver disease, a generalized bleeding tendency, and a low platelet count. Two of the patients died four and five days after onset of illness. It was established that dimethylnitrosamine had been intentionally added to lemonade and milk that were consumed by the victims.

KEY WORDS: toxicology, dimethylnitrosamine, poisons, human poisoning

Case Report

Patient 1

A one-year-old white male patient was admitted to the hospital on 12 Sept. 1978 with a two-day history of vomiting. His parents had also had a gastrointestinal upset. On the day of onset of illness, 10 Sept. 1978, they had visited relatives where they drank lemonade. A few hours later, the child and his parents developed severe abdominal cramps, vomiting, and diarrhea. On admission, the patient appeared alert but irritable. The physical examination was essentially normal except for multiple bruises. The hemoglobin level was 11 g/dL and the white blood cell count 4400/mm^3. The platelet count dropped to 19 000/mm^3 on the third hospital day. The blood urea nitrogen level was 17 mg/dL (normal, 5 to 22 mg/dL). The electrolytes and spinal fluid examination were normal. The serum glutamic pyruvic transaminase (SGPT) level was 6520 international units (IU) per litre (normal, 4 to 24 IU/L). The serum creatinine level was 0.8 mg/dL (normal, 0.6 to 1.3 mg/dL) and blood ammonia level was 297 μg/dL.

The morning after admission, the patient was unresponsive and was transferred to a children's hospital. Hepatomegaly and icterus were noted and multifocal seizures occurred at in-

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tervals. A bolt intracranial pressure monitor was placed. The monitor was later removed because of concern over the possible development of a hematoma. The thrombocytopenia remained severe. On the third day of illness, the total bilirubin level was 7.4 mg/dL (normal, 0.1 to 1.1 mg/dL), direct bilirubin level 3 mg/dL (normal, 0 to 0.2 mg/dL), and prothrombin time was more than 20 s. The alkaline phosphatase level was 850 IU (normal, 9 to 35 IU) and fibrin split products were above 40 mg/mL. Intermittent bradycardia occurred, and the next day the child died.

The following gross observations were made at autopsy:

The liver weighed 350 g and had a friable cut surface and granular appearance. The lungs showed focal atelectasis, congestion, edema, and, in the right lower lobe, irregular dark hemorrhagic areas. The gastrointestinal tract had petechial hemorrhages in the colon and the stomach contained 30 cm^3 of bloody fluid. Examination of the brain revealed burr holes in the scalp, subdural blood overlying both cerebral hemispheres to a maximal depth of 2 or 3 mm, and edematous soft cerebral substance. While the right cerebral hemisphere was uniformly coated with clotted and unclotted blood, the amount of blood over the left hemisphere was less extensive. The other organs were essentially normal. Microscopic examination of the lungs showed extensive intra-alveolar hemorrhage and edema. Areas of bronchopneumonia were also present. In the spleen, some lymphocyte depletion of the Malpighian corpuscles and lymphoid follicles was noted. The liver showed massive necrosis (Fig. 1). Only the hepatocytes immediately around the portal triads were not affected. The centrilobular areas showed complete loss of hepatocytes. In these areas, outlines of degenerated hepatocytes, red blood cells, amorphous debris, and degenerated inflammatory cells were present. The vascular wall of the central veins showed necrotic changes; the bile ducts were unaffected.

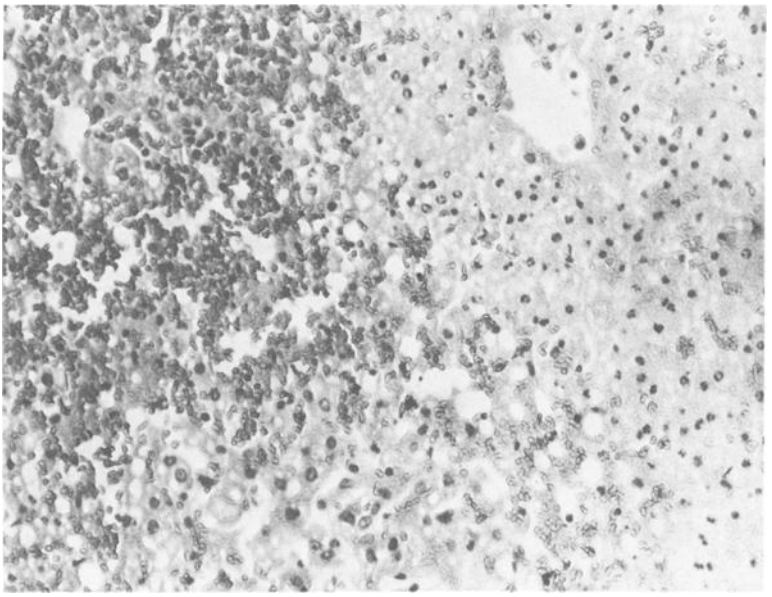

FIG. 1—*Section of liver from Patient 1. The hepatocytes in the central and mid-zonal areas are destroyed. A few inflammatory cells and necrotic debris are noted. The liver cells immediately adjacent to the bile ducts are intact.*

Patient 2

Patient 2, a 24-year-old white male, was the uncle of Patient 1. Four days before admission to the hospital, this patient, after partially painting his house, became fatigued and developed abdominal pain, which was followed by severe vomiting. That morning, he had tasted some milk that he had described as foul-tasting. He had also been seen to drink two glasses of a liquid containing ice cubes. This could have been lemonade. That same day, Patients 1, 4, and 5 had visited with Patient 2 and had drunk lemonade at his house. The following day, he continued to vomit and had chills, but no fever. Two days after onset of illness, he developed conjunctival injection, gingival bleeding, epitaxis, and a persistent headache. The epitaxis was severe enough to require packing of his nose in an emergency room. Three days after onset of illness, he became very sleepy and developed photophobia. He saw a physician. While in the physician's office, he became comatose and was admitted to the hospital.

On physical examination, periorbital ecchymoses and conjunctival hemorrhages were noted. The pupils were nonreactive to light. The patient was areflexic and there was no response to painful stimuli. The liver was barely palpable at the right coastal margin. Lumbar puncture showed bloody spinal fluid, consistent with a cerebral hemorrhage. A computerized axial tomography (CAT) scan showed an intracerebral hematoma in the right frontal lobe.

The following laboratory data were obtained: Blood ammonia level was 90 μg/dL. The serum glutamic oxalacetic transaminase (SGOT) level was 910 IU/L and later, 1208 IU/L (normal, 5 to 18 IU/L). The SGPT level was 1700 IU/L (normal, 4 to 24 IU/L). The blood urea nitrogen level was 28 mg/dL (normal, 5 to 22 mg/dL) and creatinine level, 1.3 mg/dL (normal, 0.6 to 1.3 mg/dL). The prothrombin time was 15 s (control, 10.5 s). The cholesterol level was 72 mg/dL (normal, 150 to 318 mg/dL), the alkaline phosphatase level was 326 IU/L (normal, 79 to 258 IU/L), the lactic dehydrogenase level was 396 IU/L (normal, 56 to 194 IU/L), and the serum globulin level was 2.4 g/dL (normal, 2.5 to 3.0 g/dL). The chest X-ray was normal. The hemoglobin level was initially 14.5 g/dL and later dropped to 11 g/dL. The white blood cell count was 11 000/mm^3 with a normal differential. The lowest platelet count was 6000/mm^3. Bone marrow showed normal cellularity with a slight increase in megakaryocytes.

The day after the patient was admitted, the electroencephalogram was isoelectric and he was pronounced dead.

At autopsy, marked cerebral edema and a right subarachnoid hemorrhage were noted. The heart showed myocardial and endocardial hemorrhage. The liver had a nutmeg appearance and showed marked passive congestion. The right and left lower lobes of the lungs had atelectases. The kidneys showed passive congestion. The lungs, diaphragm, stomach, and upper chest showed petechial hemorrhages.

Microscopic examination of the tissues revealed small areas of hemorrhage in the heart, fairly extensive areas of hemorrhage in the right frontal lobe area of the brain with generalized cerebral edema, and numerous red blood cells in the collecting tubules of the kidneys. The bone marrow showed normal cellularity. The liver was the organ primarily affected (Fig. 2). The hepatocytes in the periphery of the lobules showed some vacuolation of the cytoplasm but were otherwise intact with normal-appearing nuclei. There was slight bile stasis. The hepatocytes in the center of the lobules were completely necrotic or in various stages of degeneration. Congestion and hemorrhage were also prominent in the central zones. The central zones were infiltrated by inflammatory cells. Loss of endothelium of the vascular walls of the central veins was noted. The alveoli of the lungs contained many macrophages with a brown pigment. Hemorrhage was noted in many areas of the lungs as well as focal acute purulent inflammation with necrosis of the alveolar walls. Except for a few clusters of vacuolated or foamy cells in the spleen, no other findings of note were made in any other organ.

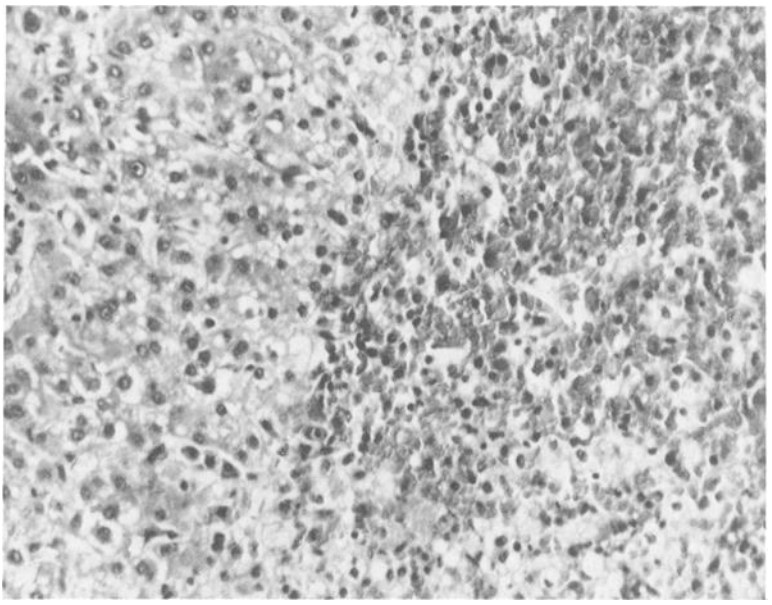

FIG. 2—*Section of liver from Patient 2. The hepatocytes in the center of the lobules are completely necrotic. Congestion and hemorrhage are prominent in these areas. The hepatocytes in the periphery of the lobules are essentially normal.*

Patient 3

A 2½-year-old white female, the daughter of Patient 2, on 10 Sept. 1978 developed nausea, vomiting, and abdominal pain four days before being admitted to the hospital. Her onset of illness occurred at about the same time as that of Patient 2. She continued to vomit and feel weak. Physical examination revealed scattered petechiae over the upper eyelids, two small ecchymoses, and scattered petechiae over the lower legs. The liver was palpable two to three fingers below the right coastal margin and the spleen tip was palpable. No other physical findings of note were made.

Laboratory data on admission were these: the SGOT level was 702 IU/L (normal, 5 to 18 IU/L) and increased to 1550 IU/L. The total bilirubin level was 1.0 mg/dL (normal, 0.1 to 1.1 mg/dL). The SGPT level was 522 IU/L (normal, 4 to 24 IU/L), the alkaline phosphatase level was 113 IU/L (normal, 9 to 35 IU/L), and the lactic dehydrogenase level was 395 IU/L (normal, 56 to 194 IU/L). The white blood cell count was 6500/mm^3, the red blood cell count was 4 110 000/mm^3; the hemoglobin level was 11 mg/dL; and the platelet counts ranged from 13 000 to 21 000/mm^3. She was tranferred to a children's hospital and discharged three weeks after onset of illness. However, follow-up as an outpatient showed continuous hepatosplenomegaly and elevated liver enzymes and a liver biopsy obtained three months after exposure showed chronic active hepatitis.

Patient 4

Patient 4 was the father of the one-year-old child that died (Patient 1). He visited relatives (Patients 2 and 3) and at their house drank some lemonade. Several hours later, he developed nausea, severe abdominal cramps, and vomiting, but no diarrhea. He was admitted to the hospital five days after onset of illness because of illness in the other family members and

a mildly elevated SGOT level. The physical examination was essentially normal. Except for a slightly elevated SGOT level of 125 IU/L (normal, 5 to 18 IU/L) and a platelet count in the range of 120 000/mm^3, all other laboratory tests were normal. He was discharged in good condition four days later.

Patient 5

Patient 5, a 21-year-old female, was the wife of Patient 4 and the mother of Patient 1. She also developed nausea, abdominal cramps, and diarrhea. She continued to have diarrhea and mild abdominal pain for the next five days, when she was hospitalized. On the day of onset of illness, she had also ingested lemonade. On admission, she was lethargic and had mild fever and slight abdominal pain. The physical examination was negative except for some mild left upper abdominal tenderness. The initial laboratory data on admission was essentially normal except for an SGOT level of 85 IU/L (normal, 5 to 18 IU/L) and a platelet count of 116 000/mm^3. Examination of a bone marrow aspirate showed normal cellularity. Eight days after onset of illness, her SGOT level had increased to 138 IU/L and peaked eleven days after onset of illness at 258 IU/L. At that time, the patient's liver was felt 6 cm below the right coastal margins and her platelet count had dropped to 12 000/mm^3 the day before. A liver needle biopsy showed necrosis of the hepatocytes in the central zones with hemorrhage and an inflammatory infiltrate composed of polymorphonuclear leukocytes, lymphocytes, and occasional plasma cells. While in the hospital, she developed an α-hemolytic streptococcus infection and was treated with penicillin. The patient improved and was discharged 16 days after onset of illness with a platelet count of 187 000/mm^3 and an SGOT level of 47 IU/L.

The Investigation

Initially, poisoning was not suspected as the cause of illness in the patients. The initial diagnosis in Patient 1 was Reye's syndrome. Aseptic meningitis was also considered. Five days after the outbreak occurred, the Virology Division of the Center for Disease Control (CDC) was contacted. Toxic and infectious causes for the outbreak were considered. The information received indicated that the patients had had vomiting and diarrhea and those that died, had died from hepatic failure.

On 15 and 16 September, meetings were held that included the attending physicians, the pathologists involved, representatives of the county health department, the state epidemiologist, and a representative of CDC. In reviewing the results of the epidemiology interviews and the pathology, it was determined that the cause of the deaths and illnesses was not viral or bacterial, nor were the symptoms consistent with any known disease. The consensus of those meetings was that a toxic substance had been placed in the lemonade that had been consumed by all of the patients. This conclusion was supported by the fact that five other family members who had been in the home of Patient 2 on and before 10 September drank no lemonade and exhibited no signs of liver dysfunction on testing. Their platelet counts were also normal. Two of the five unaffected family members had consumed coffee made from tap water in the home, one had had ice tea made from tap water, the infant son of Patient 2 had had commercially prepared infant formula, and the fifth had tasted both lemonade and milk but complained that they tasted bad and had not consumed any.

On 16 and 17 September, a detailed investigation was made at the family home. No toxic substances were located. The lemonade and milk had been discarded and the lemonade container washed. A number of samples were sent to CDC including household water, a package of unused lemonade, sugar, and the container that had held the suspected lemonade. At the same time, tissue samples were provided from the autopsy of Patient 2 to Poison Lab in Denver and CDC and histology slides from both autopsies were sent to CDC. The tap water, a package of unused lemonade, and sugar were tested in rats.

The rats did not develop signs of toxicity and were killed five days after dosing. Grossly, the rat livers were normal and microscopic examination of sections stained with hematoxylin and eosin showed essentially normal liver.

A small amount of a 5% citric acid solution was agitated for several hours in the container that had held the suspected lemonade and left over the weekend. Five millilitres of the 5% citric acid solution was given by gavage to two rats three times 2 h apart. These rats were killed eight days later. No abnormalities were noted in the livers on gross or microscopic examination.

After reviewing the medical charts and other available information, one of us (R. D. K.) suggested that an alkylating agent might be involved and that a possible source for such a compound could be a local cancer research institute. Police investigation revealed that a boyfriend of Patient 2's wife had recently been released from the state penitentiary after having been convicted of shooting at the family in 1975. He was employed while on parole at a cancer research institute where his job was to prepare diets for bioassay studies in rats.

On 3 October, a search of the suspect's home was made during which a vial containing traces of paradimethylbenzaldehyde and a bottle containing traces of arsenic and dimethylbenzanthracene were found.[3] Further discussion with employees of the institute by one of us (S. W. C.) established the possibility that dimethylnitrosamine could have caused the outbreak. Dimethylnitrosamine is a liquid, well miscible with water, and is extremely toxic on an acute basis with an oral mean lethal dose (LD_{50}) in rats of 27 to 41 mg/kg body weight [*1*]. The liver lesion it produces is consistent with the microscopic observations made in the livers of the two deceased [*2*]. Dimethylnitrosamine is also very rapidly metabolized [*3*] and excreted, making it impossible to detect above background levels four and five days after exposure. However, it is known that dimethylnitrosamine is a very potent methylating agent. Recently, a high-pressure liquid chromatography method has been developed that can detect methylation of guanine in the 7 and O^6 position [*4*]. Methylation of guanine by dimethylnitrosamine occurs primarily in the liver [*5*]. The methylated products are only gradually excreted [*6*].

Frozen liver and kidney tissue from Patient 2 and from six additional unrelated cases were selected to determine whether methylation of guanine had occurred. All tissues had been submitted in a similar manner to CDC.

The six additional specimens of liver and kidney were from an as-yet-unresolved poisoning case involving several people and three specimens from Reye's syndrome cases. These eight tissue specimens of at least 5 g each were given blind to Dr. R. C. Shank in the Atlanta Airport and analyzed in Irvine, Calif. Briefly, the results were as follows: insufficient DNA was isolated to perform the test from the kidney of Patient 2 and one liver and kidney from the as-yet-unresolved poisoning case. Sufficient DNA was isolated from the other four control cases, two livers from Reye's syndrome cases, one kidney from a Reye's syndrome case, and one liver from the as-yet-unresolved poisoning case. None had methylated guanine. The liver of Patient 2 contained 2578 μmoles 7-methylguanine per mole guanine and 273 μmoles O^6 methylguanine per mole guanine.[4]

On 5 Oct. 1979, following a three-week jury trial, the ex-boyfriend was convicted of two counts of first degree murder and three counts of poisoning [*7*].

Discussion

Many man-made and naturally occurring substances may affect the liver, but most of these compounds cause damage in other organs as well. It is unusual to find that only the liver is severely damaged by a compound and no other organs are involved.

[3]H. Fales, National Heart and Lung Institute, National Institutes of Health, Department of Health, Education and Welfare, personal communication, 11 Sept. 1979.

[4]R. C. Shank, personal letter to Mr. Samuel W. Cooper, 28 Aug. 1979.

In this poisoning outbreak, ingestion of a substance in lemonade or milk caused the illness. The toxic agent was capable of methylating guanine at rates comparable to those found in rats that had received high doses of dimethylnitrosamine [5]. Twenty-four hours after rats were given 5 mg of dimethylnitrosamine per kilogram of body weight, 1176 μmoles 7-methylguanine per mole guanine and 99 μmoles O^6 methylguanine per mole guanine were found. The ratio between the two methylguanines in the liver of Patient 2 was approximately 10 to 1, which is consistent with the ratio produced in rats given high doses of dimethylnitrosamines [5]. Furthermore, dimethylnitrosamine is miscible with water and causes the type of liver necrosis observed in the cases. The liver lesion observed in the patients differs from that produced by carbon tetrachloride in that it is more sharply circumscribed, shows more hemorrhage, and is devoid of hydropic or other slightly damaged cells. Solvents, such as carbon tetrachloride, methyl bromide, and tetrachloroethane, could be ruled out because there were no early effects on the sensorium and no kidney damage. It would also have been difficult to mix such solvents with beverages that did not contain alcohol. The victims should have noticed the presence of solvents if they had been present in amounts high enough to cause death. Poisoning cases that have resulted from the ingestion of solvents have usually occurred in association with the consumption of ethyl alcohol and many cases of carbon tetrachloride poisoning have been found among alcoholics [8].

The bleeding tendency described in these cases had also been observed in other cases of dimethylnitrosamine poisoning. Freund [2] reported subpericardial areas of bleeding and bleeding into the bronchi, the trachea, and the left lower lobe of the lungs. Occasional superficial areas of bleeding were noted throughout the entire mucous surface of the small bowel. He observed scarcity of germ centers in the lymph nodes. Apparently he did not examine the brain. In our cases, as well as in the cases reported in the literature, the bone marrow was not affected. Freund [2] did not report thrombocytopenia and neither did Hamilton and Hardy [9], who observed additional cases of dimethylnitrosamine poisoning.

Exposure of dogs, rats, and mice to dimethylnitrosamine caused anorexia, liver damage, and bleeding. The rectal temperature in dogs was elevated. The blood clotting mechanism was disrupted, but thrombocytopenia was not specifically reported [10]. It is not quite clear how carefully the thrombocytes were studied in the human poisoning cases or the animal studies. Furthermore, the exposure differed. In the human cases as well as the animal studies reported in the literature, the route of exposure was inhalation rather than ingestion and examination of the victims was not done as soon after exposure as in our cases. It is possible that the effect on platelets occurs early and is transient and was, therefore, not noticed. Prolonged prothrombin time may also be another cause of bleeding.

Other compounds considered as possible causes, such as yellow phosphorus, selenium, arsenic, and acetaminophen, were excluded because they were not found in high concentrations in the tissues or because they did not fit the disease very well. It would also have been difficult to administer these compounds in a glass of lemonade or milk in sufficient amounts to cause the outbreak.

Methotrexate, another compound causing liver damage, is soluble only in alkaline solutions and decomposes rapidly; doses of 2.5 mg per person cause loss of hair and very severely affect the bone marrow [11,12].

Aflatoxins, which are also known to cause liver damage, are produced by a mold that at times grows on corn, peanuts, and other food products. A source for this compound would be moldy food. However, the people who became ill did not have a meal common to them and separate from other people who did not get ill. Furthermore, the microscopic appearance of the liver in patients suffering from acute aflatoxin poisoning is quite different from the lesions observed in the deceased [13,14].

Pyrrolizidine is an alkaloid that occurs normally in senecio plants. It produces hepatocellular damage accompanied by obliterating vascular lesions of the hepatic veins. This was not observed in the liver of the deceased. Also, a source could not be established for this com-

pound. Pyrrolizidine is only slightly soluble in water except for the hydrochloride, and poisoning has usually occurred in animals following repeated ingestion of the plant material; however, human cases have also occurred [*15*].

Hydrazine, which is related to dimethylnitrosamine, is a colorless, caustic, oily liquid with a fishy penetrating odor. It is miscible with water. It usually causes excitement and tonic clonic convulsions soon after exposure. The microscopic appearance of the liver of the deceased was different from what has been reported for hydrazine. Hydrazine causes vacuolation of the hepatocytes throughout the liver lobules. The related compound, dimethylhydrazine, produces no liver damage on acute exposure. Hydrazine and dimethylhydrazine cause severe hemolysis [*16*], which was not observed in the cases presented here.

Quite a number of alkylating agents are known. However, many of the alkylating agents are not very soluble in water. Methyl methanesulfonate, dimethyl sulfate, dimethylnitrosamine, *N*-methyl-*N'*-nitro-*N*-nitroso-guanidine, 1,2-dimethylhydrazine, methyl chloride, methyl bromide, and methyl iodide are soluble in water and could, theoretically, methylate guanine.

Methyl bromide, methyl iodide, and methyl chloride are very weak alkylating agents. Poisoning by these three compounds usually occurs following inhalation and predominately affects the central nervous system early in the illness. Methylhydrazine has already been discussed. The other three compounds—methyl methanesulfonate, dimethyl sulfate, and *N*-methyl-*N'*-nitro-*N*-nitroso-guanidine—do not cause the type of liver damage observed in the deceased, although liver toxicity and gastrointestinal toxicity can be produced by methyl methanesulfonate [*17*]. Dimethyl sulfate would break down to sulfuric acid and methanol in the presence of water and would, therefore, not have been stable in a beverage. The liver lesion that it produces is different, consisting of fatty degeneration and scattered areas of necrosis and not uniformly involving all lobules of the liver. *N*-methyl-*N'*-nitro-*N*-nitroso-guanidine is acutely less toxic than dimethylnitrosamine. The oral LD_{50} in the rat is 400 mg/kg body weight so that to be lethal, a much larger amount would have to be given, somewhere in the range of 10 to 20 g per person.

Thus, by the process of exclusion and because symptoms as well as the liver pathology matched, dimethylnitrosamine was the only logical chemical that could have caused the illnesses and deaths. Dimethylnitrosamine has an oral LD_{50} in rats of 27 to 41 mg/kg body weight [*1*]. A lethal dose for a person weighing 60 kg (132 lb) would be roughly 1.8 g and for a child weighing 10 kg (22 lb), around 0.3 g.

The fact that these patients were poisoned was not recognized at first. Whenever unusual cases of illness occur that do not fit any specific disease pattern, poisoning should be suspected and foul play should be considered. It is highly possible that many such cases go unrecognized, particularly if chemicals are involved that are rapidly metabolized or that are beyond the usual range of compounds routinely checked for in clinical and forensic toxicology laboratories. The meticulous collection of evidence, intelligent interpretation of these findings, and the clinical observations are often more fruitful than the screening of tissue for an array of compounds that are basically known not to cause the symptoms observed in the patients.

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