Acquired Methemoglobinemia

MITCHELL E. GEFFNER, MD; DARLEEN R. POWARS, MD, and
WILLIAM T. CHOCTAW, MD, Los Angeles

Cases of acquired methemoglobinemia have been identified with increasing frequency in Los Angeles during the last several years. Among 18 patients, both infants and adults, the most commonly incriminated agent was silver nitrate used for topical antibacterial prophylaxis of burn wounds. One burned child died from overwhelming septicemia complicated by hypoxia with a methemoglobin level of 5.4 grams per dl. Other causative factors included nitrate-rich vegetables used in early infancy, additives in ethnic foods, and prescribed and overdosed drugs. Discontinuation of the precipitating agent and methylene blue therapy were usually followed by prompt improvement. In burned patients treated with silver nitrate, careful regular monitoring of serum methemoglobin levels and early initiation of specific therapy are mandatory.

That methemoglobinemia may complicate nitrate or nitrite use in infants, children and adults has been well recognized for many years. Recently, we have observed an upsurge in the incidence of this complication in four specific areas: (1) application of topical silver nitrate in the treatment of burns; (2) introduction of vegetables with high nitrate content into the diets of infants younger than 3 months of age; (3) ingestion of additives in ethnic foods among populations from Mexico, Southeast Asia and the Philippines, and (4) use of certain prescribed drugs.

We wish to report on our experience of patients with acquired methemoglobinemia in a metropolitan hospital in central-city Los Angeles between 1973 and 1978. Recently, excellent reviews of methemoglobinemia, including unresolved issues of biochemistry, have been published.\(^1,2\)

Patients, Methods and Results

All patients with known methemoglobinemia between 1973 and 1978 were evaluated. Abnormal levels of methemoglobin were considered those above 0.2 grams per dl. Methemoglobin levels were determined by the Gilford-240 spectrophotometer (Overland, Ohio), which clearly distinguishes methemoglobin from sulfhemoglobin. Table 1 includes the ages of patients, dates of diagnoses, maximum methemoglobin levels, methemoglobin levels expressed as a percent of the total hemoglobin concentration, offending agents if known and treatment modalities used. Of the 18 patients identified, 4 were younger than 1 year of age, 2 were between 1 and 18 years old and 12 were adults.

Our hospital is a major referral center for
moderately to severely burned patients. Topical silver nitrate (via continuous drip) has been the mainstay in the prevention of secondary infection in such patients; consequently, at present it is the most common identifiable cause of acquired methemoglobinemia (7 of 18 cases). Nitrate-containing prescription drugs (4 of 18), accidental overdosages (2 of 18), food additives (2 of 18) and nitrate-rich vegetables in early infancy (2 of 18) constitute the remaining causes. In only one case could no cause whatsoever be ascertained. During this six-year study period, there were no known cases of methemoglobinemia associated with exposure to aniline dyes, well water or vitamin K analogues. Table 2 lists the incriminated agents and the number of cases involved.

At our burn center we maintain a high index of suspicion for methemoglobinemia in patients who are receiving topical silver nitrate antibacterial prophylaxis. However, the identification of an altered skin appearance (that is, cyanosis) for diagnosis poses severe clinical difficulties of recognition in burned patients in view of pronounced skin disruption, dressings applied over a substantial amount of surface area, skin color changes induced by the silver nitrate itself and, often, precarious cardiovascular status. Clinical diagnosis must therefore be based primarily on the observation of dark "chocolate-colored" blood obtained during the frequent phlebotomies of these patients. In the remainder of our sample population, either clinical cyanosis was the presenting problem or methemoglobinemia was a fortuitous laboratory finding. Methemoglobin reductase levels were measured in selected patients, including a husband and wife who ingested sodium nitrate and several infants who ate nitrate-rich vegetables. Reductase levels were determined to be normal for age. Burned patients who had received multiple prior transfusions were not tested.

Discussion

In general, the cause of methemoglobinemia in adult patients relates to drugs, industrial exposures, cultural dietary patterns and recreational use of nitrates. The infant group is at risk from the ingestion of vegetables rich in nitrates such as spinach, beets, carrots, turnips and cabbage, as well as from well water, skin contact with medicines and chemicals, and accidental ingestions.

Several of our children were given spinach and other vegetables during the first three months of life. Of note is that bottles of Gerber baby spinach

---

**ACQUIRED METHEMOGLOBINEMIA**

---

**TABLE 1.—Case Descriptions of 18 Patients With Acquired Methemoglobinemia**

| Case Number | Age       | Date of Diagnosis | Maximum Methgb. Level (grams per dl) | Methgb. Level as Percent of Total Hemoglobin | Cause | Treatment       |
|-------------|-----------|-------------------|-------------------------------------|---------------------------------------------|-------|----------------|
| 1           | 1 mo      | 1/19/74           | 1.1                                 | 10                                          | Unknown | None           |
| 2           | 51 yr     | 10/28/74          | 0.3                                 | 28                                          | AgNO₃ for burn | Discontinue drug |
| 3           | 21 yr     | 5/11/75           | 2.3                                 | 28                                          | Chloroquine | Discontinue drug |
| 4           | 26 yr     | 8/15/75           | 0.5                                 | 70                                          | Sodium nitrate salt (food additive) | Change to sulfadiazine |
| 5*          | 29 yr     | 6/ 3/76           | 9.1                                 | 30                                          | Sodium nitrate | Methylen blue |
| 6*          | 27 yr     | 6/ 3/76           | 3.0                                 | 30                                          | AgNO₃ for burn | Methylen blue |
| 7           | 43 yr     | 8/ 8/76           | 3.0                                 | 30                                          | AgNO₃ for burn | change to sulfadiazine |
| 8           | 56 yr     | 8/28/76           | 0.4                                 | 30                                          | Isosorbide dinitrate | Discontinue drug |
| 9           | 3 yr      | 9/20/76           | 0.3                                 | 30                                          | AgNO₃ for burn | Methylen blue, discontinue AgNO₃ |
| 10          | 33 yr     | 10/ 6/76          | 0.3                                 | 13                                          | AgNO₃ for burn | Discontinue AgNO₃ |
| 11          | 36 yr     | 4/16/77           | 1.9                                 | 13                                          | Deodorant containing butyl nitrite | Discontinue AgNO₃ |
| 12          | 82 yr     | 6/10/77           | 0.3                                 | 4                                           | AgNO₃ for burn | Discontinue AgNO₃ |
| 13          | 44 yr     | 7/14/77           | 0.4                                 | 4                                           | Spinach water | Methylen blue |
| 14          | 1 mo      | 10/ 9/77          | 3                                   | 3                                           | Tricofuron* | Discontinue agent |
| 15          | 27 yr     | 2/19/78           | 0.3                                 | 3                                           | Phenazopyridine | Discontinue agent |
| 16          | 17 mo     | 11/16/78          | 0.4                                 | 3                                           | Gerber pureed spinach, beets | Methylen blue |
| 17          | 6 wks     | 11/26/78          | 2.8                                 | 35                                          | AgNO₃ for burn | Methylen blue |
| 18          | 3 mo      | 12/28/78          | 5.4                                 | 45                                          |                   |                 |

AgNO₃ = silver nitrate; Methgb. = methemoglobinemia

*Married Filipino couple.
†This formerly available product contains furazolidone and nifuroxamine (both of which contain nitrate groups) and was used intravaginally for the treatment of trichomoniasis.
ACQUIRED METHEMOGLOBINEMIA

TABLE 2.—Causes of Acquired Methemoglobinemia

| Cause                                | Number of Cases |
|--------------------------------------|-----------------|
| Silver nitrate                       | 7               |
| Prescribed drugs                     | 4               |
| Overdosages of drugs                 | 2               |
| High-nitrate vegetables ingested     | 2               |
| during early infancy                 |                 |
| Food additives                       | 2               |
| Unknown                              | 1               |
| **Total**                            | **18**          |

recommend—albeit in very small print—that this product is not to be given to infants younger than 12 weeks of age. Additionally, the American Academy of Pediatrics clearly recommends avoidance of spinach and other nitrate-rich vegetables in their recent report on infant feeding. Nitrates as preservatives are usually found in highest concentrations in foods not ordinarily eaten by younger children, such as hot dogs, bacon, ham, lunch meats and some imported cheeses.

In susceptible infants, as well as adults, the intake of nitrate-rich vegetables may be harmful if the nitrate is converted to hazardous nitrite. This may occur by either of two mechanisms: contamination by bacteria capable of nitrate reduction during processing or chemical reduction as a result of the plant's intrinsic enzymes. Furthermore, infants during the first few months of life are known to have a lower gastric acidity with a resultant proliferation of bacterial species capable of reducing nitrate to nitrite. This latter factor combined with the known low physiological levels of protective erythrocyte methemoglobin reductase predisposes the infant population to a risk greater than among older persons. Normal erythrocytic methemoglobin reductase is capable of reducing methemoglobin at 250 times the physiological rate of formation. Only when the toxic agent has saturated this protective mechanism does methemoglobin accumulate in erythrocytes. Methemoglobin changes the cooperativity of the hemoglobin molecule resulting in a shift of the oxygen dissociation curve to the left, thereby decreasing delivery of oxygen to the tissues.

In mild degree, dietary-induced methemoglobinemia is of minimal clinical significance. If methemoglobin levels remain below 1 gram per dl, most patients are asymptomatic. When clinically indicated, methylene blue (1 to 2 mg per kg of body weight) or ascorbic acid (200 to 500 mg per day) is effective therapy. It should be noted that in patients who are deficient in glucose-6-phosphate dehydrogenase (G-6PD), administration of methylene blue has been reported to cause a Heinz-body hemolytic anemia. We have, in addition, observed the development of a severe Heinz-body hemolytic anemia in an infant with normal values for G-6PD who was accidentally administered an excessive dose of methylene blue (10 mg per kg of body weight).

The as yet unsolved problem posed by large areas of second and third degree burns and the appropriate prophylaxis of secondary bacterial infections is of major concern in our burn center. Silver nitrate, silver sulfadiazine and combinations of them are the best and safest agents for the prophylaxis of burn wound infections. Most deaths among burned patients of all ages result from the problem of severe, overwhelming infection. Acquired methemoglobinemia in our burned patients had three prerequisites (1) a source of nitrate (silver nitrate), (2) a mechanism of nitrate reduction (the proliferation of microorganisms capable of reducing nitrate to nitrite (such as Pseudomonas aeruginosa, Enterobacter species, Escherichia coli, Serratia marcescens, and some Proteus species) and (3) an altered barrier through which the nitrite can be absorbed into the bloodstream (the surface area of burned skin).

It is the goal of topical antibiotic drugs to prevent any infection of the wound. Initiation of methylene blue therapy in patients with complicated burns must be individualized to the clinical status of each patient. The physicians at our burn center have observed tachypnea, tachycardia and other signs of hypoxia which were immediately improved following methylene blue therapy in patients with methemoglobin levels of less than 1 gram per dl (case 9). In the event that methemoglobin levels increase beyond the safe range, but no related symptomatology is seen, discontinuing application of silver nitrate for two or three days is effective. In addition, substitution of alternative topical antisepsis, such as mafenide acetate or silver sulfadiazine, should be made. It should be cautioned, however, that clinical methemoglobinemia, or more likely, sulfhemoglobinemia, has recently been reported in two 2-year-old children treated with mafenide acetate for 50 percent surface burns. Although sulfhemoglobinemia differs clinically from methemoglobinemia by the gross mauve-lavender color imparted to the blood, its irreversibility and its production of cyanosis at
lower concentrations, the two can be precisely differentiated by readily available spectrophotometric equipment.18

Of special note is one severely burned 3-month-old infant (case 18) treated with silver nitrate in whom methemoglobin levels reached 5.4 grams per dl (4 percent). The infant died three days after the burns were incurred. Findings at autopsy showed second and third degree burns over 75 percent of the child's body, septicemia, disseminated intravascular coagulation and diffuse manifestations of hypoxia. Two other children have been reported in the literature, aged 3 and 5 years in whom complications of methemoglobinemia developed after 15 and 26 days of therapy with silver nitrate, and who died on hospital days 27 and 30, respectively.16,19 Both were colonized with nitrate-reducing bacteria.15 Methemoglobinemia had developed in our infant on only the third hospital day and she died within 24 hours. Although the child's prognosis was grim by virtue of the extent of the burns and their complications, severely compromised oxygen transport may have contributed to her death. The case of this extremely ill, septic and burned infant clearly illustrates the problems encountered with methemoglobin toxicity.

Conclusion

We recommend that burn centers using silver nitrate antisepsis regularly monitor methemoglobin levels in their patients. A prospective study is needed to provide data regarding the true incidence of methemoglobinemia and the resultant clinical consequences on these severely burned patients.

REFERENCES
1. Herzog P, Feig SA: Methaemoglobinemia in the newborn infant. Clin Haematol 7:75-83, 1978
2. Committee on Nutrition: Infant methemoglobinemia: The role of dietary nitrate. Pediatrics 46:475-477, 1970
3. Hamblin DO: Aromatic nitro and amino compounds, chap 47, In Patty FA (Ed): Industrial Hygiene and Toxicology, Vol II, 2nd Ed. New York, Interscience Publishers, 1963
4. Keating JP, Lell ME, Strauss AW, et al: Infantile methemoglobinemia caused by carrot juice. N Engl J Med 288:826-826, 1973
5. Committee on Nutrition: On the feeding of supplemented foods to infants. Pediatrics 65:1178-1181, 1980
6. Magee PN: Toxicity of nitrosamines: Their possible human health hazards. Food Cosmet Toxicol 9:207-218, 1971
7. Panque A, Del Campo FF, Ramirez JM, et al: Flavin nucleotide reductase from spinach. Biochem Biophys Acta 109: 79-85, 1965
8. Nitrates and nitrites in food. Med Lett Drugs Ther 16:75-76, 1974
9. Bartos HR, Desforges JF: Erythrocyte DPNH dependent diaphorase levels in infants. Pediatrics 37:991-993, Jun 1966
10. Scott EM: Congenital methemoglobinemia due to DPNH diaphorase deficiency, In Beutler E (Ed): Hereditary Disorders of Erythrocyte Metabolism. New York, Grune and Stratton, 1968, pp 102-113
11. Enoki Y, Tokui H, Tysma I: Oxygen equilibrium of partially oxidized hemoglobin. Respir Physiol 7:300-309, 1969
12. Smith RP, Olsen MV: Drug-induced methemoglobinemia. Semin Hematol 10:253-268, 1973
13. Coluboff N, Wheaton R: Methylene blue induced cyanosis and acute hemolytic anemia complicating the treatment of methemoglobinemia. J Pediatr 58:86-89, 1961
14. Monafee WM: An overview of infection control. J Trauma 19:879-880, 1979
15. Skerman VBD: A Guide to the Identification of the Genuses of Bacteria. Baltimore, Williams & Wilkins Co, 1959, pp 61, 89-96
16. Ternberg JL, Luce E: Methemoglobinemia: A complication of the silver nitrate treatment of burns. Surgery 63:328-330, 1968
17. Ohlqisser M, Adler M, Ben-Dov D, et al: Methaemoglobinemia induced by malonid acid in children. Br J Anaesth 50: 299-301, 1978
18. Wintrobe MM, Lee GP, Boggs DR, et al: Methemoglobinemia and other disorders usually accompanied by cyanosis, In Wintrobe MM (Ed): Clinical Hematology, 6th Ed. Philadelphia, Lea and Fiehiger, 1974, pp 1009-1020
19. Cushing AH, Smith S: Methemoglobinemia with silver nitrate therapy of a burn: Report of a case. J Pediatr 74:613-615, 1969