Cause of Methemoglobinemia: Illness versus Nitrate Exposure

In their Grand Rounds article in the July 2000 issue of *EHP*, Knobeloch et al. (*1*) argued that exposure to nitrate-contaminated water remains the primary cause of infantile methemoglobinemia. As they stated in their conclusion (*1*),

> Our findings do not support Avery's conclusions regarding the roles of gastrointestinal infections and nitrate-contaminated water in the etiology of infant methemoglobinemia.

To the contrary, the information presented by Knobeloch et al. (*1*) support my conclusions (*2*).

Knobeloch et al. (*1*) described two purported cases of infantile methemoglobinemia in their paper. The diagnosis of methemoglobinemia in case 1, however, is completely speculative: a doctor did not examine the infant, and blood methemoglobin concentrations were not measured during the observed anoxia. It seems ill considered, therefore, to include this case in a serious discussion of the causes of methemoglobinemia.

Knobeloch et al. (*1*) placed undue importance on my discussion of infectious illness as a potential factor in methemoglobinemia (*2*), and their conclusion implies that I limited my discussion and conclusions to infectious illness. This is erroneous. As I discussed in my review (*2*), the case literature amply demonstrates that, along with gastrointestinal and urinary tract infections, a number of noninfectious gastrointestinal disturbances can directly cause methemoglobinemia in infants without exposure to exogenous nitrates in food or water, including copper toxicity (*3*), protein intolerance (*4*), and nonspecific diarrhea (*5*,*6*).

Although Knobeloch et al. (*1*) acknowledge that studies show "infants with diarrhea are at risk of developing methemoglobinemia, even in the absence of dietary nitrate exposure," they state that "only a small percentage of infants in these cohorts had clinically significant methemoglobin levels."

This statement seriously understates the potential severity of methemoglobinemia caused solely by diarrhea and other gastrointestinal illnesses; I found eight cases reported in the literature in which methemoglobin levels were > 34%, and three of these were > 55% (*4*,*7*–*12*). Contrary to the claims of Knobeloch et al. (*1*), secondary risk factors, such as nitrate-contaminated water, oxidant drug exposure, and inherited enzyme deficiencies, were ruled out in all of these cases, as well as in dozens of additional cases caused by diarrhea.

In fact, Knobeloch (*13*) has acknowledged that diarrhea was observed during hospitalization in case 2 of their report, undermining the conclusion that nitrates from drinking water played a critical role in this case. Knobeloch has suggested that the observed diarrhea was merely the result of the severe anoxia suffered by this infant (91.2% methemoglobin concentration) (*13*). However, the anoxia in this case was life threatening and resolved quickly following methylene blue treatment immediately after admission to the hospital. Therefore, if anoxia were the cause of the diarrhea, the diarrhea would not be expected to persist during hospitalization. Moreover, diarrhea has not been reported in cases of anoxia and methemoglobinemia caused by oxidant drug or chemical exposure.

Knobeloch et al. (*1*) stated that "infectious illnesses apparently did not contribute to her illness," yet they failed to mention the infant's diarrhea in their paper. It is worth noting that the well water in case 2 tested positive for *Escherichia coli*.

Knobeloch et al. (*1*) also failed to discuss the lengthy hospitalization of case 2. The authors stated that the infant "responded rapidly to treatment with methylene blue," yet the infant remained hospitalized for 17 days. What other health problems existed that required such a lengthy hospitalization? Could these health problems have contributed to the methemoglobinemia? Unfortunately, on several occasions Knobeloch has refused to discuss the specifics of this case with me.

Regardless, the diarrhea, the extremely high methemoglobin level, and the lengthy hospitalization indicate that the infant in case 2 was suffering from more than simple chemical nitrate poisoning.

This raises an important question, in fact, the question at the heart of my original review: What are the factors that contribute to methemoglobinemia in infants? Exposure to even high levels of exogenous nitrates in drinking water is insufficient, by itself, to cause methemoglobinemia. This was demonstrated conclusively by experiments conducted with human infants in the 1940s (*14*). Four healthy infants ranging from 2 days to 6 months of age were fed formula prepared with water containing ~100 ppm nitrate–nitrogen (nitrate-N). Despite ingesting such highly contaminated formula for more than a week, the highest methemoglobin level observed was 7.5%, with no cyanosis evident in any of the patients. Even when nitrate-contaminated formula was fed to several infants hospitalized for methemoglobinemia ostensibly linked to nitrate-contaminated water, the highest methemoglobin level recorded was 11% (*14*). As these researchers noted,

> It appeared that there were other factors in addition to the quantity of nitrate ion ingested that determined whether or not an infant became cyanotic.

All available evidence points to diarrhea, gastrointestinal inflammation, or infection as the critical factors.

Knobeloch et al. (*1*) erroneously concluded from the work of Hegesh and Shiloah (*15*) that

> Exposure to as little as 12 mg of nitrate-N per day can significantly increase an infant's methemoglobin level.

Hegesh and Shiloah (*15*) found high levels of excess nitrate excretion in the urine of infants suffering from diarrhea and methemoglobinemia without exposure to significant nitrates in food or water—a clear indication of endogenous nitrite production and oxidative stress. The excreted nitrates are merely by-products of the reaction between nitrite and hemoglobin that generates methemoglobin. The correct conclusion, therefore, would be that exposure to as little as 12 mg of nitrite-N (not nitrate) can significantly increase an infant's methemoglobin level.

The federal drinking water standard of 10 ppm nitrate-N was established after a review of data from a 1949 American Public Health Association (APHA) survey of state health departments regarding methemoglobinemia cases linked to nitrate-contaminated water. As reported by Walton in 1951 (*16*),

> Special emphasis was placed on restricting the data to those cases definitely associated with nitrate-contaminated water.

This emphasis in the APHA survey and indeed the wide and rapid acceptance by the medical community that nitrates in drinking water are the primary cause of infantile methemoglobinemia have created an inherent bias: any methemoglobinemia case with elevated nitrates in the water is assumed to be caused by the nitrates, even though it is now clear that additional factors are critical for methemoglobinemia to occur. Furthermore, these factors have now been proven to cause severe methemoglobinemia without exposure to exogenous nitrates from water or food (*4*,*7*–*12*). Thus, the available evidence suggests that exogenous nitrates from drinking water have the potential to exacerbate, but not cause, methemoglobinemia.

The Environmental Working Group has used the existence of methemoglobinemia cases at drinking-water nitrate concentrations < 10 ppm nitrate-N to argue that the current federal standard should be reduced to 5 ppm (*17*). At what point does

one stop with this logic? Does the existence of methemoglobinemia cases at water concentrations of 1 ppm nitrate-N require a standard below this level?

The current 10 ppm standard is based on very limited and poor-quality case information. Only five methemoglobinemia cases were reported at nitrate-N concentrations < 20 ppm. Moreover, the APHA survey did not report the presence of nitrite, bacteriologic contamination, gastrointestinal disease, diarrhea, or methemoglobin concentration. Walton (*16*) considered it worth noting that

> In many of these cases clinical data were insufficient for definite diagnosis, and samples of water for the analysis were sometimes collected several months following the occurrence of the case.

Walton (*16*) also addressed the 10 ppm standard:

> Although 10 ppm nitrate–nitrogen has been suggested as the permissible level, the A.P.H.A. Committee points out that most of the cases studied were associated with nitrate–nitrogen concentration in excess of 40 ppm and comments that it is impossible at this time to select any precise concentration of nitrates in potable waters fed infants which definitively will distinguish between waters which are safe or unsafe.

I stand by my conclusion that relaxing the drinking water standard for nitrate to 15 or 20 ppm nitrate-N would not appreciably increase the health risks to infants. However, my view must be corroborated through a full review by a panel of independent experts before it could reasonably be implemented as sound public health policy. Conducting such a review now is appropriate because of recent research findings. Even if the review concluded that more information was necessary, it could at least identify areas of research that could help fully elucidate methemoglobinemia etiology.

As to the "other potential health concerns" raised by Knobeloch et al. (*1*) concerning nitrate exposure through drinking water, both the National Research Council (*18*) and the U.S. Environmental Protection Agency (*19*) have concluded that there are no convincing data to suggest that nitrate is associated with any adverse effect other than methemoglobinemia because the evidence from case–control studies is both weak and contradictory. Recent studies also have shown only weak and contradictory associations. Moreover, there is no plausible mechanism whereby the relatively small contribution of nitrates from drinking water contributes to cancer or other adverse health conditions while the considerably larger nitrate exposure through vegetables and endogenous production does not (*18,19*).

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References and Notes

1. Knobeloch L, Salna B, Hogan A, Postle J, Anderson H. Blue babies and nitrate-contaminated well water. Environ Health Perspect 108:675–678 (2000).
2. Avery AA. Infantile methemoglobinemia: rexamining the role of drinking water nitrates. Environ Health Perspect 107:583–586 (1999).
3. Knobeloch L, Krenz K, Anderson H. Methemoblobinemia in an infant—Wisconsin, 1992. MMWR Morb Mortal Wkly Rep 42:217 (1993).
4. Murray KF, Christie DL. Dietary protein intolerance in infants with transient methemoglobinemia and diarrhea. J Pediatr. 122:90–92 (1993).
5. Hanukoglu A, Danon PN. Endogenous methemoglobinemia associated with diarrheal disease in infancy. J Pediatr Gastroenterol Nutr 23:1–7 (1996).
6. Lebby T, Roco JJ, Arcinue EL. Infantile methemoglobinemia associated with acute diarrheal illness. Am J Emerg Med 11:471–472 (1993)
7. Yano SS, Danish EH, Hsia YE. Transient methemoglobinemia with acidosis in infants. J Pediatr 100:415–418 (1982).
8. Gebara B, Goetting MM. Life-threatening methemoglobinemia in infants with diarrhea and acidosis. Clin Pediatr 33:370–373 (1994).
9. Dagan R, Zaltzstein E, Gorodischer R. Methemoglobinemia in young infants with diarrhea. Eur J Pediatr 147:87–89 (1988).
10. Luk G, Riggs D, Luque M. Severe methemoglobinemia in a 3-week old infant with urinary tract infection. Crit Care Med 19:1325–1327 (1991).
11. May RB. An infant with sepsis and methemoglobinemia. J Emerg Med 3:261–264 (1985).
12. Seeler RA. Methemoglobinemia in infants with enteritis [Letter]. J Pediatr 102:162 (1983).
13. Knobeloch, L. Personal communication.
14. Cornblath M, Hartmann AF. Methemoglobinemia in young infants. J Pediatr 33:421–425 (1948).
15. Hegesh E, Shiloah J. Blood nitrates and infantile methemoglobinemia. Clin Chim Acta 125:107–115 (1982).
16. Walton G. Survey of literature relating to infant methemoglobinemia due to nitrate-contaminated water. Am J Public Health 41:986–996 (1951).
17. Environmental Working Group. Pouring It On: Nitrate Contamination of Drinking Water. Washington, DC:Environmental Working Group, 1996.
18. National Research Council. Nitrate and Nitrite in Drinking Water. Washington, DC:National Academy Press, 1995.
19. US Environmental Protection Agency. Final Drinking Water Criteria Document on Nitrate/Nitrite. NTIS PB91-142836. Springfield, VA:National Technical Information Service, 1990.

Methemoglobinemia: Response to Avery

In his letter, Avery expressed concern about the accuracy and completeness of our case reports (*1*). Because his letter is quite long and touches on many different subjects, we have attempted to address his major points individually below.

Avery states that it seemed ill considered "to include this case [case 1] in a serious discussion of the causes of methemoglobinemia." Although case 1 was not confirmed by laboratory testing, the infant was seen by an experienced public health nurse. We discussed and acknowledged the presumptive nature of this infant's diagnosis in our paper (*1*). We included this case, in part, because we believe the way in which it was handled is typical of the manner in which the majority of nitrate-induced infant illnesses are handled in Wisconsin and, perhaps, throughout the United States.

As reported by Avery, the infant in case 2 experienced diarrhea during her hospital stay. However, this symptom was not mentioned on the infant's emergency room or medflight records and appears to have onset sometime after she was admitted to the pediatric intensive care unit. It should be noted that diarrhea is a common side effect of methylene blue therapy (*2*) and ceftriaxone (*3*). Both of these drugs were administered to this infant by emergency room staff. Severe hypoxia may also have contributed to this infant's gastrointestinal symptoms. Thus, although diarrhea has been implicated as a risk factor for infant methemoglobinemia, it does not appear to have contributed to the onset of this infant's illness.

We disagree with Avery's contention that diarrhea has not been reported in cases of anoxia and oxidant chemical exposure. Diarrhea, nausea, and vomiting are common symptoms associated with hypoxia caused by carbon monoxide and nitrite exposures (*4*). In a recent outbreak of methemoglobinemia among New Jersey school children, symptoms of cyanosis, nausea, abdominal pain, vomiting, headache, and dizziness onset within 1 hr of their exposure to nitrite-contaminated soup (*5*).

Avery states that "It is worth noting that the well water in case 2 tested positive for *Escherichia coli*." Although many private drinking water wells in Wisconsin test positive for *E. coli*, this contamination has not been associated with infant methemoglobinemia. The parents of this infant indicated that they boiled the well water for several minutes before using it to prepare infant formula because they were concerned about possible contamination of the well. This practice is effective in eliminating the risk of *E. coli* infection, but it could slightly increase the nitrate level. Stool cultures for this infant were negative for pathogenic *E. coli*, *Shigella* sp., *Salmonella* sp., and *Campylobacter* sp.

Avery also commented on our failure "to discuss the lengthy hospitalization of case 2." In our paper (1), we indicated that the infant (case 2) was discharged 17 days after admission. The length of a patient's hospitalization is a matter of the physician's professional judgment. The length of this infant's hospital stay was undoubtedly influenced by several factors, including the seriousness of her condition on admission,

young age, prematurity, body weight of only 5 lbs, and rural residence.

Regarding our discussion of other published cases of infant methemoglobinemia, Avery states that

> Contrary to the claims of Knobeloch et al. (*1*), secondary risk factors … were ruled out in all of these cases, as well as in dozens of additional cases caused by diarrhea.

Although we have not had an opportunity to review some of the papers cited by Avery, none of the case summaries that we have reviewed to date included detailed information on potential exposures to methemoglobin-inducing agents. The list of possible agents is extensive, including strained fruits and vegetables, vegetable broths, water that may have been contaminated by nitrite-containing boiler treatments, lidocaine, prilocaine, analine dyes, and oxides of nitrogen.

Avery believes that our conclusion from the work of Hegesh and Shiloah (*6*)—that "as little as 12 mg of nitrate-N per day can significantly increase an infant's methemoglobin level"—is erroneous. Hegesh and Shiloah (*6*) measured urinary nitrate levels, which is the measurement referenced in our paper. Because ammonia, nitrate, nitrite, and nitric oxide exist in a dynamic equilibrium in the body, it is not possible to accurately predict blood nitrite levels from a urinary nitrate measurement.

Avery also suggested that the

> emphasis in the APHA survey … has created an inherent bias: any methemoglobinemia case with elevated nitrates in the water is assumed to be caused by the nitrates, even though it is now clear that additional factors are critical for methemoglobinemia to occur.

We believe that infant exposure to nitrate and/or nitrite has the potential to cause methemoglobinemia in the absence of other risk factors. Secondary risk factors, such as diarrhea or inherited enzyme deficiencies, can exacerbate the effects of exposure to nitrate or nitrite. However, these factors are not critical to the occurrence of methemoglobinemia.

We disagree with Avery's statement that

> … there is no plausible mechanism whereby the relatively small contribution of nitrates from drinking water contributes to cancer or other adverse health conditions while the considerably larger nitrate exposure through vegetables and endogenous production does not.

Several researchers have described mechanisms whereby ingested nitrate/nitrite might induce birth defects, cancer, diabetes, and thyroid disease. Although additional research is needed in this area, we believe the proposed mechanisms are scientifically plausible.

We also disagree with Avery's assertion that nitrate from vegetables and endogenous nitrite production is "considerably larger" than exposures related to water-borne nitrate. According to Table 4-1 of the National Research Council's (NRC) report on *Nitrate and Nitrite in Drinking Water* (*7*), dietary nitrate intake for an adult averages 76 mg/day. This is equivalent to 17 mg nitrate-N per day. Endogenous nitrate production was estimated to be 62 mg nitrate/day (*7*), which is equivalent to 14 mg nitrate-N per day. In comparison, ingestion of 2 L water that contains 10 mg nitrate-N per liter would provide a nitrate-N dose of 20 mg/day. Thus, at the level of the current standard, drinking water provides more than one-third of an adult's daily nitrate intake. Ingestion of water that contains 20 mg nitrate-N per liter, the level proposed by Avery as safe, would increase an adult's daily nitrate-N exposure from about 30 mg/day to more than 70 mg/day.

Several studies cited in our paper have reported associations between nitrate-contaminated water and a variety of health problems, including cancer, thyroid disease, and diabetes. The U.S. Environmental Protection Agency (*8*) and NRC reports (*7*) cited by Avery were constrained to evaluating exposures to nitrate in municipal water supplies. Thus, both reports assumed a maximum nitrate concentration of 10 mg/L and did not address risks that might be posed by higher nitrate levels.

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References and Notes

1. Knobeloch L, Salna B, Hogan A, Postle J, Anderson H. Blue babies and nitrate-contaminated well water. Environ Health Perspect 108:675–678 (2000).
2. National Library of Medicine. Medline Plus: Methylene Blue (Systemic). Available: http://www.nlm.nih.gov/medlineplus/druginfo/methylenebluesystemic202703.html [cited 23 August 2000].
3. National Library of Medicine. Medline Plus: Cephalosporins (Systemic). Available: http://www.nlm.nih.gov/medlineplus/druginfo/cephalosporinssystemic202119.html [cited 23 August 2000].
4. Gosselin RE, Smith RP, Hodge HC. Clinical Toxicology of Commercial Products. 5th ed. Baltimore, MD:Williams & Wilkins, 1984.
5. MMWR. Methemoglobinemia attributable to nitrite contamination of potable water through boiler fluid additives–New Jersey, 1992 and 1996. MMWR Morb Mortal Wkly Rep 46(9):202–204 (1997).
6. Hegesh E, Shiloah J. Blood nitrates and infantile methemoglobinemia. Clin Chim Acta 125:107–115 (1982).
7. National Research Council. Nitrate and Nitrite in Drinking Water. Washington, DC:National Academy Press, 1995.
8. US Environmental Protection Agency. Final Drinking Water Criteria Document on Nitrate/Nitrite. NTIS PB91-142836. Springfield, VA:National Technical Information Service, 1990.

Corrections and Clarifications

In the letter by Varga and Ember published in the November 2000 issue of *EHP* [Comments on "The Worst of Both Worlds: Poverty and Politics in the Balkans." *EHP* 108:A494 (2000)], the former Soviet republics were incorrectly included in the Visegrad countries. The former Eastern bloc consists of three regions: the Balkans, the Visegrad, and the former Soviet states. The Visegrad countries include the Czech Republic, Slovakia, Poland, and Hungary. *EHP* is sorry for the error.