

COMMITTEE ON NUTRITION

INFANT METHEMOGLOBINEMIA

The Role of Dietary Nitrate

ALTHOUGH there have been no documented instances in which naturally occurring nitrates in commercially prepared food have caused infant methemoglobinemia, periodic public statements have suggested that infant foods are implicated as causes of methemoglobinemia because of their nitrate content.^{1,2} Nitrate in contaminated well water is known to cause infant methemoglobinemia.³ Because the intake of naturally occurring nitrates from such foods as spinach and beets could be as high as that from well water, these foods have been suggested as being potentially hazardous to infants. This report will briefly summarize current knowledge of infant methemoglobinemia and examine the possible reasons for the apparent nontoxicity of food nitrates.

METHEMOGLOBINEMIA

Several comprehensive reviews of methemoglobinemia have been published.^{4,5} Methemoglobin composes about 1% of the total hemoglobin of the healthy adult. Newborn or premature infants may have two to five times this level.⁶ A methemoglobin reductase system normally present in erythrocytes keeps methemoglobin at the 1 to 2% level under normal conditions.^{4,7} In the presence of a marked anemia, low methemoglobin concentrations may be fatal. On the other hand, infants and children can tolerate levels from 5 to 8% without manifesting cyanosis. Death from asphyxia may occur when the concentration of methemoglobin exceeds 70% of the total hemoglobin.^{8,9}

NITRATES VERSUS NITRITES

Nitrates, *per se*, are toxic only at levels higher than those encountered in foods.¹⁰ The potential hazard of nitrate in water or food is its conversion to nitrite either prior to or after ingestion. The nitrite ion oxidizes ferrous iron in hemoglobin to the ferric state. The resulting compound, methemo-

globin, is incapable of binding molecular oxygen.

Conditions for reducing nitrate to nitrite during digestion must exist, or nitrate will be metabolized or excreted without adverse effect. Cornblath and Hartmann¹¹ have concluded that only infants, the pH of whose gastric juice is higher than 4 and who harbor nitrate-reducing bacteria in the upper gastrointestinal tract, develop sufficient concentrations of nitrite to produce methemoglobinemia. One nonsusceptible infant 10 days of age was fed as much as 100 mg of nitrate per kilogram of body weight per day for an 8-day period without developing any signs of cyanosis. The methemoglobin level increased to only 7.5%.¹¹

Jaffe and Heller⁴ have reported other factors which may influence the incidence of methemoglobinemia in infancy. Fetal hemoglobin, the concentration of which is relatively high in the early months of life, forms oxyhemoglobin more readily than does adult hemoglobin. By analogy, it may be more susceptible to oxidation to methemoglobin by nitrite. Total circulating hemoglobin also reaches a minimum between the first and second month.¹² Gastric acidity likewise drops to a minimum level at about 10 days of age and then increases gradually.¹³ The possibility of a transient deficiency of reduced diphosphopyridine nucleotide (DPNH) methemoglobin reductase has also been suggested.⁴

These factors help to explain the relatively higher incidence of methemoglobinemia in the newborn and young infant; however, because they are variable and only limited feeding tests have been reported, it is not possible to state a specific level of nitrate intake which could be considered safe for all infants.

NITRATES IN FOODS

Extensive reviews^{5,14} have failed to identify any infants with methemoglobinemia attributable to the ingestion of plant nitrate

per se. Nitrate poisoning appears to be associated only with ingestion of nitrate in water rather than with naturally occurring nitrate in foods. The data suggest that some protective factors in food may be involved; ascorbic acid and vitamin K, although less effective than methylene blue, have been used in the treatment of methemoglobinemia.⁴ These or other naturally occurring reducing agents may prevent the formation or accumulation of methemoglobin in the erythrocytes, or plant nitrates may occur in chemical combinations that are less readily reduced to nitrite in the gastrointestinal tract than is the nitrate ion of well water. The chronicity of water consumption compared to the intermittency of nitrate ingestion from plant food may also be an important factor. As a result of these or other factors, current feeding practices are not likely to supply sufficient plant nitrate to cause methemoglobinemia, even in infants who are susceptible to the disease.

Under some conditions plant nitrates may be converted to nitrite before feeding. If ingested this nitrite may result in serious or fatal methemoglobinemia. Two infants, 2 and 3½ months of age, developed methemoglobinemia shortly after eating spinach prepared at home.¹⁵ The spinach contained only traces of nitrate but as much as 2,180 ppm of nitrite. More recently, 14 German infants, 2 to 10 months of age, developed methemoglobinemia after eating spinach.¹⁶ The spinach involved in these instances also was pureed in the home and stored under questionable conditions; apparently the spinach became toxic during storage because of conversion of nitrate to nitrite.

Schuphan¹⁷ reported that the nitrite content of spinach containing high levels of nitrate increased from 3 to 355 mg of nitrite per 100 gm of dry substance during transportation and storage of the raw leaves. Phillips¹⁸ has confirmed this observation. The conversion of nitrate to nitrite in the raw leaves may be a result of the action of a plant cell enzyme nitrate reductase known to be present in spinach,¹⁹ or it may result from the action of bacterial enzymes. The increased temperature noted during storage

and the exclusion of oxygen by tight packing during transportation are thought to be factors which increase the rate of this conversion.

Several investigators²⁰⁻²² have found only traces of nitrite in commercially canned infant foods tested under a variety of conditions which might be considered likely to foster conversion of nitrates to nitrites. Phillips^{18,23} has demonstrated that nitrite did not accumulate in canned infant foods when opened and sampled for periods of up to 35 days of storage under normal refrigeration. Differences between the canned product and fresh spinach may be attributed to the inactivation of enzymes, elimination of bacteria, and the loss of nitrate during commercial blanching and preparation. In one study as much as 80% of the nitrate originally present in raw leaves was lost during processing.¹⁸ As a precautionary measure, Brown and Smith have recommended that unused portions of spinach be discarded.²⁴

The extensive use of baby foods provides additional circumstantial evidence that is worth considering. It is conservatively estimated that more than 350 million jars of canned spinach and beets have been used in the United States and Canada over the last 20 years without causing any proven instances of methemoglobinemia.²⁵ In view of the dramatic and well recognized symptoms of infant methemoglobinemia, several instances should have been reported by a feeding test of this magnitude if commercially canned spinach and beets were causative factors.

One source of nitrate potentially capable of producing methemoglobinemia in infants has developed in the last few years—nitrate contamination of drinking water from runoff from farms fertilized with nitrates. This is a hazard whose magnitude cannot be properly measured until more systematic surveys of drinking water for nitrate and/or nitrite content have been undertaken in areas where such hazards exists.

SUMMARY

In the United States and Canada, processed infant foods have not been implicated

in methemoglobinemia associated with food or water intake in infants. Although raw spinach and beets have a higher nitrate content than do other infant foods, one or more protective factors may prevent the extrinsic or intrinsic formation of toxic levels of nitrite from these foods as commercially processed for feeding of infants.

Nitrate contamination of drinking water which may occur from run-off from fields fertilized with nitrates, represents a potential hazard.

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