Iron Deficiency Anemia among Alaska Natives May Be Due to Fecal Loss Rather than Inadequate Intake 1,2

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ABSTRACT To define more fully the nature of a persistently high prevalence of iron deficiency anemia observed among Alaska Native children, we examined dietary iron intake, hemoglobin concentrations, and storage iron (serum ferritin) based on multiple cross-sectional surveys of Alaska Natives between 1983 and 1989. Approximately 30 to 50% of the children studied <12 y of age had depleted iron stores. Anemia and depleted iron stores also were prevalent among adult men and women, about twice as prevalent as in the U.S. population based on the Second National Health and Nutrition Examination Survey (NHANES II). The higher rate of iron deficiency, occurring even when the dietary assessment found Alaska Native iron intake to be higher than the U.S. average with an ample intake of food high in bioavailable iron, suggests blood loss as a possible cause of the unusual pattern of iron deficiency observed. In a pilot study of stool blood loss in two villages, 65% of the samples had a significantly elevated stool heme concentration. Further investigation of iron deficiency due to gastrointestinal blood loss for the Alaska Native is warranted. J. Nutr. 126: 2774–2783, 1996.

INDEXING KEY WORDS:
• Alaska Natives • iron deficiency • anemia
• fecal occult blood • humans

Iron deficiency anemia is a persistent problem among Alaska Natives (Eskimo, Indian, Aleut). The earliest study documenting the high prevalence of anemia among Alaskan Eskimos was in 1953 (Scott et al. 1955). Anemia surveys from the 1960s through the mid-1980s [Margolis et al. 1982, Nobmann 1976, Peter-ersen and Grant 1984, Sauberlich et al. 1972, Thiele et al. 1988] consistently recorded a prevalence of anemia ranging from 10 to 35% of Alaska Native school-age children. By comparison, the prevalence of anemia among preschool children in the United States has been declining, reaching an estimated level of 5–8% by the mid-1980s with <3% for school-age children (Dallman et al. 1984, Yip et al. 1987). Evaluations of iron status, including transferrin saturation, serum ferritin, and correction of anemia with oral iron supplements, have clearly established that childhood anemia observed among Alaska Natives is caused by iron deficiency (Burks et al. 1976, Margolis et al. 1981). In general, the most common reason for iron deficiency anemia among children worldwide is inadequate dietary iron intake (Dallman et al. 1980). Therefore, it had been assumed that iron deficiency anemia in Alaska Native children was caused by low iron intake.

In 1984, a small survey (n = 80) measuring hemoglobin and serum ferritin concentrations of residents of two Alaska Native villages [Parkinson, unpublished data] showed that the prevalence of iron deficiency anemia among adult men and women also was higher than expected. Iron deficiency among adult women was not surprising, because the combination of low iron intake and menstrual blood loss renders women of childbearing age at risk for iron deficiency. However, the finding of iron deficiency among men was unusual. Men do not
commonly develop iron deficiency, even when their dietary iron intake is marginal. Both the First and Second National Health and Nutrition Examination Surveys [NHANES I and NHANES II] found virtually no iron deficiency anemia among U.S. men [Dallman et al., 1984, Yip and Dallman 1988]. The traditional Alaska Native diet has a high proportion of food from animal sources (marine and land mammals and fish), and is rich in heme, a highly bioavailable form of iron [Heller and Scott 1967].

This report summarizes iron nutrition status assessments and dietary iron intakes of Alaska Native children and adults that were obtained as secondary objectives of a series of investigations for other purposes among this population.

SUBJECTS AND METHODS

The series of investigations had four components: 1) a survey of residents of multiple villages to determine hemoglobin and serum ferritin concentrations among Alaska Native adults as well as children; 2) a retrospective laboratory survey of serum ferritin values obtained from a statewide sample of Alaska Native sera to define the epidemiology of iron deficiency more accurately; 3) two multiple village dietary surveys to determine iron intake levels for Alaska Natives, and 4) a preliminary study in two villages to determine the evidence for increased blood loss from the gastrointestinal tract. The locations of all of these studies are indicated on a map of Alaska divided into ethnic regions [Fig. 1].

Multiple village hemoglobin and serum ferritin surveys. A total of 2047 healthy Alaska Natives [Eskimo/Aleut], ranging in age from 6 mo to 85 y (mean 27.8 y), living in 19 villages of western Alaska, had hemoglobin and serum ferritin measured from 1988 to 1989. These 19 villages were preselected according to a specific protocol to determine the prevalence of diabetes and echi- nococcus infection, and as part of a hepatitis B vaccination study conducted by the Arctic Investigations Program, Centers for Disease Control and Prevention [CDC], and the Alaska Area Native Health Service. Blood for hemoglobin and serum ferritin was collected by venipuncture. Hemoglobin concentration was measured using a portable hemoglobinometer [HemoCue AB, Angelholm, Sweden]. The HemoCue method was verified to be fully comparable to the cyanomethemoglobin method [Schenck et al. 1986]. The CDC age- and sex-specific definitions of anemia were used [CDC 1989]. The serum ferritin was measured by immunoradiometric assay [Quantimmune Ferritin IRMA, Bio-Rad, Hercules, CA]. The assay was initially evaluated at the Arctic Investigations Program using the International Committee for Standards in Hematology ferritin reference materials supplied by the National Institute for Biological Standards and Control, London, UK. Controls [high, medium, low, and anemia] were used for each assay [Lymphochek BioRad ECS, Anaheim, CA]. For this study, we used a serum ferritin concentration of <12 μg/L as the cutoff value to define depleted iron stores.

Statewide serum ferritin survey. A serum ferritin survey representing Alaska Natives from 147 communities was conducted by using sera that had been collected from patients during a statewide hepatitis B prevalence survey conducted from 1983 to 1985 [McMahon et al. 1993]. More than 90% of all Alaska Natives resided in communities included in the sample. Only communities with a 1980 Alaska Native population of <50 persons or without adequate serum samples for testing were not included. Within each community, equal numbers of serum specimens were randomly selected from subjects in each of four age groups: 3–10 y, 11–20 y, 21–35 y and ≥36 y. A total of 3909 serum specimens, which had been stored at −30°C, were tested for ferritin by Quantimmune Ferritin IRMA.

The hemoglobin and serum ferritin concentrations found among Alaska Natives were contrasted with NHANES II values [Yip et al. 1984]. NHANES II was a multipurpose survey conducted from 1976 through 1980 and represents the latest national survey data available for direct comparison of iron status with the current series [U.S. Public Health Service 1981]. The sample design for NHANES II was a stratified, multistage probability cluster sample of households in the United States. It took into account the complex sample design and sampling probability so that age- and sex-specific findings could be generalized to the U.S. population. Hemoglobin for NHANES II was tested by the cyanomethemoglobin method using an electronic cell counter [Coulter, Hialeah, FL]. The serum ferritin concentration for the NHANES II was measured with the assay described by Miles [Life Sciences Research Office 1984].

Dietary intake assessment. From 1987 to 1988, 266 Alaska Native adults from nine villages were interviewed by trained interviewers using 24-h dietary recalls as part of a project to characterize the diet of Alaska Natives. Villages were selected to represent coastal and inland residents’ eating practices within the boundaries of the Alaska Native health corporations that were willing to participate. Communities were also selected to represent small villages and larger towns within each region. Subjects were randomly selected, except when fewer than seven subjects in the age-sex category in the smallest communities were
available, in which case all were invited to participate. Equal numbers of men and women in the age groupings of 21–40 y and 41–60 y were invited to participate. Twenty-eight people in each community were sought. Interviewers contacted each person identified from a list of Indian Health Service facility users [Alaska Native residents]. Three contacts were attempted and if no contacts were made, another subject from the list of alternates was contacted. If a subject declined to participate for any seasonal interview, an alternate was invited to participate. At least two separate dietary recalls were conducted. Up to five interviews per person were obtained, representing intakes during different seasons. Nutrient intakes were determined from the recalls by using the U.S. Department of Agriculture (USDA) food nutrient data bases, with the addition of Alaska Native foods, available at the time of the study. The iron content of all USDA food items was calculated. Twenty percent of the Alaska Native foods had missing values for iron which would suggest that the values reported here may be underreported. Detailed methods of the dietary data collection and handling were previously published (Nobmann et al. 1992).

Available iron was estimated for men and women in each community based on the following assumptions: 1) heme iron intake was multiplied by an absorption factor of 0.23 [for Kake men] or 0.28 [for all other groups], based on the relative proportion of people with low serum ferritin levels in the region in which the community was located (Table 1); 2) nonheme iron intake was multiplied by 0.08 [Monsen et al. 1978], an iron availability factor selected because large servings of fish or meat and vitamin C–rich foods such as vitamin C–fortified soft drinks are commonly consumed and enhance non-heme iron absorption. Dietary data from NHANES III, conducted from 1988 through 1991, were compared with the dietary iron intake findings among Alaska Natives (Alaimo et al. 1994).

A separate investigation among 112 children aged 4–14 y in two villages of southwest Alaska was con-
ducted in 1991. The child or parent was interviewed about the child’s intake using a 24-h dietary recall during the school year. The data were analyzed using the same data base as in the adult study.

**Stool heme study.** To determine whether increased blood loss was a potential explanation for the high prevalence of iron deficiency among Alaska Natives, a small-scale survey of stool specimens was conducted in 1988. A nonrandom sample of 23 adults from two coastal Yukon-Kuskokwim River delta villages was recruited at home to provide stool specimens for quantitative heme analysis. All participants who turned in a stool sample were questioned about whether they had eaten items containing red meat within 2 d prior to obtaining the stool. Only two persons recalled red meat consumption during that time. The stool heme concentration was estimated by measuring porphyrin compounds [HemoQuant, SmithKline Diagnostics, Sunnyvale, CA]. The normal range of stool blood concentration based on this method is <2 mg of heme/g of stool [Ahlquist et al. 1985]. A previous study found that a recent high intake of red meat can double the normal range up to 4 mg of heme/g of stool, and that fish and chicken intakes have minimal effect on stool heme content [Schwartz and Ellefson 1985]. For this study, we used >4 mg heme/g of stool as a cutoff for an elevated heme concentration in stool. A value > 8 mg heme/g of stool was regarded as markedly elevated.

All parts of the investigations described above, whether as a primary study or as supplements to other surveys, were approved by the Research and Publications Committee of the Alaska Area Native Health Service as well as the Native health boards of the regions in which the studies were performed.

**Statistical methods.** NHANES II data were weighted to reflect the U.S. population in 1978. Even though a comparison was made with the Alaskan data collected in the late 1980s, we have no evidence that the iron nutrition status of the entire U.S. population deteriorated in the past 10–15 y. The only evidence for a change of iron status is the observed improvement of iron stores and the decline in prevalence of anemia among infants and younger children in the U.S. in general [Dallman et al. 1980, Yip et al. 1987]. The proportions of persons with low hemoglobin or serum ferritin concentrations were compared using a chi-square test. Adjustment for age-group and sex was done with a Mantel-Haenszel test [Ahlbom 1993] when necessary. Median serum ferritin concentrations were compared using a Wilcoxon rank-sum test [Snedecor and Cochran 1980], and average iron intakes were compared using a t test.

### RESULTS

**Prevalence of anemia.** In the 1988–1989 19-village survey, the prevalence of anemia in all age and sex groups was nearly twice that of the U.S. population, based on the NHANES II (P < 0.001, relative risk = 1.88) (Fig. 2). Individual age group differences are significant (P < 0.05) for all except children <= 5 y (P = 0.246) and adult men 18–44 y (P = 0.054). There were few cases of severe anemia, defined as hemoglobin concentrations < 100 g/L. However, the mean hemoglobin concentrations of the various age- and sex-specific groups were 3–5 g/L lower than those of the comparable groups in the U.S. sample.

**Prevalence of depleted iron stores (serum ferritin).** The prevalence of low serum ferritin concentration (<12 μg/L) found in the 19-village survey was substantially higher than that of the U.S. population (Fig. 3). More than 50% of all sampled Alaska Native children <= 17 y had evidence of depleted iron stores; this rose to over 80% in those with anemia. Low serum ferritin was more than twice as prevalent in Alaska Native adults than in the U.S. sample. Regardless of age or sex, the serum ferritin concentrations were much lower than those for the U.S. sample (P < 0.001). Figure 4 compares the serum ferritin distribution for men and women, ages 18–44 y, in the Alaska Native and U.S. populations. The median serum ferritin for

### TABLE 1

<table>
<thead>
<tr>
<th>Region</th>
<th>2–11 y</th>
<th>12–17 y</th>
<th>18 y+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Males</td>
<td>Females</td>
</tr>
</tbody>
</table>

1 95% confidence interval.
Alaska Native men was 38 μg/L ($n = 410$) compared with 92 μg/L ($n = 807$) for U.S. men ($P < 0.001$). The Alaska Native women had a median serum ferritin of 17 μg/L ($n = 415$) which was significantly lower than the median of 30 μg/L ($n = 1031$) for the U.S. women ($P < 0.001$). Although serum for ferritin determinations was stored at −30°C for the statewide study (Table 1), there were no significant differences when the results were compared with those obtained from fresh sera in the 19-village study (Fig. 3).

Although there were regional differences ($P < 0.05$) among subgroups except for adolescent females, the 1983–1985 statewide survey of serum ferritin of nearly 4000 Alaska Native children and adults showed that iron deficiency was widespread throughout the Alaska Native population regardless of the region (Table 1).

**Dietary iron intake.** Table 2 lists iron intake for men and women for each of the nine villages surveyed. With the exception of the men in three villages and the women in one, the mean iron intake, according to village and sex, exceeded the mean intake of iron by U.S. men and women based on NHANES III (Alaimo et al. 1994). The overall daily iron intake was significantly higher than the U.S. mean intake ($P < 0.01$) and also higher than Recommended Dietary Allowances (RDA) of the U.S. (Nobmann et al. 1992). Animals were the major sources of iron for Alaska Native adults who consume highly bioavailable heme iron in fish, meat, and poultry an average of 2.3 times/d. The plant sources of iron were minor, and fiber and phytates were low because white bread is more commonly consumed than whole grain (Nobmann 1989). The mean available iron...
intake was greater than the amounts required [National Research Council 1989] to replace daily iron losses for both men (2.4 g/d intake vs. 1.1 g/d needed) and premenopausal women (1.7 g/d intake vs. 1.4 g/d needed). In the separate dietary survey of school children in two villages, the mean intake of iron was 14 mg (117% of RDA), and vitamin C intake was fourfold greater than the RDA.

**Stool heme concentration.** The heme concentration of the stool samples from 15 (65%) of the 23 adults from two villages was definitely elevated (>4 mg heme/g stool). Among these, eight (35%) samples had a heme concentration > 8 mg/g stool. Two specimens had an unusually high heme concentration, 60 and 74 mg/g stool, respectively. Even though this was a small, nonrandom sample, the rate of elevated heme in stool was considerably higher than the value of 3% in healthy volunteers [Ahlquist et al. 1985].


**DISCUSSION**

The 19-village hemoglobin survey substantiates the high prevalence of anemia among Alaska Native children and documents a higher than expected level of anemia among Alaska Native adults. The finding of low iron body stores based on serum ferritin provides unequivocal evidence that most of the anemia in this population is caused by iron deficiency. There is no evidence of hereditary anemias in the Alaska Native population [Margolis et al. 1981, Petersen and Grant 1984, Scott et al. 1955]. The magnitude of anemia and iron deficiency observed among Alaska Natives seems remarkable especially when contrasted with that of the U.S. general population based on the latest available national survey [NHANES II]. The two-site immunoradiometric assay used in NHANES II has not been directly compared with the Quantimmune Ferritin...
IRMA used in this study. More recent population-based studies [NHANES III, Hispanic HANES] have used the Quantimmune Ferritin IRMA, and pilot studies have found that age- and sex-specific serum ferritin concentrations measured in these people are higher than those that were obtained for NHANES II [Looker et al. 1991]. This may indicate that the magnitude of iron deficiency in Alaska Natives may be even higher than we report here. The findings of both the high prevalence of anemia and the low serum ferritin concentrations in villages across the state confirm that iron deficiency is a widespread disorder among Alaska Natives.

There are two unusual findings in this study which suggest that factors other than poor iron intakes are contributing to the high rates of iron deficiency in this population. First, there is the high prevalence of iron deficiency anemia among men and school-age children. Iron deficiency is rare in these two groups in the United States [Dallman et al. 1984], but in most developing and developed countries, a high prevalence of iron deficiency is commonly found among infants, younger children, and women of childbearing age because of inadequate iron intakes relative to the greater requirement related to growth, and menstrual blood loss and pregnancy. In contrast, unless there is a common reason for blood loss such as severe hookworm infestation, men are not reported to have iron deficiency even with low dietary iron intakes [Yip 1994]. In national surveys, virtually no adult men in the United States have iron deficiency anemia [Dallman et al. 1984, Yip and Dall-
TABLE 2
Iron intake in Alaska Native men and women aged 21–60 y in the summer of 1987 and winter, spring, summer, fall of 1988 compared with NHANES III (1988–1991)1

<table>
<thead>
<tr>
<th>Village</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mg</td>
</tr>
<tr>
<td>Bethel</td>
<td>16</td>
<td>21.5 ± 10.7</td>
</tr>
<tr>
<td>Kwigillingok</td>
<td>12</td>
<td>26.2 ± 13.2</td>
</tr>
<tr>
<td>Mountain Village</td>
<td>13</td>
<td>17.8 ± 4.3</td>
</tr>
<tr>
<td>Dillingham</td>
<td>19</td>
<td>20.7 ± 8.9</td>
</tr>
<tr>
<td>Pedro Bay</td>
<td>9</td>
<td>24.8 ± 16.0</td>
</tr>
<tr>
<td>Pilot Point2</td>
<td>9</td>
<td>14.6 ± 5.0</td>
</tr>
<tr>
<td>Kake</td>
<td>15</td>
<td>24.1 ± 11.8</td>
</tr>
<tr>
<td>Kotzebe3</td>
<td>10</td>
<td>16.2 ± 6.7</td>
</tr>
<tr>
<td>Selawik2</td>
<td>19</td>
<td>18.7 ± 11.7</td>
</tr>
<tr>
<td>All villages</td>
<td>122</td>
<td>20.6 ± 10.7</td>
</tr>
<tr>
<td>NHANES-III</td>
<td></td>
<td>18.1</td>
</tr>
</tbody>
</table>

1 Values are means ± SD.
2 No data for the summer of 1987.
3 No data for the summer of 1987 and fall of 1988.

When men and older women do have iron deficiency anemia, it is likely to be due to pathological blood loss from the gastrointestinal tract. In a recent clinical series (Rockey and Cello 1993), 62% of older men and women with iron deficiency anemia had an identifiable gastrointestinal lesion. It is also unusual for school-age children in the United States to have significant iron deficiency (Dallman et al. 1984). However, the prevalence of anemia and low iron stores observed among school-age Alaska Native children is high.

The second atypical finding is the prevalence of iron deficiency in a population with an adequate intake of bioavailable iron. Alaska Native foods rich in heme iron include various wild land mammals, sea mammals and birds. Fish, another source of heme iron, is frequently consumed by Alaska Natives (109 g/d compared with U.S. consumption of 17 g/d). Consumption of white bread, rolls, and crackers by village residents is ranked comparably with that of participants in the U.S. NHANES II (Nobmann et al. 1992). Therefore, the effects of phytates on iron status were not considered as atypical factors in this assessment. The effects of coffee and tea consumption on the absorption of iron were not determined for individuals in this investigation. Although coffee consumption was twice that of the general U.S. population, we were not able to identify any other factors in the study population that would reduce the availability of iron. In fact the availability of iron in our population may be underestimated because availability increases with iron deficiency (Monsen et al. 1978), and we made the conservative assumption that the average iron stores of subjects were between 250 and 500 mg. Their iron stores could be lower or negligible. Based on the factors we assessed, it appears that the bioavailable iron level is adequate. It does not seem likely that dietary intake explains the high prevalence of iron deficiency in this population. A logical alternative explanation is increased iron loss.

The pilot study of gastrointestinal blood loss, even though limited in scope, was intended to examine the hypothesis that chronic gastrointestinal blood loss may explain the high prevalence of iron deficiency anemia observed in this population. The HemoQuant, a test sensitive in detecting any heme breakdown product, provides a quantitative estimate of the amount of stool blood. Our finding of 65% of the stool samples with definitely elevated blood is also considerably different from the expected screening positivity rate of 2–5% (Ahlquist et al. 1985). This test is not specific for human hemoglobin, and a significant red meat intake can cause slight elevation of stool heme content (Schwartz and Ellefson 1985). For this reason, a more conservative cutoff of >4 mg heme/g of stool, rather than >2 mg/g, was chosen. Even though this was a small-scale pilot survey, the unusually high prevalence of elevated stool heme, as well as a very high concentration of heme among some samples, supports our hypothesis that gastrointestinal blood loss is the major cause of the atypical iron deficiency anemia.

If substantial gastrointestinal blood loss is indeed the cause for iron deficiency commonly observed among the Alaska Natives, the most intriguing question is why? Intestinal parasitic diseases, such as hookworm and diphyllobothriasis, do not contribute to anemia among Alaska Natives (Scott et al. 1955). It is possible that the high intake of [n-3] fatty acids from marine mammals and fish may alter platelet function and/or hemostasis, contributing to increased gastrointestinal blood loss. A number of studies have demonstrated the effect of fish oil supplementation on both platelet function as well as bleeding time (Dyerberg and Bang 1979, Li and Steiner 1990, Simopoulos 1991). Alaska Natives in the western part of the state have elevated [n-3] plasma fatty acid levels compared with those of non-Native persons living outside Alaska (Parkinson et al. 1994). Whether this may lead to increased intestinal blood loss is not known. However, there are suggestive regional differences in iron deficiency noted in the statewide data (Table 1), indicating more iron deficiency in the western and northern parts of the state among the Yupik and Inupiat Eskimos. Further evaluation of the possible link between diet and gastrointestinal blood loss may help to explain these regional differences.

The hemoglobin and ferritin surveys achieved broad coverage of isolated villages across Alaska, particularly in the west. Because these surveys were part of other projects requiring blood collection, one limitation of this series of investigations is that different portions of the assessment were performed in different groups of
villages with some surveys overlapping. With the exception of the pilot stool heme study and the children’s dietary survey in two villages, the other components of the investigation involved nine or more villages. The dietary as well as the biochemical findings appear to be consistent across the different Alaska Native villages. Comparable data from the non-Native population in Alaska do not exist. One of the strengths of this study is the diversity in sources of information that support the observed phenomenon that atypical iron deficiency anemia is widespread among Alaska Natives.

In summary, the recent series of investigations on iron deficiency anemia among Alaska Natives reveals unusual findings. First, iron deficiency occurs among men and older children, beyond the normal risk groups of younger children and women of childbearing age. Second, we demonstrate a high prevalence of iron deficiency in the presence of an adequate dietary iron intake. The atypical nature of the iron deficiency strongly suggests increased blood loss as the cause of the deficiency. A pilot study of stool heme concentration found high rates of increased stool blood, compatible with chronic gastrointestinal blood loss. The possibility of gastrointestinal blood loss as a cause of iron deficiency anemia in this population requires confirmation and further investigation.

ACKNOWLEDGMENT

The authors acknowledge the contributions of the participants of the Alaska interagency Ad-Hoc Iron Deficiency Committee for their guidance and work in the various phases of these investigations.

LITERATURE CITED


IRON DEFICIENCY ANEMIA IN ALASKA NATIVES