Serum ferritin and the iron status of Canadians

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Serum ferritin concentration was determined in 1105 Canadians aged 1 to 90 years. Geometric mean values (ng/ml) were as follows: children 1 to 4 years old, 12; children 5 to 9 years old, 15; adolescent girls, 17; adolescent boys, 18; women 20 to 39 years, 23; women 65 years and older, 52; men 20 to 39 years, 93; and men 40 and older, 92. Ranges were wide in all age groups, reflecting variations in size of body iron stores. From analysis of the ferritin values it is highly probable that iron stores were greatly reduced in approximately 25% of children, 30% of adolescents, 30% of menstruating women, 60% of pregnant women and 3% of men. Iron-deficiency anemia was noted in only 2% of subjects. If "normality" requires more than small amounts of storage iron to meet physiologic demands, the study results suggest a high probability of iron deficiency in 60% of the pregnant women and in 19% of the other subjects; but if normality is defined as maintenance of adequate iron stores for erythropoiesis, the prevalence of iron deficiency was zero in the pregnant women and 2% in the other subjects.

On a déterminé la concentration sérique de ferritine chez 1105 canadiens âgés de 1 à 90 ans. Les moyennes géométriques (en ng/ml) se sont établies de la façon suivante: enfants de 1 à 4 ans, 12; enfants de 5 à 9 ans, 15; adolescentes, 17; adolescents, 18; femmes de 20 à 39 ans, 23; femmes de 65 ans et plus, 52; hommes de 20 à 39 ans, 93; et hommes de 40 ans et plus, 92. Les écarts étaient grands à l'intérieur de chaque groupe, traduisant en ceci les variations individuelles des réserves de fer corporelles. L'analyse des taux de ferritine indiquent une forte probabilité pour que les réserves de fer aient été grandement réduites chez environ 25% des enfants, 30% des adolescents, 30% des femmes en âge d'activité menstruelle, 60% des femmes enceintes et 3% des hommes. Une anémie ferriprive a été observée chez seulement 2% des sujets. Si un "état normal" requiert plus que de petites quantités de fer en réserve pour rencontrer les exigences physiologiques, les résultats de cette étude suggèrent qu'il existe une forte probabilité de carence en fer chez 60% des femmes enceintes et chez 19% des autres sujets; mais si d'autre part un "état normal" se définit comme le maintien de réserves de fer suffisantes à l'érythropoïèse, la prévalence de carence en fer fut de zéro chez les femmes enceintes et de 2% chez les autres sujets.

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The serum ferritin concentration in healthy adults is proportional to the size of body iron stores,[1-3] and changes in the serum ferritin value correlate with changes in the size of these stores during normal development in infancy and childhood.[4] A highly significant correlation has been found between serum ferritin concentration and three other indices of body iron status: hemosiderin content of bone marrow,[5,6] percent absorption of iron[3,6,7] and size of body iron stores as measured by quantitative phlebotomy.[8] The mean serum ferritin concentration is higher in males than in females during adulthood but not during childhood.[2-4,9] The sensitivity of the serum ferritin assay, together with its simplicity and convenience, makes it ideal for assessing the iron status of a population. The present study was prompted by the continuing controversy about the prevalence of iron deficiency[10] and the availability of serum from a survey of the nutritional status of Canadians conducted in 1970-72.

Methods and material

Population studied

Serum ferritin assays were conducted on a random sample of the 13 689 persons who participated in the Nutrition Canada national survey.[11A] In addition, 894 women in the 3rd trimester of pregnancy, most of whom were referred by local health units, were examined; because of the mode of selection they did not constitute a probability sample. Further details are given in the Appendix.

From the present study 120 subjects were selected at random from each of 10 age–sex groups and from the group of pregnant women. An adequate sample of serum and complete data for hemoglobin and serum iron concentration and transferrin saturation were available for 1106 of the 1320 subjects.

One woman with a ferritin value exceeding 3500 ng/ml was subsequently excluded because the value was over 100 times greater than the mean value for the group.

Serum ferritin concentration

Serum ferritin concentration was measured by a two-site immunoradiometric assay.[12] The coefficient of variation of 10 measurements made on two known samples in each assay was ± 8.5% for a mean concentration of 96 ng/ml and ± 10.6% for a mean concentration of 6.6 ng/ml.

Interpretive standards

The standards used to interpret the results were derived in part from the interpretive standards developed for the analysis of Nutrition Canada data.[11] The results for hemoglobin and serum iron concentration and total iron-binding capacity (TIBC) obtained from Nutrition Canada were grouped into three categories (high, medium or low) of the probability of iron deficiency (Table I). The cut-off points that defined the limits of each probability group were similar to those used by Nutrition Canada. No account was taken of the slight decline that occurs in hemoglobin concentration as men grow older.[13] Cut-off points for serum ferritin concentration were based on comparisons of serum ferritin values with other measurements of body iron status.[1,5,6,8] Justification for the cut-off points is given in the Appendix.

Table I—Interpretive standards

Test substance	Probability of iron deficiency: High	Moderate	Low
Hemoglobin, g/dl			
0 — 1 yr, M & F	< 9.0	9.0 — 10.0	> 10.0
2 — 5 yr, M & F	< 10.0	10.0 — 11.0	> 11.0
6 — 12 yr, M & F	< 10.0	10.0 — 11.5	> 11.5
13 — 16 yr, M	< 12.0	12.0 — 13.0	> 13.0
13 — 16 yr, F	< 10.0	10.0 — 11.5	> 11.5
17+ yr, M	< 12.0	12.0 — 14.0	> 14.0
17+ yr, F	< 10.0	10.0 — 12.0	> 12.0
Pregnant women*	< 9.0	9.0 — 10.5	> 10.5
Serum transferrin, % saturation			
All ages, M & F	< 16	16 — 20	> 20
Serum ferritin, ng/ml			
≤ 12 yr, M & F	< 10	10 — 20	> 20
> 12 yr, M & F	< 15	15 — 30	> 30

*In 2nd or 3rd trimester of pregnancy.

Table II—Iron status of 1105 subjects

Age (yr) – sex group	No. of subjects	Mean age (yr)	Hemoglobin (g/dl)*	Transferrin saturation (%)*	Serum ferritin (ng/ml)†
1 — 4, M & F	87	3.1	12.7 ± 0.9 (10.0 — 14.6)	21 ± 6.6 (6 — 40)	12 (2 — 74)
5 — 9, M & F	117	7.1	13.1 ± 1.0 (9.2 — 15.2)	24 ± 7.1 (7 — 55)	15 (2 — 107)
10 — 19, M	98	14.3	14.6 ± 1.3 (12.3 — 18.8)	26 ± 6.3 (13 — 47)	18 (3 — 125)
10 — 19, F	106	14.3	13.7 ± 0.9 (11.1 — 16.2)	23 ± 6.3 (12 — 38)	17 (2 — 116)
20 — 39, M	95	28.8	16.0 ± 1.1 (12.6 — 18.4)	28 ± 8.5 (15 — 65)	93‡ (14 — 618)
20 — 39, F	100	29.4	13.8 ± 1.2 (9.0 — 16.8)	25 ± 8.1 (9 — 53)	23 (4 — 145)
40 — 64, M	103	51.8	15.7 ± 1.2 (12.2 — 18.4)	27 ± 6.3 (13 — 44)	92‡ (10 — 799)
40 — 64, F	105	50.8	13.6 ± 1.1 (9.2 — 16.0)	24 ± 8.5 (7 — 77)	29 (3 — 313)
65 — 90, M	104	73.0	15.1 ± 1.3 (11.2 — 18.0)	26 ± 7.5 (12 — 58)	92§ (13 — 651)
65 — 87, F	98	72.4	14.0 ± 1.3 (10.8 — 17.4)	24 ± 6.8 (8 — 51)	52 (4 — 665)
18 — 42, pregnant	92	26.8	12.7 ± 1.1 (10.0 — 14.9)	26 ± 9.8 (11 — 72)	11§ (1 — 129)

*Mean value ± standard deviation (and range).
†Geometric mean with 95% confidence interval.
‡§Mean value of each group significantly different from mean value of female subjects of similar age, at ‡$P < 0.01$ or §$P < 0.05$.

Results

Hemoglobin concentration, transferrin saturation and serum ferritin concentration

The mean values for hemoglobin concentration, transferrin saturation and serum ferritin concentration in the various age–sex groups and for both males and females are given in Table II. Notable findings were a slight decrease in mean hemoglobin value in men over 65 years old and a distinct sex difference for mean serum ferritin value after age 20 years, with significantly higher values in men than in women.

Serum iron concentration and TIBC

In the 25 women in the age group 20 to 39 years who were taking oral contraceptives the mean serum iron value, 108 μg/dl, and the mean TIBC, 410 μg/dl, were higher than the comparable values of 90 μg/dl and 374 μg/dl in the 24 women who had never taken these agents, but only the mean TIBC was significantly increased in the former group ($P < 0.01$). However, the mean hemoglobin values, 14.1 and 13.9 g/dl, respectively, and the mean percent transferrin saturation, 26 and 24%, respectively, were similar in the two groups. The geometric mean ferritin value of 26 ng/ml in the group taking oral contraceptives was not significantly different from the mean value of 20 ng/ml in the women who were not taking this medication ($P > 0.10$). Thus, it is unlikely that oral contraceptive therapy affected the results of this study.

The logarithmic values of serum ferritin were inversely correlated with the TIBC of the serum ($r = 0.438$, $P < 0.001$) but not with hemoglobin concentration, serum iron concentration or percent transferrin saturation.

Serum ferritin concentration

The median serum ferritin values increased with age in females but reached a plateau after 20 years of age in males (Fig. 1). The spread was broad and increased in women as they grew older. The mean concentration of serum ferritin in pregnant women was signifi-

cantly lower than the mean value in nonpregnant women aged 20 to 39 years ($P < 0.01$).

Probable iron deficiency

The percentage of subjects with a moderate or high probability of iron deficiency, based on the interpretive standards for hemoglobin concentration and transferrin saturation, is shown in Fig. 2. According to the standard developed for serum ferritin, 29 and 20%, respectively, of the children aged 1 to 4 and 5 to 9 years had a high probability, and 48 and 39%, respectively, a moderate probability that iron stores were diminished. There was also a high probability that iron stores were low in approximately 30% of adolescent boys and girls and menstruating women, and a moderate probability that they were low in an additional 30%. Beyond adolescence comparatively few men had low iron stores. For pregnant women there was a high probability that 60% had depleted iron stores and a moderate probability that another 27% had low iron reserves. Overall, in 19% of subjects the probability of iron deficiency was high.

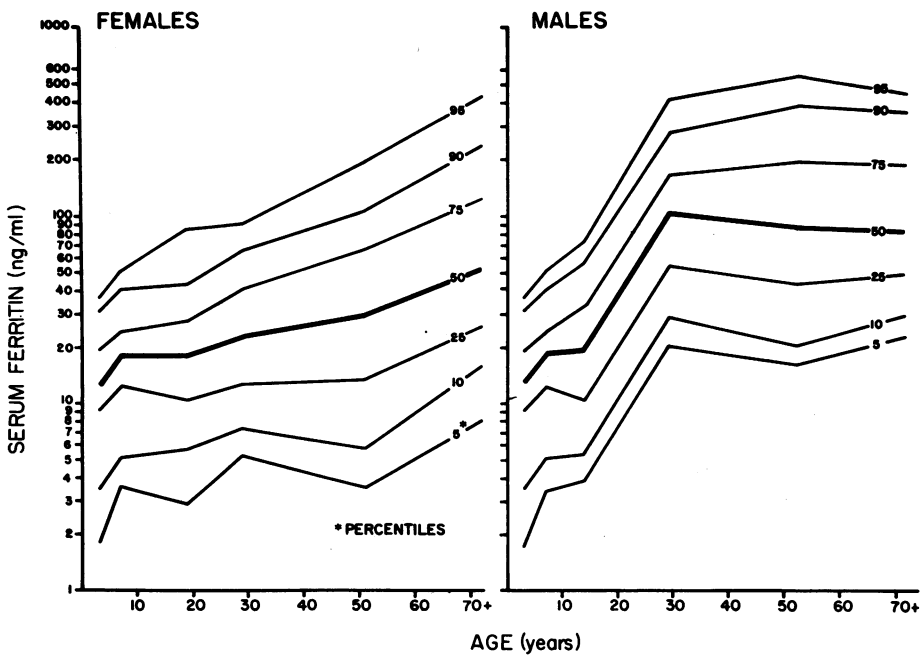

FIG. 1—Distribution of serum ferritin values expressed as percentiles. The number of the percentile refers to the position a given value holds in any series of 100 typical subjects.

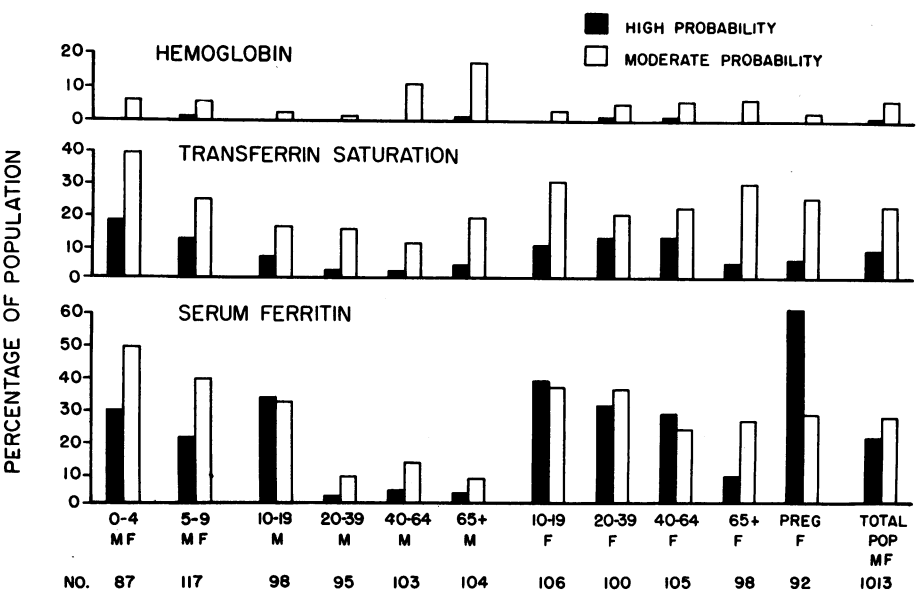

FIG. 2—Percentage probability of iron deficiency in various age–sex groups, based on hemoglobin concentration, percent transferrin saturation and serum ferritin concentration as indices of iron deficiency. "Total pop." excludes pregnant women.

Although reduced iron stores were prevalent in children, adolescents and menstruating women, iron-deficiency anemia (defined as a hemoglobin concentration in the moderate or high probability category of Table I and a serum ferritin concentration of less than 15 ng/ml) was present in only 22 persons, or 2% of the study population (Table III). According to the interpretive standard, anemia also occurred in another 47 subjects in association with serum ferritin values of 15 ng/ml or greater (Table IV). This was most prevalent in men 40 to 90 years of age.

Discussion

In evaluating body iron status it is better to determine serum ferritin concentration than hemoglobin concentration or percent transferrin saturation because the serum ferritin value is a sensitive index of the earliest stage of iron deficiency — a reduction in body iron stores.[3,5-7] Low serum ferritin values indicate iron deficiency but high values do not necessarily mean increased body iron stores. Inflammation, liver disease, hematologic malignant disease and hemolytic anemia may increase the serum ferritin concentration out of proportion to the size of body iron stores.[5] There were no reports of these disorders in the clinical records of 41 of the 52 subjects with serum ferritin values greater than 250 ng/ml, but 9 subjects had arthritis and 2 had hepatomegaly. While inflammatory joint disease may have accounted for a few of the high ferritin values, this was not considered important because there were another 148 subjects who complained of arthritis but whose ferritin values were below 250 ng/ml. Possibly, however, some of the high ferritin values were due to occult hepatic or hematologic disease that was not apparent on the screening examination.

The similarity between the relative frequencies of both low hemoglobin concentration and low percent transferrin saturation in the present study and the Nutrition Canada Survey[11] suggests that we studied a representative sample of subjects. The serum ferritin data indicate that, while the adult male appears as a standard of "normality", iron deficiency, characterized by low body iron stores, is prevalent in children, teenage boys and girls, and menstruating and pregnant women. These conclusions are similar to those drawn by Nutrition Canada for these age groups and they agree with the conclusions from studies of patients attending clinics and hospitals in Canada and the United States.[14-21] However, a reduction in iron reserves great enough to impair erythropoiesis was found in only 2% of the participants in this study. Iron-

deficiency anemia was most frequent in children and in women throughout their life span (Table III).

Our findings indicate that iron intake from the diet and other sources was sufficient in 98% of the subjects to meet the requirements for erythropoiesis but insufficient to establish any appreciable iron reserves, as defined by the interpretive standard, in approximately one quarter of the children, one third of the adolescents and one third of the young women (Fig. 1). Blood loss, apart from menstrual, did not appear to contribute greatly to the iron deficiency. Only three subjects were blood donors and abnormal blood loss was rarely reported in the clinical records.

Data on iron intake were not available for analysis but the results obtained for the groups in the national survey indicate wide variation in daily iron intake, with some exceptionally high values in infants owing to the use of iron supplements.[11B] The median daily intake of iron was 9 to 11 mg in children, 15 mg in teenage boys, 13 to 17 mg in men and 10 to 11 mg in teenage girls and women. The median iron intake in infants and children, in teenage girls and in women during the reproductive period just exceeded the adequate value specified in the interpretive standard. These results and the finding that the estimated daily iron intake in 9% of the infants, 23% of the children, 40% of the adolescents and 40% of the women was less than 6, 6, 10 and 10 mg, respectively, suggests that the dietary intake of iron was close to inadequate in these groups.

Although anemia was found in only 1 of 92 pregnant women in our study, depleted iron stores (serum ferritin concentration, < 15 ng/ml) were detected in 54 of the 92. Similar results have been reported when hemosiderin content of bone marrow was determined to assess iron stores.[22] Among the pregnant women oral iron intake in 37% was high — above 40 mg — because they were taking daily iron supplements; despite this, the median intake for the whole group was marginal — 16 mg/d — and in 30% the intake was below the adequate standard of 12 mg/d.[11B]

Table III—Prevalence of iron deficiency among subjects

Age (yr) - sex group	Total no. of subjects	No. of subjects with depleted iron stores* and hemoglobin value† that was:		
		Normal	Moderately low	Low
1 — 4, M & F	87	23	2	0
5 — 9, M & F	117	21	3	0
10 — 19, M	98	31	1	0
10 — 19, F	106	38	2	0
20 — 39, M	95	2	0	0
20 — 39, F	100	27	2	1
40 — 64, M	103	2	2	0
40 — 64, F	105	24	3	1
65 — 90, M	104	2	1	0
65 — 87, F	98	5	3	0
18 — 42, pregnant	92	54	1	0
Total	1105	229	20	2

*Defined as serum ferritin concentration < 15 ng/ml in adults and < 10 ng/ml in children.
†Defined according to which probability group of Table I the value falls into.

Table IV—Prevalence of anemia* among subjects

Group	Total no. of subjects	No. of subjects with serum ferritin value (ng/ml) that was:		
Infants and children		<10	10 — 20	>20
0 — 4, M & F	87	2	0	3
5 — 9, M & F	117	3	2	2
Adults		<15	15 — 30	>30
10 — 19, M	98	1	1	0
10 — 19, F	106	2	1	0
20 — 39, M	95	0	0	1
20 — 39, F	100	3	2	1
40 — 64, M	103	2	1	8
40 — 64, F	105	4	0	3
65 — 90, M	104	1	4	14
65 — 87, F	98	3	1	2
18 — 42, pregnant	92	1	1	0
Total	1105	22	13	34

*Defined as hemoglobin concentration in moderate or high probability group of Table I.

The finding of anemia in 47 persons (approximately 4% of the subjects) with a serum ferritin concentration of at least 10 ng/ml and 15 ng/ml in children and adults, respectively, is due, at least in part, to the placement of the cut-off points in the interpretive standard (Table I). The small normal decline in mean hemoglobin concentration in men after age 40 years[13] was reflected in an increasing number of persons classified as anemic. If the cut-off points for hemoglobin concentration had been 13.0 g/dl (40 to 65 years) and 12.5 g/dl (> 65 years) the numbers of anemic persons in these two groups would have been three and two, respectively.

Our results imply a high probability of iron deficiency in 19% of the subjects (excluding pregnant women) and in 60% of the pregnant women in this study if "normality" requires the presence of more than small amounts of storage iron to meet physiologic demands.[23] This conclusion is based on the premise that iron deficiency is highly probable if the serum ferritin concentration is less than 15 ng/ml in adults and less than 10 ng/ml in children. In patients with uncomplicated iron-deficiency anemia serum ferritin values reportedly have ranged from 1 to 14 ng/ml in adults[1,4-6] and from 0 to 9 ng/ml in children,[4] whereas values of 60 ng/ml or higher have been found in control subjects with moderate amounts of stainable bone marrow iron[5,6] or normal values for iron absorption.[6] Hence, the high prevalence of iron deficiency, based on cut-off points for serum ferritin concentration of 10 ng/ml and 15 ng/ml in children and adults, respectively, appears valid and if anything, is a conservative estimate. But if normality requires only the maintenance of sufficient body iron to ensure an adequate supply for erythropoiesis the prevalence of iron deficiency in the population was only 2%.

The main factor responsible for the high prevalence of depleted iron reserves appears to be a dietary intake of iron insufficient to ensure adequate iron reserves during growth in children and adolescents and during the reproductive period in menstruating and pregnant women, who have an increased requirement for iron. This conclusion, however, is based on crude estimates of dietary intake in the original population and the reported low incidence of abnormal blood loss in the subjects selected for this study. Furthermore, several factors in addition to the total iron content of the diet (e.g., type of iron and effect of other dietary constituents on iron absorption) determine the bioavailability of iron from a given diet.

On the basis of the 2% prevalence of iron-deficiency anemia, iron supplementation for the general population is not warranted. Whether iron supplements should be added to the diet of the general population to replenish the low iron stores in children, adolescents and women during the reproductive period is a moot point.[10,24-27] The serum ferritin assay may help to resolve the present controversy by providing a sensitive and specific method for evaluating the iron status of a population, testing the validity of models proposed for predicting the effects of iron fortification,[28] and monitoring the effect of iron fortification on the target groups at risk. If iron fortification does prove necessary our data from a randomly selected sample of the Canadian population will provide a baseline against which to compare future data.

Appendix

Nutrition Canada Survey

The Nutrition Canada Survey was designed to sample the population in five regions — Atlantic, Quebec, Ontario, Prairies and British Columbia. Census tracts, municipalities and townships formed the basis of stratification within regions to ensure representation from metropolitan, urban and rural areas, and from areas of low income and other income levels. Of 37 322 persons initially selected 46% responded. Survey teams interviewed and examined participants and obtained blood samples. The dietary interviewer asked each participant, or the adult responsible for the meal, what foods and beverages had been consumed over the previous month. Iron intake was determined from the estimated iron content of the foods.

Hemoglobin concentration was determined immediately after collection by the cyanmethemoglobin method.[29] Blood was centrifuged to obtain serum, frozen immediately after this initial processing, packed in dry ice and forwarded within 72 hours to a central laboratory in Ottawa. The serum was stored at −15°C until various biochemical tests were performed. Serum iron concentration and unsaturated iron-binding capacity were determined by the procedure of Goodwin, Murphy and Guillemette,[30] modified for the Beckman DSA 560 discrete sample analyzer.

Serum ferritin concentration

Because the blood samples were drawn during the afternoon and the evening, serum ferritin was measured in 11 healthy volunteers during the day. There was no significant difference between the average values, 92, 89 and 91 ng/ml, obtained at 8 am, 3 pm and 8 pm, respectively, or between the individual values assessed by a *t*-test for paired observations. Repeated freezing and thawing of the serum did not affect ferritin values. Some of the serum samples were cloudy but this did not affect the assay, for removal of the suspension by filtration did not alter significantly the results. Because the distribution of serum ferritin values in all age–sex groups was skewed, the geometric mean was calculated.[3,4] The mean and 95% confidence interval about the mean were calculated in logarithms and the results transformed as antilogs to recover the original units.

Interpretive standards

Comparison of serum ferritin values with measurements of body iron stores made from bone marrow aspirates suggests there is a high probability of depletion of iron stores if the serum ferritin value is less than 15 ng/ml and a low probability if it is greater than 59 ng/ml.[5,6] Another approach is to set cut-off points on the basis of "average" body iron reserves. In control subjects selected on the basis of a normal hemoglobin value arithmetic mean ferritin values were 35 ng/ml in 44 women and 69 ng/ml in 75 men.[2] When both normal hemoglobin concentration and normal percent transferrin saturation were the criteria used to select control subjects the geometric mean values were 35 and 94 ng/ml for 152 women and 174 men, respectively.[3] These values correspond to approximately 280 mg of storage iron in women and 550 mg in men.[8] If the maintenance of body iron, including iron stores in the face of physiologic demands, is considered normal, there is a low probability of iron deficiency when the serum ferritin value is greater than 30 ng/ml. This figure has been used as a cut-off point between the moderate and low probability groups for both males and females 13 years and older in the interpretive standard (Table I). A higher cut-off point was not assigned to men because their need for iron reserves to meet physiologic needs is, if anything, less than that of women.

The probability groups for children were more difficult to define. In a study of 486 nonanemic children aged 6 months to 15 years, Siimes, Addiego and Dallman[4] found a median serum ferritin value of 30 ng/ml, with 95% confidence limits of 7 to 142 ng/ml. The range of ferritin values in 13 children with iron-deficiency anemia was 0 to 9 ng/ml. Although it is evident that there is a high probability that iron reserves are depleted in children 12 years old and under if the serum ferritin value is less than 10 ng/ml, the distinction between the medium and low probability categories is not as clear cut. We chose 20 ng/ml as the cut-off point between these two categories (Table I).

Statistical methods

The significance of differences between any two mean values was calculated by Student's *t*-test.[31] The relation between serum ferritin concentration and other values for iron metabolism was determined by the least squares method for linear regression.[31]

We are indebted to Mr. C. Jones, Mrs. T. Ferreira, Mr. J. Haist and Mrs. M. McGugan for technical assistance; Mr. W. Orme for computer analysis; Dr. A. Kraus for advice; and Drs. J.B. Simon, A.W. Meyers and B.G. Shah for reviewing the manuscript.

This work was supported by a research grant from the Medical Research Council of Canada.

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