Extent and Meanings of Iron Deficiency in the U.S. (1972)

Pages
125

Size
8.5 x 10

ISBN
0309360978

Committee on Iron Nutritional Deficiencies; Food and Nutrition Board; National Research Council

SUMMARY OF PROCEEDINGS

WORKSHOP ON EXTENT AND MEANINGS OF IRON DEFICIENCY IN THE U. S.

March 8-9, 1971
Washington, D. C.

COMMITTEE ON IRON NUTRITIONAL DEFICIENCIES

FOOD AND NUTRITION BOARD
NATIONAL ACADEMY OF SCIENCES
NATIONAL RESEARCH COUNCIL
2101 Constitution Avenue
Washington, D. C. 20418

NOTICE

The workshop reported herein was undertaken under the aegis of the National Research Council with the approval of its Governing Board. Such approval indicated that the Board considered the problem of national significance; that elucidation of the problem required scientific or technical competence and that the resources of NRC were particularly suitable to the conduct of the project. The institutional responsibilities of the NRC were then discharged in the following manner:

The participants in the workshop were selected for their individual scholarly competence and judgment with due consideration for the balance and breadth of disciplines. Responsibility for all aspects of this report rests with the workshop participants, to whom sincere appreciation is expressed.

Although reports of such workshops are not submitted for approval to the Academy membership nor to the Council, each is reviewed according to procedures established and monitored by the Academy's Report Review Committee. Such reviews are intended to determine, *inter alia*, whether the major questions and relevant points of view have been addressed and whether the reported findings, conclusions and recommendations arose from the available data and information. Distribution of the report is permitted only after satisfactory completion of this review process.

P R E F A C E

The Committee on Iron Nutritional Deficiency sponsored two workshop conferences. The first, held January 22-23, 1970, dealt with measures to increase iron in foods and diets. The second, reported here considered the extent and meanings of nutritional iron deficiency in the United States. The workshop participants reviewed methods for the assessment of iron nutriture and attempted to establish the prevalence of iron deficiency, with and without anemia, in the United States, through presentation of data from the National Nutrition Survey and from additional studies of children and other population groups.

The feasibility of establishing standards and norms for the interpretation of iron nutriture were discussed, and the significance and consequences of mild, as well as severe, iron deficiency were reviewed. The significance of mild iron deficiency in children as indicated by psychological and physiological tests was reported. The systemic effects of iron deficiency and effects on reproductive performance were considered. The hazards of iron deficiency to individuals and population groups were examined.

Attention was directed, also, to measures for alleviating and preventing iron deficiency. Since knowledge of the amount and sources of iron in the diet of various segments of the population is prerequisite to designing programs to increase the dietary intake of iron, information in this area was examined.

Because it is essential that measures be devised to solve the important public health problem of iron deficiency, proposals for iron enrichment of cereals and other dietary constituents were discussed and potential hazards of corrective measures considered.

It was the aim of the workshop to suggest priorities for research and to propose tentative solutions to the problems of iron nutritional deficiency in the United States.

Committee on Iron Nutritional Deficiency
Grace A. Goldsmith, *CHAIRMAN*
William B. Bradley
Clement A. Finch
Carl V. Moore
Hilda S. White

C O N T E N T S

CRITERIA FOR EVALUATION OF THE STATUS OF IRON NUTRITION

C. A. Finch

Certain points may be emphasized with respect to criteria for recognizing iron deficiency in a public health sense as contrasted with those applied to the clinical patient.

Iron deficiency, from a laboratory standpoint, may be regarded in two ways. The first is to consider the state of iron depletion in terms of iron stores; the second is to recognize iron deficient erythropoiesis. Measurements are available to deal specifically with both of these entities.

The following discussion does not focus on the question of optimal iron stores, but rather on ways to evaluate them. Direct measurement of iron stores is accomplished by phlebotomizing individuals* and seeing how much iron can be obtained. Utilizing the phlebetomy technique, the iron stores in men approximate 1000 mg, although individual variability is not well defined. In women, the method demonstrates iron stores ranging from 300 to 400 mg, many having virtually no demonstrable iron stores.

The phlebotomy technique is not a practical way to approach population studies. The technique available for such studies is the measurement of iron absorption. As iron stores are depleted, absorption of a test dose of ferrous sulfate increases, while absorption decreases with repletion of iron stores. Given equal doses of iron, women may demonstrate an average absorption of around 15 percent and men around 7 percent. However, there is great variation of iron stores from one population to another and the so-called normal absorption in males may range between a mean of 5 percent in one area and 25 percent in another. Thus, differences in absorption values may provide an important guide to the status of iron balance in a population.

A consideration of iron deficient erythropoiesis includes measurements of plasma iron, iron binding capacity, protoporphyrin levels in red cells, and red cell

---

*Iron Metabolism--Iron Stores in Man as Measured by Phlebotomy. 1952. Haskins *et al.* J. Clin. Invest. 31:543.

indices. Such measurements reflect iron deficient erythropoiesis. They are equally affected by a depletion of total body iron or by any internal block, such as may be imposed by infection, to iron delivery to the erythroid marrow.

In a discussion of iron deficiency anemia, nutritional anemia, or other kinds of anemia, it is customary to think first of hemoglobin or red cell concentration. However, hemoglobin concentration is but one component in a complex system of oxygen transport to the tissues, a system that includes cardiac output, blood flow distribution within the body, and a number of other factors that affect oxygen release from hemoglobin within the red cell.

As a consequence of these multiple factors, all directed at maintaining optimum tissue oxygen transport, the hemoglobin level shows considerable variation that may be related to variations in other components. For example, an inverse relationship has been shown between red cell 2,3-diphosphoglycerate (DPG) and hemoglobin concentration in normal subjects. It appears that there is some internal adjustment by changes of DPG in the oxygen disassociation curve to compensate for alterations in hemoglobin, or vice versa.

The disadvantage of using hemoglobin level as an approach to nutritional anemia is the difficulty in identifying the abnormal state when the normal cannot be clearly defined. For years, it has been customary to select as a hemoglobin concentration that below which anemia exists and above which anemia does not exist. When this "critical" concentration of hemoglobin is taken, there are in fact anemic subjects above and nonanemic subjects below these levels. An anemic population as identified by hemoglobin concentration will also include some normal individuals, and as a consequence prevalence data are in considerable error. This is not to imply that the hemoglobin measurement should be discarded; it is certainly the simplest and the most easily standardized method and is affected when iron deficiency is sufficiently severe.

As for red cell indices, adequately developed automated methods may provide more accurate ways of looking at what would seem to be the most useful index, the

mean corpuscular hemoglobin. This index is useful, even though it may be lacking in sensitivity and specificity, and reflects such other abnormalities as thalassemia.

Plasma iron and iron binding capacity are measurements that bear on the iron supply available to the erythroid cell. Accurate methods exist for determining plasma iron and iron binding capacity, although there are difficulties in reaching standardization among different laboratories. It is not clear to what extent plasma iron alone, as against plasma iron and iron binding capacity or percent saturation, should be relied upon as an index of iron supply to the marrow. In some cases plasma iron measurements alone may be an imprecise index of iron supply to the bone marrow. Two conditions, nephrosis and kwashiorkor, illustrate this point. In both cases the transferrin level is greatly reduced, the total iron binding capacity is decreased to one-third the normal values, the percent saturation of transferrin is normal, and there is no evidence of iron deficient erythropoiesis.

A recent study of nutritional anemia in Latin America provides further information bearing on this point. About 15 percent of a group of pregnant and nonpregnant women had plasma iron levels below 50 μg/100 ml. Fifteen percent of the nonpregnant and 45 percent of the pregnant women had transferrin saturations below 15 percent. The latter was due to the marked increase in transferrin that occurs in pregnancy. When the two sets of figures were compared to the incidence of anemia, it became obvious that the prevalence of anemia was much higher in the pregnant group. These observations indicate that, at least with basal erythropoiesis, the percent saturation of transferrin is a more accurate measurement of iron supply to the marrow than is the plasma iron *per se*. The percent saturation of transferrin is more important than plasma iron and iron binding capacity.

The difficulty in making plasma iron and transferrin saturation measurements is the instability of the plasma iron level. Should an individual get an acute infection, the plasma iron level can drop relatively rapidly. This was particularly well shown by studies carried out in Jamaican infants who had a high incidence of infection. The use

of plasma iron and transferrin as an index of iron deficiency requires that a healthy population be surveyed and that considerable attention be paid to the detection of intercurrent infection.

Another parameter within the red cell is the amount of free protoporphyrin. As the iron supply decreases, free protoporphyrin increases. Free protoporphyrin has long been recognized as being elevated in the two conditions in which there is iron deficient erythropoiesis, namely, infection and in true deficiency. From a recent study, it would appear that protoporphyrin is not influenced by the number of reticulocytes but rather by the relationship between iron supply and marrow need. Further studies suggest that there are two types of protoporphyrin within the cell. The normal protoporphyrin that cannot be decreased by iron feeding, is not decreased in hemochromatosis, is not affected by cell age, and therefore seems to be a fixed material throughout the life of the red cell. This appears to be demonstrated by transfusion studies with erythrocytic protoporphyria. On the other hand, the protoporphyrin found in iron deficiency appears to be labile, with a half time turnover of about 3 weeks, and therefore provides a more stable tag for the red cell than does something like the plasma iron which can fluctuate very rapidly.

In summary, indices that need to be considered in relation to iron deficiency include iron absorption as an index of the overall iron status or iron stores of the individual, red cell indices as measurements of the effect of iron deficiency on the red cell population, and serum iron saturation and red cell protoporphyrin concentration as indicators of the adequacy of iron supply to the erythroid marrow. Change in hemoglobin concentration, if it can be shown to be related to iron deficiency, gives indication of the severity of the deficiency state.

It should be emphasized that the crux of any nutritional study depends on the extent to which available methods are standardized, and their absolute value thereby assured. A study that provides relative indices applicable only to that study reduces the potential value of such observations.

APPROACHES TO ANALYSIS OF SURVEY DATA ON IRON NUTRITIONAL DEFICIENCY

James D. Cook

A broadening of the physician's concern about health from the individual patient to the community as a whole has led to an increasing emphasis on surveys of anemia prevalence during the past few years. The nature of these surveys has shifted from casual clinical observations, with inadequate sampling methods, to highly complex and costly undertakings. The principle of random sampling and refinements in laboratory methods have undoubtedly improved the quality of the data obtained. At the same time, the usefulness and significance of surveys are compromised by the lack of adequate methods for interpreting the data. The majority of surveys are interpreted in terms of arbitrary criteria tailored to the study at hand. In the remaining studies, the results are buried in a maze of complex and often meaningless statistical manipulations.

This paper explores a middle ground in the interpretation of nutritional surveys and the application of some very simple and basic statistical principles to what is basically a clinical problem. The methods here described were applied to the analysis of a collaborative study conducted under the auspices of WHO and PAHO to determine the prevalence of nutritional anemia in Latin American countries. Because latent deficiencies are commonly unmasked during childbearing, women in the third trimester of pregnancy were chosen as the target population. Data for comparison were obtained from relatives and close friends of these women and are presented for men and menstruating women.

Over 95 percent of the subjects were between the ages of 15 and 45, and all belonged to the low socioeconomic classes of the countries. The measurements were carefully standardized by a Central Reference Laboratory. The composite survey comprised three groups made up of 889 pregnant women, 485 menstruating women, and 304 male subjects. The criteria for anemia were those established by a WHO scientific group in 1968, using a hemoglobin below 11 g/100 ml in late pregnancy, below 12 g/100 ml in menstruating women, and below 13 g/100 ml in the male. In the three groups studied,

39 percent of pregnant women, 17 percent of menstruating women, and 3.9 percent of the male subjects fell below these levels.

Iron deficiency, defined as a transferrin saturation below 15 percent, was significantly more prevalent than anemia and occurred in 49 percent of pregnant women, 21 percent of menstruating females and 3 percent of male subjects. The prevalence of folate deficiency defined as a serum folate less than 3 ng/ml was similar in the three study groups, about 10 percent. Vitamin B_{12} deficiency, defined as a serum B_{12} less than 80 μμg/ml as determined by microbiological assay, was high in pregnant women, 15 percent, but almost nonexistent in the remaining two groups.

A starting point for considering the criteria of anemia is to examine the frequency distribution of hemoglobin levels. If the population contains a mixture of normal and anemic subjects, the question arises as to where the anemic subjects lie in relation to the normal. There are three possibilities. To the clinician, anemia is usually considered as a disorder in which the average hemoglobin is perhaps 8 or 9 g/100 ml, he therefore often considers the distribution of hemoglobin levels in anemic subjects as being quite distinct from the normal population. The second possibility is that the hemoglobin levels in the total population are normally distributed, in which case it is clearly impossible to identify the anemics. The third possibility, which is often overlooked, is that the anemic subjects have hemoglobin levels only slightly below the normal group and that the two populations of anemic and normal subjects partially overlap. Evidence that this was indeed the case in the study under discussion appears when the distributions of hemoglobin levels in the three test groups were examined. In male subjects, the distribution was roughly symmetrical. However, in menstruating females, the distribution was skewed on the lower side, a skewness even more evident in pregnant women. The upper part of the frequency distribution of hemoglobin levels was very similar in all three test groups.

The cumulative distribution in the male series appeared as a straight line when plotted on probability paper, except that it deviated from a straight

line around the lower 2 percent of the population. One could hardly come closer to a normal distribution, whereas in menstruating females the deviation at the lower end occurred at around 15 percent and in pregnant females at around 50 percent.

If anemia is really present as a mild disorder reflected by hemoglobin levels slightly below normal, how then might its incidence be determined? The possibility that the distribution of hemoglobin levels is actually composed of two separate normal distributions merits consideration. Five measurements would be required to construct such a double population: the mean and standard deviation of the healthy population, the mean and standard deviation of the anemic population, and finally, the proportion of anemic and normal subjects. These values were obtained by searching several thousand theoretical curves with a digital computer and choosing the curve that most closely resembled the distribution actually observed. This fitted curve differed from the observed distribution by less than 1 percent at any point throughout the distribution of hemoglobin values.

These findings demonstrated a distribution of hemoglobin values in pregnant females that was comprised of an upper portion representing the normal population with a mean hemoglobin of about 12 g/100 ml and a second lower population of anemic women accounting for 22 percent of the total series. When these results were compared with the WHO criteria of anemia (11 g/100 ml), about 25 percent of the normal subjects fell below this level and were in that sense incorrectly considered anemic, while about one fourth of the anemic women fell in the range adjudged as normal by the WHO criteria. This method demonstrated in menstruating women, that the true incidence of anemia was 12 percent as compared with 17 percent based on WHO criteria. In the males series, on the other hand, the mean hemoglobin level was 15 g/100 ml, and anemia in this population accounted for no more than 2 percent of the total.

In the two series of pregnant and nonpregnant females, iron deficiency accounted for most of the anemia observed. Using WHO criteria of anemia, however, there was a group of anemic subjects that had no abnormality in iron, folate, or vitamin B_{12}.

These findings could be adequately explained by the spread of hemoglobin levels in normal subjects into the area regarded as anemia by WHO criteria.

Hemoglobin criteria as established by the National Nutrition Survey were applied to the data in a recently conducted nutritional survey carried out in the State of Washington. The subjects were males and females ranging in age from 16 to 45. The results of the study showed a prevalence of anemia of 9.7 percent in the females and 10.9 percent in the males. If hematocrit levels were employed in the same situation, the prevalence of anemia was 12 percent in the females and 35 percent in the males. This threefold higher prevalence of anemia in male subjects is certainly in contrast to almost any other nutritional survey of anemia. By performing distribution analysis on the same subjects, however, a value of 9.4 percent was obtained for the females and a less extreme prevalence of 1.7 percent for the male.

Red cell protoporphyrin measurements, which were also performed in this survey, indicated abnormal values in about 20 percent of adult females and in 4 percent of male subjects. These findings agreed well with the distribution analysis of the hemoglobin levels indicating a prevalence of iron lack about twofold greater than the prevalence of iron deficiency anemia.

There are certain limitations to the analysis of the frequency distribution as described. First the measurement being analyzed must have a normal distribution in healthy subjects. Unfortunately this occurs with very few laboratory measurements. It does apply to hemoglobin levels, however, and from preliminary data it also pertains to the red cell protoporphyrin. With measurements that are skewed, such as for plasma iron, transferrin saturation, serum folate, and many of the common laboratory measurements, an alternative approach must be employed. The difficulty can be circumvented if the measurement can be converted to a scale that shows a Gaussian distribution in normal subjects. A major advantage of distribution analysis is that no commonly established standards need be applied. The prevalence of anemia or abnormality can be defined in terms of the normal population sampled under the same conditions.

ESTABLISHMENT OF STANDARDS AND NORMS FOR INTERPRETATION OF IRON NUTRITURE
Infants

William Schubert

A well nourished infant, insofar as iron is concerned, is one in whom hemoglobin concentration and hematocrit are optimal. There should be adequate storage iron to supply the heavy requirements of the growing infant for hemoglobin production and for tissue iron in the first two years of life.

Finch and his co-workers have shown that, in adults, depletion of storage iron precedes the development of clinical iron deficiency anemia. The problem in infancy has been to develop normal values for hemoglobin concentration and hematocrit in infants in whom some demonstration of adequacy of iron stores could be made. Any discussion of normal values for iron nutrition in infancy immediately leads to a consideration of iron supplementation of diet or of dietary iron intake. Large amounts of iron, 150 to 200 mg, are needed in the first year of life, compared to the small amount of iron present in the infant's usual food. Milk contains about a half milligram of iron per quart.

This paper reports a study of the effect of iron supplementation on iron stores and compares these results with several other studies of the effect of iron supplementation in the first year of life. From this comparison standards are developed for normal values in infancy.

Despite the persistently high incidence of iron deficiency anemia in children, the prophylactic use of dietary iron supplementation remains controversial. The study was designed to test the effect of iron supplementation on the maintenance of iron stores during the first eighteen months of life. Prevention of storage iron depletion would support the importance of iron supplementation.

Twenty-two infants showing no evidence of hematologic disease either by history or physical examination on the third day of life, and having hemoglobin concentrations above 16 g/100 ml, were assigned at random to two groups. One group

was fed on iron supplemented prepared formula containing 12 mg of iron per quart, and the other on the same formula without iron. These 22 infants were part of a larger group of 118 infants in whom identical studies were made except for the evaluation of tissue iron.

The patients were members of a low income clinic population in which the incidence of iron deficiency anemia is known to be high. Nutritional management, including early introduction of strained solid foods and iron fortified cereal and routine well baby care, was performed by a single clinician. The clinician had no knowledge of the individual patient's formula status. Prepared formulas were fed for twelve months, followed by a shift to homogenized milk. Home visits were made by a nurse to deliver the formula and determine that it was being used. The incidence and types of infection were determined by retrospective history and physical examination at each clinic visit and from records of nonscheduled clinic visits.

Standard hematologic methods were used. Serum iron and iron binding capacity were measured with o-phenanthroline using 1.5 and 1 ml of serum respectively. Tissue iron was estimated by sideroblast counts of bone marrow smears at intervals of three months. In the absence of other hematologic disease, sideroblast counts have been shown to be a reliable index of available storage iron. There was no attempt to estimate stainable iron in bone marrow sections. The marrows were aspirated in the clinic from the anterior iliac crest. No difficulty arising from the procedure was observed.

One hundred normoblasts were counted on formalin fixed smears stained with Prussian blue and counterstained with saffron. The percent containing two or more granules was tabulated. The mean difference in twenty separate counts by two different observers was 7 percent, with a standard deviation of 4 percent. The mean, standard deviation, and range were calculated for each parameter and age period, and significance was determined by the t-test.

The groups were similar in sex and racial distribution. The majority of the patients were blacks. At one year of age, hemoglobin electrophoresis, sickle

cell preparations, alkali resistant hemoglobin, and red cell morphology were studied to identify and thereby exclude the common hemoglobinopathies. These studies were negative in all patients, supporting the impression that the observed anemia in fact stemmed from iron deficiency.

The number of siblings in each group was comparable. None of the infants was first born, half in each group had four or more siblings. The mothers of the infants studied were of approximately the same age and, presumably, about equally experienced.

Sideroblast counts increased with increasing age in the iron supplemented group but fell in the non-iron supplemented control group. The differences were significant ($p = 0.01$) at age 6, 12, and 15 months but at 18 months were no longer so.

On the basis of reports suggesting that iron deficiency anemia is prevented by good pediatric care and nutritional practice, it was anticipated that reduced hemoglobin concentration might not be observed in these patients and that tissue iron might provide the only evidence of iron depletion. However, beginning at eighteen weeks, hemoglobin concentration was significantly lower in the nonsupplemented group, a difference that persisted through the eighteen-month visit. The same changes in hemoglobin concentration were noted in the larger group of 118 patients as in the 22 patients in whom it was possible to make serial bone marrow observations.

The hematocrit determination showed similar differences from eighteen weeks through eighteen months. The differences in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration paralleled those of hemoglobin and hematocrit. The serum iron values were significantly lower in the nonsupplemented groups at six, nine, and twelve months, but not at eighteen months. Diurnal variation in serum iron determinations was controlled somewhat by seeing the patients at the same time every morning.

Fifty-eight patients from six to eighteen months of age received the iron supplemented diets. Eight had hemoglobins below 10 g/100 ml and none had hemoglobins below 8 g/100 ml. In the nonsupplemented group of 60 children, thirty-five had

hemoglobins below 10 g/100 ml--seven of these were below 8 g/100 ml. Both of these differences were significant at the one percent confidence level. There were no significant differences between groups as regards total protein, serum albumin, serum protein electrophoresis on cellulose acetate, stool guaiac, milk precipitins, and reticulocyte counts. Growth was similar in both groups at all visits. No significant differences in incidence of respiratory or gastrointestinal infection was noted between the groups.

These data indicate that iron supplementation prevents significant depletion of iron stores as estimated by both bone marrow sideroblast counts and iron deficiency anemia in infants who are hematologically normal at birth.

The relation of sideroblast counts to hemoglobin levels was determined in the 3, 6, 12, and 18 month age groups. The presence of tissue iron, as measured by sideroblast counts of approximately 8 percent, was associated with hemoglobin concentrations of 11 g/100 ml and above at 12 months of age, and 11.5 g/100 ml and above at 18 months of age. Such children could be considered to be in optimal iron nutrition. Although the numbers are small, the fact that tissue iron depletion can occur in the absence of anemia is illustrated by the infants with sideroblast counts below 8 percent and hemoglobin concentrations above 11.0 g/100 ml.

Bone marrow sideroblast counts are obviously not a practical way of assessing iron nutrition.

Hunter and Smith[1] have recently presented a similar study of iron supplementation in infants. They propose that the percent saturation of transferrin be used as a measure of adequacy of iron stores and that a saturation of 16 percent and above is an indication of a nonlimiting supply of iron to the bone marrow.

In this study, seventy infants, one third of whom were on an iron supplemented formula, were followed from birth. The hemoglobin values for the total group were compared to the hemoglobin value for the group with transferrin saturation of above 16 percent at 6, 12, and 18 months. Although the means of both groups were similar at each age period, the range in the total groups were much greater: from

5.9 to 13.1 g/100 ml for the total group as compared to 10.3 to 13.0 g/100 ml for those with transferrin saturation above 16 percent: 7.5 to 13.5 g/100 ml compared to 10.9 to 13.5 g/100 ml at 12 months; and 8.1 to 13.6 g/100 ml compared to 11.0 to 13.5 g/100 ml at 18 months.

Their study encompassed patients with relatively severe iron deficiency, in one instance with a hemoglobin level as low as 5.9 g/100 ml. In the group with transferrin saturation above 16 percent the range was much less, and the mean was slightly higher. Based on these data, good iron nutritional status at six months of age could be defined as a hemoglobin of 11.8 g/100 ml and a transferrin saturation of over 16 percent and at twelve months and eighteen months of age, a hemoglobin of 12.2 g/100 ml and transferrin saturation of over 16 percent. All hemoglobin values below 11 and all hematocrit values below 33 percent were associated with reduced transferrin saturation. Transferrin saturation data from the present study comparing iron-supplemented and nonsupplemented groups indicated that percent transferrin saturation was significantly increased, at least at the 95 percent confidence level, in the iron fed group at six, twelve, and eighteen months of age.

A number of prospective studies that compare iron-supplemented versus nonsupplemented infants have now been published. Sturgeon[2] (1958), studied low income patients on three levels of iron intake and compared them to low income controls and to a so-called superior group that was primarily middle class, higher income, and nonghetto. Gross *et al*[3] (1968) in Cleveland studied low income patients in the Western Reserve University family clinic program and tested the effects of protein intake as well as iron supplementation. The high protein diet was milk containing 2.4 g protein/100 ml and the low protein diet was milk containing 1.5 g protein/100 ml, the latter comparable to breast milk. Half of the children in each group received supplemental iron at 8 mg/quart. Andelman and Sered[4] (1966) compared a low protein iron supplemented formula to a high protein nonsupplemented formula.

Sturgeon (1958) found that all infants six months old fed iron-supplemented diets had a significantly higher hemoglobin (11.1 gm/100 ml) than the nonsupplemented

infants (10.8 gm/100 ml). The differences persisted at 12 and 18 months of age. Both the Andelman study, and the one here reported, demonstrated higher hemoglobin levels in the iron-supplemented group than in the unsupplemented group at the 95 percent confidence level at ages 6, 12, and 18 months. Gross *et al* (1968), on the other hand, found that hemoglobin levels were similar in all groups except the one on the high-protein milk unsupplemented with iron. In this group hemoglobin was significantly less than in the other three.

The major difference between the present study group and Gross was that the latter had better prenatal care and possibly a higher level of education, if not income, patients. The important relation of income and educational level to iron deficiency anemia is emphasized by Sturgeon's finding of a significantly higher hemoglobin level at 18 months of age (12.1 g/100 ml) in the so-called "superior" nonghetto group than in the iron-supplemented controls (11.3 g/100 ml).

Beal *et al*[5] (1962), in Denver, studied a well-educated high income group in the Child Research Council study of healthy growth. She found hemoglobins of 12 g/100 ml (range, 11-12.6) in a group receiving daily iron at a dosage of 1-2 mg/kg of body weight and hemoglobins of 12.3 g/100 ml (range, 9.8 to 14.3) in a group receiving daily iron at a dosage of 1 mg or less/kg of body weight.

In summary, it is not usually this reduction in hemoglobin of 1-2 grams in the child without iron supplementation that is significant but rather the fact that this anemia is indicative of iron malnutrition with its attendant systemic effects. Measurement of percent transferrin saturation or of sideroblasts in the bone marrow is not a practical way to assess iron nutrition. Although measurement of hemoglobin concentration and hematocrit will not detect the child who is iron depleted and not anemic, whenever there is reduction in these levels in the absence of hematologic disease, the child is certainly in a state of iron malnutrition. Therefore, hemoglobin concentrations or hematocrit levels are the most practical measures of iron nutrition. Optimal levels of hemoglobin require iron supplementation routinely during the first year of life. The present study suggests that

this is especially important in low income ghetto groups. Hemoglobin and hematocrit levels established in prospective studies of iron-supplemented infants represent optimal iron nutrition as measured by bone marrow sideroblast and transferrin saturation studies and should be taken as the minimal standard of iron nutrition in the infant.

References

[1]Hunter, R. and N. Smith: Methods and Standards in Evaluating Iron Nutrition. Iron Nutrition in Infancy II. Sixty-Second Ross Conference on Pediatric Research. Published by Ross Laboratories, Columbus, Ohio. Library of Congress Catalogue No. 53-22189.

[2]Sturgeon, P.: 1958. Studies of Iron Requirements in Infants and Children. Iron in Clinical Medicine. R. O. Wallerstein and S. R. Mettier, Editors. Berkeley, University of California Press.

[3]Gross, S., M. Vergis, and A. Good: 1968. The Relationship Between Milk Protein and Iron Content on Hematologic Values in Infancy. J. Pediat. 73:521.

[4]Andelman, M. B. and B. R. Sered: 1966. Utilization of Dietary Iron by Term Infants. Amer. J. Dis. Child. 111:45.

[5]Beal, V. A., A. J. Meyers, and R. W. McCammon: 1962. Iron Intake and Physical Growth During the First Two Years of Life. Pediatrics 30:518.

ESTABLISHMENT OF STANDARDS AND NORMS FOR INTERPRETATION OF IRON NUTRITURE
Children

Frank Oski

Finch's laboratory criteria for the diagnosis of iron deficiency (*viz.*, (1) hemoglobin less than 11.8 g/100 ml; (2) Mean Corpuscular Hemoglobin Concentration (MCHC) less than 31.6 percent; and (3) transferrin saturation less than 16 percent) have been shown to be reliable for the adult population and for children 3 to 10 years of age. It is almost impossible, however, to reach firm conclusions regarding optimum iron nutriture for the age ranges 2 1/2 to 3 and 10 to 12 years of age because there are so few data concerning these age groups.

The following presentation is a summation of data available to use in an attempt to provide criteria for determining iron nutriture in children from 2 to 10 years of age.

A study by Carl Smith and another in Denmark by Marner produced similar results. In these studies attempts were made to standardize the time of collection in relation to meals and time of day, and the effects of other diseases were eliminated. In Marner's study, children ages 3 to 6 were studied, before and after iron supplementation had been given, for periods of six weeks to three months. There was no essential change in the parameters measured. From these results it may be concluded that the children studied were in fact iron sufficient. The normal serum iron values and the percent saturations in the group studied by Marner were quite similar to those provided by Carl Smith in 1955, and establish ranges that are very similar to those reported for normal adults.

Marner also found two children in his study group who had serum iron values of 27 μg/100 ml and 35 μg/100 ml in the absence of anemia or change in the mean corpuscular hemoglobin concentration. Though these children were treated with iron, three months later their serum values were still in this low range. Apparently there can be exceptions that are difficult to interpret at the present time.

Schubert has shown that at 18 months of age the sideroblast counts in non-anemic children were above 10 percent. If these data are extrapolated it may be assumed that this situation exists in older children as well.

Nathan Smith surveyed some children 2 to 5 years of age and was unable to draw firm conclusions as to the presence or absence of iron in the marrow in relation to iron nutriture. It has been my experience that bone marrow hemosiderin stains in children in the 2 to 10 age range appear to reflect the presence of iron deficiency.

Another criterion of iron deficiency often employed is the mean corpuscular hemoglobin concentration. Marner's work showed that the mean corpuscular hemoglobin concentration in children 3 to 10 years of age was essentially like that of adults, although somewhat lower. These findings could be used as criteria of at least iron deficient erythropoiesis, if not iron depletion.

In Marner's work the hemoglobin values in children who were demonstrated to be iron sufficient, by serum iron values as well as by treatment with iron, were approximately 0.5 to 0.7 grams higher for each age group than has been reported in large surveys in the United States.

Mean corpuscular volume cannot be used as a sensitive index of the presence of iron deficiency because the mean corpuscular volume in childhood is lower than that commonly accepted as normal for adults. Mean corpuscular hemoglobin concentration is a reliable standard.

Iron absorption and the increase in iron absorption that Finch indicated is present in the iron deficient subject have not been thoroughly studied in children 3 to 10 years of age. There is evidence from Nathan Smith's work, however, that the normal amount of iron absorbed changes during this age period. In children 1, 2, and 3 years of age, for example, the amount of iron absorbed is in the range of 10 to 25 percent. The normal then drops to approximately 5 to 6 percent in the age range 5 to 9 years, and then begins to rise again as adolescence approaches.

What is considered normal iron absorption would have to be carefully examined before any attempt could be made to interpret abnormal absorption. Louis Weintraub demonstrated that an iron deficient child does not increase his iron absorption as much as do iron deficient adults, so that new norms might have to be established in the evaluation of this particular index of iron depletion.

The following summarizes criteria based on available evidence that could be applied to children 2 to 10 years of age: normality would be indicated by a hemoglobin level above 11.8 g/100 ml (11.8 was selected as two standard deviations below the mean indicated by Marner's work); a mean corpuscular hemoglobin concentration above 31.6 percent (this value is above or just at the cutoff of two standard deviations below the mean indicated by Marner's work); a transferrin saturation above 16 percent.

ESTABLISHMENT OF STANDARDS AND NORMS FOR INTERPRETATION OR IRON NUTRITURE
Adolescents

Louis K. Diamond

There are practically no data on iron deficiency in adolescents. A review of the literature for the past twelve years uncovers no more than a dozen relevant papers. In these papers considerable variation in hemoglobin levels, that have already been recognized in this workshop as being relatively poor measures of anemia, were apparent. Also, since pediatricians usually give up care of their patients at ages twelve or thirteen and internists rarely work down to this age level, the child or young adolescent between twelve or thirteen and seventeen or eighteen years of age has generally been regarded as a small adult so far as hemoglobin levels are concerned.

Ragasi and Scott of the Howard University Pediatrics Department showed that there was relatively little difference between hemoglobin levels suggested as normal in the adult and in the adolescent. These investigators studied college men and women between the ages of sixteen and twenty at Howard University. The subjects were mostly black and at a fairly good income level. It was found that if anemia was defined as a hemoglobin level of less than 11 g/100 ml, with a hematocrit of approximately 32 percent, then only 2.4 percent of the women and 0.45 percent of the men were anemic. If a hemoglobin level below 12 g/100 ml was used to define anemia then about 50 percent of the females and 12 percent of the males were anemic.

Daniel and Rowland studied adolescents in a clinic in Birmingham, Alabama. Most of the patients were from the lower income levels and included both whites and blacks. The prevalence of anemia in females was decidedly greater in the blacks than in the whites; at age fifteen, 31 percent; at age fourteen, 37 percent. In both groups the blacks were more anemic than the whites.

Howard Pearson carried out some as yet unpublished studies on 3,000 black clinic children. He considered hematocrits below 30 percent for the child of one and one-half years, below 32 percent for children one and one-half to six years, below

34 percent for children six to fourteen years, and similarly, from fourteen to seventeen years, as indicative of anemia. From these studies Pearson determined that anemia varied with age. There was considerable anemia in the infants, a diminished prevalence in older children, and a quite noticeable increase in the fourteen to seventeen year old females. The latter group included a number who were pregnant, and among these there was a high prevalence of anemia.

Studies published by Seltzer and Mayer some eight years ago were carried out on adolescent children at the Gallagher Clinic in Boston. These studies dealt not only with anemia but also with obesity and the nutritional background for this condition. The patients were not from a low income group. The diet was bizarre, however, since the children were trying to lose weight, and was particularly poor in meats, eggs, and iron-containing food and had no iron supplements.

Hemoglobin and hematocrit, as well as serum iron levels and iron binding capacity, were measured. Anemia was not particularly notable, but the observed low serum iron levels and the high percentage of unsaturated iron binding globulin were important evidences of iron deficiency. It would therefore appear that the serum iron level is a more important index of iron deficiency than is the hemoglobin level or hematocrit. If the degree of unsaturation of serum iron binding capacity and other measurements, such as red cell protoporphyrin level and possibly the siderocytes in the bone marrow, are considered, it might be possible to obtain an even better estimate of the prevalence of iron deficiency.

In adults, as the severity of anemia increases, the percentage of absorption of iron from the gut increases. This is not true in children who are anemic or are becoming increasingly anemic. Weintraub showed this very strikingly, not only by the low level of absorption in severely anemic infants, but also by the improvement that results from administering parenteral iron.

There is no knowledge on the effects of iron deficiency on metabolism, the absorption of iron, or the general activity of the adolescent. In the author's experience it was difficult to get normal hemoglobin values from adolescent patients

who were admitted to a large city hospital for various disturbances, many with severe infections (including hepatitis) since many of them were from the drug addicted and the free living group. Over 90 percent of some fifty individuals in this category, up to the ages of eighteen to nineteen, might be considered adolescents. They were anemic, with hemoglobin levels of less than 10 g/100 ml at the time that they were brought into the hospital. The low hemoglobin levels were due to infection, to poor diets, or to a combination of causes.

The few patients that were followed up showed relatively little response to diet or to iron supplements--that may or may not have been taken. Much further work and more data are needed before both the prevalence of iron deficiency and the effect of therapy in adolescents can be determined.

Discussion

Commenting on Dr. Oski's data on mean corpuscular volume in children, Dr. Finch pointed out that many problems have arisen concerning both hemoglobin concentrations and cell indices. Certainly altitude is one factor that may explain some of the differences observed. With regard to the erythrocyte size, it is difficult to believe that a child's erythrocyte would be different from that of the adult except as it was affected by physiologic factors. One such factor is erythropoietin, which at different levels appears to modify mean corpuscular volume in that at greater concentrations of erythropoietin there is more hemoglobin and the erythrocyte is larger. Another factor is the iron supply.

Dr. Nathan Smith noted that the endowment of iron at birth is not sufficient to meet the growth needs of present-day babies much beyond three to four months. Dr. Schubert agreed that the hemoglobin levels of babies on iron supplemented and nonsupplemented diets differed at 18 weeks. Sideroblast counts were not statistically significant.

The question was posed as to whether efforts should be made to prevent mild iron deficiency in infants and make all infants iron replete. What were the evidences

of harm versus benefit? Dr. Schubert indicated there was no evidence of harm from iron feeding and some indications of benefit, e.g., decrease in irritability. Dr. Smith pointed out that behavioral changes occur in severe iron deficiency that often continue into later childhood.

Dr. Crosby noted that a serious problem in children, that of pica, is alleviated by having the child iron replete. Some forms of pica are hazardous and it is becoming increasingly clear that pica is a symptom of iron deficiency.

Dr. Diamond added that pica applies not only to infants but also to children and adolescents. Recently he had been shown records of more than a dozen adolescents who practiced pica while they were anemic but who lost this habit after iron had been administered. Dr. Schubert stated that one more reason to replete all children is to avoid the occasional although rare death from iron deficiency. Over the last ten years, in his experience, about ten children have been lost from this cause.

PREVALENCE OF IRON DEFICIENCY IN THE UNITED STATES, WITH OR WITHOUT ANEMIA
National Nutrition Survey Data

General

Arnold Schaefer

The Criteria of Nutritional Risk used in the National Nutrition Survey for the adult male and female were those used for fifteen years by the Interdepartmental Committee on Nutrition for National Defense (ICNND).* They are the same criteria that were applied in all thirty-three countries in which surveys were made. The American Academy of Pediatrics, Committee on Nutrition's special *ad hoc* group developed the criteria for children and adolescents.

It should be appreciated that a survey of this kind is not designed to diagnose abnormalities in individuals, but to identify problem areas and populations at risk, and to obtain data on prevalence. Prevalence of abnormalities must be expressed in relation to some accepted or adopted guidelines. The Food and Nutrition Board of the NRC has been provided with data from ten states (over 30,000 blood determinations) giving hemoglobin and hematocrit levels by means and standard deviations, for age groups and by sex, for each of the states. These same data have been analyzed for percent unacceptable and percent acceptable, and also for *Poverty Ratios Index* percent. For all states except Washington, serum iron, transferrin saturation, and serum and red blood cell folate were determined on those blood samples designated as "unacceptable" as to hemoglobin values. All samples for the State of Washington were analyzed.

Regardless of whether a discussion concerns iron deficiency anemia or any other nutritional deficiency, there is a definite relationship with poverty. Further, regardless of whether the level of less than 14 g/100 ml or less than 12 g/100 ml of blood is accepted as indicative of low or unacceptable hemoglobin levels for an

---

*Manual for Nutrition Surveys: (ICNND) 1963. 2nd Edition, U. S. Government Printing Office.

adult male, there is an anemia problem. Using the 12 g/100 ml deficient level for New York City, the prevalence of anemia is about 8 percent and in South Carolina 11 percent. If both low (unacceptable) and deficient levels are employed for South Carolina and Louisiana as indications of anemia, the prevalence is about 37 percent in each state. California turns out to be the state with the lowest number of families in the sample with incomes less than half the poverty index. Hemoglobin levels in adult males in California are deficient in 6 percent of persons in the low income groups; for Kentucky, this occurs in 10 percent, in Massachusetts in 4 percent, and in Michigan, in 5 percent.

The criteria for defining "unacceptable" degrees of transferrin saturation for males and females was less than 20 and 15 percent respectively. In applying these criteria to the general survey, unacceptable levels were recorded in 19.9 percent of males as compared to 17.8 percent of females. Whether the guideline for transferrin saturation should be similar for male and female is an open question. I feel it should be identical. If a level of less than 16 percent saturation is used, as has so often been mentioned in this workshop, the percent of males below this is still 10 to 12 percent or more.

Higher income groups have less iron deficiency anemia than do lower income groups. About 6 or 7 percent of the females in the lower income groups were deficient, whereas this was the case in only 0.6 percent of the females in the higher income group. There is a good reason for the lower prevalence in females. They are the ones taking an iron supplement. How many males take iron tablets?

In California, hemoglobin levels were deficient and low (unacceptable) in 22 percent of low income males and in 10 percent of high income males. Similarly, hemoglobin levels were deficient in 1.7 percent of low income females and in 0.5 percent of higher income females. The same trend was found in most of the other states.

These data indicate that there are bases for concern regardless of the

criteria for iron deficiency. There are probably two to three times as many males as females who could be considered borderline or potentially at risk of anemia.

Data on red blood cell folate and serum folate levels indicate that approximately one fourth of the persons identified as having unacceptable hemoglobin values had levels of red blood cell folate that were unacceptable. The interpretive guidelines for unacceptable folate levels for males and females were identical. The prevalence of "unacceptable" red blood cell folates was greater in males than in females.

PREVALENCE OF IRON DEFICIENCY IN THE UNITED STATES, WITH OR WITHOUT ANEMIA -- NATIONAL NUTRITION SURVEY DATA

Massachusetts

Joseph Edozien

Complete data for the Massachusetts survey have not yet been received. In this survey clinical and biochemical information was obtained on 4,500 people. The mean family size for the group was 5.31. The mean annual income was $6,500. The mean poverty index ratio was 2.29*. The percentage of families below the poverty line was 19.5. A preliminary analysis of the information is presented.

Hemoglobin and hematocrit determinations were carried out on most of the participants in the survey but a special study of the extent of iron deficiency was not undertaken. Using the prescribed guidelines, approximately 8 percent of the total population surveyed had unsatisfactory hemoglobin levels. The most unsatisfactory group were males from 10 to 16 and over 60 years of age, with males 17 to 59 being almost as unsatisfactory. In all age groups, the situation for males appeared to be less satisfactory than for females. Hematocrit levels for males were also less satisfactory than for females.

More complete studies of iron deficiency and hemoglobin levels were carried out on 111 pregnant women. Most of the women were in the second half of pregnancy. Using hemoglobin levels of less than 11 g/100 ml, the proportion of pregnant women who were anemic was 16.2 percent. When hemoglobin levels of less than 11 g/100 ml, serum iron concentrations of less than 60 µg/100 ml, and transferrin saturation of less than 15 percent were used, the incidence of iron deficiency was 11.7 percent.

Pregnant women who showed both iron deficiency and anemia were 4.5 percent of the sample whereas iron deficiency without anemia was present in 7.2 percent. Anemia without evidence of iron deficiency was found in 11.7 percent of the women.

---

*M. Orshansky: 1968. The Shape of Poverty in 1966. Social Security Bulletin.

Ninety-six of the women were taking iron supplements. Of the fifteen persons who were not taking iron supplements, only five had anemia, iron deficiency, or both conditions.

PREVALENCE OF IRON DEFICIENCY IN THE UNITED STATES, WITH OR WITHOUT ANEMIA -- NATIONAL NUTRITION SURVEY DATA

Washington

Nathan Smith

There is widespread iron deficiency anemia within the population of the State of Washington as evaluated from studies of some 5,000 individuals representing 2,000 families. The sample was based on the 1960 census, and was taken from census tracts that were identified and characterized by being in the lowest quartile of incomes in 1960. There had been considerable mobility within the population since 1960 and the mean income for the families studied was $7,200. The mean income in the entire State of Washington at the time of the study was approximately $7,350. In addition to families in low income groups, a sampling of middle and upper income groups was taken. A preliminary evaluation of the data indicated that there was more severe iron deficiency in the low income groups, but the degree of this difference was not very striking. The incidence figures showed that there was almost as much iron deficiency affecting the female population in the upper income families as there was in the lower income families. The same was true for children of school age.

The infant population, preschool population, and the school age population of 6 to 12 year old children showed a rather constant pattern of iron deficiency of approximately 15 to as much as 20 percent. There did not appear to be any significant decrease in the incidence of iron deficiency in school age children. The severest iron deficiency problems arose in early infancy, however.

The criteria set up for adult males in this particular survey were a hemoglobin level of 14 g/100 ml as low and a hemoglobin level of 13 g/100 ml as deficient.

Blood levels of folic acid, iron, vitamin B_{12}, and erythrocyte protoporphyrin were measured in this survey population. By the criteria established

for hemoglobin levels, a large fraction of the male population was considered to be anemic. However, there was no evidence of deficiency as defined by the other criteria. For example, the red cell protoporphyrin levels did not indicate that the group was iron deficient.

It would appear that the hemoglobin standard will have to be critically reviewed in this particular group of adult males when detailed analysis is carried out. Also, the extent of the public health problem of iron deficiency in all socioeconomic groups appears to be greater than previously thought by many of us.

Discussion

Dr. Nathan Smith noted that to use a hemoglobin concentration of 14 g/100 ml in identifying the adult male as having an abnormal hemoglobin level necessitates further study. Dr. Wintrobe suggested that hemoglobin levels of 12 g/100 ml for deficient and less than 14 g/100 ml for low, might be more realistic criteria of anemia in the male population.

Dr. Schaefer posed the question of whether the subjects were anemic rather than the hemoglobin standards being incorrect. Dr. Nathan Smith replied that only a very small percentage of the male subjects that were recorded as having low hemoglobin levels had low serum iron, folate, or vitamin B_{12} levels. In further support of his premise that the hemoglobin standard was inapplicable was the fact that the incidence of low transferrin saturation was very low in the male population thought to be anemic as determined by the suggested hemoglobin standard.

Hemoglobin Concentrations of Children Registered* For Care in C&Y Projects During March and April 1968

Samuel J. Fomon
and
Vernon E. Weckwerth

In March of 1968, 54 Comprehensive Health Projects for Children and Youth (C&Y Projects) were in operation under funding authorized by the 1965 Amendments to Title 5 of the Social Security Act. The majority of the projects were located in urban settings with high concentrations of low-income families. Thirty-six of these projects submitted data to the Systems Development Project, University of Minnesota, concerning registrants seen during the months of March and April, 1968. The present report concerns concentrations of hemoglobin of 11,695 children less than 13 years of age. Data concerning 1033 individuals from 13 to 21 years of age are omitted.

Nineteen C&Y projects located in Kansas City, Missouri, Philadelphia, New York City, Chicago, Detroit, and Baltimore contributed more than 75 percent of the total number of determinations (Table 1). As may be seen from Table 1, C&Y projects in five other cities each contributed data concerning more than 200 children. Data concerning 100 to 200 children each were submitted by C&Y projects located in the following cities: Augusta, Georgia; Helena, Montana; Kirksville, Missouri; Minneapolis, Minnesota; Omaha, Nebraska; and San Francisco, California.

Of the 11,695 children less than 13 years of age, 65.8 percent were black, 24.8 percent were white and 9.4 percent were classified as "other." Approximately 10.5 percent were Spanish-speaking. Birth weights of 2,500 g or less were reported for 16.4 percent of the black children, 11.5 percent of the white children, and 14.6 percent of all children.

---

*Funded, in part, by Grant H-191 from the Maternal and Child Health Service, HSMHA, DHEW, to the University of Minnesota.

TABLE 1

LOCATIONS RESPONSIBLE FOR SUBMISSION OF MORE THAN 80 PERCENT OF DATA ON HEMOGLOBIN CONCENTRATIONS BY C&Y PROJECTS IN MARCH AND APRIL 1968

Location	Project	Number of Determinations *	
Kansas City, Missouri	604		3453
Philadelphia, Pennsylvania			1559
	623	918	
	619	340	
	620	172	
	618	129	
New York, New York			1422
Queens	610	1010	
Brooklyn	628	142	
Brooklyn	653	44	
Manhattan	645	92	
Manhattan	605	67	
Bronx	614A&B	67	
Chicago, Illinois	601		1347
Detroit, Michigan	616		756
Baltimore, Maryland			738
	606A	383	
	606B	187	
	606C	168	
Miami, Florida			635
	636	349	
	638	286	
Washington, D.C.	627		348
Memphis, Tennessee	626		338
Birmingham, Alabama	622		329
Kansas City, Kansas	621		221
Greensboro, North Carolina	625		202

*Applies to children of all ages (i.e., 12,728 determinations) rather than just those less than 13 years of age (11,695 determinations).

Concentrations of Hemoglobin in Relation to Age, Sex, and Birth Weight

Data concerning 9986 children with birth weights greater than 2500 g and 1709 children with birth weights of 2500 g or less are summarized in Table 2. No remarkable sex-related differences in hemoglobin concentrations are apparent. Concentrations of hemoglobin were lowest between 6 months and 2 years of age. During the first two years of life, the 10th and 50th percentiles of hemoglobin concentration were generally less for children with birth weights of 2500 g or less than for those with birth weights greater than 2500 g. Hemoglobin concentrations of children older than 2 years did not appear to be related to birth weight.

Summary of Data Concerning Children with Concentrations of Hemoglobin Less Than 11.0 g/100 ml

Because no remarkable sex-related differences were detected in hemoglobin concentrations among children of the various age categories, data pertaining to the two sexes have been combined in Table 3.

Children with birth weights greater than 2500 g: In accord with data already presented in Table 2, low concentrations of hemoglobin were most frequently encountered in children from 6 months to 2 years of age; concentrations of hemoglobin less than 10.0 g/100 ml were found in 19.7 percent of children from 6 months to 1 year of age and in 26.5 percent of children from 1 to 2 years of age. An unexpectedly high number (11.6 percent) of infants less than 6 months of age had hemoglobin concentrations less than 10.0 g/100 ml.

Concentrations of hemoglobin less than 10.0 g/100 ml were much less frequently encountered in children over three years of age than in younger children --3.1 percent of those from 3 to 4 years of age and 1.9 percent of those from 4 to 9 years of age.

Of particular medical significance was the finding of hemoglobin concentrations less than 8.0 g/100 ml. Among children with birth weights greater than 2500 g, 2.7 percent of those from 6 months to 1 year of age and 5.7 percent of those from 1 to 2 years of age had hemoglobin concentrations less than 8.0 g/100 ml.

TABLE 2

VARIOUS PERCENTILE VALUES OF HEMOGLOBIN CONCENTRATIONS OF CHILDREN LESS THAN 13 YEARS OF AGE REGISTERED IN C&Y PROJECTS DURING MARCH AND APRIL 1968

Age (years)	Males				Females			
	Number of Children	Hemoglobin (g/100 ml) Percentiles			Number of Children	Hemoglobin (g/100 ml) Percentiles		
		10th	50th	90th		10th	50th	90th
9986 Children with Birth Weights More Than 2500 g								
0.00-0.49	720	9.5	11.3	13.9	682	9.9	11.5	13.8
0.50-0.99	511	8.9	10.8	12.4	494	9.2	11.1	12.5
1.00-1.99	758	8.6	10.8	12.5	673	8.7	10.9	12.5
2.00-2.99	494	9.9	11.5	12.9	479	9.9	11.5	12.9
3.00-3.99	427	10.7	11.8	13.1	387	10.4	11.8	12.9
4.00-4.99	386	10.7	11.9	13.2	372	10.7	11.9	13.3
5.00-8.99	1114	10.9	12.0	13.4	991	10.8	12.0	13.4
9.00-12.99	796	11.1	12.5	13.8	702	11.2	12.5	13.8
1709 Children with Birth Weights 2500 g or Less								
0.00-0.49	124	8.5	10.7	12.7	137	9.3	11.0	13.3
0.50-0.99	114	8.0	10.3	11.9	118	8.7	10.9	12.4
1.00-1.99	130	7.4	10.3	12.2	138	7.8	10.6	12.7
2.00-2.99	74	10.0	11.5	13.0	107	9.7	11.4	13.4
3.00-3.99	56	10.4	11.8	13.2	75	10.4	11.9	13.0
4.00-4.99	53	10.8	11.9	13.3	69	10.6	12.0	13.0
5.00-8.99	157	10.9	12.2	13.8	163	10.8	12.0	13.6
9.00-12.99	91	11.4	12.5	14.1	103	11.1	12.3	13.5

TABLE 3

SUMMARY OF CONCENTRATIONS OF HEMOGLOBIN LESS THAN 11 G/100 ML AMONG CHILDREN REGISTERED IN C&Y PROJECTS DURING MARCH AND APRIL 1968

Age (Years)	Birth Weight >2500 g					Birth Weight 2500 g or Less				
	Number of Children	Percentage of Children With Concentrations of Hemoglobin (g/100 ml)				Number of Children	Percentage of Children With Concentrations of Hemoglobin (g/100 ml)			
		<11.0	<10.0	<9.0	<8.0		<11.0	<10.0	<9.0	<8.0
0.00-0.49	1402	35.4	11.6	2.4	0.5	261	47.5	24.1	9.2	1.5
0.50-0.99	1005	48.0	19.7	8.4	2.7	232	53.0	29.3	14.7	6.0
1.00-1.99	1431	50.7	26.5	12.7	5.7	268	58.2	38.8	21.2	11.1
2.00-2.99	973	27.7	9.7	3.1	0.7	181	30.4	8.3	2.8	1.7
3.00-3.99	814	17.0	3.1	1.1	0.5	131	19.8	3.1	1.5	1.5
4.00-8.99	2863	11.8	1.9	0.9	0.6	442	10.6	2.0	0.9	0.2
9.00-12.99	1498	5.8	1.0	0.4	0.3	194	5.7	1.0	0.5	0.0

Children with birth weights 2500 g or less: During the first 2 years of life low concentrations of hemoglobin were considerably more frequent among children with low birth weights than among those with birth weights greater than 2500 g. Among children from 1 to 2 years of age, for example, concentrations of hemoglobin less than 10 g/100 ml were found in 38.8 percent of low birth weight children compared to 26.5 percent of children with birth weights greater than 2500 g (Table 3). Concentrations of hemoglobin less than 8.0 g/100 ml were found in 6.0 percent of low birth weight children from 6 months to 1 year of age and in 11.1 percent of those from 1 to 2 years of age.

Comparison of Hemoglobin Concentrations of Black and White Children

The 10th, 50th, and 90th percentile values of hemoglobin concentrations of black and white children of various ages are presented in Table 4. The age-related prevalence of low concentrations of hemoglobin of the black children suggests that sickle cell anemia is not the major cause of the low concentrations in black children from 6 months to 2 years of age. Corresponding percentiles of hemoglobin concentrations are generally less for black than for white children in the age ranges 6 months to 2 years and 3 to 13 years.

TABLE 4

COMPARISON OF HEMOGLOBIN CONCENTRATIONS OF BLACK AND WHITE CHILDREN LESS THAN 13 YEARS OF AGE REGISTERED IN C&Y PROJECTS DURING MARCH AND APRIL 1968

Age (years)	Black				White			
	Number of Children	Hemoglobin (g/100 ml) Percentiles			Number of Children	Hemoglobin (g/100 ml) Percentiles		
		10th	50th	90th		10th	50th	90th
Birth Weights More Than 2500 g								
0.00-0.49	1017	9.7	11.3	13.5	263	9.7	11.6	15.6
0.50-0.99	725	8.9	10.8	12.4	200	9.6	11.3	12.6
1.00-1.99	1033	8.5	10.7	12.4	305	8.7	11.0	12.7
2.00-2.99	663	10.0	11.5	12.8	223	9.8	11.5	13.0
3.00-3.99	489	10.4	11.7	13.0	231	10.8	11.9	13.0
4.00-8.99	1681	10.6	11.9	13.3	837	11.0	12.3	13.5
9.00-12.99	823	10.9	12.2	13.6	507	11.6	12.8	14.0
Birth Weights 2500 g or Less								
0.00-0.49	213	8.9	10.8	13.0	35	8.9	11.2	13.2
0.50-0.99	183	8.3	10.6	12.2	36	8.7	11.0	11.9
1.00-1.99	200	7.8	10.4	12.2	56	7.1	10.7	13.0
2.00-2.99	141	10.0	11.4	13.2	30	9.5	11.3	13.3
3.00-3.99	94	10.4	11.6	13.0	28	11.2	12.0	13.2
4.00-8.99	301	10.5	12.0	13.3	104	11.0	12.1	13.8
9.00-12.99	131	11.2	12.2	13.5	45	11.5	12.8	14.4

PREVALENCE OF IRON DEFICIENCY IN THE UNITED STATES WITH OR WITHOUT ANEMIA

HEW Preschool Survey

George Owen

The study, which took place between November, 1968 and December, 1970, was limited to children between 12 and 71 months of age. It included all the preschool children in a family if there were no more than three. If there were more than three preschool children in the family, a table of random numbers was used to select only three of them.

The sampling for the study was designed by the Survey Research Center at the University of Michigan. Altogether, there were 74 sample units distributed according to population density. Sixty-two of them were included in the study only once; six of them, all in the largest metropolitan areas, were sampled on two occasions, once in each of two years. The total study included approximately 3,750 children, but data for only the first half of the sample will be discussed here.

Income quartiles were arrived at by using the take-home pay of each family unit and dividing that figure by the number of individuals in the family unit. The median per capita income for the population was approximately $1,300, which for a family of four would represent an annual income of $5,200. Having ranked the families according to per capita incomes, the population was divided into four quartiles.

The children were examined in field clinics by a pediatrician and a pedodontist. Blood samples, which were heparinized, were obtained by venipuncture from the antecubital vein. Microhematocrit and hemoglobin levels were determined in the field. Hemoglobin concentration was determined by the methemoglobin method utilizing a Fisher flow-through hemophotometer. Virtually all the determinations were carried out by the same technician.

Plasma samples were frozen in dry ice and returned to the laboratory in Columbus, Ohio, where iron and iron binding capacity determinations were carried out with a Technicon single-channel autoanalyzer.

The population was subdivided on the basis of income quartiles without respect to age (Table 1). The mean hemoglobin level for the 266 children in quartile I was 12.4 g/100 ml and 12.5 g/100 ml for children in the other three quartiles. The percent saturation of transferrin was 21.3 in children in quartile I and progressively higher in the other quartiles, reaching 24.5 percent in quartile IV.

Table 2 shows the percentage distribution of biochemical values in pre-school children in relation to age. There was an average hemoglobin level of 12.1 g/100 ml in the 182 children in the 12 to 23 month old group. As was expected, there was a progressive increase in mean hemoglobin levels with increasing age.

There was not much difference in plasma iron levels between the age groups, although the youngest age group had the lowest mean plasma iron values.

Saturation of transferrin paralleled plasma iron concentration in that the one to two year age group had significantly lower average saturation of transferrin in comparison to other age groups.

An interesting aspect of this study was the fact that children in the Northeast showed relatively little change in average hemoglobin levels with age.

Approximately 19 percent of the children in the Northeast census region, whose families had incomes below $900 per capita, had hemoglobin levels below 11 g/100 ml. In comparison, 12 percent of the children in the south in the same lower income groups had hemoglobin levels less than 11 g/100 ml.

In an attempt to answer the question whether the difference between hemoglobin levels of 10.5 and 11 g/100 ml or 10 and 11 g/100 ml was significant, a comparison of hemoglobin levels and height was carried out. There appeared to be some differences between the heights of children, as compared against the Boston grid, and their hemoglobin values. A disproportionate share of children who had shorter stature also had lower average hemoglobin levels. The same relationship did not appear to hold in the case of transferrin saturation.

Table 1 - Percentage distribution of biochemical values in first half sample, Preschool Nutrition Survey

Hemoglobin (gm/100 ml)	less than 10	10 thru 10.4	10.5 thru 10.9	11.0 thru 11.4	11.5 thru 11.9	12.0 thru 12.4	12.5 thru 12.9	13.0 thru 13.4	13.5 thru 13.9	14.0 and above	N	Mean	(S.D.)
Quartile I	2	2	4	10	12	17	21	13	10	9	266	12.4	(1.3)
II	<1	3	4	12	10	17	19	15	10	10	262	12.5	(1.2)
III	<1	3	2	9	11	25	22	13	9	8	316	12.5	(1.2)
IV	<1	1	2	6	14	21	23	15	9	8	318	12.5	(1.0)

Saturation of transferrin (%)	less than 4	5 thru 9	10 thru 14	15 thru 19	20 thru 24	25 thru 29	30 thru 34	35 thru 39	40 thru 44	45 and above	N	Mean	(S.D.)
Quartile I	2	11	19	17	14	17	8	5	3	4	197	21.3	(11.5)
II	<1	10	17	18	16	15	10	5	6	3	208	22.4	(11.0)
III	2	8	14	19	15	12	10	10	5	5	240	23.9	(12.3)
IV	0	9	11	18	15	21	8	7	6	6	238	24.5	(11.6)

Table 2 - Percentage distribution of biochemical values in preschool children in first half sample

Hemoglobin (g/100 ml)	less than 10	10 thru 10.4	10.5 thru 10.9	11.0 thru 11.4	11.5 thru 11.9	12.0 thru 12.4	12.5 thru 12.9	13.0 thru 13.4	13.5 thru 13.9	14.0 and above	N	Mean	(SD)
12-23 mos.	4	6	5	11	9	18	22	9	7	8	182	12.1	(1.2)
24-35 mos.	1	2	3	9	11	25	23	10	8	7	224	12.4	(1.1)
36-47 mos.	0	<1	1	10	11	20	22	19	9	7	271	12.5	(0.9)
48-59 mos.	<1	2	2	7	13	17	18	17	11	12	231	12.7	(1.2)
60-71 mos.	0	2	3	7	13	21	22	13	11	9	254	12.6	(1.0)

Plasma Iron (µg/100 ml)	less than 30	30 thru 39	40 thru 49	50 thru 59	60 thru 69	70 thru 79	80 thru 89	90 thru 99	100 thru 109	110 and above	N	Mean	(SD)
12-23 mos.	16	12	13	12	8	9	9	7	5	10	153	63	(31)
24-35 mos.	5	5	8	10	12	13	9	12	6	20	210	81	(35)
36-47 mos.	7	6	10	10	8	11	11	9	9	18	248	77	(33)
48-59 mos.	5	5	7	12	8	12	10	9	11	22	226	83	(38)
60-71 mos.	4	5	7	9	13	11	11	15	8	18	246	80	(31)

Saturation of transferrin (%)	less than 5	5 thru 9	10 thru 14	15 thru 19	20 thru 24	25 thru 29	30 thru 34	35 thru 39	40 thru 44	45 and above	N	Mean	(SD)
12-23 mos.	5	21	23	18	9	13	6	4	0	1	120	16	(9)
24-35 mos.	1	10	13	18	18	15	10	5	5	5	165	23	(12)
36-47 mos.	<1	8	17	18	17	16	8	8	5	4	210	23	(11)
48-59 mos.	1	6	14	16	15	13	12	8	8	7	189	26	(13)
60-71 mos.	0	6	12	20	15	20	9	7	6	4	202	25	(11)

Discussion

Dr. Nathan Smith suggested that the low stature group from which the information was collected may have included premature infants as well as small babies with low hemoglobin values. Dr. Owen agreed that this possibility existed and that it was critical to have information on birth weights when examining hemoglobin levels, particularly in the younger age group.

In response to a question, Dr. Owen pointed out that a more accurate picture of biochemical data would be obtained if the data were correctly weighted. This statement was qualified by the explanation that in the south there was a marked difference between interview response and clinic participation in the study. In the south, for example, on the basis of the 1960 census, 24 percent of the population is black. Subjects from the south interviewed in the present study regarding nutrition and dietary habits were 24.3 percent black. However, biochemical data in the same study were based on 42 percent black subjects. Obviously, unless data are weighted, biochemical measurements should be viewed only in relationship to clinical findings and dietary intakes.

PREVALENCE OF IRON DEFICIENCY IN THE UNITED STATES WITH OR WITHOUT ANEMIA

In Adult Women*

Jack Pritchard

Studies were initiated to evaluate iron stores and iron deficiency in women of reproductive age. Storage iron was evaluated by a histochemical technique using aspirated marrow particles from the iliac crest. These were blown out onto a glass slide, spread with the marrow particles intact, and stained with Prussian blue. Grading was arbitrary, but generally followed the classification proposed by Gale and associates. Two investigators did the grading independently and there was close agreement between their evaluations.

Although the technique did not permit precise quantification of the amount of iron present, attempts were made to equate the histochemical evaluation with the amount of iron in storage that was available for hemoglobin synthesis. In a group of volunteers, the amount of stainable iron present in marrow particles was examined, and the capability of the individuals to synthesize hemoglobin was measured by repeated quantitative phlebotomy. The results of sixteen quantitative phlebotomy studies showed a reasonable relationship between the iron visualized as Prussian blue over the histochemically estimated range of zero to four plus and the amount of iron converted to hemoglobin. In most instances, histochemical estimates of the iron stores were within 200 milligrams of the amount available for hemoglobin synthesis.

In some cases of megaloblastic anemia due to folate deficiency during pregnancy, where the woman was delivered before the diagnosis was made and treatment started, the amount of iron present in the marrow was determined by histochemical technique. The volunteer was then treated with folic acid and the amount of hemoglobin generated from the storage iron was measured. There was good agreement

---

*Dr. Daniel Scott collaborated in obtaining information for this study.

in conversion of storage iron into circulating hemoglobin mass whether the storage iron was removed by phlebotomy or by the removal (by folate treatment) of a block to hemoglobin synthesis.

Studies were carried out to determine if all of the storage iron was being mobilized and also to determine the amount of iron that was being absorbed and utilized from the diet. Eight women were allowed to continue for an average of five more weeks after the last phlebotomy, then circulating hemoglobin iron was remeasured. Menstrual iron loss during that time was measured. The capability for regenerating hemoglobin was very small, which indicated that these women had utilized all storage iron and that they were capturing very little iron from the diet.

It was repeatedly demonstrated in these individuals that the production of iron deficiency by this technique almost always produced a reduction in the amount of menstrual flow, which in turn reduced the amount of iron loss. The amount of iron loss was reduced to a greater degree than would be accounted for by the reduction in hemoglobin concentration. Contrary to an often repeated view that iron deficiency leads to menorrhagia, in this experience the reverse was most often true; namely, that if overt iron deficiency anemia is produced, the typical response is one of reduction in menstrual flow.

Iron stores were evaluated histochemically in 114 apparently healthy nulligravid women and equated against the standard calibration constructed from the phlebotomy data. The women were white college students enrolled in a degree nursing program and represented somewhat privileged middle class Americans in the Greater Dallas area. These individuals had been selected on the basis that they never had donated blood, suffered menorrhagia, undergone surgery, been hospitalized, and were not troubled with frequent nosebleeds. Approximately a third had essentially no storage iron, and in another third it was only about 200 milligrams. Thus two-thirds of them had iron stores equivalent to the iron content of one pint of blood or less. A rather liberal estimate of the average amount of storage iron in these young, healthy, nonpregnant women is about 350 mg.

The study was then extended to a group of predominantly black, semi-indigent women who were relatively late in the first half of pregnancy. About 50 percent of them had essentially no iron stores and another 20 percent had stores of about 200 mg or less. There appeared to be no striking difference in storage iron between the middle class whites and the blacks who were socio-economically more deprived.

The hemoglobin mass in nearly 30 normal women who were demonstrated to have iron stores was determined and the various iron contents were calculated. The results showed that the iron content of a 60 kg female was about 60 percent of that of a 70 kg male. It is interesting to speculate on the difference between iron content of the male and female. The major difference is thought to be in storage iron and lower circulating hemoglobin iron. Diet and menstruation are thought to be major factors that bring about this difference.

Halberg and his associates in Sweden demonstrated that the mean menstrual blood loss in twelve young student nurses measured through 12 cycles, was 28 ml. In Dallas, menstrual blood loss measured in 25 subjects through a total of 54 cycles was approximately the same as that found in Halberg's studies. A value of 30 ml for menstrual blood loss is probably reasonable for purposes of calculations. Using the value of 30 ml, this would represent about 400 ml per year, or a loss of nearly 200 mg of iron. If boys and girls start out with the same iron stores, or lack of iron stores, at age twelve, it is easy to see how a constant loss of iron of this magnitude over the next several years could well account for the difference in storage iron between men and women.

Quantitative phlebotomies, similar to those just described for women, have been carried out on four men. A mean value for the iron stores in healthy men was about 1100 milligrams. This is the same value found in a classic study done some years ago.

Many factors, such as use of oral contraceptives, must be evaluated in considering iron stores. In one example, a patient suffering from menorrhagia of unknown cause was overtly iron deficient, with anemia, and demonstrated the

classic changes associated with it. After treatment with oral iron, the iron deficiency anemia was corrected, but this regimen did not favorably influence menstrual loss, it simply allowed the patient to tolerate it better. Iron therapy was stopped and a commonly used oral contraceptive agent administered. Menstrual blood loss decreased remarkably from approximately 200 ml or more in each cycle to less than 50 ml. The agent was stopped, the menorrhagia recurred, and the hemoglobin returned to the previous level. The oral contraceptive was resumed with comparable results.

Data from Sweden show that oral contraceptives reduced the blood loss associated with their cyclic withdrawal to about one half that which accompanies spontaneous menstruation.

As part of the annual physical examination in a rather large family-planning project, the hemoglobin levels in collected bloods are being measured. Practically all of the women were delivered of a baby one year previously and enrolled in the program soon thereafter. In a very preliminary survey those using barrier contraceptives had a mean hemoglobin concentration of 12.8 g/100 ml, those using intrauterine devices, 12.6 g/100 ml, and those taking oral contraceptives, 13.4 g/100 ml. Hemoglobins of less than 11 g/100 ml occurred in 9 percent of those using barrier contraceptives and 12 percent of those using an intrauterine device, but in fewer than 1 percent of those taking oral contraceptives. At hemoglobin levels of less than 10 g/100 ml, the percentages were 2.6, 4.9, and 0.3 percent respectively.

The oral contraceptive typically reduces menstrual blood loss. Certainly in women who have grossly excessive bleeding, this will have considerable influence on anemia and in women who have less extensive menstrual loss, this will in time have an effect on iron stores. One 21-day cycle oral contraceptive with 7 nonhormonal tablets is presently marketed, but the 7 "blanks" contain ferrous fumarate. This approach, too, in time will have an effect on iron stores.

In a study to determine the normal hemoglobin levels in healthy adult females, three groups of 100 were chosen, and a medical history was taken and physical examination done on each woman. Bone marrow iron was determined and the presence of storage

iron identified in each subject. In addition, cytomorphological examination was carried out in search for any evidence of megaloblastic change. The mean hemoglobin value for the nonpregnant women was 13.7 g/100 ml. In one individual the hemoglobin was 11.7 g/100 ml; all others were above this value. For females at mid-pregnancy, the mean hemoglobin level was 11.5 g/100 ml, and in 29 percent of the subjects the hemoglobin level was less than 11 g/100 ml. In three individuals it was 9.8 g/100 ml, the lowest values found. For women at or very near term, 27 percent had hemoglobin levels less than 11 g/100 ml. The mean value was 12.3 g/100 ml, but in one woman the hemoglobin was 9.8 g/100 ml.

It was concluded from the study that mean hemoglobin concentration for healthy, nonpregnant, iron-sufficient women at sea level is between 13.5 and 14 g/100 ml; at mid-pregnancy it is a little greater than 11 g/100 ml; and late in pregnancy about 12 to 12.5 g/100 ml.

Discussion

Dr. Oski asked, in view of the distinct geographic variability in the incidence of iron deficiency in the first year of life, whether this might be due to a geographic variation in the technique of handling the umbilical cord since approximately one third of the blood volume can be transferred in a very short period of time. He also asked if it was more common in clinic patients to clamp the umbilical cord immediately?

In his reply, Dr. Pritchard affirmed variation in the technique of handling the cord. Immediate clamping may leave 40 percent of the blood in the placenta and distal to the clamp. This practice is perhaps more apt to occur in a clinic population. Junior personnel in training programs are harangued about the problem of aspiration in the newborn infant. As a consequence, typically, the baby is delivered, "hung by his heels," and the cord promptly clamped. As a consequence, blood may actually drain from the infant to the placenta rather than the reverse.

DIETARY INTAKE OF IRON IN THE UNITED STATES

Robert Shank, Moderator

Infants

L. J. Filer, Jr.

A substantial body of information exists concerning the dietary intake of iron by infants. However, definitive data are lacking for infants in low income families.

In each of two successive years, 1962 and 1963, approximately 4,000 questionnaires were mailed to mothers in the United States who had six-month old infants. The questionnaire, mailed with a dollar, asked the mother to supply information on the food ingested by her infant in the past 24 hours. This information was requested in terms of formula, vegetables, fruit, eggs, meats, juice, vitamins, and such other dietary components as teething biscuits or table foods that her infant might be eating. Infants were selected from a national registry of births and the sample was selected on a random basis so as to pattern itself after the Bureau of the Census data for the United States.

The male-female ratio of the sample, the percentage of primiparous and multiparous mothers, average birth weight, average age of mother, educational status, family income, and urban-rural distribution in the sample were all comparable to data reported in the United States Census.

The 50th percentile for iron intake calculated from the diets of all infants in the sample was 7.2 mg/day. This is in contrast to the recommended dietary allowance by the Food and Nutrition Board of 8 mg and the 12 mg allowance recommended by the Committee on Nutrition of the American Academy of Pediatrics.

The rural infant on the average received somewhat less iron than did his urban counterpart. Also, the mother with only a grade school education fed a diet that provided less iron for her infant than did the diets fed by the mother who had a post high school education. Furthermore, infants in families with higher incomes

received on the average diets that provided slightly more iron than did infants from families with lower incomes.

Of further interest and concern was the fact that 25 percent of the infants were receiving less than 50 percent of recommended iron allowance. In other words, the 25th percentile was receiving about 4 mg/day in contrast to a recommended allowance of somewhere between 8 and 12 mg/day. From this it may be concluded that a large segment of our infant population is not receiving an adequate amount of dietary iron.

In the U. S. Department of Agriculture survey conducted in 1965, infants 1 to 2 years of age were found to have an average daily iron intake of 5.9 mg.

For the 6 month old infant, iron fortified infant cereal provides 50 percent of total daily iron. The next most important foodstuff, as a source of iron was meat, followed by vegetables, fruit, eggs, and other. In 1970 a survey carried out on approximately 5,000 to 6,000 infants at 3, 6, 9, and 12 months of age indicated that the mean daily intake of iron for the 6 month old infant was 7.5 mg/day. Once again, 50 percent of total dietary iron came from iron fortified cereal. Meat, fruit, and vegetables provided about the same amount of daily iron as was calculated from the 1962 and 1963 surveys.

In 1970, Dr. George Owen conducted a survey on approximately 70 infants. The per capita income for the families was $600 to $2,500. Median daily iron intake at 3 months of age was 6 mg, at 6 months 5 mg, at 9 months 5 mg, and at 12 months 6 mg. These data are comparable to those obtained by the 24 hour recall questionnaire. In Dr. Owen's survey, he not only had a two-day dietary history from the mother, but a trained nutritionist went into the home and observed the feeding practice. In Dr. Owen's study 12 percent of infants received less than 3 milligrams of iron/day at 3 months of age, 35 percent received less than 3 milligrams of iron/day at 6 months of age, 19 percent at 9 months, and 10 percent at 16 months. The percentage of infants receiving more than 10 milligrams of iron per day was 15 at

3 months, 16 at 6 months, 16 at 9 months, and 15 at 12 months of age. Data from the questionnaire and from the actual household experience were comparable.

Data from the 1965 U. S. Department of Agriculture survey showed that some 5 percent of the iron intake of one-year olds and the one to two-year old infants came from milk and milk products, about 12 percent from meats and poultry, 6 percent from eggs, 5 percent from legumes, 50 percent from grain, and 20 percent from fruits and vegetables. The contribution that grain products fortified with iron make to the dietary intake of the infant is evident.

Preliminary data from the Ten State Survey show the following sources of iron in the diet of the infant. Animal protein sources contribute 47 percent of the daily intake, cereal and grain 23 percent, fruits and vegetables 15 percent, legumes 5 percent, desserts and sugar 5 percent. The ranges for the various sources of iron as indicated in the data analyzed to date are: 39 to 52 percent from animal protein sources, 19 to 32 percent from cereal and grain, 14 to 17 percent from fruits and vegetables, 1 to 10 percent from legumes, and 5 to 8 percent from desserts and sugar. Why animal protein makes a slightly greater contribution than cereals is unexplainable since it would be expected that cereal and grains contribute around 40 to 50 percent of the daily iron intake.

Through large population surveys the sources of iron in an infant's diet, and the order of magnitude of the contribution that each component makes to the daily iron intake of the infant, are well known.

DIETARY INTAKE OF IRON IN THE UNITED STATES

Preschool Children

George Owen

Iron intakes of preschool children were determined for the same population studied in the Preschool Nutrition Survey previously reported. Interviewers visited in the homes of the families and spent approximately one hour per day for three consecutive week days (day 1, 2, and 3) to obtain questionnaire and food intake information. Diet intake information was collected by recall for that portion of day 1 that preceeded the interviewer's arrival and by means of a written food record, kept by the mother, for the remainder of day 1 and for day 2. Measuring cups and spoons were provided for each respondent, and simple food models and 1,000 gram scales were used by the interviewer to verify portions of food consumed. Recipes were obtained for all home-prepared foods. Information on the kind and amount of vitamin/mineral supplement consumed was obtained for each child.

Approximately half of the children in the first half-sample routinely consumed some vitamin/mineral supplement (Table 1). Mean iron intakes were 10 mg/day for the group taking supplements, compared to 7 mg/day for those who did not take supplements. However, only a small proportion of children in the "supplemented" group received a supplement that contained iron. Table 2 indicates the relative contribution of food groups and of supplements to mean daily intakes of several nutrients including iron. Obviously, for several of the vitamins, the supplements represented a significant source of daily intake (Table 3). On the other hand, when we considered daily intakes of nutrients from only the diet alone, it became evident that the population taking supplements frequently had a greater dietary intake of nutrients than did the unsupplemented population.

In Table 4, percentage distributions of total iron intake are shown according to age and income level--neither of which seemed to be very important determinants.

Table 1

Proportion of children in first half sample of Preschool Nutrition Survey receiving vitamin/mineral supplements: by age and income quartile

Age and Income Quartile	CHILDREN	
	Total Number	Percent Supplemented
12-23 months		
I	66	34
II	65	46
III	74	57
IV	89	65
24-35 months		
I	87	34
II	60	44
III	100	59
IV	93	57
36-47 months		
I	86	30
II	83	44
III	97	50
IV	104	59
48-59 months		
I	80	21
II	80	41
III	87	53
IV	92	60
60-71 months		
I	82	20
II	74	44
III	95	51
IV	98	53

Table 2a

Percent contribution of nine food groups and of vitamin/mineral supplements to daily caloric and total nutrient intakes of preschool children (12-23 months)

NUTRIENT AND GROUP	MEAN INTAKE	PERCENT CONTRIBUTION OF DAILY INTAKE									
		Dairy foods	Meat, fish	Eggs	Legumes	Grains	Fruits	Vege-tables	Fat, oils	Sweets	Vitamin/ mineral supplements
Calories (Kcal/kg)											
National - A	102	32	11	4	4	25	7	8	3	5	--
National - B	107	35	14	4	1	22	10	6	3	5	--
Protein (gm/kg)											
National - A	4.1	44	21	6	4	16	1	6	--	1	--
National - B	4.4	46	25	7	2	14	2	4	--	1	--
Calcium (mg)											
National - A	732	80	2	2	2	9	1	3	<1	1	--
National - B	902	84	2	2	<1	8	2	2	<1	1	0
Iron (mg)											
National - A	6	6	19	7	7	40	7	12	<1	2	
National - B	9	4	20	8	2	36	7	9	<1	2	14
Vitamin A (IU/kg)											
National - A	313	25	14	8	1	5	6	38	3	0	--
National - B	593	20	9	7	<1	4	5	25	3	0	26
Thiamin (mg/1000 Kcal)											
National - A	0.6	28	11	3	3	36	7	11	<1	<1	--
National - B	1.5	18	8	2	1	20	5	5	0	<1	41
Riboflavin (mg/1000 Kcal)											
National - A	1.3	66	10	4	1	13	2	4	1	<1	--
National - B	2.5	49	7	4	<1	9	1	2	0	<1	27
Vitamin C (mg)											
National - A	40	15	2	0	2	3	51	27	<1	<1	--
National - B	101	9	2	0	<1	3	40	11	0	<1	36

A - Intake data pertain only to 142 children who did not receive supplements.
B - Intake data pertain only to 154 children who did receive supplements.

Table 2b

Percent contribution of nine food groups and of vitamin/mineral supplements to daily caloric and total nutrient intakes of preschool children (24-71 months)

NUTRIENT AND GROUP	MEAN INTAKE	PERCENT CONTRIBUTION TO DAILY INTAKE: Dairy foods	Meat, fish	Eggs	Legumes	Grains	Fruits	Vege-tables	Fat, oils	Sweets	Vitamin/ mineral supplements
Calories (Kcal/kg)											
National - A	95	22	16	3	4	29	6	8	4	8	--
National - B	100	26	15	3	3	27	7	7	4	8	0
Protein (gm/kg)											
National - A	3.6	29	34	5	5	19	1	5	1	1	--
National - B	3.8	34	32	5	3	19	2	5	1	1	0
Calcium (mg)											
National - A	786	71	3	2	2	14	2	4	1	2	--
National - B	875	76	2	1	1	13	3	3	1	1	0
Iron (mg)											
National - A	8	4	28	6	7	34	5	12	1	4	--
National - B	11	3	23	5	3	33	7	9	1	3	14
Vitamin A (IU/kg)											
National - A	239	19	19	8	1	7	8	34	5	1	--
National - B	427	17	8	5	1	7	8	26	4	1	25
Thiamin (mg/1000 Kcal)											
National - A	0.6	18	19	3	4	37	7	11	1	1	--
National - B	1.3	13	12	1	1	23	6	6	1	1	37
Riboflavin (mg/1000 Kcal)											
National - A	1.0	54	16	5	1	16	2	5	1	1	--
National - B	1.9	42	9	3	1	11	2	3	1	1	28
Vitamin C (mg)											
National - A	62	8	3	0	1	4	58	26	1	1	--
National - B	123	6	1	0	1	3	46	14	0	1	30

A - Intake data pertain only to 759 children who did not receive supplements.
B - Intake data pertain only to 641 children who did receive supplements.

Table 3

Percent increase in daily nutrient intakes of children taking vitamin/mineral supplements, first half sample, Preschool Nutrition Survey

Income Quartile	Age (mos.)	(N)	Iron	Vitamin A	Thiamin	Riboflavin	Vitamin C
I	12-23	(66)	13	17	30	20	30
	24-35	(87)	22	25	30	24	29
	36-47	(86)	0	18	26	22	26
	48-59	(80)	0	8	17	15	20
	60-71	(82)	0	6	17	13	18
II	12-23	(65)	14	43	43	30	39
	24-35	(60)	14	29	42	30	34
	36-47	(83)	11	28	36	28	29
	48-59	(80)	11	27	34	26	27
	60-71	(74)	10	26	32	25	26
III	12-23	(74)	14	41	44	30	43
	24-35	(100)	13	39	44	34	35
	36-47	(97)	11	43	38	29	33
	48-59	(87)	20	29	36	28	30
	60-71	(95)	20	29	36	27	32
IV	12-23	(89)	14	48	47	31	40
	24-35	(93)	13	42	44	34	34
	36-47	(104)	22	49	45	35	36
	48-59	(92)	11	57	40	33	32
	60-71	(98)	11	40	37	28	31

Table 4

Percentage distribution of daily iron intakes* (mg) for children in first half sample, Preschool Nutrition Survey

Income Quartile	Age (mos.)	(N)	Less than 2	2 thru 3	4 thru 5	6 thru 7	8 thru 9	10 thru 11	12 thru 13	14 thru 15	16 thru 18	19 thru 21	22 thru 24	25 and above	Mean	(S.D.)	Med.
I	12-23	(66)	0	11	23	33	11	3	0	3	3	9	3	2	8	(7)	7
	24-35	(87)	0	3	28	22	21	8	6	1	5	2	2	2	9	(7)	7
	36-47	(86)	0	5	10	33	26	9	6	2	1	6	1	1	8	(5)	8
	48-59	(80)	0	0	23	26	14	10	13	8	4	0	1	3	9	(8)	8
	60-71	(82)	0	1	10	13	27	18	20	6	2	2	0	0	9	(4)	9
II	12-23	(65)	0	34	18	18	6	5	3	3	3	6	3	0	7	(6)	5
	24-35	(60)	0	3	37	23	20	5	2	0	7	2	0	2	7	(5)	6
	36-47	(83)	0	1	16	27	19	22	1	1	1	10	1	1	9	(5)	8
	48-59	(80)	0	3	11	26	24	14	6	5	3	6	3	0	9	(5)	8
	60-71	(74)	0	0	11	18	30	19	8	1	4	3	4	3	10	(5)	9
III	12-23	(74)	0	18	32	19	8	4	4	4	5	0	1	4	7	(7)	6
	24-35	(100)	0	5	21	21	27	12	2	0	4	5	2	1	8	(5)	8
	36-47	(97)	0	2	22	26	22	7	3	2	6	4	3	3	9	(6)	8
	48-59	(87)	0	1	7	28	24	15	6	5	2	7	3	2	10	(5)	9
	60-71	(95)	0	1	13	22	25	16	4	2	5	6	4	1	10	(6)	9
IV	12-23	(89)	1	9	28	21	18	9	3	2	4	2	1	0	7	(4)	7
	24-35	(93)	0	6	16	31	15	12	3	3	8	2	0	3	8	(6)	7
	36-47	(104)	0	1	15	32	20	12	5	1	5	5	5	0	9	(5)	8
	48-59	(92)	0	0	12	37	18	13	7	0	4	3	3	2	9	(5)	8
	60-71	(98)	0	0	11	18	32	13	11	2	3	6	2	1	9	(5)	9

*Intake from all sources.

Hemoglobins below 10 gm/100 ml and below 11 gm/100 ml were considered to be unacceptable for 1-2 year-old children and 2-6 year-old children, respectively. Some differences existed between supplemented and unsupplemented groups with respect to unacceptable hemoglobins, and economic status played some role. Nine percent of lower income unsupplemented children and 5 percent of higher income unsupplemented children had unacceptable hemoglobins. For supplemented lower income and supplemented higher income groups, the figures were 7 and 3 percent, respectively.

Discussion

Dr. Crosby pointed out that in Dr. Owen's study of low income families, 12 percent of these children had daily iron intakes of more than 12 mg/day despite the low income levels. He suggested that a study of the sources of iron for this population might provide information that could assist in determining ways of providing additional iron to children with daily iron intakes of less than 12 mg.

DIETARY INTAKE OF IRON IN THE UNITED STATES

Stress Factors and Iron Nutrition with Particular Reference to Adolescents

Ray Hepner

The information for this paper comes from three years' operation of Children and Youth Project 606-A in Baltimore's inner city. The data describe children with at least two stress factors: poverty and physical growth.

The income of this group, which was approximately one-third white and two-thirds black, averaged about $50 per capita per month. The total population available was approximately 9,000 and at any given time slightly more than 6,000 were in the project.

The population characteristically had low or borderline iron intake from infancy through adolescence, even into adult life. The physical growth patterns in this population from infancy to adolescence, when compared to the Harvard growth standards, shows a mean close to the 25th percentile for height and for weight. In a comparable age group of Baltimore suburban children, height and weight means were close to the 75th percentile. Whether attempts to ascertain iron intake were carried out in the home or by 24 hour recall or by history of frequency of intake of certain foods, the results were similar, averaging 45 to 55 percent of the Recommended Dietary Allowances (RDA) from infancy through adolescence. Intake for calories and for protein were unacceptable. Intake of quality items that cost more money and furnished iron, vitamins C and A, and calcium, was poor.

Infants, preschool, elementary school, and adolescent children were studied. There was poor correlation between iron intake and manifest iron deficiency in individuals of all ages. However, the correlation between poor group intake and group anemia was excellent. In groups of not less than 88 subjects per group, there was a very high incidence (> 30 percent) of severe nutritional anemia with hemoglobin values more than two standard deviations below the mean expected for age. Thus, the "risk" of group

iron deficiency established by low intake of dietary iron was confirmed by manifest iron deficiency anemia in the groups studied.

Failure of correlation among individuals prompted further scrutiny. Factors that could change requirements were identified and studied as follows: growth spurts, changing body composition, parasitism, and psychologic stress.

Each growth spurt--the fetal-infantile, the preschool, and the adolescent --was accompanied by a sharply increased prevalence of severe iron deficiency as defined by hemoglobin values more than two standard deviations below the mean expected for age and low mean corpuscular hemoglobin concentration (MCHC) values. Prevalence in infants reached 52 percent, preschoolers rose from 2.7 percent to 8.2 percent, adolescent females from 2.1 to 4.7 percent, and adolescent males from 2.2 to 30.3 percent (all $P =< 0.01$). After each growth spurt, slow recovery from iron deficiency anemia was seen.

Growth of body mass requires 35 mg of elemental iron/kg body weight in infants and preschool children. Demand for iron is for lean body mass and erythrocytes. Body composition changes sharply during adolescence. The average male gains 70-75 pounds, 67-70 of which are lean body mass, while the average female gains 49-50 pounds, 32-35 of which are lean body mass. Therefore, male requirements for iron for growth in adolescence are double those for females. Intakes of males and females were similar. The importance of growth stress on iron requirements in this population is documented by the six times higher prevalence of manifest iron deficiency in adolescent males than in females before or after menarche.

Parasitism was not significant in this population--no hookworm disease, no amebiasis, and only two ascariasis patients having been found.

Emotional homeostasis was evaluated in two groups of children--preschoolers in the midst of their growth spurt and adolescents. The maternal-child relationship of the preschool group was evaluated by the Polansky Child Level of Living Scale. A highly significant relationship between inadequate mothering and anemia was found, whether dietary iron intake was poor, borderline, or adequate. In this disadvantaged

population, income level, education, and sex of the head of the household had no correlation with anemia.

Emotional state of the adolescent population was evaluated by Alexiou and Weiner's adolescent questionnaire, a validated, self-administered screening device indicating need for health services to secondary school children. One portion of the questionnaire identifies the child who needs psychologic or psychiatric assistance for adolescent emotional problems. Fifty-four questionnaires were returned, fourteen of which indicated emotional disturbance. Of these fourteen, twelve had low hemoglobin and MCHC values. Of the remaining forty, there were borderline emotional scores in ten, three of whom were anemic. Of the remaining thirty, three were anemic.

In summary, some stresses that influence iron nutriture have been identified: namely, a life long pattern of poor iron intake that does not allow significant storage so that the stress of normal growth spurts precipitates manifest deficiency, changes in body composition in adolescence that double the males' need for iron for growth of lean body mass in comparison with the female, and the highly significant association both in preschool and adolescent children, between emotional dyshomeostasis and iron deficiency anemia.

DIETARY INTAKE OF IRON IN THE UNITED STATES

Adults

Elmer B. Brown

Comprehensive studies of dietary iron intake by adults in the United States are not available. The paucity of data concerning iron intake of this segment of the population is dramatically illustrated in a recent review by Davis, Gershoff, and Gamble. It summarizes the results of all studies reported in the United States between 1950 and 1968. This review disclosed that about 80 percent of all dietary intake studies were made upon subjects 21 years of age or less, and there was a preponderance of subjects between the ages of 15 and 21. Data on the dietary iron intake of pregnant and lactating women were conspicuously absent. No studies were available for men between 21 and 50 years of age, and only two studies, on a total of 125 women were recorded in this 21 to 50 year age group. No efforts were made to balance economic or ethnic groups sampled, and large gaps were present in the geographic areas studied. Thus no generalizations about adult dietary iron intake are justified from the data in this review.

However, certain information about dietary iron intake for selected groups is available for small numbers of subjects.

Mean iron intake for 244 women pooled in two studies was about 10 to 11 mg of iron/day. For 368 men studied, the iron intake was about 17 mg/day. When related to daily caloric consumption, the dietary iron intake was approximately 6 mg/1000 kcal.

Approximately 50 percent of the young women failed to receive 70 percent of the recommended dietary allowance (RDA) for iron whereas, more than 95 percent of the men were above this level of iron intake.

Similar studies of small groups of older people found a mean iron intake for women of about 10 mg daily. Mean iron intake for men was about 12 mg. Again,

the iron intake was approximately 6 mg/1000 kcal, and relatively few of the older people failed to meet the 70 percent of the reference standard for iron intake.

Another small but important study was reported by Monsen, Kuhn, and Finch in 1967. For thirteen healthy young women, comparisons were made between the calculated and analyzed values for the mean and range of daily dietary iron content during a 7-day period. Mean iron intake for the women ranged from 5.2 to 14.8 mg/day by chemical analysis, and 6.4 to 16 mg/day as calculated from food composition tables. The group averages were 9.2 and 9.9 mg/day, and the comparisons between these two types of iron estimates showed a high correlation coefficient of 0.93. The extremes of daily variation were very high, 0.8 to 24.6 mg/day in the diets analyzed for iron, or 2.4 to 24 mg/day as calculated. These investigators found a calculated iron intake of 6.1 mg/1000 kcal in these otherwise generally adequate diets. None of the women met the 18 mg RDA, and all but one fell below the 70 percent of the reference standard.

In contrast to studies of diets in other countries where chemical analyses have given much higher estimates of iron intake than those obtained by calculation from food tables, the data suggest that food composition tables may provide adequate estimates for iron content of foods consumed in the United States.

Instead of examining individuals, entire household units may be examined for dietary iron intakes. The 1965 Household Food Consumption Survey estimated that in all urbanizations, each person in a household might receive an average dietary iron intake of 19.5 mg/day. Their calculated energy intake was 3211 kcal. Thus, again in this study, the dietary iron intake averaged 6.1 mg/1000 kcal. These relationships between iron and energy intakes were fairly constant in different income levels, urban and rural groups, and different geographic regions.

Mean iron intakes calculated from 24 hour recall records of food consumed by 1,946 subjects in households of five states, ranged from 12 to 14 mg of iron per day. Related to energy, iron intake was from 5.7 to 6.7 mg/1000 kcal.

Smaller samples are available for populations of both sexes 60 years of age or older. The mean daily iron intake ranged from 9 to 12 mg and 5.1 to 6.9 mg/1000 kcal. The iron intake of 116 pregnant or lactating women ranged from 10 to 16 mg/day, or 5.5 to 6.9 mg/1000 kcal. The iron intake of persons 60 or more years of age fell below 70 percent of RDA with even greater frequency than did that of those in younger age groups.

In the pregnant and lactating women, 18 to 73 percent failed to meet even 50 percent of the 18 mg/day RDA.

The following points seem clear. First, reliable and detailed information on iron intake by adults in the United States is extremely fragmentary. Second, iron intake bears a fairly constant relationship to energy intake and is approximately 6 mg/1000 kcal. Third, iron intake of large percentages of young women fall below 70 percent of RDA. Diets of pregnant and lactating women likewise fall far below the reference standards of iron allowances.

Discussion

It was noted by Dr. Filer that the infant with an iron intake of 7 or 8 mg/800 kcal was receiving about 10 mg iron/1000 kcal. It would appear that cereal is contributing 4 mg of iron since removal of this source provided the ratio of iron to calorie intake of 6 mg iron/1000 kcal described in Dr. Brown's paper.

Dr. Nathan Smith remarked that his group had examined cereal intakes of low income populations and that these data show that the intake begins to fall off pretty distinctly at 6 to 8 months of age.

Dr. Filer agreed that about 50 percent of infants stop eating cereal at approximately six months of age. Dr. Filer then went on to discuss the issue of availability of iron from certain products. A difficult question to resolve was the fact that survey data never quite compared with sales data. In brief, more cereal was sold than was accounted for. It was suggested that the cereal might go other places than into infants. He noted further that his and Dr. Durbin's figures on

the disappearance or use of cereal by infants agreed very closely, namely, about 9 grams of cereal per day for a six month old infant.

Dr. Shank examined the data on iron intakes from the National Nutrition Survey for the first five states, by poverty groups, and compared iron intakes per 1000 kcal. One of the interesting aspects of this comparison was that the mean intakes went up but the proportion of iron/1000 kcal went down, which suggests that persons in the low income groups studied in the survey were getting calories, although they were not getting as much of other nutrients.

Dr. Smith, referring to Dr. Owen's data concerning the lower and the upper income groups, noted there was no significant difference either in iron intake or in the hematological consequences. From these data he posed the question whether or not the incidence of hematological inadequacies related to iron intake were different in various population groups, and that the pediatricians who have been talking about this do so only because they have not done careful studies of the upper income groups.

Dr. Owen, in response to the question, thought that this was indeed the case. Dr. Smith felt that if this were so it would have a bearing on the dimensions of the problem being discussed, since it was important to equate iron intake either with poverty or with the early months of life for all of the population.

Dr. Owen remarked that his recent paper in the Journal of Pediatrics, based on a small study, appears to show that there is no difference in average hematological values among income groups. Dr. Owen added that in terms of the distributions of the values, they do show that there is probably a greater degree of variability in data in the lower income groups. It would seem that proportionately more children with low hematological values are accounted for by the low income groups.

SIGNIFICANCE OF IRON DEFICIENCIES

Consequences of Mild Deficiency in Children

Doris Howell

In April of 1970, a conference on iron nutrition in infancy, attended primarily by pediatricians, nutritionists, and hematologists, concluded that in the young child iron deficiency remains a high priority problem. The incidence of iron deficiency ranged from 10 to 64 percent of preschool children, depending on the geographic locale, the target population, and the zeal of the investigator. This group urged anemia be avoided by adding therapeutic iron to infant formulae.

In 1969, the Committee on Nutrition of the American Academy of Pediatrics concluded that iron deficiency in infants was probably preventable if iron fortified proprietary formulae were delivered. In its recent publications, it supported the recommendations of the Committee on Iron Nutritional Deficiencies to add iron to the milk fed to infants. This recommendation has resulted in a demand for data that would document the ill effects attributable solely to iron deficiency.

The complications of severe iron deficiency are certainly well-known, but such cases are relatively rare at the present time. The questioning practitioner, however, has the right to ask for proof that less severe or even mild iron deficiency has an effect on his patient's growth and development, particularly if he is dealing with either the young infant or with the adolescent who is about to become the young pregnant woman.

A study was carried out in collaboration with Dr. E. Cuno Beller, psychologist, to determine if the most common cause of nutritional deficiency in this country, iron deficiency, had any demonstrable effect on mental functioning. Certainly the classical symptoms of iron deprivation suggest that this might be the case.

The study was carried out in three to five-year old, low income black children enrolled in the Headstart programs in Philadelphia. A total of 8,774 children were

screened for anemia. In this study hemoglobin levels of less than 10 g/100 ml and a hematocrit of less than 31 percent were considered as defining anemia.

All laboratory tests were carried out by two technicians in the same laboratory using carefully controlled and standardized techniques. The percentage of children having hemoglobins below 10 g/100 ml was 1.9 and varied slightly between urban and rural locales.

The results of these studies differ from those previously reported in this workshop in that there was such an unexplained low incidence of iron deficiency anemia in the Philadelphia children. Even when a standard of 10.5 g/100 ml, instead of 10 g/100 ml, was applied to this group, the incidence of anemia was only increased to 5 percent. This higher incidence of anemia is still not comparable to studies carried out in other parts of the United States at the same defining hemoglobin level.

A complete medical history was taken and a physical examination was carried out on these children remaining after the total group was screened; those children having other than iron deficiency anemia were dropped from the study. Any child with a history of bleeding or evidence of infection at the time of the study or any hematologic disorder other than hypochromic microcytic anemia was also dropped. The screening diagnosis of iron deficiency anemia was carried out on red cell morphology in the anemic children.

Eighty-three children were found to be anemic. The hemoglobin determinations on the children selected for further study ranged from 9 to 10.5 g/100 ml with a median value of 9.75 g/100 ml. The hematocrit levels showed a range of 28 to 38 percent with a median of 32. Hypochromia and microcytosis on blood smear was present in 68 of the 83 children, but all smears were compatible with no other abnormality demonstrated by morphology alone.

The 83 anemic children were divided randomly into two groups. One group of 42 children received an intramuscular injectable iron preparation calculated to bring the hemoglobin level to 12 g/100 ml. The other group received the same

volume of physiological saline intramuscularly. A battery of psychological tests was administered before, and 2 to 4 months after, receiving the injection. The 53 nonanemic control group were treated similarly to the anemic untreated children and processed in the same way.

The effects of anemia on mental functioning in young children were evaluated through specific learning processes. The basic hypothesis of the study was that iron deficiency anemia in 3 to 5 year old children affects attentional processes more directly than intellectual potential as would be measured by I.Q. tests.

Intellectual potential was measured by means of the Stanford Binet scales and the Goodenough draw-a-man test. The Bender-Gestalt test was employed to rule out the possibility of brain damage in the cases under study. A battery of measures was constructed to assess attentiveness.

The choice of measures of attentiveness was built largely around the conceptual research carried out by Gardiner at the Menninger Foundation. As a result of his findings two basic factors of attentiveness, field articulation and scanning, were developed. Field articulation is a technique of finding an embedded figure within a picture. Scanning shows the ability of the child to take in the total picture and evaluate the differences. The various tests of attentiveness carried out were designed to measure initiative, resourcefulness, goal directedness, and impulse control. All the tests were carefully subjected to factor analysis, analysis of variance, and t-tests.

The measures of attentiveness yielded a factor structure in accord with the theoretical formulation. This structure emerged clearly in both the anemic and nonanemic children for whom the imbedded figure tests and the size discrimination task loaded on two separate factors. However, certain differences in the factor structure emerged between anemic and nonanemic children. The tasks of drawing a line slowly and finding an imbedded figure emerged more clearly as field articulation factors in the anemic children than in the nonanemic children. Both sensitivity to color and ability to delay response as measured by the draw-a-line-slowly task have been associated with impulse control. The indication from this finding would be that impulse control is

a more important factor in the intentional behavior of anemic children, especially with regard to field articulation.

In this context it was noted that the comparison of the factor structure for boys as compared to girls, rather than anemic as to nonanemic subjects, revealed similar characteristics in boys--that is, impulse control items played a greater role in defining the field articulation factor of boys than of girls. In the local culture, therefore, the development of impulse control presents more difficulties for boys than for girls.

Other tasks aimed at different aspects of attention were constructed. One of these tasks utilized an unstructured situation in order to find out how much attentiveness a child can mobilize in a naturalistic situation in which he is not directed to attend.

Three factors emerged in the behavior of both anemic and nonanemic children. The first of these extended from ignoring, to looking at, to touching, to aimless manipulation. The second factor might be called a motivational factor since it was defined by involvement. This factor would be the width and narrowness of the attention that the child could exert and show that he had a motive or was interested in involving himself with the item, on his thoroughness and his perseverance in pursuing the item. The third factor can be defined as structural, since it deals with the complexity of the child's purpose for manipulation of the materials.

Several of the items of this task differentiated significantly between the anemic and nonanemic children. Anemic girls manifested more aimless manipulation, less complex purposeful activity, and a narrower attention span than non-anemic girls ($p=0.5$).

A task of attention was designed to measure a child's ability to attend to the environment against the influence of a dominant stimulus in the visual field. In this task a difference emerged between anemic and nonanemic boys. Anemic boys perceived significantly fewer stimulus objects in the visual field than nonanemic

boys when a dominant stimulus was present. Thus, the relationship as predicted showed that an anemic boy is more passive and less able to respond to nondominant features of the environment when a dominant stimulus overshadows the visual field.

Finally, the I.Q. as measured by the Stanford-Binet and draw-a-man techniques yielded no significant differences between mildly anemic and nonanemic children, as measured in our laboratory.

Phase II of the study was post therapy testing. It showed no significant change in any of the groups, but in analyzing the hematologic data, it became clearly evident that the amount of injected iron that was necessary to raise the children's hemoglobin levels from the initial level of hemoglobin was miscalculated. With the dose calculated to raise the hemoglobin to 12 g/100 ml, the levels in ten children did not change at all, and in twenty of the children hemoglobin levels were raised only one gram/100 ml.

This study shows that significant iron deficiency anemia is clearly a minor problem in Philadelphia in three to five-year old low income black children enrolled in the Headstart Program. Only 1.9 percent of the children had hemoglobin levels below 10 g/100 ml and none below 9 g/100 ml.

Children with iron deficiency anemia with hemoglobin between the levels of 9 and 10.5 g/100 ml have a normal I.Q. and normal organicity but show very markedly decreased attentiveness, more aimless manipulation, less complex and purposeful activity, narrower attention span, and perceive fewer stimuli in the presence of dominant stimuli.

Significant decrease in attentiveness definitely impairs learning. Mental function may therefore be adjudged as anatomically insufficient, when in reality it may be only physiologically impaired. In any event, the study is regarded as incomplete and much additional work is required.

SIGNIFICANCE OF IRON DEFICIENCIES

Effects of Iron Deficiency on Psychological Tests in Children

Jefferson L. Sulzer

Since 1968, a team of nutritionists, biochemists, and behavioral scientists at Tulane University has conducted research on nutrition and behavior supported by the Office of Economic Opportunity. This work was initiated after results of a previous study indicated that in New Orleans a significant number of children seemed to be in the low end of the hemoglobin distribution. Results obtained by the nutrition group under the direction of the late Walter Unglaub, verified this finding. Of 469 preschool children tested, 12 percent had hemoglobin levels below 10 g/100 ml, 30 percent below 10.5 g/100 ml, and approximately 57 percent below 11.5 g/100 ml. A comparison of these data with results that the team gathered from Alabama and Mississippi showed that considerably more of the New Orleans children were anemic, possibly indicating the relative disadvantage of the urban poor in that particular area with respect to certain dietary factors.

Although these results indicated that malnutrition was present in New Orleans, very few of the blood values suggested serious clinical cases of iron deficiency anemia. Generally, the hematologic evidence obtained represented a mild form of malnutrition compared with the extreme protein-calorie deficiency encountered in some parts of the world.

Many people take it for granted that severe malnutrition retards psychological development, but the results of the studies conducted to evaluate this relationship have not been uniformly persuasive nor free of alternative explanations. There are virtually no published accounts of investigations relating milder forms of malnutrition to psychological variables and only a handful of reports dealing with behavioral concomitants of iron deficiency anemia. One of the few investigations found, in addition to the work previously reported by Dr. Howell, also dealt with Head Start children and

was carried out in Montana by Nancy Munro and her associates. She did not report a strong relationship between her index of iron levels and psychological measures. The only significant correlation she obtained showed a positive relationship between change in I.Q. and change in hemoglobin level among a group of children with the lowest levels, which were around 10, to 12 g/100 ml. That this study did not show a strong causal relationship between iron deficiency anemia and psychological function suggests several possibilities. First, the hemoglobin levels involved may have been too near normal to produce detectable effects. Second, it is possible that the measures of psychological function used were not sufficiently sensitive to detect the decrement produced by this mild type of malnutrition. Finally, it is possible that there is no demonstrable causal relationship between iron deficiency anemia and behavior.

In planning the research at Tulane, a number of behavioral measures representing different kinds of psychological functions were adopted in order to increase the chances of detecting any relationships that might exist. These included verbal and performance estimates of intelligence, measurements of conceptual function, a work endurance task, several measures of attentiveness, and a simple learning task. In the initial investigation, which was carried out in the summer of 1968, over 300 male and female black children, four to five years old, were tested with all or some of these instruments. Evidence concerning nutritional status was independently obtained from biochemical assessment of blood and urine samples and from a clinical examination carried out soon after the psychological testing was completed.

The most frequent indications of nutritional deficiency found were those associated with the hematological measures of iron deficiency. Most of the statistical analyses conducted compared groups of children above and below some accepted standard of deficiency for hemoglobin. Generally, the findings appeared to be somewhat stronger when groups were formed on the basis of more conservative standards, that is, under 10.5 or 10.0 g/100 ml.

Comparison of the scores of children defined as iron deficient or normal on the basis of hemoglobin levels showed that most of the psychological measures were not unequivocally related to hematologic status, although many differences were in the expected direction. The measures of conceptual function probably failed to produce reliable differences because the task demands were excessive for most of these young children. The work endurance task and measures of simple reactivity or short-term attentiveness were more appropriate for children at this age level, but simply failed to show a statistically significant difference between low and normal hemoglobin groups.

The major evidence of psychological decrement was produced with two measures of intelligence. Stanford-Binet and more traditional forms of intelligence measures showed no differences between these groups. One of the measures that did show a difference was the Kahn Intelligence Test, which places a premium on the kind of instruction-following that which Dr. Howell spoke about, but otherwise a rather minimal strain on verbal ability since a child does not have to respond verbally. In this test, I.Q. for the deficient children was about six points lower than for the normals. In the other intelligence measure, the Van Alstyne Vocabulary Test, which is based entirely on verbal achievement, the difference in I.Q. was about five points. Both differences were statistically significant as judged by t-tests.

Because differences in intelligence ordinarily show pervasive relationships to other measures of psychological function, it might be conjectured that the children with lower hemoglobin levels should show differences in learning ability. Of the measures that were used in the first investigation, the only one that clearly involved learning was part of the reaction time task. This battery of tests was conducted on a vertical console that contained four stimulus panels or windows and four response panels that could be independently lighted. Response time was electrically measured from the onset of the light until the child pressed the correct panel to turn it off. On the first part of this task, which was called *simple reaction time*, one window

would be lighted, and the child simply pressed it as rapidly as possible to turn it off. In the second part of the task, *disjunctive reaction time*, either of two windows might be lighted and the child pressed the panel to turn it off.

The five trials given on each of these tasks showed no difference in short-term attentiveness between the normal and deficient subjects. On the last part of the battery, the subject learned to associate each of four response panels with the appropriate stimulus window. The child was trained to learn each of these associations to a criterion of five correct trials before going on to the next one. Latency of the correct response and errors were recorded on each trial.

To the extent that the child was learning these associations, his reaction time should have decreased on each trial. Mean reaction time for the first three training trials on each of the four associations was calculated for each subject. A comparison of the performance of children with low and with normal hemoglobin levels indicated that those with normal levels were superior on every association. However, only the difference on the last association was statistically significant.

These results seemed to provide weak, but relatively clearcut, evidence of superior learning ability in the normal children. However, it is also possible that the iron deficient subjects became more bored or fatigued or less alert as training progressed, and that these motivational or attentional factors, rather than learning ability, might account for the differences.

In an attempt to provide more definitive information with respect to the responsible factors, several additional studies were carried out over the last two years. In one experiment, fifteen first-grade children with hemoglobin levels below 10.9 g/100 ml and fifteen children with normal hemoglobins, were given fifty trials on a four-window disjunctive reaction time task. That is, on any trial one of four windows might be lighted, and the child simply pressed the panel as rapidly as possible to turn it off. The performance of normal children improved after the first block of ten trials and showed little evidence of fatigue or reduced motivation, even at the end of fifty trials. By contrast, the performance of an iron

deficient group showed marked deterioration over the first four blocks and a somewhat puzzling improvement at the end of the task. Although these results indicate that learning ability is not the sole critical difference, they do not provide a clearcut basis for deciding whether iron deficient children fatigued more readily or became less attentive. The improvement in the reaction time of children with low hemoglobin levels in the last block of trials suggests that attentional or motivational factors might be more important than fatigue.

Two studies that have just been completed provide some additional information concerning these differences. Both of these studies involved first- and second-grade children classified as iron deficient and normal. In the first study, a vigilance procedure was used for fifty trials in which the subject was required to respond when one window was lit, but not when the other one was lit. For purposes of this discussion, the window the child was supposed to respond to will be referred to as Window 2 and the window he was not supposed to respond to as Window 1. To reduce motor fatigue from simply responding, Window 2 was lit only twice in each block of 10 trials, and its occurrence followed a randomized schedule so the child could not anticipate when it might come on. It was felt that this would place heavy demands upon consistent attention and motivation, while requiring relatively little work from the child.

A comparison of response latency or response time to Window 2 over the five blocks of trials showed differences between the subjects with low and normal hemoglobin levels, and also that this relationship was different for the two age groups. In both first- and second-grade subjects the reaction time of the normals was faster, but performance by the younger normals deteriorated at the end of the task. Because the deficient subjects were slower from the first trial on, it would appear that they were less attentive throughout the entire vigilance series. The relative constancy of the difference between second graders with low and normal hemoglobin levels indicates that fatigue was not the important factor in this case. However, fatigue or decreased attentiveness may be involved in the deterioration of performance in the normal first graders toward the end of these trials.

The results of another study provided clearer separation of fatigue and attentiveness. In this study, first-and second-grade children were classified as normal and deficient on the basis of hemoglobin values. First, they were given five simple reaction time trials on Window 2, next they were given forty simple reaction time trials on Window 1, and finally they were given additional trials, post-test trials, on Window 2. The important questions in this case were whether the forty trials of repeated testing on Window 1 produced evidence of fatigue and whether the suddenly changed task conditions after this fatigue task, that is, the shift back to Window 2, would find the deficient and normal subjects equally alert.

On the pretest trials on Window 2 the second-grade normals were slightly better than the other children, but no significant differences were found. On the forty trials on Window 1, the second-grade normals were consistently faster than the second-grade lows and both groups of first-graders, all of whom showed highly similar performance levels. On the first trial of the sudden shift back to Window 2, which caught the children by surprise, there was a clear separation of the groups, as we would expect on the basis of age and an attentiveness interpretation. The response latency for all four groups increased from the pretest and Window 2 levels, but this increase and the difference between deficient and normal subjects was greater for the first-graders. On the second trial following the shift, however, the means for all groups had returned to their pretest values. The mean reaction times of the subjects with low hemoglobin displayed considerable individual differences in the first post-test trial. Some of the subjects seemed so upset by the shift that they could hardly respond. Others responded, but rather slowly, and some reacted quite rapidly. The normal subjects, on the other hand showed much less variability. They responded in much more similar fashion than did the anemic subjects.

Although fatigue or ability factors cannot be ruled out entirely, it seems fairly clear that fatigue does not fully account for the differences on the first post-test trial. The evidence suggests rather that the children with low hemoglobin

levels were simply less alert or attentive, because they very rapidly returned to their original level of responding. If attentional or motivational factors were the primary determinant of these differences, then it is possible that the inferiority in I.Q. found for the deficient subjects may have been due to a lack of the necessary attentiveness to perform well on these tasks. To evaluate the extent to which this represents a generalized problem, the school performance of the iron deficient and normal children was examined. Although the records of academic performance failed to show significant differences in the first grade, ratings of the children's in-school behavior did reveal differences. Significant *chi-square* values showed that the children previously classified as iron deficient were more frequently identified as inattentive because more easily distracted, hyper- or hypo-active, lacking persistence in solving problems, and having less sense of competence. The evidence reported here, and recently by other investigators, suggests that some kind of motivational factors may underlie the apparent decrement in intellectual function associated with different indices of malnutrition. Until clearer evidence regarding these factors is developed, conclusions linking permanent brain damage to mild forms of malnutrition, such as iron deficiency, should be viewed with caution.

Discussion

Dr. Hepner remarked that in his experience in Baltimore, children stunted in height or who have low hemoglobin levels often come from the most disorganized and least well functioning families. These children rarely join the Head Start or early school admission projects, and if they do get involved, they do not stay. Also, fewer than 2 percent of the children in the Head Start program who were three years of age, had hemoglobin levels below 10 g/100 ml. In the early school admissions population, fewer than 1 percent had hemoglobin levels below 10 g/100 ml. When the clinic population is considered as a whole, 10 percent of the 3 year olds and 8 percent of the 4 year olds had hemoglobin levels less than 10 g/100 ml.

SIGNIFICANCE OF IRON DEFICIENCIES

Systemic Effects

Peter R. Dallman

In the investigation of iron deficiency the focus has understandably been on the kinetics of hemoglobin, a molecule that is readily sampled and quantitated from peripheral blood. Together with ferritin and hemosiderin it accounts for about 95 percent of total body iron. The treatment of iron deficiency anemia with appropriate doses of iron salts results in a gratifyingly prompt and complete repair of the hemoglobin deficit. However, it is becoming clear that iron deficiency is a more complex systemic disease that involves almost all cells. Thus, the manifestations and reversibility of the disorder must be reexamined, particularly in regard to the quantitation and function of the heme proteins other than hemoglobin that account for less than 5 percent of body iron. Although these compounds are widely distributed in the body, they are difficult to measure except in relatively large tissue samples from experimental animals.

The function of heme proteins involves primarily the transport, storage, and utilization of oxygen. The role of hemoglobin in the transport of oxygen is most familiar. Myoglobin, the pigment of skeletal muscle, stores oxygen for utilization during muscle contraction. The cytochromes, found in mitochondria of all aerobic cells in the body, play the major role in the utilization of oxygen for the production of cellular energy in the form of adenosine triphosphate. Other cytochromes are located in the endoplasmic reticulum of the cell. Cytochrome b5 plays a role in providing oxidative energy for protein synthesis. Cytochrome P450, found primarily in the liver, functions in the oxidative breakdown of drugs and catabolism of endogenous substrates. Thus, a very small proportion of body iron plays many roles in oxygen metabolism.

We have been interested in how heme proteins in tissues other than blood are affected by iron deficiency. In general, a deficiency of heme proteins is most

likely to develop in rapidly proliferating cells or when the whole body is growing at a fast rate. Rapidly growing nursing rats after 14 days of age can be made iron deficient within one week by withholding normal access to the iron-rich diet of the mother during the latter part of the nursing period. The normal development increase in concentration of myoglobin in skeletal muscle and cytochrome c in muscle and intestinal mucosa is arrested. At 21 days of age, the concentrations of these tissue heme proteins and of hemoglobin are about 30 percent below control values, but there is no retardation of body growth. If iron deficiency is allowed to progress past weaning for three to five weeks, growth retardation develops and differences in degree of severity of cytochrome c depletion among tissues become strikingly apparent. In the brain, which completes most of its growth and cell proliferation well before weaning, there is little, if any, deficiency of cytochrome c. In contrast, in skeletal muscle, which grows particularly rapidly during institution of the iron deficient diet, cytochrome c is reduced to less than half of normal concentrations. The similar susceptibility of intestinal mucosa is probably related to its extremely fast rate of cell replacement, a new mucosal lining being generated in about two days.

During treatment of iron deficiency, rates of cell proliferation play a role in regulating the rate of repair of deficiencies of tissue cytochrome as well as in the repair of anemia. The normal lifespan of the red blood cell is about 120 days, and there is continual replacement of aging cells by newly differentiated ones from the bone marrow. In the iron deficient patient, the red cells are small and contain a decreased concentration of hemoglobin. After treatment with iron, hemoglobin synthesis in developing cells returns toward normal. Thus, the typical blood smear after about two weeks of iron treatment shows two populations of cells. The older cells remain hypochromic and microcytic for their remaining lifespan while newly produced cells are normal in hemoglobin content and in size.

An analagous phenomenon can be observed in the cells of the intestinal mucosa. The age and state of maturation of the mucosal cells can be estimated from their anatomic position. Proliferative cells in the crypts of the small intestine

differentiate and migrate to the base of the villus and then toward the tip where they are desquamated within a period of about 48 hours. Histochemical studies of cytochrome oxidase in iron deficient animals show a marked deficiency of the enzyme in the mucosal cells of the intestinal lining. Eight to ten hours after administration of intramuscular iron, young cells at the base of the villus recover normal cytochrome oxidase activity while the older cells that line the upper part of the villus remain deficient. After twenty-four hours, the migration of this repair has progressed half way toward the tip of the villus. After 48 hours, cytochrome oxidase activity is indistinguishable from normal.

Beyond infancy most cells in the body, including muscle, liver, and neurons, have a reduced and often negligible capacity to proliferate. The recovery of these tissues from the consequences of iron deficiency cannot be assumed to be as rapid as in the blood or intestinal mucosa. Factors that might determine repair of enzyme deficiency within long-lived cells were investigated in collaboration with Dr. Joseph Goodman, by combining biochemical and ultrastructural methods. Since the cytochromes are located primarily in mitochondria, the appearance of these organelles in cells of deficient animals is of particular interest. In the iron deficient rat, mitochondria in liver cells are enlarged and radiolucent, and many appear to be dividing. In addition there are bleb-like structural abnormalities of the outer mitochondrial membrane. Similar defects are seen in the mitochondria of heart muscle and in the erythroid precursor cells of both iron deficient patients and experimental animals. In the liver, after only two days of iron administration, normal mitochondria co-exist in the same cell with those typical of the deficient animal. After five days all mitochondria return to a normal configuation, even though the rate of proliferation of liver cells during this interval is negligible. Thus, reversal of abnormal morphology of the mitochondria is possible without production of new cells.

The biochemical repair of mitochondrial cytochrome deficiency is somewhat slower and of the same order as the rate of proliferation of mitochondria, or of

the cristae of the mitochondria where the cytochromes of electron transport reside. The rate of synthesis of these subcellular structures is probably a determining factor in the rate replacement of their constituents.

Skeletal muscle cytochrome c concentrations remain markedly deficient long after red cell hemoglobin has been reconstituted. Reduced proliferative capacity of muscle cells as the animals age may be a factor responsible for the slow repair of cytochrome deficiency, requiring about eight times as long as the reversal of anemia. It is possible that very long-lived cells or slow turnover of intracellular constituents prevent the complete reversal of biochemical abnormalities.

Before concluding this discussion of the role of tissue heme proteins in the syndrome of iron deficiency, it is worth emphasizing that the secondary effects of heme protein deficits may prove to be more crucial and possibly less reversible with iron treatment than the deficiency itself--witness the long-term consequences of brief periods of hypoxia or hypoglycemia. Growth retardation in the iron deficient animal, and possibly in man, is a secondary effect of iron deficiency that may be subject to quantitation. The delineation of subtle physiological handicaps remains a greater challenge.

In summary, there are enzymatic and morphological changes in solid tissues that result from iron deficiency. These changes may not provide us with better diagnostic criteria than those discussed at this conference--namely, hemoglobin, hematocrit, serum iron, marrow iron, and others--but we should be alerted to the fact that iron deficiency is a systemic condition. The readily reversible anemia is not an early finding because several months must elapse before red blood cells deficient in hemoglobin replace the normal cell population. The other manifestations, which may result in permanent change, deserve far more attention than they have received in the past.

SIGNIFICANCE OF IRON DEFICIENCIES

In Reproductive Performance*

Jack Pritchard

A brief review of the iron requirements of pregnancy indicates that unless there is a limitation of iron or some other substance for effective hematopoiesis, the maternal hemoglobin mass increases during normal pregnancy--with a single fetus to an amount that would necessitate the utilization of about 500 mg of iron. Maternal iron excretion approximates that of the nonpregnant woman minus menstrual loss--perhaps 0.6 to 0.7 mg/day--or a total of about 200 mg during a pregnancy. Since placental and fetal requirements have been estimated to be 300 mg, the total iron requirement during pregnancy adds up to about one gram. Nearly all of this iron is utilized during the latter half of pregnancy.

In studies of obstetric clinic populations, it has been determined repeatedly that without iron supplementation the average maternal hemoglobin level is about 11 g/100 ml. With iron supplementation, however, the hemoglobin level averages 12 g/100 ml or slightly more. The interpretation of the results of supplementation has been criticized by Paynton and associates on the ground that the iron may have induced a pharmacologic rather than physiologic response, since in most instances the amount of iron administered was considerably in excess of what would seem nutritionally necessary. It has been amply demonstrated, however, that 30 mg of iron taken daily throughout the latter half of pregnancy produces an increase in maternal hemoglobin concentration comparable to that seen with larger doses and protects any preexisting iron stores.

There may be several effects of iron deficiency in pregnancy. The one obvious maternal effect--if the deficiency is severe for an extended period--is overt anemia. Data reported from Australia appear to demonstrate that in the

---

*Dr. Daniel Scott collaborated in obtaining information for this study.

presence of severe maternal anemia there is an augmentation of placental size. The anemia described was of varying kinds but was primarily iron deficiency. The significance of this is not explained. Fortunately, however, the hemoglobin concentrations in the neonate appear to be independent of maternal hemoglobin concentrations.

To test the hypothesis that lack of maternal storage iron in pregnancy might be disadvantageous to the fetus, the outcome of pregnancy in young primagravid patients was analysed. Women identified as having no storage iron early in pregnancy received an iron supplement of 30 milligrams per day; but some patients with demonstrable storage iron received no supplement, but used their stored iron to meet the demand imposed by pregnancy. From a preliminary review of the data it appeared that there was a modest difference in the frequency of low infant birthweight (< 2500 grams) when supplemental iron was administered. Thirty-two of 35 patients who received supplemental iron had marrow stainable iron at the time of delivery, whereas only 16 out of 40 subjects in the group that received no supplement had stainable iron. Six percent of the infants of the subjects with stainable iron had low birth weights, but 46 percent of the infants of the subjects with no stainable iron had low birth weights. Statistical analysis using the chi-square test, however, showed that the difference between these groups was minimally significant.

The question arises as to the importance of a maternal hemoglobin concentration of 12.5 g/100 ml over one of 9.5 g/100 ml. If the difference in hemoglobin is due solely to iron deficiency, the only firmly established distinction between these hemoglobin levels would become evident in such an obstetrical emergency as gross hemorrhage, a relatively common event during parturition. In the event of hemorrhage it is safer for the mother, and in some instances her fetus, for the maternal hemoglobin to have been at the higher level. In conclusion, lack of iron in the mother causes a lack of hemoglobin mass and hemoglobin concentration. Other adverse effects have not been clearly established at this time.

Discussion

Dr. Moore pointed out that critics question the basis for stating that a hemoglobin level of 11 g/100 ml is not as desirable as one of 12.5 g/100 ml. He felt that this is the fundamental question that must be answered. Otherwise some will continue to say that all attempts to fortify foods and to bring iron intakes up to a higher level are beside the point and may be entirely unnecessary.

Dr. Dallman felt that criticism of this nature is based on the fact that the tests for nutritional norms are biochemical and that it is necessary to establsish tests of function before such criticism can be answered objectively.

In answer to a question as to whether mitochondrial changes occur in the brain and nervous tissue, Dr. Dallman stated that he had not examined these tissues. He reported that Rabinowitz's Laboratory in Chicago used labeled dl-aminolevulinic acid to label heme proteins and found that mitochondria in heart muscle turn over at the same rate as they do in liver, yet heart is a tissue that we think of as being fairly static and stable. This may also occur in brain.

Dr. Finch asked whether mitochondrial changes that occur in iron deficiency also occur in anemia stemming from other causes. Dr. Dallman said that he was unable to answer this. Dr. Finch then discussed the question posed by Dr. Moore and noted that in considering the oxygen transport capacity of the normal individual, one must compare normal individuals with conditioned individuals, since it is well known that maximum oxygen transport capacity can be appreciably increased by conditioning, presumably both by cardiovascular changes and perhaps by changes within the cell itself. The mitochondrial changes in striated muscle, for example, occur with muscle conditioning unilaterally when one muscle is exercised. There is evidence that quite a substantial number of changes occur that make the individual capable of higher performance; increases of 50 to 100 percent would be expected with conditioning.

When the burden of anemia is imposed on the individual, it would seem reasonable to expect that some of these conditioning mechanisms might be brought

into play and that anemia might be considered one kind of conditioning device that raises the potential to a certain degree. This is not to imply that anemia may not always impose limitations on the maximum work capacity of the individual, but rather to suggest that the maximum potential work capacity of the individual may change with accommodation and give rise to a system in which the total potential is very great. With rather severe iron deficiency anemia, very severe exercise loads must be imposed in order to register changes in maximum performances or in the recovery period.

Dr. Finch felt that the changes being examined were moderate and would not be expected to impose any difficulties, any more than a reduction in cardiac output due to cardiac disease, from 100 to 90 percent, would be expected to impose any symptomatic manifestations. Perhaps the logical approach would be to examine the implication of a small reduction in the individual's potential capacity to transport oxygen as a consequence of a very mild disease.

Dr. Hegsted remarked that there is nothing unique about iron deficiency. The same question is relevant to every other problem of a nutritional requirement. The approach that differentiates the normal from conditions somewhere below normal must be defended, since the closer the conditions get to normality, the more difficult it is to demonstrate a significant difference. Studies are presently embracing smaller and smaller numbers of individuals that show abnormalities. If we are interested in normality for everyone, then there is no way to close this gap step by step until you reach a point where you would have to measure 100,000 people to show a 10 percent difference. Some kind of rational prediction, rather than actual demonstration, must be defended.

Dr. Diamond commented on Dr. Moore's question concerning the value of ensuring that the mother has optimal stores of iron and optimal hemoglobin. He stated that it has been shown over and over again, even in such severe anemias as those found in Nigeria where a woman who is folate deficient comes to term with a hemoglobin of about 3 g/100 ml and needs an exchange transfusion to survive, that the infant suffers no ill effect other than smaller size at the time of

delivery. He may be smaller than average, or smaller than he should have been, but he is born with a normal hemoglobin level. He quickly catches up, insofar as growth is concerned, with the infants of women who have not been anemic.

Dr. Clement Smith's study of women in Holland during the last year of the German occupation showed that these women were markedly deficient in all food elements, particularly protein. The delivered babies were lighter and smaller in size, but they showed no ill effects and quite rapidly caught up in weight. Eventually they were perfectly normal in growth and development. Beyond the first third, or possibly the first two-fifths of pregnancy, the infant is parasitic enough to get what it needs. Perhaps there is an advantage in having a small baby. At that point, a weak, anemic mother might have less trouble in delivery than if she had a large fat baby.

Dr. Finch felt that each of the mechanisms known to respond to oxygen levels has different controls. Apparently, 2,3-diphosphoglycerate may respond to the amount of reduced hemoglobin in the circulatory system, largely in venous circulation. Erythropoietin appears to respond to oxygen tension, the oxygen dissociation curve, and to the amount of oxygen in the blood, but not to blood flow. So, under different situations, each one of these components responds to the things it recognizes. Cardiac output probably does not respond to hypoxia in the usual sense, but responds more to vascular changes in the periphery in terms of local tissue metabolism. Certain of these responses complement each other, while others are somewhat selective.

CORRECTIVE MEASURES FOR IRON DEFICIENCY

Current Status of Proposals for Iron Enrichment

Allan L. Forbes

We are concerned here with three broad areas, namely, regulatory matters, iron assimilability studies, and the concern for followup studies subsequent to action by government health authorities.

In order to put the regulatory matters that affect the iron content of the diet in perspective, the recent Food and Drug Administration (FDA) actions and proposals concerning this area have been summarized in Table 1.

Current standards of identity specify that enriched flour shall contain 13.0 - 16.5 mg iron/lb, and that enriched bread shall contain 8.0 - 12.5 mg iron/lb. Farina has only a minimum enrichment standard of 13 mg of iron/lb. The absence of a maximum limit for farina may be explained by its frequent use in infant feeding where a high dietary level of iron is desired.

Iron enrichment of flour and bread products is a subject presently under discussion and investigation by the FDA. In the tabulated summary it may be noted that FDA recently has initiated several proposals on the subject. Also, it may be further noted that in 1970 private industry proposed that the iron enrichment of flour and bread should be increased significantly. However, the Division of Nutrition at FDA feels that more modest increases in enrichment levels of these products are more reasonable from a nutritional and technological point of view. FDA is considering single enrichment levels rather than ranges. These levels, however, will be subject to reasonable overages within the limits of good manufacturing practices.

It is interesting to speculate on the maximum logical dietary effect of the proposed increased iron enrichment of flour. In order to estimate the maximum effects on iron intake, it is necessary to make several assumptions: first that consumed flour and products derived therefrom are all enriched, either at the current minimum level of 13 mg of iron/lb or at the level currently under consideration

TABLE 1

SUMMARY OF RECENT FDA ACTIONS AND PROPOSALS AFFECTING IRON CONTENT OF THE DIET

Date Published	Petitioner	Title	Key Provisions re Iron
April 1, 1970	American Bakers Assoc. and Millers' Nat'l Fed. proposal	Enriched flour, enriched self-rising flour and enriched bread identity standards; proposal to increase required minimum and maximum iron levels	Enriched flour and self-rising flour: 50-60 mg/lb; enriched bread and rolls: 32-38 mg/lb
under current review	FDA-initiated proposal	same as above	Enriched flour and self-rising flour: 40 mg/lb; enriched bread and rolls: 25 mg/lb
Jan. 20, 1971	FDA-initiated	Labelling of non-standardized bakery products fortified with vitamins and iron	If enrichment is featured, percent MDR's must be stated (relates to use of enriched flour and cornmeal)
Oct. 29, 1970	FDA-initiated proposal	Food for special dietary uses; label statements relating to infant food	1 mg/100 calories minimum
May 7, 1970	Pillsbury Co.	Enriched flour deviating from identity standard; extension of temporary permit for market testing (extended again at USDA request to July 24, 1972)	Doubles iron from range 13.0-16.5 mg/lb to 26-33 mg/lb
Aug. 4, 1970	USDA	Enriched flour deviating from identity standard; temporary permit for market testing (expires July 24, 1971)	Doubles iron from range of 13.0-16.5 mg/lb to 26-33 mg/lb
Jan. 30, 1970	USDA	Enriched corn grits deviating from identity standard; temporary permit for market testing (expired Jan. 23,'71)	Increases iron from range of 13-26 mg/lb to 100 ± 20 mg/lb (reduced iron)

TABLE 1 (cont'd)

SUMMARY OF RECENT FDA ACTIONS AND PROPOSALS AFFECTING IRON CONTENT OF THE DIET

Date Published	Petitioner	Title	Key Provisions re Iron
Mar. 13, 1970	USDA	Enriched macaroni product deviating from identity standard; notice of temporary permit for market testing (extended to May 20, 1971)	Increases iron from range of 13.0-16.5 mg/lb to 35 mg/lb (product called "enriched yellow corn-soy-wheat macaroni")
June 9, 1970	General Foods Corp.	Enriched macaroni product deviating from identity standards; amendment of temporary permit for market tests (expires April 1971)	Increases iron from range of 13.0-16.5 mg/lb to 35 mg/lb
Mar. 3, 1971	FDA-initiated proposal	Enriched macaroni products with improved protein quality; proposal to establish identity standard	16.5 mg/lb
Jan.	FDA-initiated (via A.O.A.C.)	Hemoglobin repletion test in chicks and rats for measuring availability of iron	Tentative method of defining "assimilability"

of 40 mg/lb; second, that the highest total cereal product intakes expressed as flour equivalents from the March 1969 USDA publication "Food Intake and Nutritive Value of Diets of Men, Women, and Children in the U.S." are current. The two groups having the highest rate of intake (151 g/person/day) are 12 to 14 year old boys of families with incomes under $3,000/year and 18 to 19 year old males in the south, regardless of income.

From these cereal intake figures, the lower limit of enrichment with the present standard of 13 mg of iron/lb would provide an intake due to enrichment of 4.3 mg of iron/day. At the 40 mg/lb level as proposed, the maximum intake from the enrichment source would be 13.3 mg/day. The difference between the two enrichment levels is 9 mg/day. This increase should represent the maximum logical increase that would occur and all other segments of the population would experience smaller increases in iron intake. In the unlikely event that all cereal products consumed were made from flour enriched at the 40 mg/lb level, this would also represent the worst possible case as far as theoretical toxicity is concerned.

Among other regulatory matters is the January 20, 1971 proposal on labeling of non-standardized bakery products fortified with vitamins and iron that will probably be promulgated in a form similar to the published proposal.

All comments on the infant food proposal are now in hand and are under review. The Division of Nutrition does not anticipate any drastic changes in the proposal. This tentative order will have the effect of raising the required level of iron in infant formulas from 0.75 mg/100 kcal to 1 mg/100 kcal as a minimum.

Temporary permits have been issued for market testing of enriched products deviating from standards of identity. The Pillsbury permit for lysine enriched flour with vitamin and iron enrichment levels doubled led to extensive market testing among low income groups in Chicago. The similar USDA permit accompanies studies of use of the product among the Navajo Indians. Studies of the possible changes in nutritional status, and presumably anemia *per se*, and

other results from incorporation of the product in the Navajo diet are being carried out by the Indian Health Service.

On March 13 and June 9, 1970, the USDA and General Foods Corporation, respectively, received permits for a product that has the formal name of "enriched yellow corn-soy-wheat macaroni" with improved protein quality, standard vitamin enrichment, and substantially increased contents of iron and calcium. Market and acceptability tests have been conducted in New York City with favorable results, and the USDA is evaluating the product in the school lunch feeding program.

On March 3, 1971, a proposal to establish an identity standard for enriched macaroni products having improved protein quality was published. The proposed iron level was set at 16.5 mg/lb of finished product.

As to iron assimilability, the work of Mr. J. C. Fritz and his associates in the Division of Nutrition is summarized in Table 2. V arious sources of iron are categorized according to their relative biological values (RBV) as good sources (with RBV's of greater than 70), mediocre sources (with RBV's of 20 to 70), and poor sources (with RBV's of less than 20). Individual RBV's are determined in rats or chicks by arbitrarily assigning a value of 100 for response to ferrous sulfate. It appears from these and other data that a dilemma exists relative to the matter of iron assimilability. For example, of the four most commonly used forms of iron for enrichment purposes, ferrous sulfate is a good source, reduced iron is a mediocre source, and ferric orthophosphate and sodium iron pyrophosphate are poor sources. Detailed studies of processed foods enriched with these sources and consumed in amounts consistent with actual dietary practices are needed in both experimental animals and man, particularly now that a satisfactory method for measuring assimilability has been developed and accepted (on a "first action" basis) by the Association of Official Analytical Chemists (AOAC).

As to followup studies, there is concern regarding the limited capability of the federal health-oriented agencies to follow up on the merits and demerits of what it may do in many sets of circumstances involving nutrition. The consensus

TABLE 2

2 March 1971

PRELIMINARY RELATIVE BIOLOGICAL VALUES (RBV) 1/2/ OF POSSIBLE CHEMICAL SOURCES OF IRON FOR FOOD ADDITIVE PURPOSES

	CFR/FDA Status & Comments 3/
A. "Good" Sources (RBV greater than 70)	
1. ferrous sulfate; $FeSO_4.xH_2O$	GRAS (d)(5) & (f)
2. dihydrogen ferrous salt of EDTA (structure not known)	-
3. ferric ammonium citrate (compounds of NH_3, Fe and citric acid of undetermined structure)	GRAS (f); Regulation 121.1190
4. ferric choline citrate; $C_{11}H_{24}O_{11}NFe$	Regulation 121.1100
5. ferric citrate (combination of iron & citric acid of indefinite composition)	
6. ferric fructose; $(C_6H_9FeO_7)_n$	Used in oral drugs; not foods.
7. ferric glycerophosphate; $Fe_2[C_3H_5(OH)_2PO_4]_3$	Oral medicinal hematinic
8. ferrilactin (structure not known)	- (Merck Index)
9. ferric sulfate; $Fe_2(SO_4)_3$	GRAS (f)
10. ferrous ammonium sulfate; $(NH_4)_2Fe(SO_4)_2$	-
11. ferrous chloride; $FeCl_2$	GRAS (f)
12. ferrous citrate; $Fe(C_6H_6O_7).H_2O$ and $Fe_3(C_6H_5O_7).10H_2O$	Used in food products
13. ferrous fumarate; $FeC_4H_2O_4$	Regulation 121.1130
14. ferrous gluconate; $C_{12}H_{22}FeO_{14}.2H_2O$	GRAS (d)(5) & (f); Color Additive Regulation 8.320
15. ferrous tartrate $Fe(C_4H_4O_6)$	GRAS (DON opinion)
B. "Mediocre" Sources (RBV of 20 to 70)	
1. ferric chloride; $FeCl_3$	GRAS (f)
2. ferric pyrophosphate; $Fe_4(P_2O_7)_3.xH_2O$	GRAS (d) (5) & (f)
3. reduced iron; Fe	GRAS (d) (5) & (f)
C. "Poor" Sources (RBV less than 20)	
1. ferric orthophosphate; $FePO_4.xH_2O$	GRAS (d) (5) & (f)
2. ferric oxide; Fe_2O_3	GRAS (f); Color Additive Regulation 8.325
3. ferrous carbonate (ores); $FeCO_3$	GRAS (f)
4. ferric sodium pyrophosphate (sodium iron pyrophosphate); $Na_8Fe_4(P_2O_7)_5.xH_2O$	GRAS (d) (5)

D. Not Tested to Date (compounds with some form of use recognition)

1.	ferrous lactate; $Fe(C_3H_5O_3)_2$	GRAS (d) (5)
2.	ferrous succinate; $C_4H_4FeO_4$	GRAS (DON opinion)
3.	peptonized iron (compound of Fe_2O_3 and peptone, with sodium citrate)	GRAS (DON opinion)
4.	ferric albuminate	Oral medicinal hematinic (Merck Index)
5.	ferric and ammonium acetate solution	Oral medicinal hematinic (Merck Index)
6.	saccharated ferric oxide	I.V. medicinal hematinic (Merck Index)
7.	ferric sodium edetate; $C_{10}H_{12}FeN_2NaO_8$	Oral medicinal hematinic (Merck Index)
8.	ferroglycine sulfate (compound of glycine and ferrous sulfate)	Oral medicinal hematinic (Merck Index)
9.	ferronascin; $C_{12}H_{20}FeNaO_8$	I.V. medicinal hematinic (Merck Index)
10.	saccharated ferrous carbonate	Oral medicinal hematinic (Merck Index)

1/ see: Pla, G. W. and Fritz, J. C. Collaborative study of the hemoglobin repletion test in chicks and rats for measuring availability of iron. J. of the A.O.A.C., 54:13-17, (Jan) 1971.

2/ as determined in chicks and/or rats by Fritz *et al* FDA.

3/ GRAS (d) (5): for human food use as nutrients and/or dietary supplements (Regulation 121.101); GRAS (f): for animal feeds (Regulation 121.101); DON: Division of Nutrition, FDA.

of the majority of authorities on this particular subject of iron is that it is desirable and safe to increase significantly the levels of iron enrichment in cereal grain products for the purpose of reducing the prevalence of iron deficiency anemias. The proposed regulations now under consideration would meet these requirements.

Several workers in the field have expressed concern over the possibility of chronic iron toxicity resulting from iron fortification, with particular emphasis on the possibility of increasing the incidence or severity of hemochromatosis. Thus, there are at least two aspects that should be followed for long periods of time subsequent to increasing levels of iron enrichment: (1) the actual effects on anemias themselves, and (2) the possible undesirable effects in certain individuals.

PROJECTION OF TRENDS IN FOOD CONSUMPTION WITH SPECIAL REFERENCE TO IRON INTAKES

Marcus Wegner

One measure of the nutrients consumed by the average United States civilian comes from estimates of the nutritive value of the assortment of foods that make up our national food supply. These estimates are made yearly by the staff of the Consumer and Food Economics Research Division of the Agricultural Research Service.

The consumption figures on which these analyses are based are provided by economists in the Economic Research Service and represent food taken off the market for consumer use. These figures are divided by annual estimates of the total civilian population to give in per capita amounts. National estimates can be computed for any period of time from 1909 to the present or for any estimated projection.

Projected food use for 1980 indicates a continued increase in the use of certain foods of animal origin--for example, there is an estimated increase in the consumption of meat, poultry, and fish from 228 to 250 pounds. Per capita beef and veal consumption may rise 15 pounds above the current level.

Per capita milk consumption reached a peak of 257 quarts in 1946. Since then it has been declining but is currently still higher than in 1909. A further decline is expected during the next decade. Per capita egg consumption is projected to decrease slightly from 400 eggs to 380. Use of food fats and oils is expected to increase slightly from 56 lbs to 60 lbs per capita. The shift from animal fats to vegetable oils is expected to continue. Consumption of vegetables, including potatoes, is not expected to change substantially during the next decade, 316 lbs to 305 lbs.

The long term downward trend in wheat consumption has moderated in recent years, but per capita use is projected to decline slightly by 1980. Consumption of other grains are expected to remain fairly stable, except for rice, which is expected to increase slightly.

The amount of iron currently available as judged by consumption estimates, is 17.2 mg/capita/day and, except for mid-1940, is the highest since the beginning of the century. The projection for 1980 indicates a continued increase in the level of iron to 17.8 mg/capita/day. In making this projection, it was assumed that the enrichment and fortification of foods with iron would continue at levels reported in the most recent survey on enrichment and fortification which was conducted in the early 1960's.

In 1970, 60 percent of the iron in the food supply was provided by the two food groups, meat, poultry and fish, and flour and cereal products. Vegetables and fruits, including the legumes and nuts as a group, provided another 25 percent, with smaller amounts coming from eggs, dairy products, and sweeteners. Because of enrichment, flour and cereal products became the largest contributor of iron in the food supply and remained so until the early 1960's. The cereal products actually contributed more iron than the meat, poultry, and fish group. Today the meats occupy first place, beef alone provides 15.2 percent, pork provides 7 percent, and the outlook for 1980 is for this trend to continue. Poultry now provides over 3.5 percent, with 4.4 percent projected for 1980. The 1980 projection is that 32 percent of the iron in the food supply will come from the meat, poultry, and fish group.

If iron enrichment of flour, as presently being considered by FDA, were increased to the 40 mg level/pound of flour, it would add another five to six milligrams of iron/capita/day to the food supply in 1980. This assumes that the same proportion of flour would be enriched, as was indicated in the last enrichment survey. At that time enrichment ingredients reported as used were estimated to be sufficient to enrich about 60 percent of all white flour. This includes flour used in bread and related products.

We recognize that industry is tending to enrich more products than was common even a year ago. An increasing proportion of cookies and crackers, for example, are being enriched. If a third more flour were enriched, 80 percent

rather than 60 percent of the total white flour would have iron added at the level of 40 mg/pound, and roughly an additional 2 milligrams of iron per capita per day would be added to the food supply, bringing the total iron intake to 25.3 mg/day. The projected totals for 1980 would then become about 23 mg/person if 60 percent, and 25 mg/person if 80 percent of the flour were enriched.

What would be the potential effect of iron fortification of flour and cereal products on the diets of women, 20 to 34 years of age, one of the more vulnerable groups? For these calculations, values were based on the national survey of dietary intake conducted by the Food Economics Research Division in 1965. The present iron intake for this group of women, at all levels of income, was 11.3 mg/day. This is 63 percent of the RDA. Assuming these women ate the same diet they did in the last survey, all bakery products would need to be enriched to 35 mg iron/pound of product for them to achieve 99-100 percent of the RDA. The 25 mg level of enrichment, the range now being considered by Food and Drug, would achieve substantial improvement for this age group of women to 86 percent of the RDA.

Realistically, the "per capita" man discussed in this paper is imaginary. The true benefits to any one individual will be achieved only when the proper mix of foods is eaten.

POTENTIAL HAZARDS OF IRON OVERLOAD

William H. Crosby

One unique aspect of iron nutrition is the absence of an efficient mechanism for excretion of excess iron. The iron that is in excess must be placed in storage, and when the excess is great it seems to be injurious to the storage organs. In considering the question of adding iron to foods in order to increase the intake of certain segments of the population (the iron deficient menstruating women, pregnant women, and children), some thought should be given to the rest of the population who have no increased requirement for iron.

The need for balancing safety against the efficacy of such a program can be analyzed by examining the hoped-for benefits upon groups of people with various iron requirements, the groups with severe iron deficiency, with mild iron deficiency, with no iron deficiency, and those with iron storage diseases.

People with serious iron deficiency are usually losing important amounts of iron. Most of these are women who have excessive menstrual loss, but there are, in addition, people who have pathological bleeding. In the series of cases published by Beveridge, *et al**, 2 percent of the cases of iron deficiency anemia were caused by neoplasms.

When additional iron is provided in the diets of subjects with mild or moderate iron deficiency, an increased amount of iron is absorbed and benefits those with anemia whenever anemia is the consequence of iron deficiency. However, not all women with mild anemia are iron deficient. In a Swedish study (Garby), almost 12 percent of some 200 otherwise healthy young women with mild to moderate anemia, with hematocrits between 30 and 36 percent, had no response to the administration of therapeutic iron. Whether these anemic women absorbed unneeded iron and were unable to use it for hemoglobin synthesis was not established.

---

*Quarterly Journal of Medicine. 1965.

Persons without iron deficiency and without increased iron requirement include all healthy men and menopausal women in the United States. These people have an obligatory metabolic iron loss of about one milligram per day, and they absorb enough iron from the diet to offset this loss. It is not known how much iron they absorb when the daily dose of iron is artificially increased. In one study (Finch), several medical students were given daily pharmacologic doses of iron for six to twelve months without an appreciable accumulation of iron. On the other hand, the Bantu of South Africa have a diet that contains 50 to 100 milligrams of iron and about 20 percent of these people have severe iron storage disease. About 4 percent of the men have a heavy accumulation of iron which resembles hemochromatosis (Bothwell). The Bantu situation of course cannot be extrapolated to our civilization, but the possibility does exist that if the dose of iron is artifically increased, there may be some people in the population who would accumulate unneeded iron, perhaps to their detriment.

A final group are those with iron storage disease. The amount of iron in the body is kept at a normal level by a control system that keeps out unneeded iron. In iron deficiency, the ability of the intestine to reject available iron is reduced so that needed iron can enter the body in increased amounts. In iron storage diseases the control system malfunctions, thus permitting the absorption of unneeded iron. The iron cannot be excreted, so it accumulates and is placed in storage, and the iron stores become overloaded.

Most of these iron storage diseases are genetically determined. Some of them, like thalassemia, are associated with anemia; others, like familial hemochromatosis, are not. In all it is evident that the patient's diet must be the source of the iron that accumulates and eventually injures the liver, pancreas, heart, etc. By increasing the amount of iron in the diet, the rate of accumulation is accelerated and so also the damage that results from the accumulation. These diseases are insidious. The victim is unaware of the existence of iron storage disease until he develops diabetes or cirrhosis or congestive heart failure. Being unaware of the disease he does not avoid iron-enriched foods. Also, these diseases are potentially

lethal. Finch and Finch in a 1955 survey reported that the average life expectancy after diagnosis of hemochromatosis was five years. The number of people in the United States who are at risk from these iron storage diseases is not inconsiderable. There are an estimated 20,000 cases of hemochromatosis in the United States. The clinical evidence of the disease usually appears after the age of 45.

A second disease is sickle cell anemia. Approximately 50,000 American blacks have homozygous Hemoglobin S and a serious hemolytic disease. Some of these patients are iron-loaded because of multiple transfusions. These patients might be especially apt to absorb excess iron if the dietary iron load were artificially increased.

A third example is thalassemia or Mediterranean anemia. This is a common disorder in Americans of Mediterranean ancestry. For example, it occurs in 4 percent of the Italian population of Rochester, New York. Children with the homozygous form of thalassemia, Cooley's anemia, develop hemochromatosis in childhood. Some patients with a heterozygous disease also acquire abnormal accumulations of iron. It is not known to what extent an increased amount of iron in the diet would accelerate iron accumulation by these patients and provoke iron accumulation in those with thalassemia minor, whose absorptive control can cope with a normal amount of dietary iron.

Laennec's cirrhosis poses yet another problem. It is estimated that approximately a half-million Americans have overt cirrhosis and that there is an equal number of preclinical cases. From 5 to 10 percent of people with cirrhosis have iron accumulations so high as to indicate the existence of iron storage disease. The accumulation of iron in the cirrhotic liver may hasten damage. The addition of excessive iron to the diet may hasten the accumulation.

It is probable that all who have existing or potential iron storage disease will be placed at additional risk if the amount of iron added to the American diet is manipulated upward. In preparing the iron enrichment proposal, the increased risk to people with iron storage disease may not have been taken sufficiently into account.

STUDIES AND RESEARCH NEEDED TO ESTABLISH HEMATOLOGICAL STANDARDS TO EVALUATE EFFICACY OF FOOD SUPPLEMENTATION

Clement Finch - Moderator

It was apparent from the workshop discussions that much more work is required to determine the prevalence of iron deficiencies both in the United States and elsewhere. Several Federal and state supported population studies of hematological values in the United States are presently in progress; others are being organized for the immediate future. Older studies that included hematological values were: (1) investigations of nutritional status in 39 states by the U. S. Dept. of Agriculture* and (2) investigations in the North Central Region dealing with constitutents of blood of healthy women 30 to 90 years of age.**

The Health and Nutrition Evaluation Study known as the HANES project just commencing was mentioned by Dr. Nathan Smith. It is a health and nutrition evaluation of a probability sample taken across the United States. Some 30,000 subjects will be studied in considerable depth with regard to health and nutrition. The sample will be taken from 64 locations in the United States and the study will examine 15,000 subjects a year for two years. Dr. Owen, in collaboration with Dr. Wentworth's group at Minnesota, is collecting information on hemoglobins and hematocrits in a number of children. The children will be taken from youth projects in 18 states. The object of the study is to secure hemoglobin and hematocrit information from 30,000 children by the end of 1971.

In addition to the studies already described, Dr. Crosby pointed out that more and more large industrial companies, as part of their employee relations, are having health surveys carried out on all employees. These surveys involve a battery of biochemical studies of blood. It was suggested that commercial laboratories carrying out these studies should be encouraged to include routine serum iron determinations in addition to consideration of the other parameters that make up a health profile.

---

*California Agricultural Experiment Station Bulletin 769. 1959.
**Nebraska Research Bulletin. June, 1961.

As for other countries, Canada is carrying out a nutrition survey that was initiated in 1970 and will in all include 20,000 people. Dr. Shah reported that half of the sample will come from those with incomes below $5,000/year and the other half from those with incomes above this figure. Blood samples are being taken, and serum iron, iron binding capacity, hemoglobin, and hematocrit are being determined.

On the question of methodology, Dr. Finch suggested that protoporphyrin levels were one of the best potential measurements of an individual's iron status. Although the measurement has been severely limited in the past by technological problems, Dr. Labbé has developed a simplified method that permits a technician to carry out 50 to 60 determinations a day. The possibility also exists that this methodology will soon be automated.

Dr. Filer suggested that electroencephalographic measurements of the so-called evoked response in an iron deficient infant before and after treatment might provide useful information with regard to the importance of cytochromes in terms of central nervous system metabolism.

On the subject of iron fortified foods, it was the consensus that, although this enrichment program would be useful in bringing a large segment of the population closer to optimal iron nutrition, adequate studies should be carried out to determine whether fortification was efficacious in those segments of the population that are at risk and at the same time not deleterious to other population groups. Levels now suggested for iron fortification of foods could be inadequate in some cases and excessive in others.

One facet of the question of fortification of foods with iron is the form of iron that is used. Another is the paucity of knowledge concerning those factors in the diet that interfere with iron absorption. As an example, the WHO Advisory Group in its latest publication on iron requirements has taken the position that iron in foods in the absence of animal protein has half the availability of iron that it has in the presence of animal protein. As a consequence, the value of a fixed figure of so many mg/day would be subject to considerable variation. Also,

there is some evidence that animal protein not only supplies a different form of iron--heme iron--but also has a facilitating effect on absorption of iron in the soluble iron pool that is separate from the heme iron pool. Dr. Cook has some interesting data showing high correlation between albumin levels and iron deficiency indices. The role of ascorbic acid and other reducing substances in the absorption of iron is recognized but needs further investigation. Likewise the question of the ability of phosphates and phytates to compete for iron and the tendency for it to become unavailable needs to be addressed.

Dr. Goldsmith pointed out that more iron is needed in the diet of certain target groups than in the general population. One difficulty is the determination of foodstuffs consumed by these groups and the amounts consumed so that these foods can be fortified with iron. There are many potential vehicles for fortification, even soft drinks, salt, and sugar.

On the subject of target groups, the discussants felt that it was difficult to find a single food that is consumed by all women in the 18 to 55 year bracket. For the young child, however, whole milk appeared to be the best vehicle for providing additional iron to this age group.

One difficulty in selecting foods for fortification is the greater intake of particular foodstuffs by the affluent child. As an example, the child from an impoverished background may get very little milk from the time bottle feeding is discontinued until he enters the school meal program. Another problem is the lack of toxicity data on continued iron intake over extended periods of time. Apparently in persons with hemachromatosis, any amount of iron over requirement is deleterious.

It was the general feeling of the group that iron fortification of foodstuffs would benefit a significant portion of the population. Subjects for future investigation should include how to administer iron, in what form, and in what foodstuffs, and evaluation of the prolonged effect of such administration on all segments of the population.

Dr. Diamond commented on the question of toxicity and indicated that we do not know whether iron can be toxic to normal individuals or whether Dr. Crosby's conclusions are based on experience with abnormal individuals. Although no figures are available on the number of children who have received iron medication for long periods of time, sometimes for years, purely inadvertently because some physician forgot to stop the prescription, we have not seen any cases of ehmochromatosis in such children nor in hemophilic children who were placed on iron medication prophylactically for long periods.

Dr. Finch commented that iron overload seems to be a matter of opinion. There are no firm data available. The Bantu takes in iron with alcohol, which certainly has additional effects. The Ethiopian takes it in as dirt, but this can be criticized as not the type of iron being discussed. As an experimental approach, it was suggested that an attempt be made to determine at what point iron stores became stabilized in the normal individual so that they remain at a suitable level and frank iron overload does not occur.

Dr. Crosby stated that we do not know whether iron supplementation at the proposed levels will be harmful to anyone but that we ought to find out before doing anything. He suggested models in which this type of problem could be studied, namely, penitentiaries, monasteries, or other closed communities where food intake could be controlled. He stated that if the intake was increased from 15 to 30 milligrams per day, and by this an individual forced to absorb a milligram of iron daily that he doesn't need, in three years time this would amount to an extra gram of storage iron. By using the method of phlebotomy in these people, it would be possible to learn the amount of their iron stores.

Dr. Moore suggested that the experiment that was being discussed probably had been carried on for generations, but that we do not recognize it. Past generations probably had a bigger iron intake than the current one, merely because cooking in the past commonly used iron vessels. Dr. Moore also indicated the danger of

transferring information obtained in using pure iron preparations in experimental animals to the question of iron fortification of foods in man.

Dr. Finch indicated his support of the proposal to expose a population under controlled conditions to high doses of iron. He indicated that he did not accept completely the implication that any increase in stores should be regarded as hazardous. He suggested that if man's intake was doubled his stores might go up from 1000 to 2000 mg., but if the stores were held at 1 to 4 grams, and did not move above this, he would consider it safe.

Dr. Goldsmith indicated that it would be necessary to carry out the other half of the experiment, namely, to determine if giving food fortified with iron to a population group that needs it is efficacious in either preventing or mitigating the severity of anemia.

Dr. Filer commented on the position of the Committee on Nutrition of the Academy of Pediatrics--namely, that when physicians are prescribing a formula for the infant this formula should be one that contains iron. The import on the hemoglobin level of the infant of adding iron to the formula has indicated that the iron is available and that milk phosphates apparently do not interfere with iron absorption. Factors that facilitate iron absorption from milk, are probably, the natural content of citrates and certain amino acids, e.g., lysine, that complex with iron. Lactose probably facilitates iron transport. The new standards for minimum safe levels for infant formulas under the revised FDA regulations will specify, as Dr. Forbes pointed out, 1 milligram of iron per 100 kcal, which is about 7 milligrams per liter.

Dr. Diamond indicated that the infant receives the formula for only the first six months of life and yet there is a greater risk of anemia between the ages of 6 and 18 months.

Dr. Filer added that the Committee on Nutrition of the Academy of Pediatrics hopes that the milk industry will fortify whole milk, but in some states, such as Georgia, it is now against the law.

The question was asked whether children with hemochromatosis might be identified early as in the case of phenylketonuria. Dr. Crosby answered that this was not possible at the present time.

SUMMARY AND CONCLUSION

Max M. Wintrobe

Dr. Finch's discussion on criteria for evaluating the status of iron nutrition emphasized the importance of determining iron stores and the methods, such as phlebotomy or percentage of absorption, that can be used for determining them. Evidence has been offered to support the assumption that the iron content of the body to some extent controls the degree of absorption of iron. Also, now that automated methods are available, the measurement not only of hemoglobin values but of red cell indices is readily carried out.

Dr. Finch has made an important point over the years regarding the significance of serum iron saturation. Saturation of iron binding capacity of less than 15 percent suggests iron deficiency. He pointed out, however, that there are circumstances when this can be misleading; for example, when there is urinary loss of protein in conditions such as nephrosis and when protein nutrition is inadequate, as in kwashiorkor.

He also discussed two additional indices of iron nutrition, the sideroblast and free erythrocyte protoporphyrin. Sideroblasts are nucleated red cells that on staining with Prussian blue are found to contain iron granules in their cytoplasm. The presence of sideroblasts in substantial numbers, such as 30 percent or so, certainly does not suggest iron deficiency, whereas a decrease down to 10 percent would be suspect. This, however, is not a very practical method, because it requires a bone marrow examination, and in any large scale study this is totally impractical.

Free erythrocyte protoporphyrin (FEP) is a measure that has been recognized as an index of iron deficiency for some years but the difficulties of methods for its measurement have limited its usefulness. If Dr. Labbé has developed a method whereby a technician can run 50 of these a day, then the measurement of FEP becomes practical.

Standards of normality were discussed by Drs. Schubert, Oski, and Diamond. It is more than a philosophical question to ask what is normal, and how it can be adequately judged. Dr. Cook's observations on this matter were extremely interesting. His discussion of statistical methods and his approach to their interpretation suggest that there may be some people who have hemoglobin values above an arbitrary value of 12 g/100 ml who may be iron deficient, whereas some whose hemoglobin value is below this arbitrary value may not be iron deficient.

Dr. Schubert mentioned that he had encountered some instances in which the hemoglobin level was satisfactory, but there was other evidence of iron deficiency. Dr. Cook's method of analysis probably will be very useful in evaluating the results of surveys in which hemoglobin or hematocrit levels have been measured, but it does not apply, of course, to the individual subject.

It has been assumed by some investigators that if an individual whose hemoglobin level is low is given iron in a form that is absorbable and the hemoglobin level rises, then that person has been shown to be iron deficient. This conclusion is not necessarily valid, since it is not known whether the mechanism for controlling the hemoglobin level in the body is so perfect that when an individual is given iron the hemoglobin will not rise to some degree even though he may not be iron deficient. Or should we define adequate iron nutrition as that state in which administration of iron will not cause the hemoglobin level to rise? Are control mechanisms as perfect as has been assumed?

Several presentations addressed themselves to surveys designed to determine the prevalence of iron deficiency in the United States. I am impressed with the fact that in these surveys the accuracy of the measures used differed widely. When hemoglobin levels or serum iron levels are measured, one has a value that can be determined fairly precisely even though interpretation must be guarded. Serum iron, for example, can be low, not only in iron deficiency, but in such other circumstances as chronic diseases of various kinds.

In dietary surveys, on the other hand, the observations are subject to a great deal more inaccuracy than the laboratory measurements referred to above. The sources of error are numerous.

Other presentations dealt with several psychological tests of the effects of iron deficiency. Dr. Howell's discussion was extremely interesting, as was Dr. Sulzer's. But what do these tests mean? It would appear that many factors besides iron deficiency must influence the results of such tests. Perhaps the investigators were working with individuals who had only modest degrees of iron deficiency. It might be better to test subjects having substantial iron deficiencies to see if psychological abnormalities can be clearly demonstrated, and then to examine those with milder degrees of iron deficiency to see if in such individuals one can detect differences. To try to demonstrate small differences before proving that the method is capable of demonstrating the effects of large differences, seems to add to the difficulties.

As to the significance of systemic effects of iron deficiency, when the capacity of the body for adjustment is considered, how much deficiency is truly important? Is it of advantage to the individual to be exactly average normal? Does that make him significantly better functionally? Or is there room for some plus or minus? Doubtless iron deficiency is harmful if it is severe, but is it harmful if it is very mild?

With regard to the proposals for iron enrichment of cereals and for dietary iron fortification there was nothing said in the discussion concerning the effects of such fortified foods. What proportion of the iron in the various fortified foods, in the cereals for example, is actually absorbed by the individual and used? This important question should not be overlooked.

The survey studies that have been presented show that there is a great deal of variation in the alleged prevalence of iron deficiency. In some areas the figures are high. In other areas they are appreciably lower. Such factors as economic conditions and educational status seem to play an important role. Mothers

who had gone to high school seemed to take better care of their children than those who had less education. The age of the mother, and whether or not they were experienced also was important. There is much variation from one part of the country to another. Since there are such group and individual variations, is it appropriate to apply one procedure to the country as a whole?

It was suggested that such target populations as children, infants, menstruating women, and women who have had a number of pregnancies be recognized, that these are the persons likely to be iron deficient. However, it is difficult to provide this population with the needed iron by means of iron enrichment of foods without running medical risks. From the standpoint of good clinical medicine, it must not be forgotten that iron deficiency is an important clue to the presence of such diseases, as peptic ulcer or cancer of the gastro-intestinal tract. There is a very good rule in clinical medicine that if an adult male has reached adulthood with a normal hemoglobin level and thereafter develops iron deficiency, there must be a leak somewhere, and that leak is most likely in the gastrointestinal tract.

A number of questions remain to be answered. One may ask whether food fortification at twice or three times the present level is wise and whether this should take precedence over medical care directed at those individuals who specifically need iron. It is perhaps better to treat the individual iron depleted subject than to mask the whole population by throwing an iron curtain over them all.

Discussion

Considerable discussion followed the summary presentation by Dr. Wintrobe. Dr. Hegsted asked Dr. Hepner if there was clear evidence that iron-fortified milk was effective and if so, what kind of iron was used in milk? The response was that the iron was utilized by infants who were part of a blindly-selected population that received milk with and without added iron delivered to the home. The group receiving no iron fortification had a very high incidence of iron deficiency anemia

whereas the other group given the highly fortified product had essentially no deficiency. Thus, in this case, it was obvious that the iron--as ferrous sulphate--was available.

Dr. Filer referred to a study reported in the Scandinavian literature in which an iron fortified cereal product was administered to infants at a level supplying 12 milligrams of iron per day. A hematologic response occurred that would be comparable to putting 12 milligrams of iron in milk, so apparently there is no question that when you put the right form of iron in an infant cereal it is available.

Dr. Finch indicated that in previous studies of the effects of iron fortification on nutritional status, it was not possible to characterize the population in terms of iron stores. In view of better techniques presently available, further attempts should be made with long-term studies of population groups.

Dr. Brown commented on the effects of oral contraceptives on the group of menstruating women as reported by Dr. Pritchard. It was shown that the amount of blood loss went down dramatically in these women. Also, the addition of iron to the seven blank tablets used each month should further improve the iron nutrition. He suggested that this might be a valuable therapy for the future. Dr. Pritchard indicated that he felt the salutary effects occurred as a result of reduction in menstrual loss, plus iron supplementation in the blank preparation, and the absence of pregnancy. This might add up to a significant improvement in iron stores and certainly would reduce overt iron deficiency.

CONCLUDING REMARKS

Grace A. Goldsmith

What did this second workshop on The Extent and Meaning of Nutritional Iron Deficiency in the United States accomplish? A few highlights of the discussions may be pointed out. In the evaluation of iron nutritional status, the importance of determining iron stores was emphasized, including a consideration of methods that can be used for such determinations. Estimation of transferrin saturation was considered to be an important technique for the diagnosis of iron deficiency. The determination of free erythrocyte protoporphyrin was suggested as a new and promising method of estimating the status of iron nutriture.

Pitfalls in the interpretation of hemoglobin values obtained in surveys were pointed out. It was strongly urged that findings be reported as distribution ranges so that more use could be made of data in future compilations.

The discussions emphasized that iron deficiency produces more than a reversible anemia and suggested that attention be directed to these other findings. Enzymatic and morphological changes occur in bodily tissues, but at the present time it appears unlikely that these will provide better diagnostic criteria in the diagnosis of iron deficiency than hemoglobin or hematocrit determinations, mean corpuscular hemoglobin concentration, transferrin saturation, and bone marrow iron.

PARTICIPANTS

Dr. Aaron Arnold
c/o Sterling Winthrop Research Institute
Columbia Turnpike
Renssalaer, New York 12144

Dr. Ernest J. Beutler
City of Hope Medical Center
Los Angeles, California 90014

Dr. Ernest J. Briskey
Campbell Soup Company
100 Market Street
Camden, New Jersey 08102

Dr. Elmer B. Brown
School of Medicine
Washington University
St. Louis, Missouri 63110

Miss Marianna Burt
University of Maryland
College Park, Maryland 20742

Dr. Joginder Chopra
Pan American Health Organization
525 - 23rd Street, N.W.
Washington, D.C. 20037

Miss Gretchen Collins
Nutrition Program, CDC
CDC Building No. 1
1600 Clifton Road, N.E.
Atlanta, Georgia 30333

Dr. Gerald F. Combs
Food Science Coordinator
Room 332E, Administration Bldg.
U. S. Dept. of Agriculture
Washington, D. C. 20250

Dr. Marcel E. Conrad
Walter Reed Medical Research Center
6825 - 16th Street, N.W.
Washington, D.C. 20012

Dr. James D. Cook
Division of Hematology
School of Medicine
University of Washington
Seattle, Washington 98105

Dr. William H. Crosby
Tufts University
136 Harrison Avenue
Boston, Massachusetts 02111

Dr. Peter R. Dallman
Dept. of Pediatrics
University of California
San Francisco, California 94122

Dr. William J. Darby
School of Medicine
Vanderbilt University
Nashville, Tennessee 37203

Dr. Louis K. Diamond
Dept. of Pediatrics
University of California
San Francisco, California 94122

Dr. Joseph A. Edozien
Dept. of Nutrition and Food Science
M. I. T.
Cambridge, Massachusetts 02139

Miss Mary C. Egan
Maternal Health Services/DHEW
Room 12A43, Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20852

Dr. Lloyd J. Filer, Jr.
University of Iowa College of Medicine
Iowa City, Iowa 52240

Dr. Clement A. Finch
School of Medicine
University of Washington
Seattle, Washington 98105

Dr. Allan L. Forbes
Dept. of Nutrition
Food and Drug Administration
BF-127, Federal Building #8
Washington, D.C. 20204

Dr. Grace A. Goldsmith
Dean, School of Public Health and Tropical Medicine
Tulane University
New Orleans, Louisiana 70112

Dr. Willis A. Gortner
Human Nutrition Research
Agricultural Research Service
Beltsville, Maryland 20705

Mr. Paul A. Hamnes
Quinton Research Laboratories
Merck & Company
Rahway, New Jersey 07065

Mr. Frank Hepburn
American Institute of Baking
400 E. Ontario Street
Chicago, Illinois 60611

Dr. Ray Hepner
Community Pediatric Center
University of Maryland
214-420 West Redwood Street
Baltimore, Maryland 21201

Dr. Homer T. Hopkins
4500 Elmwood Road
Beltsville, Maryland 20705

Dr. Hartley W. Howard
Borden, Inc.
350 Madison Avenue
New York, New York 10017

Dr. Eugene E. Howe
Quinton Research Laboratories
Merck & Company
Rahway, New Jersey 07065

Dr. Doris A. Howell
Dept. of Pediatrics
Medical College of Pennsylvania
3300 Henry Avenue
Philadelphia, Pennsylvania 19129

Miss Carole Jenny
Office of Health & Scientific Affairs
Dept. of Health, Education, and
Welfare
Washington, D.C. 20204

Dr. Ruth M. Leverton
Agricultural Research Service
U. S. Dept. of Agriculture
Washington, D.C. 20250

Dr. Earl E. Lockhart
The Coca Cola Company
P. O. Drawer 1734
Atlanta, Georgia 30301

Dr. Karl E. Mason
NIAMD
National Institutes of Health
Bethesda, Maryland 20014

Dr. Mary McCann
Nutrition Program, CDC
CDC Building No. 1
1600 Clifton Road, N.E.
Atlanta, Georgia 30333

Dr. William J. McGanity
Dept. of Obstetrics and Gynecology
University of Texas Medical Branch
Galveston, Texas 77551

Dr. John McKigney
NICHD
National Institutes of Health
Bethesda, Maryland 20014

Dr. Walter Mertz
Human Nutrition Research
Agricultural Research Service
U. S. Dept. of Agriculture
Hyattsville, Maryland 20705

Mr. Donald F. Miller
Food and Drug Administration
Federal Building #8, BF-127
Washington, D.C. 20204

Dr. J. E. Monagle
Chief, Nutrition Division
Room 7, Food and Drug Building
Ottawa 4, Canada

Dr. Carl V. Moore
School of Medicine
Washington University
St. Louis, Missouri 63110

Dr. Eugene R. Morris
Agricultural Research Service
U. S. Dept. of Agriculture
Washington, D.C. 20250

Dr. Milton Z. Nichaman
Room 405, Building B.
Center for Disease Control
Atlanta, Georgia 30333

Mr. C. W. Ofelt
Sterwin Chemicals, Inc.
90 Park Avenue
New York, New York 10016

Miss Helen Ger Olson
Indian Health Service, USPHS
Room 5A-25 Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20852

Dr. Frank Oski
Children's Hospital
18th and Bainbridge Streets
University of Pennsylvania
Philadelphia, Pennsylvania 19146

Dr. George M. Owen
Children's Hospital
561 South 17th Street
Columbus, Ohio 43205

Dr. Jack A. Pritchard
Dept. of Obstetrics and Gynecology
University of Texas Southwest
Medical School
Dallas, Texas 75222

Dr. Merrill S. Read
NICHD
National Institutes of Health
Bethesda, Maryland 20014

Dr. Harold Rice
Office of Nutrition
Technical Assistance Bureau/AID
Room 2489, New State Building
Washington, D.C. 20523

Dr. C. S. Rollinson
University of Maryland
College Park, Maryland 20742

Miss Eleanor W. Rosenbloom
University of Maryland
College Park, Maryland 20742

Miss Carol Rothman
National Academy of Sciences
2101 Constitution Avenue
Washington, D.C. 20418

Dr. Roberto Rueda-Williamson
Pan American Health Organization
525 - 23rd Street, N.W.
Washington, D.C. 20037

Dr. Arnold E. Schaefer
Pan American Health Organization
525 - 23rd Street, N.W.
Washington, D.C. 20037

Dr. John Schubert
Executive Secretary
Nutrition Study Section
National Institutes of Health
Bethesda, Maryland 20014

Dr. William K. Schubert
Children's Hospital Research Foundation
Elland and Bethesda Avenue
Cincinnati, Ohio 45229

Dr. W. H. Sebrell, Jr.
Director, Institute of Human Nutrition
511 West 166th Street
New York, New York 10032

Dr. B. G. Shah
Dept. of National Health and Welfare
Food and Drug Directorate
Tunney's Pasture
Ottawa 3, CANADA

Dr. Robert E. Shank
School of Medicine
Washington University
St. Louis, Missouri 63110

Dr. Horace L. Sipple
Executive Secretary
The Nutrition Foundation, Inc.
Ninety-Nine Park Avenue
New York, New York 10016

Dr. Nathan J. Smith
Office of Asst. Secretary for Health
and Scientific Affairs/DHEW
330 Independence Avenue
Washington, D.C. 20204

current address for Dr. Nathan J. Smith:
Dept. of Pediatrics
University of Washington
Seattle, Washington 98105

Dr. Robert A. Stewart
Director of Research
Gerber Products Co.
Fremont, Michigan 49412

Dr. Jefferson L. Sulzer
Early Childhood Research Center
Tulane University
Tulane University Station Box 5039
New Orleans, Louisiana 70118

Mr. John J. Watson
Watson Foods
57-01 32nd Avenue
Woodside, New York 11377

Dr. Byron H. Webb
Agricultural Research Service
U. S. Dept. of Agriculture
Washington, D.C. 20250

Dr. Marcus I. Wegner
Agricultural Research Service
U. S. Dept. of Agriculture
Hyattsville, Maryland 20705

Dr. Hilda S. White
Dept. of Home Economics
Room 307, Fisk Hall
Northwestern University
Evanston, Illinois 60201

Dr. Philip L. White
American Medical Association
535 North Dearborn Street
Chicago, Illinois 60610

Dr. Max M. Wintrobe
University of Utah
School of Medicine
Salt Lake City, Utah 84112

Mr. Frank O. Wood
The Salt Institute
206 North Washington Street
Alexandria, Virginia 22314

FNB/NRC Staff

Dr. LeRoy Voris
Dr. Paul E. Johnson
Dr. Philip L. Harris
Mr. Durward L. Dodgen