Iron deficiency and behavior

The literature bearing on the behavioral correlates of sideropenia in animals and man is reviewed. There is evidence to support the contention that sideropenia, per se, is causally related to the subjective complaints of the iron-deficient and/or anemic individual. And, although important biochemical pathways involving electron transport, catecholamine catabolism, and porphyrin synthesis have been shown to be deranged in iron-deficient animals and human beings, the role of these alterations in any putative behavioral aberration is conjectural at present. Given the high prevalence of iron deficiency in the world's population, these issues should be addressed by appropriate biochemical and psychologic studies in animals and human beings.


The term "iron deficiency," as used in this article, refers to a state in which body iron stores have been depleted. It implies neither the degree of depletion nor the presence of anemia. "Iron deficiency anemia" refers to a hematologic state resulting from "iron deficiency"; its occurrence implies that body iron stores are severely depleted. Thus an individual may be iron deficient without manifesting iron deficiency anemia; the converse, however, does not occur. This article reviews the literature concerning the effects of iron deficiency, both with and without anemia, on behavior and learning in animals and man. Our purpose is also to specify, wherever possible, the extent to which the mineral deficiency, per se, or its associated hematologic conditions are etiologically related to the behavioral correlates of iron deficiency.

It is generally agreed that iron deficiency is the most prevalent nutritional disorder in the United States. The Ten-State Nutritional Survey found that it maintained this status regardless of socioeconomic class, age, and sex.

Determination of the prevalence of iron deficiency anemia is complicated by disagreement over the hematocrit level and/or hemoglobin concentration that should define this condition. The World Health Organization (WHO) has proposed that a Hgb of less than 11 gm/dl, or a Hct of less than 33% may be used to identify anemia in children between the ages of 6 months and 6 years. However, recent studies by Marner and Moe indicate that the use of the WHO definition results in an underestimation of the frequency of iron deplete status in children (Table I).

### Abbreviations used

- **WHO**: World Health Organization
- **Hct**: hematocrit
- **Hgb**: hemoglobin
- **TCA**: tricarboxylic acid
- **MAO**: monoamine oxidase
- **NE**: norepinephrine
- **DOPA**: dihydroxyphenylalanine

Even if the conservative WHO Hgb values are used, the prevalence of iron deficiency anemia among young children in the United States is high, as indicated by the recently published Preschool Nutritional Survey. Table II, prepared on the basis of data from this survey, presents the cumulative percentage distribution of low Hgb values by age and socioeconomic ranking. The prevalence varies little with age, and in most cases 5% of the children have...
Hgb values below 10.9 gm/dl. However, a slight elevation of the lower acceptable limit would result in a marked increase in prevalence. For example, use of a Hgb level of 11.4 gm/dl results in a prevalence rate in excess of 20% among all age ranges within the lowest socioeconomic group.

A series of studies have been conducted to assess the contribution of prevailing forms of malnutrition to intellectual retardation. Most have focused on protein-calorie malnutrition because of its high frequency in developing countries. Evidence currently available indicates that chronic, severe protein-calorie malnutrition, occurring during a period of rapid brain growth, is likely to result in anatomic and biochemical alterations of that organ, and in moderate retardation of intellectual functioning. Data on the possible relationship between the more prevalent chronic, mild-to-moderate undernutrition and cognitive development are less conclusive. No data are available on anatomic or metabolic changes in the central nervous system of moderately or mildly malnourished children. In addition, the complex ecology of malnutrition introduces methodologic limitations in evaluating intellectual deficiency among these children. The possible contributory role of malnutrition is obscured by a host of biological and social-psychological correlates which, by themselves, can seriously impair mental development. Finally, although altered brain growth and impaired intellectual functioning may be concomitants of early malnutrition, these structural and functional correlates are not necessarily causally related.

A review by Read indicates that only a few studies exist on the behavioral effects of iron deficiency. These reports suggest that iron deficiency anemia may affect an organism's response to its physical and social environment. Anorexia and irritability are prominent when Hgb levels fall below 5 gm/dl; apathy and listlessness are also reported. Such clinical descriptions, however, have not been supported by systematic studies to define precisely the effects on behavior of iron deficiency, with or without anemia.

### Table I. Hematocrit and hemoglobin values of presumably iron-replete children (data from Marner and Moe)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Hct</th>
<th>SD</th>
<th>Hgb</th>
<th>SD</th>
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<tr>
<td>1½-3</td>
<td>38.9</td>
<td>2.20</td>
<td>11.8</td>
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<tr>
<td>3</td>
<td>38.0</td>
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<tr>
<td>4</td>
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</tr>
<tr>
<td>5</td>
<td>40.0</td>
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<td>13.8</td>
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</tr>
<tr>
<td>6</td>
<td>41.0</td>
<td>2.78</td>
<td>14.0</td>
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### Table II. Cumulative percentage distribution of hemoglobin (gm/dl) values by age and Warner Rank of children in Preschool Nutritional Survey (adapted from Owen, Lubin, and Garry)

<table>
<thead>
<tr>
<th>Age and Warner rank*</th>
<th>&lt; 10</th>
<th>&lt; 10.4</th>
<th>&lt; 10.9</th>
<th>&lt; 11.4</th>
<th>Mean Hgb value</th>
<th>SD</th>
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<tr>
<td>12-23 mo</td>
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<td></td>
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<td></td>
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<tr>
<td>I</td>
<td>16</td>
<td>22</td>
<td>32</td>
<td>11.6</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>8</td>
<td>12</td>
<td>17</td>
<td>33</td>
<td>12.0</td>
<td>1.4</td>
</tr>
<tr>
<td>III</td>
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<td>6</td>
<td>7</td>
<td>15</td>
<td>12.4</td>
<td>1.1</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>3</td>
<td>9</td>
<td>12.5</td>
<td>0.9</td>
<td></td>
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<tr>
<td>24-35 mo</td>
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<td></td>
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<td></td>
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<tr>
<td>I</td>
<td>4</td>
<td>5</td>
<td>10</td>
<td>22</td>
<td>12.3</td>
<td>1.2</td>
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<tr>
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<td>14</td>
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<td>0.9</td>
</tr>
<tr>
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<td>3</td>
<td>10</td>
<td>12.5</td>
<td>0.9</td>
</tr>
<tr>
<td>IV</td>
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<td>8</td>
<td>12.8</td>
<td>0.9</td>
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<td>48-59 mo</td>
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<tr>
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<td>0</td>
<td>1</td>
<td>2</td>
<td>19</td>
<td>12.4</td>
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<td>II</td>
<td>2</td>
<td>4</td>
<td>11</td>
<td>12.6</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>12.7</td>
<td>1.4</td>
</tr>
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<td>IV</td>
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<td>2</td>
<td>9</td>
<td>12.7</td>
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<tr>
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<tr>
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<td>0</td>
<td>1</td>
<td>2</td>
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<td>II</td>
<td>3</td>
<td>4</td>
<td>11</td>
<td>12.6</td>
<td>1.0</td>
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</tr>
<tr>
<td>III</td>
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<td>4</td>
<td>9</td>
<td>12.7</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>12.8</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* I = lower lower; II = upper lower; III = lower middle; IV = upper middle.

### IRON KINETICS AND TISSUE BIOCHEMISTRY

Studies of the effects of iron deficiency on behavior have focused on the extreme form: iron deficiency anemia. In human studies, the discrimination process generally has been based on hemoglobin or hematocrit values, rather than on more direct measures of body iron stores. Iron kinetics are such that body iron stores, transferrin saturation, and even tissue levels of essential heme-containing enzymes can be exhausted or markedly diminished before the circulating mass of red cells is affected. Beutler has demonstrated deficiencies in heme-containing enzymes (cytochrome C, cytochrome oxidase) and iron-dependent enzymes (succinic dehydrogenase, aconitase) in the tissues of animals with latent iron deficiency (sideropenia without significant anemia). Many of the Krebs tricarboxylic acid cycle enzymes and cofactors contain iron, and in vitro studies have demon-
strated increased oxygen consumption in the leukocytes of iron-deficient patients. Conversely, a study by Dagg and colleagues, which showed tissue (buccal mucosa) cytochrome oxidase deficiency in sideropenic patients, failed to establish a correlation between the enzymopathy and the presence and/or severity of buccal mucosa atrophy.

Although the three studies mentioned above tend to invalidate the classical concept that tissue iron-containing enzymes are "inviolate" even in the face of extreme body iron depletion, they do not address the crucial issue of whether such enzymopathies contribute to the symptoms of iron deficiency anemia. Ascertainment of such data is further complicated by the fact that different iron-containing enzymes are affected to different extents by an equivalent degree of iron lack, and that the same enzymes are variably affected in different organs.

Although these heme-containing and iron-dependent enzymes account for only a few tenths of one per cent of total body iron, their location in the Krebs TCA cycle and the cytochrome system render them essential to cellular oxidative metabolism. The brain, like most other organs, depends upon these enzymes for the efficient utilization of blood-borne energy substrates, although there is only an approximate correlation between brain iron content and that organ's respiratory activity.

The extra-pyramidal system of the adult human brain contains concentrations of non-heme iron up to 21 mg (per 100 gm fresh weight), which are equivalent to those found in the liver, a major storage site for iron. The remainder of the brain contains 2 to 5 mg iron per 100 gm of tissue (with concentrations proportionate to the phylogenetic age of the brain part), an amount greater than that which can be accounted for by the levels of various known iron-containing enzymes and cofactors. Some of this iron is apparently present in the form of ferritin. Brain iron concentration increases gradually with age, being about 10% of adult values at birth, 50% at age 10 years, and achieving maximal levels in most parts of the brain between the ages of 20 and 50 years. This gentle rise parallels neither the developmental pattern of brain cytochromes, which increase to adult levels concurrent with myelinization, nor the fluctuations of total body iron stores. Hallgren and Sourander, however, remark that "in three cases of ulcerating intestinal carcinomas associated with large hemorrhages somewhat lowered values of non-haem iron in the extra-pyramidal system have been observed. Further, in a case of severe anemia lowered values were also found in the cortical areas." These findings imply that brain iron, in its non-heme form, is not an inviolate sanctuary. Dallman and Schwartz showed that, in rats, mild iron deficiency reduced tissue levels of cytochrome C by as much as 30% in intestinal mucosa and skeletal muscle, but that little or no decrease in this cytochrome occurred in the brain and cardiac muscle of severely iron-deficient animals. Despite this indication that there is a functional hierarchy to somatic and nervous system iron depletion, the behavioral correlates of sideropenia and/or iron deficiency anemia might conceivably be related to disordered cerebral oxidative metabolism secondary to suboptimal levels of various heme-containing and iron-dependent enzymes.

Dallman and Schwartz emphasize that the susceptibility (as reflected in reduced cytochrome levels) of a given tissue to iron lack is a product of organ function, growth rate, and cell turnover. With regard to the last two factors it is important to recall that human CNS susceptibility would be greatest in utero and during the first two years of life and that permanent impact might result from such a transient deficiency state via effects on cerebral oxidative metabolism neurotransmitter synthesis or brain cell mitosis.

Another enzyme apparently sensitive to the state of body iron stores is mitochondrial monoamine oxidase. Crucial in the catabolism of monoamines in the brain and elsewhere, this enzyme has been shown to be functionally deranged, both in vitro and in vivo, in severely iron-deficient rats. In the latter study, substrate oxidation returned to normal by Day 6 of iron refeeding—before restoration of Hgb mass—implying that the acquired metabolic dysfunction had not been the result of anemia, per se. The role of iron in the action of this enzyme is unclear, although Symes and colleagues have suggested that the enzyme may serve as a prosthetic group of MAO. Given the putative function of various monoamines in brain neurotransmission and the affective and behavioral changes associated with the administration of MAO-blocking agents, it seems possible that at least a portion of the behavioral aberrations commonly attributed to iron deficiency may be caused by impaired MAO function and associated excesses of CNS catechols. Voorhees and associates provide evidence of such a conjunction in a recent article, which showed that children with iron deficiency anemia had elevated urinary norepinephrine excretion rates prior to therapy with intramuscular iron. Urinary NE excretion did not vary directly with the degree of anemia, serum iron level, or percentage of saturation, but patients with anemias unrelated to iron deficiency failed to show any significant alterations in NE excretion before or after transfusion. The clinical observations regarding the rapidity of symptomatic relief, as opposed to the longer time needed to raise hemoglobin level in iron repletion therapy, is particularly interesting in view of the fact that urinary NE excretion rates were normalized in the above patients within one week of parenteral iron.
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The iron-deficient state might be expected to suppress the activity of this rate-limiting enzyme in NE synthesis to partially compensate for the effect of diminished MAO activity. Finally, in considering the impact of iron deficiency on nonhematologic behavior-related systems, the status of muscle, which normally accounts for 10% of total body iron and includes more than 50% of the body's mitochondrial cytochromes, must be examined. Although the effect of iron deficiency on myoglobin in man is unknown, the rat shows reduced muscle myoglobin and cytochrome C early in the development of iron deficiency. The possible impact of these biochemical alterations on behavior are somewhat mooted by the fact that isolated muscle from these animals performs normally in response to electrical stimulation. No reduction in myocardial myoglobin or cytochrome C concentrations is noted in iron deficiency without anemia.

In adults, a serum iron level of less than 70 µg/dl and/or transferrin saturation of less than 16 to 20% are well correlated with a failure to deliver to the marrow a quantity of iron sufficient for full proliferative capacity of the red cell line. Hunter and Smith showed that in 6- to 18-month-old children, a transferrin saturation of greater than 16% was virtually always associated with hematocrit and hemoglobin levels equal to or greater than 33% and 11 gm/dl, respectively. The converse, however, did not hold. Many children with hematocrit and hemoglobin levels greater than 33% and 11 gm/dl, respectively, had transferrin saturations of less than 16%. Thus the iron depleted state, at least in its incipiency, is frequently not reflected in the Hgb or Hct levels. Therefore, studies using Hct and Hgb alone to identify the prospective iron-deficient individual must always underestimate the prevalence of the iron-deficient state.

At present, according to Harris and Kellermeyer, determining the iron content of a bone marrow needle aspirate provides the most accurate, readily available, direct assessment of body iron stores. Ferritin assays have reported that protoporphyrin, the immediate precursor of heme, is increased in the red blood cells of the iron-deficient (but not necessarily anemic) individual. Assay for this compound can thus be used as a screening device for the presence of early iron deficiency. In young children, however, the frequent existence of increased body lead, which results in increased red cell porphyrin levels even in the absence of iron deficiency, often confounds the results of this assay. Consequently, the young child with an acquired elevated red blood cell protoporphyrin level may be suffering from lead poisoning and/or iron deficiency.

Many behavioral abnormalities attributed to the iron-deficient state are similar to those described in plumbism and, for that matter, in the congenital disorders of porphyrin metabolism. The work described earlier regarding the effects of iron lack on oxidative metabolism and MAO function notwithstanding, it is possible that the true proximate biochemical lesion influencing behavior in iron deficiency results from excess heme precursors.

**Iron Deficiency and Animal Behavior**

Few reports are available on the effects of iron deficiency on behavior in laboratory animals, and, except for a well-designed and controlled experiment on physical activity, most reported research is methodologically weak. A study by Bernhardt with rats showed that experimentally induced postweaning iron deficiency anemia adversely affected maze learning. Conversely, a later study showed that the offspring of rats fed iron-deficient diets during pregnancy performed similarly in a maze-learning task to the offspring of animals placed on well-balanced diets. This study, in which testing began when the animals were 42 days old, made use of food rewards for experimental motivation. A byproduct of the study was the finding that, during pregnancy, control animals were active, whereas experimental subjects had decreased appetite and were less active.

The validity of the two investigations described above can be questioned on the ground that both used food as a positive reinforcer. Hungry animals, after an experience of food deprivation early in life, show an exaggerated response to food. Moreover, such behavior is not simply mediated by the actual memory of deprivation; there is evidence that as adults, the progeny of mothers that were deprived of food during pregnancy differ from control subjects in their behavior toward food. Furthermore, in human beings at least, maternal iron status appears to have little impact on the sufficiency of fetal iron stores.
With an activity meter, Glover and Jacobs\(^\text{44}\) monitored total and large body movements of three groups of male Wistar rats of similar weights that had been placed on a standard, an iron-free, or an iron-deficient diet since weaning. Each group included three animals, and no between-group statistical comparisons were reported. Nonetheless, there were clear differences between the two depleted and the control groups; the iron-depleted rats had a considerable reduction in body movements. Large increases in activity were observed in all but the control animals after two and four days of iron-repletion therapy; there was a decline in activity after iron was again withheld.

A well-controlled study by Edgerton and associates\(^\text{47}\) on the effects of diet- and phenylhydrazine-induced anemia on the physical performance of laboratory rats showed that iron deficiency anemia caused a decrement in forced-exercise performance. The decrement, however, was quickly ameliorated by iron repletion therapy. The severity of the anemia was more important than its duration in determining the activity decrement. A clear correspondence between hemoglobin values and performance levels was evident, regardless of the duration of the deficiency; short-term anemia was associated with performance characteristics similar to those found with diet-induced iron deficiency anemia.

Despite a failure to demonstrate a correlation between physical performance parameters and muscle content of myoglobin/cytochromes, Edgerton and colleagues\(^\text{47}\) suggested that the apparent salutary effect of iron repletion might not be solely the result of an increment in Hgb mass. They commented that the reconstitution of tissue iron stores might be a more important factor in the behavioral response to iron therapy.

**IRON DEFICIENCY AND HUMAN BEHAVIOR**

The anemic state, regardless of its etiology, represents a threat to sufficient tissue oxygenation.\(^\text{39}\) From the viewpoint of general organismic homeostasis, this threat is the most significant effect of anemia. Several mechanisms exist to preserve tissue oxygenation in the face of diminishing hemoglobin levels.\(^\text{56}, 57\) These include an intrerythrocytic adaptation, which permits the release of oxygen at higher tissue oxygen levels, a rise in cardiac output, and the selective deviation of blood flow to the most vital organs. These compensatory devices are invoked in succession as the hemoglobin level falls—the first occurs linearly over hemoglobin levels ranging from 12 to 8 gm/dl, and the last is not employed until the hemoglobin level is less than 7 gm/dl.

An appreciation of the existence of these compensatory mechanisms is crucial to any effort to isolate behavioral correlates specific to a particular type of anemia. Certain symptoms/signs occurring at a low Hgb level will be a generic reflection of anemia, per se, and not type specific. Therefore, appropriate controls are crucial in studies purporting to assess the somatic and/or psychological impact of a specific type of anemia. The majority of such studies to date suffer from a lack of such controls.

Investigations of the effects of iron deficiency anemia on human behavior have focused on alterations in physical activity and cognitive test performance. Data have also been published on verbalizations of iron-deficient subjects regarding cognitive-emotional experiences stemming from their malnourished state.

Clinical reports on patients with iron deficiency anemia indicate that the subjects complain of fatigue, weakness, and lack of ability to concentrate.\(^\text{24}\) Some studies\(^\text{53}\) suggest that iron-deficient, anemic children are irritable and anorexic. However, Harris and Kellermeyer\(^\text{55}\) point out that the subjective response to iron therapy in anemic, iron-deficient patients often considerably precedes the rise in hemoglobin values. Thus, three to five days after the institution of iron therapy, the patient may note a return of strength, appetite, and a feeling of well being that could not have been caused by an alteration of red cell mass. Likewise, pagophagia (pathologic craving for ice), which appears to be a specific symptom of iron deficiency (but not necessarily of anemia), is rapidly and completely corrected by dosages of iron less than those required to correct anemia or reconstitute the iron stores.\(^\text{56}, 60\) Such clinical observations tend to support the contention that much of the symptomatology attributed to the iron-deficient, anemic state is, in fact, not the result of anemia, per se, but rather of some other metabolic correlate of iron depletion. As mentioned previously, the iron-dependent enzymes and heme-containing cofactors of the Krebs cycle, altered porphyrin metabolism, and MAO dysfunction have seemed logical candidates for a role in the behavioral disturbances described in iron deficiency. However, proof of their role in either animals or human beings is currently lacking.

Available information shows, with few exceptions, that physical endurance, activity, and manual labor productivity are significantly curtailed in adults with Hgb values below 11 gm/dl.\(^\text{51-64}\) Basta\(^\text{65}\) however, has shown that there is a significant increment in productivity after iron repletion therapy. These studies made no attempt to differentiate the effects of iron repletion and rehabilitation from anemia. Beutler and associates\(^\text{50}\) were unable to demonstrate a difference in oxygen consumption or heart rate with a fixed exercise load in iron-deficient patients before and after iron therapy. However, as Dallman\(^\text{71}\)
points out, a decrease in mitochondrial cytochromes would be more likely to affect maximal oxygen utilization and ATP production. Thus endurance or maximal response to a work load would be better parameters for evaluation.

Studies on intellectual function in iron-deficient children have purported to demonstrate varying adverse effects of anemia on one or more cognitive processes. A study of Eldwood and Hughes using adults as experimental subjects showed that anemia had a nonsignificant effect on psychological test performance. In this study, 47 women with Hgb values below 10.5 gm/dl were randomly divided into two treatment groups for an 8-week period; one group received a placebo, while the other received 150 mg of elemental iron as ferrous carbonate daily. Before and after treatment they were given a battery of tests covering a range of psychomotor functions. Statistical analysis showed nonsignificant intrapersonal differences in the tests before and after treatment; there were also no significant interindividual differences after treatment. The only trend found among the results was the improved performance observed among those women with the largest rise in Hgb level.

Except for a few instances, available reports on investigations of children are published in the Proceedings of Conferences. With the exception of the report by Sulzer and associates, they provide brief descriptions of methods and subjects, which make it difficult to assess the methodologic rigor and the exact objective(s) of the studies. The following review is limited to the more detailed and informative reports, and to one brief abstract from a longitudinal study.

In one project, Sulzer and associates studied over 230 male and female, 4- to 5-year-old black children enrolled in a Head Start Program in New Orleans. Of this group, 11.7% had hemoglobin values below 10.5 gm/dl. Two batteries of psychological tests were used. The first included a global, allegedly culture-free IQ test, a vocabulary test, and measures of moral development and grouping behavior. The other battery comprised reaction time, attentive recall, and cranking tasks. When compared with control subjects, the performance of anemic subjects (Hgb < 10 gm/dl) was significantly poorer on the vocabulary tests and showed similar, but not significant, trends on all other measures. The score differentials between groups became more statistically evident when the cutoff point in hemoglobin values was 10.5 gm/dl, which increased the sample of anemic subjects. Compared with the control group, the anemic subjects had significantly lower scores on the IQ measure, the vocabulary test, and the latency and associative reaction measures. An important finding was that younger anemic children were unable to integrate effectively experience accumulated during different steps of the associative reaction test. The authors suggested that the younger group may have been more vulnerable to the possible effects of iron deficiency anemia on cognition. It is also possible, of course, that the timing of iron deficiency relative to the ontogenesis of the CNS is a factor in terms of possible permanent sequelae.

Recognizing that the nutritional history of the child (independent of current anemia) may have contributed to the observed results, the investigators compared the test scores of tall and short children. (Physical growth is an accepted indicator of nutritional status.) When the age variable was controlled, differences (the authors do not specify which tests differed) between tall and short children were small. The data did indicate, however, that the combination of a history of inadequate nutrition and current low hemoglobin value was the best predictor of inferior performance.

Education of the father was the only social factor that distinguished anemic from nonanemic children; the educational level of the fathers of children in the anemic group was lower. Family size, occupation of the head of the household, housing characteristics, health, and many other social characteristics failed to differentiate the groups.

This study had a series of methodologic flaws, (e.g., the testing environment was far from ideal, and there was not time to establish rapport with the children), and therefore, the investigators considered the results inconclusive. However, the data were used to develop relevant hypotheses for subsequent testing. Two alternatives were presented to explain the better performance of the nonanemic children: (a) better learning ability and (b) higher motivation. The investigators add that their observations excluded the possibility that the differences were caused by attentional factors.

In contrast, Howell has reported markedly decreased attentiveness, narrow attention span, and perceptual restriction among 3- to 5-year-old iron-deficient children (hemoglobin levels of less than 10 gm/dl). Howell's report, unfortunately, is too incomplete to establish the validity of her data, or the possible source of their conflict with findings of Sulzer and colleagues.

Iron deficiency anemia and scholastic achievement in young adolescents was investigated in Philadelphia by Webb and Oski. Subjects were 12- to 14-year-old male and female junior high school students in an economically deprived, mostly black community. Following a hematologic survey of 1,807 children, 92 subjects were considered anemic (hemoglobin values ranged from 10.1 to 11.4 gm/dl). All anemic subjects had hypochromic, microcytic
red cell indices and evidenced neither sickle cell hemoglobin nor red cell glucose-6-phosphate dehydrogenase deficiency. It was presumed that all were iron deficient, although no attempt was made to exclude either alpha- or beta-thalassemia traits. A control group of 101 students with hemoglobin values ranging from 14.0 to 14.9 gm/dl was also tested. A measure of scholastic performance was obtained from the composite score on the Iowa Tests of Basic Skills, Levels A-F/Form 3. This score represented performance across the following subtests: vocabulary, reading knowledge and use of reference materials, arithmetic concepts, and problem solving.

The scores of the anemic subjects were significantly lower (P < 0.025) than those of nonanemic students. Further, the older anemic male subjects displayed a progressive departure in performance from the nonanemic control subjects. The authors acknowledged that they had insufficient information to interpret the sex difference in the decline of scores as a function of age. In a subsequent study the performance of both groups of children on a standard visual afterimage task was investigated. The subjects' reports on the visualization of an afterimage showed that the iron-deficient anemic children had a longer latency period than the nonanemic subjects.

A third study by Webb and Oski, on 74 of these 92 anemic children and 36 control subjects, employed a Behavior Problem Checklist and showed a differential trend between the two groups. Observational ratings from 13 English teachers, who did not know the group to which each child belonged, provided the basis for behavioral comparisons. The information provided by the checklist focused on: (a) conduct problems, (b) personality disturbances, and (c) inadequacy-immaturity. The results showed a nonsignificant between-group difference in the scores on personality disturbances and inadequacy-immaturity. The difference in the conduct scale reached the 0.10 level of probability; the authors interpreted this difference to mean that the anemic subjects tended to have more conduct disturbances than the nonanemic subjects. The age by hematologic condition interaction in the statistical analysis proved to be statistically insignificant for each of the scales. In summary, the authors conclude that the scholastic performance of the anemic children was compromised by disturbances in attention and perception.

It is unclear from the above data whether the poor performance, perceptual disturbances, and conduct problems observed in the anemic subjects were consequences of anemia, per se, iron deficiency alone, or a general nutritional inadequacy of which iron deficiency was only a readily identifiable component. The possibility that anemia, per se, was the determining factor in the low performance of these students must be questioned, because two other studies found no significant relationship between IQ measures and the degree of anemia, secondary to sickle cell disease, among children.

The reported investigations in New Orleans and Philadelphia suffer from weak study designs that raise critical questions about their internal validity. They were ex post facto limited to a static-group comparison, and neither provided a way to certify that the groups would have been equivalent had it not been for the iron deficiency.

A longitudinal study by Cantwell, undertaken to determine whether hypoxemia from anemia causes brain damage, involved 61 full-term infants from comparable socioeconomic groups. At 6 to 18 months of age, 32 of the infants exhibited iron deficiency anemia (Hgb values ranged from 6.1 to 9.5 gm/dl). Twenty-nine infants had received neonatal iron dextran injections and were not anemic (Hgb ranged from 11.5 to 12.9 gm/dl). Neurologic examinations were done at 6 to 7 years of age, and the examiners had no knowledge of the presence or absence of previous anemia. The anemic group had a higher incidence of "soft" neurologic signs, such as clumsiness in balancing on one foot, tandem walking, and repetitive hand or foot movements. They were also less attentive and more hyperactive than control subjects. The authors do not include statistical data in their abstract and report that IQ scores averaged 98 and 92 for the nonanemic and anemic groups, respectively. In the absence of protein-calorie malnutrition, the authors specify that anemia in infancy appears to be one cause of possibly permanent minimal brain dysfunction.

**SOCIOECONOMIC CORRELATES OF IRON DEFICIENCY ANEMIA**

Investigators of possible relationships between dietary protein-calorie deficiency and behavior recognize that economic and social correlates of nutritional status must be controlled in any such assessment. Regression equations derived from studies attempting to separate malnutrition's effects on cognition from those of various socioeconomic factors reveal that both sets of variables can independently account for parts of the variance in cognitive performance. Thus, if the specific contribution of such socioeconomic variables is not measured and discounted, there may be an overestimation of the effects of the nutritional factor.

Data from a pilot study by Kallen and associates on maternal socioeconomic correlates of iron deficiency anemia in infants in East Lansing suggest that environmental factors may also covary with iron status. Mothers
of 11 iron-deficient infants (Hgb not specified) ranging from 6.5 to 26 months of age differed in a number of social dimensions from the mothers of a matched group of nonanemic children of the same age. Mothers of the deficient children tended to be younger at the time of pregnancy, to have had more children more closely spaced, and to have had fewer years of schooling. A 1963 study in the District of Columbia also showed that iron deficiency anemia was related to low socioeconomic status, depression, and apathy in the mothers of affected children.

The above data suggest that some of the behavioral characteristics of iron-deficient children described in the previous section may have been partly caused by social and economic factors covarying with nutritional deficiency. Unless the environmental conditions in which the children were raised are taken into account, it seems doubtful that the exact nature of the apparent relationship between behavior and nutrition can be clarified.

CONCLUSIONS

In the United States, iron deficiency (sideropenia) and iron-lack anemia represent highly prevalent, readily identifiable hematologic states. Research on the effects of iron deficiency on behavior has been limited to assessing the effects of iron-lack anemia. Psychological consequences of sideropenia without anemia have not been investigated. Clinical reports suggest, however, that after the initiation of iron repletion therapy, but before a significant augmentation of Hgb mass, there may be a reversal of some of the subjective states (e.g., irritability and lassitude) commonly associated with anemia. This conjunction implies that iron lack, per se, may be the cause of such symptoms.

Evidence has accumulated in support of the hypothesis that iron deficiency anemia among adults reduces the capacity for vigorous exercise or hard physical labor. The predominant mechanism of this limitation seems to be tissue hypoxemia, secondary to a gross reduction in circulating Hgb mass. Nevertheless, the question of whether sideropenic subjects without anemia are also handicapped in physical stamina remains unanswered.

Except for one article by Cantwell, the available studies on behavioral consequences of iron deficiency in children have all used ex post facto design; there is no evidence regarding experimental and control group equality prior to iron depletion. Thus no conclusive inferences can be derived because the environmental conditions in which the children were raised were not taken into account. As it stands, available information suggests that motivation to persist in intellectually challenging tasks may be lowered, attention span shortened, and over-all intellectual performance diminished. The abstract available on the longitudinal study is too short to allow a fair evaluation. The data reported are insufficient to estimate whether the anemic and nonanemic groups were exposed to similar environmental conditions, or to determine whether differences between the groups were caused by differences in specific caretaking practices. The study does not address itself to the issue of whether the effects are dependent on iron levels or on the hematologic condition.

Given the striking prevalence of sideropenia in children in the United States—particularly those of less advantaged socioeconomic status—and given the possible contribution of this state to the development of common behavioral and intellectual problems in children, it would seem imperative that the nature of the relationship (if any) between these two rather ubiquitous conditions be determined as soon as possible.

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