IRON DEFICIENCY IN THE PREMATURE INFANT
Significance, and Prevention by the Intramuscular Administration of Iron-dextran

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INFANTS born prematurely experience a greater than usual number of serious illnesses throughout the first 2 years of life. We have previously reported that 1 out of every 4 premature infants discharged from our nursery required re-admission to the hospital before the second birthday, usually for treatment of pneumonia or diarrheal disease. The great majority of these babies were also found to have iron deficiency anemia. In view of the widely-held clinical belief that iron deficiency anemia is associated with an increased incidence of infections, it seemed desirable to study the health record of a group of premature infants maintained in a state of abundant iron nutrition; evidence that the number of infections in such a group was reduced would be of considerable theoretic and clinical interest. Another object of this study was to determine whether the "prophylactic" use of intramuscular injections of iron-dextran during the nursery stay was a method of preventing iron deficiency anemia suitable for use in clinical practice.

SUBJECTS AND METHODS

Two hundred and five, consecutive, prematurely born babies, who weighed 2,000 grams or less and had survived for at least 24 hours, were allocated by random selection to a group to receive iron-dextran and a control group. On reaching 2,000 grams in weight, babies in the iron-dextran group were given 1 ml of iron-dextran daily by deep intramuscular injection in alternate buttocks for 5 days. This dosage supplied a total of 250 mg of elemental iron, the quantity used in a similar study; according to the calculations of Sturgeon, this quantity should be sufficient to provide the iron requirements necessitated by growth during the first year in most infants, even if no additional iron was absorbed from the intestinal tract. After discharge from the nursery, the babies were seen in the premature clinic monthly by one of us and both groups were given similar advice regarding increases of milk formula and introduction of solid foods.

Duplicate determinations of hemoglobin (oxyhemoglobin) and the micro-hematocrit were carried out weekly in the nursery and monthly at follow-up visits; blood smears and sickle-cell preparations were examined in all anemic infants. Babies in the control group usually received no supplemental iron, unless the hemoglobin declined below 7 gm/100 ml; then, oral administration of iron preparations (supplying 60 mg of elemental iron daily) was used for 1 or 2 months.

Additional data concerning morbidity and mortality in both groups of infants were obtained from study of the hospital records and from the Vital Statistics of the Dallas City and County Health Departments, which frequently yielded information about infants whose clinic follow-up record was deficient. Since some of the babies lost to follow-up may have become ill or died in hospitals outside the city area, these data may not be complete, but there seems no reason to suppose that this would affect comparison between the two groups.

* Either ferrous sulfate (Fer-in-Sol, supplied through courtesy of Mead Johnson and Company), or iron choline citrate (Chel-Iron, courtesy of Kinney and Company, Inc.).

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TABLE I
DISTRIBUTION OF INFANTS SURVIVING THE NEONATAL PERIOD

<table>
<thead>
<tr>
<th>Weight (gm)</th>
<th>Treated with Iron-dextran</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1,250</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>1,250–1,499</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>1,500–1,749</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>1,750–1,999</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>Totals</td>
<td>84</td>
<td>97</td>
</tr>
</tbody>
</table>

RESULTS

Of 205 infants entering the study, 181 survived the neonatal period; of the latter, 84 received iron-dextran and 97 did not. No febrile reactions to the intramuscular injections of iron-dextran were observed. One infant developed a sterile abscess at the site of injection, and two others developed flaccid paralysis of one leg below the knee.*

Distribution by birth weight is shown in Table I. Among the babies weighing less than 1,250 grams, 8 received iron-dextran and 16 did not. Because of the small number of cases, this difference is probably not sufficient to affect over-all comparisons made between the two groups, although the smaller infants usually show a high incidence of iron deficiency and post-neonatal illness.7

The follow-up record is shown in Table II. There were five deaths known to occur in the iron-dextran group and three in the control group, during the first year. Of the surviving babies in the iron-dextran group, 38% were followed in the clinic for 11 months or more, and 62% were followed for at least 6 months. In the untreated group the corresponding figures were 51% and 72%. Over 30% of the total number of surviving infants were lost to follow-up before 6 months of age, mostly for social and economic reasons. The better clinic attendance record of infants in the control group suggests a greater maternal desire to provide good care; it is unlikely that the development of iron deficiency anemia in these infants was in itself responsible for their better attendance, because this condition is usually asymptomatic during this period.

The mean values for hemoglobin in the treated and untreated babies are shown in Table III. Hemoglobin values were slightly lower in the iron-dextran treated babies at 1 week of age but identical with the values in the control group at 4 weeks. By 7 to 8 weeks of age, hemoglobin values were by guest on April 28, 2017

TABLE II
PERIODS OF FOLLOW-UP OF SURVIVING INFANTS

<table>
<thead>
<tr>
<th>Duration</th>
<th>Treated with Iron-dextran (%)</th>
<th>Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 11 months</td>
<td>38</td>
<td>51</td>
</tr>
<tr>
<td>6–11 months</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Less than 6 months</td>
<td>38</td>
<td>28</td>
</tr>
</tbody>
</table>

* Both babies received intragluteal injections of antibiotics in addition to iron-dextran. Similar lesions following the injection of antibiotics in young infants have been reported by one of us8 and by others.9 Personal communications from other workers using intramuscular injections of iron-dextran in premature infants10–12 state that they have not experienced this difficulty. However, it is possible that despite efforts to keep the injection confined to the upper and outer quadrant, inappropriate placement of the iron injection may have been responsible for these lesions. We are now using the mid-anterior thigh as the site for all intramuscular injections in young infants.13

TABLE III
CONCENTRATION OF HEMOGLOBIN (GM/100 ML) DURING THE EARLY WEEKS OF LIFE

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>Treated With Iron-dextran</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.5 (67)*</td>
<td>17.8 (88)</td>
<td>&gt; .1</td>
</tr>
<tr>
<td>4</td>
<td>17.2 (58)</td>
<td>17.2 (71)</td>
<td>—</td>
</tr>
<tr>
<td>7–8</td>
<td>9.9 (50)</td>
<td>9.6 (55)</td>
<td>&gt; .1</td>
</tr>
<tr>
<td>9–10</td>
<td>10.5 (68)</td>
<td>9.6 (51)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>11–12</td>
<td>10.7 (30)</td>
<td>9.8 (37)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>13–16</td>
<td>11.5 (40)</td>
<td>9.5 (50)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>17–20</td>
<td>12.0 (40)</td>
<td>9.7 (52)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>21–24</td>
<td>12.3 (42)</td>
<td>8.8 (44)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Over 1 year</td>
<td>11.5 (28)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* (Number of determinations).
higher in the iron-dextran group; by 9 to 10 weeks, the difference between the groups became statistically significant and remained so thereafter. None of the babies receiving iron-dextran showed any significant anemia during the period of follow-up; the mean hemoglobin level in this group at 1 year of age was 11.5 gm/100 ml (range 9.3 to 13.4 gm/100 ml).

Forty-eight of the control group were followed in the clinic for at least 11 months. The data indicate that almost all the control babies developed a significant degree of iron deficiency anemia during the first year of life. Hemoglobin values below 7.5 gm/100 ml, and a hypochromic blood picture, were observed in 24 (50%) and values below 5 gm/100 ml occurred in 4 infants. Values between 7.5 and 9.5 gm/100 ml were observed in an additional 18 infants. Only five infants reached the age of 1 year with a hemoglobin level greater than 9.5 gm/100 ml without having received supplemental iron.

Weight curves for babies in the ranges of 1,500 to 1,749 grams and 1,750 to 2,000 grams are compared in Figure 1. There is no significant difference between the groups that received iron-dextran and those that did not. This is in accordance with the clinical impression that iron-deficient infants seldom appear underweight, but differs from observations made in some iron-deficient animal species (e.g., growing piglets in which administration of iron supplements causes a striking increase in weight gain and nitrogen retention). We did not obtain the impression that there was any significant difference in general development between the control group and the group treated with iron-dextran.

Data concerning morbidity and mortality are shown in Tables IV and V. The number of respiratory infections and diarrheal disorders requiring outpatient visits and hospital admissions were compared in the iron-dextran and control groups. It will be seen that there is no significant difference in the number of inpatient or outpatient attendances, or in the number of outpatient ill-
Diagnosis treated with iron-dextran (84) Controls (97)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treated with Iron-dextran</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants admitted</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Number of admissions</td>
<td>82</td>
<td>90</td>
</tr>
<tr>
<td>Deaths</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Attending outpatient dept.</td>
<td>85</td>
<td>47</td>
</tr>
<tr>
<td>Number of outpatient illnesses</td>
<td>64</td>
<td>87</td>
</tr>
<tr>
<td>Average number of illnesses per infant attending outpatient dept.</td>
<td>1.83</td>
<td>1.85</td>
</tr>
</tbody>
</table>

Discussion

The prematurely born infant almost invariably develops iron deficiency anemia unless supplemental iron is given. The adequacy of iron nutrition of the mother, perinatal factors and variations in dietary iron intake may affect the degree of anemia or the rapidity with which it develops, but the principal causative factor in these babies is the rapid rate of growth. Analyses of animal and human fetuses of various ages show that the iron content per unit of fetal weight is normally rather constant throughout pregnancy. Since the small premature infant may often attain six times his birth weight or more by 1 year of age, it can readily be seen that the meager quantity of iron present in the body at birth soon becomes insufficient to supply the needs for the synthesis of hemoglobin and myoglobin, as the blood volume and muscle mass expand. Insufficient iron is absorbed from conventional diets to keep up with this demand.

Although early administration of strained meat or the use of milk fortified with iron may provide dietary iron sufficient to meet requirements, the common practice at the present time involves the oral use of supplemental iron salts. The latter procedure is entirely effective when properly used, but the results of this study and others in medically indigent clinic populations show that optimal results are often not obtained. Patients may default from the clinic and never receive a prescription for iron, or the iron preparation may not be procured for financial or other reasons. Other mothers fail to give the medication for the prolonged period required or give it incorrectly. Facilities for making the indicated hematologic determinations are not available in many well-child clinics so that the need for treatment and the response to it cannot be evaluated.

Intramuscular injection of iron-dextran complex is a rapid and effective method for the correction of iron deficiency. Side effects from the use of the material in clinical practice are relatively rare; allergic and febrile responses have been reported in adult patients and staining of the tissues at the site of injection may occur. The use of massive doses in rats has led to siderosis of organs and deposition of ceroid pigment in the tissues (similar to that induced by vita-
min E deficiency; testicular fibrosis and sarcomas at the sites of injection may also occur, but these effects seem to have little bearing on the customary use of the material in clinical circumstances. The injection of 250 mg of iron-dextran in a 2,000-gm premature infant (125 mg/kg), when the infant does not have iron deficiency, may reasonably be expected to lead to some temporary organ siderosis; however, histologic evidence concerning the tissue distribution of intramuscularly injected iron in human infants is lacking. Much of the injected iron is apparently incorporated into hemoglobin later in the first year of life, and it therefore seems most improbable that temporary overloading of this degree could lead to harmful effects in later life. Preliminary studies indicate that the injection of much larger doses of iron-dextran (1,500 mg/kg) into newborn rats results in some siderosis of the liver, spleen, lung and pancreas, but the testes have been unaffected.

The results of the present study are in agreement with other reports and leave no doubt that the iron deficiency anemia of prematurity can be prevented by the prophylactic use of intramuscular injections of iron in the nursery. Of interest was the statistically significant finding that the concentration of hemoglobin was higher in the babies treated with iron-dextran as early as 10 weeks of age, which is in contrast to the results obtained by Smith et al. in full-term babies of a higher socio-economic group. These workers were unable to find evidence that dietary iron was incorporated into circulating hemoglobin before 3 or 4 months of age. The present data and those of others suggest either a) that the iron economy of these premature babies was under stress as early as the second month or b) that the injected iron was used for hemoglobin synthesis in preference to, and earlier than, endogenous sources of iron in storage.

The results in the control group of infants offer ample confirmation of the frequency with which iron deficiency anemia develops in prematurely born babies who do not receive supplemental iron. It has been shown that the circulating hemoglobin mass is reduced in infants born to mothers with severe iron deficiency, and it is probable that this factor accounts in part for the frequency of anemia seen in the present group of infants. There is no experimental evidence that the iron content of the human fetus can be raised above normal by parenteral administration of iron to the mother, although this effect has been demonstrated in the rabbit.

There is a widespread clinical impression that babies with iron deficiency anemia have lowered resistance to infections. A general metabolic disturbance in iron deficiency is reflected in the diminished activity of iron-containing enzyme systems (catalase and cytochrome C) in the tissues of iron deficient animals. Until the advent of a suitable iron preparation for parenteral use, it was impossible to separate the effects of iron deficiency per se from those of poor nutrition and inadequate housing and the accompanying high risk of cross-infection. The number of cases involved is small, but the results of the present study do not show a direct association between infection and poor iron nutrition; iron deficiency does not seem to be a major cause for the high incidence of infections observed in prematurely born infants.

Severe iron deficiency anemia is, nevertheless, a cause for many hospital admissions and outpatient visits; therefore there is justification for the prophylactic use of intramuscular injections of iron in the premature infant while still in the nursery, when oral treatment with iron later in the first year may be difficult to carry out. A dose of 100 mg of iron-dextran may be sufficient to prevent severe degrees of anemia, while minimizing the possible hazards of repeated injections and an excessive load of iron.

This approach should in no way be regarded as a substitute for education of parents in sound dietary principles. It should be emphasized that if anemia should develop in a baby previously treated with intramuscular administration of iron, the
cause of the anemia should be thoroughly investigated. A hemolytic process, blood loss, or some other serious condition are likely possibilities in an infant whose requirements for iron have supposedly been met.

SUMMARY
Iron-dextran was given intramuscularly to 84 small prematurely born babies during their stay in the nursery; 97 similar babies were not so treated and served as controls.

By 8 to 10 weeks of age, values for hemoglobin in the babies who received iron-dextran were significantly higher than in the controls and remained high throughout the first year. Virtually all of the control babies became anemic and hemoglobin levels below 5 gm/100 ml were observed in four infants.

There was no difference in the rate of growth or in the incidence of common infections in the two groups.

It is concluded that intramuscular injections of iron given prophylactically in the nursery will effectively prevent iron-deficiency anemia in premature infants and that this practice has definite clinical applicability. (See Addendum.)

Prevention of iron deficiency anemia does not reduce the high incidence of common infections experienced by prematurely born infants.

Acknowledgment
Our thanks are due to Mrs. Barbara Hunter and the premature nursery staff, and to the nurses of the Dallas City and County Health Departments for their interest and cooperation; also to Genevieve Thompson, Jene Nelson and Frances Anderson for technical assistance.

Addendum
Since this paper was submitted, Imferon has been withdrawn from the market by the manufacturers because of the finding that very large doses have a carcinogenic effect in animals (Editorial: Brit. Med. J., 1:788, March 12, 1960). Whether these results are pertinent to the clinical use of this iron-dextran preparation is not known, and this question raises important ethical and medicolegal problems for future drug-testing programs. No reports of neoplasms complicating injections of iron-dextran in man have yet appeared despite extensive clinical use of this preparation. It is to be hoped that an expert assessment of the accumulated evidence will soon be forthcoming.

In the meantime, intramuscular injection of iron-dextran should not be used for the purpose suggested in this study. It may be repeated here that similar hematologic results can be obtained with oral preparations of iron, provided an adequate treatment program is ensured.

REFERENCES
13. Combes, M. A., Clark, W. K., Gregory,


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