PREVIOUS experience has shown that premature infants are subject to anemia at 6 to 9 months of age and that this anemia is most marked in those infants having the lowest birth weights. It has, furthermore, been demonstrated by one of us (J.A.W.), as well as others, that this late anemia of prematurity responds to oral administration of iron. Since Wallerstein has shown the beneficial effects of intramuscular administration of iron-dextran in the treatment of iron deficiency anemia in full-term infants, the present study was undertaken to evaluate the efficacy of intramuscularly administered iron in the premature.

SUBJECTS AND METHODS

A group of 100 premature infants admitted to the Babies Hospital Premature Unit between September 1957 and July 1958 were studied. Only those infants having a birth weight of less than 1,800 grams were included, and these only if they had not had previous transfusions or complications of a sort that might be conducive to anemia, such as gastrointestinal bleeding, surgical intervention or severe infections. Of the 100 infants started on the program, 20 were lost to follow-up, including 4 patients known to have died. Among the 80 infants who remained in the study, 64 were followed for 9 months or longer.

Consecutive patients received alternately ferrous sulfate, orally, or iron-dextran complex, intramuscularly, beginning at the time the subjects reached a weight of 2,100 grams. Those receiving the ferrous sulfate preparation were given 0.6 ml daily until the age of 2 to 3 months, at which time the dose was doubled. The dosage of iron-dextran was calculated according to a formula as follows:

\[
\text{Desired Hemoglobin} - \text{Present Hemoglobin} \times \frac{100}{\text{Estimated Blood Volume}} \times 0.0034 \times 1.5 \times \text{Blood in ml of Iron}
\]

Although full-term infants at the age of 1 year have a mean hemoglobin level of 11.2 gm/100 ml, in the formula the desired hemoglobin was set at 12.0 gm/100 ml in order not to underestimate the iron dosage that might be required for prophylaxis. The blood volume at 1 year of age was calculated at 80 ml/kg for an assumed body weight of 10.6 kg. The calculated amount was administered intramuscularly by the Z-technique over a period of several consecutive days in a dosage not exceeding 100 mg/day. The largest total dose given was 250 mg.

For evaluation the subjects were divided into three groups according to birth weight: Group I, less than 1,200 grams; Group II, 1,200-1,499 grams; and Group III, 1,500-1,799 grams (Table I). The dosage of intramuscular iron for each weight group is tabulated in Table II.

The following laboratory data were obtained for all patients: Hemoglobin, erythrocyte count, reticulocyte count, and erythrocyte indices. Hemoglobin was determined by a cyanmethemoglobin method in a Coleman spectrophotometer which had been standardized with a specimen of cyanmethemoglobin.

* Skin over injection site is pulled aside gently before injection and thus covers the needle tract when allowed to return to its normal position.
intra
muscular
Iron
Oral
Iron

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg)</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
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<tbody>
<tr>
<td>I</td>
<td>50</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td></td>
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<td></td>
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<td>200</td>
<td>4</td>
<td>2</td>
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</tr>
<tr>
<td></td>
<td>250</td>
<td>1</td>
<td>1</td>
<td>2</td>
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</tbody>
</table>

(continued from the Department of Hematology of the Walter Reed Army Institute of Research in Washington, D.C.). The indices were calculated on a Best Blood Constants Calculator, with specimens for hematocrit determination collected in heparinized capillary tubes and centrifuged 4 to 5 minutes at 10,000 rev/min in an International Hematocrit Centrifuge. The determinations were performed by one technician.

The laboratory tests were performed in the nursery just prior to the start of therapy when the subjects reached a weight of 2,100 grams, and in the Premature Follow-up Clinic at 1 to 2 months after discharge from the nursery, at 6 months, at 9 months and, when possible, also at 1 year of age. The children were evaluated for general health at each visit in an attempt to identify intercurrent conditions which might affect the results. The mothers of patients receiving ferrous sulfate were carefully questioned regarding the amount of medication actually given to the child.

For comparison, the results in the present series of treated infants were contrasted with the findings in a group of untreated infants from the same nursery, who had been studied in 1954 and were of comparable weight. Hematocrits and erythrocyte indices had not been obtained for these untreated subjects.

RESULTS

Because orally prescribed medication is frequently taken irregularly, an attempt was made to determine at each visit how much iron each child actually received. It was found that of the 37 patients who had been started on ferrous sulfate 14 received the medication as outlined, 20 were given some iron during the study period though less than the prescribed amount, and 3 received no iron after discharge from the nursery despite the recommendations. Since one of the purposes of this study was to determine how regularly the oral medication would be given, we retained for evaluation all patients who returned to clinic, even if only for one visit, and even if they did not follow directions fully. In the following figures patients who received ferrous sulfate are designated by three types of lines in accordance with the amount of medication they received: the broken lines represent those who received the prescribed dosage, the solid lines those who received less than the prescribed medication, and the dot-and-dash lines those who to our knowledge received no iron after discharge. Normal values for hemoglobin, erythrocyte count, hematocrit, reticulocyte count or erythrocyte indices at 1 year of age in untreated premature infants for each of the weight groups studied have not been found in the literature. Therefore we have taken the values found in untreated normal full-term infants for comparative purposes in the following paragraphs.

Group I (Fig. 1)

HEMOGLOBIN: The initial hemoglobin concentrations of the study patients were lower than those of the untreated group because the mean age was greater at the time, i.e., 2 months versus 1 month for the un-
treated ones. The mean hemoglobin levels at 9 to 12 months of age were 11.4 gm and 11.5 gm/100 ml, respectively, in the ferrous-sulfate treated and iron-dextran treated groups. In the untreated group the mean hemoglobin was 7.7 gm/100 ml at the same age (Table III). As stated previously, the mean hemoglobin level in full-term infants at 1 year of age is 11.2 gm/100 ml. 

**ERYTHROCYTE COUNTS** Values for erythrocyte counts at 9 to 12 months of age increased to means of 4,690,000 and 4,410,000
TABLE III

<table>
<thead>
<tr>
<th></th>
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<th>Intramuscular Iron</th>
</tr>
</thead>
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<tr>
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<td>7.7</td>
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<tr>
<td>Group II</td>
<td>10.1</td>
<td>10.9</td>
</tr>
<tr>
<td>Group III</td>
<td>9.3</td>
<td>11.0</td>
</tr>
</tbody>
</table>

* From previous study\(^1\) carried out in same nursery.

\(^{1}\) From previous study carried out in same nursery.

\(\text{gm}\) in the ferrous-sulfate treated and iron-dextran treated groups, respectively. The untreated group had a mean erythrocyte count of \(4,100,000/\text{mm}^3\) at 9 to 12 months of age. In full-term infants the mean erythrocyte count is \(4,500,000/\text{mm}^3\) at 1 year of age.\(^7\)

**Hematocrit:** At 9 to 12 months of age, the mean hematocrit was 35.8\% in both treatment groups. The mean hematocrit at 1 year of age in full-term infants is 35\%.\(^7\)

**Group II (Fig. 2)**

**Hemoglobin:** The mean age of the treated groups was 1½ months at the time of the initial hemoglobin determination versus 1 month for the untreated infants. It is of note that a striking early decline of hemoglobin level occurred in the untreated group, which in some cases necessitated eliminating them from further study because they required treatment. This did not occur in the treated group. At 9 to 12 months of age, the mean hemoglobin levels were 10.9 gm/100 ml in the ferrous-sulfate treated group and 9.8 gm/100 ml in the iron-dextran treated group. The hemoglobin level in the untreated group at this age was 10.1 gm/100 ml (Table III); too few untreated infants remained in the study this length of time, however, for the value to be significant. The hemoglobin levels of the iron-dextran treated infants in this weight group did not increase above those of the untreated patients.

**Erythrocyte Count:** At 9 to 12 months of age, the mean erythrocyte counts were 4,310,000 and 4,370,000/mm\(^3\) in the ferrous-sulfate treated and iron-dextran treated groups, respectively. In the untreated group the mean value was 3,820,000/mm\(^3\). Although the hemoglobin levels of the iron-dextran treated infants in this weight group did not increase above those of the untreated group, the erythrocyte counts did.

**Hematocrit:** The mean hematocrit value was 33.3\% in the ferrous-sulfate treated group and 31.5\% in the iron-dextran treated group. Like the hemoglobin levels in this weight group, the hematocrit values were not as high as those achieved in infants of lower birth weight.

**Group III (Fig. 3)**

**Hemoglobin:** The initial values in the untreated patients were lower because these infants were slightly older than the treated patients at first comparison, i.e., 4 weeks versus 3 weeks. In the ferrous-sulfate treated group the mean hemoglobin level at 9 to 12 months of age was 11.0 gm/100 ml and in the iron-dextran treated group it was 11.4 gm/100 ml. The mean hemoglobin level in the untreated group was 9.3 gm/100 ml (Table III), but the number of untreated infants was again too small to be of value. Unlike Group II, the hemoglobin levels in this weight group were comparable to those in Group I as well as to those of normal 1-year-old infants.

**Erythrocyte Count:** At 9 to 12 months of age, the mean erythrocyte counts were 4,490,000 and 4,420,000/mm\(^3\) in the ferrous-sulfate treated and iron-dextran treated groups, respectively. In the untreated infants at this age the mean value was 4,000,000/mm\(^3\).

**Hematocrit:** The mean hematocrit in the ferrous-sulfate treated group was 35.8\% and in the iron-dextran treated group was 35.0\%.

**Reticulocytes (Fig. 4)**

The reticulocyte response was similar in all three weight groups and with both treatment regimens. It is of interest that the untreated groups maintained consistently higher reticulocyte levels throughout.
the study period, presumably a reflection of lower hemoglobin levels. The initial reticulocyte levels in all groups probably represent the second physiologic peak seen in prematures.\textsuperscript{1}

**Erythrocyte Indices (Figs. 5-7)**

**Mean Corpuscular Volume (MCV):**

The mean value at 1 year of age is 78 \( \mu^3 \) (cubic microns) in full-term infants.\textsuperscript{7} The patients in the ferrous-sulfate treated group
had a mean MCV of 77.7 µ and in the iron-dextran treated group a mean of 78.5 µ, at 9 to 12 months of age.

**Mean Corpuscular Hemoglobin (MCH):** In full-term infants the mean MCH at 1 year of age is 25 µ (micromicrograms). At 9 to 12 months of age, the patients who received ferrous sulfate had a mean of 24.9 µ and those who received iron-dextran a mean of 24.8 µ.
Mean Corpuscular Hemoglobin Concentration (MCHC): A mean value of 32% for MCHC is found in full-term infants at 1 year of age. The infants in the ferrous-sulfate treated group had a mean MCHC of 31.9% and those in the iron-dextran treated group a mean of 31.5%.

Discussion
The results of this study indicate that...
intramuscular administration of iron-dextran has as good an effect in preventing the late anemia of prematurity as does oral administration of ferrous sulfate. Hemoglobin levels at 1 year of age in iron-dextran treated patients in Groups I and III were equivalent to hemoglobin levels found at this age in full-term infants and in ferrous-sulfate treated patients in this study, but well above those observed in untreated pre-
mature infants. Only in Group II was this goal not reached by iron-dextran treated infants. In this weight group hemoglobin levels were relatively high at the time a weight of 2,100 gm was reached, as compared to infants in Group I. As compared to infants in Group III, whose hemoglobin levels were also high at the time a weight of 2,100 gm was reached, the rate of growth was considerably more rapid in Group II.
Because of these circumstances, it is likely that the formula utilized for calculation of the total amount of intramuscular iron failed only in Group II to provide a sufficient amount of iron for complete prophylaxis. This may explain why a Negro infant in this weight group, who had a hemoglobin level at 9 months of 6.8 gm/100 ml, subsequently responded to additional iron given orally.
It is of considerable interest that the hemoglobin levels of those infants given iron by mouth irregularly, as a result of failure to follow instructions, were comparable to those of infants given the prescribed amount and to those achieved by intramuscular administration of iron. Although the need for iron therapy to prevent the late anemia of prematurity is established, this observation suggests that the amount of iron prescribed orally for prophylaxis in this study is greater than that actually required.

No untoward side effects were experienced to the administration of iron-dextran in the manner described, and there was no evidence of toxicity. In a study reported by Richmond, rats receiving iron-dextran weekly over a period of many months in amounts equivalent to 200 to 300 times the dose used in humans, subsequently developed sarcoma of muscle at the injection site in a high percentage of cases. Although this report is disturbing, we have found no evidence of adverse effect after 1 year in the present series of treated patients who received a much smaller dosage.

In the past, we have encountered considerable difficulty in obtaining good cooperation in carrying out instructions concerning oral use of iron therapy after discharge of the infants from the nursery. These difficulties have been associated with language barriers, economic factors and, in many cases, lack of understanding or indifference. Despite the fact that the present study gives evidence that the amount of iron prescribed orally may be more than is needed to achieve the desired results, there have been many instances where the deviations from prescribed treatment were so gross that anemia has resulted. We are fully in accord with those who are attempting to correct this deficiency by providing better educational programs and facilities for infant care. Nevertheless, at the present time, because of our past experience, we advocate intramuscular administration of iron therapy in those groups where it is anticipated that oral form of iron will not be given. When it is probable that patients will be seen regularly and instructions followed, iron should be given orally because the danger of over-dosage is less likely to occur via this route. Moreover, although the present study has not shown any side effects from intramuscular use of iron-dextran, the occurrence of sarcomas in rats as well as reports of hypersensitivity reactions of a local or systemic nature in humans would contraindicate the intramuscular use of iron except in the special circumstances already outlined. The present study shows that intramuscular administration of iron is effective in the prevention of the late anemia of prematurity—not that it is the most desirable treatment. Further investigation of possible toxic effects of intramuscular administration of iron-dextran is required before widespread use can be considered.

CONCLUSIONS

Intramuscular administration of iron, given at the time a weight of 2,100 grams is reached, is as effective as oral use of iron in the treatment of the late anemia of prematurity.

No toxicity or untoward side effects were noted when iron was given intramuscularly in the manner and dosage described.

Intramuscular administration of iron is preferred when follow-up of infants after discharge from the nursery is difficult. Where follow-up is assured, orally administered iron remains the treatment of choice. (See Addendum.)

Acknowledgment

We gratefully acknowledge the technical assistance of Mrs. Geraldine Adams and the follow-up of patients by Mrs. Judith Cohen. We also wish to thank Dr. Memee King, as well as Miss Priscilla Parke and her staff in the Premature Nursery, for their kind cooperation.

Addendum

Since this article was accepted for publication Imferon has been withdrawn from the
market by the Lakeside Laboratories. Although no further experimental data have been forthcoming relative to the toxicity of Imferon in animals, we have discontinued, at least temporarily, further use of this drug in the Premature Nursery.

REFERENCES

COMPARISON OF ORAL AND INTRAMUSCULAR ADMINISTRATION OF IRON FOR PREVENTION OF THE LATE ANEMIA OF PREMATURE INFANTS
Anneliese L. Sitarz, James A. Wolff and Frederick H. Von Hofe

Pediatrics 1960;26;375

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