The Immediate Hematologic Effects of Intravenous Saccharated Iron Oxide

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It has long been recognized that the level of leukocytes circulating in the peripheral blood is capable of large and rapid fluctuations. Recently, Brown et al. noted that the intravenous injection of saccharated iron oxide is followed by a sudden profound leukopenia. As their studies were directed to the effects of such injections on hemoglobin, this leukopenia was not further characterized. Because of the interest in rapid changes in the leukocyte number of the peripheral blood this phenomenon was investigated to determine the locus and modus operandi of the leukopenia.

SUBJECTS AND METHODS

Saccharated iron oxide was administered intravenously on 17 occasions to 13 patients all of whom had neoplastic diseases, usually with widespread metastatic involvement. The iron preparations employed were stable colloidal suspensions of saccharated ferric oxide,* at pH 11, containing 20 mg. of elemental iron per ml. Single doses of 100 to 1,000 mg. were administered at rates which varied from 100 to 2,000 mg. per minute.

Blood samples were taken simultaneously from artery and vein, every 30 seconds for the first 5 minutes, and every minute for the next 5 to 55 minutes. In four studies venous blood was obtained through an intracardiac catheter; in 1 instance from the pulmonary conus, in 1 from the right ventricle, and in 2 patients from the inferior vena cava. In the remaining cases venous samples were taken through a large bore needle, clearly implanted within a large peripheral vein without the use of a tourniquet. The arterial samples were drawn through an indwelling needle in the femoral artery. The venous blood was drawn by syringes, and the arterial samples were collected directly into chemically clean glass tubes, with heparin added as the anticoagulant. In 3 preliminary cases finger blood was studied.

All counts were completed as rapidly as possible. National Bureau of Standards certified Trenner automatic filling pipets and certified hemocytometers were used exclusively. Platelet counts were determined by the direct method using Tocantin's solution. Confirming duplicate chambers and other scrupulously careful counting techniques previously described were again employed. At least 600 cells were counted for each determination computing the average of confirming duplicate chambers. In counts between 5,000 to 10,000 per cu.mm., counting all nine squares on each of two chambers from a single pipet, the 70 per cent confidence limits of the value obtained are ±8.5 per cent. This ignores the added significance of serial results.

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* Kindly supplied by Smith, Kline and French as Feojectin through the courtesy of Dr. Edward B. MacLean, and as Ferr-Ox by the Merrell Co., through the courtesy of Dr. R. C. Pogge.
<table>
<thead>
<tr>
<th>Patient data</th>
<th>Diagnosis</th>
<th>FeO₂ rate mg./min.</th>
<th>Injected total mg.</th>
<th>Sampling site*</th>
<th>Leukocyte count per cu.mm.</th>
<th>Onset of leukopenia</th>
<th>Time of nadir from onset of injection</th>
<th>Duration of leukopenia</th>
<th>% fall in WBC</th>
<th>Remarks</th>
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</thead>
<tbody>
<tr>
<td>ISB</td>
<td>Careinoma Colon</td>
<td>200</td>
<td>100</td>
<td>BV</td>
<td>6,400</td>
<td>N.C.</td>
<td>-</td>
<td>-</td>
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<td>% 53</td>
<td></td>
<td></td>
<td></td>
<td>FA</td>
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<td>150</td>
<td>IV</td>
<td>2,500</td>
<td>N.C.</td>
<td>-</td>
<td>-</td>
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<td></td>
<td>FA</td>
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<td>100</td>
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<td>200</td>
<td>IVC</td>
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<td>4,200</td>
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<td>4 1/2 min.</td>
<td>8 1/2 min. +</td>
<td>Specimens taken for 10 min. Counts low at last Specimens</td>
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<td>% 44</td>
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<td></td>
<td></td>
<td>FA</td>
<td>6,900</td>
<td>4,600</td>
<td>90 sec.</td>
<td>4 min.</td>
<td>9 min. +</td>
<td>Specimens at 0, 30, 120 and 300 sec. only</td>
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<td>FA</td>
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<td>RV</td>
<td>FA</td>
<td>RV</td>
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<td>800</td>
<td>15,500</td>
<td>14,100</td>
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<td>?</td>
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<td>6,000</td>
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<td>920</td>
<td>90 sec.</td>
<td>60 sec.</td>
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<td>26,800</td>
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<td>?</td>
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<td>?</td>
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* Sampling Site Code
  - FA—Femoral artery
  - BV—Basilic vein
  - IV—Innominate vein
  - IVC—Inferior vena cava
  - RV—Rt. ventricle
  - PC—Pulmonary conus

† N.C. = no change
EFFECTS OF INTRAVENOUS SACCHARATED IRON OXIDE

Results

No fall in leukocyte count occurred in 3 patients who received 100, 100 and 150 mg. of iron (table 1). In 14 studies in which 200 mg. or more of iron was given, a significant decrease in the leukocyte number, which varied from 35 to 85 per cent of the original level, was observed. The developing leukopenia was first manifest on the arterial side of the pulmonary circulation, and was followed 30 to 90 seconds later by a similar leukopenia in the venous blood (fig. 1). The onset of the leukopenia occurred within 30 seconds to 5 minutes, and the nadir of the fall was reached in 3 to 20 minutes after the start of the injection (table 1, fig. 2). Although the rate, magnitude and duration of the leukocyte depression bore no relationship to the rate of administration of the material, there was a definite correlation with the total amount of iron injected (fig. 3).

Serial differential leukocyte counts showed no significant change in those patients in whom no leukopenia was observed. The leukopenia was not confined exclusively to one cell type in any patient in whom a leukocyte fall was observed. In the nonleukemic patients the fall was predominately in the granulocytic series (fig. 3). In 2 patients with lymphatic leukemia the few remaining granulocytes disappeared simultaneously with a considerable fall in absolute lymphocyte number within 5 minutes after the injection of iron. In patient JOH, who had monocytic leukemia, the induced leukopenia was equally divided between granulocytes, lymphocytes and monocytes, so that a 45 per cent fall in the leukocyte number produced essentially no change in the differential count.

No significant change in the platelet counts occurred in 4 patients who developed a leukopenia. There was no change in the hematocrit level of serial samples of blood in 1 case in which it was measured, although there was a very significant fall in the leukocyte count.

![Graph](image-url)
In the patients whose venous specimens were drawn through catheters in the pulmonary artery or right ventricle, i.e. directly downstream in the vascular channel from the site of injection of the iron, clotting of the venous samples occurred during the period of injection of iron. Immediately after completion of the injection clotting was no longer noted (fig. 4). Arterial specimens drawn

Fig. 2.—Greater fluctuation in counts, and rise in arterial number between 5 and 10 minutes. Arterial fall in leukocytes is again faster and of greater magnitude than venous.

Fig. 3.—Direct comparison of dose-response in same patient on same day. Large dose produced greater fall in leukocyte count although rate of administration was identical. Comparison of differentials shows fall to be predominately in granulocytic series. Venous specimens drawn from inferior vena cava through catheter.
simultaneously did not clot. In two cases in which the tip of the catheter was out of the direct stream of the iron-containing blood, i.e. in the inferior vena cava, there was no cloting in any of the specimens (fig. 3). The addition of 20 mg. of saccharated iron oxide to 5 ml. of blood in vitro showed no alteration in the clotting time.

There were no serious reactions to the injection of these preparations of saccharated iron oxide despite the massive doses and rapid injection. All patients who received more than 200 mg. of iron experienced slight to severe cutaneous flushing. Some complained of moderate abdominal and muscle cramps. One patient developed a transient syncope, which lasted 60 seconds. In 3 other patients a transient hypotension was noted.

**JOH 25· MONOCYTIC LEUKEMIA**

![Graph showing leukocyte count over time](image)

**Fig. 4.**—Injection of iron from 0 to 4 minutes. Note clotting of all venous specimens during iron injection, not immediately after its termination. Such clotting did not take place in venous samples taken peripherally or when catheter tip was out of direct stream of iron.

**DISCUSSION**

The time sequence of the leukopenia which was observed indicated that the major immediate site of disappearance of the leukocytes was the pulmonary vascular system. In every instance in which a fall was observed it occurred first, and usually most markedly, in the arterial blood. The transient nature of the leukopenia suggested temporary sequestration of these cells in the pulmonary circulation. Following the cessation of the leukopenic stimulus it is probable that many of the same cells were returned to the circulation from the lungs. The higher leukocyte counts in the arterial blood during the recovery from leukopenia support this hypothesis.

It is unlikely that the pH of the material or its chemical nature were responsible for the drop in the leukocyte count. Other colloidal substances have been found to produce the same phenomenon. The colloidal nature of the iron preparation would therefore seem to be involved in the genesis of the leukopenia.

It is uncertain what role vasodilatation plays in the production of iron-incited
leukopenia. All patients who received large amounts of iron showed evidences of vasodilatation. Vejlens\textsuperscript{4} has shown that vasodilatation will decrease the leukocyte count of specimens of blood taken distal to the site of dilatation, presumably due to increased margination of the leukocytes, particularly the granulocytes.

Tait and Elvidge\textsuperscript{5} have reported an increased coagulability of blood in animals after the intravenous injection of colloidal materials. In two of these studies the clotting power of the venous blood containing the highest initial level of iron was markedly increased. No change in platelets was observed. Essex and Grana\textsuperscript{6} have shown by direct observations on vessels in situ in the rabbit's ear that the intravenous injection of colloidal materials such as gelatin and dextran produced marked clumping of leukocytes. At the same time they found a fall in the level of circulating white cells in the blood taken distal to the site of clumping. Vejlens\textsuperscript{4} reported similar results using gelatin and fibrinogen. The leukocytic reaction following the injection of colloidal saccharated iron appears to be the same, and it is plausible to suggest that a similar mechanism may be in operation.

**SUMMARY AND CONCLUSIONS**

1. Saccharated ferric oxide in colloidal suspension was administered intravenously on 17 occasions to 13 patients in doses of 100 to 1,000 mg. A prompt arterial leukopenia, followed within 30 to 90 seconds by a similar fall in the venous blood, was observed in all patients who received more than 200 mg. of iron. This leukopenia involved all white cell types.

2. The magnitude of the fall in leukocytes was directly proportional to the amount of material injected, and independent of the rate of injection under the conditions of the study.

3. There was no significant change in the platelet number in arterial or venous blood of 4 patients. In 2 patients an increased clotting power of venous blood containing large amounts of iron was observed only during the period of injection.

4. The colloidal nature of the material is probably the responsible factor in producing the leukopenia.

**REFERENCES**


\textsuperscript{5} Tait, J. and Elvidge, A. R.: Effect upon platelets and on blood coagulation of injecting foreign particles into the blood stream. J. Physiol. 68: 129-144, 1926.

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