THE TREATMENT OF IRON DEFICIENCY*

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Table 1
ORAL IRON COMPOUNDS

<table>
<thead>
<tr>
<th>Author</th>
<th>Compound</th>
<th>Effective Dose</th>
<th>Utilisation %</th>
<th>Daily Haemoglobin Rise</th>
<th>Toleration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witts (1936) (Witts 1931, 1933; Heath, 1933; Fullerton, 1934.)</td>
<td>Iron and ammonium citrate.</td>
<td>4.0–8.0 gm. (800–1,000 mg.) Fe.</td>
<td>1.5–3.0</td>
<td>Approx. 1%</td>
<td>Intolerance rare.</td>
</tr>
<tr>
<td></td>
<td>Ferrous sulphate</td>
<td>0.6 gm. (180 mg. Fe)</td>
<td>14–15.7</td>
<td>Approx. 1%</td>
<td></td>
</tr>
<tr>
<td>Reznikoff and Goebel, 1937 Haler, 1952</td>
<td>Ferrous gluconate Ditto</td>
<td>108 mg. Fe</td>
<td>17.2–37.5</td>
<td>1.2–1.5%</td>
<td>? None</td>
</tr>
<tr>
<td>Gillhespy, 1955</td>
<td>Ferrous succinate</td>
<td>105 mg. Fe</td>
<td>Max. 40</td>
<td>1.2%</td>
<td>1 in 150 intolerant</td>
</tr>
<tr>
<td></td>
<td>Iron choline citrate</td>
<td>160 mg. Fe</td>
<td>16.7</td>
<td>0.16 g.</td>
<td>4.6% intol.</td>
</tr>
</tbody>
</table>

Many new iron preparations have been and are being introduced on the market for the treatment of anaemia. Each of these is accompanied by the support of intensive advertising. Under these circumstances there is a danger of confusion as to the true value of these compounds. In order to obtain a clear picture of the situation one must look at the published work of the past.

In 1936 Witts published his paper on the therapeutic action of iron in which was embodied all the recent work of that time (Heath, 1933; Fullerton, 1934; Witts, 1931; 1933). The dose of the different iron compounds required for effective treatment of iron deficiency had only then become accurately known. The effective therapeutic amounts of ferrous sulphate, and iron and ammonium citrate are shown in Table 1. These two compounds remain today perfectly satisfactory in the treatment of iron deficiency. As was pointed out by Witts, these compounds, and others such as ferrous lactate, ferrous chloride, ferric hydroxide, and Blaud's pill, are all capable of causing regeneration of haemoglobin at the rate of 1 per cent. (0.15 g.) per day when effective doses are used. It was considered then, and has been since confirmed (Goetsch et al., 1946), who used massive doses of intravenous iron, that a rise of above 2 per cent. (or 0.3 g.) haemoglobin per day is very rarely attained when treating iron deficiency anaemia.

In 1937, Reznikoff and Goebel introduced ferrous gluconate (Table 1), and they claimed satisfactory results with this compound. The next study in English literature on this preparation appears to have been that by Haler in 1952, who believed it superior to inorganic compounds of iron. Ferrous succinate, introduced in 1955, produces a somewhat similar haematological response though it is claimed that utilisation is greater.

The paper by O’Sullivan, Higgins and Wilkinson

in 1955, seems to be the most reliable work of recent years on the comparative value of different oral iron compounds. Their results are given briefly in Table I and it can be seen that when identical doses of elemental iron are used there is no appreciable difference in the rate of haemoglobin regeneration.

However, the commercial race continues and now attention has turned from the organic compounds of iron to the chelated compounds. This is despite the original papers on the action of an iron chelate, ferric sodium ethylene-diamine tetra-acetic acid, in iron deficiency anaemia, where it was clearly shown that there was no greater absorption of iron with it than with similar doses of ferrous sulphate (Seeberg et al., 1954; Will and Vilter, 1954).

This year Franklin et al. (1958), published results using the chelated compound, iron choline citrate, and the results are almost exactly the same as with all other recognised compounds.

To turn from consideration of the various oral iron compounds to the practical problem of iron deficiency of the present day, it seems that severe iron deficiency is becoming rarer. Furthermore it is being emphasised in recent years that iron deficiency is rarely 'idiopathic' and that it is usually the result of occult bleeding recently or in the past. However, iron deficiency anaemia remains predominantly a disease of women during their reproductive life, and it is in the attendance at a maternity hospital or antenatal clinic that cases of iron deficiency will be found in the greatest numbers. Figure 1 shows the situation at the Rotunda Hospital, Dublin where the author has been one of those concerned in managing the iron deficiency problem over the past five years. This shows the approximate numbers we deal with each year, and what proportions are treated with oral and parenteral iron. A similarly high incidence of iron deficiency may be present in various centres in Britain. Within the last 15 months the incidence of anaemia in pregnancy at the City General Hospital, Stoke-on-Trent, was 16.5 per cent. (below 9.5 g.) (C. Giles, 1958).

Table 2 shows the results we have obtained in pregnancy with different iron compounds. The results are much the same except with regard to tolerance. These figures suggest that the tolerance rate is proportional to the amount of elemental iron in the preparation. Nevertheless from the study of O'Sullivan et al. (1955), where the same amount of elemental iron was present in each compound tested, intolerance was still considerably greater with ferrous sulphate than with ferrous gluconate or succinate.

Table 3 shows the haemoglobin response to ferrous gluconate and ferrous succinate in more detail. Here the dosages used are virtually the same. Note that the haemoglobin rise is greater when the initial level is low.

If iron preparations in effective dosage all produce a similar haematological response, then only cost and tolerability remain questions of importance. Intolerance to oral iron in pregnancy has received considerable attention in recent years and the results are very different (Table 4). It was Benstead and Theobald in 1952 who particularly raised the problem by stating that 30 to 40 per cent. of pregnant women could not
Tolerate ferrous sulphate. At the time of their paper, Girdwood in a letter stated that from experiments he had conducted he believed intolerance was largely psychological and often depended on the colour of the tablets, and in fact despite the evidence largely to the contrary (Fisher and Biggs, 1955; Gatenby and Lillie, 1955), Edgar and Rice (1956) reported only 5 per cent. intolerance to ferrous sulphate when using white tablets. This is of importance from the financial aspect as ferrous sulphate remains the cheapest of the ferrous compounds on the market.

**Parenteral Iron**

The indications for giving iron by injection are listed below:

1. Intolerance to oral iron particularly in pregnancy.
2. Gastrointestinal disorders e.g., ulcerative colitis.
3. Inability to absorb iron. Steatorrhoea.
4. Anaemia associated with rheumatoid arthritis.
5. Replenishment of iron stores in recurrent anaemia.

Of these, persistent intolerance to oral iron in pregnancy is probably the most important. Coleman et al. (1955) state that in iron deficiency many months of oral iron therapy are required to replenish tissue iron stores after blood values have been returned to normal. If this is accepted, iron by injection should, in theory anyway, be given in

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### Table 2
**Comparison of Ferrous Compounds in Pregnancy**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tablet Dosage</th>
<th>Available Daily Fe</th>
<th>Range of Hb. Rise from 24-36 Weeks' Gestation</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulphate</td>
<td>6 x 200 mg.</td>
<td>420 mg.</td>
<td>Initial values being 8.0—8.9 1.6—4.0, Average 2.4 (13 cases)</td>
<td>46% (207 cases)</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>6 x 300 mg.</td>
<td>204 mg.</td>
<td>1.8—3.9, Average 2.6 (13 cases)</td>
<td>84% (109 cases)</td>
</tr>
<tr>
<td>Ferrous succinate</td>
<td>6 x 150 mg.</td>
<td>210 mg.</td>
<td>1.6—4.8, Average 3.0 (9 cases)</td>
<td>69% (74 cases)</td>
</tr>
</tbody>
</table>

### Table 3
**Comparison of Ferrous Gluconate and Ferrous Succinate in Pregnancy**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tablet Dosage</th>
<th>Available Daily Fe</th>
<th>Range of Hb. Rise from 24-36 Weeks' Gestation</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous Gluconate</td>
<td>6 x 300 mg. (204 mg. Fe) Daily dose</td>
<td>7.0—7.9</td>
<td>8.0—8.9</td>
<td>9.0—9.9</td>
</tr>
<tr>
<td>Ferrous Succinate</td>
<td>6 x 150 mg. (210 mg. Fe) Daily dose</td>
<td>7.0—7.9</td>
<td>8.0—8.9</td>
<td>9.0—9.9</td>
</tr>
</tbody>
</table>

### Table 4
**Toleration to Oral Iron Compounds in Pregnancy**

<table>
<thead>
<tr>
<th>Author</th>
<th>Compound</th>
<th>Iron Compound Daily Dose</th>
<th>Intolerance Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benstead and Theobald (1952)</td>
<td>Ferrous sulphate Mol-iron</td>
<td>6 x 200 mg.</td>
<td>30—40% 15%</td>
</tr>
<tr>
<td>Fisher and Biggs (1955)</td>
<td>Ferrous sulphate Ferrous sulphate and Vitamin C</td>
<td>3 x 200 mg.</td>
<td>Approx. 50% Better tolerated</td>
</tr>
<tr>
<td>Gatenby and Lillie (1955)</td>
<td>Ferrous sulphate Mol-iron Ferrous gluconate</td>
<td>6 x 200 mg. 6 x 195 mg. 6 x 300 mg.</td>
<td>48% 41% 8%</td>
</tr>
<tr>
<td>Edgar and Rice (1956)</td>
<td>Ferrous sulphate (white)</td>
<td>3 x 200 mg.</td>
<td>5.6%</td>
</tr>
</tbody>
</table>
virtually all cases of iron deficiency where there is a possibility of relapse to the anaemic state. Obviously to incorporate this idea in to practice would surely encourage unnecessary treatment with parenteral iron and would only increase the growing habit of giving indiscriminate iron injections where there is no clear indication for them. Figure 2 shows a rare type of problem when parenteral iron was repeatedly successful and oral iron totally useless. This was a case with ulcerative colitis.

Scott and Govan (1954), Jennison and Ellis (1954), and Scott (1956) have all studied the use of 'imferon' in iron deficiency anaemia of pregnancy.
and they all concluded that this preparation produces results comparable to those found with ‘ferrivenin,’ though the initial effect may be somewhat slower. It seems generally accepted that intramuscular iron should be used in place of intravenous iron because of greater convenience in administration and a reduction in the tendency to reactions. Nevertheless at the Rotunda we have tended to revert to the use of ferrivenin because it was found that imferon was sometimes unsatisfactorily slow and we disliked the staining of the tissues. Figure 3 shows the results in two similar groups of cases treated with ferrivenin and imferon respectively. It can be seen that there is little difference in response rate except that imferon is somewhat slower in its effect. It seemed that a more rapid response with imferon would be obtained by using this preparation intravenously. Also one should require fewer injections as imferon is two and a half times more concentrated form of iron than ferrivenin.

Figure 4 shows the results of a trial in non-pregnant cases where ferrivenin, imferon intramuscularly, and imferon intravenously are compared. Note that the time saved in using parenteral iron instead of oral iron is only two to three weeks. The interrupted line in Figure 4 indicates a rise in haemoglobin at the rate of 1 per cent. daily, which is the usual response to be expected with oral iron. There is no great difference in response between the different parenteral methods and the only advantage might be in the fewer injections required with imferon intravenously. However, in view of the increased likelihood of reactions with intravenous injections it seems that imferon intramuscularly will remain the parenteral treatment of choice. On the other hand reactions to intravenous iron therapy are very rare, when care is taken in administration, and when this mode of treatment is used only in cases of marked iron deficiency.

**Conclusion**

The newer oral iron compounds have little or no advantage over the cheaper ferrous sulphate as regards haematological response in iron deficiency anaemia. They are often better tolerated and this is of particular value in pregnancy. Psychological factors may be important in producing nausea and vomiting.

The indications for giving iron by injection are limited but it is particularly valuable for severe iron deficiency in late pregnancy when there is troublesome intolerance to oral iron.

**ADDENDUM**

Since this article was submitted for publication two important contributions to this subject have been published by Kerr and Davidson (1958). They have found no difference between ferrous sulphate and ferrous gluconate, as regards gastrointestinal side-effects, in a most carefully controlled trial. They conclude from their studies that intolerance to oral iron preparations is ‘mainly psychological in origin.’ Their observations were made in pregnant women with initial haemoglobin values between 10.4 g. per 100 ml. and above, and in a series of 93 nurses with initial haemoglobin ranging from 11.7 to 15.5 g. per 100 ml. One of these cases was suffering from only mild degrees of anaemia and intolerance to oral iron appears more common in severe degrees of anaemia with which the present paper is largely concerned.

*Bibliography continued on page 23*
femoral vein. A stripper is passed along it from the ankle.

In recurrent long saphenous vein incompetence, exposure of the sapheno-femoral junction is difficult, due to scar tissue, and the mass of veins which follow an incomplete procedure. These can be avoided if the femoral sheath is opened at Poupart's ligament and the femoral vein traced down to the sapheno-femoral union, where the long saphenous vein is terminally secured beneath the cicatrix of the previous procedure.

Hunter's canal is opened through a separate incision, and the varicose communicating veins are divided as described.

Other Incompetent Veins

These may be ankle communicating veins, or the short saphenous vein with other varicose tributaries of the popliteal vein. The ankle veins are divided immediately after the Hunter's canal veins, but the short saphenous vein is done two to three days later. The writer is reluctant to undertake two major vein procedures at one operation session because of the danger of thrombosis and a breach in asepsis.

Conclusion

Varicose communicating veins passing into the superficial femoral vein through Hunter's canal are described. They are often missed in diagnosing varicose veins, and are a cause of persistent varices after operation. They contribute to eczema and ulceration at the ankle. The diagnosis and treatment are detailed.

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