The mechanism of the rise in the urinary white-cell excretion in these cases is of interest. Perhaps the most important point is the urinary excretion of about 33% of injected iron-sorbitol within a few hours. Wöhler (1962) has demonstrated in experimental animals that the iron-sorbitol complex crosses Bowman's capsule of the glomerulus, presumably because of the low molecular weight of the complex—namely, 5,000. Furthermore, this author has also shown that iron has a predisposition to localize in areas of infection. These findings may explain the provocation of white-cell excretion after iron-sorbitol in patients with a chronic infection of the urinary tract.

The results raise two questions. Firstly, is the intramuscular injection of iron-sorbitol an effective agent, comparable to intravenous pyrogen or prednisolone, in the diagnosis of latent states of chronic urinary infection? The fact that a significant rise, over 100%, in the urinary white-cell excretion occurred in seven out of nine cases suggests that this method is worthy of further consideration. In addition, iron-sorbitol is administered intramuscularly and, unlike pyrogen, no side-reactions occurred in any case.

A second question of importance is the relevance of these findings to the possible provocation of infection of the urinary tract after iron-sorbitol injections. This was noted by Scott (1962), although she could cite only a single patient. There was, however, no clinical deterioration in any of the present cases; nor was there evidence of an increase in the bacterial count. Furthermore, Walquist (1962) failed to find deterioration of renal function in patients with chronic renal disease given iron-sorbitol. Nevertheless, the fact that a significant urinary cellular increase was obtained in the majority of patients suggests that the association of an iron-sorbitol injection with a urinary infection noted by Scott (1962) was not entirely fortuitous. For this reason it may be a wise precaution to avoid the use of iron-sorbitol in patients with an active infection of the urinary tract.

Summary

The urinary white-cell excretion rate after the intramuscular injection of iron-sorbitol-citric-acid complex ("jectofer") was observed in 10 healthy subjects, in 9 patients with chronic infection of the urinary tract, and in 5 patients with other renal diseases. The white-cell excretion rate rose by more than 100% in seven of the nine patients, with infection of the urinary tract, while there was no significant rise in the other two groups.

This observation may be explained by the urinary excretion of iron-sorbitol to an extent of one-third of the intramuscular dose, as well as the known predisposition of iron to localize in infected tissues.

Iron-sorbitol, used in this way, may be of value in the diagnosis of chronic infection of the urinary tract.

A single case has been previously reported in which the injection of iron-sorbitol may have provoked an infection of the urinary tract.

For these reasons it is suggested that iron-sorbitol should not be administered to patients with an active urinary infection.

We would like to thank Dr. J. McGeachie for carrying out the bacterial counts.

Addendum

Since this paper was written the urinary white-cell excretion after the intramuscular injection of iron-sorbitol

has been studied in a further group of 33 patients. Twelve suffered from non-infective renal disease and in 11 of these there was no significant alteration in the white-cell excretion after the injection. The one patient who showed a rise in white-cell excretion of more than 100% after the injection had the clinical features typical of focal glomerulonephritis.

The remaining 21 patients had proved infection of the urinary tract of whom three were on treatment at the time of the test. In 13 patients the white-cell excretion rate rose by more than 100% after the injection, while in eight there was no significant alteration. Two of these eight patients were on treatment at the time of the test.

Of the 30 patients therefore in the complete series with proved infection of the urinary tract 20 showed a rise of more than 100% in the urinary white-cell excretion rate after the intramuscular injection of iron-sorbitol. In none of these additional patients was there any evidence of untoward effects from administration of the iron.

REFERENCES

- Little, P. J., and de Wardener, H. E. (1962). *Lancet*, **1**, 1145.
 McGeachie, J., and Kennedy, A. C. (1963). *J. clin. Path.*, **16**, 32.
 Pears, M. A., and Houghton, B. J. (1958). *Lancet*, **2**, 128.
 — (1959). *Ibid.*, **2**, 1167.
 Pringle, A., Goldberg, A., Macdonald, E., and Johnston, S. (1962). *Ibid.*, **2**, 749.
 Scott, Jean M. (1962). *Brit. med. J.*, **2**, 480.
 Wahlquist, S. (1962). Symposium on Jectofer organized by Astra Pharmaceutical Products Inc. September, 1962, at Worcester, Mass., U.S.A.
 Wetherley-Mein, G., Buchanan, J. G., Glass, U. H., and Pearce, L. C. (1962). *Brit. med. J.*, **1**, 1796.
 Wöhler, F. (1962). Symposium on Jectofer organized by Astra Pharmaceutical Products Inc. September, 1962, at Worcester, Mass., U.S.A.

IRON-SORBITOL-CITRATE IN PREGNANCY ANAEMIA

BY

JEAN M. SCOTT, M.D.

Research Department, Glasgow Royal Maternity Hospital

During pregnancy parenteral-iron therapy is invaluable in the treatment of iron-deficiency anaemia, especially in patients near term. Thus when Richmond (1959, 1960) and Haddow and Horning (1960) published their findings on the induction of sarcoma at injection sites in rats and mice after massive doses of iron dextran ("imferon") it was natural that other intramuscular preparations should be sought, no matter how remote the clinical application of these animal experiments. Iron-sorbitol-citric-acid complex ("jectofer") appeared to be a suitable alternative, and it had already been used to advantage in non-pregnant patients (Andersson, 1961) when the present trial was undertaken.

Materials and Methods

The majority of patients reviewed received treatment at the antenatal blood clinic, held thrice weekly. At their first visit a full blood count, including reticulocytes, was made and blood films and buffy coats were screened. The marrow was also examined in some patients. Haemoglobin estimations were made on an EEL colorimeter, and reticulocyte counts were done daily in hospital patients or at each clinic visit in the others. Repeat blood counts were carried out at weekly intervals.

This regime was the same as that adopted in an earlier trial with imferon (Scott, 1956) except that less iron could be administered with each injection, as the recommended

dose for jectofer was only 100 mg. compared with 250 mg. for imferon. Treatment therefore took longer, and since it was felt that this might affect the rate of haemoglobin regeneration a smaller number of patients, mainly those nearer term, were admitted to the antenatal wards and given daily injections. This seemed preferable to changing clinic procedures and asking patients to report each day.

Dosage requirements were based on the results of the earlier imferon trial, where it was found that 100 mg. of iron raised the haemoglobin by 0.3 g./100 ml. on the average, and each patient was given enough iron to raise her haemoglobin to 10 g./100 ml. In this way, by slightly undertreating the patients, it was hoped that most of the iron administered, with the exception of that deviated to the foetus, would be utilized for haemoglobin production and not deposited in reserve stores.

Results

In all, 80 patients were reviewed—60 at the blood clinic, the remainder in hospital. Of the 60 out-patients all but five were more than 30 weeks pregnant when first seen, and their average haemoglobin level was 9 g./100 ml. Forty-four responded well to treatment. The remaining 16 eventually showed signs of folic-acid deficiency and will be discussed later. The weekly increases in haemoglobin were calculated for the 44 cases of simple iron-deficiency anaemia and found to be 0.58, 0.59, and 0.44 g./100 ml. during the first, second, and third weeks respectively (see Table). These increments were less than those obtained with imferon (0.77, 0.8, 0.4 g./100 ml.); but, as already mentioned, the rate of administration of iron was slower, and when this was corrected by giving daily injections to hospital patients the average rise in the first week of treatment in 15 antenatal patients was 1 g./100 ml. and in five

Results of Treatment

Treatment	Weekly dose (mg. Fe)	No. of Patients	Average Weekly Hb Increases (g./100 ml.)		
			1	2	3
Jectofer ..	300	44 (clinic)	0.58	0.59	0.44
" ..	700	15 (hospital)	1.0	0.77	
" ..	700	5 (puerperium)	1.5		
Imferon ..	650	200 (clinic)	0.77	0.8	0.4

puerperal patients 1.5 g./100 ml. Thus under optimum conditions the rate of improvement with jectofer was actually greater than that of imferon and the reticulocyte peaks were also higher (maximum 7.4%).

The utilization of the iron in terms of maternal haemoglobin increase was also calculated in the clinic patients. Ten patients had to be discarded because they were still responding when delivered. In the remaining 34 it was found that 100 mg. of jectofer raised the haemoglobin on the average by 0.25 g./100 ml. This was less than that obtained with imferon (0.3 g./100 ml.); it is therefore not surprising that only 10 patients reached the expected haemoglobin level of 10 g./100 ml., and a further 17 (39%) had actually begun to deteriorate as their pregnancy advanced. Frequently, second and even third courses of treatment were required to maintain a level of 10 g./100 ml., and this was especially true in those women who became anaemic before the 36th week.

Complications

Folic-acid Deficiency and Iron Therapy

It is now fairly well recognized that in iron-deficiency anaemia of pregnancy an unsuspected folic-acid deficiency may become overt after parenteral-iron therapy (Scott,

1954; MacKenzie and Abbott, 1960). At one time such a complication was thought to be relatively infrequent because the diagnosis depended largely on the finding of megaloblasts in the peripheral blood or marrow. Nowadays haematologists recognize this condition at a much earlier stage, with the result that more and more cases are being noted, and in the present series 18 patients showed this change either during or after jectofer treatment: 16 of these were clinic patients, and two were in the hospital series; yet initially all appeared to be cases of simple iron-deficiency anaemia, their average haemoglobin being 8.9 g./100 ml. and M.C.H.C. 30%. With treatment the weekly haemoglobin increments were 0.34 g. and 0.3 g./100 ml., but in fact four patients failed to show any improvement whatsoever and in five others the increments were small (total increase 0.5 g./100 ml.). Signs of folic-acid deficiency appeared relatively early in these nine—after one to three weeks. In the remainder, however, the initial increments were good (more than 0.5 g./100 ml. per week) and reticulocyte peaks averaged 5%. Signs of folic-acid deficiency were later in appearing, and the longest interval of 14 weeks occurred after two repeat courses of jectofer.

The earliest signs were failure to improve, failure to maintain improvement, or an actual drop in the haemoglobin level. Buffy coats were screened at this stage and "megaloid" (transitional) cells (two cases) and white-cell changes (18) found. Marrows in the two hospital patients showed similar features, no frank megaloblastic change being seen. Histidine-loading tests were positive in every case. Folic-acid therapy was started and further improvement with a secondary reticulocytosis resulted, the average increase in haemoglobin being 1.1 g./100 ml. Only one patient failed to show satisfactory improvement, and she will be discussed later.

Of the 80 patients in the series 18 (22%) became obviously deficient in folic acid. This, of course, could happen with any iron preparation, but its significance here is stressed because of the toxic reactions that may develop in such patients if jectofer is unwittingly continued. These reactions will be discussed later.

Urinary Infection and Iron Therapy

In the present survey several cases of pyelitis were seen either during or subsequent to treatment. In cases of simple iron-deficiency anaemia 5 (11.4%) developed this additional complication though only two gave a history of a previous attack. Symptoms appeared in four during treatment, but the fifth patient did not have any complaint until the puerperium.

On the other hand, pyelitis was more common in patients who developed folic-acid deficiency, and in one patient, already mentioned, this seemed to be responsible for her failure to improve with folic acid. Of the 18 women in this group 7 (39%) developed this complaint and only two gave histories of previous attacks. One was still under treatment for this, and she developed albuminuria amounting to 1 part Esbach during jectofer therapy, but there was no recrudescence of symptoms. Three patients developed pyelitis during or immediately after completion of jectofer therapy. In the remainder the onset was delayed, two cases occurring in the puerperium. In all patients mid-stream specimens of urine were examined. These were cultured and the sediment was also examined microscopically.

Pyelitis was reported as occurring (Scott, 1962) in a patient who was having both oral iron and jectofer. Toxic symptoms were at first thought to be coincidental in this

case and had been present for two days; she then had a rigor, and on investigation was found to have an *E. coli* urinary infection. A similar case has since been noted, except that in this instance jectofer was given twice daily and the urinary infection, which was proteus in type, did not develop until the fifth day.

No other cases of pyelitis were recorded in the few other patients who received both oral iron and jectofer, but by then toxic symptoms were recognized immediately and oral iron was discontinued.

Reactions

Local.—Only two local reactions were noted. Both patients complained of pain, heat, and swelling, which developed some hours later at the injection site. On examination an area approximately 10 cm. in diameter, dull red in colour, and showing considerable local oedema was observed. Within 36 hours most of this had subsided, leaving only a localized area of brown staining similar to that seen with imferon.

General.—General reactions were infrequent, provided oral iron was not being given (Scott, 1962). Toxic reactions, such as headache, vomiting, and occasionally even nervous manifestations were seen when both forms of therapy were combined, and it was felt that this could be related to the saturation of transferrin.

As already mentioned, reactions to jectofer may occur in patients who have a folic-acid deficiency anaemia. None of the 18 cases under review showed any toxic signs, but they were closely supervised haematologically and treatment was altered immediately evidence of folic-acid deficiency appeared. Until we were fully aware of this problem, however, reactions similar to those described above with oral iron were noted in certain anaemic women who were admitted to the antenatal wards as emergencies near term and given jectofer empirically, before the results of their blood counts or marrow smears were known. It was possible to examine four of these cases more fully before any further treatment was given, and details are given below.

The first patient was also receiving oral iron, which was started on the day of admission. Her blood count, taken at the same time, showed Hb 8 g./100 ml. and M.C.H.C. 30%. In the buffy coat a few "megaloid" cells and hypersegmented polymorphs were seen, but before this result was reported she had already been given jectofer 100 mg. Ten minutes later she complained of nausea and vomiting. Her bone-marrow was examined the next day. It showed changes similar to those seen in the buffy coat and was classified as Grade III (Dawson, 1962). A histidine-loading test was also carried out and found to be strongly positive. Folic-acid therapy was then started, and two days later jectofer 100 mg. was administered without any undue effect. Daily injections were continued thereafter, the patient showing a good response.

The second and third cases were very similar except that they were not given oral iron. Reactions did not occur until after the second and third injections of jectofer had been given. Marrow smears were then examined. One was found to be frankly megaloblastic (Grade IV), the other Grade III (Dawson, 1962). Histidine loading tests were again strongly positive, and once folic acid had been given for two days jectofer therapy was restarted, causing no further reactions.

The fourth patient was slightly different. She had been receiving oral iron at a clinic for several months and was admitted to hospital for haematological investigation as her haemoglobin had fallen from 11.1 to 9.9 g./100 ml. at 38

weeks. Typical giant hypersegmented polymorphs were seen in her buffy coat, and her histidine-loading test was strongly positive. Oral iron was discontinued and jectofer 100 mg. was given on the day of admission and repeated daily. Folic acid was started next day. On the third day of treatment she had a reaction to jectofer, although by this time she had already been taking folic acid for 24 hours.

In her case the important factor appears to have been the delay in starting folic acid, and this is borne out by the fact that since then many patients with folic-acid-deficiency anaemia and even frankly megaloblastic anaemia have begun treatment simultaneously with jectofer and folic acid and no reactions have been observed. Certain patients even had 100 mg. of jectofer twice daily without untoward effect.

Discussion

The present results undoubtedly show that jectofer is a useful iron preparation for intramuscular injection. Given in daily injections of 100 mg. it produces a rate of haemoglobin regeneration more rapid than that found with imferon, and this is reflected in the higher reticulocyte responses produced. In the treatment of out-patients, which includes most of our anaemias, the necessity of giving daily injections is a drawback, as one naturally hesitates to ask these women to attend daily, especially if this involves travelling. On the other hand, thrice-weekly injections inevitably reduce the amount of iron administered to 300 mg. and if one assumes that a third of this is lost in the urine (Andersson, 1961; Pringle *et al.*, 1962; Wetherley-Mein *et al.*, 1962) it is not surprising that the rate of haemoglobin regeneration should be curtailed. Thus the advantage of rapid absorption and utilization is lost and the weekly haemoglobin increments were actually less than those obtained with imferon. In pregnancy, where time is a factor, this is a consideration worthy of note.

When the amount of iron injected is related to the actual increase in maternal haemoglobin the findings show that the increments with jectofer are less than those with imferon. For example, 100 mg. of imferon raised the haemoglobin by 0.3 g./100 ml. on the average (Scott, 1956). With jectofer this figure is only 0.25 g./100 ml. Presumably the 30% loss of jectofer in the urine is responsible for this, but Andersson (1961) claimed that in non-pregnant patients the utilization of both preparations was the same, and he felt that the amount lost in the urine with jectofer was equivalent to that remaining at the injection site with imferon. In pregnancy, however, where there is a constant demand for iron by the conceptus, it is doubtful if much iron is eventually left at the injection sites apart from that accidentally retained in fat. Indeed, the gradual withdrawal from these sites is probably the reason why fewer patients on imferon require repeat courses to maintain their haemoglobin.

With jectofer this was a common occurrence, especially when treatment was started before the 36th week. In the present series one was often faced with the problem of a falling haemoglobin level developing after a satisfactory response, and one had to decide whether this was due to inadequate treatment or an early folic-acid deficiency. Of course, the latter complication may arise with any form of iron therapy (Scott, 1954; MacKenzie and Abbott, 1960) and is not peculiar to jectofer. The higher incidence in the present series is mainly due to earlier recognition of the deficiency at a stage long before it produces a megaloblastic anaemia. Indeed, of the 80 patients followed up 18 (22.5%) eventually showed signs of folic-acid deficiency, and presumably this was precipitated by additional demand

for the vitamin, secondary to increased erythropoietic activity.

It should be remembered, however, that once folic-acid deficiency becomes overt further injections of jectofer may produce toxic reactions. These may appear at any time, depending on the status of iron in the body. For example, it was found that where oral iron was being given the reaction appeared with the first injection, but in untreated cases it might be delayed until the second or even the third injection.

Normally, folic-acid therapy produces a sharp fall in serum-iron levels within 48 to 72 hours of beginning treatment (Scott, 1957; Giles and Shuttleworth, 1958), but it is important to realize that a time lag does exist, and unless jectofer and folic acid are commenced simultaneously reactions may still occur during this period.

Pyelitis was also more frequent in those patients who developed signs of folic-acid deficiency. Of the iron-deficiency-anaemia cases in the present series 11.1% had pyelitis and this incidence is similar to that reported from other centres (Giles and Brown, 1962). In contrast, patients who developed signs of folic-acid deficiency during jectofer therapy had an incidence almost four times higher. The reasons for this high incidence, and its aetiology, are not clear. Giles and Brown (1962) found that, in pregnancy, pyelitis was twice as common in anaemic patients as in non-anaemic controls, but they were unable to find any relationship with folic-acid deficiency. It is to be noted, however, that their patients received folic acid prophylactically. The problem is to understand why in the present series symptoms of urinary infection should arise so frequently during treatment. It may be that in these cases jectofer acts as a pyrogen, and indeed Goldberg (1963) has actually used it for this purpose. As stated previously, 30% of jectofer is excreted via the kidneys, and, although Andersson (1961) could demonstrate no untoward effect on renal function, in the presence of latent renal infection it could stimulate the inflammatory process.

Whether or not the coexistence of a folic-acid deficiency potentiates this effect awaits to be seen. Certainly it would seem that pyelitis is more likely to occur in patients who, for various reasons, cannot fully utilize the jectofer presented to them. One is tempted to suggest that this may in part be related to increased excretion of the iron, and certainly Wetherley-Mein *et al.* (1962) have shown that the rate of loss in the urine is related to plasma-iron levels. One would expect these to be higher where utilization is incomplete, and in this respect it is interesting to note that in the present series the most acute attacks of pyelitis, heralded by rigors, occurred in two patients who had a previous history of pyelitis and were intolerant to combined oral iron and jectofer therapy.

Thus though jectofer may be an excellent haematinic there are definite contraindications to its use. Among these should be included any history of urinary infection or folic-acid-deficiency anaemia. Even so, one cannot at present be sure that the latter deficiency is not potentially present and will not become overt as a result of treatment. Under such circumstances a constant watch is obviously necessary.

Summary

Iron-sorbitol-citrate complex has been used under clinical trial in the treatment of iron-deficiency anaemia of pregnancy.

The results in 80 patients have been reviewed.

With daily injections of 100 mg. the weekly haemoglobin increments are excellent—better than those obtained with imferon—but in treating out-patients the daily visit to a

clinic is a drawback. Any attempt to spread the injections over a longer period inevitably slows the rate of haemoglobin regeneration.

Utilization in terms of increase in maternal haemoglobin is not as good as for imferon, probably because of the 30% loss in the urine, and repeat courses were necessary in 39% of patients in order to maintain the haemoglobin level.

Signs of folic-acid deficiency appeared in 22.5% of patients during or subsequent to treatment. Earlier diagnosis of this deficiency rather than any specific effect of jectofer accounted for the higher incidence reported.

Its occurrence is stressed, however, because these patients are liable to show toxic reactions to jectofer which are similar in nature to those already described in patients receiving combined oral iron and jectofer therapy.

Pyelitis is also four times commoner in such patients, and the question of whether jectofer has a pyrogen-like effect in such circumstances is discussed.

In view of these findings it is considered that among the contraindications to its use should be included any history of previous urinary infection or folic-acid deficiency.

I should like to convey my thanks to my clinical colleagues for their co-operation in the treatment of these patients and to acknowledge the helpful criticism of this work received from Dr. A. D. T. Govan, Director of Research. We are grateful to Astra-Hewlett Ltd. for supplies of jectofer.

REFERENCES

- Andersson, N. S. E. (1961). *Brit. med. J.*, **2**, 275.
 Dawson, D. W. (1962). *J. Obstet. Gynaec. Brit. Cwlth.*, **69**, 38.
 Giles, C., and Brown, J. A. H. (1962). *Brit. med. J.*, **2**, 10.
 — and Shuttleworth, E. M. (1958). *Lancet*, **2**, 1341.
 Goldberg, A. (1963). Personal communication. *Scot. med. J.* (in press).
 Haddow, A., and Horning, E. S. (1960). *J. nat. Cancer Inst.*, **24**, 109.
 MacKenzie, A., and Abbott, J. (1960). *Brit. med. J.*, **2**, 1114.
 Pringle, A., Goldberg, A., MacDonald, E., and Johnston, S. (1962). *Lancet*, **2**, 749.
 Richmond, H. G. (1959). *Brit. med. J.*, **1**, 947.
 — (1960). In *Cancer Progress*, edited by R. W. Raven, p. 24. Butterworths, London.
 Scott, J. M. (1954). *J. Obstet. Gynaec. Brit. Emp.*, **61**, 646.
 — (1956). *Brit. med. J.*, **2**, 635.
 — (1957). *Ibid.*, **2**, 270.
 — (1962). *Ibid.*, **2**, 480.
 Wetherley-Mein, G., Buchanan, J. G., Glass, U. H., and Pearce, L. C. (1962). *Ibid.*, **1**, 1796.

During the last financial year, £155,739 was made available by the Oxford Committee for Famine Relief specifically for medical work. Grants were made to medical organizations and individual hospitals in 25 different countries. In the first half of the current year (October, 1962, to April, 1963) Oxfam made medical grants totalling £106,670, an increase of nearly 50% over those made in the corresponding period last year. These figures only include funds allocated to purely medical programmes. Part of many other grants, made for famine relief or refugee aid, is used for medical work. Oxfam has recently made a number of grants to fight leprosy in consultation with the British Leprosy Relief Association. Aid to the sum of £13,050 has been given so far to nine projects of leprosy relief—six of them in India—and £14,300 went to seven schemes to help sufferers from tuberculosis. Three of these grants covered the cost of feeding poor patients, three were for building purposes. The African Medical and Research Foundation has received £10,000 from Oxfam's funds in support of its mobile clinics in Kenya and Tanganyika.