effective, non-toxic, and easily administered intramuscular iron preparation should not be made an excuse for the indiscriminate use of parenteral iron therapy.

Summary

A preliminary account is given of the successful clinical trial, in 15 patients, of a newly elaborated proprietary dextran-iron haematinic ("imferon"). The agent proved non-irritating when given intramuscularly and was readily absorbed, giving serum iron levels of 600 μg. within eighteen hours; absorption via the lymphatics was demonstrated histologically. The complex proved an effective haematinic, giving average haemoglobin regeneration rates of between 3.5 and 11.3% Hb per week over the first four weeks of treatment.

We wish to thank the Medical Director, Research Department, Benger's Ltd., for supplies of imferon.

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ANAEMIA OF PREGNANCY TREATED WITH INTRAMUSCULAR IRON

BY

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AND

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The injection of iron intramuscularly as a therapeutic measure is no new procedure. As early as 1893 Stockman recognized the efficacy of this mode of administration, but, as he and subsequent authors (Barlow and Cunningham, 1911; Bullock and Peters, 1911; Witts, 1933; Heath, Strauss, and Castle, 1932) pointed out, the toxicity of the solutions employed was so great that only small quantities could be injected. Consequently, the rate of haemoglobin regeneration was actually less than that found with oral iron therapy. At the same time Heath *et al.* (1932) showed that the utilization of the injected iron for haemoglobin formation was nearly 100%. Fowler and Barer (1937) did not wholly agree with this. They stated that in all their cases the iron was retained, but in three out of four of their patients no improvement in haemoglobin level occurred. It was generally felt that until a less toxic preparation was available there was no real case for the intramuscular administration of iron.

The following is a report on the results obtained by the treatment of iron-deficiency anaemias of pregnancy with a new preparation "imferon" which can be given intramuscularly as well as intravenously.

Materials and Methods

Fifty pregnant women with iron-deficiency anaemia were treated with this preparation. All had haemoglobin values less than 10 g.%* In 14 the anaemia was mild—9 to 9.5 g.%; in 28 the haemoglobin lay between 8 and 8.9%, and in the remainder the anaemia was severe, haemoglobin being less than 8 g.%. All but one had a red-cell count over 3,000,000 per c.mm. This patient had a red count of 2,850,000 with a haemoglobin reading of 5.7 g.%. All were of microcytic hypochromic type with normoblastic marrows. Serum iron levels estimated by the method of Sven Dahl (1948) were uniformly low—from 10 to 65 γ per 100 ml., the average being 35 γ per 100 ml. Four of the patients were treated in hospital; the remainder were out-patients. Initially, two schemes of dosage were employed. Thirteen patients, including the four in hospital, were given daily injections equivalent to 100 mg. of elemental iron. Others received larger doses, representing 250 mg. of elemental iron, twice weekly. Subsequently all patients were treated with the larger dose. This preparation of iron is much more concentrated than the intravenous forms involving the use of the saccharated oxide. Each millilitre contains 50 mg. of elemental iron.

Daily estimations of haemoglobin, haematocrit values, and reticulocytes were made on those patients receiving daily injections. Similar estimations were made at regular intervals on other patients. Each week a complete investigation was made on all patients. Serial estimations of serum iron were made in selected cases.

*68% on the scale of 14.8 g. ≡ 100%.

Results

Daily haemoglobin and haematocrit readings, carried out on those patients receiving the smaller dose, revealed a characteristic pattern of changes somewhat similar to that found in patients treated with intravenous saccharated iron. The haemoglobin rose slightly during the first 24–48 hours. Thereafter a fall occurred, a minimum value being reached by the fourth day of therapy. Subsequently there was a rapid improvement. These sudden initial changes in haemoglobin were probably due in part to variations in blood volume. Curiously, however, the haematocrit reading increased from the beginning and there was a similar increase in mean cell volume. It is likely that these increases were caused by an outpouring of normocytes from the marrow, and this might tend to mask blood-volume changes.

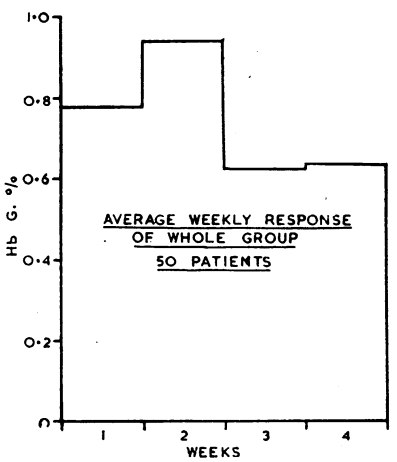

FIG. 1.—Average weekly haemoglobin increments of whole group.

The average haemoglobin increments during the first three weeks following treatment are shown in Fig. 1. During the first week the average increase was 0.77 g.%. The average increment for the whole group during the second week was 0.94 g.%. By the third week many of the cases were almost normal, and the percentage increase for the group was only 0.62 g.%. Study of the cases, however, indicated that, as with all forms of iron therapy during pregnancy, two main types of response were shown. Adopting an arbitrary response of 0.5 g. as a significant figure, it could be shown that, during the first week of therapy, in the greater proportion of patients (42) the haemoglobin increased by 1.1 g. In the remaining eight patients the increase during this period amounted to only 0.22 g. During subsequent weeks the response of both groups was similar. Haemoglobin increments of the two groups are shown in Figs. 2 and 3.

Reticulocytes, from an initial value of less than 1%, showed a significant rise by the fourth day and reached a maximum on the seventh. Levels were higher in the more severe cases, and the greatest increase, 6.8%, was found in a young patient whose initial haemoglobin was 6.2%. The average for the whole group was 3.8%.

Utilization for haemoglobin production was extremely good. An average haemoglobin increase of 0.3 g. was recorded for every 100 mg. of elemental iron injected. The smallest increase, 0.21 g., occurred in a patient with a twin pregnancy, and the highest, 0.66 g., in a case of early pregnancy. These findings, however, will have to be confirmed over a larger series, since the response will naturally vary with the weight of the patient and her blood volume.

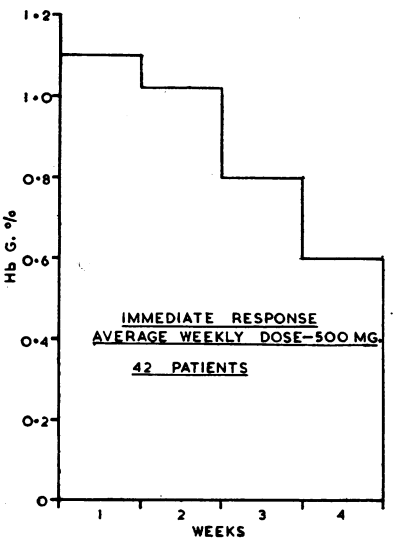

FIG. 2.—Haemoglobin increments in patients showing rapid response to treatment.

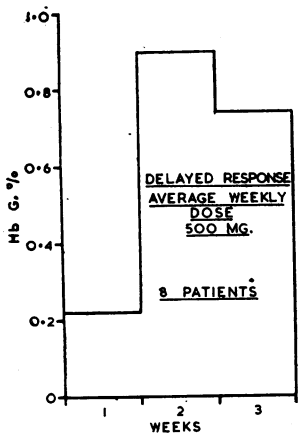

FIG. 3.—Haemoglobin increments in patients in whom response is delayed.

Serum Iron

Serial estimations of serum iron were made in nine patients. Five received daily injections of 2 ml. of the preparation (≡ 100 mg. of elemental iron), and the serum iron was estimated at the same time each morning before the injection was given. Twenty-four hours after the first dose the readings, previously low, were remarkably high, 335 to 820 γ per 100 ml.; and the levels mounted steadily with each injection. In the more severe cases the levels were not so high, suggesting possibly that the utilization was more rapid. The number of cases is small, however, and no doubt other factors, such as marrow activity, play a part.

With larger doses the serum iron increases were less regular, but extremely high levels were often found. In two patients given 5 ml. daily for four and five days respectively, the serum iron readings 24 hours after the last injection were 2.26 mg. and 1.87 mg. per 100 ml.

Serial readings following a single intramuscular injection equivalent to 250 mg. of elemental iron showed a steadily rising curve during the subsequent 36 hours. This preparation can be given equally well intravenously. Estimations following a single intravenous injection of 250 mg. of elemental iron showed very high readings immediately, with a fall to a level at 48 hours almost the same as that recorded with the intramuscular route (Fig. 4). Successive intravenous injections produced further augmentation of the serum iron level, and readings as high as 7.5 mg. per 100 ml. have been found.

General

The most remarkable features of this new preparation are the facility with which it can be administered, and the absence of reactions, either local or general, provided care is taken to give the injection properly. It must be made deep into the muscle of the upper and outer quadrant of the buttock, using a large-size needle. If it is injected into the superficial fat a persistent brown staining of the subcutaneous tissue will result and there will be a lack of absorption. Apart from a slight initial stiffness common to all intramuscular inoculations, no untoward effect has been observed. Similarly, despite the very high serum iron levels, no general reaction which could be clearly attributed to the preparation was encountered. One patient developed a maculopapular rash on the extensor surfaces of both arms. This patient, however, had previously suffered from dermatitis. After the rash disappeared further treatment failed to provoke any reaction, and it is considered that the skin rash was merely coincidental. Since large amounts of iron may be given in a single dose the number of injections can be reduced. It is often found that patients treated with oral iron fail to respond until they are admitted to hospital. This may be due to some defect of absorption corrected by rest, or merely because the patient fails to take the medicine as prescribed. With this simply administered preparation the need for admission to hospital is eliminated.

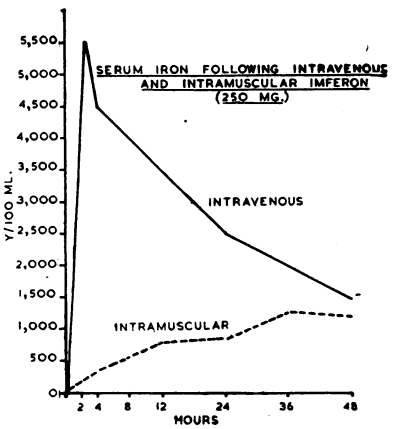

FIG. 4.—Serum iron curves following intramuscular and intravenous injections of 250 mg. of "imferon."

Commentary

This preparation naturally invites comparison with the widely used saccharated oxide of iron, which can only be administered intravenously (Govan and Scott, 1949; Scott and Govan, 1951). As already stated, the ease with which the injections may be made and the absence of reactions, despite the relatively high doses of iron, are among the most important characteristics of this preparation. The response is equal to that obtained with intravenous saccharated oxide of iron. In a previous series of 91 patients treated with the intravenous preparation (Scott and Govan, 1951) the average haemoglobin increments during the first three weeks of treatment were 1.0 g., 0.9 g., and 0.4 g. per 100 ml. The present results of 0.77 g., 0.94 g., and 0.62 g. per 100 ml. are equally good. Utilization of the iron for haemoglobin production is exactly the same for the two compounds, both resulting in an increase of 0.3 g. of haemoglobin per 100 mg. of elemental iron. As with the intravenous preparation, significant improvement may be delayed for a week. This is characteristic of many cases of simple anaemia of pregnancy no matter how or in what form the iron is administered. With oral iron preparations improvement may be delayed for as long as one month.

With the higher concentration of elemental iron (50 mg. per ml.), as compared with intravenous saccharated oxide of iron (20 mg. per ml.), a higher dosage schedule may be instituted, thus reducing the number of injections.

The extremely high serum iron readings, combined with the absence of reactions, is interesting. Similarly high readings were obtained with saccharated oxide of iron only when very large quantities, up to 1 g., were injected, and this was associated with a greatly increased incidence of reactions. Obviously the serum iron readings *per se* have no direct relationship to the onset of reaction. In the present series, levels well above the plasma iron binding

power (Klopper, 1951) were obtained without having any undue effect. It would appear that the nature of the iron compound and its stability are more important than the amount given. Our results would tend to support the view of Nissim (1954) that reactions following use of saccharated oxide of iron are due to precipitation of an inherently unstable compound.

Summary

The results of treatment with a new intramuscular preparation of iron in 50 cases of anaemia of pregnancy are recorded. All patients were in the antenatal period.

In 14 patients the condition was of mild degree, in 28 it was moderate, and in 8 it was severe. All responded satisfactorily. An average weekly dose equivalent to 500 mg. of elemental iron produced an increase of slightly more than 1 g.—that is, 6% on the Haldane scale. Utilization of the iron was good, the haemoglobin increasing on the average by 0.3 g. for every 100 mg. of elemental iron injected. These results are almost identical with those obtained by the use of intravenous saccharated oxide of iron. As with all forms of iron therapy, response to treatment was sometimes delayed, but by the second week of treatment all patients showed similar haemoglobin increases.

The preparation contains 5% elemental iron compared with 2% in those utilizing the saccharated oxide of iron. With this concentration the number of injections may be reduced considerably. Many cases of mild anaemia require only two 5-ml. ampoules. Very high serum iron readings result from the injection of this highly concentrated solution, but no reactions, either local or general, have so far been encountered.

We would like to thank Benger's Ltd. for generous supplies of imferon for clinical trial.

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The General Board of Cambridge University, in a Notice in the *Reporter* of November 17, state that they consider that former University teaching officers should not be employed to give regular courses of instruction unless it is clear that by so doing they will not block the way to promotion for others. With certain exceptions, continues the Notice, the Board "will therefore not approve the estimates of a Faculty or Department which desires to employ a former University teaching officer unless they have received an assurance that other teachers will not thereby be precluded from appointment to office or from having their fitness for promotion tested. The Board will be prepared to consider the approval of estimates which include provision for the payment at the normal rates of a former University teaching officer to give a regular course of instruction when a University teaching officer falls ill or is away on leave and is therefore unable to carry out his regular teaching duties, and it is found difficult to replace his teaching work without seriously disorganizing the work of other members of the staff. They will also consider the approval of estimates which include provisions for the payment at the normal rates of former University teaching officers to give specialized courses to meet particular needs not forming part of the instruction for a Tripos or Part of a Tripos."

A PREVENTIVE APPROACH TO COMMON DISEASES OF THE LUNG*

BY

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Preventive medicine, together with a rising standard of living and recent therapeutic developments, has led to a marked rise in the expectation of life of children born into our community. Since 1841 this has amounted to 27½ years—but there has been no equivalent increase for those aged 60. In fact, during the same 110 years the expectation of life at this age has risen only one year for men and four years for women (Logan, 1953). The great killing diseases at this time of life are those affecting the cardiovascular system and the lungs. A preventive approach to these should pay handsome dividends. However, despite much research, the problems of cardiovascular disease remain unsolved. The major lung diseases—bronchitis, pneumonia, cancer, and tuberculosis—do not present such baffling problems. Sufficient is known of their aetiology now to make prevention possible in a community alive to the simple facts governing these lesions of the chest. The deaths, mainly in the older age groups, amount probably to 100,000 per year, but death is preceded by months and often years of invalidism in many cases. This is certainly true of the too common condition of bronchitis. In 1950 it was responsible for the loss of 16,500,000 working days amongst our insured population. A high incidence of chronic chest disease is accepted by us—but a careful study will show that most of this is avoidable. This study is essential in a community where healthy ageing is one of the most pressing problems of society.

The industrial revolution brought great wealth to our country, but resulted in a growth of industrial cities where a spectacular rise in morbidity and mortality took place. Between 1831 and 1841 the crude death rate per thousand in Birmingham, Leeds, Bristol, Manchester, and Liverpool rose from 20.6 to 30.8 (Griffith, 1926). Great efforts were made subsequently to deal with intestinal diseases which were responsible for the most spectacular part of the rise. Cholera, typhoid, and dysentery were gradually controlled. This was achieved, after many bitter struggles, by the supply of clean water and the effective clearing of sewage.

Respiratory diseases remained, but the need for attention to the grossly polluted air was apparent to the great reformers Chadwick and Simon—in fact, Chadwick projected a "pure air company" to suck down pure air from specially constructed towers into the dwellings and workshops of city populations. Coal was abundant and cheap. Industrial cities had grown up, consisting of houses, surrounding factories, foundries, and mines. "The towns sprang up at a nightmare rate and of a nightmare character. Fastest of all grew the cotton towns; the iron towns, the woollen towns, the pottery towns followed hardly less swiftly, while all about the coalfields gaunt mining villages grew side by side with fiery waste heaps in the very shadow of the pitheads, often enough in the pit yards themselves." (Sharp, 1950.) Here the air was and still is heavy with smoke, fumes, oxides of sulphur, and other products of combustion. The urge for hygienic reform spent itself before clean

*Based on a lecture given to the Salford Division of the British Medical Association, May, 1954.