undertaken solely by them. Throughout this period I have received the utmost consideration and help from this company, particularly from their Mr. F. Hodson. My thanks are due to Mrs. Shirley East for her line illustrations, to Dr. Donald Chisholm for his x-ray plates, and to my general surgical colleagues for their encouragement and for agreeing to the name chosen for this valve.

IRON THERAPY IN PRIMARY IRON-DEFICIENCY ANAEMIA

BY

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Recently much attention has been paid to the relative merits of various iron compounds in the treatment of iron-deficiency anaemia. Organic iron preparations such as chelates and salts of organic acids have been recommended on various grounds, including better utilization and lower toxicity (but never economy). On the basis of these trials it has been claimed that some of the new iron preparations give better results than the widely used ferrous sulphate tablets. However, as O'Sullivan *et al.* (1955) point out, the significance of such trials is doubtful for two reasons. Firstly, they have often been carried out on pregnant women with mild or moderate anaemia who tend to recover spontaneously after pregnancy. Secondly, the doses of the iron salts used have not been comparable in terms of their content of elemental iron.

In young men there is a form of anaemia in which exhaustive investigation fails to show evidence of organic origin. To this condition the name primary iron-deficiency anaemia has been given (Brumfitt, 1958). In these patients complicating factors which might interfere with or modify a normal response to iron therapy are absent. In the series described (Brumfitt, 1958) all the patients were young soldiers who were kept in hospital throughout the period of treatment. The risk of the patient forgetting to take the prescribed dose of iron was thereby avoided, and samples of blood could be obtained at frequent and regular intervals. In addition, it was possible to follow the patients for periods of up to one year after correction of the

anaemia. Such conditions provided a good opportunity to compare the response of two commonly used iron salts—ferrous sulphate and ferrous gluconate.

Patients and Methods

The patients were 30 soldiers between the ages of 18 and 20 years in whom organic disease had been excluded (Brumfitt, 1958). The extent of the anaemia varied from 6.4 to 11.1 g. of haemoglobin per 100 ml. The fasting serum iron level was always low and ranged from 23 to 45 $\mu\text{g.}/100\text{ ml.}$ The patients were divided by random selection into two groups: 16 were treated with ferrous sulphate and the other 14 by ferrous gluconate. The comparability of the treatment groups is shown in Table I.

The dose of ferrous sulphate and ferrous gluconate was adjusted so that each patient received 149 mg. of bivalent iron daily. The tablets were given between meals and were taken at once in the presence of the ward sister. Therapy was continued for five weeks unless the haemoglobin rose to the arbitrary level of 13.5 g./100 ml., in which event iron was discontinued.

Haemoglobin and reticulocyte estimations were made daily for the first 14 days and thereafter twice weekly. In view of the diurnal variation in haemoglobin level (McCarthy and Van Slyke, 1939; Brown and Goodall, 1946) blood for haemoglobin estimations was taken between 10 and 11.30 a.m. The pipettes were calibrated gravimetrically (Stevenson *et al.*, 1951) and the

TABLE I

Average	Treatment Group	
	Ferrous Sulphate	Ferrous Gluconate
Age	18.3 years	18.4 years
Weight	10 st. 7 lb. (66.7 kg.)	10 st. 10 lb. (68 kg.)
Haemoglobin	8.8 g.	8.9 g.
P.C.V.	35.9%	35.9%
M.C.H.C.	24.5%	24.7%
Fasting serum iron	34 $\mu\text{g.}/100\text{ ml.}$	34 $\mu\text{g.}/100\text{ ml.}$
Histamine-fast achlorhydria	30%	42%

estimations made photoelectrically. Indices were calculated before starting treatment, after 1, 3, 5, and 12 weeks, and at follow-up.

Before beginning treatment, uptake of iron given by mouth was studied. The fasting serum iron level was

FIG. 1.—Comparison between response to ferrous sulphate (●—●) and ferrous gluconate (×—×).

estimated and a dose of ferrous gluconate containing 69 mg. of elemental iron given orally. The serum iron was re-estimated after two hours. The fasting serum iron was also determined at the time of follow-up.

Results

Although there was variation between individual patients in the average increments for haemoglobin, P.C.V., and M.C.H.C., there is close agreement when the whole groups are compared (Fig. 1, Table II). In

TABLE II.—Summary of Peripheral Blood Findings Before, During, and After Treatment

	Ferrous Sulphate				Ferrous Gluconate			
	Mean Hb g./100 ml.	Weekly Rise g./100 ml.	P.C.V. (%)	M.C.H.C. (%)	Mean Hb g./100 ml.	Weekly Rise g./100 ml.	P.C.V. (%)	M.C.H.C. (%)
Before treatment	8.8		35.9	24.5	8.9		35.9	24.7
After 1 week	10.0		39.1	25.6	10.0		39.8	25.7
„ 2 weeks	11.3	1.3			11.3	1.3		
„ 3 „	12.3	1.0	43.0	28.4	12.2	0.9	43.7	28.0
„ 4 „	13.0	0.7			13.0	0.8		
„ 5 „	13.6	0.6	45.3	30.0	13.6	0.6	46.1	29.2
„ approx. 12 weeks	15.2		46.0	32.9	14.9		46.6	31.7

both groups the rate of increase in the haemoglobin level was greatest in the second week and thereafter gradually declined. It is seen that the P.C.V. increases more rapidly than the M.C.H.C. This is presumably due to the production of red cells of normal size which are deficient in haemoglobin content.

Table III shows the fasting serum iron levels in the two treatment groups. In addition the levels in 10

TABLE III.—Fasting Serum Iron Levels of the Two Treatment Groups Before and After Oral Iron Therapy. Fasting Serum Iron Levels of 10 Healthy Males are Given for Comparison

	Fasting Serum Iron (μg./100 ml.)		
	Normal Controls	Ferrous Sulphate	Ferrous Gluconate
Before treatment	115 98–160	34 23–45	36 24–43
3–12 months after completing treatment	—	114 95–148	113 90–159

healthy males are given for comparison. It is seen also that at the time of follow-up, which was at least three months after the course of treatment had been completed, all values were within normal limits.

The maximum reticulocytosis occurred between the sixth and tenth days. Fig. 2 shows that there is an

FIG. 2.—Relationship of maximum reticulocyte response to severity of anaemia.

obvious relationship between the severity of the anaemia and the reticulocyte response.

Discussion

In two groups of young men suffering from uncomplicated iron-deficiency anaemia there was no significant difference in the effectiveness of

ferrous gluconate and ferrous sulphate when administered in doses which contained the same amount of elemental iron. These results agree with those of O'Sullivan *et al.* (1955), but are contrary to the findings of Haler (1952), who found ferrous gluconate to have a much higher percentage utilization than ferrous sulphate. Haler's results can be explained by the fact that in terms of elemental iron he used a much smaller dose of ferrous gluconate than ferrous sulphate, and Smith (1957) and Smith and Pannacchiulli (1958) have shown that the percentage absorption of an iron salt is inversely proportional to the dose.

The same criticism can be levelled at the widespread use which is made of the utilization factor as a means of estimating the relative value of iron salts in the treatment of iron-deficiency anaemia. The figures given by Witts (1936), which are often quoted in commercial literature, are assembled from a number of sources and the doses used vary greatly in their content of elemental iron. Apart from this difficulty, the patients treated are frequently not comparable. For example, idiopathic iron-deficiency anaemia of middle-aged women and iron-deficiency anaemia of pregnancy may respond differently to treatment. Another point of importance is the period over which the response to iron is calculated, since it has already been pointed out that the haemoglobin generation is most rapid in the second week of treatment and thereafter declines. Therefore, in comparing two groups it is important that the response should be calculated over the same interval of time.

Gatenby and Lillie (1955) compared ferrous sulphate and ferrous gluconate in pregnant women suffering from iron-deficiency anaemia. Symptoms due to intolerance were much more frequent with ferrous sulphate, but if cases showing intolerance are omitted and the results calculated on the basis of the quantity of elemental iron given, the findings do not differ significantly between the two groups.

Leonard (1954) treated a group of young airmen suffering from primary iron-deficiency anaemia with intravenous iron, giving the equivalent of 25 mg. of elemental iron for each 1% deficiency of haemoglobin. These patients were entirely comparable with those in the present trial, and it is interesting that, apart from rapidity of initial response, the results were very similar. This lends support to the idea that if iron is well absorbed from the intestine nothing is to be gained by using the parenteral route.

One problem which requires consideration in choosing a suitable iron preparation is that of intolerance. Intolerance to ferrous sulphate was found in 30 to 40% of pregnant women by Benstead and Theobald (1952) and in 50% by Gatenby and Lillie (1955), who found only 10% intolerance to ferrous gluconate. Edgar and Rice (1956), noting the view of Girdwood (1952) that intolerance was partly psychological, replaced the familiar green tablets, usually issued at antenatal clinics, with white sugar-coated tablets containing the same quantity of ferrous sulphate. Of the 179 patients investigated, only 8 (5.4%) showed intolerance.

In the present series no case showed intolerance to either drug. Furthermore, of 50 out-patients suffering from iron-deficiency anaemia treated with the same dose of ferrous sulphate, none showed symptoms of intolerance and the anaemia responded to the treatment.

It would therefore seem that, apart from psychological factors, intolerance is related to the size of the dose. The idea that large doses of iron are required stems partly from the suggestion of Brock and Hunter (1937) that, owing to the avidity of storage depots for iron, the plasma level must be raised above the physiological level before the bone marrow can be stimulated. No doubt this idea arose in part from the difficulty in treating patients with absorption defects, such as steatorrhoea, who are resistant to oral iron therapy. The present findings indicate that cases of iron deficiency should be treated with relatively small doses of oral iron and those who do not respond should be further investigated.

Some authors recommend that iron therapy should be continued for some time after correction of the anaemia in order to replace iron stores (Jasiński, 1949, 1950; Dunlop *et al.*, 1958). This idea is based on the views of Finch *et al.* (1950) that, after anaemia has been corrected and the erythropoietic activity has returned to normal, the absorption of iron returns to a basal level despite the depletion of the iron stores. In the present cases iron was discontinued after five weeks, or less if the haemoglobin reached 13.5 g./100 ml., and in no instance did relapse occur. At follow-up the fasting serum iron level was invariably within normal limits. All patients with symptoms were completely cured by iron therapy and were aware of a sense of well-being.

The findings in the present investigation uphold the view of Minot and Heath (1932) that the reticulocyte response is proportional to the severity of the anaemia and is correlated more closely with the initial haemoglobin level than with the initial red-cell count.

Summary and Conclusions

The results of treatment in young men suffering from uncomplicated iron-deficiency anaemia are described. All responded to oral iron, and no difference between treatment with ferrous sulphate and ferrous gluconate was found. In primary iron-deficiency anaemia an excellent clinical and haematological response can be obtained by giving doses of 600 mg. of ferrous sulphate or 1,500 mg. of ferrous gluconate daily. With this dosage no patient complained of symptoms of intolerance. At follow-up 3 to 12 months after treatment all symptoms were completely cured and no case had relapsed. Therefore, iron therapy after the blood picture has been restored to normal is unnecessary.

It is suggested that cases of iron deficiency anaemia should be treated with small doses of oral iron. Those who do not respond require further investigation.

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MEGALOBlastic ANAEMIA INDUCED BY PHENYLBUTAZONE

BY

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The production of megaloblastic anaemia by anti-convulsant drugs has been recorded in at least 40 cases, and has recently been reviewed (Stokes and Fortune, 1958). In the case described below, megaloblastic anaemia appeared to follow the administration of phenylbutazone and responded to oral folic acid. Many other toxic effects of phenylbutazone on the bone marrow have been described, notably agranulocytosis, but no case of megaloblastic anaemia has previously been reported to our knowledge.

Case History

A housewife aged 36, who had lived in South Australia since birth, was admitted to the Royal Adelaide Hospital in June, 1956. She had suffered from joint pains for some years, and had been taking phenylbutazone ("butazolidin") 400 mg. daily for the last five months. During the month before admission she had lost weight and complained of nausea, attacks of palpitation, and giddiness on bending forward. Her menses had been irregular for three years and she had had amenorrhoea for the last four months. There was no history of pernicious anaemia in relatives, and the only other drugs she had taken were thyroid extract and dexamphetamine sulphate, both prescribed for moderate obesity. During this time she continued to eat a varied and adequate diet.

The patient was pale and her tongue smooth, but otherwise she appeared to be well nourished. Her sternum was tender and the spleen tip was palpable, but there was no lymph-node enlargement. Tendon reflexes were present in the legs but sluggish. The ankle-joints were swollen, red, and tender.

The blood picture was: red-cell count, 1,100,000 per c.mm.; haemoglobin, 4 g. per 100 ml.; M.C.V., 100 cubic microns; M.C.H., 36 μ g.; M.C.H.C., 36%; platelets "plentiful"; reticulocytes, 3.4%; leucocytes, 6,800 per c.mm. (myelocytes 1%, metamyelocytes 2%, polymorphs 65%, lymphocytes 26%, monocytes 6%). Red cells showed marked anisocytosis and some poikilocytosis. Polymorphs showed a mild degree of hypersegmentation. There were six nucleated red blood cells per 100 leucocytes, and about half showed megaloblastic characteristics. The bone marrow was hyperplastic with many fully formed megaloblasts as well as intermediate types. An augmented histamine test meal with radiological control on two occasions revealed no free hydrochloric acid.

Liver-function tests showed nothing abnormal; the icteric index was 7, the serum colloidal gold 0, the cephalin-