STUDIES ON THE RETENTION OF IRON IN CHILDHOOD

BY

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The efficacy of iron therapy in nutritional anaemia, which has been shown to be of such common occurrence in infants and adults (Mackay¹⁶; Faber⁶; Davidson et al⁵; Fullerton⁹) is apparently dependent on the administration of large doses of iron if given orally (Heath¹¹; Witts³¹). In this connection it is interesting to recall that the use of large doses was first advocated in 1832 by Blaud¹. Only a small amount of the iron ingested goes to the formation of haemoglobin and there has been much speculation as to the reason why it has to be given in such large doses, and as to the fate of the remainder of the iron which has not been utilized in haemoglobin building. That the body can store large amounts of iron has been shown by Reznikoff, Toscani and Fullerton²⁴, who found that, after the administration of phenylhydrazine hydrochloride to a case of polycythaemia, there was a blood destruction equivalent to 2.1 grammes of iron without any extra excretion of this metal. Ramage and Sheldon²¹, recovered as much as 50 grammes of iron from the tissues in a case of haemochromatosis. The necessity for the use of massive doses of inorganic iron salts has until recently caused many workers to doubt if iron deficiency is the sole factor in the etiology of the nutritional anaemias (Whipple and Robschey-Robins³⁰). Heath, Strauss and Castle¹² showed that the parenteral administration of iron in inorganic form resulted in 100 per cent. utilization, and because of this Fullerton⁸ sees no reason to postulate the existence of another factor, and suggests that the necessity for large doses is dependent, among other things, upon imperfect absorption. There are, however, few observations regarding the absorption of iron, and the importance of further investigation on its fate after ingestion is obvious. With a view to throwing some light on this problem, a series of iron-balance studies has been conducted on in-patients at the Royal Hospital for Sick Children in Glasgow.

Method of investigation

The subject was given a diet of known iron content for a period of four days before the beginning of the experiment. Thereafter, for a period of seven days on the weighed diet, the faeces were collected for analysis; then ferrous sulphate was added to the diet in doses which amounted to 4 grammes

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or 8 grammes of the sulphate, the equivalent of 803.45 milligrammes or 1606.9 milligrammes of iron per week, and the collection of the faeces continued. The ferrous sulphate was given in aqueous solution with the addition of glucose syrup to minimize oxidation as recommended by Parsons and Hawksley¹⁹. The iron content of the urine was neglected, as all workers agree that urinary excretion of iron is negligible (Tompsett²⁷; Hunter and Brock³. Weekly determinations of the haemoglobin, red blood cells and colour index, were made in every case. The haemoglobin levels were determined by the Sahli method. The haemoglobinometer was standardized against blood, the iron content of which had been estimated, and it was found that a reading of 100 per cent. on the haemoglobinometer represented a haemoglobin content of 17.3 grammes per 100 c.c. blood. After completion of the study, examination of the gastric contents, following a test-meal, was carried out in every case by the Rehfuß method, a Ryle's tube being used for the aspiration of the gastric contents.

The total faeces for each period were placed in a porcelain evaporating dish (the weight of which was known), and treated with methylated spirits. Thereafter, the faeces were dried on a hot plate until constant weighings were obtained on three consecutive days, and the weight of the dried faeces thus obtained. The dried faeces were then finely divided by grinding in a mortar and stored in a stoppered glass jar. By calculating the iron content of aliquot samples of faeces from each period, the total iron output for each period was determined. The method used for determining the iron content of the faeces was that described by Taylor and Brock²⁶, in which sulphuric acid digestion makes possible the volumetric estimation of iron by the permanganate titration method of Margueritte (Treadwell and Hall). Before the beginning of the metabolism studies the method was tested thoroughly and found to be accurate and satisfactory.

Like all macromethods for the determination of iron in biological material, this method is time-consuming, each estimation taking about eight days. When to this is added the ten to fourteen days required for drying the faeces it is about three weeks from the end of any one weekly experimental period before the determination of the iron retention during that period can be estimated. This led to certain difficulties in planning experiments but could not be overcome by the adoption of any one of the many microcolorimetric methods for biological assay, because the errors entailed in those methods are greatly exaggerated when amounts of iron between 1 and 10 milligrammes are being estimated.

The results of iron balance studies which have been carried out on six patients over long periods are presented. The duration of the experiments varied from eight to sixteen weeks and comprised in some cases as many as sixteen weekly periods. Of these six patients, four gave normal or almost normal values for haemoglobin and red blood cells at the beginning of the metabolism studies, and the remaining two were cases of severe hypochromic anaemia. The findings of the normal and anaemic cases are discussed separately.

Results : Non-anaemic subjects

Case 1. E. S., a girl aged eleven years, was admitted to the wards with chorea minor. The iron-balance study, the results from which are shown in table 1, was begun after complete cessation of choreiform movements.

The first weekly period was in the nature of a control period during which no iron was administered apart from the small amount (37·87 milligrammes) contained in the food. Throughout the second, third, fourth, fifth and sixth periods, 4 grammes of ferrous sulphate (equivalent to 803·45 milligrammes of iron) were administered orally each week, the total iron intake of 841·32 milligrammes per period being the sum of the food iron and the inorganic iron given in the form of ferrous sulphate. The total iron output was not determined for the fourth and fifth periods. During the seventh, eighth, ninth and tenth periods the child received 8 grammes of ferrous sulphate (equivalent to 1606·90 milligrammes of iron) per week, the total iron intake during each period being 1644·77 milligrammes. After completion of the tenth period the administration of ferrous sulphate was stopped.

From table 1 it can be seen that this girl, who constantly presented a normal blood picture, retained remarkably large amounts of the iron administered: 72–87 per cent. of the total intake per period was retained when the weekly intake amounted to 4 grammes of ferrous sulphate, and from 27–76 per cent. of the intake with 8 grammes of ferrous sulphate. Another feature of interest is the wide variation of the retention of iron during different weekly periods. These differences are probably to be explained, in part, by the possibility that an apparently large retention during one period, may be due to constipation with accumulation in the bowel of non-absorbed iron, which being passed in the faeces of the next period produces an apparently small retention of iron for that period. Thus, when there was a positive iron balance of 1254·91 milligrammes during the ninth period, and a negative balance of 211·02 milligrammes during the tenth period, the amount of faeces passed during these periods were 39·62 grammes and 112·20 grammes respectively. This artefact could be abolished by the use of long periods and it is of interest and significance in this connection that Brock and Hunter³ using three-day periods in contrast to the seven-day periods used in these experiments, found much larger variations in the retention of iron. From table 1 it is also apparent that when the administration of ferrous sulphate was discontinued on completion of the tenth period, re-excretion of some of the iron retained took place during the eleventh, twelfth and thirteenth periods. In brief, the total amount of iron retained by the child over the fourteen weeks was approximately 3·5 grammes. The normal iron content of a child of this age is about 1·5 grammes, so that presumably the body stores of iron were trebled in amount.

Case 2. A. C., a boy aged ten years, was admitted suffering from subacute rheumatism. An iron-balance study (table 2) was begun as soon as the sedimentation rate had fallen to normal. The first period was, as in the preceding case, a control period. From the second to the end of the seventh period 4 grammes of ferrous sulphate per week were administered, and from the eighth to the end of the twelfth period, 8 grammes

TABLE 1.
ABSORPTION AND RETENTION OF IRON IN A NORMAL SUBJECT.
E. S., AGED 10 $\frac{1}{2}$ YEARS. CHOREA.
Wt. : 24.72 KG. BLOOD VOLUME : $\frac{24.72}{15} = 1.65$ LITRES.

PERIOD.	INTAKE MGM. FE.	OUTPUT MGM. FE.	RETENTION MGM. FE.	PER CENT. RETENTION.	Hb. PER CENT.	R.B.C. PER C.MM.	IRON (MGM.) AS Hb.	IRON (MGM.) RETAINED AS Hb.	PER CENT. OF RETENTION UTILIZED.	PER CENT. OF INTAKE UTILIZED.
1	37.87	4.08	33.79	90	90	5,100,000	871			
2	841.32	107.49	733.73	87	90	4,960,000	871	Nil	Nil	Nil
3	841.32	220.58	620.74	74	92	5,380,000	890	21	3.4	2.5
4	841.32	—	—	—	92	4,980,000	890	Nil	—	—
5	841.32	—	—	—	92	4,980,000	890	Nil	—	—
6	841.32	236.37	604.95	72	95	5,000,000	919	29	4.8	3.4
7	1644.77	699.03	945.74	57	95	4,970,000	919	Nil	Nil	Nil
8	1644.77	1177.26	467.51	27	95	5,190,000	919	Nil	Nil	Nil
9	1644.77	389.86	1254.91	76	95	4,960,000	919	Nil	Nil	Nil
10	1644.77	1855.79	-211.02	Nil	95	5,270,000	919	Nil	Nil	Nil
11	37.87	1631.62	-1593.84	Nil	95	5,040,000	919	Nil	Nil	Nil
12	37.87	783.77	-745.90	Nil	95	5,070,000	919	Nil	Nil	Nil
13	37.87	1107.28	-69.41	Nil	95	5,020,000	919	Nil	Nil	Nil
14	37.87	23.58	+14.29	+37	95	5,130,000	919	Nil	Nil	Nil

TABLE 2.
ABSORPTION AND RETENTION OF IRON IN A NORMAL SUBJECT.
A. C., AGED 9½ YEARS. RHEUMATISM.
WT.: 20.79 KGm. BLOOD VOLUME: $\frac{20.79}{15}$ = 1.39 LITRES.

PERIOD.	INTAKE MGm. FE.	OUTPUT MGm. FE.	RETENTION MGm. FE.	PER CENT. RETENTION.	Hb. PER CENT.	R.B.C. PER C.MM.	IRON (MGm.) AS Hb.	IRON (MGm.) RETAINED AS Hb.	PER CENT. OF RETENTION UTILIZED.	PER CENT. OF INTAKE UTILIZED.
1	39.48	105.13	-65.64	Nil	85	4,880,000	683			
2	842.93	410.21	432.72	51	85	4,570,000	683	Nil	Nil	Nil
3	842.93	948.09	-105.16	Nil	85	4,780,000	683	44	21.1	5.2
4	842.93	633.92	209.01	25	90	4,960,000	727	Nil	Nil	Nil
5	842.93	—	—	—	90	5,120,000	727	Nil	Nil	Nil
6	842.93	—	—	—	90	5,000,000	727	Nil	Nil	Nil
7	842.93	585.38	257.55	30	90	4,750,000	727	Nil	Nil	Nil
8	1646.38	1055.97	590.41	36	90	5,010,000	727	Nil	Nil	Nil
9	1646.38	1583.45	62.93	4	90	4,870,000	727	Nil	Nil	Nil
10	1646.38	1930.09	-283.71	Nil	90	5,230,000	727	Nil	Nil	Nil
11	1646.38	1577.74	68.64	4	90	5,160,000	727	Nil	Nil	Nil
12	1646.38	1644.80	1.58	0.9	90	5,020,000	727	Nil	Nil	Nil

TABLE 3.
ABSORPTION AND RETENTION OF IRON IN A NORMAL SUBJECT.
G. N., AGED $1\frac{1}{2}$ YEARS. INFANTILE ATROPHY.
Wt.: 4.68 KGM. BLOOD VOLUME: $\frac{4.68}{15} = 0.312$ LITRES.

PERIOD.	INTAKE MGM. FE.	OUTPUT MGM. FE.	RETENTION MGM. FE.	PER CENT. RETENTION.	Hb. PER CENT.	R.B.C. PER C.MM.	IRON (MGM.) AS Hb.	IRON (MGM.) RETAINED AS Hb.	PER CENT. OF RETENTION UTILIZED.	PER CENT. OF INTAKE UTILIZED.
1	820.11	430.76	389.35	47	85	4,620,000	156			
2	820.11	207.12	612.99	75	85	4,660,000	156	Nil	Nil	Nil
6	820.11	317.65	502.46	66	85	4,950,000	156	Nil	Nil	Nil
7	16.66	-81.59	-64.93	Nil	85	4,730,000	156	Nil	Nil	Nil
8	16.66	12.91	3.75	22	85	4,740,000	156	Nil	Nil	Nil

TABLE 4.
ABSORPTION AND RETENTION OF IRON IN A NORMAL SUBJECT.
J. McE., AGED 1½ YEARS. INFANTILE ATROPHY.
WT.: 5.94 KG. BLOOD VOLUME: 5.94 = 0.396 LITRES.
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PERIOD.	INTAKE MGM. FE.	OUTPUT MGM. FE.	RETENTION MGM. FE.	PER CENT. RETENTION.	Hb. PER CENT.	R.B.C. PER C.MM.	IRON (MGM.) AS Hb.	IRON (MGM.) RETAINED AS Hb.	PER CENT. OF RETENTION UTILIZED.	PER CENT. OF INTAKE UTILIZED.
*1	744.37	322.30	422.27	56	75	4,010,000	174			
2	821.09	—	—	—	70	4,490,000	163	-11	—	—
3	821.09	—	—	—	80	5,450,000	186	+23	—	—
4	821.09	612.05	209.04	25	85	5,150,000	197	11	5.3	1.3
5	821.09	641.00	180.09	22	90	5,100,000	208	11	6.1	1.3
6	821.09	730.79	90.30	11	90	5,100,000	208	Nil	Nil	Nil
7	821.09	626.04	195.05	24	90	4,750,000	203	Nil	Nil	Nil
8	17.64	104.72	-87.08	Nil	90	4,970,000	203	Nil	Nil	Nil
9	17.64	9.27	8.37	45	90					

* The total iron intake during the first period is less than those given for the other periods up to the seventh. This is due to the fact that the infant vomited two doses of iron during this period, and thus the figures given for this period are less accurate than is the case in the other periods.

TABLE 5.
ABSORPTION AND RETENTION OF IRON IN A CASE OF NUTRITIONAL ANAEMIA.
I. D., AGED 3 YEARS. NUTRITIONAL ANAEMIA.
WT.: 12 KG. BLOOD VOLUME: 15

PERIOD.	INTAKE MG. FE.	OUTPUT MG. FE.	RETENTION MG. FE.	PER CENT. RETENTION.	Hb. PER CENT.	R.B.C. PER C.MM.	IRON (MG. FE.) AS Hb.	IRON (MG. FE.) RETAINED AS Hb.	PER CENT. OF RETENTION UTILIZED.	PER CENT. OF INTAKE UTILIZED.
1	23.31	20.23	3.08	13	35	3,430,000	163			
2	826.76	845.80	479.96	58	39	3,870,000	196	33	6.9	4.0
3	826.76	385.89	440.87	53	52	4,360,000	244	48	10.9	5.8
4	826.76	339.32	487.44	59	63	5,040,000	295	51	10.5	6.2
5	826.76	245.76	581.00	70	78	4,980,000	365	70	12.0	8.4
6	826.76	178.29	638.47	77	85	5,290,000	399	34	5.3	4.1
7	826.76	584.64	242.12	27	87	5,000,000	405	6	2.5	0.7
8	835.51	812.61	22.90	3	90	5,070,000	422	17	73.9	2.0
9	835.51	676.18	159.33	19	90	5,070,000	422	Nil	Nil	Nil
10	835.51	1113.15	-277.64	Nil	90	5,010,000	422	Nil	Nil	Nil
11	835.51	523.91	311.60	37	90	5,050,000	422	Nil	Nil	Nil
12	82.06	390.41	-358.35	Nil	90	5,070,000	422	Nil	Nil	Nil
13	82.06	33.69	-1.63	Nil	90	5,010,000	422	Nil	Nil	Nil
14	82.06	44.79	-12.73	Nil	90	5,000,000	422	Nil	Nil	Nil
15	82.06	24.47	7.59	24	90	5,020,000	422	Nil	Nil	Nil
16	82.06	17.86	14.20	44	90	5,040,000	422	Nil	Nil	Nil

per week. The blood picture was normal throughout the period of observation. During the second period the retention of iron was equivalent to 51 per cent. of the intake, while during the third and tenth periods, on the other hand, there were negative balances of 105·16 and 283·71 milligrammes respectively. It is obvious that the total retention of iron for the duration of the study was proportionately much less than was seen to occur in case 1.

Case 3. G. N., aged seven months, was admitted with infantile atrophy. The results from the iron-balance study on this infant are shown in table 3. During the first six periods on metabolism the infant received orally 4 grammes of ferrous sulphate per week, the iron intake per weekly period being 820·11 milligrammes. The administration of ferrous iron was stopped during the last two periods of the experiment (that is the seventh and eighth), the iron intake of 16·66 milligrammes per period being derived in those periods from the food which consisted of cow's milk. The development of excoriation of the buttocks prevented the determination of the iron retention during the third, fourth and fifth periods. Table 3 shows that the infant retained large amounts of the iron ingested. The total iron retention in the body over the eight weeks of the metabolism study (at the rate shown in periods one, two and six) amounted approximately to the remarkable figure of 2·5 grammes which is several times the amount of iron normally present in the whole body of an infant at this age. An accumulation of such magnitude raises the question as the possibility of toxic effects resulting from saturation of the tissues with iron. No untoward symptoms were observed, and it is of interest to note in passing that a careful perusal of the literature has brought to light only one authentic case of toxic effects following the administration of iron (Hurst¹³).

Case 4. J. McE., aged eight months, was admitted with infantile atrophy. Table 4 summarizes the results obtained from an iron-balance study, lasting over a period of nine weeks. Throughout each of the first seven weekly periods 4 grammes of ferrous sulphate were administered orally. Thereafter the iron was omitted. This infant also retained large amounts of iron, although the retention did not approach the huge amounts recorded in case 3 in spite of the fact, noted in table 4, that the infant exhibited a mild hypochromic anaemia at the commencement of the study, whereas in case 3 high haemoglobin values were obtained throughout.

Results : Patients with hypochromic anaemia

Case 5. P. C., a boy aged three years was admitted suffering from a profound hypochromic anaemia. The haemoglobin was 35 per cent., red blood cells, 3,430,000 per c.mm., and colour index, 0·51. An iron-balance study was carried out while the boy was being treated with 4 grammes of ferrous sulphate per week. The results are tabulated in table 5.

In this case, as in the others, the iron-content of the circulating haemoglobin as noted in the accompanying tables, was calculated by taking the blood volume to be $\frac{\text{body weight in kilogrammes}}{15}$ litres, and the iron-

content of the haemoglobin to be 0·335 per cent. (White House Conference²⁹). In this way the iron utilized for the formation of the new haemoglobin could be estimated, and the percentage of the retained iron so used calculated with a reasonable degree of accuracy (table 5). It is observed that this patient retained a large percentage of the iron administered. It is also seen that during all the periods of observation only a small percentage of the

large total iron retention was utilized in the building of new haemoglobin, the remainder being stored presumably in the liver as inert metal as far as haemoglobin formation is concerned. This point is more forcibly brought home, if it is realized that between the first period and the end of the eighth period 2895.84 milligrammes of iron were retained, although the rise of 55 per cent. in the haemoglobin during that period represented the addition to an 0.8 litre circulation of only 259 milligrammes of iron (equivalent to only 9 per cent. of the total retention of 2895.84 milligrammes). These figures, obtained from observations over a much longer period, agree very closely with the figures published by Brock² for similar experiments on adults suffering from idiopathic hypochromic anaemia.

Case 6. J. C., aged ten months, presented, on admission to hospital, the picture of hypochromic anaemia of moderately severe degree. As in case 5 an iron-balance study was performed while the infant was under treatment for anaemia (table 6). In this case also the haemoglobin increase bore little relationship to the iron retained. The haemoglobin rose by 6 per cent. in the seven days of the second weekly period (blood examinations being performed on the last day of each period); whereas the amount of iron retained by the body in those seven days (528.78 milligrammes) would have allowed an increase to more than 100 per cent. if the iron had been fully utilized for haemoglobin formation. The total amount of iron retained by this infant, during the second, third, fourth, fifth and sixth periods on metabolism, that is, during the time taken for the haemoglobin to rise from 50 to 85 per cent., was enough to produce a rise in the haemoglobin of more than 17 per cent. per day during that same period of time. The actual daily rise in haemoglobin was only 1 per cent.

Relation of gastric acidity to retention

It has been shown by Heath¹¹ that the haemoglobin and reticulocytes respond better to a given dose of iron when the gastric secretion is normal; he therefore draws the conclusion that the 'absence of free HCl in the gastric contents probably is a factor in preventing the adequate absorption of iron.' Mettier and Minot¹⁷ from a series of experiments with acid-buffered meat mixtures came to the following conclusions:—'The studies appear to indicate that soluble iron compounds are absorbed from the gastro-intestinal tract or utilized more readily for blood formation when administered with acid than with alkaline meals.'

With these facts and ideas in mind it was decided to perform a test-meal on every case at the completion of the iron-balance study. The accompanying six charts depict the results of the gastric analyses in the customary manner in the six cases already described. The numbers of the charts correspond to the cases to which they refer.

Scrutiny of the charts reveal certain interesting facts. Case 2 in which, it will be remembered, comparatively small amounts of iron were retained, showed a high gastric acidity. Case 3 which retained remarkably large amounts of iron over a period of eight weeks, showed not only the absence of free hydrochloric acid in the stomach under the conditions of the Rehfuß

TABLE 6.
ABSORPTION AND RETENTION OF IRON IN A CASE OF NUTRITIONAL ANAEMIA.
J. C., AGED $1\frac{9}{12}$ YEARS. NUTRITIONAL ANAEMIA.
WT.: 9.31 KGM. BLOOD VOLUME: $\frac{9.31}{15} = 0.62$ LITRES.

PERIOD.	INTAKE MGM. FE.	OUTPUT MGM. FE.	RETENTION MGM. FE.	PER CENT. RETENTION.	Hb. PER CENT.	R.B.C. PER C.MM.	IRON (MGM.) AS Hb.	IRON (MGM.) RETAINED AS Hb.	PER CENT. OF RETENTION UTILIZED.	PER CENT. OF INTAKE UTILIZED.
1	18.18	5.62	12.56	61	50	4,580,000	182			
2	824.66	295.93	528.73	64	56	4,320,000	204	22	4.1	2.6
3	824.66	221.54	600.12	73	65	5,050,000	286	32	5.3	3.9
4	824.66	522.35	302.31	37	73	5,000,000	265	29	9.6	3.5
5	824.66	429.86	394.80	47	83	5,080,000	301	36	9.1	4.4
6	824.66	411.88	412.78	49	85	5,040,000	309	8	1.9	0.9
7	824.66	354.95	469.71	57	85	5,080,000	309	Nil	Nil	Nil
8	824.66	537.66	287.00	35	85	5,030,000	309	Nil	Nil	Nil

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CHART I.

RESULTS OF GASTRIC ANALYSIS IN CASE 1.

E. S. CHOREA.

CHART II.

RESULTS OF GASTRIC ANALYSIS IN CASE 2.

A.C. RHEUMATIC INFECTION.

CHART III.

RESULT OF GASTRIC ANALYSIS IN CASE 3.

G.N. INFANTILE ATROPHY.

CHART IV.

RESULTS OF GASTRIC ANALYSIS IN CASE 4.

J.McE. INFANTILE ATROPHY.

N.B.—After histamine injection there was no free HCl.

CHART V.

RESULTS OF GASTRIC ANALYSIS IN CASE 5.

P.D. NUTRITIONAL ANAEMIA.

CHART VI.

RESULTS OF GASTRIC ANALYSIS IN CASE 6.

J.C. NUTRITIONAL ANAEMIA.

test meal, but its absence even after stimulation of the acid-secreting glands with histamine.

This case, therefore, presented a true achylia gastrica in conjunction with the capacity to absorb large amounts of iron from the intestine. Cases 5 and 6 presented hypochlorhydria, a not uncommon finding in nutritional anaemia of infancy and childhood. (Hawksley, Lightwood and Bailey¹⁰; Ogilvie¹⁸.) Case 5 absorbed enough iron in the first eight weeks of treatment to allow of an increase in haemoglobin of 13 per cent. per day and case 6 it will be recalled, absorbed enough iron to allow of an increase in haemoglobin of over 17 per cent. per day.

It is realized that there is hardly justification for drawing conclusions from so small a series of gastric analyses, but the results show that a low degree of gastric acidity does not preclude the ready retention of iron, which in the presence of anaemia may be used for haemoglobin building. Stewart²⁵ has approached this question from a more clinical aspect, and is inclined to attach less importance than other workers to the diminished gastric acidity as a factor in the etiology of the nutritional anaemias of infants (Faber, Mermod, Gleason and Watkins⁷). She concludes that it would appear extremely likely that the impairment of the gastric secretion is the result rather than the cause of the anaemia.

Discussion

The results of the metabolism studies carried out in this series of cases demonstrate clearly that the body is capable of retaining remarkably large amounts of iron administered in the inorganic state. Nor is it possible, in view of these results, to assume that the necessity for large doses of iron in the treatment of nutritional anaemia is dependent on the poor absorption of iron-salts from the intestine. Other workers (Brock and Hunter³, Reimann, Fritsch and Schick²³) have formulated similar conclusions upon the results of iron-balance studies in adults.

It would appear also that high rates of iron retention can be maintained over long periods, with resulting accumulation in the body of large amounts of iron. This was seen to be the case not only in the two patients showing anaemia, but also in three of the four non-anaemic patients. Even in case 2 considerable amounts of iron were retained, although the total retention for the duration of the study was proportionately much less than was seen to occur in case 1. The reason for this variation in the ability to retain iron is not obvious, but a similar observation has been made by Brock and Hunter³ and Reimann, Fritsch and Schick²³.

Apart from the fact that for a period of three weeks after the administration of ferrous sulphate was discontinued case 1 appeared to re-excrete some of the iron retained, there is no definite evidence forthcoming from the above results to indicate that the capacity to store iron is limited. Case 5 after ten weeks' administration of 4 grammes of ferrous sulphate per week, had retained 3086.05 milligrammes of iron, of which only 259 milli-

grammes were used in the synthesis of haemoglobin, and only 372·71 milligrammes of iron were excreted after discontinuance of the administration of iron on completion of the eleventh period, before a positive iron-balance was again established during the fifteenth period. Cases 3 and 4 after retaining large amounts of iron over periods of six and seven weeks respectively, presented negative iron-balances for one weekly period only, after the stopping of massive iron-dosage; this can be explained by the fact that there is always a certain lag in the excretion of unabsorbed iron by the faeces.

It would appear, then, that the body is capable of storing in the tissues a large excess of iron over an indefinite period of time, and this again raises the question as to the possibility of toxic effects resulting. Polson²⁰ maintained a high iron content in the livers of rabbits over periods of one to four years by means of repeated administration of iron subcutaneously and intraperitoneally and found no evidence of hepatic cirrhosis or pancreatic damage in any of the rabbits. He concluded that excess of iron in the body over long periods caused neither liver cirrhosis nor haemochromatosis in rabbits, and it is unlikely that excess of iron is responsible for the hepatic and pancreatic lesions of human haemochromatosis. Cappell⁴ after giving large doses of iron to mice and rats for as long as fourteen months found no evidence of haemochromatosis in the organs. The most outstanding contra-indication to the use of massive iron therapy can therefore be discontinued.

Once again it is necessary to seek an explanation of the need for such large doses, and of the inefficacy of smaller doses which only supply enough iron for haemoglobin formation. Brock² suggests the possibility that large doses of iron are necessary in order to obtain a sufficiency of the copper impurity present in most iron preparations. He admits, however, that the claims of some workers, that the copper is effective as an adjuvant to iron in certain cases (Waddell, Hart, Steenbock and Elvehjem²⁸; Lewis¹⁵; Josephs¹⁴) have not been generally confirmed. Against this theory also is the fact that ferrous sulphate used in the metabolism studies here reported contained less than 0·0005 per cent. of copper, so that no such interpretation can be put on the results of this series. Another possible explanation also advanced by Brock² is that large quantities of iron may alter the chemical composition of the intestinal contents and thereby increase the absorption of some undetected haemopoietic factor. It is admitted, however, that there is no real evidence as to the existence of such a haemopoietic factor.

There is another explanation, however, which can be advanced as a result of the foregoing metabolism studies. Assuming that iron once deposited in the tissues is not available for the regeneration of haemoglobin, unless it has been derived originally from the destruction of haemoglobin in the body, it follows that the great bulk of iron absorbed from the intestine during massive dosage with inorganic salts, would not be available as it would first find its way to the liver where it would be stored and thus

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rendered inactive for haemoglobin synthesis. It is reasonable to suppose then, that only by giving massive doses of iron can the rate at which it is stored by the liver be overcome and the excess iron be pushed past the liver directly into the blood serum, from whence it may be utilized for haemoglobin formation. This would explain the 100 per cent. utilization of parenterally administered inorganic iron, as demonstrated by Heath, Strauss and Castle¹², such iron presumably being absorbed directly into the systemic circulation, whereas orally administered iron is absorbed into the portal circulation and stored in the liver. Of interest in this connection also, is the finding of Reicker²² that the level of the serum iron can be raised by the administration orally of large doses.

It is probable, however, that the final explanation of the reason why it is necessary to administer iron in amounts far in excess of the actual requirements for the regeneration of haemoglobin will only be attained when knowledge regarding the chemical combinations in which iron occurs in the tissues is more precise, and also when a fuller understanding of the functions of the various components of the haemopoietic tissues is available.

Summary

(i) Observations on the retention of iron over long periods have been made in four non-anaemic and two anaemic children. The body is capable of retaining large amounts of iron. Only a small percentage of this iron is utilized for the synthesis of haemoglobin, even in those cases showing severe anaemia.

(ii) The necessity for giving large doses of iron by mouth does not depend on the poor absorption by the intestine.

(iii) No evidence was obtained that variations in gastric acidity influenced the retention of iron.

(iv) The suggestion is made that the iron stored in the liver is unavailable for haemoglobin formation, and only iron which overflows from the liver into the circulation can be utilized for haemoglobin formation. Massive doses are necessary to effect this.

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