We intend to incorporate this method into the practical side of a growth study, as it will not only greatly increase our accuracy but provide us with permanent records of the tissue growth.

We are grateful to Dr. T. H. Hills and Dr. E. A. Miskin for many helpful suggestions.

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THE THERAPEUTIC RESPONSE OF SECONDARY ANAEMIAS TO ORGANIC AND INORGANIC IRON SALTS

BY

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In 1926 Starkenstein discovered that only ferrous iron is utilizable by the haemopoietic system. Since then inorganic ferrous salts have provided the standard form of ferrotherapy. In particular, ferrous sulphate has been widely used in various official and proprietary presentations. The *National Formulary 1952* informs us that there is need for only two oral preparations of iron in the treatment of ferro-sensitive anaemias. These are those containing either ferrous sulphate or iron and ammonium citrate.

Benstead and Theobald (1952), in their work on the incidence of anaemia in pregnancy, showed in their series of cases that in one group of patients 33%, and in another group 40.2%, found it difficult or impossible to tolerate ferrous sulphate tablets. They concluded that 30–40% of antenatal patients do not, in fact, consume these tablets when prescribed as routine in antenatal departments. It therefore seems that, although ferrous sulphate tablets are widely ordered, their therapeutic value, owing to gastric intolerance, leaves much to be desired.

Following their publication I wrote (Haler, 1952) that I was investigating the therapeutic effects of the organic ferrous gluconate in ferro-sensitive anaemias. The results are herewith appended.

Ferrous gluconate is the normal ferrous salt of D-gluconic acid; it is a dihydrate crystal and contains 11.5% of ferrous iron.

Staub (1949), Jasinki (1949), and others have shown that this salt is the most easily absorbed of all ferrous salts. It does not appear to produce gastric upsets. The following figures result from the decision to compare the therapeutic response of ferro-sensitive anaemias when treated with the standard inorganic iron preparations with those obtained from the use of ferrous gluconate.

The Investigation

The cases investigated are classified as follows:

Anaemia following post-partum haemorrhage	..	25	cases
" " normal delivery	..	13	"
" " illness	..	6	"

TABLE I

Code	No. of Cases	Key	Daily Dosage of Available Iron
Group A. Inorganic Iron Preparations			
A	5	Proprietary ferrous sulphate and folic acid in capsules	184 mg.
B	1	Proprietary ferrous sulphate capsules	184 "
C	11	Tab. ferrous sulphate Co. N.F.	180 "
D	1	Ferri dia'sata	180 "
F	1	Proprietary saccharated iron for intravenous use	216 "
J	1	Proprietary iron and folic acid tablets	100 "
			184 "
Group B. Organic Iron Preparations			
I	23	Ferrous gluconate	105 "

The cases were selected at random, the average Hb value (King and Gilchrist, 1947; King *et al.*, 1947, 1948a, 1948b, 1948c, 1951; Macfarlane *et al.*, 1948; Donaldson *et al.*, 1951) over the series being 65%; organic and inorganic iron preparations were given to alternate cases. The organic preparation of iron was available as a liquid proprietary preparation which in addition contained aneurin hydrochloride, nicotinamide, and riboflavin in blackcurrant juice syrup, which also provided 5 mg. of natural vitamin C per drachm.

In Group A cases (Table I) supplementary vitamins were given to those patients in whom avitaminosis was suspected.

TABLE II

Case No.	Group	Hb Initial	Hb Final	Hb Increase	Hb Mean Daily Increase %	Total Fe++ Administered	% Fe++ Utilized	Coef. ficient
Group A. Inorganic Iron Preparations								
1	A	62 (9.25)	90 (13.5)	28 (4.25)	1.16	4,416	19.02	16.4
2	A	70 (10.45)	92 (13.80)	22 (3.35)	0.54	7,554	8.7	16.1
3	A	80 (12.0)	86 (12.9)	6 (0.90)	1.2	920	19.6	16.3
4	A	68 (10.15)	80 (12.0)	12 (1.85)	1.5	1,288	28.0	16.45
5	A	32 (4.75)	41 (6.1)	9 (1.35)	1.0	900	30.0	30.0
6	C	52 (7.7)	74 (11.05)	22 (3.35)	2.2	1,800	36.0	16.4
7	C	60 (9.0)	76 (11.4)	16 (2.4)	0.67	2,880	18.8	28.0
8	C	54 (8.05)	68 (10.15)	14 (2.1)	0.67	3,780	11.1	16.6
9	C	70 (10.5)	90 (13.5)	20 (3.0)	0.57	6,300	9.5	16.7
10	C	68 (10.15)	90 (13.5)	22 (3.35)	0.43	8,820	7.5	17.4
11	C	48 (7.2)	72 (10.7)	24 (3.5)	0.84	5,580	13.9	16.6
12	C	68 (10.15)	82 (12.3)	14 (2.15)	0.5	5,040	8.3	16.6
13	C	34 (5.00)	76 (11.4)	42 (6.4)	0.875	8,640	14.5	16.7
14	C	58 (8.65)	84 (12.6)	26 (3.95)	0.74	6,300	12.4	16.75
15	C	60 (9.0)	78 (11.7)	18 (2.7)	0.47	13,680	4.0	8.5
16	C	50 (7.5)	58 (8.65)	8 (1.15)	0.53	5,400	4.5	8.5
17	B	76 (11.4)	80 (12.0)	4 (0.60)	1.0	736	16.3	16.3
18	D	48 (7.2)	70 (10.5)	22 (3.30)	1.0	7,560	8.8	8.8
19	F	45 (6.7)	75 (11.2)	30 (4.5)	1.4	4,536	13.9	10.0
20	H	41 (6.1)	58 (8.65)	17 (2.55)	3.4	525	97.0	28.6
21	J	55 (8.2)	82 (12.3)	27 (4.10)	0.77	6,440	7.9	10.2
Group B. Organic Iron Preparation								
23	I	62 (9.2)	92 (13.8)	30 (4.6)	1.67	1,890	47.6	29.5
24	I	58 (8.65)	92 (13.8)	34 (5.15)	1.88	1,890	52.9	28.0
25	I	76 (11.4)	90 (13.5)	14 (2.1)	1.2	1,890	22.2	18.5
26	I	72 (10.7)	94 (14.1)	22 (3.4)	1.8	1,890	50.8	28.2
27	I	70 (10.5)	98 (14.85)	28 (4.35)	1.6	1,890	44.4	27.8
28	I	80 (12.0)	98 (14.85)	18 (2.85)	1.0	1,890	28.6	28.6
29	I	47 (7.0)	84 (12.6)	37 (5.6)	1.8	2,205	50.2	27.9
30	I	80 (12.0)	98 (14.85)	18 (2.85)	1.5	1,260	42.9	28.6
31	I	54 (8.0)	92 (13.8)	38 (5.8)	2.1	1,890	60.3	28.8
32	I	72 (10.7)	90 (13.5)	18 (2.8)	2.6	735	75.2	28.9
33	I	72 (10.7)	88 (13.2)	16 (2.5)	1.33	1,260	38.1	28.7
34	I	77 (11.5)	95 (14.2)	18 (2.7)	1.5	1,260	42.9	28.6
35	I	76 (11.4)	96 (14.4)	20 (3.0)	1.67	1,890	47.6	28.5
36	I	78 (11.7)	96 (14.4)	18 (2.7)	2.33	1,260	66.6	28.6
37	I	68 (10.15)	90 (13.50)	22 (3.35)	1.2	1,890	34.9	29.0
38	I	78 (11.7)	93 (14.0)	15 (2.3)	1.5	1,050	42.8	28.8
39	I	90 (13.5)	96 (14.4)	6 (0.9)	0.85	735	25.0	29.4
40	I	60 (9.0)	82 (12.3)	22 (3.3)	1.8	1,260	52.4	29.0
41	I	74 (11.05)	96 (14.4)	22 (3.35)	1.0	2,205	30.0	30.0
42	I	70 (10.5)	94 (14.1)	24 (3.6)	0.85	2,940	24.5	28.8
43	I	72 (10.7)	98 (14.85)	26 (4.15)	0.62	4,410	17.7	28.6
44	I	65 (9.7)	100 (15.0)	35 (5.3)	1.2	2,940	35.7	29.8
45	I	68 (10.15)	78 (11.7)	10 (1.55)	1.4	735	40.8	29.2

	Available Fe++/day
A = "Plastules" with folic acid	 184 mg.
B = "Plastules" plain	 184 "
C = "Ferso'ate"	 180 "
D = Tab ferri sulph. co.	 180 "
F = Ferri dia'sat.	 216 "
G = Ferri ammon. cit.	 189 "
H = "Ferrivenin"	 100 "
I = "Cerevon"	 105 "
J = "Folvite" with iron ("Folvron")	 184 "

Assessment of the therapeutic response was based on the following factors: (1) total increase in grammes of Hb per 100 ml.; (2) average daily Hb increase per 100 ml. (taking 15 g. Hb as 100%); (3) the iron utilization coefficient, calculated on the basis that 30 mg. of iron is required to raise the Hb by 1%; and (4) the average number of treatment-days required to raise the Hb value to within normal limits. Routine haematological investigation was carried out before and during treatment, and the results were carefully recorded.

Study of the Therapeutic Response

Group A (Table II) shows the results of treatment in those cases treated with inorganic iron. The average total dosage of available iron administered was 4,900 mg. The average Hb increase in this group was 2.9 g. per 100 ml. It can therefore be deduced that the iron utilization coefficient for this group was 18.1. This approximates to the findings of Witts (1936) for the iron utilization coefficient of ferrous sulphate as 14. The mean daily Hb increase was 1.02%, which confirms the therapeutic response to be expected. The average period of treatment over this group was 21.7 days.

In Group B the average total dosage of available organic iron given was 1,359 mg. The average Hb increase was 3.4 g. per 100 ml., indicating an iron utilization coefficient of 28.3. This compares favourably with the finding of Staub following his study of ferrous gluconate in tablet form, which showed an iron utilization coefficient of $22 \pm 5\%$. The mean daily Hb increase in this group was 1.49% and the average period of treatment 17.8 days.

The analysis of the haemoglobin response in both the groups indicates that the organic iron-treated group shows a remarkably constant iron utilization coefficient of 28.3. This compares with the inorganic iron-treated group, which shows an average utilization coefficient of 18.1. This increased haemoglobin response was achieved in a shorter period of time, and with a reduced overall dosage of iron.

An Interesting Case Noted During Study

Case 20.—A full report on this case of post-natal anaemia following post-partum haemorrhage is given, as iron therapy was started with intravenous iron and completed with the ferrous gluconate preparation. The findings were as follows:

	Date	R.B.C. (mill.)	Hb Haldane (%)	C.I.	M.C.D. (μ)	Retics.	
						%	Total
Ferrivenin, 100 mg. daily ..	20/5/52	2.0	32	0.8	6.85	0.6	12,000
	23/5/52	2.1	34	0.81	6.8	0.6	12,000
Ferrous gluconate, 105 mg. available iron daily ..	27/5/52	2.5	41	0.82	6.85	0.45	10,000
After 5 days	31/5/52	3.12	58	0.92	6.9	1.4	43,000
" 10 "	9/6/52	4.32	74	0.84	6.7	1.9	82,000

Tolerance and Side-effects

It is usually stated that ferrous sulphate tablets are well tolerated. I first learnt to doubt this when I was treated for anaemia arising during a severe pneumonia. My gastric experiences during that treatment led me to watch for other people's intolerance to iron. It has been found that quite 25% of out-patients treated with the standard therapy voluntarily discontinue treatment because they are unwilling or unable to tolerate the gastric side-effects.

Graph showing group positions in relation to average daily haemoglobin increase.

The liquid ferrous gluconate has proved so effective that patients in the ward have asked to be taken off the tablets and to be put on to the "liquid tonic."

Summary

Of all the preparations used in this trial, the liquid ferrous gluconate preparation was far and away the most popular with patients, and produced a therapeutic response out of all expectations.

A study was made of the relative therapeutic values of organic and inorganic iron salts in the treatment of ferro-sensitive anaemia. The inorganic iron preparations provided ferrous sulphate in various presentations, the daily intake of available iron being approximately 180 mg. a day.

The organic iron salt administered was a proprietary liquid ferrous gluconate preparation giving a daily intake of available iron of 105 mg. a day, with the addition of aneurin hydrochloride, nicotinamide, riboflavin, and natural vitamin C which in the dosage given provided 15 mg. of ascorbic acid a day.

An evaluation of the therapeutic response indicates that the group treated with the inorganic iron salt showed a mean daily increase of 1.02% haemoglobin and an iron utilization coefficient of 18.1.

The group treated with the organic preparation showed a mean daily haemoglobin increase of 1.49% and an iron utilization coefficient of 28.3.

The period of treatment required to raise the haemoglobin value to normal limits was 21.7 days in the inorganic iron group and 17.8 days in the organic iron group. The average total dosage of available iron administered in the inorganic group was 4,900 mg. and in the organic group 1,359 mg.

I suggest that the organic iron salt ferrous gluconate seems to produce a more satisfactory haemoglobin response within a shorter period of time than that obtained by the well-known ferrous sulphate preparation.

I wish to acknowledge my indebtedness to my personal laboratory staff for their great and invaluable assistance with the laborious assessment of this mass of figures; to my secretarial

staff for their careful typing in this detailed work; to Messrs. Calmic for their generous supply of ferrous gluconate used in this test; to all those clinicians who have assisted so kindly in placing clinical material at my disposal; and, above all, to all patients who shared in this stimulating piece of laboriously built-up research.

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Medical Memorandum

Vasa Praevia

Vasa praevia may be defined as a condition in which the foetal blood vessels, unsupported by either umbilical cord or placental tissue, traverse the foetal membranes of the lower uterine segment in front of the presenting part. As a rule it is impossible to diagnose abnormalities of the placenta until after delivery. Vasa praevia is an exception to this rule, as on rare occasions the condition has been recognized before rupture of the vessels has occurred. It is a rare condition: a survey of the literature reveals only 52 recorded cases, and for this reason the following case is of interest as an example of an uncommon cause of stillbirth.

CASE REPORT

A primipara first attended the antenatal clinic on October 26, 1951. Her menses had always been regular, and her last menstrual period was on June 24. No abnormality was detected on examination, the height of the uterine fundus corresponding with an 18-weeks pregnancy. She remained well throughout pregnancy. On March 24, 1952, when she was 39 weeks pregnant, premature rupture of the membranes occurred at 5.45 a.m., and she noticed that the liquor was blood-stained. No foetal movements were felt after 6 a.m., and she was admitted to hospital at 9 a.m.

On admission she was having no pains, but was draining liquor which was mixed with a little fresh blood. The blood pressure was 140/80 and there was no albumin in the urine. On abdominal palpation the height and girth of the uterus were compatible with a full-term pregnancy. The lie of the foetus was longitudinal, and the head was deeply engaged. The uterus was not tender to palpation and foetal parts were readily felt. No foetal heart could be heard. On vaginal examination the cervix was partly effaced and one finger dilated. The membranes were ruptured and the vertex was presenting. No umbilical cord could be felt and the liquor was blood-stained. A diagnosis of revealed accidental haemorrhage was made.

Labour began at 1 p.m.; seven hours later the cervix was fully dilated. Throughout the first stage the loss of blood-stained liquor continued, and it was estimated that the total blood loss was about 120 ml. The mother had not felt any foetal movements, nor had the foetal heart been heard since admission. Forceps delivery was performed in the second stage of labour because of maternal distress. The infant was stillborn, weighing 7 lb. 2 oz. (3.2 kg.). No cord was felt on examination under anaesthesia. After delivery of the infant it was noticed that the umbilical cord was pale and that the umbilical vessels, particularly the arteries, contained very little blood. The puerperium was uneventful and the mother left hospital on the tenth day.

Placenta.—This was of normal size and the maternal surface appeared normal. There was no evidence of any retroplacental haematoma. A velamentous insertion of the cord was present, the umbilical vessels traversing the membranes for a distance of about 10 cm. before reaching the foetal surface of the placenta. One of these vessels, an artery, was divided in two by the rent in the membranes through which the baby had been delivered (see illustration).

Necropsy.—At post-mortem examination of the foetus the findings were compatible with foetal death due to anoxia consequent upon blood loss and interference with the foetal circulation. No other cause for death was found.

Edge of placenta, showing a velamentous insertion of the umbilical cord and vasa praevia. A small metal probe has been inserted into the lumen of the divided umbilical artery. (Owing to preservation of the specimen in formalin before photography, the membranes have shrunk.)

COMMENT

Velamentous insertion of the cord is almost a prerequisite for the occurrence of vasa praevia. Only very rarely may it be attributed to vessels running between the lobes of a multipartite placenta; to the vessels of a succenturiate lobe crossing the lower segment; or to a marginal insertion of the cord, in which condition aberrant vessels sometimes traverse the membranes before finally penetrating placental tissue. Rucker and Tureman (1945) state that the incidence of velamentous cord insertion has been given by various authors as between 0.4 and 0.9%. De Lee (1913) declares that there is a much higher incidence in multiple pregnancy. It is often associated with other placental abnormalities—namely, multilobed placentae, placenta succenturiata, and, in particular, placenta praevia. Although in most cases when bleeding from velamentous vessels occurs the vessels are praevia, five cases have been recorded in which vessels in the fundus have been ruptured.

The risk to the foetus is considerable, and foetal death *in utero* may occur from either asphyxia or exsanguination. Asphyxia is due to compression of the aberrant vessels in the lower segment by the presenting part. It is probably the greater of the two dangers to the foetus. Exsanguination may occur if the vessels are torn across.

Should a vasa praevia rupture, the child, even if born alive, may be severely anaemic and neonatal death may occur. The foetal loss in the 53 cases so far recorded has been 55%. This is very similar to the figure of 58% quoted by Graff (1921) in reviewing all cases up to that time. But in the 41 cases (67%) in which rupture of the vessels was known to have occurred the foetal loss was 73%. It must, however, be emphasized that vasa praevia is essentially a foetal complication. The only added hazards to the mother are those attendant upon interference by the accoucheur, such interference being undertaken solely on behalf of the foetus. Caesarean section is indicated in those cases discovered early in labour with the membranes intact, but the operation should only be considered before the vessels rupture, for once haemorrhage has occurred the prognosis for the infant is too bad to justify the increased risk to the mother. McNair (1921) and Vogt (1943) obtained living infants by abdominal delivery.

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