

Iron deficiency after partial gastrectomy

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SYNOPSIS Iron-deficiency anaemia will develop in half the males and nearly all females after partial gastrectomy, and in addition to causing the anaemia the sideropenia may cause any general symptoms such as lassitude, failure to maintain weight, or dumping symptoms.

The variable response to treatment is due to the fact that ferrous iron is not adequately released from coated tablets taken after meals and rapidly emptied from the gastric remnant. Treatment with chelated iron is more reliable, and one tablet taken on lying down each night is adequate in the treatment of mild anaemia and for its prevention in women during the reproductive life.

PART I: AETIOLOGY

After partial gastrectomy iron deficiency is common and notoriously difficult to treat orally (Owren, 1952; Goldeck and Gadermann, 1954; Wallensten, 1954). The object of this study was to clarify the relative importance of the many suggested causes with a view to clinical management.

MATERIAL

All patients of this hospital who underwent partial gastrectomy for a benign ulcer in 1954 and 1955 were followed up with the results shown in Table I.

TABLE I

RESULTS OF FOLLOW-UP OF 347 PATIENTS SUBMITTED TO PARTIAL GASTRECTOMY FOR BENIGN ULCERS DURING 1954 AND 1955

Sex	Male		Female	
	Billroth I	Polya	Billroth I	Polya
Dead	6	12	1	0
Untraced	17	38	3	4
Did not attend	0	1	1	1
Excluded because of a disease with effects on the haematology	2	2	0	0
Seen in person	56	124	18	26
Seen at local hospital	7	5	3	3
Totals seen	63	129	21	29
	242			

The patients were evenly distributed with regard to age, had had similar pre-operative selection and care throughout, were all within three to five years

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of operation, and were well documented, thus being suitable subjects for statistical analysis.

METHODS

After an interview to elicit details of post-operative diet (from which the average daily intake of iron in food was calculated, using Scientific Tables, J. R. Geigy, S.A., Basle, 1956) consumption of alkali and aspirin, and any blood loss or treatment, patients were weighed and venepuncture performed.

Haemoglobin was determined (Gibson and Harrison, 1945) in duplicate, reducing the technical error to $\pm 0.5\%$. The 6% to 11% variation (McCarthy and Van Slyke, 1939) associated with exercise, meals, menses, etc., was minimized by collecting all blood samples at the same time of day and menstrual cycle from subjects who had rested half an hour or more and whose last meal had been taken at least four hours previously. Preliminary tests had shown these precautions reduced the variation to 2%.

Wallensten (1954) used as normal haemoglobin levels 15.4 ± 0.9 g./100 ml. for males and 13.4 ± 0.9 g./100 ml. for females, so that the criteria for anaemia were levels below 13.6 g. for males and below 11.5 g. for females. Levels before operation or haemorrhage were available in 181 of 192 male patients and agree well apart from the wider scatter of random sampling; 15.1 ± 1.3 g./100 ml. Subsequent experience showed (Fig. 1) that after treatment the haemoglobin levels of females rose to within the range expected for normal males, so that one doubts whether the sex difference is physiological.

Haematocrits were determined on all blood samples, and in general the calculated M.C.H.C. confirmed cases of iron deficiency; however, as 16 patients with a normal M.C.H.C. responded to iron therapy, this index is of limited value as an indicator of the need for treatment with iron.

Serum iron was estimated (King and Wootton, 1956) in duplicate, yielding a technical error of $\pm 5\mu\text{g./100 ml.}$

TABLE III
ANAEMIA CAUSED IN 84 MALES AFTER
PARTIAL GASTRECTOMY

		% from Table III
Abnormal iron losses	Pre-operative	12
	Per-operative	3
	Post-operative	5
Abnormal iron intake	Less than 10 mg./day	9
	Aspirin consumption	5
	Total	34

half the females were anaemic, but if the same standards are applied to females as to males, nearly all the females were anaemic (Table IV). After treat-

TABLE IV
INCIDENCE OF ANAEMIA AFTER PARTIAL GASTRECTOMY¹

<i>Present Series Alone</i>			<i>Present series and series of Watson (1947), Lyngar (1950), and Wallensten (1954)</i>	
<i>No. of Patients</i>	<i>No. with Criterion</i>	<i>% Anaemia</i>	<i>No. of Patients</i>	<i>% Anaemia</i>
	Hb < 11.5g.			
Females	21	42	227	40
	Hb < 13.6g.			
Males	84	40	715	49
Females	50	48	207	94

¹This series includes five patients treated for anaemia who are assumed to have had a haemoglobin level below 13.6 g./100 ml.

ment, the haemoglobin levels of both males and females fell within the normal male range except for one man (13.3 g.) and three women (12.6, 12.8, 13.3 g.). The view that iron deficiency was clinically significant is supported by the observation that even when the haemoglobin rise was small, the patient often felt markedly better and 24 of 108 gained weight for the first time since operation. Of the non-anaemic males 23% had serum iron levels below 60 µg./100 ml. which was considered to constitute sideropenia (Waldenström, 1946), and the few of these who were treated responded subjectively in the same way as anaemic patients and gained weight. These observations confirm those of Reimann (1956) and Beutler, Larsh, and Gurney (1959) who have shown that sideropenia has a profound effect on energy, muscle mass, and sexual libido, and support those of Ott and Jasinski (1954) who often cured patients of their dumping symptoms by treating the sideropenia which was invariably present.

THE PATHOGENESIS OF THE IRON DEFICIENCY Iron deficiency in all these cases must be due to present or past blood loss, or to an inadequate supply of

iron. Women who have not passed the menopause lose 500 to 3,000 ml. of blood a year, and of 23 such patients all had a haemoglobin level below 13.6 g., which was exceeded in all cases after treatment. Because of this apparently dominant effect of menstruation, other factors were analysed only in male patients.

Before transfusion became freely available (Morley and Roberts, 1928), survivors from partial gastrectomy for haematemesis were grossly anaemic. Nowadays pre-operative iron loss is less important (Table II) and its contribution can be abolished by adequate transfusion and treatment with iron during convalescence. These same measures minimized the subsequent effects of pre-operative loss, which initially rendered over half the patients anaemic. In the years following operation, overt blood loss, chiefly from haemorrhoids, was of little general significance and individual cases are treated on their own merits. Occult blood loss is rare (Table V) and the speculations of Smith and

TABLE V
OCCULT BLOOD LOSS AFTER PARTIAL GASTRECTOMY

<i>Series</i>	<i>No. of Patients Examined</i>	<i>No. of Patients Found to be Positive</i>
Dedichen (1934)	47	1
Hartfall (1934)	20	1
Lyngar (1950)	146	Rarely
Blake and Rechnitzer (1953)	104	4
Baird and Wilson (1959)		
Not anaemic	32	6
Anaemic	30	3
Choudhury and Williams (1959)	40	0
Stevens <i>et al.</i> (1959) Over 1 year	5	0
This series	84	1

Mallett (1957) are without foundation. There is good evidence against the hypothesis of intermittent loss in that only eight weakly positive occult blood reactions were found in 321 random stools, corresponding to a loss from the average patient of 24 ml. of blood in 321 days, whereas the physiological loss over this period is about 90 ml. Three cases of acute melaena have been ascribed to aspirin consumption, but if these are excluded only 5% of the anaemia could have been caused by aspirin. A low dietary iron intake, possibly causing 9% of the anaemia, was usually due to the eating of small meals as an adaptation to the symptoms of dumping: this constitutes a vicious circle as the dumping symptoms are aggravated by iron deficiency. The age of the patient and the site of the ulcer appear irrelevant.

The factors considered above account for only one third of the anaemia so that the only factor not yet considered, that is, defective iron absorption, must account for the remaining two thirds.

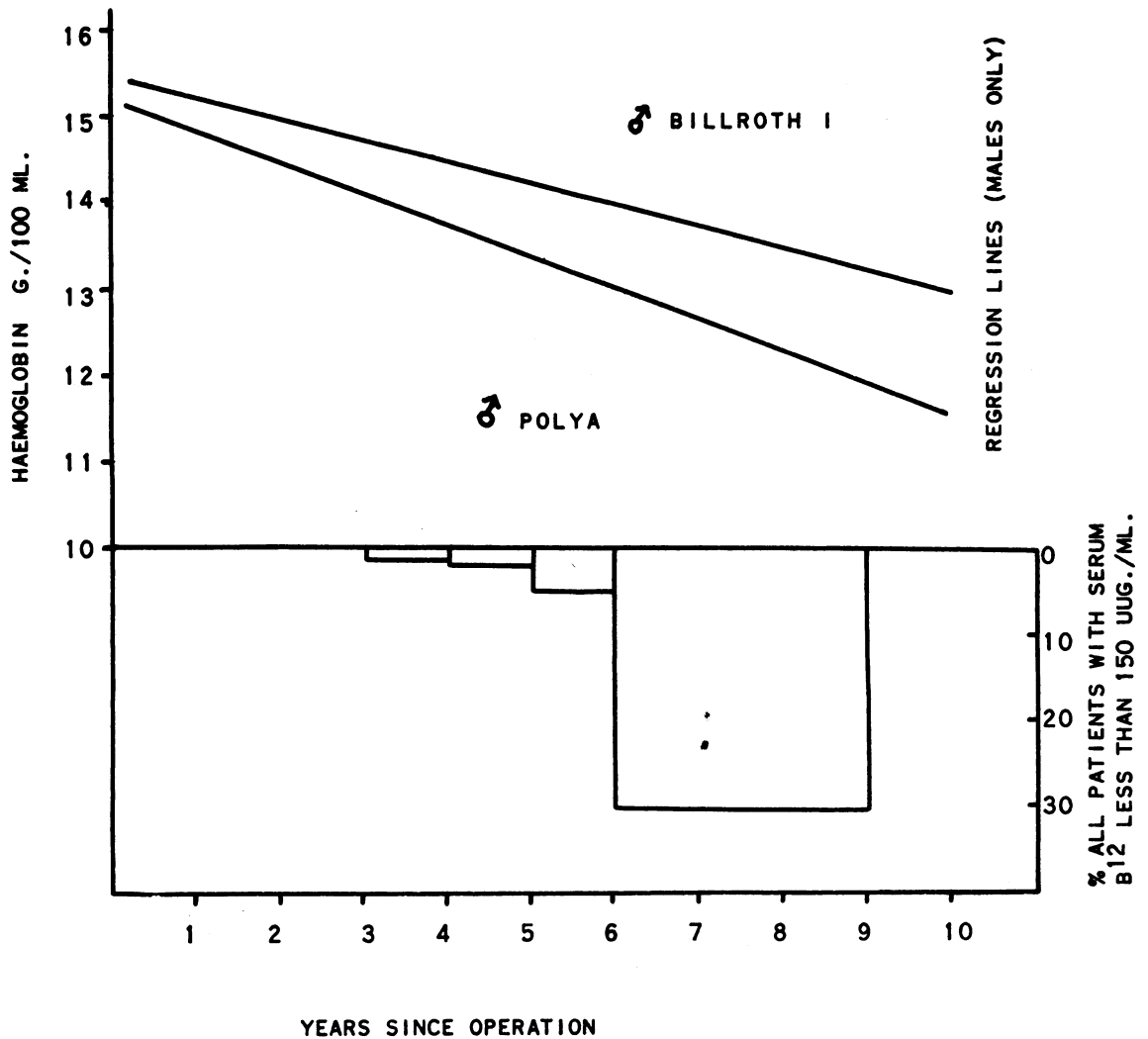


FIG. 2. The degree of anaemia (after Baird and Wilson, 1959) and percentage of subnormal serum B₁₂ levels (after Sewell) in patients over time after partial gastrectomy.

THE ABSORPTION OF IRON Were iron absorption suddenly to cease, a normal man with 1,000 mg. of iron in store and 2,500 mg. in haemoglobin (15 g./100 ml.) would live for three and a half years before his haemoglobin fell below 13.6 g./100 ml., assuming the reasonable loss of 1 mg. of iron daily (Moore, 1955). As most patients were seen more than three and a half years after operation, the criterion of 13.6 g. used in this series and Wallensten's fails to detect an increasing incidence of anaemia with the later years. However, by using a criterion of 12.6 g. (Burge, 1960), or better still, by plotting haemoglobin levels directly against time (Baird and Wilson,

1959), the effect of time since operation is clear (Fig. 2). Sewell (data to be published) has shown that serum B₁₂ levels behave similarly (Fig. 2), and their correlation with the iron deficiency suggests that 'sideropenic gastritis' may impair the absorption of B₁₂: since the achylia is initially reversible (Brumfitt, 1960). This hypothesis could explain the spontaneous rise of serum B₁₂ levels after iron therapy alone (Cox, Meynell, Gaddie, and Cooke, 1959).

If ferrous ions are presented to any level of the small gut of the cat (Jacobi, Pflieger, and Rummel, 1956) or of man (Holmberg, Vahlquist, and

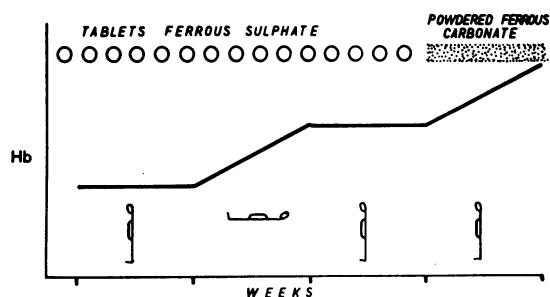


FIG. 3. The influence of posture and disintegration of tablets on iron absorption after partial gastrectomy (after Owren, 1952).

Waldenström, 1944) they are absorbed. In healthy individuals the pancreatic secretion renders the contents of the duodenum neutral or slightly alkaline, so lowering the concentration of ferrous ions that iron is mainly absorbed in the duodenum. It is known that the Polya gastrectomy is followed by more severe anaemia than the Billroth I operation, and Wallensten suggests that this is due to exclusion of the duodenum. Choudhury and Williams (1959) confirmed this difference, but found that patients with gastroenterostomy, in whom the duodenum was no longer a pathway for digesting food, absorbed iron normally. Anaemia only seems to occur when the distal part of the stomach is resected (or excluded, Lublin, 1936), and this area is known to regulate the rate of emptying of the stomach (Thomas, 1957). An alternative hypothesis thus seems to be that failure of absorption is due more to the rapid passage of iron through the upper gut; not only is there less time for ferrous ions to be split off from food (or

therapeutic tablets) but they are shorter lived. Radiologically, hurried emptying of the gastric remnant was recorded by Hartfall in 1934, and in 1952 Owren (confirmed by Goldeck and Gadermann, 1954) showed that in the erect posture tablets might reach the terminal ileum within 20 min. and that these patients would only respond when confined to bed, as lying down slowed the transit of the ferrous sulphate tablets so that they disintegrated in the stomach (Fig. 3). Powdered ferrous carbonate in large doses could be effective while patients are ambulant, but Owren admits it is difficult to persuade patients to take this.

These authors alone, among the many who have studied iron absorption after partial gastrectomy (Table VI), have considered the influence of posture and of the physical form in which iron is presented. If ferrous iron in solution is administered to fasting subjects (especially in bed), maximum absorption must occur, yet the presence of food can halve such absorption (Bothwell, Pirzio-Biroli, and Finch, 1958). Consequently such studies reproduce neither the usual conditions of clinical treatment (tablets after meals) nor the natural dietary background against which the iron deficiency develops.

Malabsorption of iron in food has, in fact, been demonstrated after partial gastrectomy (Table VI), and alkali consumption (Table II); achylia *per se* (Bothwell *et al.*, 1958), jejunitis, and steatorrhoea are of little significance in its causation.

Unsaturated serum iron-binding capacity may be of importance in iron absorption (Hallberg, 1960), and in iron-deficiency anaemia levels above normal (over 300 $\mu\text{g.}/100\text{ ml.}$) are found in association with the known increased ability to absorb iron. The

TABLE VI

RESULTS OF STUDIES ON IRON ABSORPTION AFTER PARTIAL GASTRECTOMY

Authors	Method	No. of Patients	Evidence for Malabsorption
<i>Using inorganic iron in fasting patients</i>			
Owren (1952)	} Radiological	2	Yes
Goldeck and Gadermann (1954)		3	Yes
Wallensten (1954)	} Plasma iron absorption curves, which can be misleading (Bothwell <i>et al.</i> , 1955)	4	Yes
Heinrich (1954)		7	Yes
Murray <i>et al.</i> (1957)		2	Yes
Zingg <i>et al.</i> (1959)		83	No
Smith and Mallett (1957)	} Radioiron balance	43	No
Baird and Wilson (1959)		13	No
Duthie (1959)		4	No
<i>Using inorganic iron added to food</i>			
Bothwell <i>et al.</i> (1958)	} Double isotope balance	5	Yes
Stevens <i>et al.</i> (1959)		8	Yes
Choudhury and Williams (1959)	Radioiron balance	25	Yes
<i>Using radioiron incorporated in food</i>			
Chodos <i>et al.</i> (1957)	} Radioiron balance	1	Yes
Baird and Wilson (1959)		4	Yes

latter could not be demonstrated after partial gastrectomy (Baird and Wilson, 1959), and in 84 anaemic patients no such increase in unsaturated serum iron-binding capacity could be found ($225 \pm 64 \mu\text{g./100 ml.}$): however these results probably reflect the insidious onset of the chronic anaemia, for the described increases (Laurell, 1947) were found in acute cases.

After consideration of the many factors affecting iron absorption after partial gastrectomy it can be said that the most significant cause of the observed malabsorption is an increased rate of emptying of the gastric remnant.

SUMMARY

An analysis of the literature and a study of 242 patients reveals that, after partial gastrectomy, iron deficiency (1) leads to anaemia in half the males and, because of menstruation, in nearly all the females; (2) apart from causing anaemia, can have far-reaching effects on the other tissues of the body; (3) insidiously develops over the years as a result of the malabsorption of iron from food due chiefly to the rapid emptying of the gastric remnant.

This study has enabled the following principles of management to be defined: (1) Haemoglobin levels should be determined every three months in menstruating women and yearly in other patients. (2) Iron therapy should be given to all patients with a haemoglobin level below 13.6 g./100 ml.; continuously, as prophylaxis, to menstruating women; and is worth a trial if sideropenia without anaemia is suspected; in patients complaining of lassitude, failure to maintain weight, or dumping symptoms.

PART II: TREATMENT

PRINCIPLES

The case for iron therapy has been stated in Part I of this paper: and parenteral treatment should only be used when there is no alternative.

The object of oral therapy is to present soluble iron to the small gut. Solutions of ferrous salts are unpalatable, are rapidly rendered insoluble by the alkaline contents of the upper small intestine, and are unstable, being readily oxidized to the ferric state with its obnoxious staining and side-effects. They need to be freshly prepared as an elixir and this is expensive and impractical. Tablets, although convenient, would require very rapid dispersal unless taken lying down. Disintegration times *in vitro* can be misleading as to what actually happens *in vivo* (Weiner, 1960) but it will be shown that they are of

value in iron therapy. Tablets harden with age (Table VII) and a small survey of current iron preparations from the shelves of local pharmacies revealed that, as judged by disintegration times¹ (Table VII), many of the tablets would be unsuitable for patients after gastrectomy.

TABLE VII

CONDITION OF IRON TABLETS BEFORE REACHING PATIENTS

	<i>Disintegration Time (min.)</i>
<i>Ferrous sulphate tablets of a reputable firm</i>	
Time since manufacture	
Fresh	20
One month	30
Three months	40
Six months	60
Twelve months	85
<i>Tablets of various ferrous salts from shelves of local pharmacies</i>	
Range	20-140
Average	40-80

Chelated iron preparations consist of iron combined to an organic complex by NH_2 groups in such a way that they are stable in alkaline solutions (Arden, 1950) and are thus available for absorption along the entire small gut. It has been suggested that they by-pass the ferritin mechanism for very high blood levels were achieved rapidly in cats (Jacobi *et al.*, 1956). The ferritin mechanism itself seems to operate by chelating ferrous ions from the gut, so that chelated iron can be loosely regarded as 'pre-digested'. Of the preparations then available, ferrous glycine sulphate was chosen, being the simplest chelate and also the cheapest. It is not stable in acid solutions, the ferrous moiety becoming ionic at about $\text{pH } 1.5$, so that in stomachs with normal acidity it has no advantage over ordinary ferrous salts. However, after partial gastrectomy, it seemed to offer an ideal treatment.

METHODS

Each patient was given one of four régimes (Table IX) for one month, and then, if the response was bad, the treatment was changed to one of the remaining three and continued until the haemoglobin had risen above 13.6 g./100 ml. (Fig. 4). Only those patients who claimed to have taken over 90% of the prescribed doses are included in the 214 treatments reported. The criteria of response are arbitrary, taking into account the initial haemoglobin level (Table VIII). The monthly gains may seem small, being about half of what would be expected in patients with intact stomachs, but after partial gastrectomy even parenteral therapy results in a slow response; probably because the 7.5 g. of globin, required for each 1% (0.15g.) rise, have to come from a protein balance that is critical (Pattarin, 1958).

¹Disintegration times were determined by Messrs. Coates & Cooper Ltd., using the rotating gauze method of the British Pharmacopoeia.

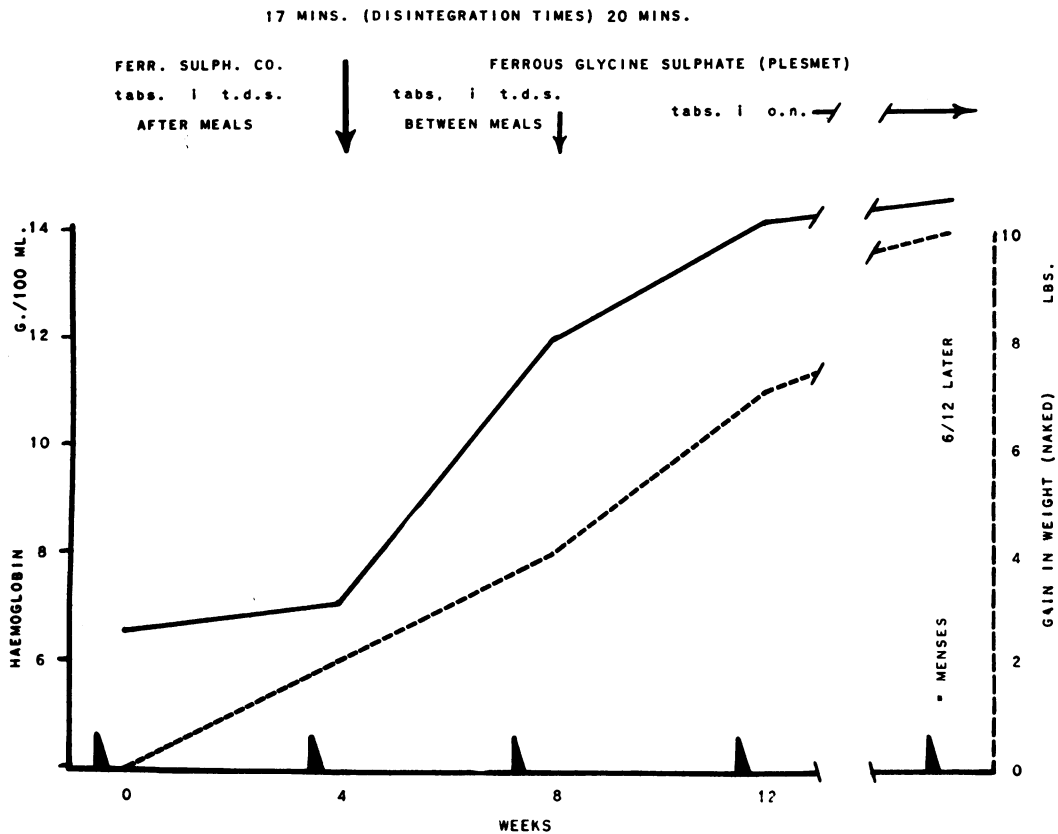


FIG. 4. The treatment of a female patient after the failure of a 6/52 course of ferrous gluconate tablets (ii t.d.s.p.c.). Though all the tablets rapidly disintegrate in vitro, the Plesmet régime was the better and provided adequate maintenance over six months. The weight gain was independent of the haemoglobin response.

TABLE VIII

CRITERIA OF RESPONSE TO ORAL TREATMENT OF IRON-DEFICIENCY ANAEMIA AFTER PARTIAL GASTRECTOMY

Initial HB (g./100 ml.)	Rise per Month		
	<9.5	9.5-11.5	>11.5
None	—	—	—
Unsatisfactory	<1.05	<0.90	>0.60
Satisfactory	1.05-2.05	0.90-1.65	0.60-0.90
Excellent	>2.05	>1.65	>0.90

RESULTS

The first régime, used routinely in this hospital in the treatment of iron deficiency, is satisfactory for patients with intact stomachs. Table IX shows that after Polya gastrectomy this régime is virtually useless. Even after the Billroth I operation it is not very efficient.

Using treatment, identical except for a more rapid dispersal of the iron tablets, the results after Polya gastrectomy approach those after Billroth I gastrectomy. This supports the hypothesis (Part I) that the rate of emptying of the gastric remnant is more important than duodenal exclusion in the causation of iron malabsorption.

This régime is still inefficient in half the included patients, and as it could not be tolerated by an excluded 20% of patients, it was not tried between meals.

Ferrous glycine sulphate tablets taken between meals yield excellent results, the more remarkable in that all patients to whom it was given had already failed to respond to ferrous sulphate tablets: further, patients with haemoglobins of 11.5 to 13.6 g./100 ml. had taken only one tablet (50 mg. Fe) daily, on lying down at night.

The chelated iron, given as a stable syrup, was

TABLE IX
RESULTS OF ORAL IRON THERAPY AFTER PARTIAL GASTRECTOMY

Regime	1	2	3	4
Daily mg. iron	215	215	50 or 150	50
	Ferrous Sulphate		Ferrous Glycine Sulphate	
	Co. N.F. tabs i with ascorbic acid 100 mg. three times daily After meals		Tabs iii/day or tabs i nocte Between meals The syrup I teaspoonful twice daily	
Rate of intolerance	8%	20%	0%	0%
Disintegration time of tablets (min.)	80	17	21	0
Response of patients (%)				
Type of operation	Polya		Billroth I	
	21	6	14	6
	4	5	5	5
	3	9	10	5
	2	1	14	5
Number of patients	30	21	49	12
				29
				10

immediately available for absorption. This was satisfactory in the three Billroth I and 11 Polya patients who had failed to respond adequately to all tablets taken by day, when presumably 'hurry' had prevented adequate absorption.

The four patients with unsatisfactory response to the syrup all had haemoglobin levels below 11.5 g./100 ml. Their treatment was changed to ferrous glycine sulphate tablets, one b.d. between meals and

one taken on lying down at night. At this higher dosage of 150 mg. of iron, they all responded excellently.

DISCUSSION

When tablets, all with a disintegration time of 30 minutes, are given to ordinary patients in a double-blind trial, no difference in efficacy is

detected between many of the current ferrous salts, and a genuine intolerance can be shown in 8% of patients, quite apart from psychological factors (Berlin, 1960). This coincides with that found in régime 1; thus the 20% rejection of more rapidly distintegrating (17 minutes) ferrous sulphate may be considered as genuine intolerance.

Any attempt to speed up the release of inorganic iron, in an effort to improve absorption, is likely to be rejected by many patients. On the other hand, ferrous glycine sulphate causes minimal side-effects, a finding in agreement with Jennison (1958) and Barnes (1960), presumably because chelation prevents oxidation of the ferrous moiety to obnoxious ferric ions.

It is likely that any tablet, releasing its iron within 30 minutes, will give a satisfactory response if taken lying down. Here, this has only been demonstrated with ferrous glycine sulphate, and one tablet taken last thing every night has been found during the past year to be convenient and adequate in the prevention of a recurrence of anaemia in our menstruating women.

Finally, only the consecutive (unselected) cases from the survey (Part I) are reported here. Experience with some hundred other cases of anaemia after partial gastrectomy supports the findings.

SUMMARY

The notorious difficulties encountered in the oral treatment of iron deficiency after partial gastrectomy are probably due to an inadequate release of ferrous ions from coated tablets, taken after meals and rapidly emptied from the gastric remnant.

Treatment with tablets of the iron chelate, ferrous glycine sulphate, taken between meals is reliable, though a few patients respond better to the stable syrup.

One tablet, taken on lying down each night, is adequate in the treatment of mild anaemia (haemoglobin 11.5 to 13.6 g./100 ml.) and its prophylaxis in women so long as menstruation continues.

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