such cases admitted between May 1 and October 31, 1935. Similar periods were chosen in order to exclude the possibility that seasonal variations might affect the incidence and severity of the condition.

The results are given in Tables II and III. Out of ten severe cases admitted in 1935 and treated conservatively, four developed fits, and two patients died; while out of twelve severe cases treated in 1936 with corpus luteum hormone none developed fits and none died. The results therefore appear to be suggestive and encouraging.

In an investigation of the possible value of progesterone in the treatment of certain toxæmias of pregnancy it was obviously desirable to select severe cases, since the significance of results obtained could then be more easily estimated. At the same time it is well realized that if the treatment was definitely shown to be effective it would be advisable to apply it at an earlier stage, and to determine whether under such conditions it might not be of prophylactic value.

Summary

1. Certain experiments, in which toxic conditions leading to death were produced in pregnant rabbits, are described; these conditions were associated with a failure in the secretion of the luteal hormone.

2. The results obtained following the administration of progesterone in twelve cases suffering from severe pre-eclamptic symptoms are given. Clinical improvement appears to have been produced in these cases.

3. It is evident that the numbers are too small to establish formal proof of the efficacy of the treatment, and the results are published at this stage because it would take many years to collect adequate data in a single hospital. The results appear to be sufficiently encouraging to deserve testing on a wider scale without delay.

We should like to express our gratitude to the honorary staff of the Elsie Inglis Memorial Hospital for permission to use some of their cases, and to the Medical Research Council for defraying the expenses of the experimental part of this investigation.

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C. Kroetz (*Med. Klinik*, November 6, 1936, p. 1521) points out that carbon monoxide poisoning is a danger which may arise in garages, streets, factories, tunnels, and domestic houses. It may produce in the heart muscle haemorrhages and necrotic patches especially close to the papillary muscles of the mitral valve. Entering the upper respiratory passages it affects the vagus, causing spasm of the coronary blood vessels. Later, arteriosclerotic changes occur in the vessel walls. The electrocardiogram often gives evidence of these pathological changes. Clinically, a heart with necrotic foci following carbon monoxide poisoning reacts more quickly with attacks of angina pectoris. Kroetz, acting as referee in a compensation case, showed that symptoms of cardiac stenosis must be carefully looked for in cases of CO poisoning. In 1915 an engine driver of 38 had an attack of angina pectoris after working in a tunnel with a known high CO content. Two other well-authenticated attacks occurred in the same manner in 1922 and 1928. Previous to 1915 the patient had had no heart trouble. Although he was off work for 285 days between 1915 and 1922, his symptoms were put down to neurosis. He was pensioned off in 1933. In 1936, upon re-examination, his condition had not deteriorated. Syphilis and senile arteriosclerosis had been excluded in 1915.

THE RELATION BETWEEN THE HYPOCHROMIC ANAEMIAS AND IRON DEFICIENCY

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There has been much speculation as to the mode of action of iron in the hypochromic anaemias, and especially as to the reason why it requires to be given in large doses. The successful treatment of the hypochromic anaemias with large doses of iron has been one of the most encouraging chapters in medicine during the last decade, and iron can now be regarded as a specific remedy.

Schulten (1930) has emphasized the importance of large doses in the case of ferrum redactum. He showed that in some cases this preparation could be given for four weeks in doses of 2 grammes (30 grains) daily without any response, but when the dose was raised to 6 grammes (90 grains) there was an immediate rise of reticulocytes and return of the blood picture to normal. In this country and in the U.S.A. the preparations of iron most in vogue until recently have been iron and ammonium citrate in doses of from 60 to 90 grains daily, and pil. ferri carb. (Blaud's pill) in doses of from 45 to 90 grains daily. Although it has been recognized that some patients respond to considerably smaller doses (Witts, 1933), the necessity for the large doses mentioned as average optimum doses has been very clearly established in clinical experience (Dameshek, 1934; Heath, 1933; Schulten, 1930; Witts, 1933). And there is no question that the specificity of iron therapy has only been generally accepted since these preparations have been used in large doses as originally suggested by Blaud (1832).

Definition of Hypochromic Anaemia

A hypochromic type of blood picture may be found in association with almost any disease picture, and may respond to a greater or less degree to iron therapy. The term "hypochromic anaemia" is, however, used in this paper to signify a certain group of cases. The blood picture is characterized by a low colour index, hypochromia and microcytosis in the stained film, and a low mean corpuscular haemoglobin concentration. The number of white blood corpuscles is at or below the normal level. In the absence of treatment the course of the anaemia is chronic or torpid; the reticulocytes are within normal limits, and there is no spontaneous recovery. In the absence of complications such as fever, sepsis, cancer, nephritis, or pronounced arteriosclerosis, iron therapy causes the blood picture to return to normal provided it is adequate and, if necessary, prolonged. In one of its purest forms hypochromic anaemia is found in women of the child-bearing epoch, and is commonly associated with achlorhydria or hypochlorhydria. This syndrome has been very fully described in the literature as idiopathic hypochromic anaemia or chronic microcytic anaemia (Faber, 1913; Witts, 1930; Waugh, 1931; Minot, 1932; Dameshek, 1933). Quite frequently chronic blood loss or dietetic inadequacy are believed to be aetiological factors. Heath (1933) found that of eighty-four cases responding to iron 93 per cent. were idiopathic in association with reduced gastric acidity, or were associated with chronic haemorrhage or dietary deficiency. It is this group of cases in an uncomplicated state which is used for the study of the relation of hypochromic anaemia to iron deficiency.

Iron Exchange of the Body

Examination of the facts of the distribution and exchange of iron in the body lends support to the view that the hypochromic anaemias are the result of a state of iron deficiency in the body. These facts are given in the table. It will be seen that more than half of the iron

Iron Stores and Exchange: Normal Human Approximate	Authority
Total in body ... 4-4.5 grammes	White House Conference, 1932
Circulating blood ... 2.44 "	Fullerton et al., 1933
Circulating haemoglobin * 2.31 "	
Liver ... 0.15-0.25 gramme	Ashby, 1912
Daily Iron Exchange	
Average diet, total ... 10-20 mg.	Reznikoff et al., 1934
" " available... 7-9 mg.	Widdowson and McCance, 1936
Poor diet, total ... 5-10 mg.	Davidson and Fullerton, 1933
Faeces ... 5-20 mg.	and 1935 Reznikoff et al., 1934
Urine ... 0.5-1 mg.	Marlow and Taylor, 1934
Haemolysis of effete red cells 80 mg.	Wright, 1934
Iron in bile ... 0.5 mg.	Henrique and Roland, 1928
Special Sources of Loss in Female	
Menstruation (per month), normal 3.8-78.4 mg.	Baldrige, 1935; Barer et al., 1935; Gillett et al., 1918; Ohlson and Daum, 1935
Iron content in full-term foetus 375 mg.	White House Conference, 1932
Iron secreted in lactation ... 750 mg.	Fullerton, 1936

* 5 litres of blood, 13.8 grammes haemoglobin per cent., 0.335 gramme iron per cent. in haemoglobin.

of the body is present as circulating haemoglobin. It might be expected, therefore, that a state of iron deficiency would manifest itself as a deficiency of haemoglobin, and that chronic loss of blood would seriously deplete the body's stores of iron. Actually the character of the blood picture in hypochromic anaemia with its low colour index and its low mean corpuscular haemoglobin concentration suggests that the essential fault is a failure of the erythron to produce haemoglobin for the developing red cells, and this blood picture is always associated with conditions which deplete the body of iron. The menstrual drain of blood accounts partly for the preponderance of females which is observed clinically. In men hypochromic anaemia is often associated with chronic blood loss from haemorrhoids.

The supply of iron in the food is very small, and of this only a part is available (Elvehjem, 1932; Widdowson and McCance, 1936), so it is not surprising to find dietary deficiency frequently associated with hypochromic anaemia (Davidson, Fullerton, *et al.*, 1933; Heath, 1933). There is evidence that iron is better utilized when administered to patients with a normal gastric secretion (Heath, 1933; Minot and Heath, 1932) or in an acid-buffered medium (Mettier and Minot, 1931), and these observations fit in with the high incidence of achlorhydria or hypochlorhydria among cases of hypochromic anaemia. The role of pregnancy in producing hypochromic anaemia can be attributed partly to the drain of iron into the foetus and in lactation, not fully compensated for by the omission of menstruation, and partly to the temporary hypochlorhydria (Strauss and Castle, 1932).

In short, the repeated association of hypochromic anaemia with conditions which would be expected to lead to iron deficiency and the specific cure of the anaemia with iron strongly favour the view that the hypochromic anaemias are conditioned by a state of iron deficiency in the body.

Dose in Relation to Iron Need

A rise of 1 per cent. per day in the circulating haemoglobin represents the addition of only 23 milligrammes (1/3 grain) of metallic iron per day to the circulation. If the mode of action of iron is simply to correct the iron deficiency in the body it is difficult to explain why large doses are required. The discrepancy between iron need in the body and the size of the average optimum dose led Schulten (1930) to reject the view (Fullerton, 1934; Heath, Strauss, and Castle, 1932) that iron therapy was effective by virtue of correcting a deficiency. He quoted the possibility of a catalytic (*fermentartigen*) action, although admitting that this explained nothing, and appeared to lean towards the explanation attributed to Elvehjem (Dameshek, 1934) that the large doses were effective in virtue of their supplying by contamination another haemopoietic factor such as copper.

Heath, Strauss, and Castle (1932), however, showed on a number of cases of hypochromic anaemia treated by injections of iron that the iron content of the haemoglobin formed as a result of treatment was roughly equal to the amount of iron injected, or in other words that the utilization of injected iron was 100 per cent. This has been taken (Fullerton, 1934) as establishing the view that the hypochromic anaemias are conditioned solely by a state of iron deficiency, and that iron therapy acts solely in virtue of rectifying a state of iron deficiency. This assumption is not necessarily justified, for the cases observed by Heath, Strauss, and Castle were not treated throughout the whole recovery period by iron injections, and even in the short periods of observation there were significant variations from 100 per cent. utilization. Moreover, it leads to the conclusion that iron and ammonium citrate and Bland's pill in the average optimum doses are very poorly absorbed from the intestine (Clark, 1932). Brock and Hunter (1937) have recently demonstrated that these iron preparations are very well absorbed, and have shown how big is the discrepancy between retention and utilization.

This latter work has therefore raised again the question, apparently settled by the work of Heath, Strauss, and Castle, why it is necessary to give large doses of iron. If the hypochromic anaemias are conditioned solely by a state of iron deficiency, and iron therapy is effective in virtue of correcting this deficiency, why is it necessary to give doses of iron which lead to the accumulation in the body of a great excess of iron? Why are smaller doses not effective?

Iron Retention and Iron Utilization

In considering the response of the blood to iron reaching the body via the intestine in patients with hypochromic anaemia three selected cases are described because they illustrate different forms of response. The cases are selected from a small series in which the amount of iron retained as a result of a short period of therapy was measured by balance experiments (Brock and Hunter, 1937) and the resultant haemoglobin rise measured. The further course of the patients was observed over a period of two years or more. Haemoglobin was estimated by the Haldane method, using a calibrated standard on which 100 per cent. represented 13.8 grammes of haemoglobin per 100 c.cm. of blood. The iron content or iron

FIG 1.—Case II. In the upper chart is a detailed record of the response of the blood to a brief period of treatment. In the lower chart the patient's subsequent progress is recorded. In the lower chart the period of time represented in the upper chart is condensed on a smaller scale between the dotted lines. Iron retention, May 12–May 21, was 2,491 mg. Haemoglobin rise, May 12–May 26, was 29 per cent., representing 670 mg. of iron.

equivalent of the newly formed haemoglobin was calculated in each case on a presumed circulating blood volume of 5 litres, using 0.335 per cent. as the iron content of haemoglobin. In this way it was possible to observe the haemoglobin response of patients when the amount of iron actually reaching the body from the intestine was known.

Case I

This was a case of hypochromic anaemia associated with a gastric ulcer, and presumably due to chronic blood loss in the past. The patient was a male aged 17, treated three years before (that is, in 1931) for anaemia. On March 9, 1931, his blood count was: red cells, 3,500,000; haemoglobin, 25 per cent. On March 16, after iron therapy, haemoglobin was 71 per cent. 1934: complaining of epigastric pain and lassitude. X-ray examination showed a large lesser curve ulcer. Test meal: free hydrochloric acid, 0.26 per cent.; no occult blood in stools on repeated examination. Red blood count, 5,370,000 per c.mm.; haemoglobin, 62 per cent.; white blood count, 7,700 per c.mm.

The patient's iron balance was measured, and 90 grains a day of Bland's pill were given for ten days. Of this he retained 639 mg. of iron. He received no further treatment for three weeks. At the end of this period his haemoglobin had risen to 92 per cent. This rise of 30 per cent. would represent 693 mg. of iron added to the circulation if the patient had a blood volume of 5 litres. He was a small individual, however, and the new haemoglobin must therefore have represented an addition of iron to the circulation about equal to the amount of iron retained. When iron therapy was renewed the haemoglobin rose to 110 per cent., and two years later the patient is still well.

Case II

This was a case of idiopathic hypochromic anaemia in a female, single, aged 30. She complained of shortness of breath and pallor for two months. Moderate diet. Catamenia not excessive. No other blood loss. Test meal: no free hydrochloric acid after gruel, but after histamine 0.25 per cent. X-ray examination showed no abnormality of stomach or duodenum. Red blood count, 3,460,000 per

FIG. 2.—Case III. In the upper chart is a detailed record of the lower chart the patient's subsequent progress is recorded. In the lower chart the period of time recorded in the upper chart is condensed on to a smaller scale between the dotted lines. May 23–June 9, was 13 per cent., representing 300 mg. of iron.

c.mm.; haemoglobin 45 per cent.; white blood count, 3,800 per c.mm. She was given Bland's mass in gelatin capsules, 102 grains a day for six days and 153 grains a day for a further three days. As a result of this she retained 2,491 mg. of iron, or more than is contained in the whole circulating haemoglobin. The resultant rise of 29 per cent. in the haemoglobin (Fig. 1) represented the addition of 644 mg. of iron to a 5-litre circulation. When iron therapy was renewed the haemoglobin continued to rise, and reached 100 per cent.

Case III

The patient—a case of idiopathic hypochromic anaemia resistant to iron therapy—was a female aged 38, single. Lassitude, pallor, and shortness of breath for two years. Finger-nails brittle. No serious illness in the past. Diet moderately satisfactory. No indigestion. Catamenia not excessive. On examination: well-nourished, pale, with bluish sclerotics; koilonychia. Slight marginal atrophy of mucous membrane of tongue. No temperature. No septic foci. No

haemorrhoids. All other systems normal to clinical examination. X-ray examination showed no abnormality in stomach or duodenum. Fractional test meal: no free hydrochloric acid after gruel; meal repeated with histamine—free hydrochloric acid 0.15 per cent., total acid 30. No occult blood in stools. Red cells, 4,900,000 per c.mm.; haemoglobin, 55 per cent.; colour index, 0.56; white cells, 5,500 per c.mm. Urine and renal function normal.

Details of her blood are given in Fig. 2. She took 90 grains a day of iron and ammonium citrate for nine days. Of this she retained 1,665 mg. At the end of sixteen days her haemoglobin had only risen 13 per cent., representing the addition of 299 mg. of iron to a 5-litre circulation. She was put on to 90 grains a day of Bland's pill, but at the end of four months her haemoglobin was only 80 per cent. If only 5 per cent. of the Bland's pill had been retained, an improbably low estimate (Brock and Hunter, 1937), she would still have retained another 3 grammes in addition to the 1.66 grammes retained in the experimental period. This is twice as much

iron as is contained in the whole circulating haemoglobin. And yet in September, 1934 (Fig. 2), the change from Bland's pill to iron and ammonium citrate, which doubled the amount of iron in the intestine, was followed by a sharp rise of haemoglobin to 110 per cent. This patient was in no way different clinically from cases of hypochromic anaemia which respond rapidly to iron; she had none of the complications which are recognized as delaying the response to iron, and although she has been under observation for two years since the balance experiment she has remained well. But in 1936 there was a drop in the haemoglobin, in spite of all the excess iron which was stored.

Discussion of Cases

In Case I the haemoglobin increase was a quantitative measure of the amount of iron absorbed and retained by the body, and it can be argued from this case, as from the cases treated by Heath, Strauss, and Castle (1932) with injections of iron, that the anaemia was conditioned solely by the absence from the body of iron available for haemoglobin formation.

In Case II the haemoglobin increase was not a measure of the amount of iron retained. It rose by 29 per cent. in fourteen days, whereas the amount of iron retained by the body in nine days of treatment would have allowed it to rise to more than 100 per cent. if the iron had been fully utilized for haemoglobin formation. We do not know the maximum possible rate of haemoglobin formation. The highest rate recorded by Fullerton (1934) in periods varying from twenty-five to forty days after the inception of treatment was 2.88 per cent. per day. In one case which I studied intensively the haemoglobin rose 34 per cent. in twelve days (2.8 per cent. per day) following the commencement of iron therapy, when iron balance had shown that sufficient iron had been retained to allow of an even greater rise.

In Case II the iron retained was enough to allow the haemoglobin to rise by more than 7 per cent. per day during the first fourteen days. It can be said of this case that the rate of regeneration of the haemoglobin was limited by some factor other than the rate at which iron could be introduced into the body, but that it was so satisfactory that there is no reason to believe that the anaemia was conditioned by any factor other than a deficiency of iron.

In Case III the rate of haemoglobin regeneration was quite clearly unsatisfactory. During the first sixteen days her haemoglobin rose only 13 per cent., which is below the accepted standards of satisfactory response (Fullerton, 1934; Heath, 1933), and thereafter the rate of recovery steadily declined in spite of the fact that during the first nine days of iron therapy alone enough iron was retained to allow the haemoglobin to rise to 100 per cent.

It is difficult to define accurately what is the lower limit of a satisfactory response to iron therapy. Heath (1933) has suggested as a rough working rule a rise of at least 1 per cent. per day when the initial haemoglobin is below 70 per cent. Without defining the limits any more accurately it is plain that the response in Cases I and II was, and in Case III was not, satisfactory.

Efficacy of Excess Iron

How do these three cases fit in with the theory that the hypochromic anaemias are conditioned solely by a deficiency of iron available for haemoglobin formation? Case I is in line with the results of Heath, Strauss, and Castle, and supports the thesis. On the other hand, Case III is an extreme example of failure to respond in the presence of enough iron. The amount of iron retained

by this patient in the first ten days of treatment (Fig. 2) was enough, if fully utilized, to allow her haemoglobin to rise to 100 per cent., but this result was only achieved after amounts of iron had been given in the next six months which must have led to the accumulation of a great excess in the tissues. The amounts of iron in question, moreover, were too great to allow of the explanation that some of the retained iron was stored in other iron-hungry tissues (see Table), and hence was not available for haemoglobin formation. Resistant cases of this sort have in the past been attributed to failure to absorb iron. It is now apparent that this explanation is inadequate, and it must be allowed that certain cases of hypochromic anaemia do not recover when iron has been absorbed into the body in amounts sufficient for haemoglobin formation.

Case II presents another aspect of the problem. Here the haemoglobin response was satisfactory, and it might be thought that the dose of iron was unnecessarily large. But in Fig. 1 it appears that the haemoglobin rise began to tail off between May 23 and 26 after the cessation of therapy, in spite of the fact that enough iron had already been retained to allow it to rise to 100 per cent. The haemoglobin rise was renewed when iron therapy was instituted again. If this observation is correct, then even in cases which respond satisfactorily and when iron absorption is rapid an *excess* of iron may be more effective than *enough* iron. This single observation could not be accepted in itself, but it is strongly supported by the large discrepancy demonstrated by Brock and Hunter (1937) between the figures for iron utilization and those for iron retention when the preparation is taken by mouth in the average optimum doses. It is supported also by the sort of case reported by Schulten (1930), in which 2 grammes of reduced iron had no effect, while 6 grammes produced a prompt response in the blood picture. Schulten's experience can be confirmed by anyone who has treated a large series of cases of hypochromic anaemia, and has been commented on by other writers (Dameshek, 1934; Heath, 1933; Wits, 1933).

In view of the figures for iron retention published by Brock and Hunter (1937) it is no longer possible to assume that the large doses are necessary in order to get *enough* iron into the body. Such cases are strong evidence that *excess* iron may be more effective than *enough* iron. It might be argued that there is a sort of mass action in the intestine, and that no iron is absorbed at all until large doses are given. There is, however, no evidence of mass action in the figures supplied by Brock and Hunter, and Reimann and Fritsch (1931) have shown by balance experiments that small doses of iron are readily absorbed.

In short, it may be said that Cases II and III, supported by a considerable body of corroborating evidence, suggest that large doses of iron which lead to the accumulation of a great excess of iron in the tissues are more effective in certain cases of hypochromic anaemia than are smaller doses which allow of absorption of enough iron for haemoglobin formation. It is this mysterious efficacy of large doses which is the baffling problem of the relation of the hypochromic anaemias to iron deficiency.

Soluble Ferrous Preparations

Up to this point the argument has been simplified by omitting all reference to recent work on the use of small doses of soluble ferrous preparations (Davidson, 1933; Fullerton, 1934; Heubner, 1924 and 1926; Lintzel, 1931; Reimann and Fritsch, 1933; Starkenstein, 1926; Starkenstein and Weden, 1928; Wagner, 1931). It has been

claimed that these are efficacious in smaller doses than can be used in the case of the preparations referred to above. The claim is justified only in part. Reimann and Fritsch (1931) have shown that small doses of ferrous chloride are very readily absorbed and retained (up to 53.8 per cent. of the amount administered). This means that a daily dose of 9 grains ferrous sulphate exsiccatus, if it is absorbed anywhere near as readily as ferrous chloride, would allow the body to retain enough iron for an optimal haemoglobin response and a margin for replenishing reserves. But in spite of this Fullerton (1934) found that only ten out of twenty-one cases had a satisfactory haemoglobin response on this dose. So that even with the soluble ferrous preparations the anaemia apparently does not always respond to the provision of *enough* iron.

There has been a tendency to put 9 grains of ferrous sulphate exsiccatus on a par with 90 grains of Blaud's pill as an average optimum daily dose. Such a claim cannot be accepted. Favourable cases (ten out of twenty-one in Fullerton's experience) will respond to 9 grains of ferrous sulphate; but they will also respond to 30 grains daily of Blaud's pill, which contains about the same amount of iron. Sixty to ninety grains of Blaud's pill is an average optimum dose which will cause a satisfactory remission in all but the most resistant cases, and the equivalent dose of ferrous sulphate exsiccatus is probably about 18 to 27 grains. There is no reason at all why the iron of ferrous sulphate exsiccatus should be better absorbed than that of freshly prepared Blaud's pill, and indeed there is no evidence of a difference in utilization as between the two preparations in Fullerton's Table III (1934).

Mode of Action of Large Doses of Iron

The purpose of this paper is to present the evidence for the greater effectiveness of *excess* iron as compared with *enough* iron, not to explain it. Any attempt to do so involves us in the present state of knowledge in pure speculation. Recent work on the potentiation of iron as briefly reviewed by Witts (1936) may have some bearing on the problem. Two possible explanations will be outlined as exemplified in Case III, but it must be insisted that they are highly speculative and that there is at present no real evidence in support of either of them.

One is that the iron and ammonium citrate administered in November (Fig. 2) contained copper which was needed by the individual, whereas the Blaud's pill previously given contained no copper. It is still claimed by some workers (Dameshek, 1934; Mills, 1930) that copper is effective as an adjuvant to iron in certain cases, although their experience has not been generally confirmed, and Davidson (1933) has given reasons for believing that the modern adult never suffers from copper deficiency.

The other possible explanation is that the presence of large amounts of iron in the intestine *per se* has some effect. It is significant that so soon as iron therapy was omitted in Case III (Fig. 2) in January, 1935, the haemoglobin immediately dropped from 110 to 86 per cent. The presence of large quantities of iron in the intestine must change conditions there very markedly. It alters the bacterial flora (Lotze, 1933) and interferes with the absorption of other minerals (Brock and Diamond, 1934; Brock, 1937; Waltner, 1927). It is conceivable that it might aid the absorption of other substances necessary for haemopoiesis. There are still many unexplained features in the relation between achlorhydria and the hypochromic anaemias. It has been shown that the haemoglobin and reticulocytes respond better to a given dose of iron in the presence of a normal gastric secretion

(Heath, 1933) and when it is given in an acid-buffered meat mixture (Mettier and Minot, 1931), but there is still no proof that iron is better absorbed under these conditions. Recent work by Mettier, Kellogg, and Rinehart (1933) is interpreted by them as indicating that the absence of pepsin in cases of achlorhydria prevents them from freeing iron from its organic combinations in food. But it is apparent that the new-formed haemoglobin in their cases contained more iron than had been contained in the whole of the predigested meals administered, so if their observations are correct they must mean that some additional factor necessary for haemopoiesis had been formed under the influence of peptic digestion.

It is at least conceivable that the presence of large quantities of iron in the intestine, by altering the chemical environment, increases the absorption of some undetected haemopoietic factor which is necessary in iron-resistant cases. The final rise of haemoglobin in Case III which occurred in November, 1934 (see Fig. 2), followed on the doubling of the amount of iron in the intestine of a patient whose body was already saturated with iron. It is possible that the relation between these two events was really *propter hoc* instead of just *post hoc*. This suggestion is, however, only a hypothesis for which there is no real evidence at all, and it must be frankly admitted that there is at present no rational explanation of the value of large doses of iron.

Rational Iron Therapy

It is clearly established that the hypochromic anaemias are conditioned mainly, if not solely, by a state of iron deficiency, and that they cannot respond properly to any form of therapy which does not supply enough iron to be incorporated in the new haemoglobin. A satisfactory response to iron is a rise of haemoglobin of from 1 to 2 per cent. per day, which represents the addition to the circulation of from 23 to 46 mg. of iron. The administration of this amount by any form of injection, even when given every day, is an extremely uncomfortable and even dangerous procedure for the patient (Heath, Strauss, and Castle, 1932). The well-known preparations on the market of iron for injection contain less than 3 mg. per dose, and their use in anaemia is ridiculous. Even *injectio ferri B.P.* is entirely inadequate (Burger and Witts, 1934). It can be said to-day that there is never any indication for injections of iron in the treatment of anaemia.

In some cases of hypochromic anaemia all that is required is sufficient iron by mouth to supply about 50 mg. daily for new haemoglobin and an undetermined but probably smaller amount for the replenishment of other tissues in the body which have become iron-deficient.

Another group of hypochromic anaemias appears to respond only when iron is given in doses which lead to the accumulation in the body of amounts up to 200 mg. per day (Brock and Hunter, 1937). There is at present no rational explanation of the necessity for such large doses. Their use is empirical, but their value is very well attested in clinical experience (Dameshek, 1934; Heath, 1933; Schulten, 1930; Witts, 1933). It is important to note that there is no way of distinguishing clinically between those cases in which small amounts of iron are adequate and those which require larger doses. It is advisable, therefore, to have an average optimum dose for the benefit of practitioners who have to treat patients without facilities for frequent haemoglobin estimations. The average optimum dose of iron and ammonium citrate is 60 to 90 grains a day, and of Blaud's pill 45 to 90 grains

a day, as judged by clinical experience with large series of cases (Dameshek, 1934; Heath, 1933; Witts, 1933). There is no reason to believe that tablets of ferrous sulphate or ferrous chloride are any better absorbed than is the iron in freshly prepared Bland's pill, so that they should be given in doses containing the same quantity of iron—for example, 15 to 30 grains daily in the case of ferrous sulphate exsiccatus. Many cases will respond to smaller doses just as they will to doses of Bland's pill smaller than 45 grains daily, but, as has been shown, there is no way of distinguishing clinically between those needing small and those needing large doses. Fullerton (1934) found that only ten cases out of twenty-one responded satisfactorily to ferrous sulphate exsiccatus in a dose of 9 grains daily.

Various preparations of soluble ferrous salts are being put on the market which, because of their smaller bulk, will probably replace the familiar Bland's pill. But whatever the preparation there must be a reasonable assurance that the iron will remain in a ferrous state, and they must be given in a dose which contains a minimum of 300 mg. of metallic iron daily. Tablets of ferrous sulphate as made by Glaxo appear to fulfil these requirements, and are very convenient and palatable. The dose of 9 grains per day, however, which is frequently recommended, cannot be regarded as an average optimum dose. About 50 per cent. of cases will respond adequately (Fullerton, 1934), but unless frequent haemoglobin estimations are being performed the dose should always be at least 15 grains a day, and may have to be larger. If ferrous chloride is being used in a syrup solution, as recommended by Witts (1936), an average optimum dose varies from 9 to 18 grains a day at least (300 mg. of metallic iron), according to whether the ferrous chloride is anhydrous or not.

In resistant cases the dose should always be raised to the maximum before despairing of iron, and since there are still many unexplained factors in the aetiology of hypochromic anaemia a diet rich in first-class protein and vitamins should always be insisted on.*

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J. P. Strömbeck (*Nord. med. Tidskr.*, December 5, 1936, p. 1996) finds from a study of the literature that opinions are still divided as to the merits of the excision and suture of recent wounds as advocated for the first time by Friedrich in 1893. The author has therefore tried to throw light on this treatment, which has been applied since 1928 at the Serafimer Hospital in Stockholm to wounds accidentally inflicted. Since September, 1932, records have been kept with special reference to the nature of the wounds according as they were inflicted by cutting or blunt objects, or were associated with suppuration, necroses, haematomata, reopening of the wound, and other complications. In the course of three years about 3,000 cases were treated, approximately three-quarters of the patients being males. In nearly every case the injuries did not entail residence in hospital, and those cases were excluded from the analysis in which compound fractures of the long bones had occurred or in which the wounds were very deep and extensive. The treatment consisted in washing with a soap solution and then with alcohol after local anaesthesia had been induced. The walls and floor of the wound were then excised to a depth of one millimetre. Before, during, and after this excision the wound was irrigated by a solution of chloramine. Ligatures and sunk sutures (except tendon sutures) were avoided as much as possible, and silk was employed for the skin sutures. The author's findings are reproduced in several tables in which information is given about the character and site of the injuries and various other data. The author's conclusion is favourable to this procedure, which he does not, however, recommend unreservedly in general practice. It is most suitable for hospital practice, and even here care must be taken in the after-treatment lest secondary opening of the wound ensue.

* Since the publication of the work of Brock and Hunter (1937) on the absorption of large quantities of iron my attention has been drawn to a note by Fowler and Barer (1935) indicating that they have obtained similar results by balance experiments.