IDIOPATHIC HYPOCHROMIC ANAEMIA IN MALES

BY

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Idiopathic hypochromic anaemia is a disease which occurs mainly in females, and its incidence in males appears to be very low. Chlorosis was thought to occur almost entirely in young females, but the following quotations suggest that Shakespeare was aware of the possibility that the disease might appear in males. In *Antony and Cleopatra*, III, ii, 4:

> Caesar is sad; and Lepidus,
> Since Pompey's feast, as Menas says, is troubled
> With the green sickness.

and in *II King Henry IV*, IV, iii, 96, referring to Prince John:

> There's never none of these demure boys come to any proof; for thin drink doth so over-cool their blood, and making many fish-meals, that they fall into a kind of male green-sickness.

From the series of cases which have been reported previously it seems that between 4 and 8% of cases of idiopathic hypochromic anaemia are males. Davies (1931) reported four cases in males out of 55 cases; Britton (1936) reported four cases in males out of 66 cases; and Wintrobe and Beebe (1933) reviewed a total of 498 cases, of which 18 were males. Other published series of cases in males include 26 cases reported by Burger and Witts (1934) and 10 cases by Thomson (1943).

Two recent series of cases have consisted entirely of national service recruits. Shorthouse and King (1951) reported 20 cases among young recruits in the Royal Army Ordnance Corps, and Leonard (1954) detected 47 cases by routine blood examination of 4,221 R.A.F. recruits. The incidence of idiopathic hypochromic anaemia of 1.1% among these R.A.F. recruits suggests that this condition may be more common than has been indicated by the small numbers attending hospital.

The majority of case reports of idiopathic hypochromic anaemia in males have been by British workers. The prevalent opinion of American haematologists, however, is that idiopathic hypochromic anaemia does not occur in males. Heath and Patek (1937) and Wintrobe (1951) believe that hypochromic anaemia in males is almost always due to occult haemorrhage, and Moore (1950) thinks that there is no justification now for the term idiopathic because the cause of the anaemia is always evident. He believes that, while an inadequate diet and poor iron absorption frequently contribute to the pathogenesis of iron deficiency, they do not seem able to precipitate its development unless there is an increased iron loss from the body, and in his experience (1953, personal communication) he has been unable to find a male patient with hypochromic anaemia in whom careful study has revealed no evidence of haemorrhage.

In view of this difference of opinion about the existence of idiopathic hypochromic anaemia in men, 11 further cases are reported, and the aetiology of the condition is discussed.

Review of Cases

The cases were obtained from the records of the David Lewis Northern Hospital, Liverpool, between September, 1948, and September, 1952, and from the records of the Liverpool Stanley Hospital between October, 1949, and January, 1954. All the cases were primarily diagnosed as hypochromic anaemia, microcytic anaemia, or iron-deficiency anaemia, and cases in which the anaemia was obviously secondary to some other disease have not been included. Fourteen cases—six from the David Lewis Northern Hospital and eight from the Liverpool Stanley Hospital—were selected originally, but the follow-up study revealed that in two cases the anaemia was due to carcinoma of the stomach and one case developed haematuria due to benign prostatic hypertrophy, which suggested that the anaemia might have been due to previous persistent microscopic haematuria. Of the remaining 11 patients, one has been followed up for four months, three for between six months and a year, two for between one and two years, two for between two and three years, one for three and a half years, and two for between five and six years. With two exceptions, the patients were all seen personally. Five patients were first seen at the time of their original attendance at hospital and four were first seen at the time of their follow-up attendance.

At the time of their first attendance, nine patients were under the age of 25, and the other two were aged 53 and 61, which is similar to the age distribution in the 26 male patients of Burger and Witts (1934). Lassitude and dyspnoea were the presenting symptoms in eight patients, and of the other three, two boys (Cases 1 and 2) had no definite symptoms of anaemia but were noted to be pale by their parents, and one young man (Case 7) during convalescence from pneumonia was noted to be pale by his doctor.

The tip of the spleen was palpable in four patients, and in one patient (Case 9) there was marked enlargement of both liver and spleen, which led at first to the mistaken diagnosis of Banti's disease. The palpable spleen disappeared in four patients after the anaemia had been corrected, and the other patient, whose spleen is still palpable after correcting the anaemia, has been followed up for only four months. Koilonychia was noted in only one case. There was a loud systolic murmur over the praecordium in three patients, in one of whom (Case 1) it had led to a previous diagnosis of patent interventricular septum. In all of these the murmur disappeared after the anaemia was corrected.

The blood picture showed a severe or moderate degree of hypochromic anaemia in all the patients, and the colour index was always reduced below 0.8 (see Table). The mean

Blood Findings

Case No.	Age	R.B.C. (Millions per c.mm.)	Hb (g.%)	Hb %	Colour Index	W.B.C. (per c.mm.)
1	7	3·8	5·9	41	0·53	10,200
2	14	5·5	8·5	58	0·53	—
3	14	4·5	7·4	50	0·55	8,000
4	14	3·9	8·2	56	0·7	9,400
5	14	4·8	7·0	47	0·48	4,500
6	15	3·8	5·3	37	0·5	11,400
7	19	4·0	6·7	45	0·56	8,000
8	20	3·1	5·8	39	0·62	—
9	24	2·5	4·4	30	0·6	5,700
10	53	3·0	5·6	38	0·63	—
11	61	3·0	7·1	48	0·79	9,600

corpuscular haemoglobin concentration, which was estimated in only three patients, was very much reduced—namely, 19, 19, and 25%. The white-cell count, which was estimated in eight patients, was always within normal limits.

The gastric acidity was estimated in seven patients, of whom six had a histamine-fast achlorhydria and one had hypochlorhydria.

There were no features in the previous history or during the follow-up period to suggest that gastro-intestinal bleeding or steatorrhoea was the cause of the anaemia. In seven patients the faeces were tested for occult blood on several

occasions and the results were all negative. The faecal fat was estimated in two patients and a fat-balance test was carried out on one patient, the results of these investigations being normal. Other possible aetiological factors were teeth extraction, apparently without much haemorrhage, at about the time of the onset of symptoms in one patient, and poor diet in four patients. It is difficult, however, to decide with any certainty whether a diet has an adequate iron content by questioning patients about their menu.

The anaemia was corrected invariably by iron therapy. Nine patients were given oral iron only. One patient (Case 10) was given 1 pint (570 ml.) of blood and intravenous iron initially, followed by oral iron, and one patient was given 2 pints (1,140 ml.) of blood at the onset of treatment, but the subsequent good response to iron therapy showed that the blood transfusion was unnecessary. The reticulocyte response, which was estimated in two patients in whom the anaemia was rapidly corrected by oral iron, was very small —namely, 1% and 1.4%. Sporadic administration of iron before attending hospital was the probable reason for this small reticulocyte response.

The prognosis as regards the anaemia was good and none of the 10 patients who were followed up for longer than six months relapsed. Two of these patients had not taken any medicinal iron during the previous two years, and two had not taken any during the previous year.

Case Reports

The features of the disease are illustrated by the following selection of case reports.

Case 1.—A boy aged 7 was admitted to the Liverpool Stanley Hospital in October, 1953. He was noted to have been pale for several years, and congenital heart disease had been diagnosed previously. He had plenty of energy and there were no symptoms of anaemia. On examination there was pallor of the face and mucous membranes; the tip of the spleen was palpable; there was clinical and radiological evidence of cardiac enlargement; a loud systolic murmur was heard over the praecordium, maximal at the apex; and the nasal septum was deviated, producing nasal obstruction. Laboratory investigations showed: R.B.C., 3,800,000 per c.mm.; Hb, 5.9 g.%; M.C.H.C., 19%; W.B.C., 10,200 per c.mm.; serum calcium, 11.6 mg. per 100 ml.; faecal fat, 7.5%. Occult blood tests on four specimens of faeces were negative. Treatment with "colliron," ½ dr. (1.8 ml.) t.d.s., was started in October, 1953, and produced a reticulocyte response of only 1%. In May, 1954, the mucous membranes were a good colour, the spleen was not palpable, there were no cardiac murmurs, chest *x*-ray examination showed a decrease in heart size to within normal limits, and the Hb had risen to 13 g.%.

Case 3.—A boy aged 14 attended the David Lewis Northern Hospital in November, 1950, complaining of lassitude, dyspnoea, and anorexia for about five weeks. He was taking a poor diet on account of anorexia. The chest *x*-ray examination showed slight cardiac enlargement. A blood count showed: R.B.C., 4,500,000 per c.mm.; Hb, 7.4 g.%; C.I., 0.55; W.B.C., 8,000 per c.mm. He did not take iron therapy as advised, and next attended hospital in September, 1952, when he complained that his symptoms had persisted. On examination the face and mucous membranes were pale, and the tip of the spleen was palpable. A blood count showed: R.B.C., 4,640,000 per c.mm.; Hb, 9.8 g.%; C.I., 0.72. Occult blood tests on two specimens of faeces were negative. There was no excess of faecal fat. A fractional test meal showed histamine-fast achlorhydria. Treatment with 2 tablets of "fersolate" t.d.s. was started in September, 1952, and in November the spleen was not palpable and the blood count was as follows: R.B.C., 4,200,000 per c.mm.; Hb, 12 g.%; C.I., 0.97; W.B.C., 7,200 per c.mm. In April, 1954, he wrote to say that he was feeling well and was in the R.A.F. He had not taken any iron during the last year.

Case 6.—A boy aged 15 was admitted to the Liverpool Stanley Hospital in January, 1954, complaining of lassitude and dyspnoea during the previous two years. His appetite was quite good, but he did not eat meat or fish and only few green vegetables. On examination the face and mucous membranes were pale, the tip of the spleen was palpable, and there was a loud systolic murmur over the praecordium, maximal at the apex. The chest *x*-ray examination was normal. Laboratory investigations: R.B.C., 3,800,000 per c.mm.; Hb, 5.3 g.%; M.C.H.C., 19%; W.B.C., 11,400 per c.mm.; E.S.R., 7-mm. drop per hour; serum calcium, 10.5 mg./100 ml.; fat-balance test normal. Occult blood tests on four specimens of faeces were negative. A fractional test meal showed histamine-fast achlorhydria. Treatment with colliron, 1 dr. (3.5 ml.) t.d.s., was started in February and produced a reticulocyte response of only 1.4%. In May he was feeling very well, and the Hb had risen to 13.3 g.%. The tip of the spleen was still palpable.

Case 9.—A man aged 24 was admitted to the Liverpool Stanley Hospital in August, 1951. He had been discharged from his job because the works medical officer thought he looked very anaemic, but at first he would not admit to having any symptoms. On further questioning, he thought that he had been slightly more breathless on exertion than usual for several months. His teeth had been extracted two months previously, but he did not think that there had been much haemorrhage. On examination there was pallor of the mucous membranes, a systolic murmur was heard at the cardiac apex, and both liver and spleen were much enlarged, so that Banti's disease was diagnosed at first. Laboratory investigations: R.B.C., 2,500,000 per c.mm.; Hb, 4.4 g.%; C.I., 0.6; W.B.C., 5,700 per c.mm. Occult blood tests on faeces were negative. Liver-function tests were normal. Treatment with 2 tablets of fersolate t.d.s. was started in August, 1951, and one month later the haemoglobin had risen to 14.4 g.%. In November, 1952, he was feeling very well, the liver and spleen were not palpable, and the blood count was as follows: R.B.C., 5,500,000 per c.mm.; Hb, 14.8 g.%; W.B.C., 5,800 per c.mm. He had not taken any medicinal iron during the previous year. In April, 1954, he wrote to say that he was feeling well.

Discussion

Idiopathic hypochromic anaemia in males is a rare disease in hospital practice, and only 11 cases were collected from the records of three general medical firms, each containing about 35 beds, over a period of four years. The majority of these patients are below the age of 25, and the diagnosis of idiopathic hypochromic anaemia should not be made in middle-aged and elderly men until they have been followed up for at least a year. The present follow-up study showed that of three middle-aged men who were originally included in the series, two had died from carcinoma of the stomach and one had developed haematuria due to prostatic hypertrophy.

The diagnosis of idiopathic hypochromic anaemia is made in these patients because the aetiological factors are not evident. The cause of the anaemia, however, must be haemorrhage, inadequate iron intake, or poor iron absorption, either together or singly, and these three factors are now considered.

1. *Haemorrhage.*—If haemorrhage produces hypochromic anaemia it is usually chronic and not acute, and so would be expected to continue after the patients attended hospital and to produce a relapse after stopping iron treatment. In none of these patients, however, was there any evidence of haemorrhage during the follow-up period, and the absence of relapse has been a constant feature.

2. *Inadequate Iron Intake.*—The average total daily iron loss in adult men is about 1.2 mg., consisting of 0.4 mg. in the urine (Barer and Fowler, 1937) and 0.8 mg. in the bile (Whitby, 1949). The daily iron requirements for growth are about 0.2 mg. in the 8th year, 0.54 mg. in the 13th year, 0.86 mg. in the 14th year, rising to a maximum of almost 1 mg. in the 16th year, and ceasing completely in the 22nd year (Heath and Patek, 1937). If in normal subjects about 15% of the iron in the intestine is absorbed (Dubach *et al.*,

1948), then adult men require a diet which contains about 8 mg. of iron daily and youths of 16 require a diet containing about 14 mg. of iron daily.

In the National Food Survey for 1950 (Ministry of Food, 1952) it was estimated that the average daily iron intake for adults of both sexes was 13.6 mg., and for a group of adolescents and children it was 13.9 mg. The size of the family, however, influenced the average daily iron intake; it was only 10.9 mg. in families with four or more children. These figures show that even the poorest diet should provide enough iron for adult men and for boys under the age of 14, but that a poor diet may lead to iron deficiency in youths between the ages of 14 and 17, which is the age period when the incidence of the disease is greatest.

3. *Poor Iron Absorption.*—Hawkins *et al.* (1950) found evidence of steatorrhoea in six cases of hypochromic anaemia which were refractory to oral iron therapy, and Badenoch and Callender (1954) have shown that the poor iron utilization in steatorrhoea is due to poor absorption. It should be emphasized, therefore, that intravenous iron preparations should not be given before a trial of oral iron therapy, because the absence of a response to oral iron therapy may be the first evidence which suggests the diagnosis of steatorrhoea. Fat-balance studies were done on only one of the present series of patients, but there was nothing in the histories of the other patients to suggest the diagnosis of steatorrhoea, and they all responded to oral iron therapy.

It has been shown that, except in cases of steatorrhoea, iron absorption is partly controlled by the body's needs for the element and that the average absorption is much higher in patients with hypochromic anaemia than in normal subjects (Brock and Hunter, 1937; Moore *et al.*, 1939; Balfour *et al.*, 1942; Dubach *et al.*, 1948). There is, however, a considerable variation in the amount of iron absorbed by both patients with hypochromic anaemia and by normal subjects (Dubach *et al.*, 1948; Badenoch and Callender, 1954). In these studies, the hypochromic anaemia has usually been due to haemorrhage, which would account for the high average absorption. On the other hand, Balfour *et al.* (1942) found that the amount of radioactive iron which was absorbed by a patient with hypochromic anaemia with no evidence of blood loss was less than the average amount absorbed by patients with anaemia due to haemorrhage, and Badenoch and Callender (1954) found that in a male patient with hypochromic anaemia and no evidence of haemorrhage only 11% of administered radioactive iron was utilized.

In these experiments, which have been discussed, the absorption of iron, which has been given in addition to the normal food, has been studied. However, the work of Moore and Dubach (1951), who measured the iron absorption from foods tagged with radioactive iron, suggests that the absorption of food iron differs from that of medicinal iron salts. They found little difference between the average iron absorption in normal subjects and in patients with untreated hypochromic anaemia, but the variation in the amount of iron absorbed was considerable, ranging between 1.1 and 33.1% (average 6.5%) in 17 normal subjects, and between 1.4 and 17.7% (average 5.8%) in 7 patients with hypochromic anaemia. As they have accepted the amount of iron appearing in the circulating haemoglobin as a measure of the iron absorbed, it is probable that their figures in the cases of hypochromic anaemia are a good indication of absorption, as almost 100% of the absorbed iron is utilized (Dubach *et al.*, 1948). On the other hand, in the normal subjects, in whom less than 50% of absorbed iron is utilized, the iron absorption was probably much more than they calculated in the haemoglobin.

In conclusion, it seems probable that in some patients with hypochromic anaemia the absorption of food iron may be inadequate even when the patient is taking a normal diet, and it is postulated that this is an important aetiological factor in male patients with idiopathic hypochromic anaemia. This view, however, requires confirmation by further studies on iron absorption, using food tagged with radioactive iron. On the other hand, the measurement of the absorption of radioactive iron salts is unlikely to be of value because these patients respond to oral iron therapy.

Summary

Eleven male patients with hypochromic anaemia and with no evidence of haemorrhage or steatorrhoea are described.

All responded to oral iron therapy. None relapsed during the follow-up period, and four of the patients had not taken any iron during the previous year.

The aetiology is discussed, and it is concluded that poor iron absorption and, during adolescence, inadequate iron intake are the aetiological factors.

My thanks are due to the physicians of the David Lewis Northern Hospital and the Liverpool Stanley Hospital for permission to study and follow up their cases. I also wish to thank Sir Lionel Whitby for his permission to publish this paper, part of which was included in a thesis for the Cambridge M.D.

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HAEMOGLOBIN LEVELS OF NORMAL MEN AND WOMEN LIVING IN A TROPICAL CLIMATE

BY

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There is some doubt about the effects of high environmental temperatures on the haemoglobin level of man. Exposure of a few days to a few weeks are accompanied by a decrease of the haemoglobin concentration (Barcroft *et al.*, 1923; Bazett *et al.*, 1940; Maxfield *et al.*, 1941; Post and Spealman, 1948). The evidence about haemoglobin levels of people who are permanently living in a hot climate is contradictory (MacGregor and Loh, 1941), but it has been shown that such people have normal packed red-cell volumes (Wadsworth, 1952a) and red-cell counts (Wadsworth, 1952b). The present investigation was designed to show if prolonged exposure to high environmental temperature affected haemoglobin levels. The opportunity was also taken to compare haemoglobin levels of different racial groups.

Material

The investigation was made at Singapore, where the environmental temperature varies very little throughout the year and is usually between 23 and 32° C. (73.4 and 89.6° F.), with a humidity of 70 to 90%. There is an absence of