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IDIOPATHIC HYPOCHROMIC ANAEMIA IN YOUNG ADULT MALES

BY

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Idiopathic hypochromic anaemia is described by Whitby and Britton (1946) as a chronic anaemia chiefly found in middle-aged women and characterized by a low mean corpuscular haemoglobin concentration and mean cell volume; achlorhydria and glossitis are usual, while koilonychia is common. Attention was first drawn to the condition by Faber (1913) and since that time ample descriptions of the disease in women have appeared in the literature.

According to Whitby and Britton the disease is uncommon in males, while Wintrobe (1946) states that 4% of cases are found in men. Faber's original account of 22 cases contained three males. Witts (1930a) analysed a series of 50 cases, one of which was a man; while Davies (1931a) later reviewed the subject of achlorhydria and anaemia and found no males in a series of 15 cases of hypochromic anaemia. In a further series recorded by Davies (1931b) there were four males in a total of 55 cases. Parkes Weber and Weisswange (1933) described four cases of anaemia of unexplained origin occurring in men, only two of which were of the true hypochromic type. Bethell *et al.* (1934) found two males in a series of 33 cases; Britton (1936) recorded four cases of idio-

pathic hypochromic anaemia occurring in men in a series of 66. Reviewing the incidence of chronic nutritional anaemia, Davidson and Fullerton (1938) found no cases in a series of 167 adolescent and adult males, while the Medical Research Council (1945) showed that between 2 and 3% of adult males had a haemoglobin level below 80%, and 0.2% of adolescent males under the age of 20 years had a haemoglobin level below 70%. In that survey no cause was apparently sought for the anaemia.

The occurrence of idiopathic hypochromic anaemia in the young adult male is, however, very rarely described. Wintrobe states that of the cases occurring in men, 82% are found between the ages of 20 and 50 years. Thomson (1943) recorded nine cases occurring in adolescent males whose ages ranged from 17 to 19 years, and Beckert (1938) described two cases of apparent chlorosis in youths aged 16 and 17. The five cases of chlorosis recorded by Witts (1930b) were found in young men with ages varying from 18 to 28 years, while of the series of 26 cases of idiopathic hypochromic anaemia in males described by Witts and Burger (1934) eight were males below the age of 30.

The present series of 20 cases in young soldiers has been seen by us over the course of the past two years at the Cambridge Military Hospital, Aldershot. Although the ages of patients (all male) attending the hospital range from 18 to 60 years, cases of idiopathic hypochromic anaemia have been observed only in soldiers from 18 to 23 years of age. All but one of the cases were found in men with less than three months' service, and an interesting point for which we can offer no explanation is that of the 20 patients 11 came from the Royal Army Ordnance Corps. In none was there any relevant past history, and in one case only was there any familial history of anaemia. This man had an anaemic brother. On close questioning no abnormal food habits were found. Clinical examination and special investigations revealed no evidence of gross organic disease such as chronic infection, gastro-intestinal disorders, chronic nephritis, recurrent rheumatism, or neoplasm. A particular search for gastro-intestinal haemorrhage or bleeding haemorrhoids failed to disclose a cause for the anaemia.

A summary of the main clinical findings is shown in Tables I and II. Some representative case histories are given below.

Case 5

Aged 19. Service, one week. Civilian occupation, plasterer's labourer. History: was examined one year previously by civilian medical board and call-up deferred owing to anaemia; not investigated, but advised to take iron tablets, which he did not do; no symptoms before joining Army, but marked dyspnoea on exertion since recruitment; had "gastritis" five years previously; no relevant family history. Physical examination: mucous membranes very pale; sparse axillary and pubic hair, fine in quality; skin thick and dry, nails fluted; tongue, teeth, and pharynx healthy; spleen just palpable; no haemorrhoids.

Investigations.—Hb, 7.6 g.% (Sahli); R.B.C., 5,000,000; C.I., 0.52; P.C.V., 32%; M.C.V., 64 μ^3 ; M.C.H., 15.2 μg ; M.C.H.C., 23.7%; W.B.C., 6,400 (P. 54%, L. 42%, M. 2%, E. 2%); red-cell fragility within normal limits; chest radiograph normal; F.T.M., histamine-fast achlorhydria; stools, negative for O.B. (six specimens).

Treatment: ferrous sulphate, 6 gr. (0.4 g.) t.d.s.; dilute HCl, 15 min. (0.9 ml.) t.d.s., a.c. Result: Hb, 14.2 g%; R.B.C., 4,800,000; C.I., 1, after 11 weeks; no return of symptoms after two years.

Case 9

Aged 18. Service, four weeks. Civilian occupation, plumber's mate. History: had noticed marked dyspnoea and palpitations on exertion for three months; more severe since joining Army; had always been pale; appetite good, no abdominal pain, bowels opened regularly; no relevant past or family history. Physical examination: slightly built; pallor of skin and mucous membranes; nails thin and transversely ridged; tongue, teeth, and pharynx healthy; soft systolic murmur localized to mitral area; tip of spleen easily felt. Liver just palpable. No haemorrhoids.

Investigations.—Hb, 8.8 g.% (Sahli); R.B.C., 4,700,000; C.I., 0.69; P.C.V., 35%; M.C.V., 74 μ^3 ; M.C.H.C., 25%; stained film of red blood cells showed marked anisocytosis and poikilocytosis, but no polychromasia or stippling; W.B.C., 8,800 (P. 49%, L. 50%, M. 1%); reticulocytes, 0.5%; fragility of red blood cells, within normal limits; blood bilirubin, 0.3 mg./100 ml.; F.T.M., complete achlorhydria; stools, three specimens negative for O.B.; chest radiograph normal; barium meal normal. The fact that this man had worked with lead as a plumber's mate for three years may have contributed to the production of the anaemia. But there were no other symptoms or signs suggestive of lead-poisoning. The presence of a normal red-cell fragility and a normal serum-bilirubin level, together with the absence of stippling, make it extremely unlikely that the anaemia was a toxic manifestation of lead.

Treatment: ferrous sulphate, 6 gr. t.d.s., dilute HCl 15 min. t.d.s., a.c. Result: Hb, 12.6 g.%; R.B.C., 5,400,000; C.I., 0.8 after eight weeks; no return of symptoms after 18 months.

Case 6

Aged 18. Service, four weeks. Civilian employment, shop assistant. History: marked dyspnoea on exertion since joining Army; had previously felt quite fit; no relevant past or family history. Physical examination: poor physique; skin dry and coarse; marked pallor of mucous membranes; pharynx, teeth, and tongue healthy; no koilonychia; liver and spleen not felt; no haemorrhoids.

Investigations.—Hb, 6.9 g.% (Sahli); R.B.C., 4,240,000; C.I., 0.57; P.C.V., 27%; M.C.V., 66 μ^3 ; M.C.H., 16.2 $\mu\mu\text{g.}$; M.C.H.C., 25.3%; W.B.C., 7,600 (P. 53%, L. 42%, M. 3%, E. 1%, B. 1%); reticulocytes, 2%; red-cell fragility within normal limits; chest radiograph normal; F.T.M., complete achlorhydria with slight histamine response; stools, negative for O.B. (five specimens, first specimen weakly positive); barium meal normal; Kahn test negative.

Treatment: ferri et ammon. cit., 40 gr. (2.6 g.) t.d.s., dilute HCl, 15 min. t.d.s., a.c.; "multivite" tablets, 1 t.d.s. Result: Hb, 11.2 g.%; R.B.C., 5,000,000; C.I., 0.78 after 10½ weeks; no return of symptoms after two years.

Case 13

Aged 20. Service, three weeks. Civilian occupation, farm labourer. History: vague epigastric ache present spasmodically for previous four weeks, unrelated to food; appetite good; no vomiting; bowels opened regularly; no melaena; dyspnoea on exertion; no relevant past or family history. Physical examination: marked pallor of skin and mucous membranes; koilonychia; tongue, teeth, and pharynx healthy; liver and spleen not felt; no haemorrhoids.

Investigations.—Hb, 9.5 g.% (photoelectric); R.B.C., 5,200,000; C.I., 0.62; W.B.C., 4,500 (P. 50%, L. 31%, M. 15%, E. 4%); fragility of red blood cells within normal limits; chest radiograph normal; F.T.M., hypochlorhydria; stools, negative for O.B. (three specimens).

Treatment: ferrous sulphate, 6 gr. t.d.s., dilute HCl, 15 min. t.d.s., a.c. Result: Hb, 14.7 g.%; R.B.C., 5,250,000; C.I., 0.97; quite fit after 11 months.

Comments on Table I

The duration of the symptoms was short in all cases. The commonest complaint was of dyspnoea; 15 of the cases complained of some degree of undue breathlessness on exertion. The severity of the dyspnoea did not appear to bear any constant relation to the degree of anaemia. In only three instances were there dyspeptic symptoms, consisting of epigastric pain. Bloating after food, dysphagia, and diarrhoea, symptoms often found with achlorhydria, were not encountered. In common with Witts and Burger (1934) we observed a definite tendency to immaturity, all appearing some few years younger than their actual ages. This immaturity and the "sneaking college look" (Wycherley, 1972) may have, albeit unconsciously, prompted the personnel selection officer in his choice of posting for these men.

There was no tendency to eunuchoidism or under-development of the genitalia, which Gardiner-Hill (1931) and Filo (1933) associate with anaemia. The patients' skins were smooth, and the hair fine; acne was absent in all cases. Glossitis and soreness of the tongue were

TABLE I.—Main Clinical Findings

Case No.	Age	Symptoms		Physical Signs			
		Dyspnoea	Other Symptoms	Pallor	Spleno-megaly	Apical Murmurs	Miscellaneous
1	18	Nil	Nil	Marked	—	—	Poor physique
2	18	Mild	Would-be blood donor. Anaemia discovered on routine blood examination	Slight	—	—	—
3	18	Severe	Nil	Marked	—	—	Immature
4	18	Mild	Lassitude. Generally unwell	—	—	—	Nails fluted; skin hard and dry; pubic hair scarce
5	19	Severe	Anaemia noted by civilian medical board; enlistment deferred	"	Palp.	Systolic	Poor physique
6	18	"	Nil	"	—	—	Poor physique; koilonychia; dental sepsis
7	18	Mild	Pains in calves on exercise	"	—	Systolic	Koilonychia
8	18	Nil	Headaches	"	—	—	Poor physique; nails thin; transversely ridged; liver palpable
9	18	Severe	Palpitations	"	Palp.	Systolic	No abnormal C.N.S. signs
10	18	Mild	Occasional pins-and-needles in feet	"	—	—	—
11	23	Severe	Attacks of dizziness	"	—	—	—
12	18	Nil	Epigastric pain not related to meals	"	—	—	—
13	20	Mild	Would-be blood donor. Anaemia discovered on routine blood examination	"	—	—	Koilonychia
14	18	Marked	Nil	"	—	—	Poor physique
15	18	Mild	Epigastric pain. Palpitations	"	—	—	" "
16	18	Nil	Would-be blood donor. Anaemia discovered on routine blood examination	"	—	Systolic	" "
17	18	"	Lassitude, headaches, dizziness	"	Palp.	—	Liver palpable
18	20	Severe	Lassitude, headaches	"	Palp.	Systolic	Nails flattened; poor physique
19	18	"	Nil	"	—	"	Poor physique; gross koilonychia
20	20	"	Nil	"	—	"	"

not seen and oral sepsis, so beloved of the elder clinician, was in no case a marked feature. Changes in the nails were present in seven cases, frank koilonychia in four, brittleness and fluting in three. Witts and Burger (1934) described no changes in the nails, whereas Thomson (1943) found 4 with changes in 10 cases. In Case 20 the koilonychia was gross, the depression in the thumbnail holding eight drops of water. Splenomegaly was found in four of our cases. This proportion is similar to that described by Witts and Burger (1934). In Thomson's cases, however, the spleen was enlarged and palpable in 5 cases out of 10. These observations are to some extent in agreement with those of Witts and Burger (1934) in that "the typical syndrome of hypochromic anaemia as it appears in women with microcytic anaemia, achlorhydria, splenomegaly, and dystrophic changes in the tongue, the pharynx, and the nails is rarely encountered in the adult male."

Comments on Table II

The haemoglobin levels are expressed as grammes per 100 ml., and were estimated either by the methods of Haldane or Sahli, or by means of a photoelectric colorimeter standardized against the Gibson-Harrison artificial standard. The figure of 14.5 g. per 100 ml. was taken as 100% for the purposes of colour-index calculation. The fractional test meals were performed using 50 ml. of 7% ethyl alcohol as the primary stimulus, with the addition in some cases of 0.5 mg. of histamine subcutaneously.

Examination of the stained films invariably revealed variations in shape, size, and colour of the red blood

cells, in some cases out of proportion to the degree of the anaemia. Red-cell fragility and platelet and reticulocyte counts were within normal limits. The leucocyte counts varied between 4,000 to 10,000 per cm., and most cases showed some degree of neutropenia. Chest radiographs showed no evidence of pulmonary or cardiac disease, and the examinations of stools for occult blood were without significant exception negative.

Thirteen cases showed complete achlorhydria. Normal gastric acidity was present in Case 17 and hyperchlorhydria was demonstrated in Cases 14 and 16. In none of these was there any radiological evidence of gastric or duodenal abnormalities. The remaining case with hyperchlorhydria did not have a peptic ulcer excluded radiologically, but examinations of the stools for occult blood were consistently negative. These cases of hypochromic anaemia associated with a normal or high gastric acidity are presumably examples of the chlorotic type of anaemia seen more often in former days in adolescent females.

Treatment

Treatment was conducted on routine lines with the patients at rest in bed on a normal diet. All cases were given iron preparations in the form of ferrous sulphate, 6 gr. (0.4 g.) t.d.s., or ferri et ammon. cit. 40 gr. (2.6 g.) t.d.s., together with vitamin supplements. Those with achlorhydria were given dilute HCl 15 min. (0.9 ml.) t.d.s., in addition. Patients were advised to continue treatment after discharge from hospital.

The results of treatment as indicated in Table II were in most cases satisfactory. The patients have been

TABLE II

Case No.	Hb g %	R.B.C. (mils.)	C.I.	P.C.V. %	M.C.V. (μ3)	M.C.H.C. %	W.B.C. Diff. %	Comment on Film	F.T.M.	Results of Treatment			Duration of Treatment
										Hb	R.B.C.	C.I.	
1	7.87 (H)	4.1	0.66	33	80	24	8,400 P58, L36, M2, E4	Hypochromia, anisocytosis, poikilocytosis	Achlorhydria	14.7	5.3	0.93	8 weeks
2	9.4 (S)	3.83	0.84	36	94	26	7,800 P64, L32, M3, E1		"	14.5	5.2	0.95	6 "
3	6.8 (S)	3.62	0.65				7,300 P69, L29, M1, B1	Anisocytosis, polychromasia	Histamine-fast achlorhydria	14.0	5.35	0.90	6 "
4	8.0 (H)	4.06	0.69				6,700 P54, L36, M5, E5	Hypochromia, anisocytosis, poikilocytosis	Achlorhydria	13.8	5.02	0.91	6 "
5	7.6 (S)	5.0	0.52	32	64	23.7	6,400 P54, L42, M2, E2	Gross anisocytosis and poikilocytosis, hypochromia	Histamine-fast achlorhydria	14.2	4.8	1.0	11 "
6	6.9 (S)	4.24	0.57	27	66	25.3	7,600 P53, L42, M3, E1, B1	Hypochromia, anisocytosis, poikilocytosis	Achlorhydria, slight histamine response	11.2	5.0	0.78	10 "
7	7.29 (H)	4.15	0.60	30.5	73.5	23.9	6,000 P70, L26, M3, E1	"	Achlorhydria	14.17	5.0	0.98	12 "
8	7.87 (H)	3.96	0.68				5,200 P30, L59, M11	Hypochromia, anisocytosis	"	12.0	5.3	0.77	4 "
9	8.8 (S)	4.70	0.69	35	74	25	8,800 P49, L50, M1	Anisocytosis, hypochromia, poikilocytosis; no stippling	"	12.6	5.4	0.80	8 "
10	7.9 (P)	4.75	0.57				7,600 P55, L37, M4, E3, B1	Anisocytosis, poikilocytosis	"	12.6	5.0	0.87	6 "
11	10.4 (S)	5.0	0.72				6,800 P60, L35, M4, E1	Red cells appear normal	"	13.7	4.84	0.97	7 "
12	7.7 (S)	4.18	0.63				8,200 P57, L40, E2, M1	Marked hypochromia some polychromasia	Hyperchlorhydria	12.9	4.9	0.90	6 "
13	9.45 (P)	5.2	0.62				4,500 P45, L50, M3, E2		Hypochlorhydria	14.7	5.25	0.97	6 "
14	8.37 (H)	3.5	0.80				7,000 P58, L39, M2, E1		Hyperchlorhydria	13.1	4.93	0.9	5 "
15	8.0 (H)	3.61	0.77	30	83.3	26.6	7,000 P60, L26, M8, E6	Hypochromia, anisocytosis, poikilocytosis	Achlorhydria	13.8	5.6	0.85	6 "
16	8.2 (P)	4.48	0.65	34	75.5	23.1	9,100 P72, L25, M3	"	Hyperchlorhydria	14.2	5.2	0.93	8 "
17	9.66 (H)	4.8	0.70	40	84	24.1	8,200 P69, L26, M4, E1	Anisocytosis, hypochromia	Normal acidity	15.66	5.0	1.1	5 "
18	10.3 (H)	5.0	0.71	36	92	22.4	7,200 P65, L30, M3, E2	Hypochromia	Histamine-fast achlorhydria	14.3	5.2	0.9	4 "
19	11.0 (P)	5.0	0.75				9,000 P72, L25, M3	Sl. anisocytosis and poikilocytosis	"	16.0	5.0	1.1	5 "
20	6.3 (S)	3.5	0.60				7,800 P60, L32, M4, E3, B1	Anisocytosis, hypochromia, poikilocytosis	"	14.5	5.3	0.92	10 "

H = Haldane. S = Sahli. P = Photoelectric colorimeter.

followed up for periods varying from three months to two years, and, although it has not been possible to obtain follow-up blood pictures, in no cases have symptoms returned.

Discussion

The fact that these cases of anaemia are labelled idiopathic indicates that their aetiology is obscure. A combination of factors has probably rendered insufficient the amount of iron available for haemoglobin synthesis. It is less likely that there was an excessive iron loss by way of chronic haemorrhage, although the possibility that this had occurred in the past cannot be ruled out. The deficiency of hydrochloric acid in the gastric secretions was probably one of the determining factors, but it cannot have been the primary cause, as four of the patients were not achlorhydric. Also, as noted by Davidson and Fullerton (1938), not all achlorhydric people are anaemic, and, whereas the incidence of achlorhydria increases with advancing years, idiopathic hypochromic anaemia in old people is rare.

The possibility that the anaemia in Case 9 was a toxic manifestation of lead has already been considered. We have also pointed out that all but one of the men had less than three months' service. Probably the amount of extra physical exertion involved in their basic training was sufficient to produce symptoms in subjects previously anaemic but hitherto symptomless. This certainly was true of Case 20, in which the gross degree of koilonychia was evidence of a long-standing anaemia, and also of Case 5, in which an anaemic state had been demonstrated twelve months previously.

There is, however, a further possible explanation. Cantarow (1947) states that 23% of the minimal iron intake is required for the manufacture of muscle haemoglobin and for use in muscle and other parenchymal cells. This iron is not available for blood haemoglobin formation, and blood haemoglobin may constitute an important source of iron necessary for growth. Davidson *et al.* (1933) have shown that persons with achlorhydria exist on an intake of iron which is very near the borderline. In most cases the first few months of the recruits' lives in the Army are accompanied by a marked increase in weight, due, in part, to enhanced development and hypertrophy of the musculature. This change is more pronounced in those previously immature and of poor physique. It may be that this abnormal demand for iron cannot be met by increased intake, on account of impaired absorption from the gut, and iron for the enhanced development is obtained at the expense of the blood haemoglobin. Thus either an anaemic state is produced or a latent anaemia is rendered obvious.

Summary

An account is given of 20 cases of idiopathic hypochromic anaemia occurring in young men.

The majority of cases showed a definite tendency to immaturity, and nail changes were present in some. The typical syndrome of hypochromic anaemia as it occurs in women was not seen.

Achlorhydria or hypochlorhydria was present in 16 of the cases. Of the remainder, normal gastric acidity was present in one and hyperchlorhydria in three.

The blood pictures rapidly improved, and in most cases became normal on treatment with adequate amounts of iron.

There was no indication that the anaemias were the result of blood loss. They were probably due to an increased demand for iron coupled with defective intestinal absorption.

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ORAL HEXAMETHONIUM BROMIDE IN ESSENTIAL HYPERTENSION

BY

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The group of compounds known for convenience as methonium halides emerged in the course of a systematic search for synthetic substitutes for curare. The pharmacological researches of Paton and Zaimis (1949) showed that compounds with carbon chains of intermediate length (five or six atoms) exert their action at ganglionic synapses rather than at neuromuscular junctions and that they are capable of influencing profoundly the functions of the autonomic nervous system. An opportunity was thus provided for a new approach to the management of diseases, such as peptic ulceration and essential hypertension, in which hyperactivity of the autonomic nervous system might be conceived to play a part.

These drugs are stable and soluble, and are apparently absorbed freely unchanged from the alimentary tract. As soon as adequate amounts became available Kay and Smith (1950), working on peptic ulcer, showed that hexamethonium bromide is pharmacologically active when given orally. We were fortunate in having direct access to Kay and Smith's work in progress. It seemed to suggest the possibility that a simple effective method might be devised of controlling by oral drug therapy the manifestations of essential hypertension. A clinical investigation along these lines was begun early in 1950. As the methonium drugs are now freely marketed we feel it appropriate that we publish our results and attempt to indicate provisional tentative conclusions.