Anaemia Associated With Unexplained Occult Blood Loss*

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In the course of a study of patients with hypochromic anaemia investigated by this unit (Beveridge, Bannerman, Evanson, and Witts, in preparation) a surprisingly large number were found to have unexplained occult alimentary bleeding. Iron-deficiency anaemia associated with unexplained occult blood loss is a recognized clinical problem and has been referred to in several papers (Heath and Patek, 1937; Bedford and Wollner, 1958; Bel, 1959; Retzlaff, Hagedorn, and Bartholomew, 1961; Kay, 1962). However, there is little or no information about the long-term prognosis. We therefore report the results of a follow-up study on 68 patients in whom this diagnosis was made.

Methods

Selection of Patients

The patients are drawn from a group of 378 in-patients of the Nuffield Department of Clinical Medicine investigated in the twenty years 1941 to 1960, in whom the diagnosis of "hypochromic anaemia" was made. These patients all had "anaemia" recorded in their final diagnoses, an initial haemoglobin level of less than 12 g./100 ml., and hypochromia of the erythrocytes as shown by an M.C.H.C. of 30% or less, or where this was not available a colour index of 0.8 or less. In 371 of these patients iron deficiency was the apparent cause of the anaemia and 73 had unexplained positive tests for occult blood at the time of their first investigation. We exclude from further consideration here five of these patients in whom a positive occult-blood test was obtained on only one occasion, and have analysed the data on the remaining 68. Thirty-six of these had had full clinical and radiological investigations, including barium meal and barium enema (Group A), while in 32, the majority of whom were investigated before 1954, radiological investigations were not complete (Group B).

Occult-blood Tests

These were performed throughout the period 1941-60 in the Nuffield Department of Clinical Biochemistry by the benzidine method, using 2.5% benzidine base and hydrogen peroxide solution, with boiled faeces. This method gives identical results to those obtained by Gregersen's modification, in which benzidine hydrochloride and barium peroxide powder are used, as shown by Mendeloff (1953) and confirmed by one of us. A positive result usually indicates the loss of at least 5 ml. of blood from the alimentary tract (Needham and Simpson, 1952; Bannerman, 1957; Huntsman and Liddell, 1961). In this study we have included only patients in whom two or more tests were positive.

Follow-up

At follow-up and review two to 21 years after they were first investigated we were able to trace all 68 patients. Local patients were seen by one of us and patients who lived at a distance were seen by their general practitioner. Haemoglobin and packed cell volume were determined on all surviving

patients, and blood smears and estimations of serum iron were obtained where possible. Further information that had accrued during the intervening years was obtained from hospital and general practitioners' records, and the death certificates or necropsy reports of the nine patients who had died were scrutinized.

Because the part played by the ingestion of salicylate in causing gastro-intestinal bleeding has only been fully appreciated in recent years (Alvarez and Summerskill, 1958) all surviving patients were asked either at interview or by means of a detailed questionnaire about their intake of aspirin or aspirin-containing medicines. Replies were obtained from all except two.

Results

Patients Reclassified at Follow-up

Information that had come to light since the initial investigation or at follow-up allowed the reclassification of 17 patients. In 12 of these (in nine as a result of specific questioning at follow-up) the ingestion of salicylate was thought likely to have been a major cause of blood loss. Two patients gave a history of bleeding haemorrhoids that they had not disclosed initially, and in one other patient a gastric ulcer was demonstrated by a further barium meal. The last two patients are of special interest. One, a woman of 52, was readmitted 14 months after complete initial investigation, and a second barium enema revealed a carcinoma of the hepatic flexure from which she died two years later. In the other, a man of 75 who complained of constipation, bright blood was observed on the stools and at proctoscopy the rectal mucosa bled easily. Attempts at sigmoidoscopy and barium enema failed because of hard faeces. Laparotomy was considered but rejected because of the patient's general condition, and he died at home eight months later. Death was attributed to "pulmonary embolus" and "gastro-enteritis," but the patient has been included here because it seems likely that he was suffering from carcinoma of the rectum or haemorrhagic proctitis. In the entire group of 378 patients these are the only two in whom there has been any evidence that a malignant lesion was overlooked at the original investigation.

The details of the 51 remaining cases are set out in Tables I and II¹ and the further analysis and discussion of results will be confined to them.

Age and Sex

The patients' ages when they were first seen ranged from 14 to 80 years, and were more or less evenly distributed by decades. There were 30 female and 21 male patients. This age and sex

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distribution differs markedly from that of our larger group with iron-deficiency anaemia from all causes, in which there is a fourfold preponderance of females with a very high incidence in the 30–50 age group (Beveridge *et al.*).

Anaemia and Epithelial Changes

The mean haemoglobin value for the group was 7.9 g./100 ml. and was the same for each sex (males 8.0 g./100 ml.; females 7.9 g./100 ml.). The incidence of epithelial changes, including achlorhydria, is similar to that in other series of cases of iron-deficiency anaemia, including our own larger group.

Contributing Causes of Iron Deficiency

Iron-deficiency anaemia is a syndrome often due to multiple causes, and while we believe that gastro-intestinal bleeding was an important cause in the cases considered here other factors certainly contributed. Thus, 17 female patients were menstruating and seven gave a history of menorrhagia. Some degree of malabsorption of iron may have been present in 10 patients: five had had a partial gastrectomy, two a gastro-enterostomy, and the other three had high faecal-fat excretion. The patients who had undergone gastric surgery were all men, and constitute much the same proportion of the males in this series (seven out of 21) as in the original larger survey (22 out of 83). The diet of nine patients was considered to contain insufficient iron for normal needs.

Follow-up

The results of follow-up are set out in Tables III and IV.¹ The average time between initial investigation and follow-up or death was seven years. The most striking finding was that none of these 51 patients had obvious organic disease of the gastro-intestinal tract. Many of them had been investigated several times without any lesion of the gastro-intestinal tract being found, though in some of them occult blood was repeatedly present. In the nine patients who died the cause of death did not appear to be related in any way to the anaemia.

Of the 42 surviving patients, though over half had had one or more recurrences of anaemia during the intervening years (approximately the same recurrence rate as in our total group of 371 patients), only five had a haemoglobin level below 12 g./100 ml. at follow-up. This is in contrast to the high incidence of anaemia found at follow-up in larger unselected groups of patients with iron-deficiency anaemia (Fry, 1961; Beveridge *et al.*) and may be attributed to the fact that 24 patients were regularly taking oral iron or had taken it within the previous year.

Discussion

The 51 patients reported here with positive tests for occult blood for which no cause has been found represent 14% of all patients with iron-deficiency anaemia in our larger survey. They are thus a numerically important part of the total picture of iron deficiency as seen by this department. It is important to decide whether the positive tests for occult blood are merely a coincidental finding in patients with iron deficiency from some other cause or whether, as we believe, they represent an important though unexplained factor in the anaemia. The marked difference in age and sex between this group and our total series of patients with iron-deficiency anaemia (more than 85% of whom had stools examined for occult blood) is very much

against positive occult-blood tests being a purely random phenomenon.

The incidence of positive tests for occult blood in a normal population is unknown. Mendeloff (1953), using Gregersen's method with 0.5% benzidine hydrochloride, obtained positive tests in 79 out of 248 stool specimens from healthy students who were taking 180 mg. of ferrous iron daily. However, the faeces had not been previously boiled to destroy peroxidases. Using a method essentially the same as that employed with our patients, Huntsman and Liddell (1961) found no positive tests in 83 specimens from 18 normal adults on a full diet. In 117 specimens from children on a full diet, however, there were 24 positive results.

There is evidence that positive tests are not uncommon in infants (Hoag, Wallerstein, and Pollycove, 1961) and in hospital patients more than 65 years of age (Bedford and Wollner, 1958). In both these age-groups, however, they are much more frequently found in patients with iron-deficiency anaemia. The quantitative importance of occult bleeding as a source of iron loss has been confirmed by studies of individual patients, using the radio-isotopes ⁵⁹Fe or ⁵¹Cr (Bannerman, 1957; Ebaugh, Clemens, Rodnan, and Peterson, 1958; Hoag *et al.*, 1961). In one patient in our series (No. 19) ⁵¹Cr studies showed faecal blood loss of approximately 2.5 ml. per day, and in similar patients too recently investigated for inclusion in the series unexplained losses of up to 20 ml. of blood per day have been determined.

In how many of our 51 patients whose loss of blood is still unexplained would a lesion have been discovered had they been submitted to more elaborate investigations along the lines suggested by Kay (1962), or to laparotomy? In 21 cases at the Mayo Clinic in whom a laparotomy was performed because of hypochromic anaemia with unexplained loss of occult gastro-intestinal blood, no cause was found in 15 despite careful examination of the gastro-intestinal tract (Retzlaff *et al.*, 1961). The lesions discovered in the remaining six were carcinoma of the colon (three) and peptic ulcer, jejunal haemangioma, and "roentgen-ray enteritis" (one each). As noted above, one case of carcinoma of the colon was discovered in the course of follow-up in our original total of 68 patients. Clearly this is one lesion that it is essential not to overlook, and this is the main reason why laparotomy should be seriously considered in the management of these cases. Had laparotomy been carried out routinely in our patients, the carcinoma of the colon and the gastric ulcer which later became evident would doubtless have been discovered at an earlier stage. An unknown number of other organic sources of bleeding might also have been found, but the subsequent course of our patients makes it unlikely that serious organic disease exists in many of them.

It is commonly taught that in such cases a cause will always be discovered if investigation is pursued with sufficient zeal (Moore, 1950; de Gruchy, 1958). A possible cause in some of our cases would be bleeding from chronic gastritis (Wood and Taft, 1958). Thirteen patients had achlorhydria demonstrated by a histamine test (Tables I and II) and two others had gastric atrophy diagnosed radiologically; both these phenomena may be taken as indications of an abnormal gastric mucosa (Badenoch, Evans, and Richards, 1957; Wood and Taft, 1958; Joske and Vaughan, 1962; Bock, Kemp, and Richards, 1963). It is possible that bleeding was occurring from a chronic anastomotic ulcer in the seven patients who had had previous gastric operations, though at least one barium meal had been performed on all these patients. Acute gastric lesions are frequently invoked as a cause of unexplained bleeding in patients with otherwise normal stomachs (Avery Jones and Gummer, 1960) and without gastroscopy at the time of bleeding we cannot say that this possibility has been entirely excluded in our cases. It seems unlikely, however, that chronic gastritis, acute erosions, or rarer disorders could account for all or even a large proportion of our cases.

¹ Available on application to the authors.

Conclusions

Occult bleeding from the gastro-intestinal tract for which no cause can be found is not uncommon in cases of iron-deficiency anaemia.

A follow-up study of 68 patients in whom this diagnosis was made after initial investigation has revealed only 17 in whom some cause of bleeding became apparent (in 12 aspirin ingestion, in two bleeding piles, in one a gastric ulcer, in one a possible carcinoma of the rectum, and in one a carcinoma of the colon). The great majority of the remaining 51 patients were in good health two to 21 years after their initial investigation. Recurrence of the anaemia was frequent, occurring in over half the group, but it appeared to respond satisfactorily to oral iron.

We are grateful to the large number of general practitioners who actively co-operated with us in the follow-up study, to Mr. J. R. P. O'Brien, director of the Nuffield Department of Clinical Biochemistry, whose department performed the occult blood tests, and to Dr. Sheila Callender and other colleagues in the Nuffield Department of Clinical Medicine.

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Non-toxic Goitre in Males

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In most surveys of the incidence of non-toxic goitre it has been noted that women are predominantly affected. This is true of most forms of thyroid disease and is one of the puzzling features of disorders of this gland. There is evidence that in the west of Scotland, where goitre is seen relatively infrequently, the commonest form of non-toxic goitre is associated with iodine deficiency (Koutras *et al.*, 1960 ; Wayne *et al.*, 1964). However, some patients have inborn errors of thyroid hormone synthesis (McGirr, 1960 ; Dimitriadou *et al.*, 1961). It has been suggested that goitrogens in the milk may be important (Kilpatrick *et al.*, 1963). Other forms of non-toxic goitre—for example, Hashimoto's disease, drug-induced goitre, and thyroid neoplasms—are seen relatively infrequently, at least in women. We have investigated a group of males with non-toxic goitre to see whether these aetiological factors were of greater importance in this sex.

Methods

In 1961 and 1962 24 males with non-toxic goitre were referred to the thyroid clinic of the Western Infirmary, Glasgow, for investigation. Details of these patients are shown in Table I. The serum protein-bound iodine (P.B.I.) was measured by the method of Farrell and Richmond (1961). Standard radioiodine (¹³¹I) tests including measurements of 4- and 48-hour thyroid uptake and P.B.¹³¹I levels at 48 hours were carried out as described by Macgregor and Wayne (1958).

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The thyroid clearance of iodine, plasma inorganic iodine (P.I.I.), absolute iodine uptake of the thyroid gland (A.I.U.), and renal clearance of iodine were measured using the methods described by Alexander *et al.* (1962). The normal ranges in our laboratory are shown in Table II. In patients taking iodides, thyroxine in the serum was measured by separation from other iodine-containing compounds on a resin column, as described by Pileggi *et al.* (1961). The urine was tested for monoiodotyro-

TABLE I.—Goitre in Males

Case No.	Age in Years	Estimated Size of Goitre	Associated Diseases	Diagnosis
1	41	100 g.	"Allergy to fish"	Iodine-deficient goitre
2	18	75 "	—	
3	37	75 "	Klinefelter's syndrome	
4	45	75 "	Mental deficiency	
5	41	75 "	—	
6	45	75 "	Bronchial asthma	Drug-induced goitre
7	28	50 "	" "	
8	19	100 "	" "	
9	42	200 "	Treated thyrotoxicosis	
10	63	75 "	—	Autoimmune thyroiditis
11	61	50 "	—	
12	43	50 "	—	
13	52	75 "	—	
14	67	75 "	Systemic lupus and rheumatoid arthritis	
15	48	50 "	Klinefelter's syndrome	Thyroid adenoma
16	39	50 "	—	
17	57	50 "	—	Thyroid carcinoma
18	65	75 "	—	
19	22	50 "	—	
20	30	100 "	—	
21	76	50 "	—	Uncertain
22	42	70 "	—	
23	54	100 "	—	
24	37	50 "	—	