BLOOD

The Journal of Hematology

VOL. IV, NO. 7 JULY, 1949

THE CLINICAL ASSOCIATION OF MACROCYTIC ANEMIA WITH INTESTINAL STRICTURE AND ANASTOMOSIS

By D. G. CAMERON, M.D., G. M. WATSON, M.B., D.PHIL., AND L. J. WITTS, M.D.

BEFORE 1900, several Scandinavian authors had observed that intestinal stricture might be associated with an anemia resembling pernicious anemia. Faber,[11] who described a case of pernicious anemia in a young woman with multiple intestinal strictures, was the first to recognize the relationship between the two conditions. Other reports followed, and Meulengracht[20] reviewed 22 cases of macrocytic anemia associated with intestinal stricture. Little, Zerfas and Trusler[17] described a case of anemia, with a blood picture typical of pernicous anemia, in a young man on whom a series of operations had been performed to cure a fistula, the sequel of acute appendicitis. In this case, anastomoses were present and it appears to be the first recorded in which the anemia was associated with the presence of anastomoses. This patient responded well to liver therapy and relapsed when this was discontinued. Since 1929, further cases of both stricture and anastomotic anemia have been described, though it has not always been possible to separate the two conditions. Barker and Hummel[1] reviewed 51 cases, 2 of their own and 49 collected from the literature. Since their publication, additional cases have been reviewed by Jensenius,[16] and a recent case has been reported by J. E. Richardson.[22]

The main features of the published cases of this anemia are analyzed in table 1. This table is based on the figures given by Barker and Hummel, but has been amended by the inclusion of cases published since their review and a further case admitted to the Radcliffe Infirmary in 1944 (R.I. 26019/44) which is described below. Two other cases have been reported briefly by Wintrobe[32] but as no details are given they have been omitted from the table. Anastomosis was the basic abnormality in 23 cases, while in 37 cases one or more strictures were present. One case had multiple diverticula. Of the anastomoses, 15 were entero-enterostomies or entero-colostomies, 2 of which had fecal fistulae in addition, and 8 were gastro-colic or high jejuno-colic fistulae. The strictures were mostly of the small intestine but 6 were in the colon. In 12 cases, the strictures were shown to be tuberculous, in 3 others regional ileitis was present or had been resected, and some cases reported as tuberculous, but without definite proof, may properly belong in this category. In other cases, the stricture was secondary to adhesions, and in some no cause for the stricture could be found. In some of the 8 cases where there was gastro-colic or

From the Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford, England.

jejuno-colic fistula the anemia may be partly attributed to an underlying lesion: carcinoma or peptic ulcer. In a few cases, the intestine had been resected to a varying extent, but in no case more than 60 cm., and it is unlikely that resection was an important factor in the production of anemia, as Jensenius[16] has shown that much more extensive resections are necessary to produce anemia, both in man and in the experimental animal.

Case Report (R.I. 26019/44)

The patient was a woman of 42 whose mother was known to have pernicious anemia. In 1938, this patient first developed symptoms of subacute intestinal obstruction. After three months a laparotomy was done and adjacent loops of ileum anastomosed with relief of the abdominal symptoms. In 1939, she again became ill and was found to have a severe hyperchromic anemia with a hemoglobin value of 5.9 Gm. per cent and an erythrocyte count of 1.69 millions. The blood film showed macrocytosis, anisocytosis and poikilocytosis. Treatment at this time with an oral liver preparation was very effective.

In the summer of 1943, she was unable to obtain oral liver extract and was treated with an intramuscular preparation. In spite of intensive therapy, she began to get sore tongue and indigestion, she lost weight and the anemia recurred. She complained of abdominal discomfort and distension and of paraesthesia in the hands and feet. The stool was unformed with a bowel action usually twice a day.

She was admitted to this hospital in April, 1944. There was slight clubbing of the fingers. There was extensive edema of the legs and a little glossitis. The abdomen was distended in the center by a swelling apparently composed of firm coils of bowel and there was visible and noisy peristalsis. Physical examination was otherwise negative. The blood pressure was 135/90, the urine was normal and there was no objective evidence of neurologic disease. Laboratory investigation at this time gave the following results.

Blood
Hemoglobin, 9.4 Gm.
Erythrocytes, 2,630,000
Color index, 1.2
Reticulocytes, 1.6%
Leukocytes, 3,200
Platelets, 260,000
Hematocrit, 33%
Mean cell volume, 125 μ^3
Mean cell diameter, 8.24 μ
Prothrombin time, Normal

Blood urea, 22 mg. %
Plasma bilirubin, 0.2 mg. %
Plasma phosphatase, 3 units
Plasma phosphate, 3.33 mg. %
Serum calcium, 7.8 mg. %
Plasma cholesterol, 120 mg. %
Plasma ascorbic acid, 0.2 mg. %
Plasma protein (total), 4.17 Gm. %
Plasma albumin, 2.10 Gm. %
Plasma globulin, 1.70 Gm. %
Plasma fibrinogen, 0.37 Gm. %

Sternal marrow. Smears showed an active marrow with both normoblastic and megaloblastic hemopoiesis. There were 12 per cent megaloblasts and 21 per cent normoblasts in the film.

Fractional test meal. Free hydrochloric acid was present (this was still true in 1947).

Barium meal. Evidence of relative small bowel obstruction with hypermotility.

Absorption tests. Glucose and sucrose tolerance tests were within normal limits.

Fat balance. For this test the diet contained 70 Gm. of fat daily.

	1st day	*2nd day*	*3rd day*
Total fat as per cent of dried feces	18.7	16.2	27.5
Split fat as per cent of total	91	97	99
Total fat excreted	6.36 Gm.	3.03 Gm.	6.57 Gm.

There was no occult blood in the feces.

She was treated with a low fat, high protein diet, together with yeast and proteolyzed extract of liver by mouth. Plasma protein levels rose to a total of 6.1 Gm. per cent, with 3.32 Gm. albumin, and edema diminished. Finally, as a preliminary to operation, a transfusion of two pints of blood was given. Mr.

D. C. Corry operated on the patient on May 24, 1944, through a right paramedian incision. The previous anastomosis was identified an inch above the ileo-caecal valve. The excluded coil of bowel, which was about two feet in length, contained several strictures and the intervening musculature was greatly dilatated and hypertrophied. The mesentery was thickened in a way similar to that of regional ileitis, but the bowel wall was not so rough as in regional ileitis and appeared whiter. Mr. Corry resected the excluded loop and did a side-to-side anastomosis to reconstitute the bowel. Dr. J. R. O'Brien reported as follows on the specimen:

> The specimen consists of about 70 cms. of small intestine, the two ends of which are bound together to form a rough circle. There are at least nine constrictions in the wall, with dilatation in between, giving a beaded effect. The largest cavity measures 12.0 × 7.0 cms. in diameter, and the narrowest constriction appears to be only about 0.5 cm. wide. The wall is slightly thickened throughout. The average thickness is 0.4 cm., while at each constriction there is considerable increase in the thickness of the wall, which appears to be mainly due to muscular hypertrophy with a maximum thickness of 1.1 cms.
>
> The mucosa appears natural, except for the absence in places of rugae, due presumably to the distension, and there is necrosis and ulceration of the mucosa in relation to the stomata. Also in relation to these there are many polypoid outgrowths, the largest being 1.0 cm. in diameter, and 0.8 cm. high. This one is sessile, some are pedunculated. At one place the constriction has extended for about 4.0 cms. in length, while the majority of constrictions are only about 1.0 cm. wide. There is considerable increase of fat in the mesentery in places, particularly in relation to the stenotic areas.
>
> Microscopically the mucosa appears to be natural, but there is a very marked hypertrophy of both the muscularis mucosae and the circular and longitudinal muscles. It is the muscular hypertrophy which produces the preponderance of the increase in thickness of the wall. There is a very extensive chronic inflammatory change with a moderate amount of scarring. On top of the chronic change there is also an acute inflammatory process extending through into the muscle layer. In addition, there are a large number of lymphoid aggregates scattered in the muscle layer and more particularly on the peripheral surface of the muscle in the attachment of the mesentery. There are areas of early calcification in the muscle layer. The microscopic picture is in fact disappointing, the predominant features being the acute inflammatory process with polymorphs extending into the muscle layer, the muscular hypertrophy, and a background of chronic inflammation.

After operation the patient made a good recovery in all respects. Diarrhea was a little troublesome at first, but it responded to treatment with syrup of codeine and prepared chalk, and by the end of two months the bowel rhythm had been re-established at one motion a day without medication. It was still necessary, however, for her to be careful with her diet and to avoid fresh fruit, salads and coarse vegetables. She rapidly gained weight. Parenteral liver extract was continued until October, 1944, when she became sensitized to liver and had severe reactions after the injections. At this time the blood count was, red cells 5.03 million per cu. mm., hemoglobin 13.2 Gm. per cent, color index 0.9, white cells 7,600. The Price-Jones curve, which had been displaced to the right, had come back to normal. The plasma proteins were 6.35 Gm. per cent, with 4.2 Gm. albumin. It was decided to see the effect of discontinuing liver.

The patient remained well for a little less than a year. There was then a sharp relapse, and in October, 1945, the hemoglobin had fallen to 5.6 Gm. per cent. She was therefore desensitized to liver and intramuscular treatment was resumed. All went well again until the beginning of 1947, when her father died. The patient, who is a rather emotional woman, collapsed after this and later had an illness which was called gastric influenza.

She was readmitted to hospital on April 24, 1947. She had lost about 10 kilos in the last six months and there was slight clubbing of the fingers. Physical examination was otherwise negative. The stools showed no gross abnormality on microscopy or culture and no occult blood. There was moderate anemia, red cells 4,400,000 per cu. mm., hemoglobin 11.6 Gm. per cent, mean corpuscular volume 99 μ^3, white cells 7,100, E.S.R. 9 mm. The plasma proteins totalled 5.1 Gm. per cent with 3.0 Gm. albumin. Free acid was present in the test meal in high normal concentrations. On x-ray examination, there was practically no gas in the abdomen. The small bowel was much shorter than normal and the terminal loops showed a moderate degree of dilatation. There were changes in the pattern which strongly suggested an extensive recurrence of the original lesion.

Further surgery was not advised and she resumed treatment with a low residue, high protein diet,

extra vitamins and intramuscular liver extract. By May, 1948, she had regained 6 kilos and was relatively free from symptoms.

Discussion

In the present patient, anemia developed after anastomosis had been performed to short-circuit a stricture due to regional ileitis, and its persistence after resection of the bypassed loop appears to be due to an extension of the disease process up the small intestine. In view of the repeated finding of free hydrochloric acid in the gastric juice, and the failure of the anemia to respond to intramuscular liver therapy until the anastomosis had been corrected, it is unlikely that the case represents the fortuitous association of Addisonian anemia with gross intestinal disease. Nevertheless, it is of interest that the patient's mother had pernicous anemia and an inherited predisposition may have been a factor. A further point worth making about this woman is that there was no obstruction to the passage of food along the small intestine; stagnation was confined to the bypassed loop.

Table 1.—*Analysis of 61 Cases of Intestinal Stricture or Anastomosis Associated with an Anemia Resembling Pernicious Anemia*

	Present	Absent	Not recorded
Gastro-intestinal symptoms	52	2	7
Glossitis	33	6	22
Neurologic disease	12	19	30
Icterus	19	19	23
Macrocytosis	49	1	11
Hyperchromia	41	11	9
Poikilocytosis	24	—	37
Leukopenia	35	7	19
Free HCl in gastric juice	24	20	17

The main features of the macrocytic anemia of intestinal stricture and anastomosis have been discussed by Barker and Hummel and by Jensenius, and they are summarized in table 1. In the 11 cases where the presence of macrocytosis has not been recorded, the blood picture has been described only as resembling that of pernicious anemia. In general, the blood picture in these anemias closely resembles that of pernicous anemia in that hyperchromia, macrocytosis and anisocytosis are prominent features. Poikilocytosis also is often prominent; in most of the cases where its presence has not been recorded, there has been no detailed description of the blood. In some cases, however, it has been noted that poikilocytosis has been slight and less than might be expected in pernicous anemia of the same degree.[1,4,5,12,19] These reports include 4 cases of stricture anemia and 4 of gastro-jejuno-colic fistula. In the macrocytic anemia of sprue, poikilocytosis is less prominent than in pernicous anemia. In the present series of cases, there are 9 in which steatorrhea has been demonstrated by analysis of the stool; in 4 of these, poikilocytosis was recorded as slight, in the other 5 there is no record. Nucleated red cells have been seen occasionally in peripheral blood films, and in three cases[14,27,33] megaloblasts have been reported.

The Bone Marrow

For most of the cases, there is either no record of the bone marrow or it has simply been described as red and hyperplastic. In 8 cases, megaloblasts have been reported in the marrow. Zadek[33] found megaloblasts in the marrow in his two cases, Hartmann[27] in his, Fairley and Kilner[12] in their third case, Hawksley and Meulengracht[15] in their case, Barker and Hummel[1] in their 2 cases and the sternal marrow was megaloblastic in our own case. In one case, Zadek found only 1 per cent of megaloblasts in sternal marrow smears. In Barker and Hummel's first case, the sternal marrow film was said to resemble that of pernicous anemia but contained only 2.5 per cent of megaloblasts. After liver therapy, it became normal. Fairley and Kilner remark that in their case the megaloblastic transformation was far from complete. Evidently a megaloblastic transformation may be seen in the marrow similar to that of pernicous anemia, but the change may be to a lesser degree. In one case,[10] the marrow was aplastic, infection was present and this patient did not respond to liver therapy.

The Effect of Liver Therapy

The effect of liver therapy in these cases has been reviewed by Barker and Hummel[1] and Jensenius.[16] Liver therapy was used in 27 of the 61 cases reviewed here; in 5 of these, it was without effect and in the remaining 22 a response was obtained. This response varied considerably in degree, being often less than might be expected in pernicious anemia of comparable severity. In 8 of these cases, oral administration of a liver preparation was effective, and it is important to note that in 5 cases, parenteral therapy was effective where oral administration had failed. Treatment with liver seems to have been less certain in its effect than in true pernicious anemia but it should be remembered that some of the patients who derived little benefit from liver therapy were extremely debilitated or had some complicating lesion such as carcinoma. In 4 of the 5 cases where liver therapy produced no response at all, the patients were moribund, and the fifth had active pulmonary tuberculosis from which he died after operation.

The Effect of Surgical Correction of the Intestinal Lesion

The direct relation of the anemia to the intestinal lesion has been shown by the fact that, in several cases, surgical correction of the intestinal abnormality has led to cure of the anemia. In this series, operative treatment was carried out in 25 cases. The results of operation are shown in table 2. Fifteen of the cases had liver therapy in addition to surgical treatment. The mortality appears high, but in many cases the technical difficulties were considerable, and in others the presence of carcinoma as the underlying cause made success improbable. The earliest cases were undertaken before liver therapy and blood transfusion were available to improve the preoperative condition. The importance of a high protein diet to repair the hypoproteinemia and edema is also better recognized today.

The cases which survived operation will be described briefly. Sturgis and Goldhamer[30] (case 7) reported a case of ileo-cecal fistula with macrocytic anemia, in which an attempt was made to correct the fistula, but this was unsuccessful.

In 5 cases, operation was of no benefit or produced only a temporary remission of the anemia. Little, Zerfas and Trusler[17] described a case of anemia in association with two jejunal anastomoses. These were undone and 25 cm. of distended jejunum excised. Improvement followed but the anemia later recurred. Another case was noted by Bethell[3]; here details are lacking but resection of a stricture gave relief from a macrocytic anemia, without liver therapy, for 8 months; relapse then followed the formation of fresh adhesions. The 3 remaining cases in which operation did not lead to cure of the anemia were all diagnosed as regional ileitis, and it is to be expected that the lesion would recur (Barker and Hummel,[1] case 1; Sturgis and Goldhamer,[30] case 6; and our own case). It is interesting that in the case reported by Barker and Hummel an anastomosis performed to bypass a stricture made the anemia worse.

The first case in which operation was successful was reported by Seyderhelm,[28] excision of a stricture curing the anemia. Another case of stricture anemia was described by Scherer.[25] In this instance, ileo-colostomy was performed to bypass a tuberculous stricture of the ileum, marked improvement followed during a short observation period. Butt and Watkins[6] described a similar case in which ileo-

TABLE 2.—*The Results of Surgical Correction*

	Number of cases
Death from operation	11
Operation technically unsuccessful	1
Failure to correct anemia	5
Cure of anemia	8
Total cases	25

colostomy was performed for terminal ileitis; the operation was claimed to cure the anemia but the patient was not followed up. In these 2 cases, prolonged observation might have shown that the improvement was not maintained. Cases of gastro-jejuno-colic fistula with accompanying macrocytic anemia which was cured by surgical correction of the fistula have been reported by Fairley and Kilner[12] (case 1) and Bennett and Hardwick.[2] Christopher[8] described a case of macrocytic anemia in association with multiple anastomoses between the ileum and the colon; surgical correction of the intestinal lesions led to cure of the anemia, and liver therapy was not needed. W. Richardson[23] reported a case of macrocytic anemia in a young man in whom an entero-enterostomy had been performed as a sequel to acute appendicitis. This patient responded partly to liver therapy but jaundice remained. At a further operation it was found that about half the small intestine had been short-circuited, this was corrected and the patient became completely well and needed no further liver. In a case reported by J. E. Richardson,[22] a high jejuno-colostomy was performed after appendicitis, and this patient developed a macrocytic anemia. Surgical correction led to complete cure.

From these results it is clear that where it has been practicable to correct the intestinal abnormality the anemia has been cured or greatly improved. In 4 of the

5 cases in which operation was unsuccessful, or produced only a temporary remission, there was an underlying abnormality which was progressive and could not be permanently eradicated by surgical measures.

The Relation of Steatorrhea to the Macrocytic Anemia

Macrocytic anemia may be found in other intestinal disorders, notably the steatorrheas, and as steatorrhea has been found in some of the cases reviewed here it is necessary to consider whether the macrocytic anemia of stricture or anastomosis might not arise from the presence of steatorrhea rather than directly from the intestinal lesions.

In 10 of the 61 cases, the fat content of the feces has been estimated, 9 of these providing evidence of steatorrhea. In 2 other cases,[1] blood fat levels have been followed after ingestion of a fatty meal. In 2 cases, the stools have been described

TABLE 3.—*Steatorrhea and Macrocytic Anemia*

Author	Diagnosis	Fecal fat figures	
			Total fat, %
Fairley and Kilner[12]	Gastro-jejuno-colic fistula		33.9 (dry)
Fairley and Kilner[12]	Gastro-jejuno-colic fistula		47 (dry)
Fairley and Kilner[12]	Gastro-jejuno-colic fistula		31.8 (dry)
Hawksley and Meulengracht[15]	Tuberculous strictures of intestine		51 (dry)
Mindline and Rosenheim[21]	Duodeno-colic fistula		92 (dry)
Brock[4]	Multiple strictures of intestine	28 Gm. 7 Gm. 27 Gm. 13 Gm.	4-day period. Diet 45 Gm daily.
Salvesen and Kobro[24]	Gastro-jejuno-colic fistula		7 (moist)
Salvesen and Kobro[24]	Stricture of middle gut		15.3 (moist)
Bennett and Hardwick[2]	High jejuno-colic fistula		56 (dry)

as resembling those of sprue,[9,22] in one case the stool was said not to be fatty,[11] and in another the stool is said not to have been that of sprue.[25] In the remaining cases, there is no specific information on the nature of the stool. In some of these cases, the stool has been noted to be offensive or pale, and steatorrhea may have been present; in most cases the presence of diarrhea, often watery, has been mentioned, and it seems likely that the majority did not have steatorrhea. Table 3 shows the cases in which laboratory evidence of steatorrhea is available.

From table 3 it is seen that 6 of the 9 cases in which there was positive evidence of steatorrhea were patients with gastro-jejuno-colic, duodeno-colic or high jejuno-colic fistual. There are 3 further cases of this description in the series; in one of these,[9] a diagnosis of sprue had been made originally, and in another[22] the stools were like those of sprue. In the third[1] (case 2) the blood fat curve after ingestion of a fatty meal was normal, but this method cannot be relied upon to detect abnormalities of fat absorption. It is clear that cases with gastro-colic or other high

anastomoses usually have steatorrhea, but steatorrhea has been demonstrated in only 3 of the remaining 52 cases of stricture or anastomosis, though it may have escaped observation in some of these. Our own case, in which the fecal fat output over a three-day period on a constant diet was within the normal range, demonstrates that steatorrhea is not essential to the development of macrocytic anemia in these cases. Further evidence is provided by the 2 cases, referred to above, in which the macroscopic appearance of the stool did not suggest steatorrhea. It was noted earlier that poikilocytosis, which is not a feature of sprue, was less in evidence in the cases in this series with steatorrhea, and the anemia of these cases may resemble that of sprue rather than that of pernicious anemia. Jensenius[16] considers that stricture anemia resembles pernicous anemia very closely, but that anastomotic anemia resembles spure. This appears to be the case only where there is a gastrocolic or high jejuno-colic fistula.

Pathogenesis of Stricture Anemia

Pernicous anemia is a disease of the latter half of life which, if untreated, follows a remittent course to a fatal ending. It is characterized by a severe macrocytic and hyperchromic anemia, megaloblastic change in the bone marrow, leukopenia and a therapeutic response to liver extract. In addition to abnormalities of blood formation there is evidence of increased blood destruction. The gastric secretion as a whole is reduced and achlorhydria is almost invariably present. The gastric mucosa is atrophied; this change may involve more of the alimentary tract and glossitis is common. Pathologic changes in the central nervous system are frequently present.

It is clear that most the features of pernicous anemia, given in this brief description, are present in the macrocytic anemia associated with intestinal stricture or anastomosis. Though there are some important differences the similarity is such that it is probable that the two conditions are closely related, and that the abnormal hemopoiesis present in both has a common origin. That the occurrence of macrocytic anemia with intestinal lesions does not represent the fortuitous association of the two diseases is shown by several points. The age distribution differs from that of pernicous anemia in that younger subjects are equally susceptible; free hydrochloric acid is frequently present in the gastric juice and intrinsic factor has been shown to be present in one case,[26] although it was absent in the only other case in which its activity was investigated.[7] Finally, there is the point that the anemia may be cured by surgical correction of the intestinal abnormality.

With regard to the pathogenesis of stricture anemia, Faber[11] originally postulated the absorption of a poison from the stagnant bowel content. Meulengracht[18] held the same view and considered it to support the theory of the intestinal origin of pernicious anemia, while Seyderhelm[28] went so far as to practice, with some success, ileostomy and lavage for pernicous anemia. After Castle's work, these views needed some modification and Barker and Hummel[1] considered various possibilities. It might be thought that stagnation interferes with the absorption of hemopoietic principles, but these authors found that, in general, absorption tests in these anemias were usually good. Lack of extrinsic factor in the diet or the presence of disease of the liver could not be incriminated. They concluded that the liver prin-

ciple did not act directly on the bone marrow but promoted detoxification of compounds of intestinal origin which might cause harmful changes throughout the body. It seems more probable that those compounds act by interfering with the formation, absorption or utilization of materials necessary for normal erythropoiesis.

It seems established that macrocytic anemia of intestinal origin is different from Addisonian pernicious anemia inasmuch as the secretion of hydrochloric acid and intrinsic factor by the stomach may be normal. There need be no steatorrhea. The only essential factor is stagnation, whether from intestinal stenosis or a stagnant loop. Acting on this hypothesis, we have produced blind loops in the small intestine of rats and have shown that if these loops are designed so as to be filled by peristalsis, a macrocytic anemia develops in a high proportion of the animals.[31] This anemia is usually fatal, but in some of the rats it has responded to treatment by injection of refined liver extract. The results of further experiments will be reported in subsequent papers.

Summary

1. The case is reported of a woman in whom a macrocytic anemia developed after a short-circuit operation for regional ileitis. At a second operation, multiple constrictions and distentions were present in the bypassed loop.

2. The literature of macrocytic anemia associated with intestinal stenosis and anastomosis is reviewed. The anemia differs from Addisonian pernicious anemia in that the gastric secretion of hydrochloric acid and intrinsic factor may be normal. There need be no steatorrhea. It is concluded that the anemia is probably due to stagnation of intestinal contents and the absorption of toxic substances.

3. The production of blind loops in the small intestine of experimental animals offers a promising approach to the study of the macrocytic anemias.

REFERENCES

[1] Barker, W. H., and Hummel, L. E.: Macrocytic anemia in association with intestinal strictures and anastomoses. Bull. Johns Hopkins Hosp. *64:* 215, 1939.

[2] Bennett, T. I., and Hardwick, C.: Chronic jejuno-ileal insufficiency. Lancet *2:* 381, 1940.

[3] Bethell, F. H.: Unpublished, cited by Barker and Hummel.[1]

[4] Brock, J. F.: Intestinal stricture and megalocytic anaemia. Lancet *1:* 72, 1939.

[5] Butt, H. R., and Watkins, C. H.: Occurrence of macrocytic anemia in association with lesions of the bowel. Ann. Int. Med. *10–1:* 222, 1936.

[6] ——, and——: Unpublished, cited by Barker and Hummel.[1]

[7] Castle, W. B., Heath, C. W., and Strauss, M. B.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia. Am. J. M. Sc. *182:* 741, 1931.

[8] Christopher, F.: Vicious jejuno-colostomy with chronic ileac obstruction. Am. J. Surg. *29:* 124, 1935.

[9] de Rivas, D. Übstract of discussion on sprue; 81st. annual session of the A. M. A., Detroit. J. A. M. A. *95:* 1964, 1930.

[10] Emile-Weil, P., Stieffel, R., and Bousser, J.: Un cas d'anémie grave aplastique au cours de sténoses intestinales. Sang *7:* 540, 1933.

[11] Faber, K.: Perniciöse Anämie bei Dünndarmstricturen. Berlin. klin. Wchnschr. *34:* 643, 1897.

[12] Fairley, N. H., and Kilner, T. P.: Gastro-jejuno-colic fistula with megalocytic anaemia simulating sprue. Lancet *2:* 1335, 1931.

[14] Hartmann, E.: Hyperchrome Anämie bei Stagnation des Darminhaltes in einer Seitentasche des Dünndarms. Klin. Wchnschr. *2:* 1359, 1929.

[15] Hawksley, J. C., and Meulengracht, E.: Intestinal stricture and its association with pernicious anaemia. Lancet *2:* 124, 1936.

[16] Jensenius, H.: Results of Experimental Resection of the Small Intestine on Dogs. Copenhagen, 1945.

[17] Little, W. D., Zerfas, L. G., and Trusler, H. M.: Chronic obstruction of the small bowel. J. A.-M. A. *93:* 1290, 1929.

[18] Meulengracht, E.: Darmstriktur und perniziöse Anämie. Arch. f. Verdauungskr. *28:* 216, 1921.

[19] ——: Dünndarmstrikturen und perniziöse Anämie. Darmresection. Acta Med. Scand. *56:* 432, 1922.

[20] ——: Pernicious anaemia in intestinal stricture. Acta Med. Scand. *72:* 231, 1929.

[21] Mindline, J., and Rosenheim, M. L.: Duodeno-colic fistula simulating idiopathic steatorrhoea. Lancet *2:* 764, 1935.

[22] Richardson, J. E.: Addisonian anaemia following enteroanastomosis. Brit. J. Surg. *33:* 71, 1946.

[23] Richardson, W.: Pernicious anemia due to entero-enterostomy. New England J. Med. *218:* 374, 1938.

[24] Salvesen, H. M., and Kobro, M.: Symptomatic sprue. Acta Med. Scand. *102:* 277, 1939.

[25] Scherer, E.: Hyperchrome Anämie und Dünndarmstriktur. Klin. Wchnschr. *9:* 790, 1930.

[26] Schlesinger, A.: Nachweis des Antiperniciosa-Prinzips in Magensaft einer Patientin mit perniziös-anämischen Blutbild bei Dünndarmstenose. Klin. Wchnschr. *12:* 298, 1933.

[27] Schmidt, W.: Dysfunktion des Intestinaltraktus und perniziöse Anämie. Zeitschr. f. klin. Med. *106:* 337, 1927.

[28] Seyderhelm, R.: Die Pathogenese der perniziösen Anämie. Ergbn. d. inn. Med. u. Kinderheit. *21:* 361, 1922.

[29] ——, Lehmann, W., and Wichels, P.: Experimentelle intestinale perniziöse Anämie beim Hund. Klin. Wchnschr. *2:* 1439, 1924.

[30] Sturgis, C. C., and Goldhamer, S. M.: Macrocytic anemia other than pernicious anemia, associated with lesions of the gastrointestinal tract. Ann. Int. Med. *12–2:* 1245, 1939.

[31] Watson, G. M., Cameron, D. G., and Witts, L. J.: Experimental macrocytic anaemia in the rat. Lancet *2:* 404, 1948.

[32] Wintrobe, M. M.: Clinical Hematology. London, 1946.

[33] Zadek, I.: Darmulcera und Strikturen bei perniziöse Anämie. Munch. med. Wchnschr. *73:* 2165, 1926.

1949 4: 793-802

THE CLINICAL ASSOCIATION OF MACROCYTIC ANEMIA WITH INTESTINAL STRICTURE AND ANASTOMOSIS

D. G. CAMERON, G. M. WATSON and L. J. WITTS

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.