Section of Medicine

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Late Post-gastrectomy Syndromes

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Observations on the Nature and Pathogenesis of Anæmia following Partial Gastrectomy

The purpose of this paper is to discuss the nature and pathogenesis of the anæmias which occur after partial gastrectomy, with particular emphasis on the significance of vitamin B_{12} and folic acid deficiency. Studies have been restricted to patients who had either Billroth I or Polya-type partial gastrectomy for benign peptic ulcer of either the stomach or duodenum.

INCIDENCE OF ANÆMIA FOLLOWING PARTIAL GASTRECTOMY

Though anæmia has long been recognized as a complication following partial gastrectomy, the reported incidence varies from 4% (Björnebo *et al.* 1951) to 80% (Dedichen 1934). These differences are largely due to the different criteria employed in defining anæmia, to differences in time following surgery when investigations were undertaken, and to whether or not the patients had received treatment for anæmia before hæmatological investigation (Baird *et al.* 1959, Deller & Witts 1962).

Employing Wallensten's criteria for defining anæmia (1954) whereby a male is considered anæmic if his hæmoglobin concentration is less than 13·6 g/100 ml and a female if her hæmoglobin concentration is less than 11·6 g/100 ml, we found the incidence of anæmia to be 46% in 212 unselected and previously untreated patients; in 17% the hæmoglobin concentration was less than 10 g/100 ml. These patients were investigated from one to fourteen years after partial gastrectomy. As others have observed (Deller & Witts 1962, Baird *et al.* 1959) the incidence of severe anæmia was found to increase with time after partial gastrectomy.

MEGALOBLASTIC ANÆMIA AFTER PARTIAL GASTRECTOMY

Until recently, iron deficiency was considered to be the sole cause of the anæmia encountered after partial gastrectomy (Baird *et al.* 1959, Jones & Gummer 1960). The incidence of megaloblastic change in anæmia after partial gastrectomy was under-estimated, partly because the significance of so-called 'intermediate megaloblastic change' (Dacie & White 1949) was not appreciated, but chiefly because megaloblastic change in these patients was associated with iron deficiency which may 'mask' megaloblastic change almost completely (Tasker *et al.* 1958, Pedersen *et al.* 1957).

Within the last six years at Hammersmith hospital, we have had the opportunity to investigate 52 patients with megaloblastic anæmia following partial gastrectomy. There were 26 males and 26 females; 21 of the patients had a Billroth I operation while 31 had a Polya gastrectomy.

Hæmatological Features

The 52 patients could be divided into three groups on the basis of their hæmatological features:

Group 1 consisted of 14 patients, in whom peripheral blood and bone marrow findings were those of uncomplicated megaloblastic anæmia. The hæmoglobin concentrations ranged from 5·0 to 13·4 g/100 ml with a mean of 10·1 g/100 ml. The anæmia was macrocytic and normochromic; the mean corpuscular volume (MCV) ranged from 110 to 150 cu.μ and the mean corpuscular hæmoglobin concentration (MCHC) from 32 to 36%. Stainable iron was present in the bone marrow and the degree of megaloblastic change in the bone marrow was compatible with the degree of anæmia.

Group 2 was made up of 12 patients whose hæmatological features were essentially similar to Group 1, except that mild iron deficiency was demonstrated in all these patients. Their hæmo-

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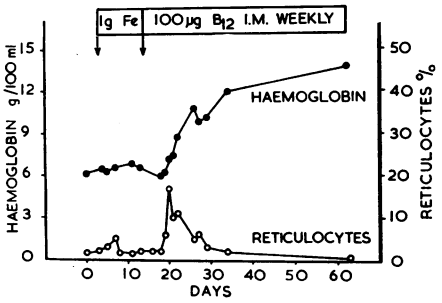

Fig 1 *The hæmatological response of a patient with iron deficiency and megaloblastic anæmia following partial gastrectomy, who was treated first with iron 1g I.V. and then with vitamin B_{12}. There was no significant response until vitamin B_{12} was given*

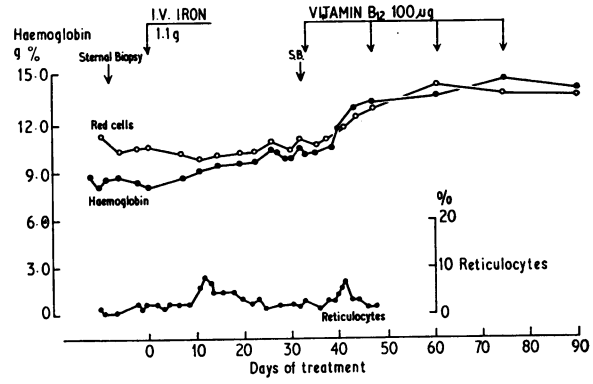

Fig 2 *The hæmatological response of a woman with iron deficiency and megaloblastic anæmia following partial gastrectomy, who was treated first with iron and then with vitamin B_{12}. The response was suboptimal until vitamin B_{12} was given*

globin ranged from 7·0 to 13·8 g/100 ml with a mean of 11·0 g/100 ml; the anæmia was macrocytic, the MCV ranged from 112 to 140 cu.μ but the MCHC was subnormal, the range being between 29 and 31%. The red cells were *mildly* hypochromic and stainable iron was absent from the marrow. The degree of megaloblastic change in this group was usually similar to that observed in the first group. If treated with vitamin B_{12} and/or folic acid, patients in this group developed signs of iron deficiency anæmia, whereas if treated with iron alone the blood picture became identical with that observed in the first group.

Group 3 was made up of the remaining 26 patients in whom the signs of iron deficiency were much more obvious and the blood picture closely resembled that seen in severe or moderate iron deficiency anæmia. The hæmoglobin concentrations ranged from 5·0 to 12 g/100 ml, the mean being 8·7 g/100 ml, the MCV was low or normal, ranging from 66–98 cu.μ and the MCHC was always less than 29%. The serum iron was low, the serum iron binding capacity unsaturated and stainable iron was absent from the bone marrow. However, the blood picture differed from simple iron deficiency in a number of ways. Thus, the stained blood film invariably showed a dimorphic picture, a number of normochromic or only slightly hypochromic macrocytes always being present among the hypochromic erythrocytes. Furthermore, abnormal polymorphs were always present and the average count of the lobes of the polymorphs was always increased. Giant metamyelocytes were present in the bone marrow, and megaloblastic change might also be present in the erythroblasts, but this was masked to a variable degree by the changes of iron deficiency. The degree of megaloblastic change was therefore always less than one would expect for the degree of anæmia, and was frequently difficult to recognize.

Effect of iron therapy in Group 3: When the patients in Group 3 were treated with iron, the signs of iron deficiency disappeared and the mean hæmoglobin concentration increased to levels similar to that seen in the first and second groups. After iron therapy, the underlying megaloblastic change either became more obvious or was revealed for the first time. The extent of the response to iron varied widely in different patients. In some, the administration of iron produced a reticulocyte response without significant increase in hæmoglobin concentration (Fig 1). The erythroblasts in the bone marrow of such patients are always frankly megaloblastic shortly after the start of treatment with iron. If no other treatment but iron is given, the hypochromic cells in these patients are gradually replaced by normochromic macrocytes and the blood picture is gradually transformed into that seen in moderately severe megaloblastic anæmia. More commonly, treatment with iron produces a reticulocyte response and a slow increase in the hæmoglobin concentration (Fig 2), which in some patients may reach normal levels (Fig 3). Megaloblastic change is again revealed or accentuated after treatment with iron and persists even in patients whose hæmoglobin concentrations reach normal levels until these patients are treated with B_{12} or folic acid.

PATHOGENESIS OF THE MEGALOBLASTIC ANÆMIA AFTER PARTIAL GASTRECTOMY

The cause of the megaloblastic anæmia in these patients was investigated by measuring the serum vitamin B_{12} levels using the *Euglena gracilis* assay (Hutner *et al.* 1956) and the serum folate levels using the *Lactobacillus casei* assay (Baker *et al.* 1959, Waters & Mollin 1961). In addition, the

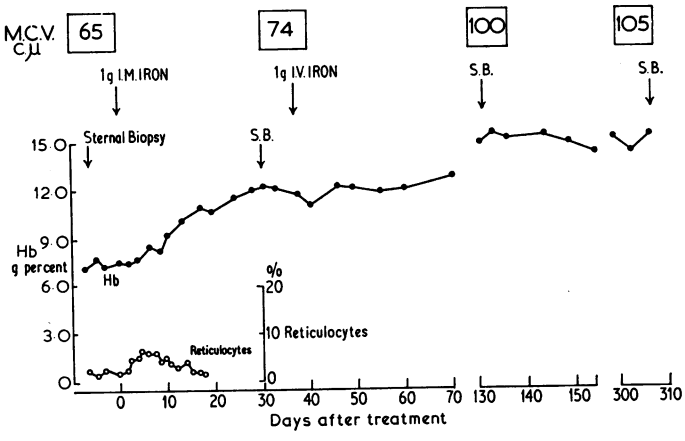

Fig 3 *The hæmatological response of a woman with iron deficiency and megaloblastic anæmia following partial gastrectomy (Polya), who was treated with iron. The response to iron was complete, but abnormalities persisted in the blood film and bone marrow*

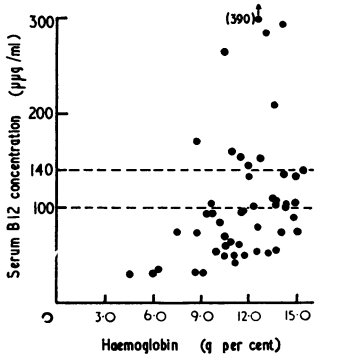

Fig 4 *The serum vitamin B_{12} levels in 52 patients with megaloblastic anæmia after partial gastrectomy are plotted against hæmoglobin concentration after previous treatment with iron. The upper dotted line in the figure represents the lowest limit of normal and the lower dotted line represents the upper limit found in patients with untreated pernicious anæmia*

hæmatological responses of patients to treatment either with vitamin B_{12} or folic acid were also studied. Wherever possible, small ('physiological') doses of vitamin B_{12} or folic acid were used. In 35 of the 52 patients, the absorption of radioactive vitamin B_{12} was determined using an oral dose of 1 μg of ^{58}Co vitamin B_{12} employing the fæcal excretion method (Mollin *et al.* 1957). The dose was first given alone, and then in a subsequent test with 40 mg of hog intrinsic factor concentrate (IFC).

Serum Vitamin B_{12} Concentrations

Previous reports suggest that although serum vitamin B_{12} levels in patients with megaloblastic anæmia due to partial gastrectomy are usually subnormal, levels in many patients may not be as low as those found in pernicious anæmia (Badenoch *et al.* 1955, Mollin & Ross 1957). In some instances, levels within the normal range have been found in patients with this condition (Deller & Witts 1962). The results in the 52 patients studied by us are summarized in Fig 4, in which the serum vitamin B_{12} concentration of each patient is plotted against the hæmoglobin concentration at the time the assay was carried out. As many of these patients were iron deficient, the serum vitamin B_{12} levels and hæmoglobin concentrations plotted are those found when the hæmatological response to iron was complete. In 79% of the patients, the vitamin B_{12} level was subnormal (less than 140 μμg/ml); in more than half of the patients, the levels were within the range found in untreated pernicious anæmia (less than 100 μμg/ml). In the remaining 21% of patients, the serum vitamin B_{12} levels were within the normal range. Normal serum vitamin B_{12} levels were not found in patients who were severely anæmic.

Deficiency of vitamin B_{12} was therefore the sole or contributing cause of megaloblastic change in approximately four-fifths of patients after partial gastrectomy. In the remaining patients, that is, in those in whom serum vitamin B_{12} levels were within the normal range, megaloblastic change was presumably due to deficiency of folic acid.

Serum Folate Levels

This view is supported by the observation that the serum folate levels may be low in patients after partial gastrectomy (Waters 1963). Fig 5 compares the serum folate levels of our patients with partial gastrectomy megaloblastic anæmia with the levels found in patients with untreated pernicious anæmia. In the majority of patients with pernicious anæmia, the serum folate levels were normal or above normal; in two-thirds of the patients with megaloblastic anæmia due to partial gastrectomy, the levels were below the normal range (less than 6·0 mμg/ml, and in one-third, the levels were within the range found in severe folate deficiency (less than 3·0 mμg/ml). Low serum folate levels were always found in patients with normal vitamin B_{12} levels, but subnormal or borderline folate levels were also found in a number of patients with low vitamin B_{12} levels. The latter observation is surprising, for folate levels in patients with vitamin B_{12} deficiency and mild megaloblastic anæmia due to pernicious anæmia are often above normal (Waters & Mollin 1963).

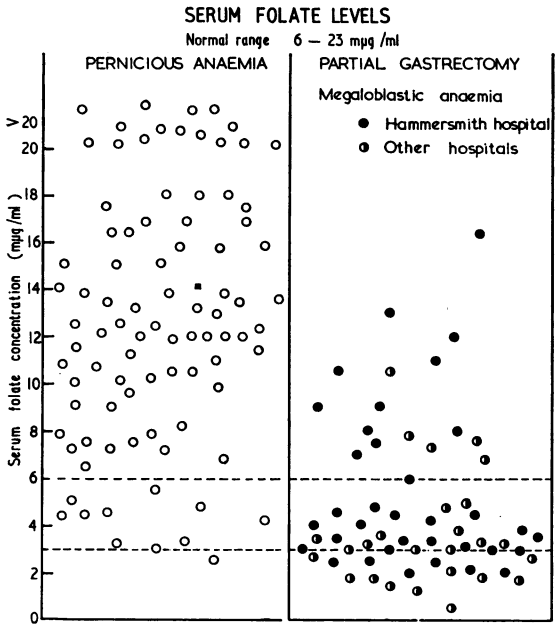

Fig 5 *A comparison of the serum folate levels in patients with partial gastrectomy megaloblastic anæmia with the levels found in patients with untreated pernicious anæmia. The upper dotted line indicates the lowest limit of normal (normal range 6–23 mμg/ml) whilst the lower dotted line represents the level below which are found patients with megaloblastic anæmia due to folic acid deficiency*

Hæmatological Responses to Vitamin B_{12} and Folic Acid

If folic acid deficiency contributes significantly to the megaloblastic anæmia after partial gastrectomy, it might be expected that patients with this condition would not respond fully until treated with folic acid. However, it has been reported that patients with megaloblastic anæmia after partial gastrectomy, with low or with *normal* serum vitamin B_{12} levels, respond optimally to treatment with vitamin B_{12} once the pre-existing iron deficiency has been corrected (Badenoch *et al.* 1955, Deller 1962). However, the doses of vitamin B_{12} used, where specified, were large and these patients presumably were also given an unrestricted hospital diet. Under these conditions, considerable hæmatological responses to treatment with vitamin B_{12} might be expected in patients with folate deficiency, for large unphysiological doses of vitamin B_{12} may produce dramatic hæmatological responses in such patients (Zalusky *et al.* 1962). If, instead of large doses, small intramuscular injections of vitamin B_{12} are given (doses of 0·5–1·0 μg per day), and the intake of folic acid is restricted to that taken before hospital admission, then only the patients with low serum vitamin B_{12} levels will respond optimally; patients with low folate levels either fail to respond or respond inadequately. This is illustrated in Fig 6, which indicates the hæmatological response of a patient with low serum vitamin B_{12} and folate levels to treatment with varying doses of vitamin B_{12}. The patient failed to respond adequately to treatment with daily doses of either 0·5 or 1·0 μg of vitamin B_{12}, but responded optimally when large injections of 100 μg of vitamin B_{12} per week were given.

The Cause of Vitamin B_{12} Deficiency

The cause of the vitamin B_{12} deficiency in patients with partial gastrectomy and megaloblastic anæmia is uncertain. Defective absorption of vitamin B_{12} which is improved by the administration of a source of intrinsic factor has been reported in a number of these patients (Badenoch

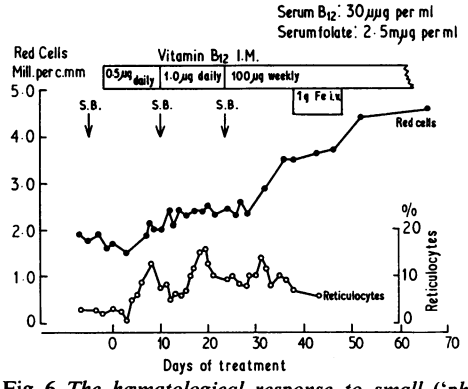

Fig 6 *The hæmatological response to small ('physiological') and large doses of intramuscular vitamin B_{12} in a patient with combined vitamin B_{12} and folic acid deficiency after partial gastrectomy. Although reticulocyte peaks of 12% and 15% respectively followed the administration of 0·5 μg/day and 1·0 μg/day doses of vitamin B_{12}, there was no adequate increase in hæmoglobin concentration until the patient was treated with injections of 100 μg vitamin B_{12} I.M. weekly*

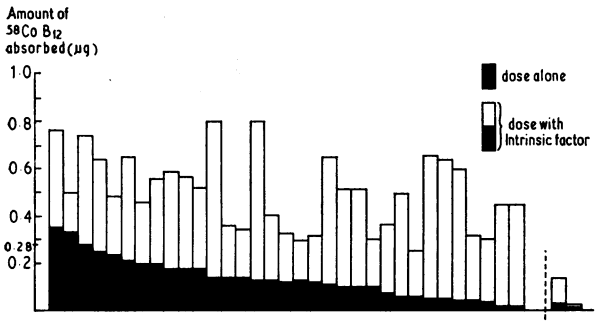

Fig 7 *The absorption of ^{58}Co-labelled vitamin B_{12} in 35 patients with megaloblastic anæmia after partial gastrectomy, showing the effect of intrinsic factor. The height of the black column represents the amount absorbed from a dose alone, while the height of the total column represents absorption from the dose plus hog intrinsic factor concentrate*

et al. 1955, Mollin & Baker 1955, Lous & Schwartz 1959, Deller & Witts 1962, Mollin 1962), but low serum vitamin B_{12} levels have been reported in patients who appear to have absorbed vitamin B_{12} normally (Deller & Witts 1962). The results of vitamin B_{12} absorption tests carried out on 35 of our patients with megaloblastic anæmia due to partial gastrectomy are given in Fig 7. Patients with pernicious anæmia absorb less than 0·28 μg from an oral dose of 1·0 μg of ^{58}Co vitamin B_{12}, and entirely normal subjects absorb more than 0·45 μg from this dose (Mollin *et al.* 1957, Whiteside *et al.* 1964). The absorption of vitamin B_{12} was subnormal in all the patients tested, and in all except 3 the absorption was within the range found in pernicious anæmia. The mean vitamin B_{12} absorption in these patients was, however, significantly greater than the mean absorption in patients with pernicious anæmia (Mollin 1962).

When the dose was given with hog IFC the increase in absorption in 33 patients was similar to that seen in patients with pernicious anæmia given the same dose of intrinsic factor. In these patients defective secretion of intrinsic factor would seem to be the main cause of the abnormal absorption of vitamin B_{12}. In the other 2 patients administration of hog IFC or of human gastric juice had no effect on absorption in one, and produced only a slight improvement in absorption in the other. In these 2 patients there appeared to be a defect in the intestinal absorption of the vitamin B_{12} – intrinsic factor complex. Both patients were found to have abnormally large duodenal 'afferent' loops and the absorption of radioactive vitamin B_{12} with intrinsic factor increased significantly in both patients after treatment with tetracycline.

Thus it would appear that the principal cause of the subnormal vitamin B_{12} levels in patients with megaloblastic anæmia due to partial gastrectomy is defective absorption of vitamin B_{12}, the result of inadequate secretion of intrinsic factor. This is presumably secondary to the atrophic process which occurs in the gastric remnant (Badenoch *et al.* 1955, Deller & Witts 1962). However, as previously pointed out, the absorption of vitamin B_{12} in these patients is not reduced as severely as in patients with total gastrectomy or with overt pernicious anæmia (Mollin 1962) and it may well be that factors such as inadequate dietary intake of vitamin B_{12}, or an increased requirement for vitamin B_{12} due to the chronic iron deficiency anæmia contribute to the production of the vitamin B_{12} deficiency.

The Cause of the Folic Acid Deficiency

The cause of the folic acid deficiency in these patients is uncertain. Although defective absorption of crystalline pteroyl-glutamic acid may occur in some patients after partial gastrectomy, adequate studies of folate absorption in these patients have not been reported. There is no doubt that many patients take an inadequate diet. In our series, detailed dietary histories were taken in 20 of the 52 patients. In 7 the dietary intake of folic acid was as low as that found in patients with megaloblastic anæmia due to dietary deficiency of folic acid. An inadequate intake of folic acid may therefore contribute to the folic acid deficiency found in these patients. It is probable, too, that increased demands for folic acid due to chronic iron deficiency anæmia also plays a part.

INCIDENCE OF VITAMIN B_{12} AND FOLIC ACID DEFICIENCY AFTER PARTIAL GASTRECTOMY

So far we have been discussing the incidence of subnormal serum levels of vitamin B_{12} and folic acid in patients with megaloblastic anæmia after partial gastrectomy. How frequently are these low levels observed in patients following partial gastric resection? The incidence of subnormal serum vitamin B_{12} levels has been found by Deller & Witts (1962) to be 14% in 265 patients following partial gastrectomy, and in our own series of 212 patients investigated from one to fourteen years after partial gastrectomy at Hammersmith Hospital, an almost identical incidence was found (15%). Jones *et al.* (1962), however, have reported an incidence of 51% in 100 patients who were

investigated five to six years after gastric surgery. All agree that the incidence of low serum vitamin B_{12} levels in these patients increases with time after surgery.

Subnormal serum folate levels were found in nearly 40% (32) of 81 patients investigated from one to eight years after partial gastrectomy. In only 6 patients, however, was the serum folate level in the range found in severe folate deficiency.

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Postgastrectomy Bone Disease

Osteomalacia has been recognized as a rare complication of partial gastrectomy, but only recently has it become apparent that a disturbance of calcium metabolism is common in patients after gastrectomy (Jones *et al.* 1962, Clark 1963). Nickolaysen & Ragaard (1955) showed that after gastrectomy many patients are in negative calcium balance. Prolonged negative balance depletes the skeleton of calcium, and some years after operation these patients might be expected to show radiological evidence of this. Demineralization of the skeleton is difficult to measure but the radiological method of Barnett & Nordin (1960) provides a convenient technique for survey purposes. This is based on a scoring system using standard X-rays of the hand, femur and spine. The hand and femur scores are derived from a ratio of cortical to total bone width and these when added together are described as a peripheral score, the measure of bone density used in this study.

This technique has now been used to examine 150 patients who had undergone Polya gastrectomy. They were drawn from two out-patient screening surveys. There were 51 patients operated on between the years 1945 and 1955 from one of the surgical services and representative of a larger group of unselected patients, all of whom had had Polya gastrectomy (Clark *et al.* 1964). The second survey was carried out by medical students as part of a vacation exercise (Amar *et al.* 1964) when an attempt was made to trace all patients with peptic ulcer treated by gastrectomy during the years 1948–50. Some patients were common to both groups but the second survey provided 99 further cases for consideration. All patients were in the age group 40–65 years and the results of the radiological screening procedure showed that 18% of the gastrectomy patients had diminished radiological bone density.

Barnett & Nordin (1960) described their scoring system as an osteoporotic index, but the abnormality seen in the gastrectomy patients could also be due to osteomalacia, which in the early stages can be difficult to differentiate from osteoporosis. In osteomalacia there is an associated biochemical disturbance characterized by a lowered serum calcium and later a fall in serum phosphorus. The reduced calcium × phosphorus product leads to inefficient calcification of newly formed osteoid, and increased osteoblastic activity is reflected in a raised serum alkaline phosphatase. In osteoporosis there is no associated biochemical disorder and though it may be primarily a disease of