Metabolic effects of partial gastrectomy with special reference to calcium and folic acid

Part I Changes in calcium metabolism and the bones

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EDITORIAL SYNOPSIS Spinal rarefaction is greater in patients who have had a partial gastrectomy than in matched controls. The nature of the bone lesion after operation was mainly osteoporosis but there was some biochemical and histological evidence of osteomalacia as well.

It is surprising that osteomalacia has been infrequently reported as a late complication of gastric surgery. Many gastrectomies have been performed and steatorrhoea is not unusual after this operation (Wollaeger, Comfort, Weir, and Osterberg, 1946). Furthermore, it has been suggested that steatorrhoea is the commonest cause of osteomalacia in North America (Albright and Reifstein, 1948) and in Britain (Dent, 1957; Nordin, 1961a). Patients with osteomalacia following partial gastrectomy have been found to have either steatorrhoea (Pyrah and Smith, 1956; Baird and Oleesky, 1957; Hillemand, Mialaret, and Boutelier, 1960) or else an inadequate diet (Sarasin, 1941; Melick and Benson, 1959). Another factor contributing to a deficiency of vitamin D, and consequently to the development of osteomalacia, has been inadequate exposure to sunshine, either due to the wearing of religious habits (Groult, 1945; Arne, Mouton and Seilhean, 1960), or to residence in industrial cities in the more northerly latitudes (Schrade, 1953; Reinwein, 1962, amongst others).

Radiological studies of the bones of selected groups of patients after partial gastrectomy have shown spinal rarefaction in 20 to 95% of patients, the frequency of these changes varying with the selection of cases and the criteria adopted in recognizing bone rarefaction (Udaondo and Castex, 1944; Baronchelli and D'Antuono, 1958; Candiani, Dalla Costa, and Furlan, 1959). Spinal rarefaction is more typical of osteoporosis than osteomalacia and consequently these radiological studies suggest that gastrectomy may play a role in the development of spinal osteoporosis. Experimental support for this suggestion is seen in the production of severe

osteoporosis in puppies by gastrectomy (Bussabarger Freeman, and Ivy, 1938). For these reasons we decided to investigate the frequency and nature of bone changes after partial gastrectomy in a random sample of 100 patients and in a similar number of control subjects.

PATIENTS STUDIED

The gastrectomy group consisted of 68 men and 32 women. The diagnosis at operation was duodenal ulcer in 55 patients and gastric ulcer in 54. Eighty-two patients had the Polya partial gastrectomy and 18 the Billroth I. The interval between operation and the study by us was two to 15 years with a mean of 8.9 years. The operation had been performed more than six years previously in 76 patients.

The control group of the same number of men and women was selected to match as closely as possible the gastrectomy group for sex, age, and economic status. All were ambulant in-patients or out-patients and they were excluded from selection only if the reason for hospital attendance was a condition generally recognized to affect bone metabolism. Selection was not influenced on account of backache alone. Most patients were convalescing in hospital following an acute illness.

Table I shows the distribution of the two groups according to age and sex. The mean age of patients after partial gastrectomy was 61.9 years and of control subjects 60.1 years. Fifty-six patients in the gastrectomy group and 51 in the control group were 60 years or more in age. The two groups were comparable in a number of other respects. The frequency of natural or artificial menopause in women was

TABLE I

SEX AND AGE OF 100 PATIENTS AFTER PARTIAL GASTRECTOMY AND 100 CONTROL SUBJECTS

Sex	Group	Age (yr.)							
		11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
Male	Gastrectomy	0	1	5	6	22	20	12	2
Male	Control	2	1	1	15	12	19	13	5
Female	Gastrectomy	0	2	1	6	6	10	7	0
Female	Control	0	2	2	4	5	11	6	2

similar. The social status was comparable as the majority were working people.

METHODS

RADIOLOGY The radiological examination in each patient consisted of lateral views of the dorsal and lumbar spine. Eighteen patients who had had a partial gastrectomy and who complained of generalized skeletal pains had a complete radiological survey of the bones. Spinal rarefaction was assessed subjectively and objectively and the readings were made by the one observer who was not provided with the clinical details of the patients. In the subjective assessment, spinal rarefaction was stated to be present or absent and any vertebral deformity was noted. The objective method of assessment consisted of the measurement of the degree of wedging of the dorsal spine and of biconcavity of the lumbar spine. In the case of the dorsal spine, the vertical height of the anterior body of the 'most wedged' thoracic vertebra was divided by the vertical height of the same body posteriorly. The fraction obtained was multiplied by 100 to yield the dorsal score. We have followed Barnett and Nordin (1960) in defining the lumbar score as the vertical height of the middle of the best centred lumbar vertebra divided by the height of the same body anteriorly, the fraction so obtained being multiplied by 100. The sum of the dorsal score and lumbar score was called the 'spinal score' and we have arbitrarily defined spinal rarefaction as a spinal score of 160 or less (Deller and Begley, 1963).

BIOCHEMISTRY One hundred patients after partial gastrectomy and 50 control subjects had blood taken for the estimation of serum calcium (Baron and Bell, 1957), phosphate (Fiske and Subbarow, 1925), and alkaline phosphatase (Marsh, Fingerhut, and Kirsch, 1959). The level of serum calcium when estimated by the E.D.T.A. method of Baron and Bell (1957) is lower than that

obtained using other methods. Twenty-two of the patients who had had partial gastrectomy were further investigated by iliac crest bone biopsy, the calcium infusion test (Finlay, Nordin, and Fraser, 1956), and faecal fat estimations (van de Kamer, Huinink, and Weyers, 1949). The patients selected for intensive investigation were those who on clinical grounds were suspected of having a severe grade of bone disorder. Eight control subjects also had the calcium infusion test.

RESULTS

SPINAL RAREFACTION When spinal rarefaction was assessed by the subjective method it was detected in 22% of controls and 50% of patients after partial gastrectomy (Table II). The skeletal abnormality, furthermore, was more severe in the patients after operation: eight patients had crush fractures of the vertebrae after gastrectomy (Fig. 1) whereas spinal fractures were not observed in the controls. Pseudo-fractures (Looser's zones) typical of osteomalacia were detected in only one patient, although 18 patients in whom the diagnosis of osteomalacia was suspected had a complete skeletal radiological study.

Figure 2 shows the distribution of the spinal scores. Spinal rarefaction according to these morphological measurements was present in 35% of patients after partial gastrectomy and in 15% of control subjects.

There was a disproportionate increase in spinal rarefaction in males who had had partial gastrectomy (Table II). The ratio of females to males with spinal rarefaction in the control group was 3.1/1, whereas the ratio in the gastrectomy group was 1.7/1. In both groups spinal rarefaction was recognized more frequently in the aged. Even so, rarefaction in

TABLE II

FREQUENCY OF SPINAL RAREFACTION IN PATIENTS AFTER PARTIAL GASTRECTOMY AND IN CONTROL SUBJECTS

Group	Patients with Spinal Rarefaction ¹			Significance of Difference between Percentages
	Males	Females	Total	
	No.	No.	No.	
Gastrectomy	28 (41.3%)	22 (68.7%)	50 (50%)	p < 0.01
Control	9 (13.2%)	13 (40.6%)	22 (22%)	

¹Spinal rarefaction was assessed subjectively.

FIG. 1

FIG. 1. Radiograph of the thoracic spine of a patient who had undergone partial gastrectomy showing spinal rarefaction with compression fractures of the vertebrae.

FIG. 2

FIG. 2. Spinal scores of 100 control subjects and 100 patients after partial gastrectomy. The dotted line represents the arbitrary lower limit of normal, values below which have been taken to represent spinal rarefaction.

patients less than 65 years in age was three times as frequent in the patients after gastrectomy than in the controls.

The frequency of spinal rarefaction in patients after gastrectomy was influenced by the interval of time after operation and the presence of post-gastrectomy sequelae. Spinal rarefaction in patients operated on less than six years was not significantly more frequent than in the control group. However, rarefaction was three times more frequent in patients examined more than six years after operation. The effect of the time on the prevalence of rarefaction could not be ascribed to age, as there was no significant correlation between the age of the patients and the interval after operation ($r = 0.11$, $p > 0.05$). Spinal rarefaction was also detected more often in patients with delayed complications

of operation. Thus anaemia, loss of weight, symptoms of the 'dumping' syndrome, and diarrhoea were all more frequent in patients with spinal rarefaction than in patients with normal bones. Indeed the patients usually regarded the skeletal symptoms as the least of their troubles.

Neither the reason for the operation nor the type of operation influenced the frequency of spinal rarefaction to a degree that could not be explained by the various factors previously detailed. However, the majority of subjects with severe skeletal symptoms had had gastric ulcers and had been operated on by the Polya partial gastrectomy.

SERUM CALCIUM, PHOSPHATE, AND ALKALINE PHOSPHATASE The normal range for serum calcium, phosphate, and alkaline phosphatase was taken as

FIG. 3. Serum calcium levels in 50 control subjects and 100 patients after partial gastrectomy. The dotted line represents the lower limit of normal.

FIG. 4. Serum phosphate levels. The dotted line represents the lower limit of normal.

the mean $\pm$ 2 S.D. of the values for the control subjects. Abnormal results were found in a number of patients after partial gastrectomy: low serum calcium levels (below 8.0 mg. per 100 ml.) were present in six (Fig. 3); low serum phosphate levels (below 2.8 mg. per 100 ml.) in five (Fig. 4); and raised serum alkaline phosphatase levels (above 13 King-Armstrong units) in 15 (Fig. 5). Hypocalcaemia was not associated with hypoalbuminaemia in any of the cases studied.

FIG. 5. Serum alkaline phosphatase levels. The dotted line represents the upper limit of normal.

CALCIUM INFUSION TEST The 'four-hour skeletal retention' of calcium was calculated as the proportion of the infused calcium which was neither recovered in the urine nor estimated to be present in the extracellular fluid (Finlay *et al.*, 1956). The retention of calcium has been shown to be invariably increased in osteomalacia, and only occasionally reduced in osteoporosis. Nine of the 22 patients after partial gastrectomy retained an abnormally large percentage of the infused calcium (more than 62.6%) and two had reduced retention (less than 40.2%) (Fig. 6).

FAECAL FAT EXCRETION Eight of the 22 patients who had had partial gastrectomy excreted 7 g. or

FIG. 6. *Skeletal retention of calcium during the calcium infusion test. The dotted lines represent the mean 4-hr. retention $\pm$ 2 S.D. of the eight control subjects.*

more fat in the stools daily, and so were considered to have steatorrhoea.

BONE BIOPSY The major abnormality in the bone biopsies was osteoporosis. In 17 of 20 biopsies the amount of cortical and trabecular bone was considerably reduced. Evidence of early osteomalacia, however, was also frequently present (Fig. 7). The osteoid seams in decalcified sections of bone measured 0 to 6 μ in seven; 7 to 12 μ in one; 13 to 20 μ in 10; and 21 to 40 μ in two. In undecalcified sections the upper limit of normality of the seams is 12 μ (Ball, 1960). In decalcified sections the seams are usually inconspicuous and do not measure more than 6 μ (Deller, Edwards, and Addison, 1963). In classical osteomalacia, however, the width of the osteoid seams is generally in excess of 20 μ . Therefore the osteoid seams in this series of patients after gastrectomy usually differed from the typical findings in osteomalacia in being narrower and also less frequent and more irregular.

DISCUSSION

These observations have shown that spinal rarefaction is unusually frequent in patients examined six or more years after partial gastrectomy, and that the bone lesion is predominantly osteoporosis, although some degree of osteomalacia is usually present as well. The results of previous radiological surveys of the bones after gastric surgery have also

FIG. 7. *Iliac crest bone biopsy from a patient who had undergone partial gastrectomy, showing a widened osteoid seam characteristic of osteomalacia. (Undecalcified section stained with von Kossa stain, $\times$ 80.)*

suggested that bone rarefaction is more frequent after operation (Udaondo and Castex, 1944; Baronchelli and D'Antuono, 1958; Candiani *et al.*, 1959). Udaondo and Castex (1944) observed spinal rarefaction in the radiographs of 39 of 41 patients after gastric surgery, although the disorder was marked in only 15 (36%). In the radiological study of Baronchelli and D'Antuono (1958), spinal rarefaction was detected in nine of 45 patients (20%). The patients in this study were 45 years or less, so that the bone changes are unlikely to be ascribed to the effect of age. Baronchelli and D'Antuono (1958) further found that spinal rarefaction was present in two of 30 (6%) subjects studied less than six years after operation, whereas seven of 15 (47%) patients studied after this time had bone rarefaction. Candiani *et al.* (1959) reported bone rarefaction in seven of 30 (23%) patients following the Polya partial gastrectomy. Most of the subjects were

middle-aged men and all but one had been operated on less than six years.

These studies have been made on selected groups of patients after operation and the criterion for the diagnosis of spinal rarefaction has not been clearly stated. Moreover the incidence of rarefaction after operation has not been given in relation to the incidence in a sample of the population which is similar in age and sex but which has not been subject to operation. These objections have been met in the present study where spinal rarefaction was detected in 50% of the patients after partial gastrectomy and in 22% of the control group when rarefaction was assessed by subjective visual criteria, and in 35% of patients after gastrectomy and in 15% of control subjects when rarefaction was diagnosed by morphological measurements. The measurement of lumbar biconcavity as an index of vertebral bone density has been variously considered reliable (Nordin, Barnett, MacGregor, and Nisbet, 1962) and unreliable (Virtama, Gästrin, and Telkkä, 1962; Caldwell, 1962). However, in the present study, two methods of assessing bone density were used. The frequency of skeletal rarefaction was compared in two groups of subjects, and the radiological study was undertaken in a 'blind' manner by the one observer. There was a satisfactory correlation between the morphological and visual assessments, although rarefaction was diagnosed more frequently by the latter technique and it was recognized with ease, visually, at the stage when the morphological measurements were abnormal.

We feel that there is a significant increase in bone rarefaction after partial gastrectomy, because the frequency of the bone disorder was related to the interval after operation and to the presence of post-gastrectomy sequelae. However, the condition of the bones after operation is obviously influenced by the skeletal status before the surgery and factors associated with peptic ulceration in the form of an inadequate diet or abnormal endocrine influences may also be important in the pathogenesis of the bone lesion. Furthermore some of the changes observed in patients after partial gastrectomy would have occurred irrespective of the operation, as one fifth of the controls, mainly elderly males and post-menopausal women, had spinal osteoporosis.

In the present study the major abnormality in the bones was osteoporosis. The evidence for osteoporosis was the predilection of the spine in the rarefying disorder, the normal serum chemistry in the majority of cases, and the histological changes in the bone biopsies. However, evidence of osteomalacia was present as well in some patients after operation, judged by the serum chemistry, the

response to calcium infusion, and the histology of the bone: the serum calcium was reduced in 6%; the serum phosphate in 5%; the serum alkaline phosphatase was elevated in 15%; nine of the 22 subjects retained an abnormally large proportion of calcium in the calcium infusion test; and widening of the osteoid seams was present in 13 of 20 biopsies. In previous studies of smaller groups of patients after partial gastrectomy the serum alkaline phosphatase level has been found to be elevated in 14% (Campanacci, 1955), 23% (Candiani *et al.*, 1959), and 26% (Jones, Williams, Cox, Meynell, Cooke, and Stammers, 1962) of the patients who were investigated. A raised serum alkaline phosphatase level is probably indicative of osteomalacia after gastric surgery if other causes for the increase can be excluded. Five patients in the present study and the same number of patients reported by Jones *et al.* (1962) had raised serum alkaline phosphatase levels and some degree of osteomalacia was present in bone biopsy specimens in every case. However, eight of our patients with widened osteoid seams did not show alterations in the serum alkaline phosphatase level.

Discomfort due to bone disease in the patients we studied could not be regarded as a major factor in assessing the success or failure of the operation. More frequently the bone symptoms were part of a complex consisting of lassitude, loss of weight, symptoms of anaemia, and post-prandial discomfort. Pain in the back was a feature of eight patients with crush fractures of the spinal vertebrae, and in one of these patients considerable loss of height resulted from the 'telescoping' of many vertebrae. A patient with multiple pseudo-fractures of the ribs complained of severe pain and audible 'cracking' whenever pressure was applied to her thorax. Eighteen patients, including four patients with vertebral fractures and the patient with pseudo-fractures, complained of multiple skeletal pains and had bone tenderness. In this respect they resembled osteomalacia rather than osteoporosis. None of the cases, however, could be regarded as examples of classical osteomalacia. The radiological features resembled osteoporosis in all but one patient. Furthermore of 13 patients submitted to thorough study, the serum alkaline phosphatase was raised in five and an abnormally high retention of infused calcium was shown in seven. The bone biopsies from these patients showed a major degree of osteoporosis with only early evidence of osteomalacia. We have used the term 'osteomalacic' syndrome to describe this condition with features of mixed osteoporosis and osteomalacia (Deller *et al.*, 1963). Louyot, Mathieu, and Gaucher (1961) classified the skeletal status of 50 patients who had been submitted to

partial gastrectomy and who were being investigated in hospital for various post-gastrectomy disabilities as follows: no bone disease in 13; classical osteomalacia with pseudo-fractures in four; osteoporosis in five; and a 'malacic' syndrome in 28. We would agree that the skeletal symptoms which are most frequently complained of after gastrectomy suggest osteomalacia. Investigation usually shows osteoporosis to be the major abnormality. The accepted distinctions in the pathogenesis of osteoporosis and osteomalacia, however, may not be as mutually exclusive as previously considered, and experimentally at least, osteoporosis and osteomalacia are sometimes inter-convertible (Storey, 1961).

The cause of osteomalacia in steatorrhoea is impaired absorption of vitamin D leading to a fall in the plasma calcium primarily because of the lack of the direct 'calcaemic' action of vitamin D on the skeleton (Nordin, 1960). Malabsorption of calcium, either the result of steatorrhoea or due to vitamin D deficiency, would tend to produce a negative calcium balance. According to Nordin (1961b) and Harrison, Fraser, and Mullan (1961), prolonged calcium deficiency can lead to spinal osteoporosis. The Albright and Reifstein concept of the pathogenesis of spinal osteoporosis places prime importance on the steroidal imbalance of old age and the post-menopausal state wherein there is a relative excess of anti-anabolic steroids over anabolic steroids producing a condition qualitatively similar to that of Cushing's disease (Reifstein, 1960). The present study was not designed to provide evidence in the debate on the factors involved in the development of spinal osteoporosis. Moreover, the occurrence of osteoporosis combined with osteomalacia makes the task of separating the different aetiologies exceedingly difficult. However, it was observed that spinal rarefaction was significantly more frequent in the gastrectomy group after an interval of six years. Prolonged negative calcium balance for this period of time could theoretically produce a degree of bone rarefaction which would be detected radiologically (Cooke, 1955).

Factors of importance in the production of bone disease after gastrectomy are dietary deficiency of calcium, protein, and vitamin D (Deller *et al.*, 1963) and impaired absorption of calcium (Nicolaysen and Ragård, 1955). Defective absorption of calcium may result from by-passing the duodenum in the Polya operation, as it has been shown that the duodenum is the major site of calcium absorption (Schachter and Rosen, 1959). Intestinal hurry, the formation of insoluble calcium soaps in steatorrhoea, and vitamin D deficiency are additional factors contributing to impaired absorption of calcium.

In the present study patients with features of

osteomalacia have been treated with calcium and vitamin D, whereas patients with osteoporosis have been given calcium and an anabolic hormone (1 methyl- Δ^1 -androstenolone oenanthate). The response to this treatment is currently being assessed.

SUMMARY

The frequency and severity of spinal rarefaction were greater in 100 patients investigated after partial gastrectomy than in 100 control subjects, matched for age and sex. The difference in the frequency of the bone lesion was statistically significant.

The incidence of spinal rarefaction within the group of patients after partial gastrectomy was highest in those patients examined more than six years after operation, and in those with other post-gastrectomy disabilities.

The nature of the bone lesion after operation was mainly osteoporosis but there was some biochemical and histological evidence of osteomalacia as well.

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Part II The contribution of folic acid deficiency to the anaemia

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EDITORIAL SYNOPSIS Folic acid deficiency has been detected in 12% of randomly selected patients after partial gastrectomy. A megaloblastic reaction was found in seven of the patients of whom four had evidence of folic acid deficiency, one being regarded as due to primary folic acid deficiency. Attention is drawn to the dangers of therapy with folic acid and multi-vitamin preparations without full haematological investigation of the patient.

Megaloblastic anaemia following partial gastrectomy had usually been attributed to a deficiency of vitamin B_{12} (Badenoch, Evans, Richards, and Witts, 1955; Doig and Girdwood, 1960; Deller and Witts, 1962). The role of folic acid deficiency in the pathogenesis of anaemia following partial gastrectomy is uncertain, and only infrequently has folic acid deficiency been mentioned as a cause for the anaemia (Deller, 1962; Pitney, 1963).

Until recent years the diagnosis of folic acid deficiency in cases of megaloblastic anaemia has rested upon the exclusion of vitamin B_{12} deficiency;

by the finding of a normal serum level of vitamin B_{12} ; an inadequate response to vitamin B_{12} ; and a complete remission with folic acid therapy. More recently Chanarin, Mollin, and Anderson (1958) have used the rate of clearance from the plasma of intravenously administered folic acid as a measure of the folic acid stores, and they have reported an increased clearance rate in some patients with megaloblastic anaemia following gastric surgery. Rapid clearance of folic acid, however, was observed in haematological conditions other than folic acid deficiency.