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Serum gastrin concentrations in colorectal cancer patients

Richard M Charnley DM FRCS
Research Fellow

Julie Stanley
Senior Technician

W Michael Thomas MB FRCS
Research Fellow

David L Morris MD FRCS*
Senior Lecturer

Department of Surgery, University Hospital, Nottingham

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Fasting serum gastrin concentrations were shown to be elevated in colorectal cancer patients compared with controls ($P = 0.0037$), which was mainly accounted for by a subgroup of patients who had significantly elevated levels. In cancer patients there was no difference in gastrin concentrations in blood taken from a tumour-draining mesenteric vein and from a peripheral vein at the time of colonic resection. Serum gastrin concentrations were significantly lower after apparently curative resection for colorectal cancer ($P = 0.028$), suggesting that the elevated serum gastrin seen in these patients may be due, at least in part, to secretion of gastrin by the tumour.

It is well established that breast, prostate and some other cancers are under hormonal control *(1,2)*. Gastrointestinal hormones, including gastrin, glucagon, secretin, cholecystokinin, cerulin and bombesin, have been shown to influence the growth of tumour cells *(3)*. Gastrin has a trophic effect on normal epithelial cells in the gastrointestinal tract *(4,5)*. Colorectal and gastric tumour cells cultured *in vitro* respond trophically to gastrin *(6)*, and colorectal neoplasms in the rat are stimulated by gastrin *(7)*. Fresh human colorectal cancer cells are stimulated by gastrin in early *in vitro* culture *(8)* and some gastrointestinal tumours have also been shown to secrete gastrin *(9)*. It has been reported that some patients with colorectal cancer have elevated serum gastrin concentrations *(10,11)*. If this is the case, is the tumour the origin of the elevated gastrin?

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* Present appointment: Professor of Surgery, St George Hospital, Sydney, Australia

Correspondence to: Mr R M Charnley, Department of Surgery, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH

Patients and methods

Estimation of fasting serum gastrin concentrations was carried out in 65 patients with histologically proven colorectal cancer (median age 69 years, range 42–84 years) and in 19 patients who had a normal complete colonoscopy (two of these patients had colonoscopy to the hepatic flexure followed by right-sided, double-contrast barium enema) and no other signs of malignancy (median age 63 years, range 29–76 years). None of the patients in either group were known to have pre-existing conditions which might cause elevated serum gastrin, such as previous gastric surgery, pernicious anaemia or hypercalcaemia. Patients taking H_2 receptor antagonists were also excluded.

Fasting serum gastrin concentrations were measured in 52 patients with colorectal cancer at the time of resection of their primary carcinoma. Blood samples were taken simultaneously from a peripheral vein (usually the antecubital vein) by the anaesthetist and from the tumour-draining mesenteric vein by the surgeon.

To determine if there was a difference in preresection and postresection serum gastrin concentrations, fasting serum gastrin concentrations were also measured in 25 patients on one occasion 2–6 months after resection. None of these 25 patients had evidence of residual or metastatic carcinoma.

In all cases, estimation of the serum gastrin concentration was carried out by radioimmunoassay (CIS, UK).

The statistical analyses were carried out using the Mann–Whitney *U* test for comparing gastrin concentrations in cancer patients and normals, and by using the

correlation coefficient to find a difference between mesenteric vein and peripheral vein gastrin levels. The Wilcoxon signed pair rank test was used to evaluate the difference between preresection and postresection serum gastrin concentrations.

Results

Fasting serum gastrins in colorectal cancer patients and controls

The results are shown in Fig. 1. Fasting serum gastrins in cancer patients had a median value of 47.6 ng/l (range 7.5–1100 ng/l) and in controls 36.6 ng/l (range 5.5–53.3 ng/l). There was a significant difference between the two groups, $P = 0.0037$. If the subgroup of patients with cancer who had serum gastrin levels greater than 100 ng/l are removed from the analysis, there is still a significant difference between the two groups with $P = 0.013$.

Fasting serum gastrins in mesenteric vein and peripheral vein at operation

The results are shown in Fig 2. Tumour-draining mesenteric vein gastrin concentrations had a median value of 44.5 ng/l (range 6.0–1001.8 ng/l). Peripheral vein gastrin concentrations had a median value of 47.6 ng/l (range 7.5–1100.0 ng/l). There was no significant difference between the concentrations in the mesenteric vein and those in the peripheral vein, and values in individual patients were very similar (correlation coefficient, $r = 0.99$).

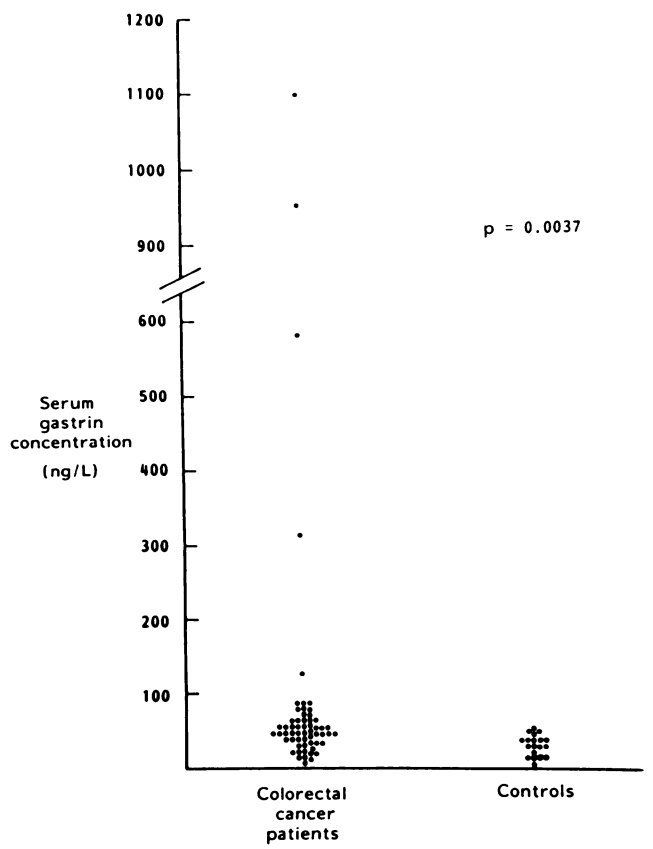

Figure 1. Fasting serum gastrin concentrations in colorectal cancer patients and in controls.

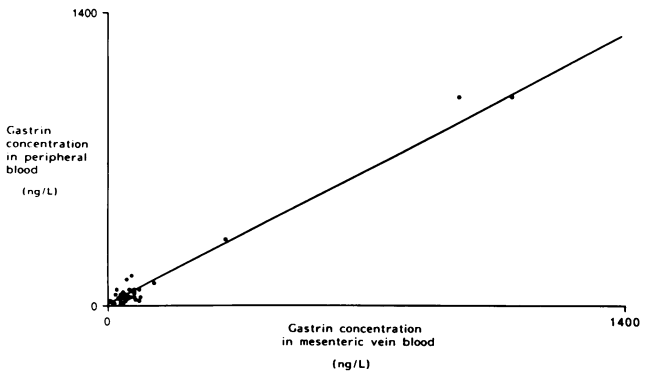

Figure 2. Fasting serum gastrin concentrations in mesenteric vein and peripheral vein at operation.

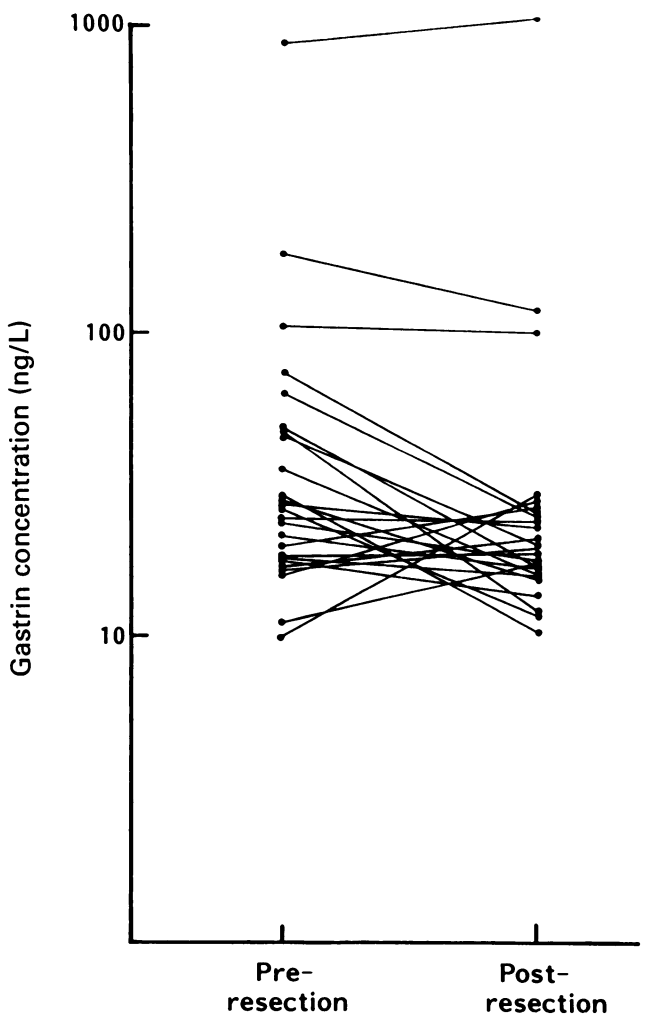

Figure 3. Preresection and postresection gastrin concentrations in colorectal cancer patients who had a 'curative' resection.

Preresection and postresection gastrin concentrations

The results are seen in Fig 3. For preresection gastrin concentrations the range was 10.0–953.0 ng/l (median 48.9 ng/l). For postresection concentrations the range was 11.1–1111.3 ng/l (median 35.0 ng/l). There was a significant difference in these results ($P = 0.028$).

Discussion

While Smith *et al. (10)* and Seitz *et al. (11)* have shown that serum gastrin is elevated in patients with colorectal cancer, Suzuki *et al. (12)* found no difference in levels between controls and patients with colorectal neoplasia. We have again demonstrated an elevated serum gastrin in colorectal cancer patients. The majority (74%) of our cancer patients had serum gastrins within the normal range (mean of the normals + 2 SD). Most of the remaining 26% with elevated gastrins had modestly elevated levels, but there were five patients with serum gastrin concentrations above 100 ng/l. Even if this group of patients is removed from the analysis, there is still a significant difference between the serum gastrin of cancer patients and the controls. Patients with elevated gastrins did not display any particular feature. In particular, there was no correlation with age, nor did patients with metastases have higher gastrins than those with localised disease. The relationship between the raised serum gastrin and colorectal cancer is unknown, but the post-operative fall in gastrin at least suggests that this may be due partly to tumour production of gastrin. There was no difference in the concentration of gastrin in peripheral and mesenteric vein blood, although gastrin production by tumour would not necessarily produce a difference.

It has been postulated that malignant transformation of cells may be linked to growth modulating polypeptides or growth factors *(13,14)*. Gastrin may be such a factor. The fact that gastrin is produced by some colorectal cancers and that these tumours have gastrin receptors *(15)* also points to gastrin functioning as an autocrine growth factor in colonic cancer, as suggested by Hoosein *et al. (16)*. Some patients, however, do have elevated serum gastrin even after their tumours have been removed. Even if there is an autocrine element, there may also be a source of the increased gastrin secretion other than the tumour. This is most likely to be the stomach. Patients with achlorhydria, atrophic gastritis and pernicious anaemia have elevated serum gastrins *(17–19)*. These conditions may be predisposing factors to the development of colorectal cancer as well as gastric cancer.

Gastrin receptor antagonists have been shown to have strong antiproliferative effects on colonic tumour cells *(16)*, and studies are in progress to determine if they have an effect on the growth of colorectal cancers *(20)*. However, if circulating gastrin proves to be an important factor in the growth of colorectal cancers, substances which decrease the levels of circulating gastrin will be as useful in regulating tumour growth as gastrin receptor antagonists.

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