

Postprandial hypergastrinaemia in patients with colorectal cancer

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Abstract

Gastrin is trophic to colon cancers that possess gastrin receptors. Whether fasting serum gastrin concentrations are high in patients with colon cancer is controversial. We therefore studied the effect of food on serum gastrin concentrations in patients with colon cancer and control subjects. Fasting serum gastrin was greater, though not significantly so, in patients with colon cancer before surgery (mean (SD) 17.4 (3.6) pmol/l, n=16) compared with control subjects (12.6 (1.9) pmol/l, n=14). Postprandial increases in serum gastrin were significantly and persistently higher than normal in the cancer patients. These increases were due to a subset of six patients with serum gastrin concentrations greater than the control mean+2 SD at 20 and 40 minutes (62 pmol/l-146 pmol/l). Four of the six patients had intra-abdominal metastases. The extent of the increase may well correlate with that of the disease. Surgical resection of the tumour resulted in a fall in serum gastrin values and probably reflects the cause of the hypergastrinaemia. Hypergastrinaemia may, therefore, be an important aetiological factor in colon carcinogenesis.

Colon cancer is the third commonest malignant disease in the United Kingdom with some 14 000 new patients seen annually, more than half of whom will die from their cancer.

It has been clear for some time that gastrin is trophic to the normal colonic mucosa of rats.¹ Recent work has shown that exogenously administered gastrin is trophic to colon cancer that possesses gastrin receptors,^{2,3} while administration of the gastrin receptor antagonist, proglumide, prolongs tumour doubling time and increases survival in mice with xenografted colon cancer.⁴ In animal models of colon carcinogenesis, endogenous hypergastrinaemia increases the number of rats that develop colon cancer⁵ and also the growth rate of epithelial tumours.⁶ Gastrin and its analogue pentagastrin stimulate the growth of human colon cancer cell lines *in vitro*.⁷⁻⁹ Recently, Palmer-Smith *et al* showed raised fasting serum gastrin concentrations in patients with adenomatous polyps and colon cancer. In their studies, a particular subset of patients (nearly a third in both cases) had fasting serum gastrin values more than 2 SD greater than the mean control value.¹⁰ Similar findings have been shown by others,¹¹ although some investigators have been unable to verify these.¹²

In healthy humans fasting serum gastrin values occur only in the few hours before dawn. The purpose of this study is therefore twofold. Firstly, to further examine the relation between

colon cancer and fasting serum gastrin values, and, more importantly, to examine the effect of food on serum gastrin values in patients with colon cancer.

Patients and methods

We studied 16 patients (eight men, eight women; median age 70 years, range 48-82 years) undergoing colonic resection for colorectal cancer and 14 healthy age and sex matched control subjects (nine men, five women; median age 70 years, range 50-86 years). None of these patients had a previous history of gastrointestinal surgery, peptic ulcers, or recent use of H₂ receptor antagonists.

Blood samples were taken while fasting and then at 10, 20, 40, 60, 90, and 120 minutes after a standardised hospital meal. In the patients with cancer, these studies were performed on the day of admission before bowel preparation, and were repeated 10 days after surgery, immediately before hospital discharge. The blood was drawn into EDTA bottles containing 10 units of Trasylol (Bayer UK, Reading) and immediately placed on ice. Plasma was separated by centrifugation (3000 rpm for five minutes) within 30 minutes of collection and was stored at -70°C before gastrin assay.

At surgery, samples (1 g) of tumour and healthy colonic mucosa from the distant resection margin were collected and stored dry at -70°C. These specimens were then extracted by mincing and boiling in distilled water for 30 minutes at a volume of 5 ml water/g tissue (1:5 dilution). The supernatant was separated by centrifugation and stored again at -70°C for subsequent analysis. As a positive control for our extraction procedure, samples of normal gastric antrum taken at gastric surgery were also examined for gastrin concentration.

Determination of the gastrin concentration in both serum and tissue extracts was by radioimmunoassay using antibody G179 (a gift of Professor S R Bloom) which recognises the large C terminal fragments of gastrin - that is, G-34 and G-17 - with less than 2% cross reactivity to CCK-8, CCK-33, and CCK-39.¹³ The data were analysed using a two way analysis of variance (ANOVA), and where the ANOVA showed a significant difference, the groups at each time point were compared using a Student's *t* test (*p*<0.05 considered significant).

Results

The results of the effect of feeding on serum gastrin are summarised in Figure 1. Fasting serum gastrin values were higher in the colon cancer patients before surgery (mean (SD) 17.4

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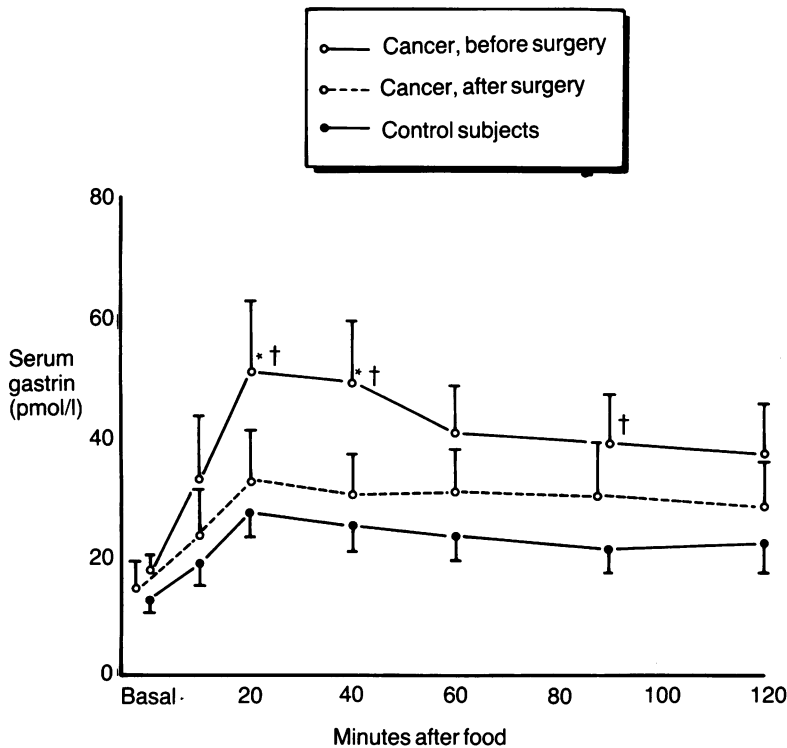


Figure 1: Serum gastrin concentrations (pmol/l) in the three study groups after food stimulation. Postprandial serum gastrin was persistently higher in colon cancer patients before surgery than in the other two groups and these differences were significant at 20 and 40 minutes (*). Serum gastrin values between the presurgery group and the controls were significant at 20, 40, and 90 minutes (+).

(3.6) pmol/l) than in patients after surgery (14.4 (4.5) pmol/l) and control subjects (12.6 (1.9) pmol/l) but these differences were not significant. Postprandial serum gastrin concentrations, however, were persistently higher in the colon cancer patients before surgery than in the other two groups, and these differences were significant 20 and 40 minutes after food.

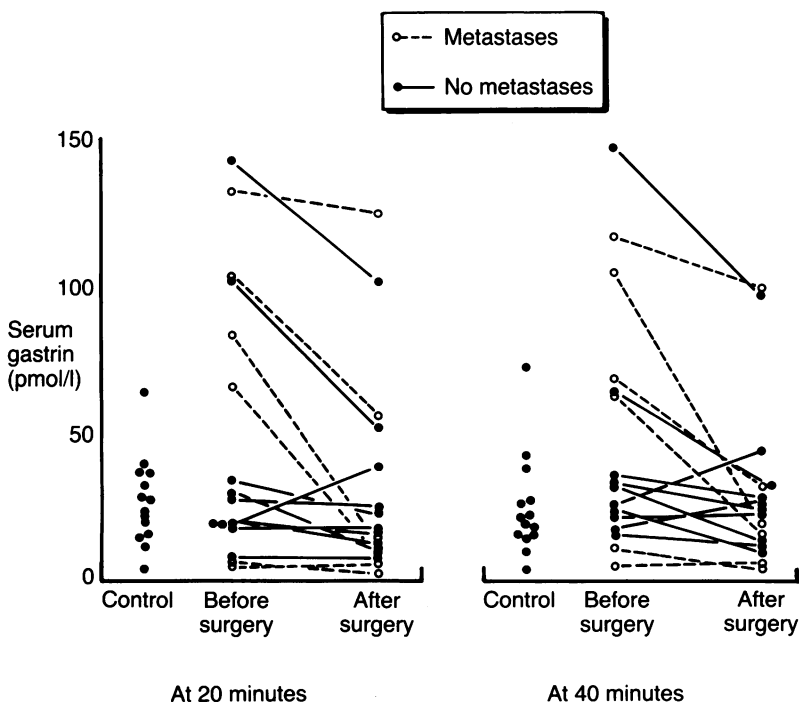


Figure 2: Serum gastrin values of the individual patients and subjects in the three groups at 20 and 40 minutes. In the patients with cancer, the open circles (○) represent those patients with intra-abdominal metastases found at surgery. Four of the six patients with metastases had serum gastrin concentrations greater than the control group mean + 2 SD (57 pmol/l at 20 minutes and 59.1 pmol/l at 40 minutes).

Before surgery, six of the 16 cancer patients had gastrin values greater than 2 SD from the mean of the control group at 20 minutes (control mean + 2 SD, 57 pmol/l; range, 66–142 pmol/l) and at 40 minutes (control mean + 2 SD, 59.1 pmol/l; range, 62–146 pmol/l). The other cancer patients had serum gastrin values ranging from 5–34 pmol/l at 20 minutes and 5–37 pmol/l at 40 minutes. Four of these six patients with very high serum gastrin values had intra-abdominal metastases at laparotomy, whereas only two of the other 10 patients with lower serum gastrin values had documented metastases at the time of surgery (Fig 2).

No gastrin was detected in either normal colonic mucosa or colon cancer in any of the specimens. As a positive control, extraction of normal human gastric antral mucosa yielded a concentration of 47.5 nmol/g tissue.

Discussion

We have shown that patients with colorectal cancer may have significantly raised postprandial serum gastrin values compared with the normal population. The role of growth factors and intestinal neoplasm has recently been reviewed by Townsend *et al.*¹⁴ By convention, the term growth factor is normally limited to substances produced by normal or neoplastic cells which are thought to act largely in a paracrine or autocrine manner. Our data suggest that the postprandial hypergastrinaemia seen in patients with colon cancer was not derived directly from the cancer; nor would it be expected that the presence of food in the stomach could promote and increase the release of gastrin from a tumour in the colon. However, it is possible that tumours produce a factor or factors that stimulate endogenous hypergastrinaemia either by increasing synthesis or promoting gastrin release from the gastric mucosa.

Our results also bear out the findings of Palmer-Smith *et al* that there seems to be a subset of about a third of patients with colorectal neoplasms who have very high serum gastrin concentrations compared with the normal population. Although our sample is small and not easily amenable to accurate statistical interpretation, it seems from the data on prevalence of metastases that the degree of increase in the serum gastrin value may correlate with the extent or aggressiveness of the disease.

Gastrin receptors have been identified on colon cancer cell lines from humans (LoVo, WiDr, LS180) and mice (MC-26)^{3,14} and the trophic effect of gastrin on MC-26 is mediated by the interaction of gastrin with its receptor.¹⁵ These receptors can be regulated by exposure to gastrin^{16,17} and inhibited by the gastrin antagonist, proglumide,¹⁸ which causes a decrease in the number of high affinity gastrin receptors expressed by the colon cancer cells. Interestingly, these same researchers went on to show an inverse relation between the numbers of gastrin receptors expressed in human colon cancer cells and the Duke's staging of the tumours.¹⁴

In conclusion, the presence of colon cancer is associated with endogenous postprandial hypergastrinaemia, which resolves after resection of

the tumour. Abnormally high serum gastrin concentrations after meals may have an aetiological role in the development of colon cancer, particularly in the transition from benign adenoma to carcinoma. Finally, it is possible that the colon tumours may be producing an agent that promotes abnormally excessive production of gastrin after food and this phenomenon is now being investigated by our group.

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