Gastrins and gastrinomas

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Introduction

Gastrin was first postulated by Edkins in 1906 as the hormone responsible for gastric acid secretion but it took a further 65 years of debate before Gregory and Tracey (1961) reported on the properties and structure of this hormone. With the elucidation of the complete amino acid structure and synthesis of the peptide, immunochemical and immunocytocchemical methods quickly led to measurement of the hormone in blood and other biological fluids, localization, physiology and pathophysiology. Although gastrointestinal hormones were not amongst Avery Jones' primary interests in gastroenterology, the unit's expertise in peptic ulcer particularly with reference to bleeding led to the author's search for a possible role of gastrin in the pathophysiology of ulcer and to general studies of gastrin by radioimmuno assay.

This review will describe the advances in the past 20 years in gastrin physiology and pathophysiology with particular reference to gastrinoma.

Radioimmunoassay of gastrin

The ability to measure femtomol (10^{-15} M) amounts of gastrin by radioimmunoassay has led to intensive study of the release of the hormone. Since McGuigan (1968) first developed this assay for gastrin, numerous groups have followed and the assay is now widely available. The most useful gastrin antibodies are those that are directed against the C-terminus, measure all forms equally and do not cross react with other peptides that share the C-terminus such as cholecystokinin or caerulein. Using such antibodies, serum gastrin can be detected in unextracted samples at a dilution of 1:10 and usually measures amounts of 10–50 fmol ml^{-1} in the fasting normal subject. Region specific antisera have been generated for the C and N terminus of gastrin 17, for unsulphated G17, for G34 and the N terminus of G34. Utilizing these region specific antisera, the characterization of the various molecular forms of gastrin in plasma or tissues can be made without resort to gel filtration or affinity chromatography (Dockray, 1979).

The gastrins

Gastrin exists in multiple molecular forms that not only differ in one or two amino acids in different species but also occur in different chain lengths within species. It is thought that a large precursor molecule, Pre-Pro-Gastrin, is synthesized in cells and undergoes post-translational enzymatic cleavage at specific arginine or lysine residue to yield first gastrin 34 and then gastrin 17 (Yanahaira, 1980). In addition to these molecules of different chain length, the molecules may have the single tyrosine sulphated or unsulphated. There is little doubt about six molecular forms of gastrin in mammals—G34 sulphated or unsulphated, G17 sulphated and unsulphated and G14 sulphated and unsulphated. A form larger than G34 has been identified on gel chromatography and named 'Component I’ but its structure has not yet been elucidated (Rehfeld, Stadil and Vikelsoe, 1974). There has also been a peak eluting in the void volume of sephadex columns called 'big big gastrin’ but this is probably an artefact. There is also controversy whether G4 exists in cells. The most abundant forms in blood and tissues are G34 and G17. G34 accounts for most of the fasting serum gastrin and for about half of that released by a stimulius. The predominant site of extractable gastrin is the antrum and the form is as G17. Gastrin can also be extracted from the duodenum where about half is G34. Sulphated and unsulphated forms are equally distributed.

Actions of gastrin and role in physiology

The full range of biological actions of gastrin reside in the C terminal tetrapeptide amide. G17 and G14 are equipotent in stimulating gastric acid secretion whereas G34 has about 1/6 the potency in the circulation. When infused exogenously, all three are equipotent on a molar basis. Table 1 shows the actions of gastrin on the gastrointestinal tract: of these, the effect on gastric acid secretion, antral motility and gastric and intestinal growth may be
physiological. The other effects are almost certainly pharmacological.

<table>
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<th>TABLE 1. Actions of gastrin</th>
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<td>Inhibits:</td>
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*Physiological.

Release of gastrin

The factors which stimulate and inhibit the release of gastrin have been fully elucidated with the advent of radioimmunoassay in its measurement. The factors which stimulate gastrin release are shown in Table 2. Small peptides, amino acids and calcium in the gastric lumen stimulate gastrin release. Low doses of atropine enhance release of gastrin in response to food, an increase also seen after all forms of gastric vagotomy suggesting removal of cholinergic inhibitory fibres. Vagal stimulation by insulin hypoglycaemia and sham feeding result in gastrin release. This suggests that cholinergic influences on gastrin release are complex and both stimulatory and inhibitory mechanisms operate. Intravenous infusion of catecholamines, calcium and bombesin stimulate gastrin release by mechanisms not fully determined. There is increasing evidence that gastrin is released into the lumen of the gut as well as into the blood stream.

<table>
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<th>TABLE 2. Release of gastrin</th>
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<td>Luminal:</td>
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Table 3 shows the factors which inhibit gastrin release. Decreasing the pH of the contents bathing the antrum inhibit gastrin—this commences at a pH of 3-0 and is maximal at a pH of 1-0 or less. Presumably this is part of the normal feedback control of gastrin release. Topical prostaglandins and local anaesthetics have also been shown to inhibit the release of antral gastrin.

<table>
<thead>
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<th>TABLE 3. Inhibition of gastrin release</th>
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<td>Luminal:</td>
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Intravenous injection of somatostatin and calcitonin inhibit gastrin release as do some members of the 'secretin' family. In particular vasoactive intestinal peptide, glucagon and secretin lead to a fall in circulating gastrin levels. This is of some clinical importance in that in normal subjects or where gastrin is originating from the antrum (e.g. antral G cell hyperfunction or retained excluded antrum), secretin injection leads to a fall in gastrin whilst in Zollinger-Ellison syndrome it leads to a paradoxical rise (Korman et al., 1972). The role of these hormones in the physiology of gastrin release is not known and the effects may be pharmacological (Hansky, Soveny and Korman, 1971).

Pathophysiology of gastrin release

Ulcer disease. In duodenal ulcer, fasting serum gastrin levels are generally within the normal range but food stimulated gastrin levels are greater than in normal subjects (Hansky and Korman, 1973). This, together with the finding that parietal cell hyperfunction in duodenal ulcer disease are more sensitive to gastrin (Lam et al., 1980) indicates some role for gastrin in the pathophysiology of duodenal ulcer. In gastric ulcer, basal levels of gastrin are elevated and there is a large release of food stimulated gastrin. This is probably consequent on the diminished acidity in the antrum due to concomitant gastritis (Hansky and Korman, 1973). All forms of vagotomy in man lead to an increase in fasting serum gastrin and increased release after food stimulation. It is considered that this may be due to both removal of a vagal inhibitory mechanism and an increase in the gastrin cell mass (Hansen, Larsen and Svendsen, 1979).

Hypergastrinaemia. The causes of an increase in fasting serum gastrin are shown in Table 4. The group associated with hyperacidity, hypergastrinaemia and usually peptic ulceration form the most interesting and probably the commonest group. Gastrinoma will be considered separately and the hypergastrinaemia associated with massive small bowel resection has been reported only by Strauss, Berson and Yalow (1974) but not confirmed by others. Retained excluded antrum and antral G cell hyperfunction are uncommon but definite entities. Retained excluded antrum was first described by Korman et al. in 1972, but only a few patients have been reported. Recently Basso et al. (1981) have assessed bombesin in differentiating between gastrinoma.
of antral origin and that from other sites. They found an increase in gastrin after bombesin in five patients with the retained antrum syndrome and postulated this as a good differentiating test. Antral G cell hyperfunction (hyperplasia) has been reported sporadically and consists of hypergastrinaemia, hyperacidity and peptic ulceration in the absence of definite evidence of a gastrinoma with a major distinguishing feature being a grossly exaggerated gastrin release after food. Some reports have indicated an increased number of G cells in these patients but the feature which distinguishes them from gastrinoma is that the serum gastrin returns to normal levels following antrectomy (Walsh, 1979).

The differentiation of these three causes of hypergastrinaemia and hyperacidity is shown in Table 5 and is mainly based on the serum gastrin response to food and intravenous secretin injection as well as the fasting serum gastrin. Generally patients with gastrinoma have a very high fasting gastrin, a normal gastrin response to food and a paradoxical increase in gastrin to secretin. Antral G cell hyperfunction shows a moderately elevated fasting gastrin, an exaggerated response to food (over 400%) and a fall in gastrin with secretin. Retained antrum is the same as antral G cell hyperfunction except that the response to food is poor. All three show a response to intravenous calcium infusion whilst the experience with bombe-

**Table 4. Causes of hypergastrinaemia**

<table>
<thead>
<tr>
<th>Type of Hypergastrinaemia</th>
<th>Causes</th>
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| With increased gastric acid secretion: | Gastrinoma (Zollinger-Ellison Syndrome)  
Antral G cell hyperfunction  
Retained excluded antrum  
Massive small bowel resection |
| With variable gastric acid secretion: | Chronic renal failure  
Rheumatoid arthritis |
| With decreased/absent gastric acid secretion: | Type A gastritis  
Post vagotomy |

**Table 5. Differentiation of hypergastrinaemia: response to food, secretin, calcium and bombesin**

| Gastrin response to Food | Gastrinoma  
Retained antrum | Antral G cell hyperfunction  
Chronic renal failure  
Type A gastritis  
(Pernicious anaemia) |
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<tbody>
<tr>
<td>Gastrin response to Food</td>
<td>Gastrin response to Food</td>
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</table>
| IV Secretin  
IV Calcium  
IV Bombesin |
| Gastrinoma  
Retained antrum | ↑↑  
>500  
N |
| ↑↑  
100–300  
N |
| ↑  
↑↑  
↑ |
| ↑  
↑  
? |

† Increased; † Decreased; N = Normal.

**Chronic renal failure**

Studies on the metabolism of gastrin suggest that the kidneys are a major site of gastrin breakdown particularly for the G34 form. Hypergastrinaemia has been reported in patients with acute renal failure, after nephrectomy and in chronic renal failure. In a study on a large number of patients, it has been shown that the serum gastrin rises proportionally with the serum creatinine, the higher the creatinine, the higher the gastrin. The relationships of this increase in gastrin to acid secretion and peptic ulceration in this group of patients with chronic renal failure is not clear as most patients do not have ulcer problems (Hansky, 1979).

**Type A chronic atrophic gastritis**

Elevated serum gastrin is usually found in patients with type A chronic atrophic gastritis. This gastritis is characterized by a positive titre for parietal cell antibody, gastritis limited to the acid secreting part of the stomach with antral sparing and propensity towards development of pernicious anaemia. Gastrin levels are often the highest seen, increase with age and there is an exaggerated response to food suggest...
Gastrinoma (Zollinger-Ellison syndrome)

The commonest causes of hypergastrinaemia, hyperacidity and peptic ulceration are gastrin secreting tumours. Since the syndrome was first described in 1955, a vast literature has accumulated and changes have occurred in diagnosis and management. The clinical features have been well documented and generally consist of duodenal ulceration or more uncommonly diarrhoea and steatorrhea. Clinical suspicion is aroused by the presence of recurrent or intractable duodenal or jejunal ulcer; stomal ulceration after adequate gastric surgery; failure of ulcer to heal on adequate medical therapy; the combination of duodenal ulcer with gastric hypersecretion, hypokalaemia, hypercalcæmia, hypoglycaemia, diarrhoea, or steatorrhea, and large volume diarrhoea or steatorrhea. All clinical features can be ascribed to either increased gastric acid secretion or associated endocrinopathies. Pathogenesis is that the tumour secretes increased amounts of gastrin which stimulates increased gastric acid secretion. The steatorrhea or diarrhoea is due to inactivation of pancreatic lipase and damage to small bowel mucosa by the acidity within the intestinal lumen.

Approximately 20% of gastrinoma patients form part of the multiple endocrine adenomatosis (MEA) type I syndrome. The commonest associated endocrine abnormality is hyperparathyroidism with hypercalcæmia followed by insulinoma and pituitary chromophobe adenoma.

Most tumours are found in the pancreas, from 3–15% in the duodenum and rarely functioning gastrinomas are found in the kidney or ovary. Tumours are frequently small, multiple and malignant; metastatic disease is present in 20–40% of patients at initial onset.

Diagnosis. The diagnosis is confirmed by measuring the fasting serum gastrin—this is usually above 300 fmol/ml depending on the laboratory’s normal range. Gastric acid studies are usually not necessary if the patient has peptic ulceration but if performed, these will show a basal acid output of over 15 mmol per hour and a basal: maximal output ratio of over 0.6. Barium studies may show large resting gastric volume, very prominent gastric folds or an ulcer in the post bulbary duodenum; in most patients barium meal is unremarkable apart from showing ulcer disease. The best confirmatory test for gastrinoma is secretin or calcium challenge and this has been recently reviewed by McGuigan and Wolfe (1980). The secretin stimulus is the most reliable and easiest to perform and it is also our experience that a rise in gastrin after secretin of 100% is virtually diagnostic of gastrinoma. The occasional patient will have no rise and the precise incidence of false negative tests is difficult to determine. As shown in Table 5, calcium infusion also gives an increase in gastrin whereas food has little effect.

Tumour localization. Techniques such as abdominal ultrasonography, CT scanning and visceral angiography will find a tumour in only 25–30% of patients who have all the other criteria for gastrinoma. The technique of percutaneous transhepatic portal venous sampling to localize gastrinomas has been advocated by Burcharth et al. (1979). They studied six patients and were successful in four in removing all gastrin producing tissue. However this procedure is technically difficult and may not be universally successful. Thus, using all available modalities, at best tumour localization is possible in some 35% of patients.

Management. Before the discovery of powerful inhibitors of gastric acid secretion such as histamine H₂ receptor antagonists, treatment of gastrinoma relied on either tumorectomy and/or total gastrectomy. With the advent of antisecretory agents such as cimetidine, ranitidine and omeprazole effective medical therapy became available for the treatment of gastric acid hypersecretion with a real alternative to total gastrectomy. Despite these developments, controversy still exists as to the best way to manage these patients and a number of treatment schemes have come into vogue. Surgical exploration with complete removal of the tumour varies from 5–30% so that this option is not very successful. The reasons for this are failure to locate the tumour, multiple tumours and metastatic spread (Zollinger et al., 1980; Deveney, Deveney and Way, 1978; Bonfils et al., 1981). The results of medical therapy are difficult to assess. Most patients have been subjected to an exploratory laparotomy and the tumour has not been found; but given this premise, most large series report that cimetidine in doses of 1–5 g per day keep the majority of patients well. If breakthrough occurs or side effects such as gynaecomastia and impotence, patients can be successfully changed to ranitidine therapy with only about 10–15% requiring total gastrectomy because of failure of medical treatment (Stadil and Stage, 1978; McCarthy, 1978). Others have reported more failures with medical treatment with a greater incidence of total gastrectomy (Bonfils, Mignon and Gratton, 1979; Deveney et al., 1978). A recent paper from the Mayo Clinic (Malagelada et al., 1983) reported experience in 53 patients with gastrinoma. They explored 44 patients, found a tumour in 31 of whom 13 were unresectable and 18 were resected. Of this 18, only seven have shown no
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recurrence and there were five duodenal wall tumours in this subgroup. Eighteen patients had a total gastrectomy (before introduction of the receptor blockers) and a further 18 had had cimetidine therapy with excellent results. They concluded that patients without MEA I or metastasis should undergo exploratory laparotomy with a view to resection of tumour and that chronic therapy with \( H_2 \) receptor antagonists is preferable to total gastrectomy. Passaro and Stabile (1983) have suggested a complex scheme based on their analysis of all the available data and initially subdivide their patients into non MEA I + no metastases and either MEA I or liver metastases. The former group is treated medically for a year and if controlled, young and good risk, or fail, are explored. If old and poor risk they continue on chronic therapy. Patients in the group with liver metastases or MEA I have chronic medical therapy.

Another approach has been to explore the patient and if the tumour is not found or is unresectable, to do a truncal vagotomy as this may decrease the amount of cimetidine required to control acid secretion (Richardson et al., 1979).

Our own experience with medical therapy is based on 46 patients with gastrinoma. Twenty seven have been treated with cimetidine in doses ranging from 0.8-1 g daily; of these nine have had vagotomy and/or partial gastrectomy and are well controlled on cimetidine; 13 are controlled on larger doses of 1–5 g daily and five have failed cimetidine and are now controlled with ranitidine. Side effects from medication are minimal and all 27 patients are well. The 19 patients not treated with \( H_2 \) receptor antagonists comprise four with tumour removal whose gastrins normalized, nine with total gastrectomy, two with MEA I who responded to parathyroidectomy and four patients who died from metastatic disease (Hansky, 1983).

Based on our experience and the available literature, the recommended management option for gastrinoma is shown in Table 6. If a tumour can be demonstrated on ultrasound, CT scanning, portal vein sampling or angiography then explore and attempt removal. If no tumour is found, cimetidine or ranitidine are commenced and the patient followed closely. Gastrin estimations are performed 3 monthly and if there is a sudden increase the patient is re-studied sooner than 2 years. Medical therapy is dictated by side effects and relapse. Start the patient on cimetidine 1–1.2 g daily and if not held will increase the dose up to 3 g daily then change to ranitidine at a dose of 300–600 mg daily. The alternative is to begin ranitidine from the outset. Failure on ranitidine previously meant total gastrectomy; with the availability of omeprazole, a substituted benzimidazole, this should be tried first or perhaps an anticholinergic can be added to the \( H_2 \) receptor blocker. Patients with MEA I should have their other endocrinopathies treated and often the hyperacidity diminishes. If not, they are treated medically. The role of streptozotocin in metastatic disease is not clear but it does not seem to be as valuable as in other types of islet cell tumours.

This scheme is a guide to management and will certainly not apply to all patients, particularly those with fulminating ulcer disease which requires urgent gastrectomy. It is of some interest that in the 1950s and 60s these patients were not infrequently seen; more recently, they seem to have become much rarer, perhaps reflecting earlier diagnosis.

Summary

The past 20 years have seen gastrin attain true hormonal status. Its structure has been characterized,
it has been synthesized, radioimmunoassays for its measurement in blood and tissues have been developed and its physiology and metabolism elucidated. Of much interest to clinicians has been the association between gastrin and tumours of the pancreas (gastrinomas) and atrophic gastritis. The advent of gastrin measurement has facilitated the diagnosis of gastrinoma and the availability of powerful acid suppressants has altered the therapy of gastrinoma.

References


