

Laboratory Diagnosis of Gastrinoma remains difficult.

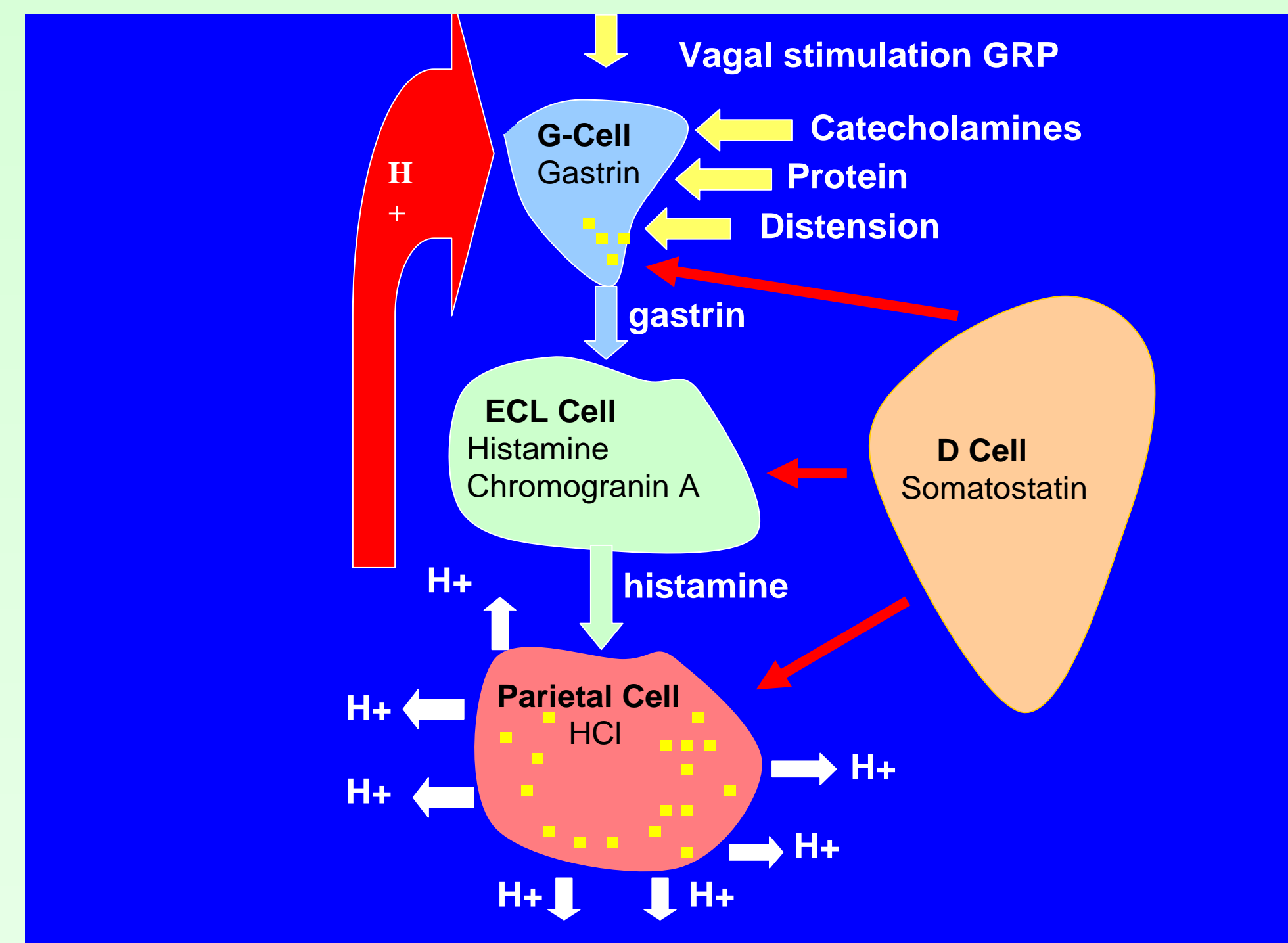
Ardill JES, Armstrong E, McCance DR, Johnston BT.

Regional Regulatory Peptide Laboratory & Neuroendocrine Tumour Group, Royal Victoria Hospital Belfast UK

Introduction

In a diagnostic laboratory the main utilization of gastrin assay is for the diagnosis of gastrinoma. However, gastrinoma is uncommon 1-2/million/year and many other, more common conditions present with similar GI symptoms including diarrhoea, abdominal pain and gastric reflux all suggestive of peptic ulcer disease. In the last year, in this laboratory 28% of specimens processed for gastrin measurement gave results above the reference range yet <5% were from patients with gastrinoma. More commonly hypergastrinaemia is a result of non-fasting specimen collection, the use of proton pump inhibitor (PPI) or H2 antagonist therapy, H-pylori infection (Hp), atrophic gastritis or renal failure. To compound the problem about 20% of patients with gastrinoma present with circulating gastrin only marginally above the reference range

Although Chromogranin A (CgA) is the best general circulating marker for neuroendocrine tumours (NETs) measurement of CgA is not usually helpful in the diagnosis of gastrinoma as in all conditions where gastrin is elevated due to over-production of gastrin or lack of the negative feedback from gastric acid, chromogranin A is also raised.



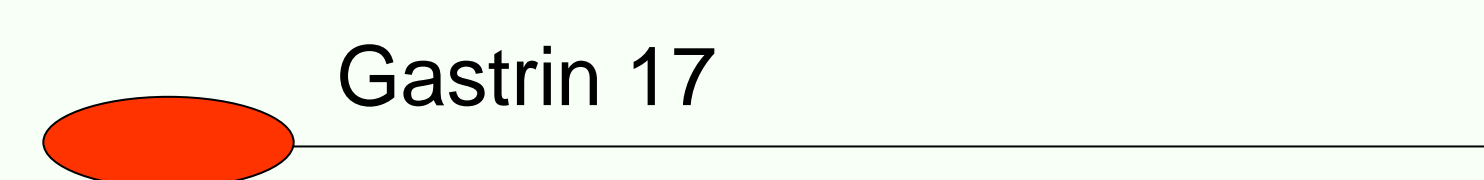
Methods

STUDY 1 In a specialized laboratory we have studied requests for gastrin and CgA in patients undergoing investigation for gastrinoma. An in-house assay for amidated gastrin is routinely used for gastrin assay (The reference range (RR) is <45pmol/l. The DAKO CgA kit is used routinely for the measurement of CgA. RR<30U/l.

STUDY 2 We have investigated the following groups of subjects: normal healthy controls both Hp-ve and Hp +ve and patients with gastrinoma, autoimmune atrophic gastritis (AIAG), idiopathic gastric achlorhydria (IGA), renal failure (RF), Hp +ve duodenal ulcer (DU) and subjects on PPI therapy for 1 and 6 months. Subjects were tested both after an overnight fast and post-prandially (50g protein) and also using three different gastrin antisera described below



Antibody raised to the N-terminus of G34 which measures G34 and C-terminally extended G34



Antibody raised to the N-terminus of G17 which measures G17 and C-terminally extended G17



Antibody raised to the N-terminus of G17 measures all amidated gastrin. This gastrin assay is in routine diagnostic use in this laboratory. RR is <45pmol/l.

Results

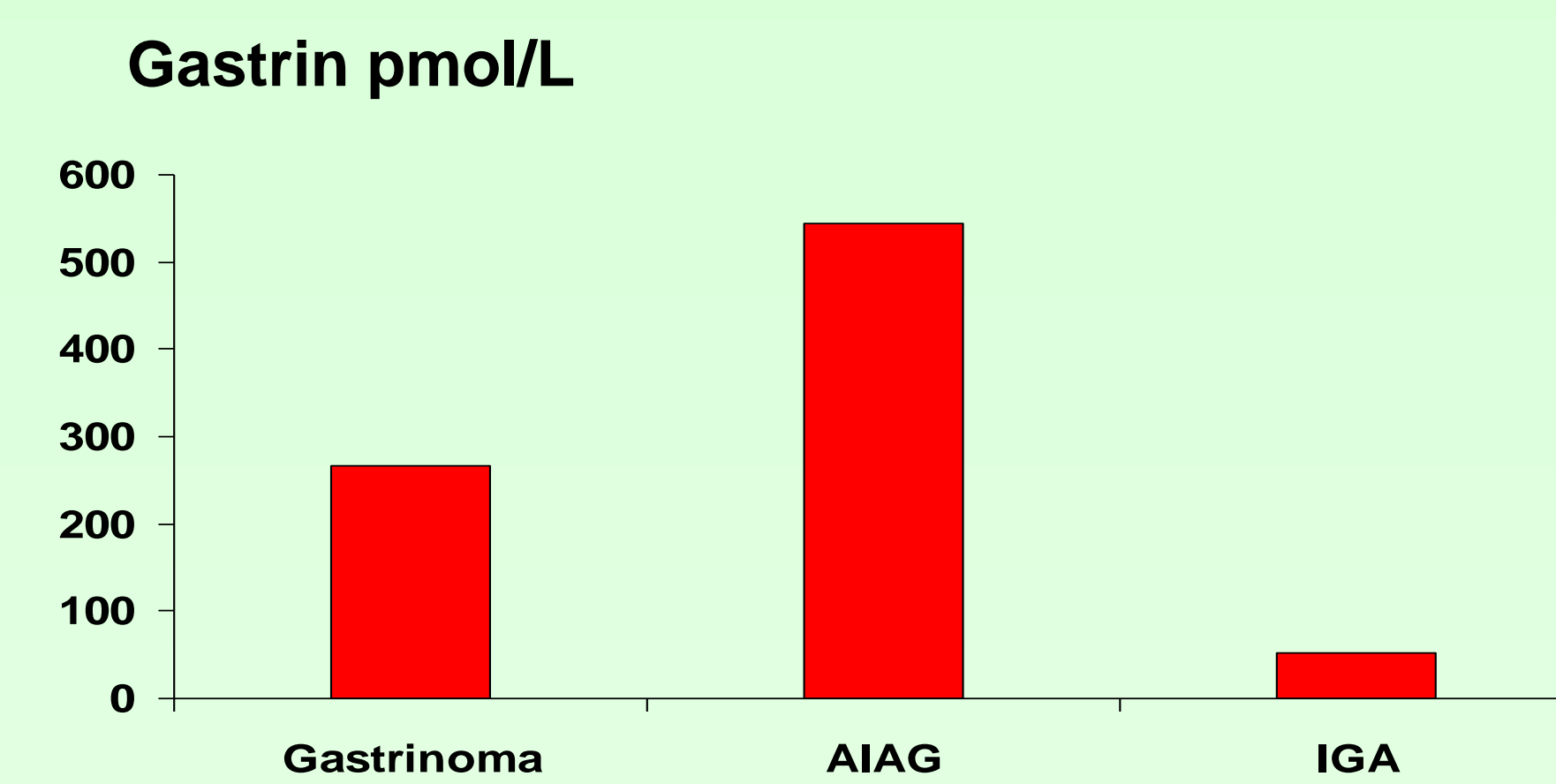
STUDY 1

Of 500 consecutive specimens under investigation for gastrinoma, 28% showed gastrin above the RR and 47% showed CgA above the RR. Five percent were shown to have gastrinoma (within a 6 month period) 12% had a different NET (most commonly midgut carcinoid) at least 22 % had AIAG, at least 45% were taking PPI therapy and at least 37% were not fasted.

STUDY 2

All patients with gastrinoma presented with gastrin above the RR, the lowest concentration was 50 pmol/L. There was 100% overlap between plasma gastrin in gastrinoma and in AIAG and 56% overlap with IGA.

Median fasting Amidated Gastrin



Overlap between plasma gastrin in gastrinoma and Hp+ve DU was 34%, normal healthy controls Hp+ve 22%, those on PPI therapy for one month 26% and those on PPI therapy for 6 months 92%. Only healthy control subjects who were Hp-ve showed no overlap with gastrinoma. See table below.

	Number	Number gastrin >RR	Above RR
Gastrinoma	50	50	100%
AIAG	50	50	100%
IGA	25	14	56%
RF	50	50	100%
DU Hp+ve	50	17	34%
DU on PPI (1 month)	50	13	26%
DU on PPI (6 months)	50	46	92%
Control Hp+ve	50	10	20%
Control Hp-ve	50	0	0%

More than 10% of patients with gastrinoma present with gastrin <5% above the RR and more than 20% with gastrin <20% above the RR in contrast some patients present with gastrin concentrations >10,000 pmol/l

Many specimens delivered to the laboratory have not been taken after an overnight fast. It is important to be aware of the effect of food on circulating gastrin concentrations. Within 30 minutes post-prandially amidated gastrin rises to within the gastrinoma range in almost all subjects, including those who are Hp-ve, therefore all new patients who present with circulating gastrin 45-200 pmol/l are re-tested after an overnight fast.

Patients with AIAG present with a wide range of circulating gastrin and in >15% of this group gastrin is greater than 10,000 pmol/l.

Ninety nine percent of patients with gastrinoma presented with elevated CgA. However very many circulating CgA concentrations are above the reference range. One thousand consecutive specimens tested for CgA in routine diagnostic assay gave the following results.

CgA (U/l)	% within each range
<30 (RR)	47%
31-100	24%
101-200	8%
>201	21%

When the three antisera were used to measure circulating gastrin, after an overnight fast and post prandially then the concentrations measured did not clarify the diagnosis of gastrinoma. There was no advantage in using an antisera raised to the N-terminus of G34 which measures G34 and C-terminally extended G34 or the antibody to N-terminus of G17 which measures amidated gastrin and C-terminally extended G17. With these antibodies even Hp-ve controls showed a considerable overlap with gastrinoma patients. Median fasting and post-prandial measurements of gastrin using the 3 antisera are shown in the table below.

	Amidated gastrin		G34 & extended		G17 & extended	
	fasting	fed	fasting	fed	fasting	fed
Gastrinoma	295	325	348	365	685	785
AIAG	714	1643	335	527	726	2918
DU Hp+	40	105	45	48	34	82
DU on PPI (1m)	43	89	45	52	38	88
DU on PPI (6m)	55	125	51	60	49	138
Control Hp+	37	90	42	38	20	66
Control Hp-	33	76	37	36	12	29

Discussion

- 1 Clinical diagnosis for gastrinoma is difficult and many patients will remain undiagnosed for years because the symptoms frequently occur in common conditions. PPI therapy is used to relieve symptoms and this, although potentially life saving, obscures the syndrome delaying diagnosis.
- 2 Laboratory diagnosis also remains problematic. Only subjects who are Hp-ve show no overlap with gastrinoma patients with regards to circulating fasting gastrin when the routine antibody is used. There is no advantage to using N-terminal G17 or G34 antisera for the measurement of gastrin except for the occasional patient.
- 3 CgA measurement does not clarify diagnosis.
- 4 Patients with AIAG are common but may be excluded by measuring parietal cell antibody in serum, or by the histological examination of gastric biopsies.
- 5 Subjects who are Hp+ve or those on PPI therapy remain problematic as both gastrin and CgA are elevated. Hp should be eradicated in patients with DU symptoms. PPI therapy should be withdrawn only under careful supervision in patients suspected of having a gastrinoma as perforation may occur.