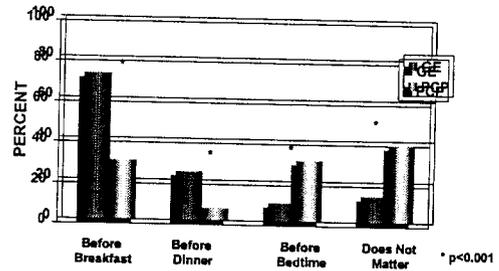


### Gastrin Stimulates Receptor-Mediated Proliferation of Human Esophageal Adenocarcinoma Cells

T. C. Moore,\* L.I. Jepeal,\* M.O. Boylan,\* S.K. Singh,\*  
N. Boyd,\* D.G. Beer,§ M.M. Wolfe\*

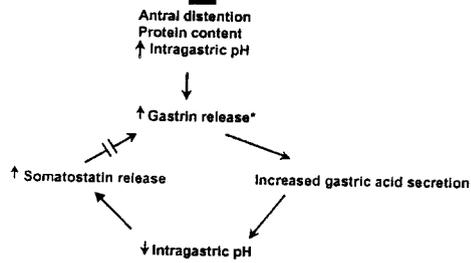
\*Section of Gastroenterology, Boston University School of Medicine; §Department of Surgery, University of Michigan.

### Administration of PPIs



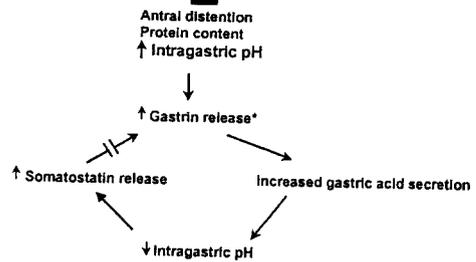
Barrison AF et al. Amer J Med 2001; 111:469-73.

### Gastric Phase of Acid Secretion



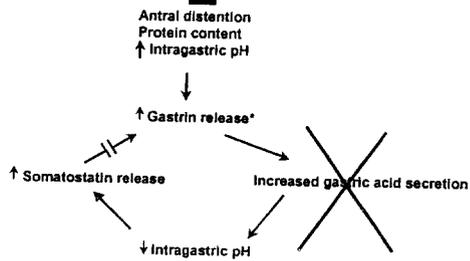
\* mediates 92% of the response

### Gastric Phase of Acid Secretion



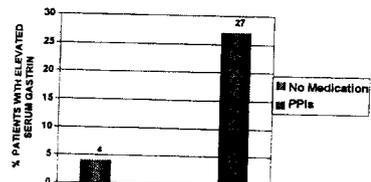
\* mediates 92% of the response

### Gastric Phase of Acid Secretion



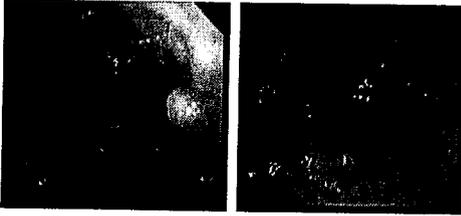
\* mediates 92% of the response

### Serum Gastrin Levels During PPI Therapy



Bonapace ES et al. Dig Dis Sci 2000;43:34-39.

## Gastric Polyps in Patients on Long-Term PPI Therapy

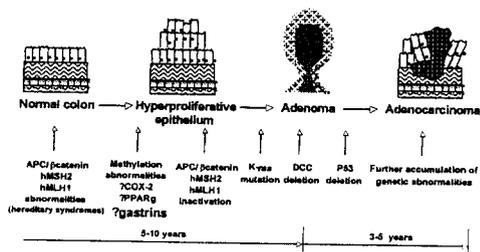


## Gastrin and Colorectal Cancer

"... a gastrin level above normal was associated with increased risk for colorectal malignancy (odds ratio, 3.9; 95% confidence 1.5-9.8). If this association is causal, 8.6% of colorectal cancers could be attributed to high serum gastrin level.  
**Conclusion:** Hypergastrinemia is associated with an increased risk of colorectal carcinoma."

Thorburn CM et al. *Gastroenterology* 1998;113:275-80.

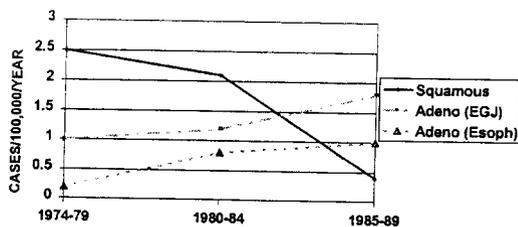
## Molecular Genesis of Colorectal Neoplasia



## Gastroesophageal Reflux Disease

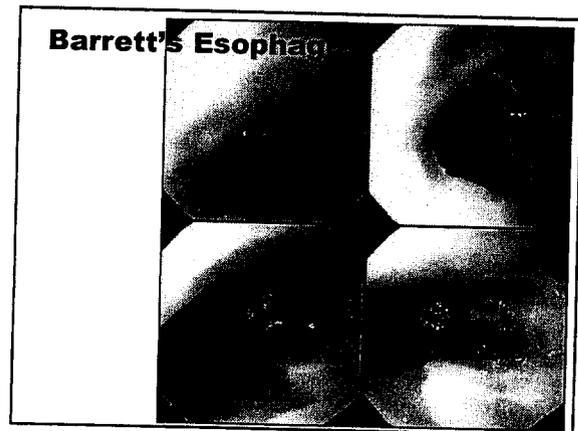
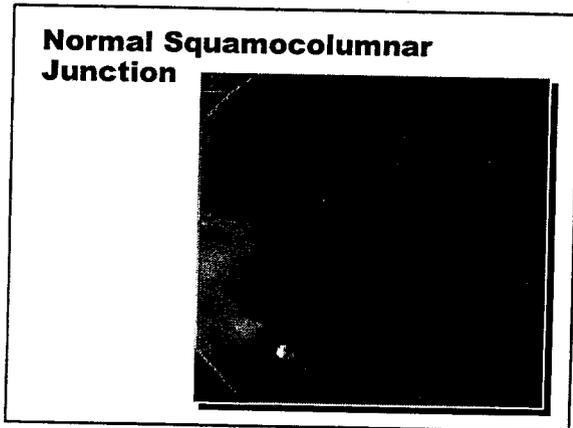
Epidemiology of heartburn: 40% monthly, 15% weekly, 7-10% daily.  
 In most, GERD is a nuisance.  
 10-20% develop complications.  
 3-7% have Barrett's esophagus.  
 Cancer of esophagus is the fastest growing cancer in the U.S. for unknown reasons, *despite the best GERD therapy ever available.*  
 Complications may occur without severe symptoms; poor correlation.

## Esophageal Cancer Incidence



Pera M et al. *Gastroenterology* 1993;104:510-513.

It is perplexing that the incidence of this neoplasm has increased dramatically during the very period in which highly effective acid-reducing therapies have provided symptomatic relief and healing in those individuals with mucosal injury due to the erosive effects of acid and other gastric contents.



### Prospective Studies on Cancer Incidence in Barrett's Esophagus

Study Author	No. of Patients	Follow-Up (Patient-Yrs)	Annual Cancer Incidence (%)
Hammeeteman	50	260	1.9
Bonelli	71	110	1.8
Robertson	56	224	1.8
Miros	81	289	1.0
Iftikhar	102	462	0.8
Drewitz	170	834	0.5
<b>Total</b>	<b>530</b>	<b>2179</b>	<b>1.0</b>

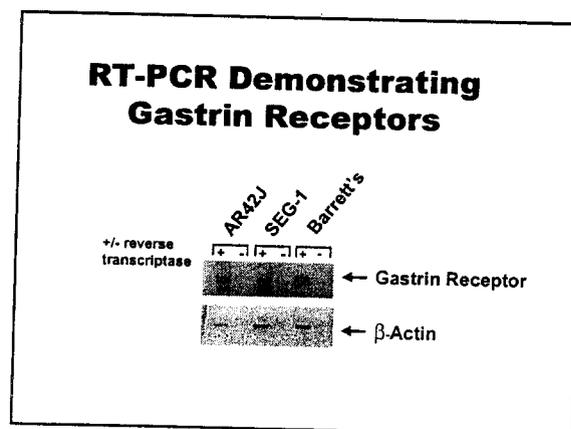
Adapted from Drewitz D.J. Am J Gastroenterol. 1997;92:212.

### Purpose

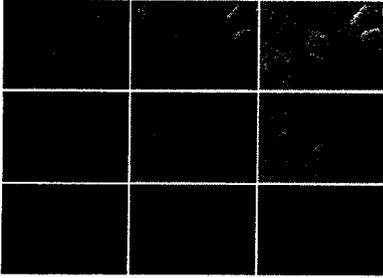
To determine whether functional gastrin receptors are present on esophageal adenocarcinoma cells.

### Experimental Method

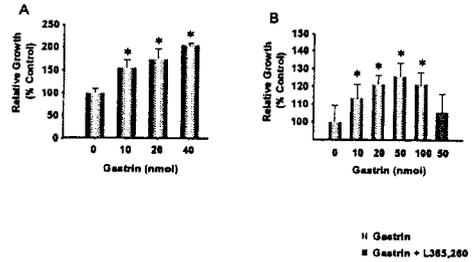
- Studies were performed utilizing the human esophageal adenocarcinoma cell line SEG-1.
- This cell line was derived from human esophageal adenocarcinoma in the setting of GERD-associated Barrett's esophagus.
- In these studies, we used the 17-amino acid  $\alpha$ -amidated form of gastrin (G17).



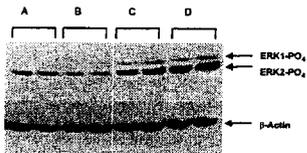
### Confocal Microscopy



### Growth Assays in SEG-1 Cells



### MAP Kinase Signaling



### Study Conclusion

The presence of functional gastrin receptors on esophageal adenocarcinoma cells indicates that gastrin may play a role in the pathogenesis of esophageal adenocarcinoma. This raises the possibility that secondary hypergastrinemia associated with proton pump inhibitor therapy may stimulate the proliferation of pre-existing esophageal adenocarcinoma.