

Core Lecture: GERD and Barrett's Esophagus

John M. Wo, M.D.

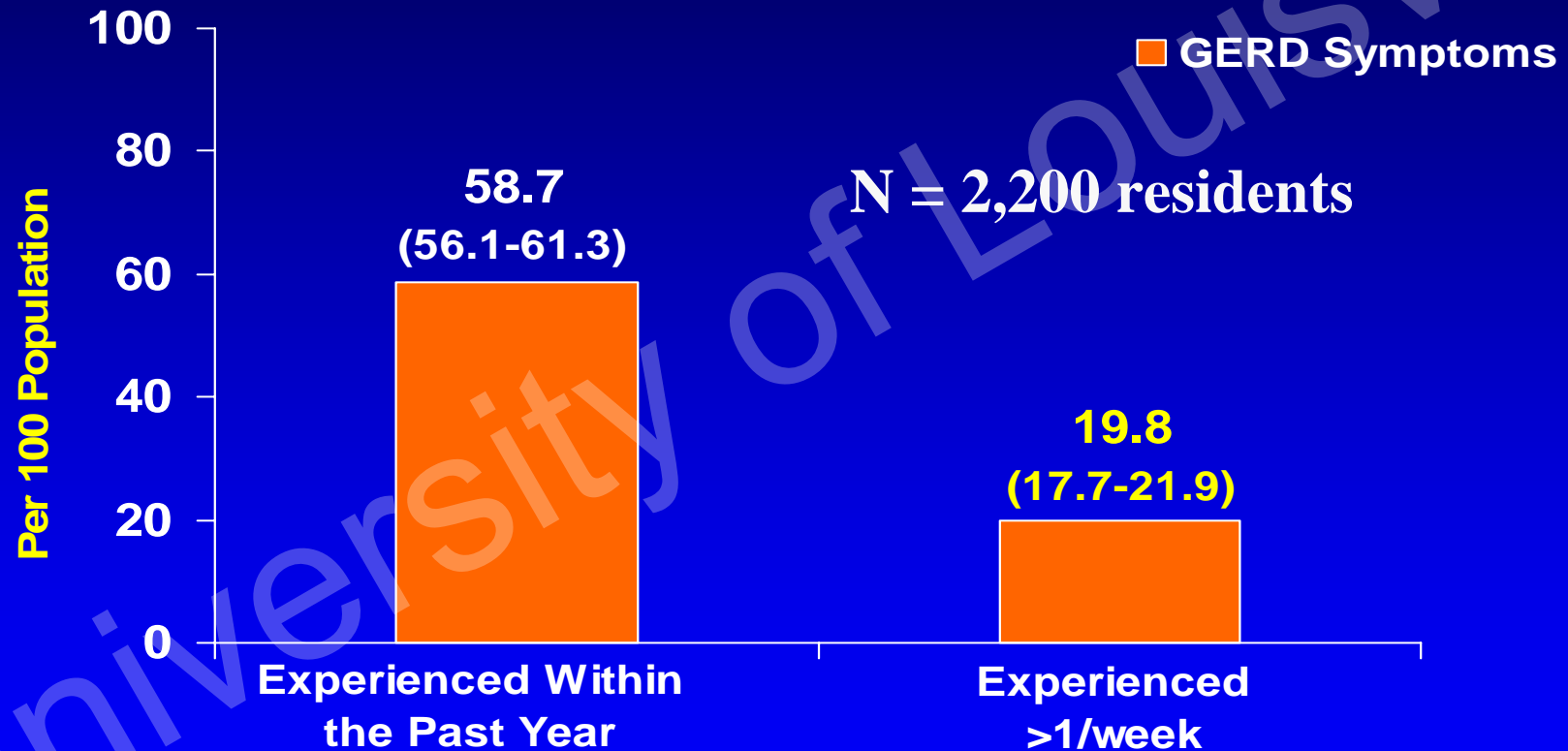
Director, Swallowing and Motility Center

Division of Gastroenterology/Hepatology

January 4, 2006



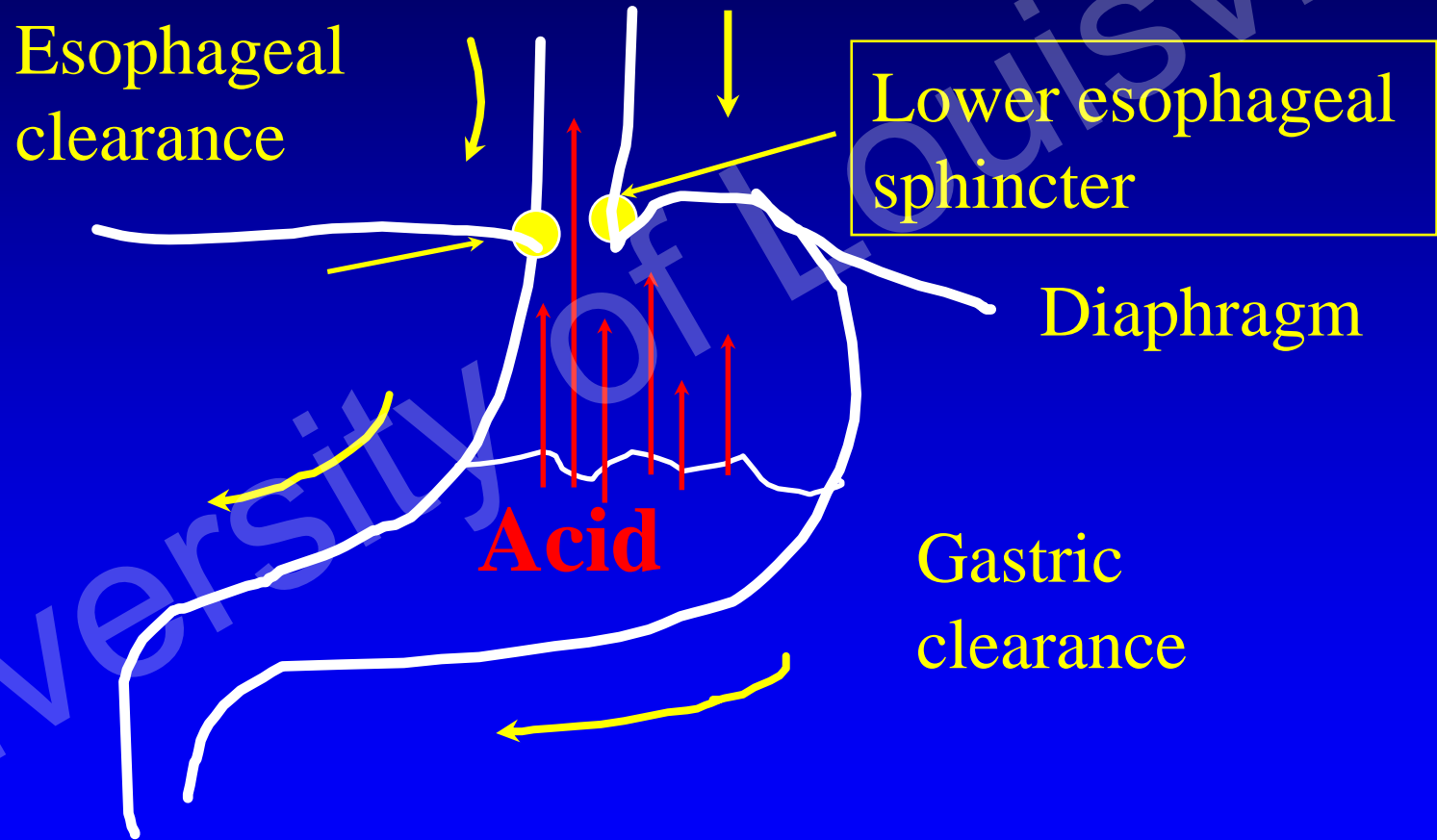
Prevalence of GERD Symptoms: The Olmsted County Study*



*Data collected by self-report questionnaire.

Locke et al. *Gastroenterology*. 1997;112:1448-1456.

Protection from Acid Reflux



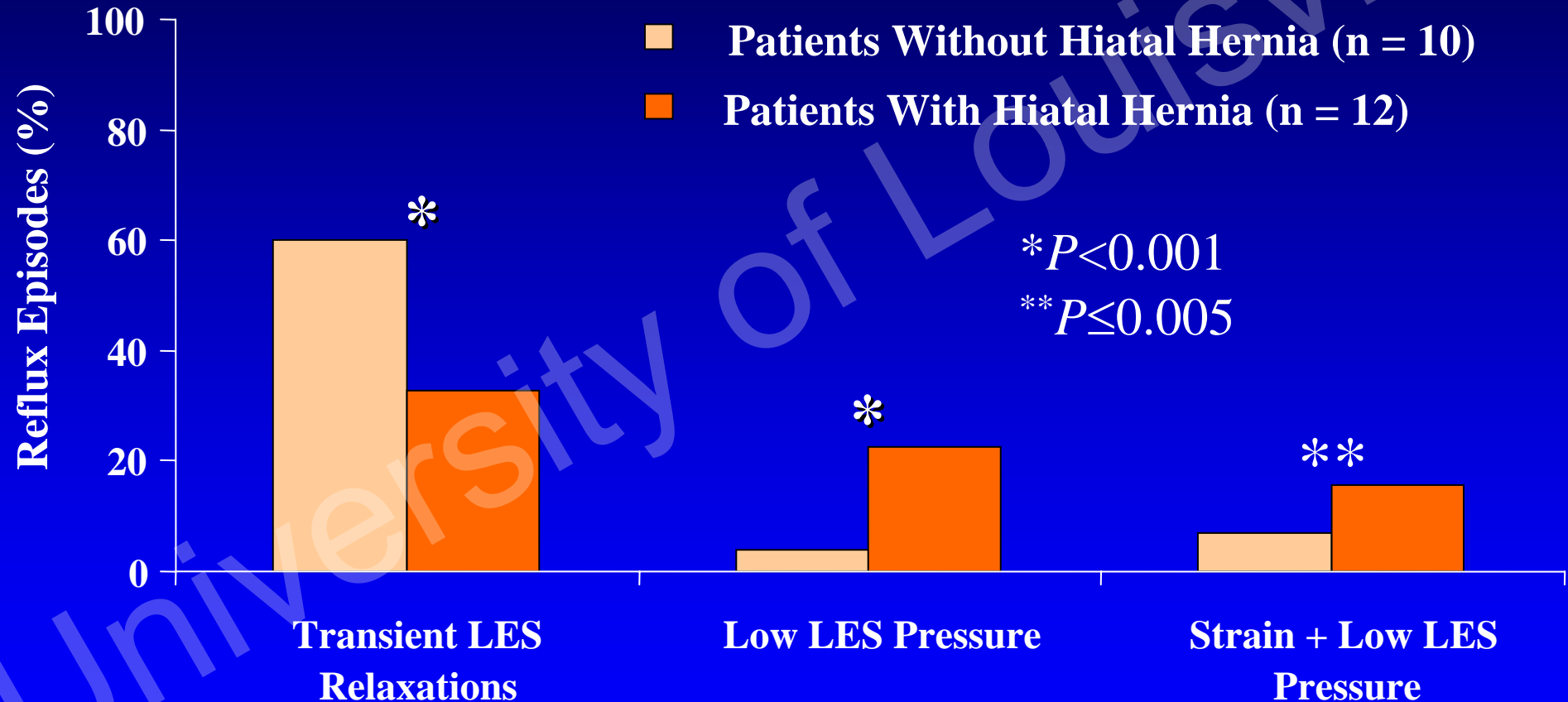
Significant of Intragastric pH >4 in GERD

- Pepsin inactive at pH >4
- Most bile acids and pancreatic enzymes inactive at pH >4
- Injury rare at pH >4

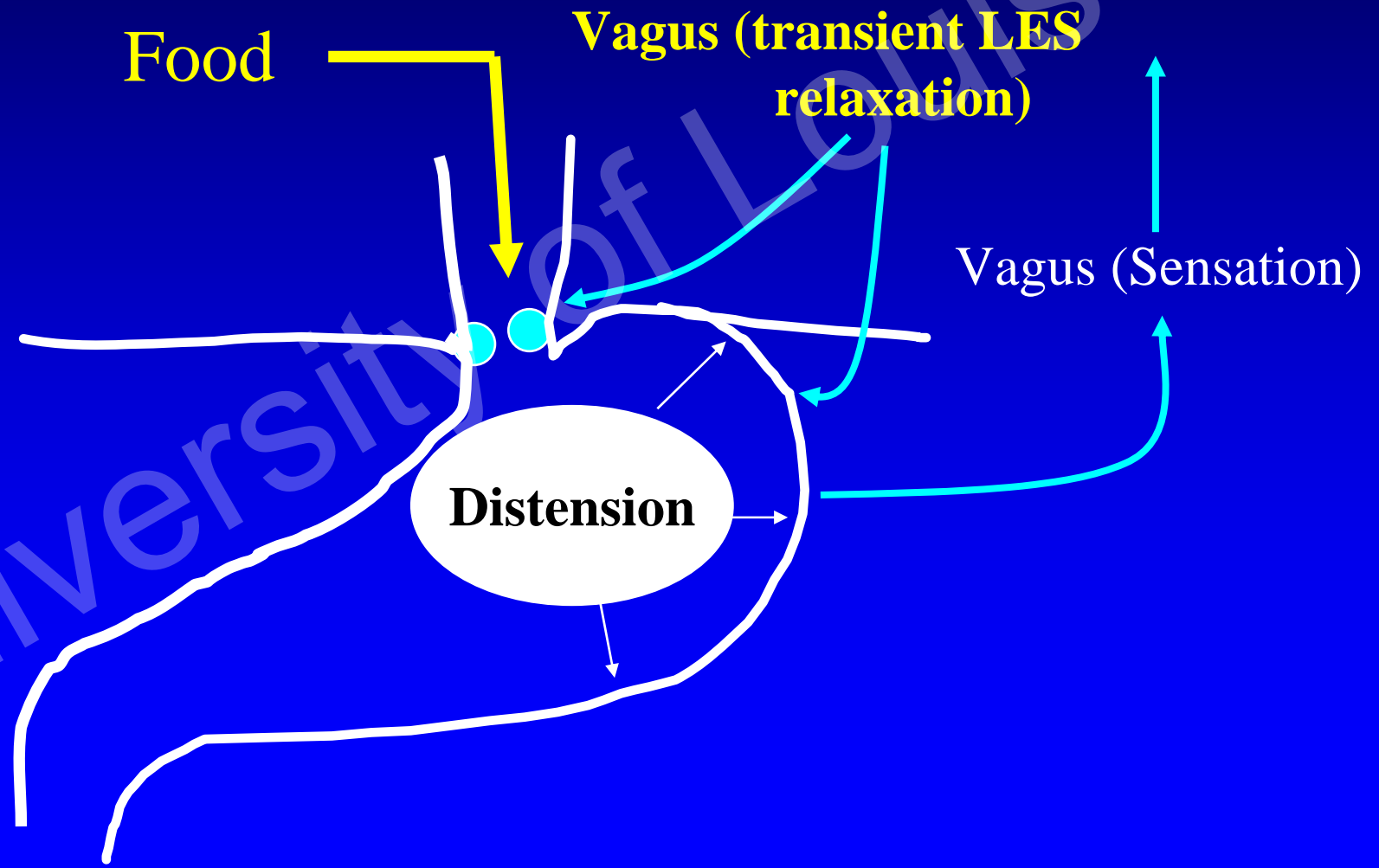
Hunt. *Arch Intern Med.* 1999;159:649-657.

Smith et al. *Gastroenterology.* 1989;96:683-689.

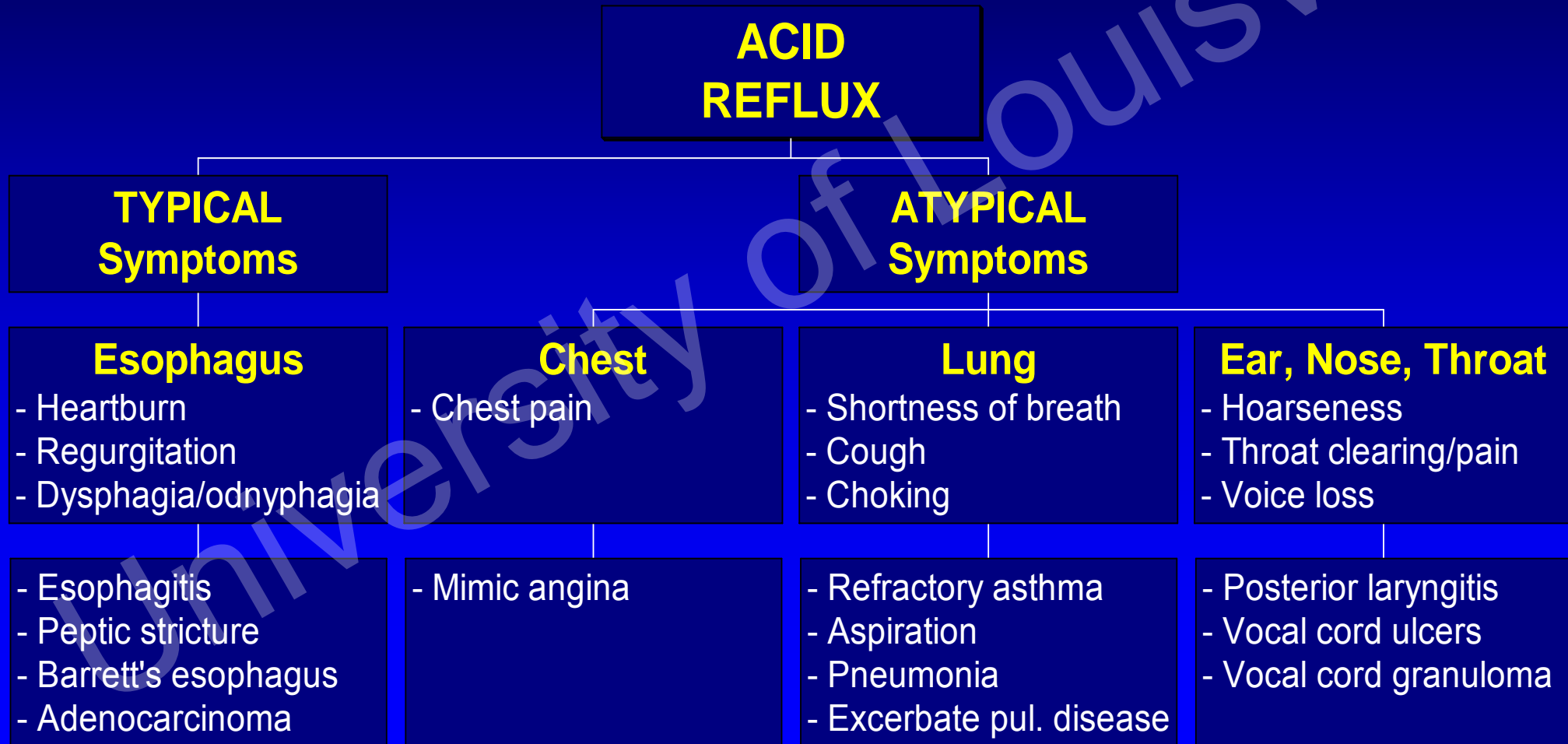
Three Mechanisms Causing Pathologic Acid Reflux



Transient LES Relaxation



Acid Reflux is More Than Just Heartburn



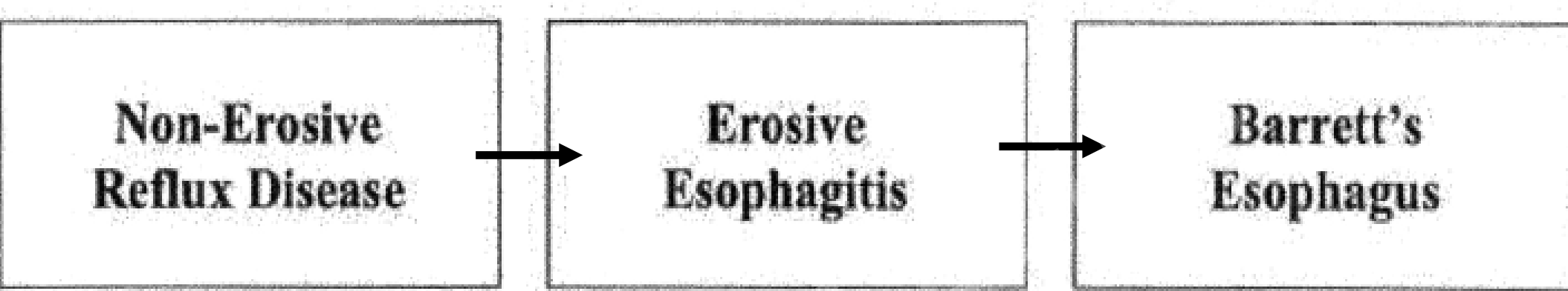
Typical vs. Atypical GERD

	<u>Typical</u>	<u>Atypical</u>
Symptoms	consistent	variable
Esophagitis/Barrett's	common	uncommon
Causes	reflux	reflux + others
Treatment response	rapid	variable
Therapy	step-therapy	more aggressive + longer duration

Empiric Therapy is Appropriate in Patients with Typical Heartburn

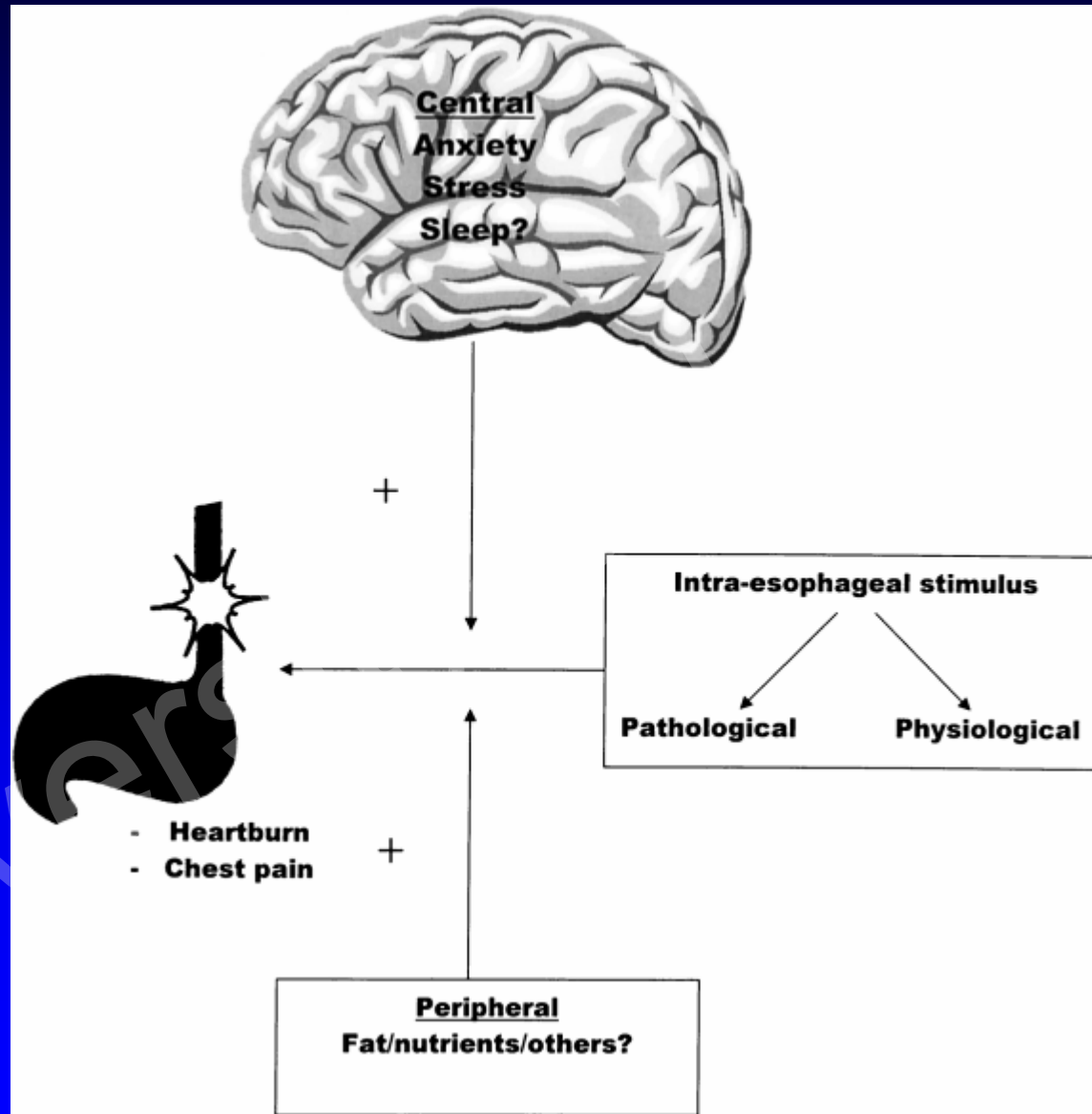


Old Conceptual Model for GERD

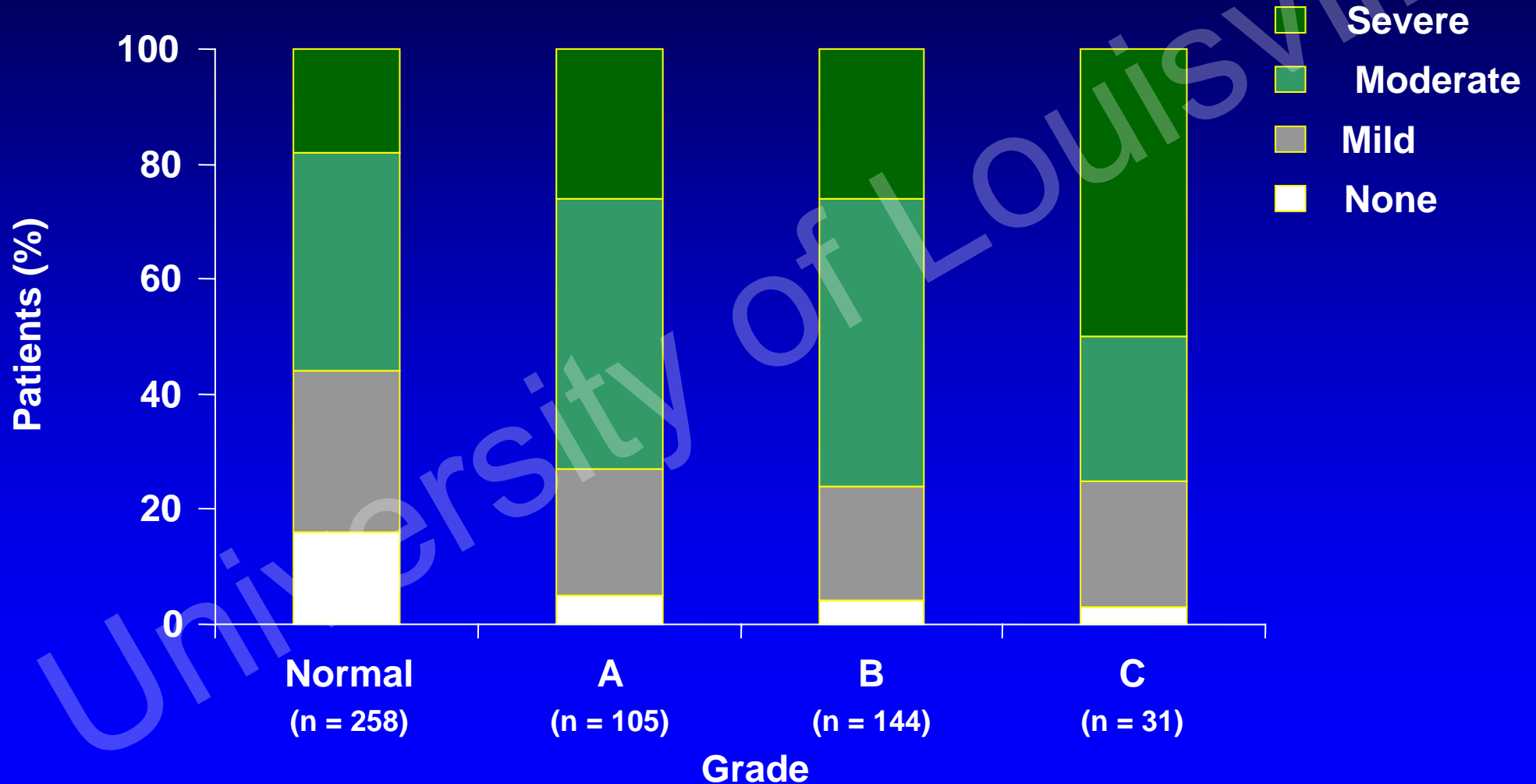


Brain-Gut Axis for Non-Erosive Reflux Disease

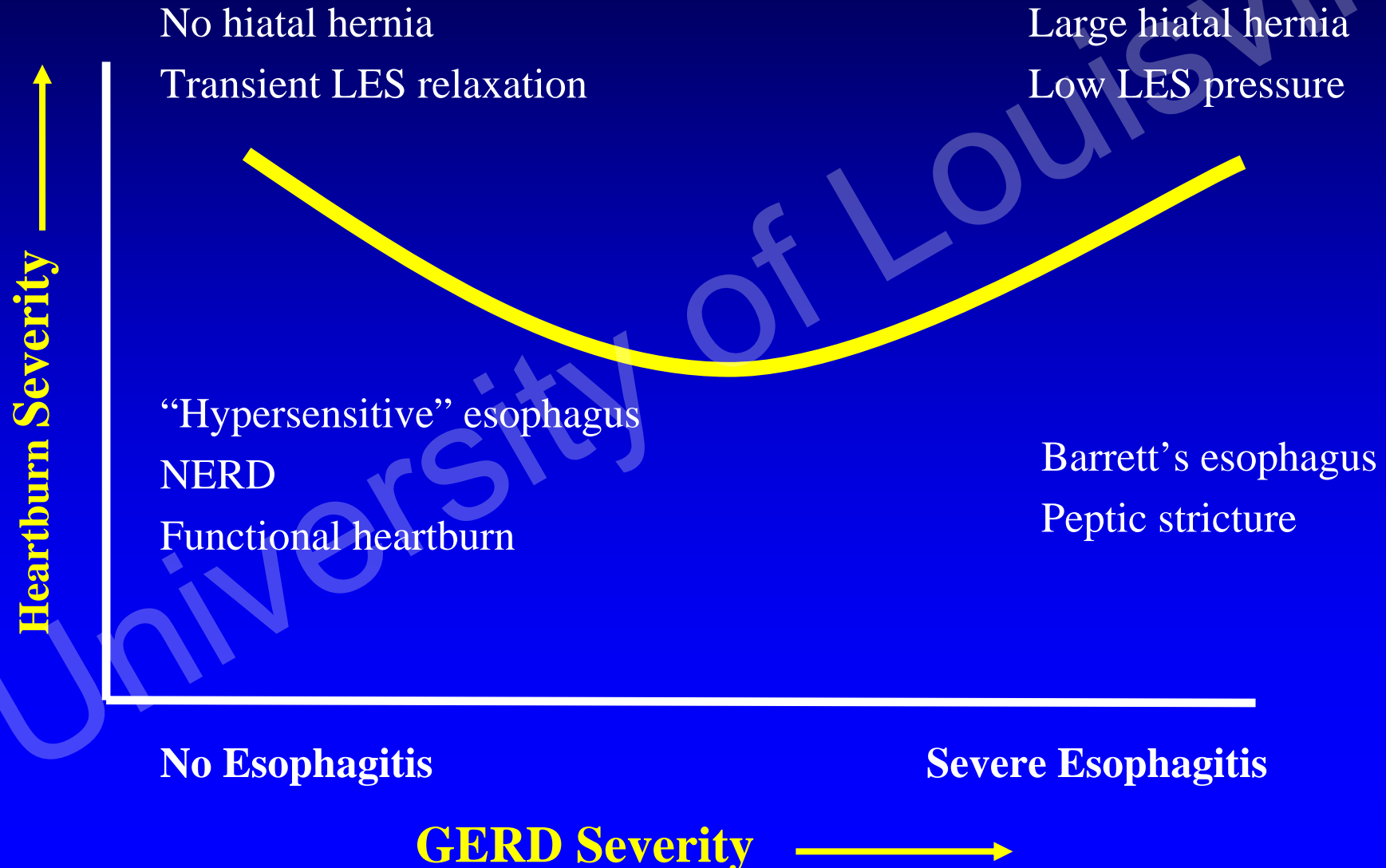
Acid
Hypersensitivity



Heartburn Severity Does Not Correlate with Erosive Esophagitis



Heartburn Severity May Not Correlate with Disease Severity in GERD



Eight Reasons Why Acid Suppression Not Working

1. Not taking the medication correctly
2. Inadequate acid suppression
3. Large hiatal hernia
4. Impaired esophageal motility
5. Gastroparesis
6. Wrong diagnosis
7. Non-acidic reflux
8. Hypersecretion of acid

Diagnostic Tests for GERD

	Sensitivity (%)	Specificity (%)
Empiric Trial With a PPI	70-80	60-85
Endoscopy	40-70	90-95
Esophageal pH Monitoring	70-90	80-95
Barium Swallow	30-35	60-75
Esophageal Manometry	15-30	20-40

When is Upper Endoscopy Indicated?

1. Alarm symptoms of GERD
 - Dysphagia, odynophagia, GI bleed, weight loss
2. Refractory heartburn
3. Recurrent disease
4. At risk for Barrett's esophagus

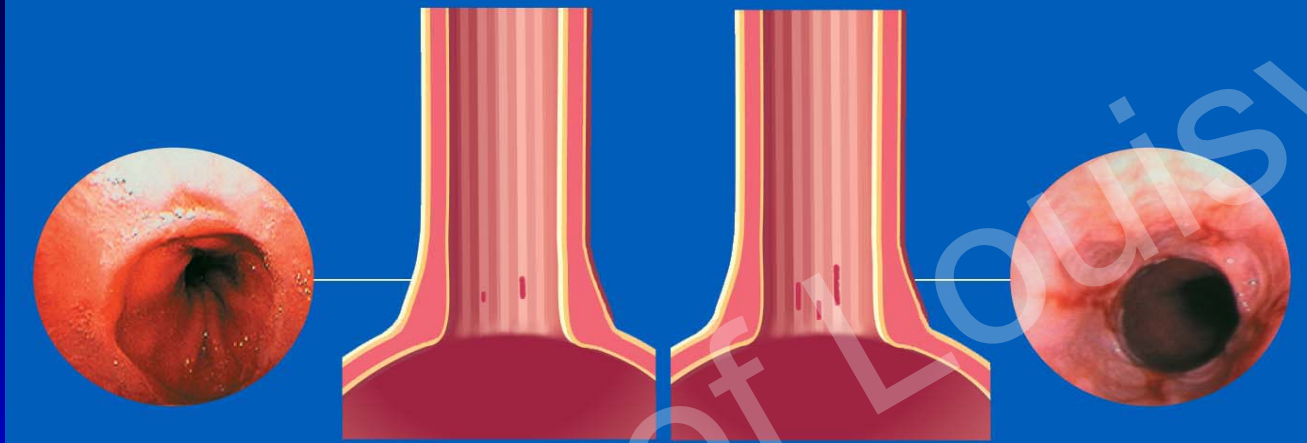
GERD Complications

- Esophagitis
- Esophageal stricture
- Barrett's esophagus
- Adenocarcinoma

LA Classification of Erosive Esophagitis

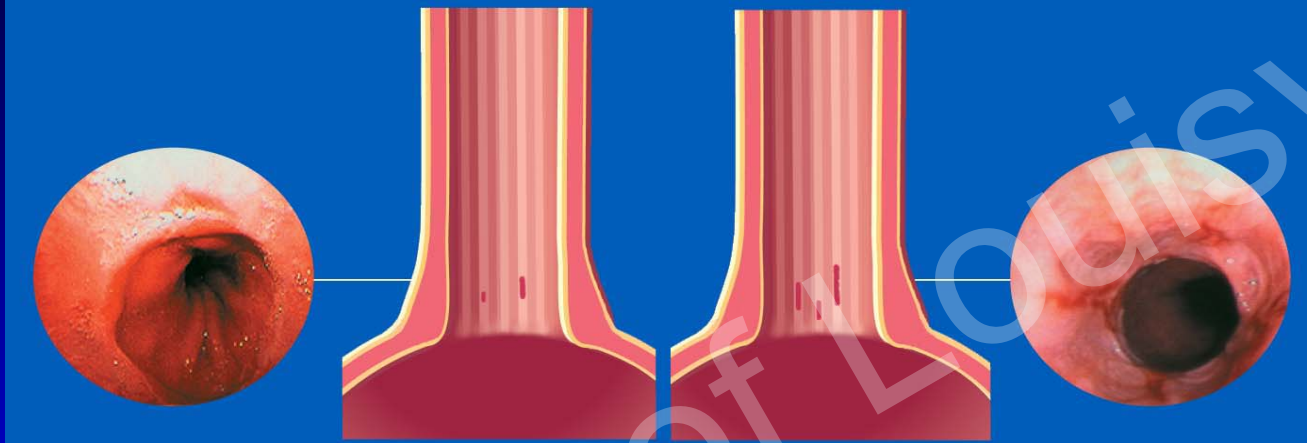
LA Grade A

Isolated mucosal breaks ≤ 5 mm long



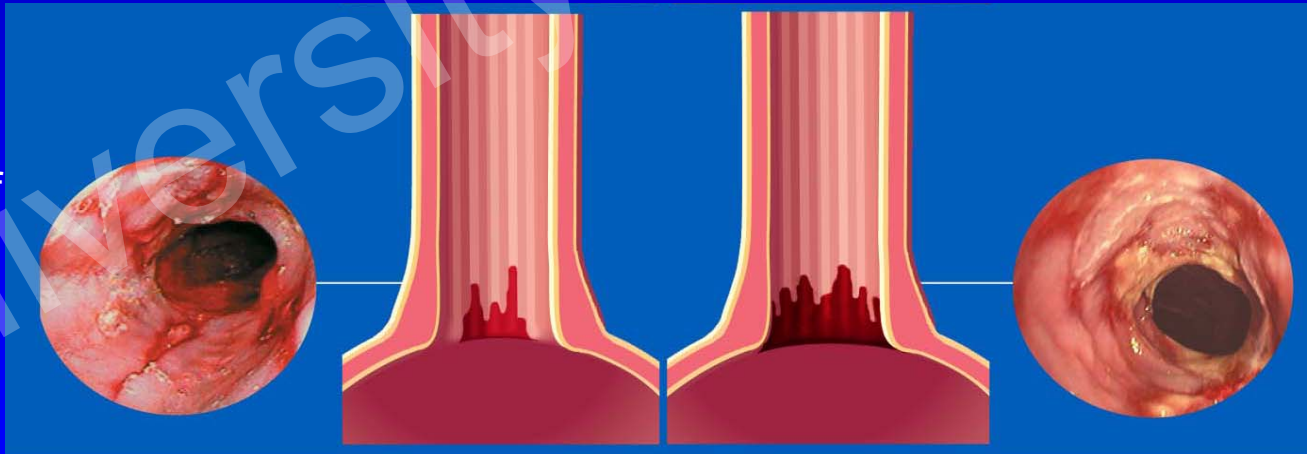
LA Grade B

Isolated mucosal breaks > 5 mm long



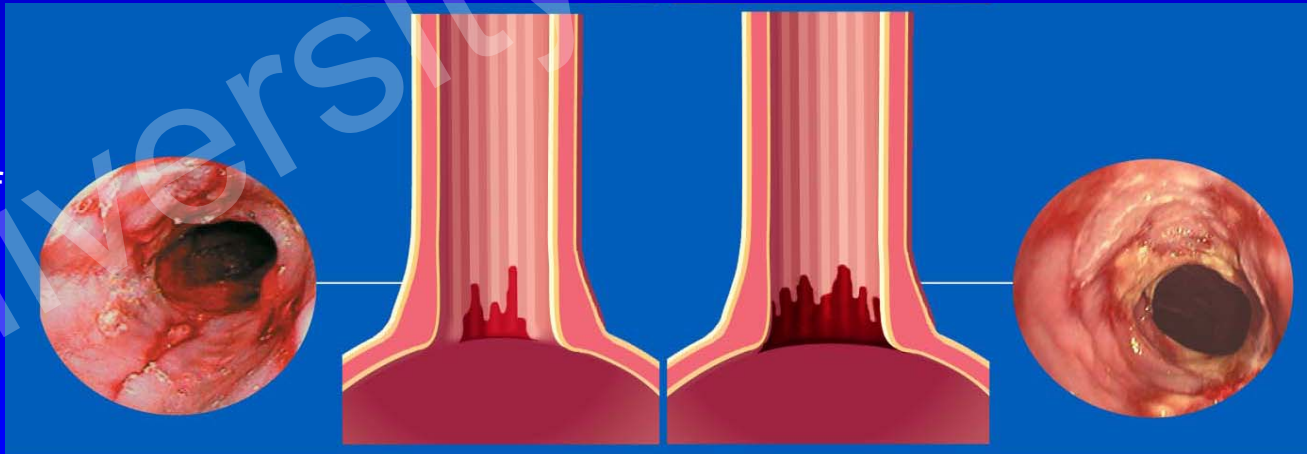
LA Grade C

Mucosal breaks bridging the tops of folds but involving $< 75\%$ of the circumference



LA Grade D

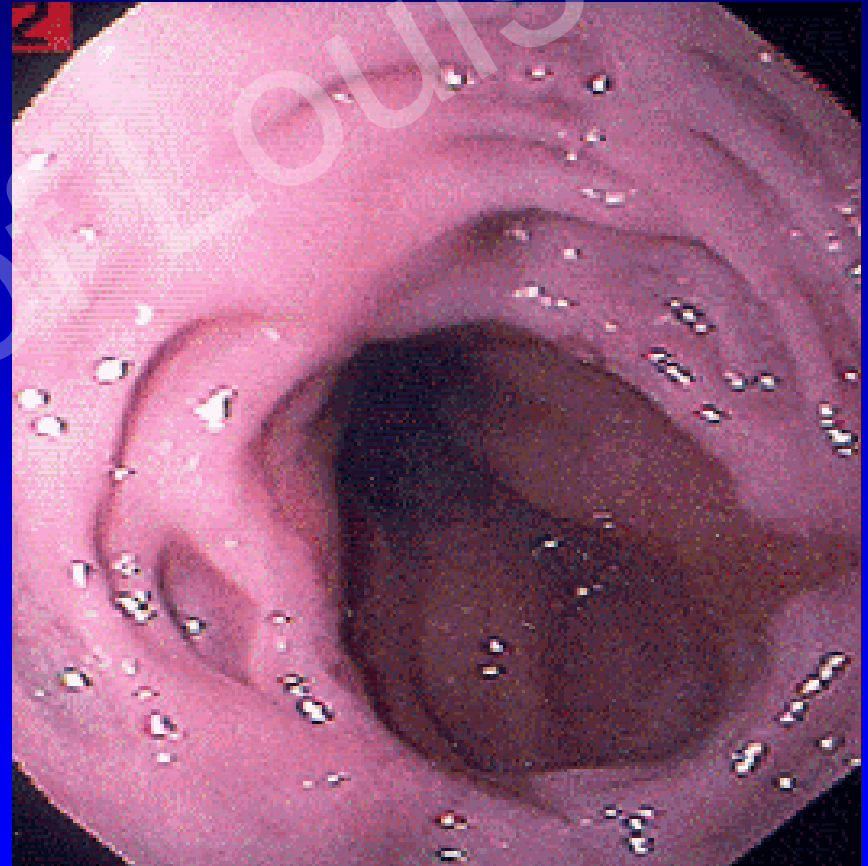
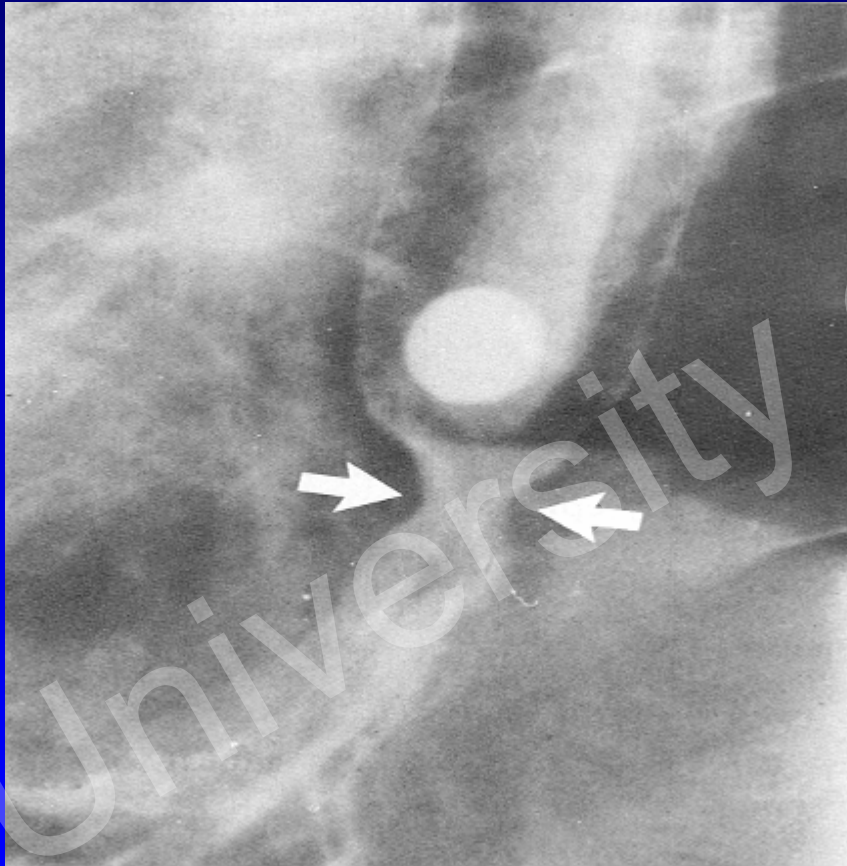
Mucosal breaks bridging the tops of folds and involving $> 75\%$ of the circumference



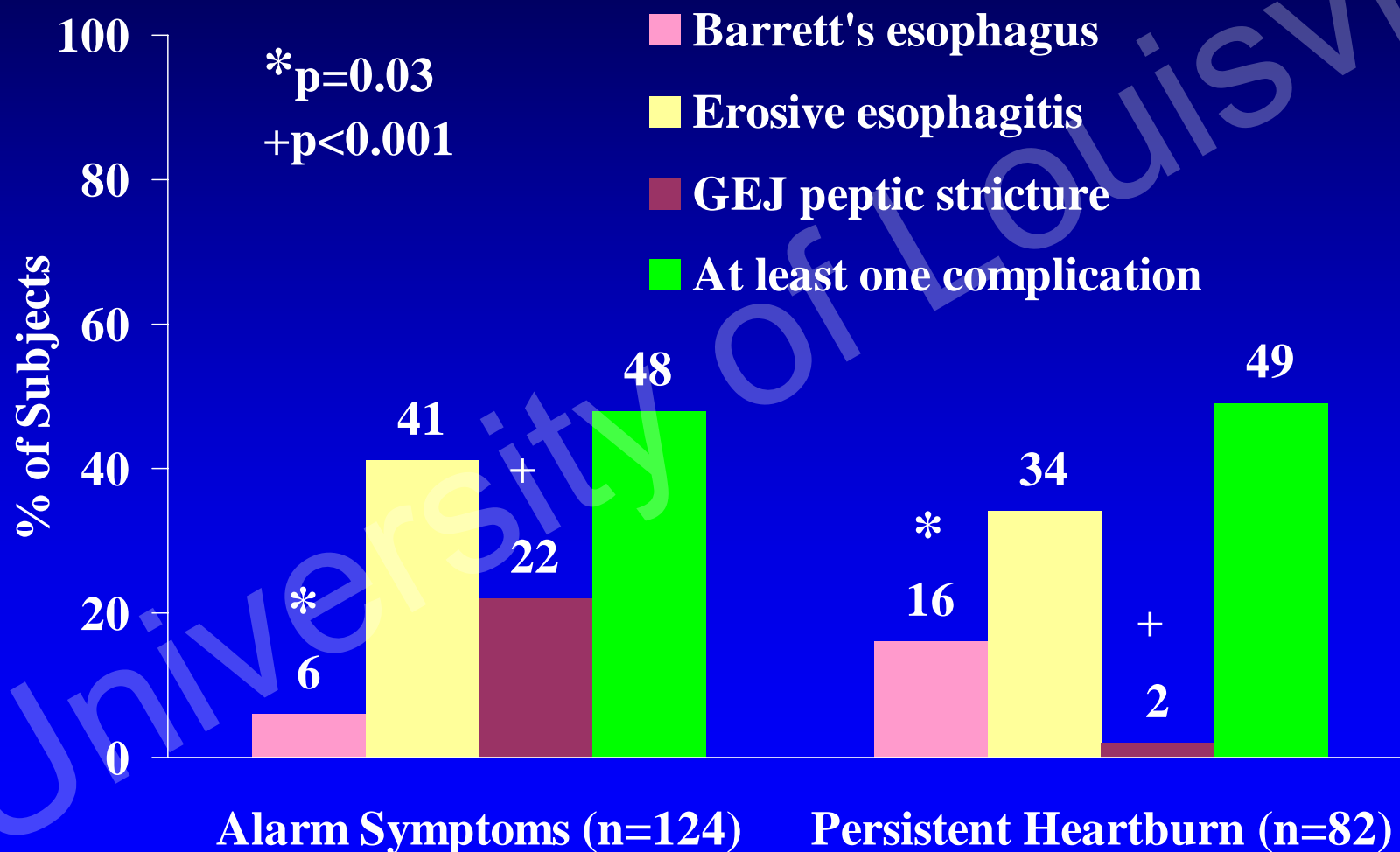
LA Class C Esophagitis



Esophageal Peptic Stricture



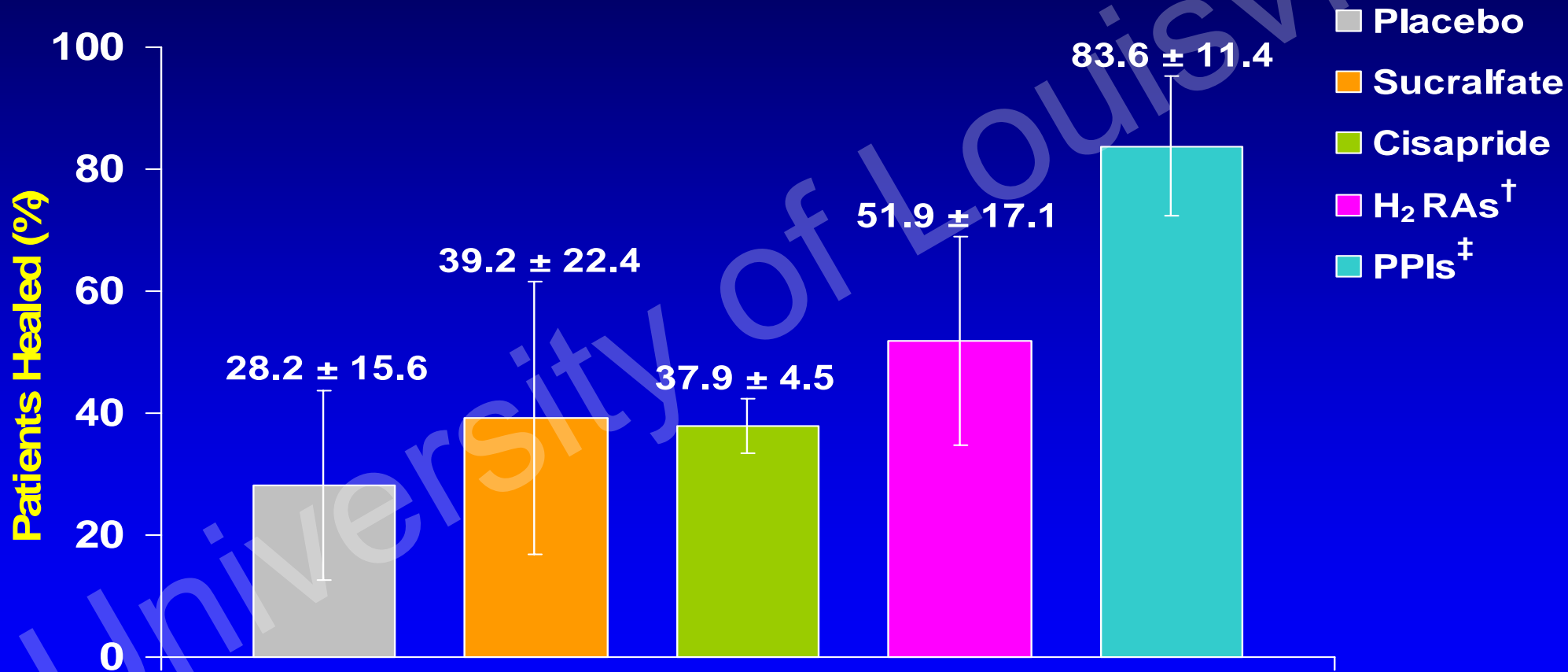
Prevalence of GERD Complication



Treatment Options for GERD

- Lifestyle and dietary modification
- **Medical**
 - **Acid suppression**
 - Prokinetic
- Surgical

Healing of Erosive Esophagitis



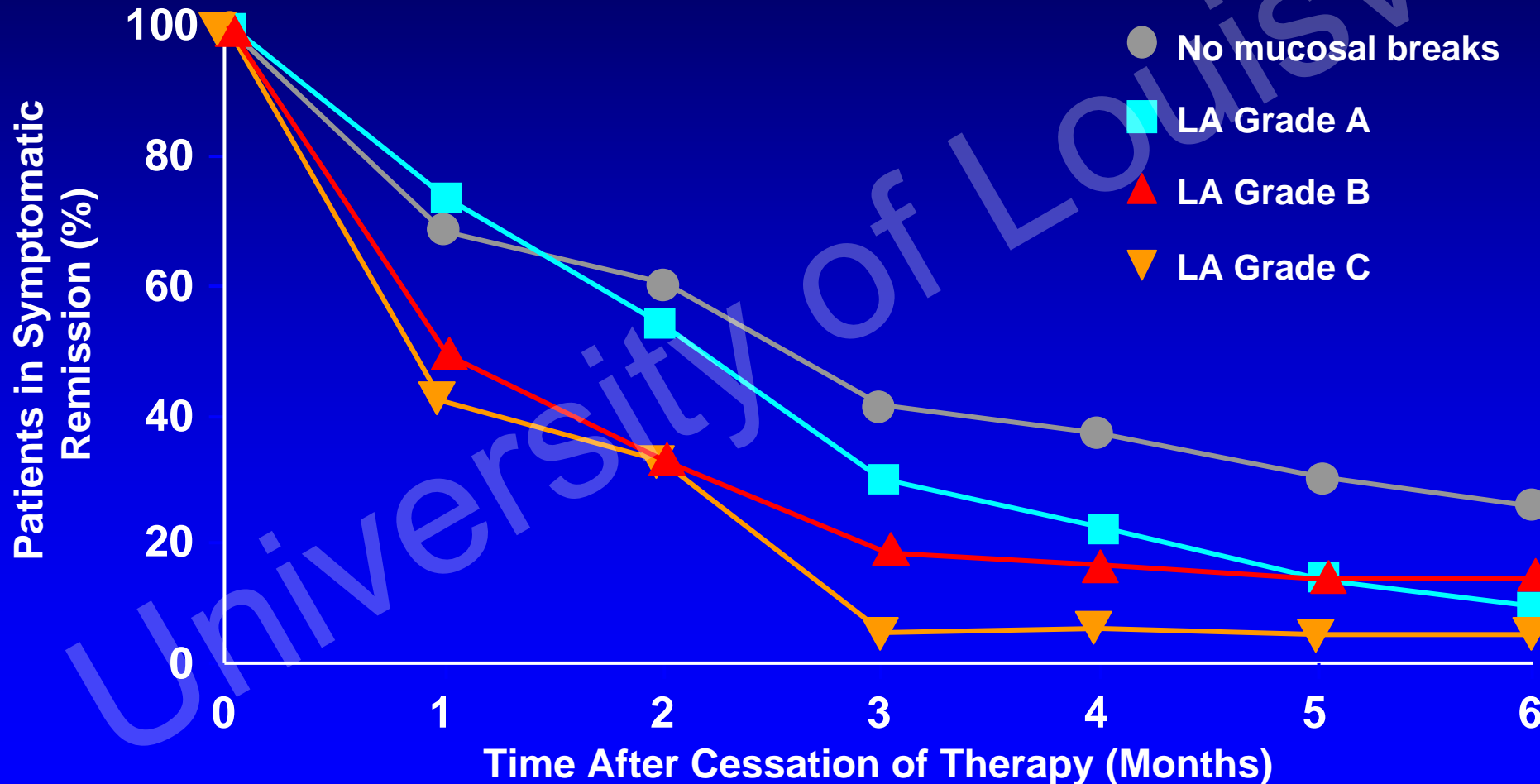
Meta-analysis from 23 placebo-controlled trials with grade II to grade IV EE.

Chiba et al. *Gastroenterology*. 1997;112:1798-1810.

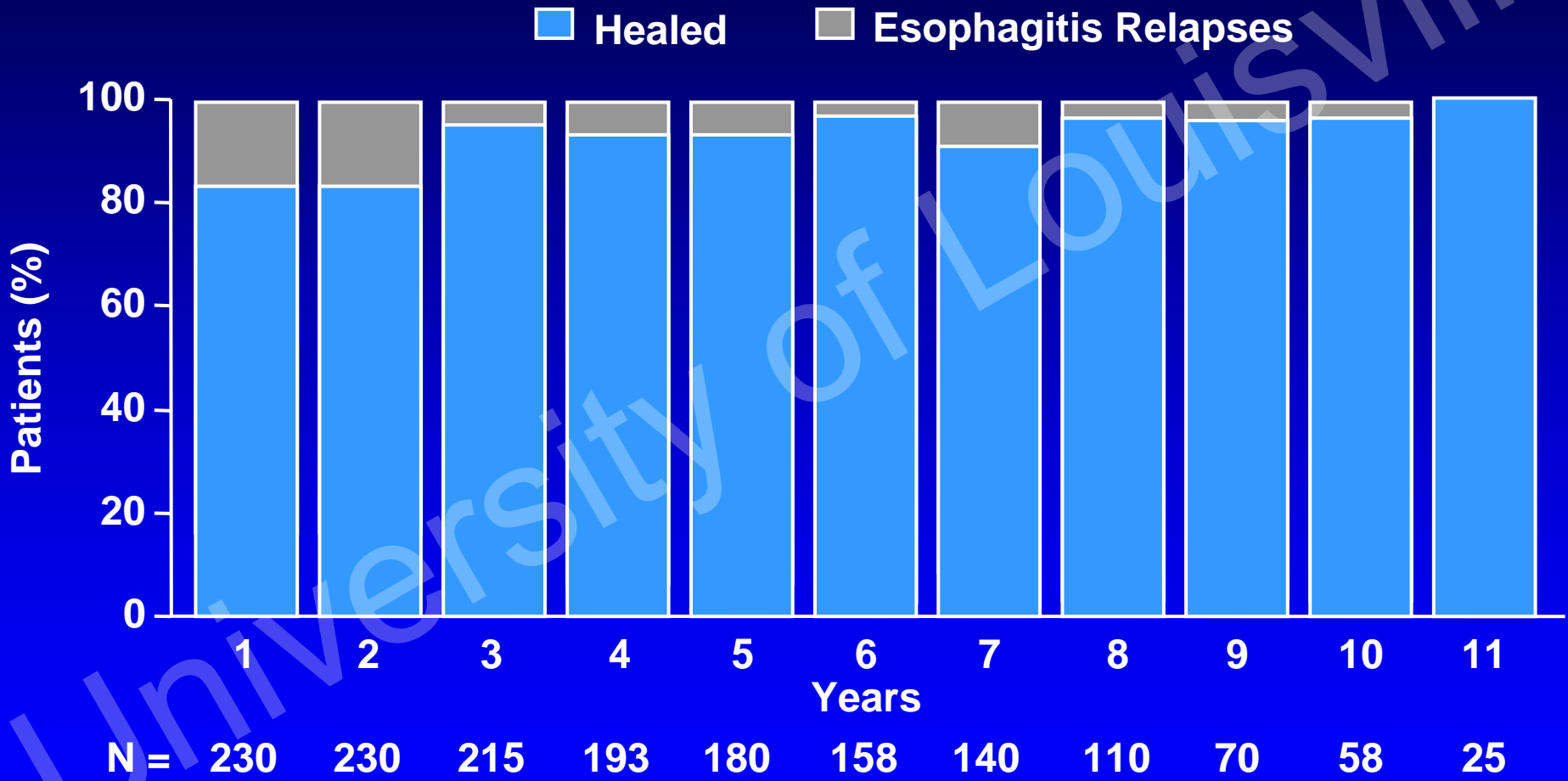
Formulations for Proton Pump Inhibitors

- Pill & Capsule
- Powder
- Chewable
- Non-coated with bicarbonate
- Intravenous injection

GERD is a Chronic Condition that is Likely to Relapse



Long-Term PPI for Reflux Esophagitis

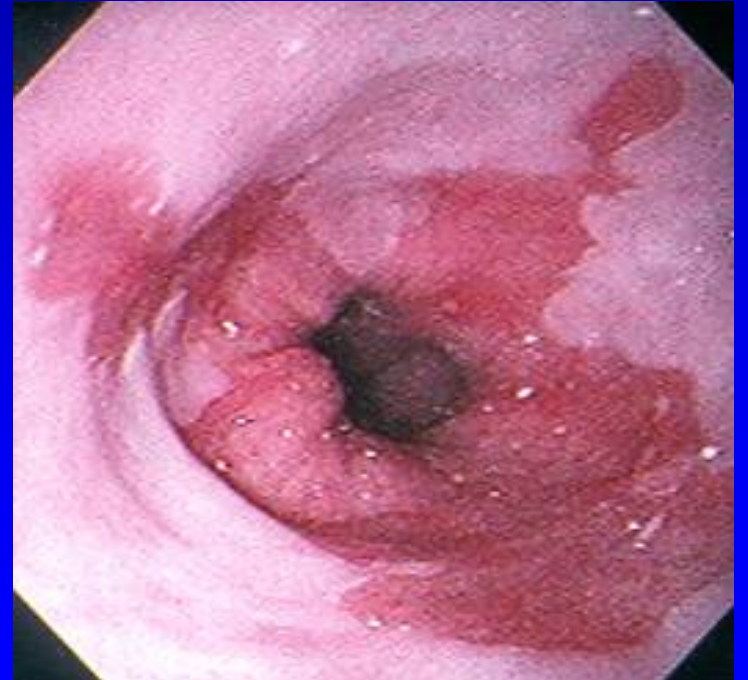


Omeprazole ≥ 20 mg.
Klinkenberg-Knol et al. *Gastroenterology*. 2000;118:661-669.

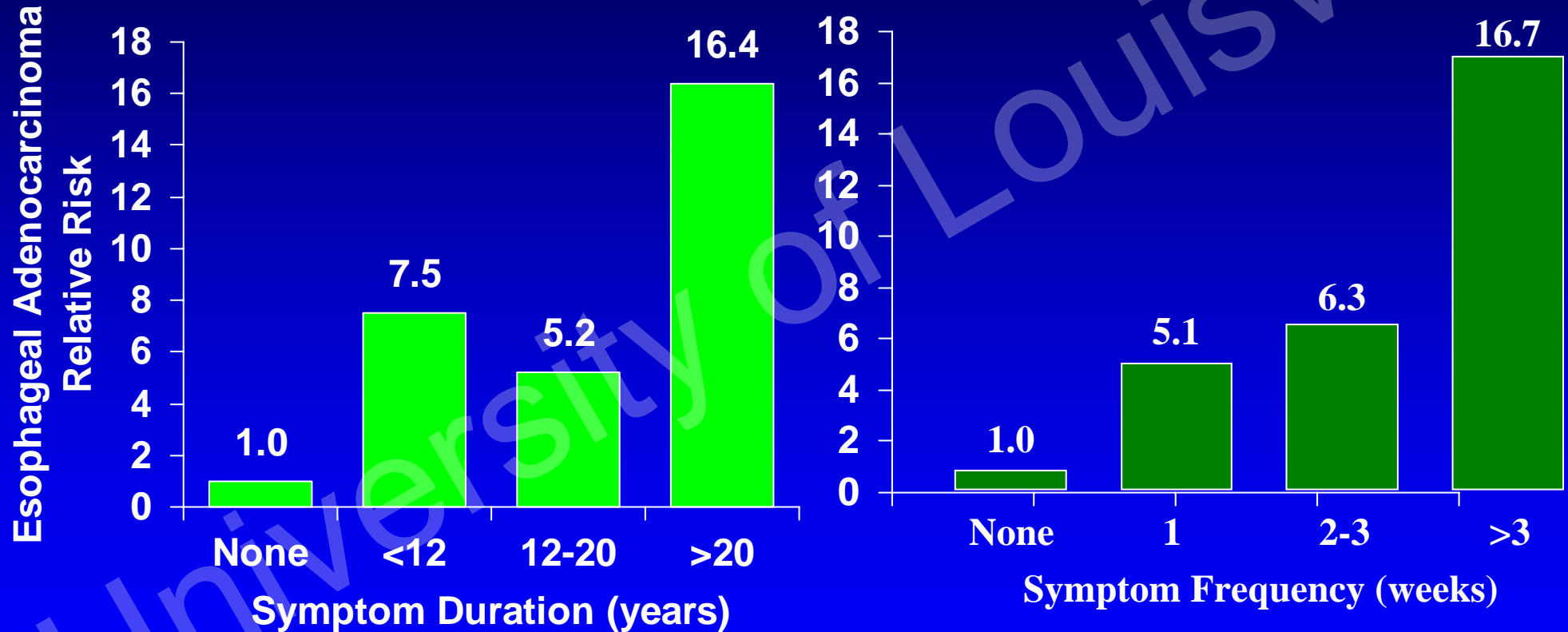
Summary (GERD)

- Pathophysiologic mechanisms of GERD are many
- All GERD patients are not the same
 - NERD vs. EE vs. BE
- Acid suppression is the first-line of therapy
- Reflux complications require maintenance therapy

Barrett's Esophagus



Heartburn Duration and Frequency is Associated with Esophageal Adenocarcinoma



N = 1,438 (n = 189 with esophageal adenocarcinoma).

Lagergren et al. *N Engl J Med*. 1999;340:825-831.

Risk of Adenocarcinoma in Patients with Barrett's Esophagus

- Spechler (1984) 1/175 pt-yr
- Cameron (1985) 1/442 pt-yr
- Achkar (1988) 1/166 pt-yr
- Robertson (1988) 1/56 pt-yr
- Vanderveen (1988) 1/170 pt-yr
- Hameetman (1989) 1/52 pt-yr
- Ovaska (1989) 1/55 pt-yr
- Drewitz (1995) 1/278 pt-yr

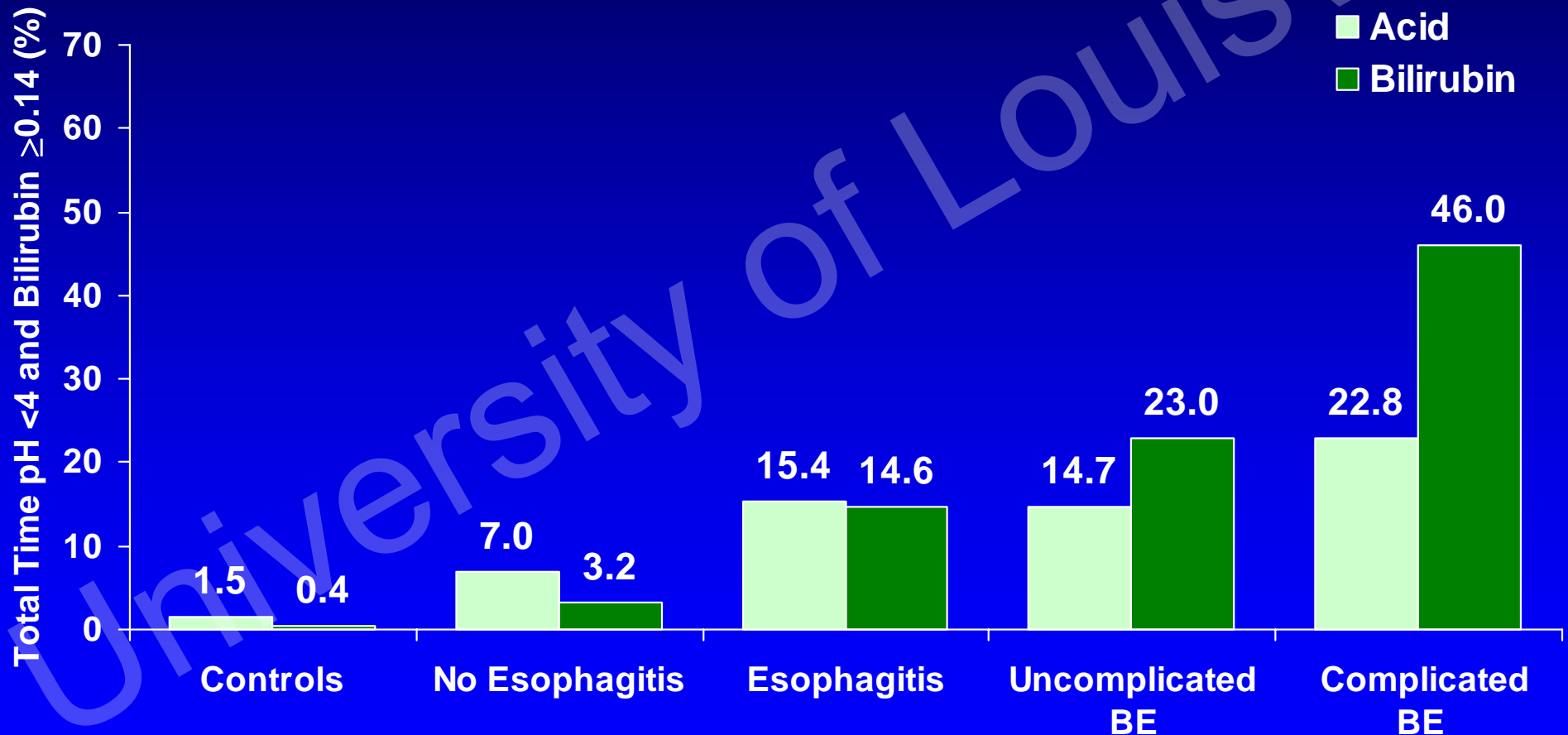
Average risk of developing adenocarcinoma: 0.4% per patient-year

“Natural” History of Barrett’s Esophagus

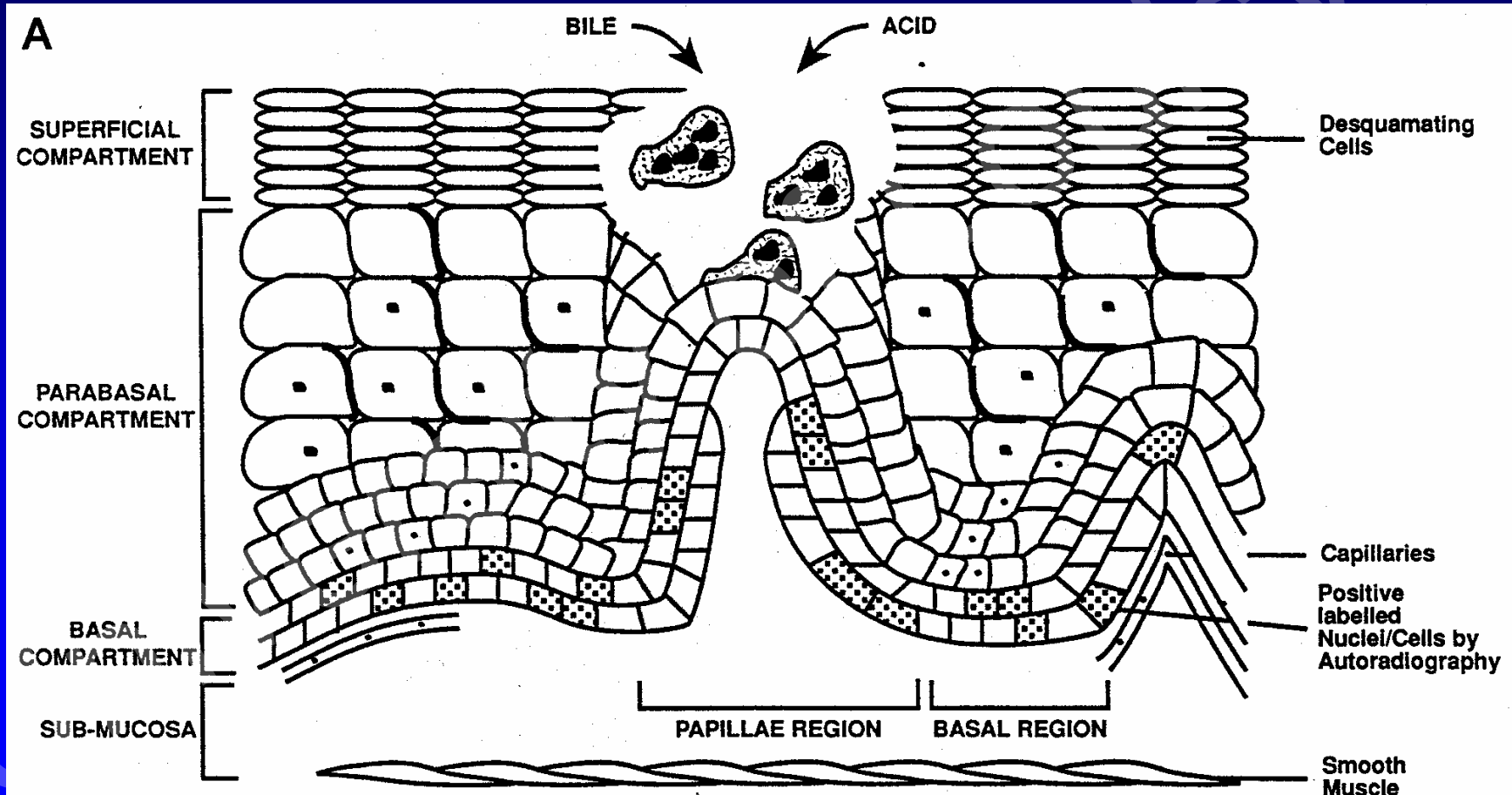
Published Data From Prospective Registry

<u>Dysplasia</u>	<u>Ca / # of pts</u>	<u>% progressed to Ca</u>	<u>F/U (yrs)</u>
None	5/150	3%	3.4-10
Low grade	8/45	18%	1.5-4.3
High grade	44/161	27%	0.2-9

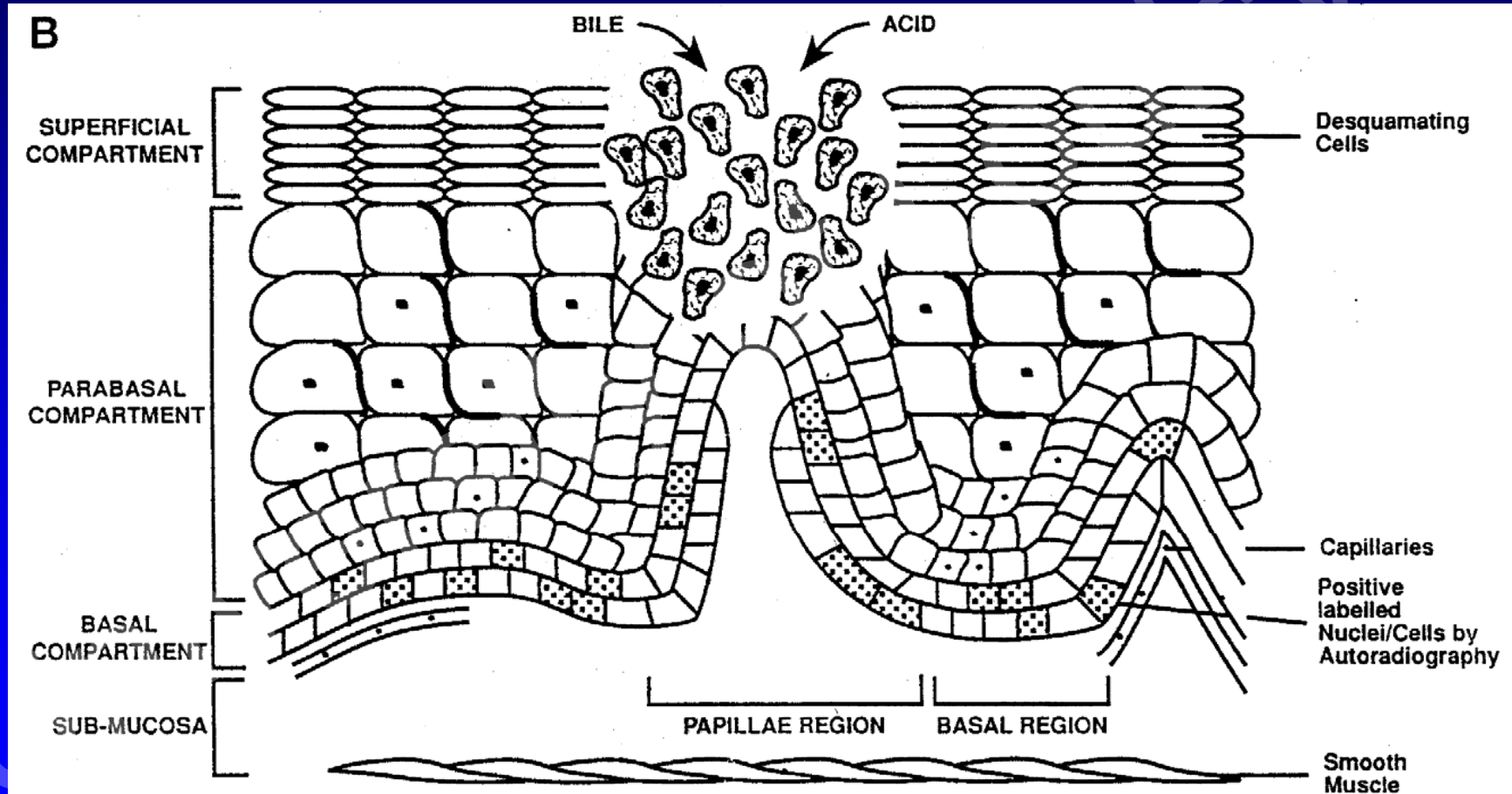
Relationship of Acid and Bile Exposure to Barrett's Esophagus



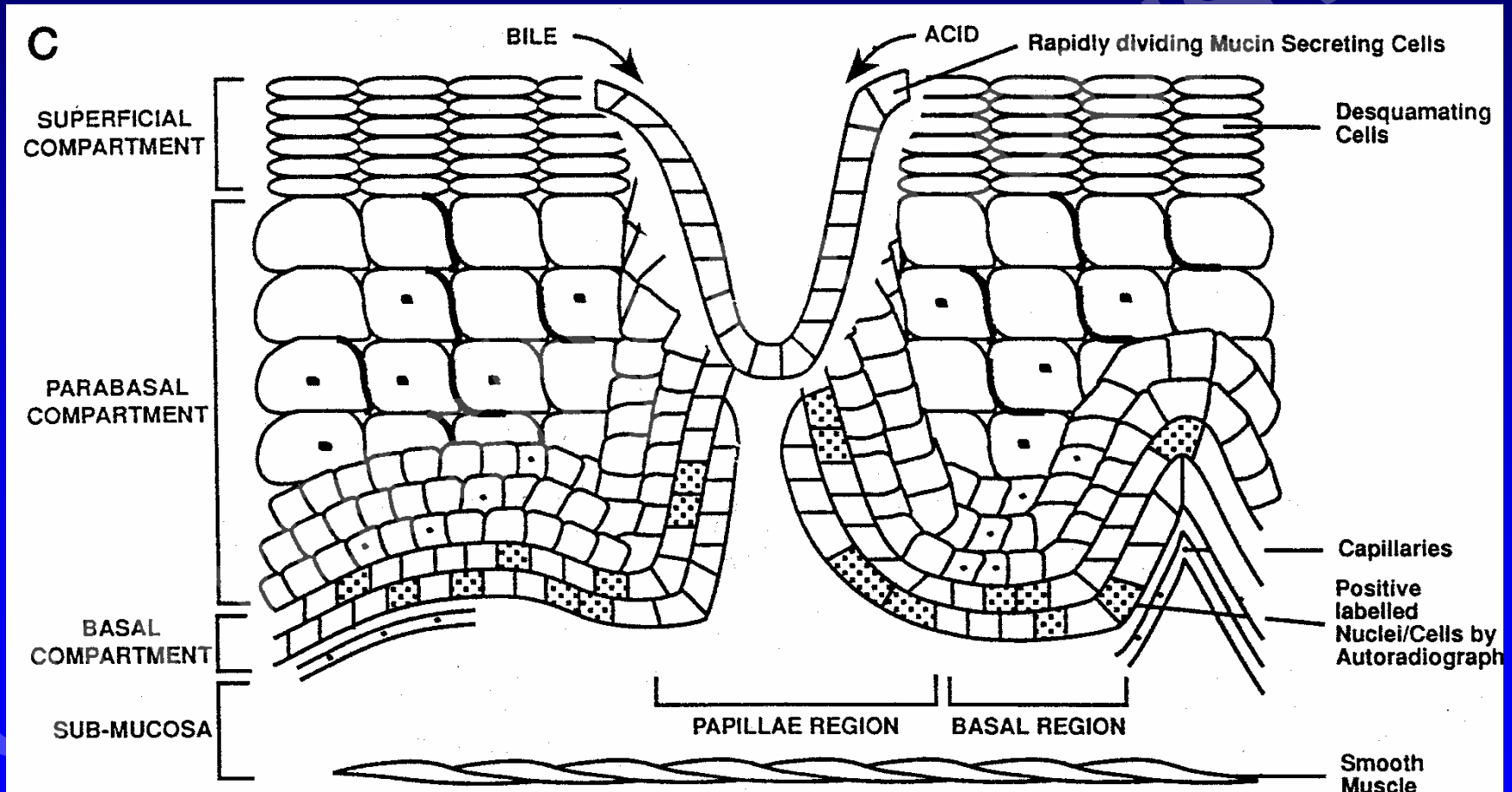
Esophagus Lining is Damaged by Acid Reflux



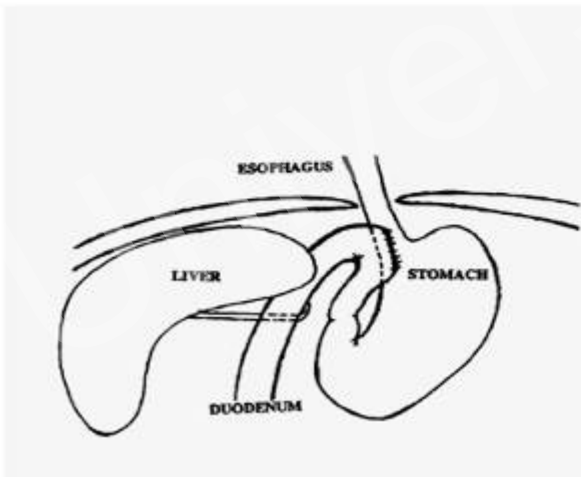
Hyperproliferation Occurs, Esophagus Stem Cells are Damaged



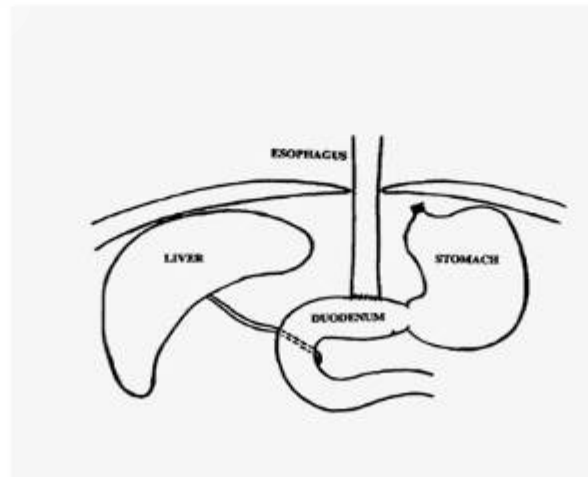
Instead of Healing with Squamous Cells, Mucous-Secreting Cells are Generated



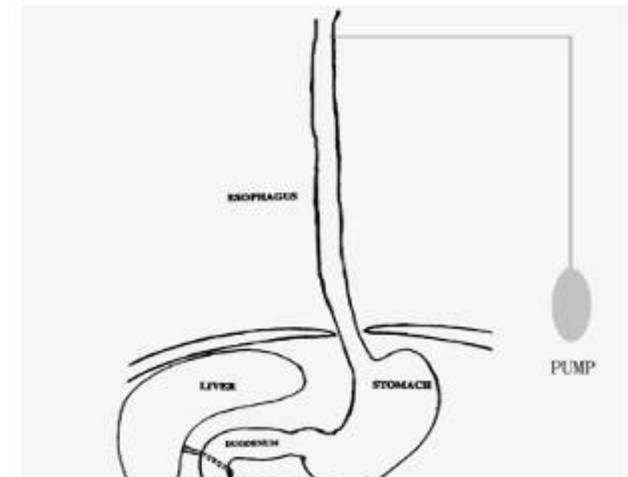
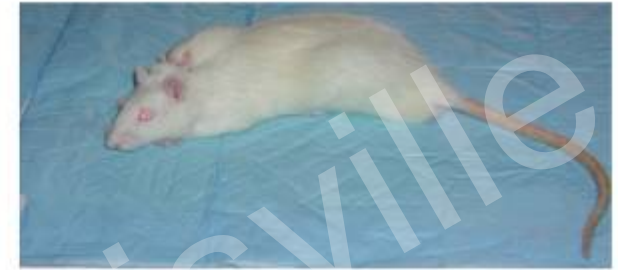
Esophagogastroduodenostomy



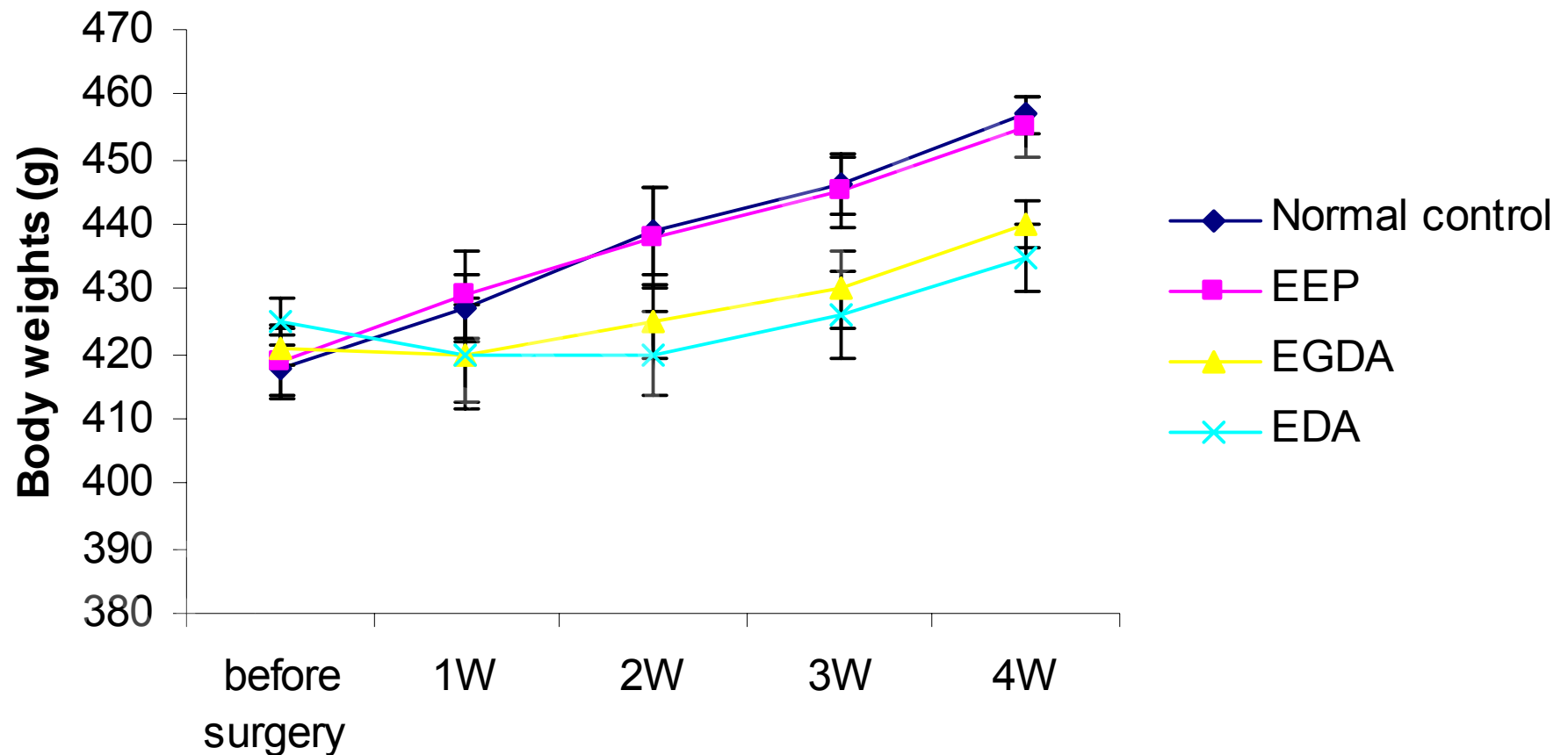
Esophagoduodenostomy



External Esophageal Perfusion

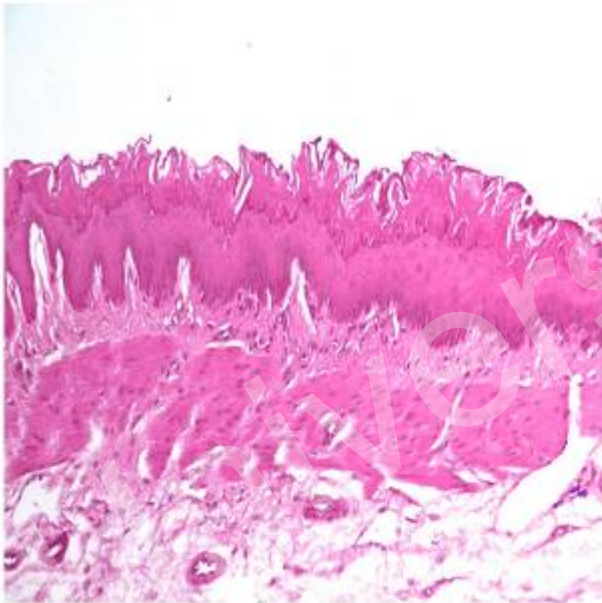


Comparing Post-Op Stress Among Animal Models of Erosive Esophagitis

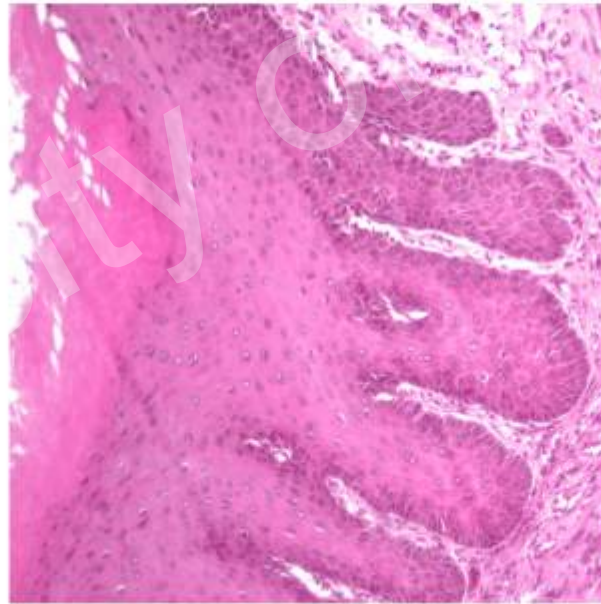


External Esophageal Perfusion Model (after 7 days)

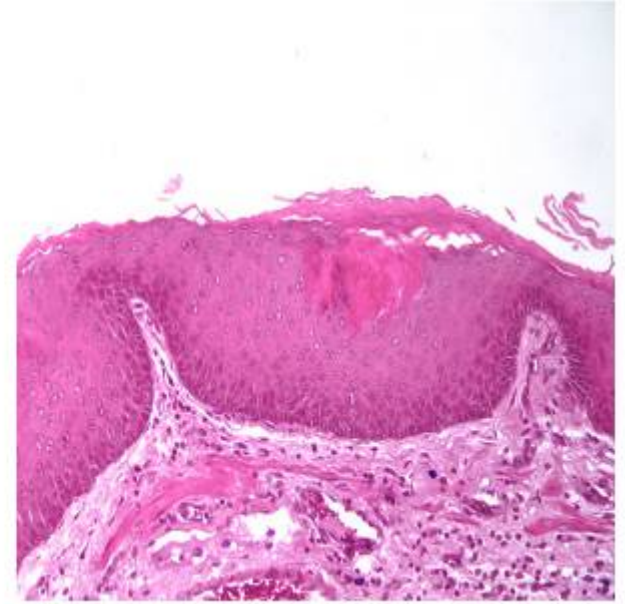
Saline Control



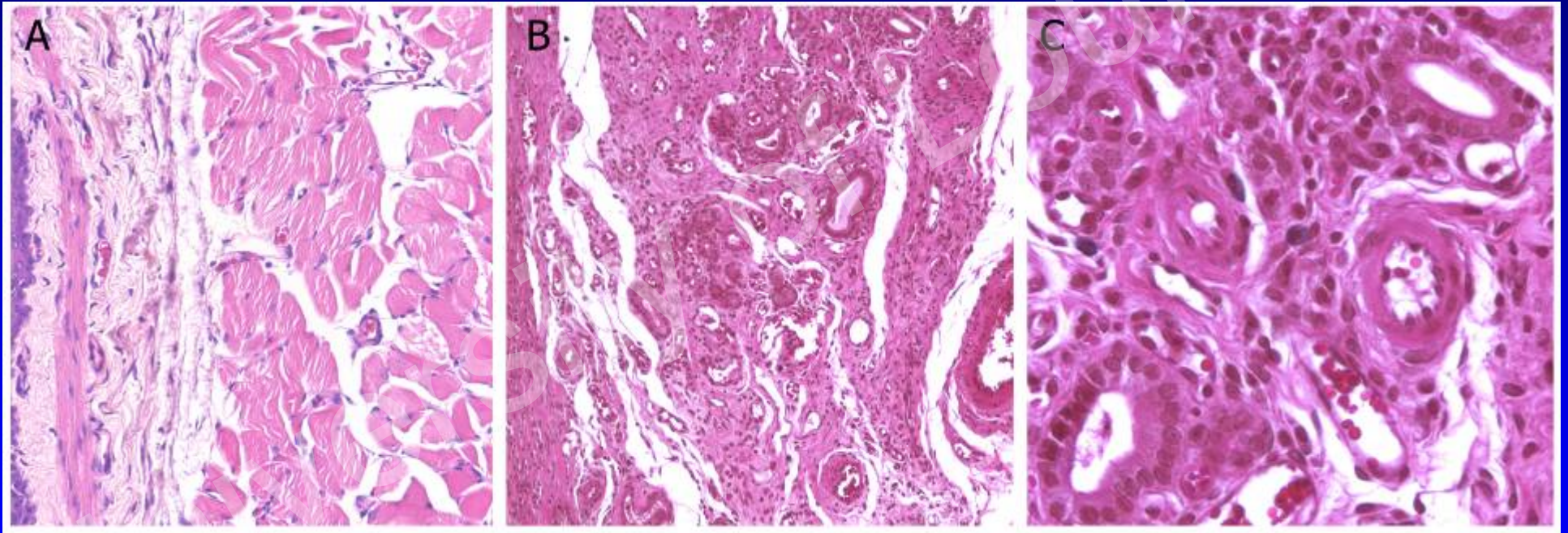
Acid



Bile

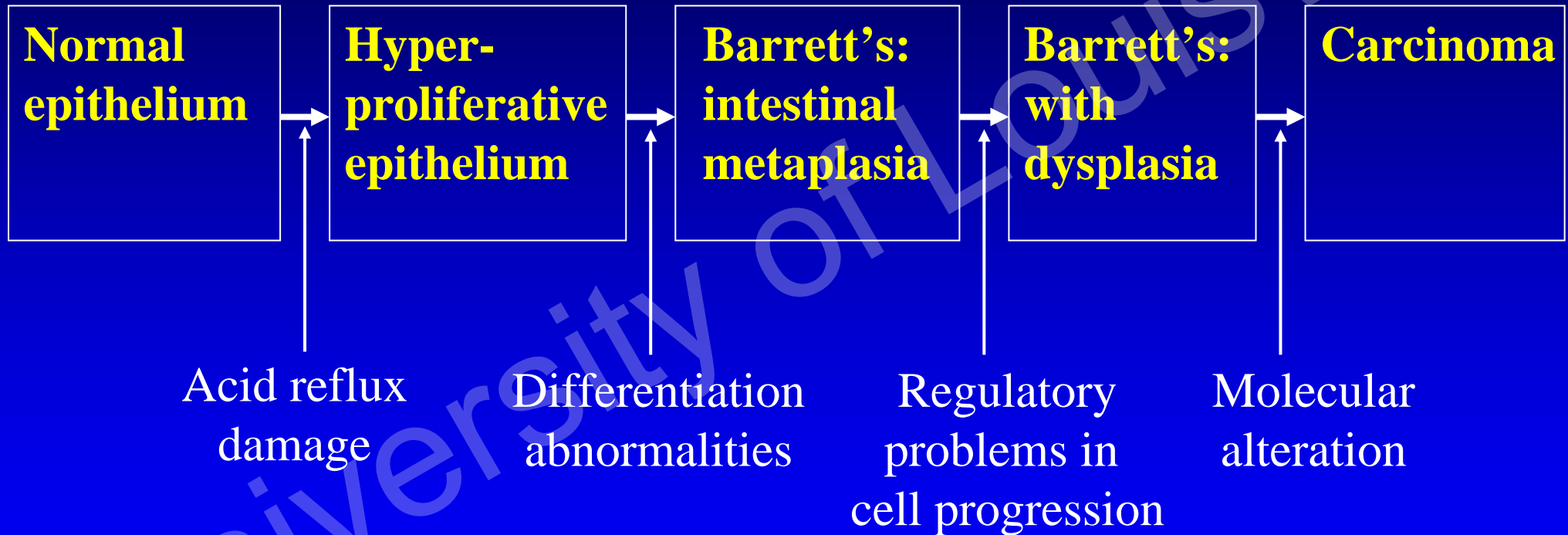


External Esophageal Perfusion Model with Implantation of Bone Marrow Cells

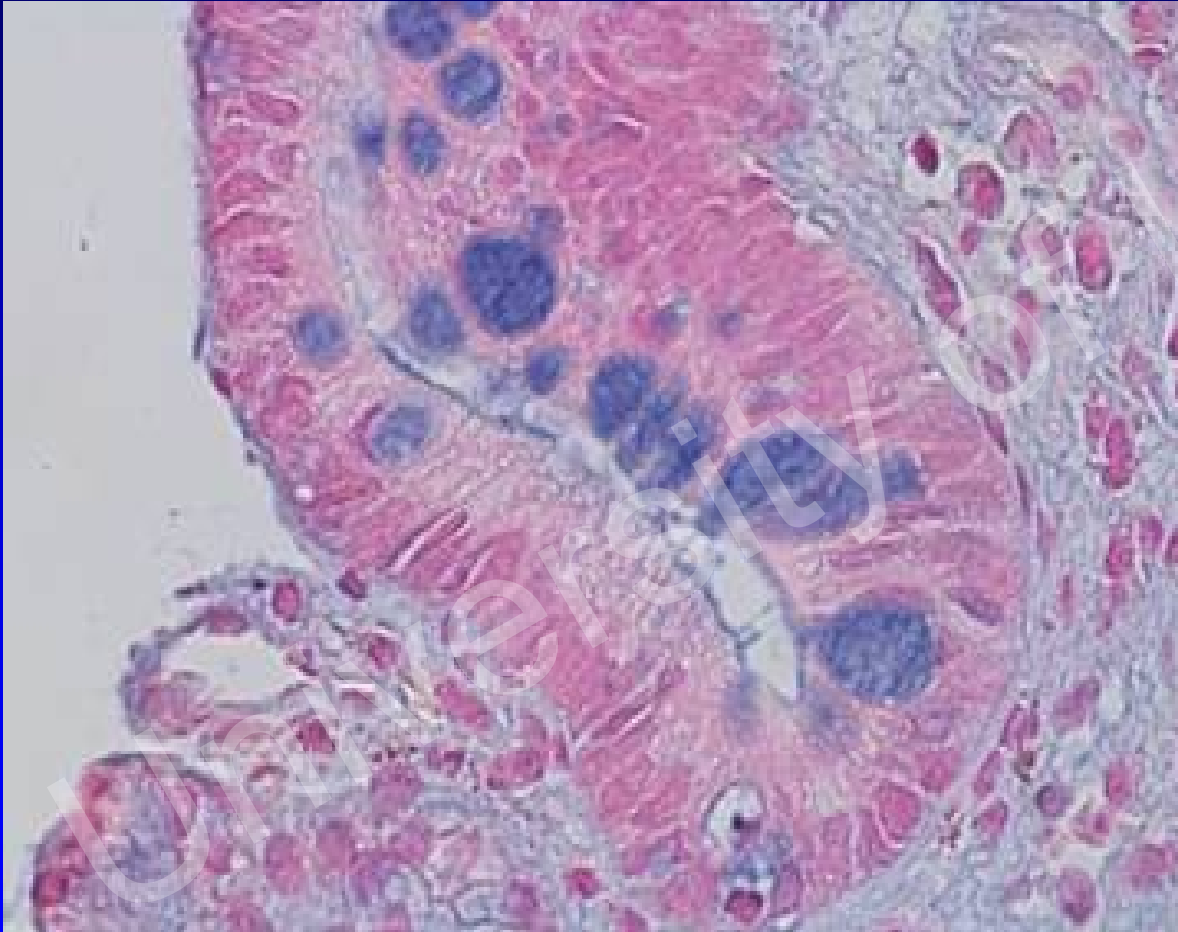


Metaplasia-Dysplasia-Adenocarcinoma

Sequence of Barrett's Esophagus

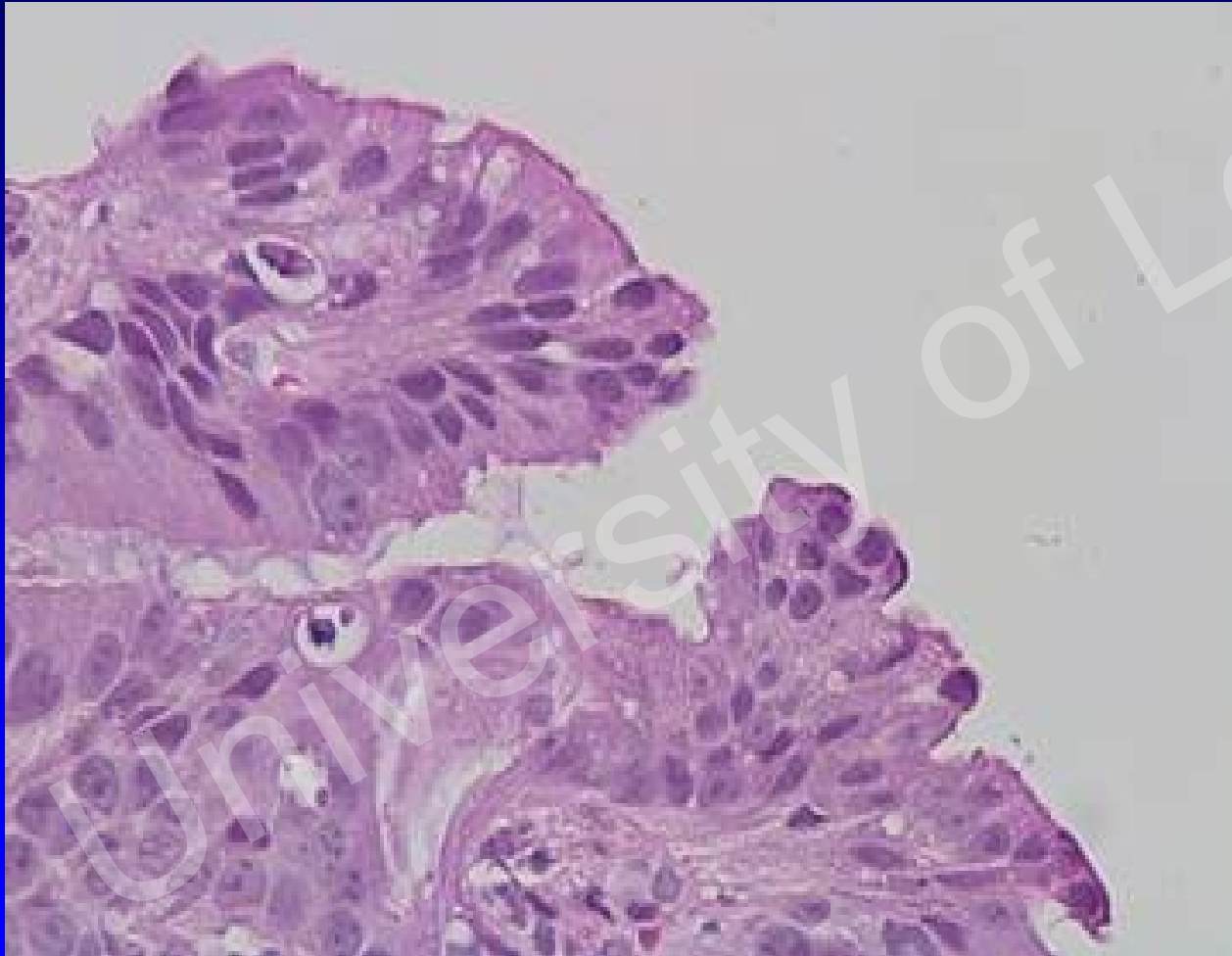


Barrett's Esophagus: Specialized Intestinal Metaplasia (SIM)



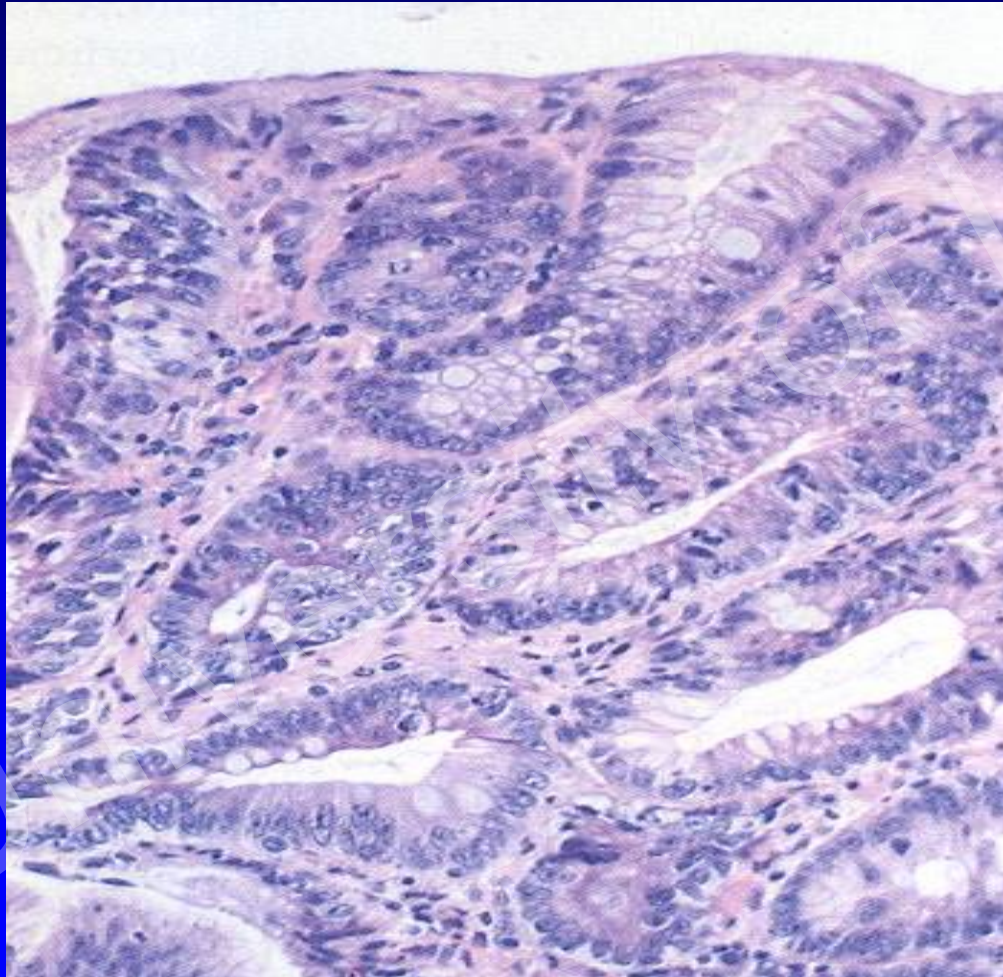
- Goblet cells
- Resemble cells from the small intestine

Barrett's Esophagus: Indeterminate/Low Grade Dysplasia



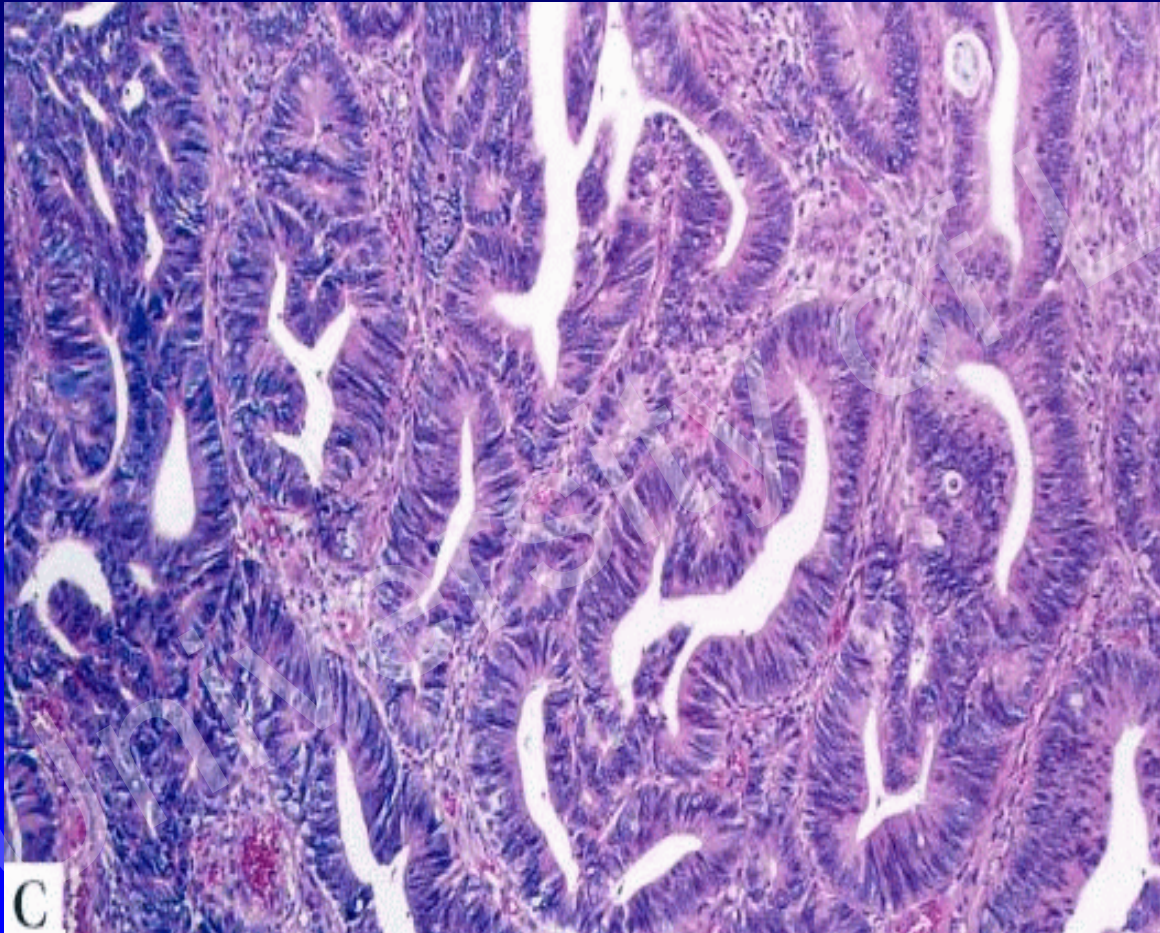
- Prominent and crowded nuclei
- Diminished mucus cells
- Preserved architecture

Barrett's Esophagus: High Grade Dysplasia



- Hyperchromatic nuclei
- Prominent nucleoli
- Diminished mucus cells
- Distorted architecture
- No invasion of lamina propria

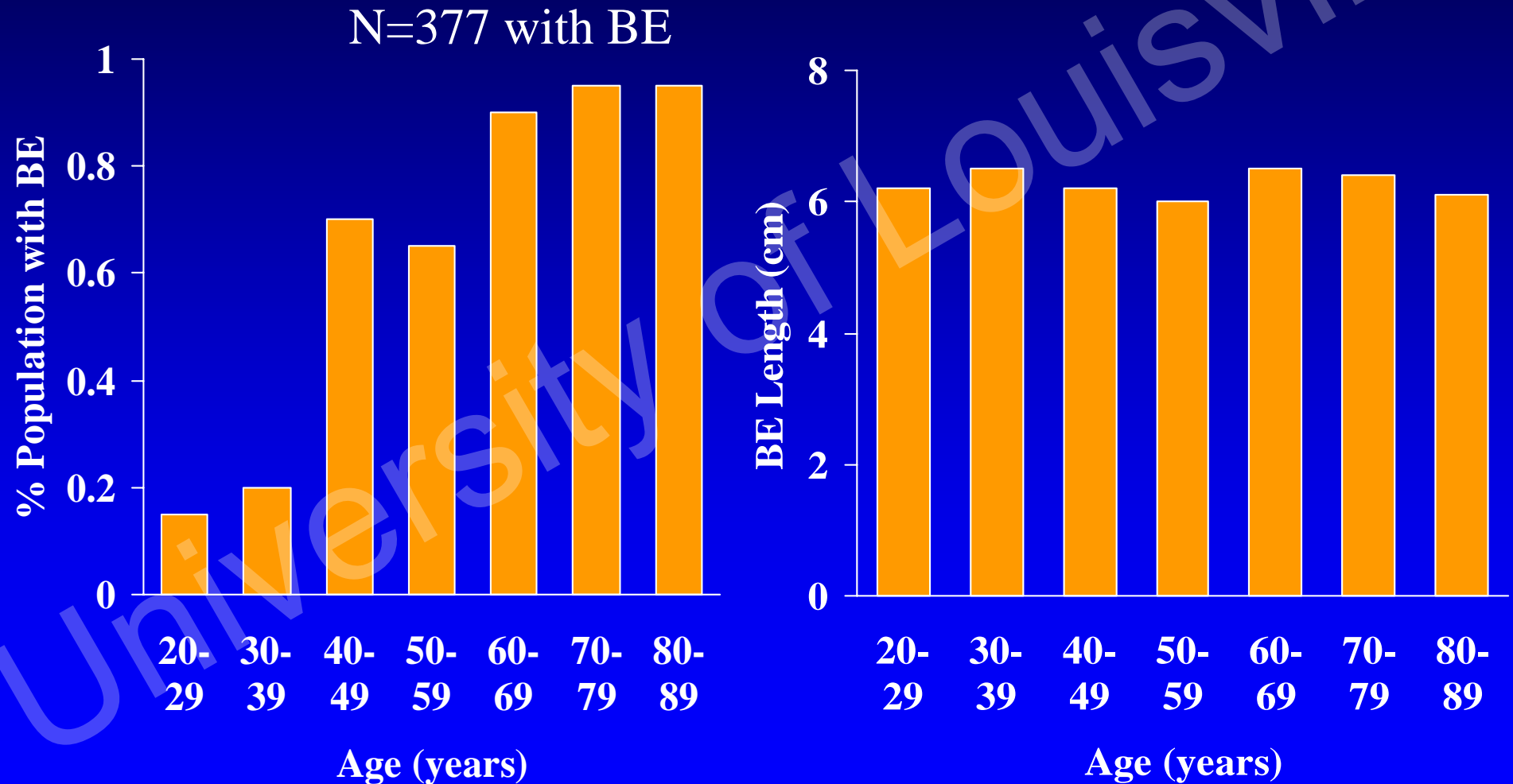
Barrett's Esophagus: Adenocarcinoma



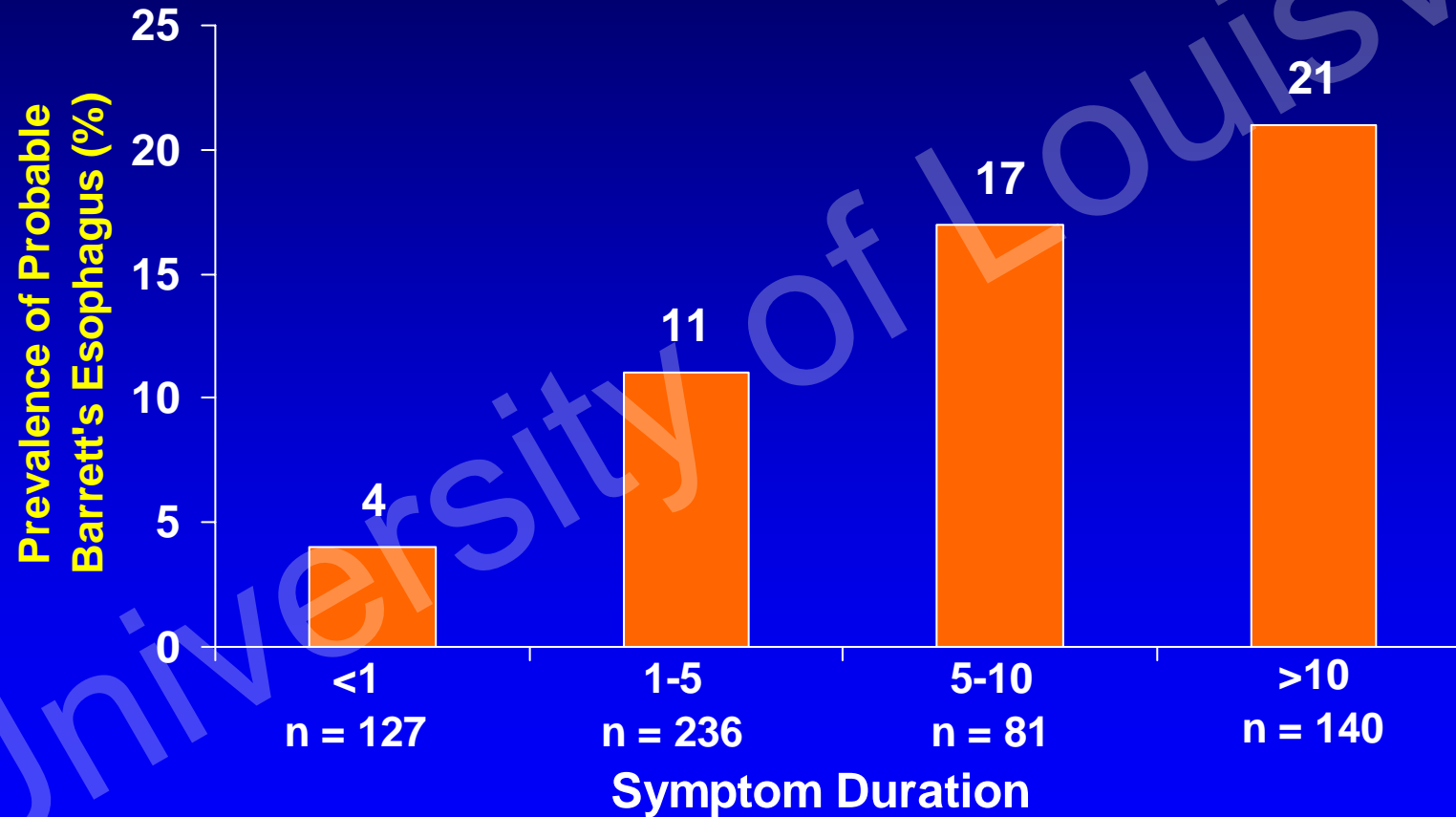
- Back-to-back glands
- Markedly hyperchromatic nuclei
- Loss of architecture
- Invade lamina propria

Who should be Screened for Barrett's Esophagus?

Prevalence of Barrett's Esophagus Increases with Age



Prevalence of Barrett's Esophagus is Associated with Duration of Heartburn

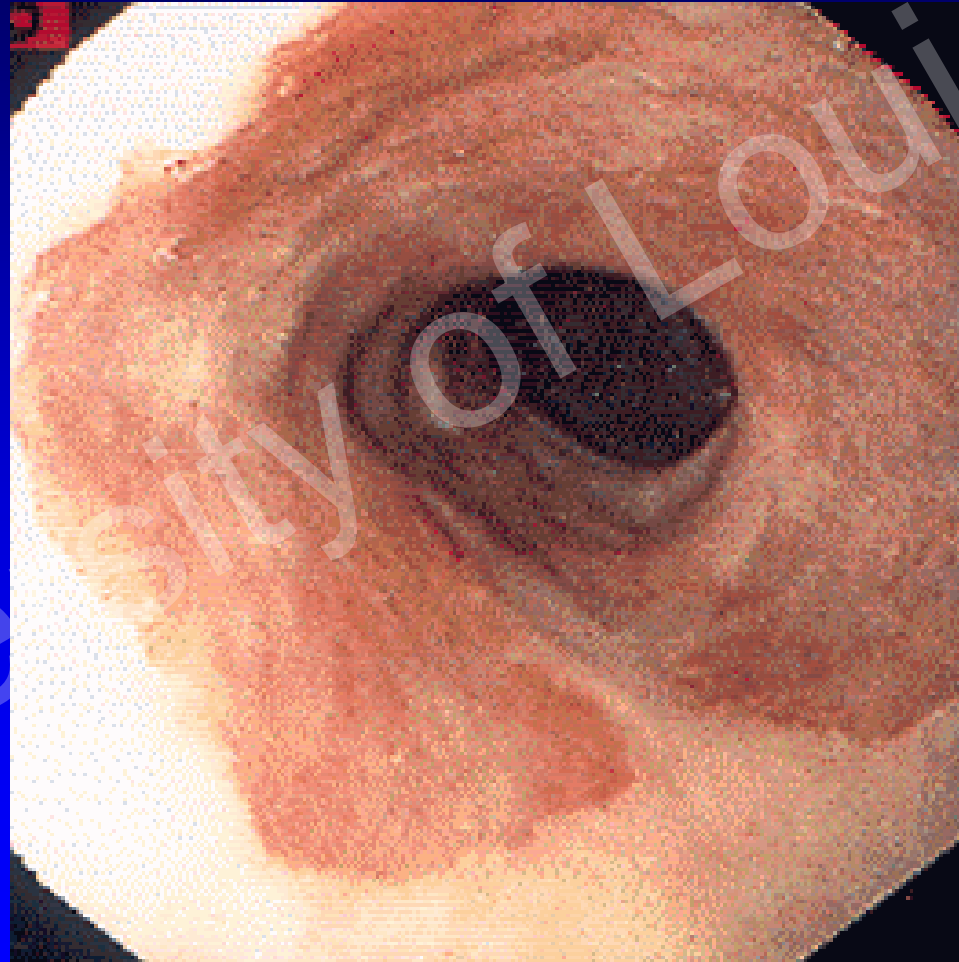


Screening for Barrett's Esophagus

- > 10 years of heartburn
- > 50 years old
- Caucasians
- Males
- (Patients with long standing heartburn who require maintenance medications to control symptoms)

Diagnosing Barrett's Esophagus and Dysplasia

Where are the Dysplasia?



Systematic Mapping of Esophagectomy Specimens

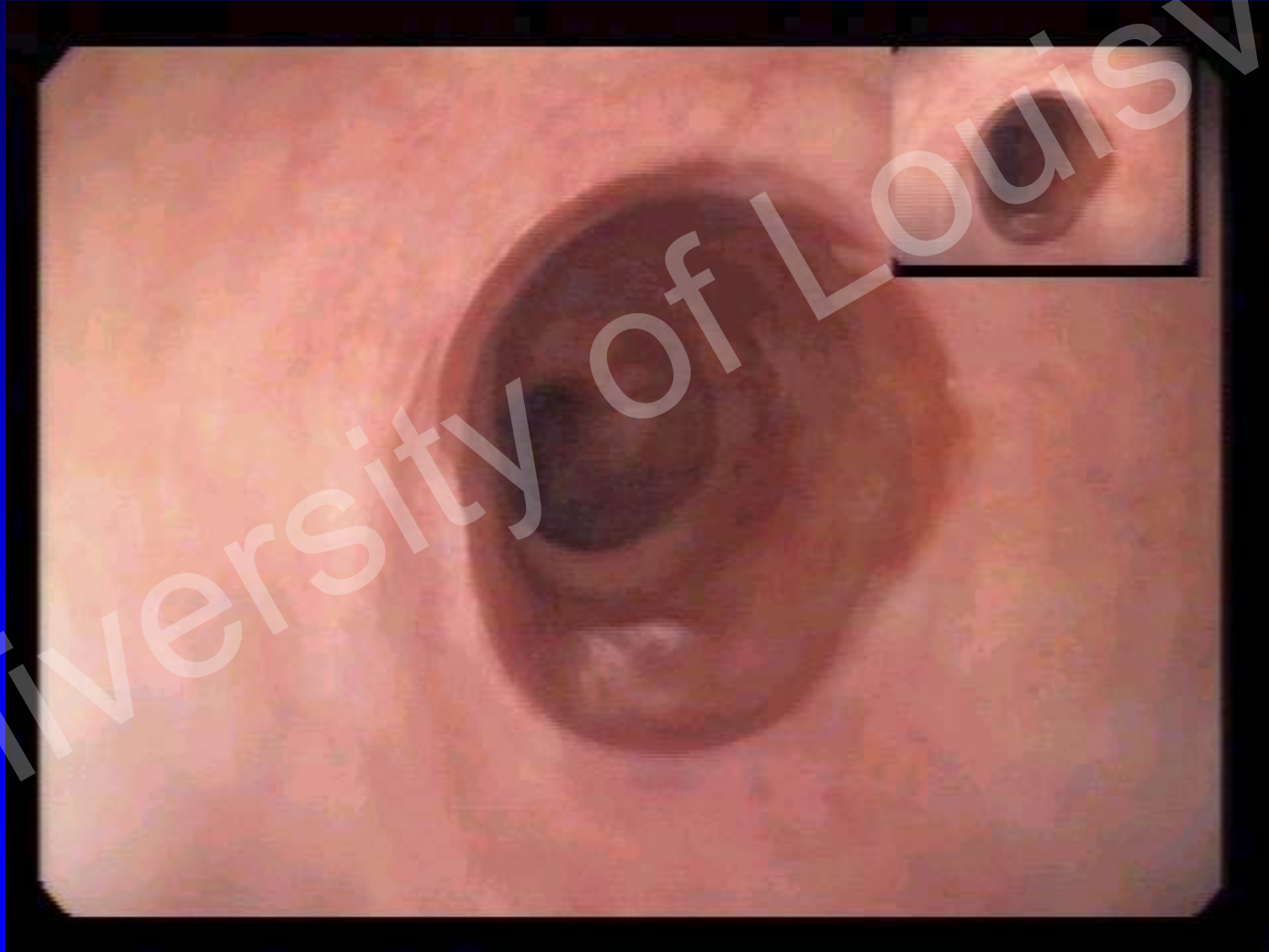
	<u>Surface Area</u>
Total Barrett's mucosa	32 cm ²
Low grade dysplasia	13 cm ²
High grade dysplasia	1.3 cm ²
Adenocarcinoma	1.1 cm ²

Cameron et al. Am J Gastroenterol 1997;92:586-91. (N=30 pts without endoscopic evidence of cancer)

Barrett's with Ulcer



Barrett's with Stricture



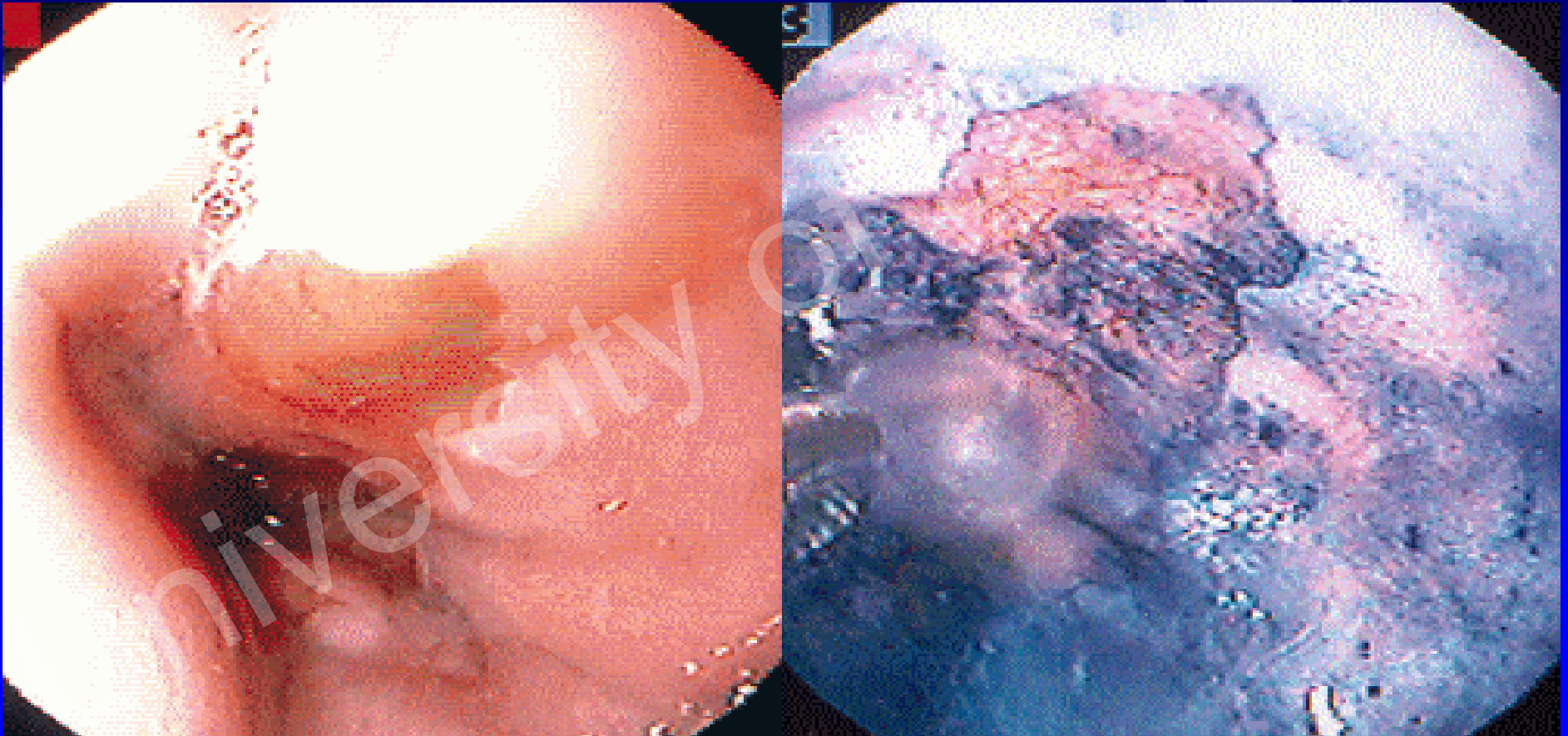
Barrett's with Nodular Mucosa



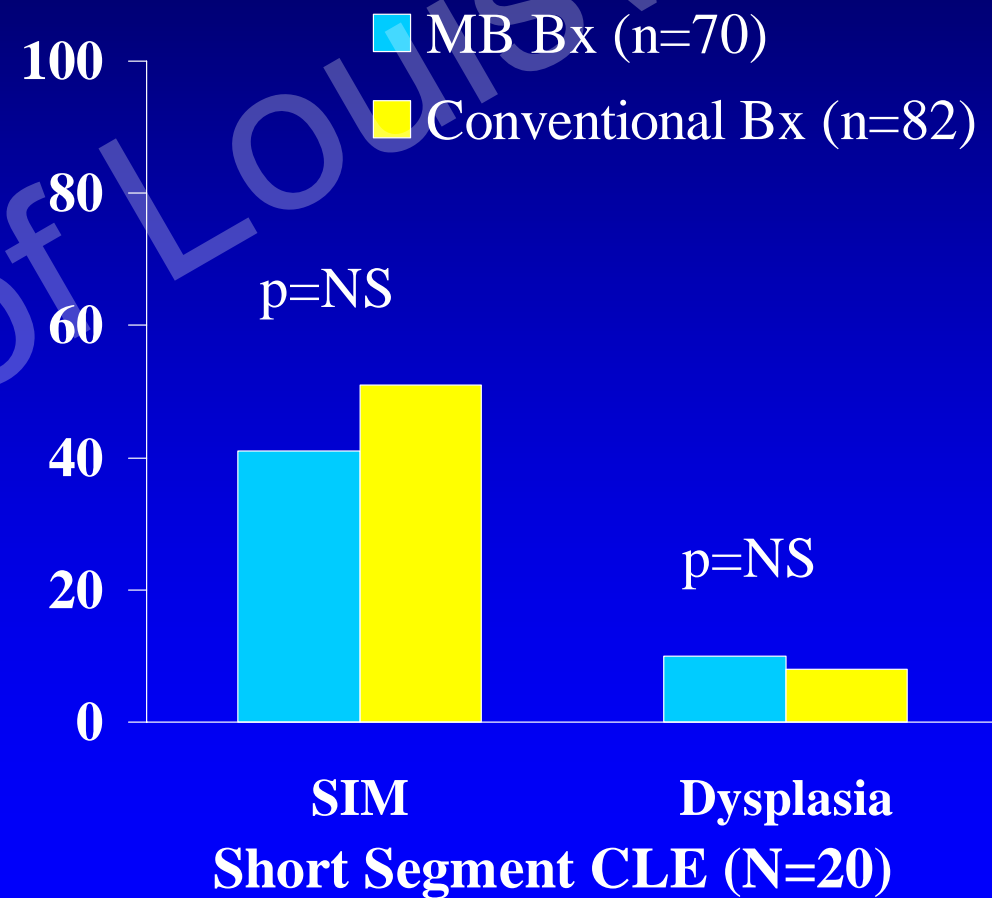
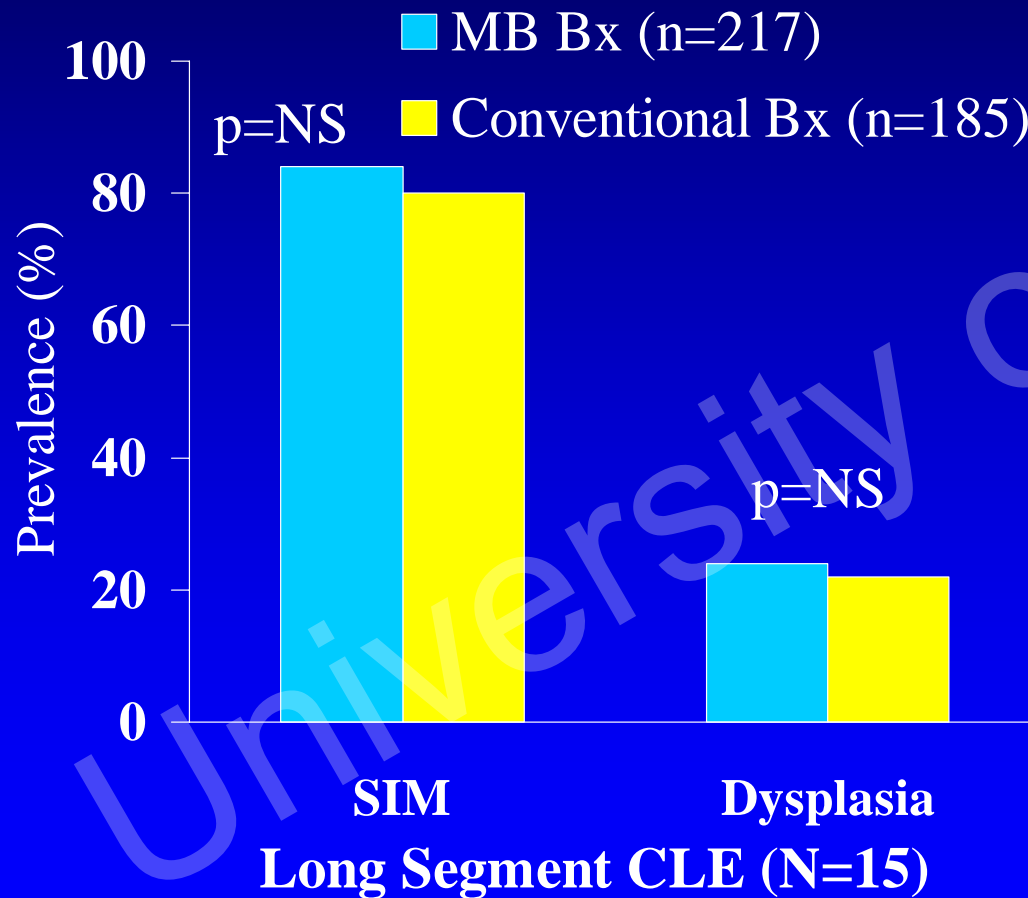
Real-Time Endoscopy to Detect Dysplasia

- Chromoendoscopy
 - Methylene blue, crystal violet, indo
- Optical devices
 - Fluorescence spectroscopy
 - Confocal fluorescence microendoscopy
 - Light scattering spectroscopy
 - Raman spectroscopy
- Magnification endoscopy
- Blue-light endoscopy

Methylene-Blue Chromoendoscopy



Results of MB-directed vs. Conventional Biopsy for Barrett's Esophagus

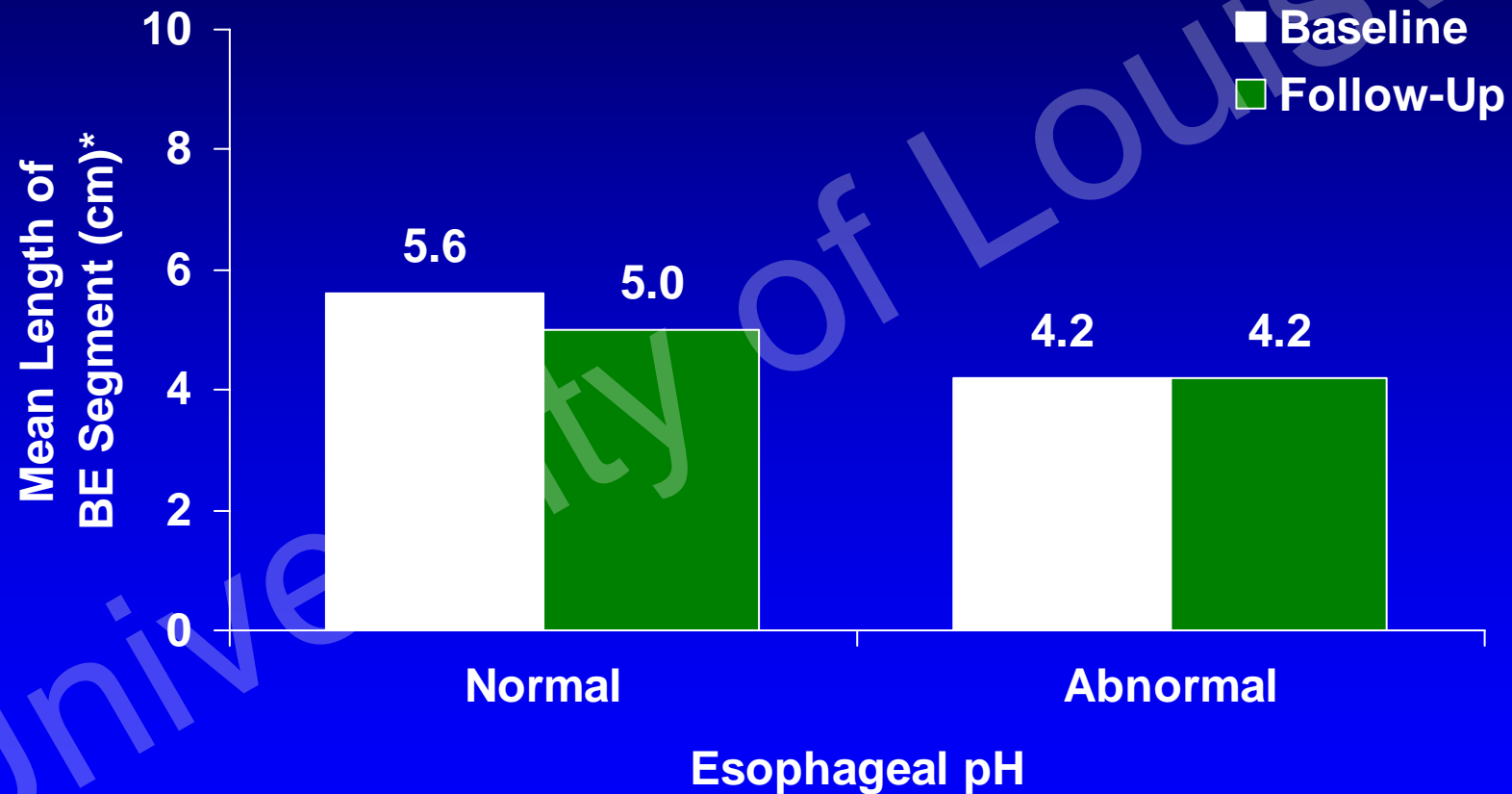


Crystal Violet and Magnification Endoscopy



Treatment and Surveillance for Barrett's Esophagus

Efficacy of High-Dose PPI Therapy in Regression of Barrett's Esophagus



N = 13 patients treated with lansoprazole 60 mg daily for a mean of 5.7 years.

Sharma et al. *Am J Gastroenterol* 1997;92:582-585

Does Treatment Alter Barrett's Esophagus?

- No clear evidence that antireflux therapy reduces the extent of Barrett's esophagus or risk of adenocarcinoma

Goals for Surveillance in Barrett's Esophagus

- Detect dysplasia before becoming cancer
- Identify which patient is at high risk for developing cancer
- Early intervention to prolong quality of life

Management of Barrett's Esophagus with No Dysplasia

ACG Practice Guidelines for No Dysplasia	
New diagnosis	Repeat in 1 year* (for long segment) (Repeat in 3 years for short segment)
Confirm on repeat	Surveillance every 3 years

*To avoid sampling error

Management of Barrett's Esophagus with Low-Grade Dysplasia

- Prescribe aggressive antisecretory therapy to eliminate confounding inflammation

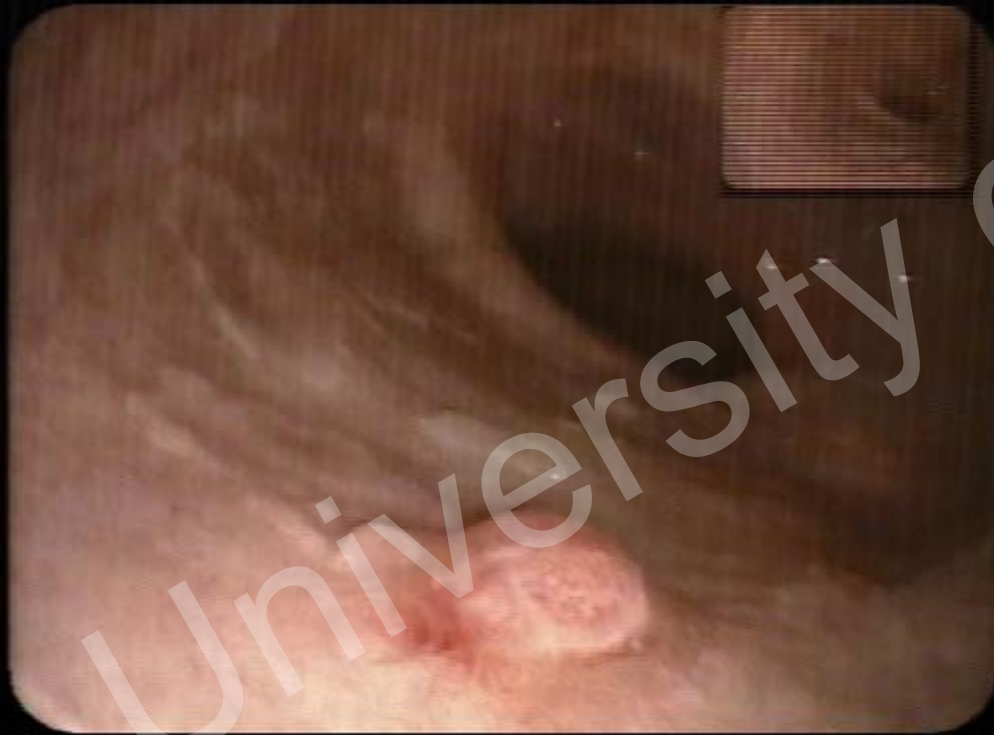
ACG Practice Guidelines for Low Grade Dysplasia	
New diagnosis	Repeat in 6 months
Confirm on repeat	Surveillance every 1 year

Management of Barrett's Esophagus with High-Grade Dysplasia

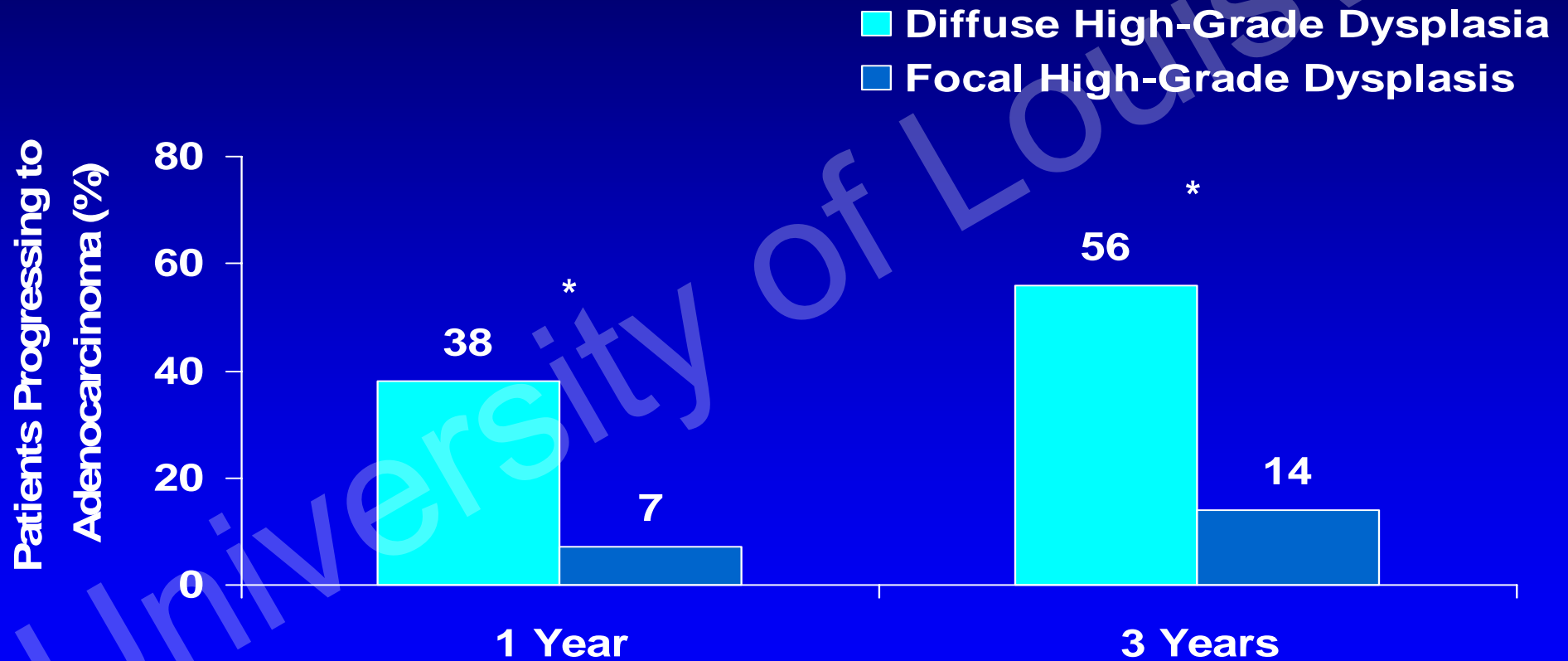
- Difficult to differentiate from cancer; requires intensive biopsy protocol

ACG Practice Guidelines for HGD	
Mucosal irregularity	Endoscopic mucosal resection
Focal high-grade dysplasia	Follow-up EGD every 3 months
Multifocal (diffuse) high-grade dysplasia	a. Surgery <u>or</u> b. Photodynamic therapy <u>or</u> c. EGD every 3 months

Endoscopic Mucosal Resection for Barrett's Esophagus



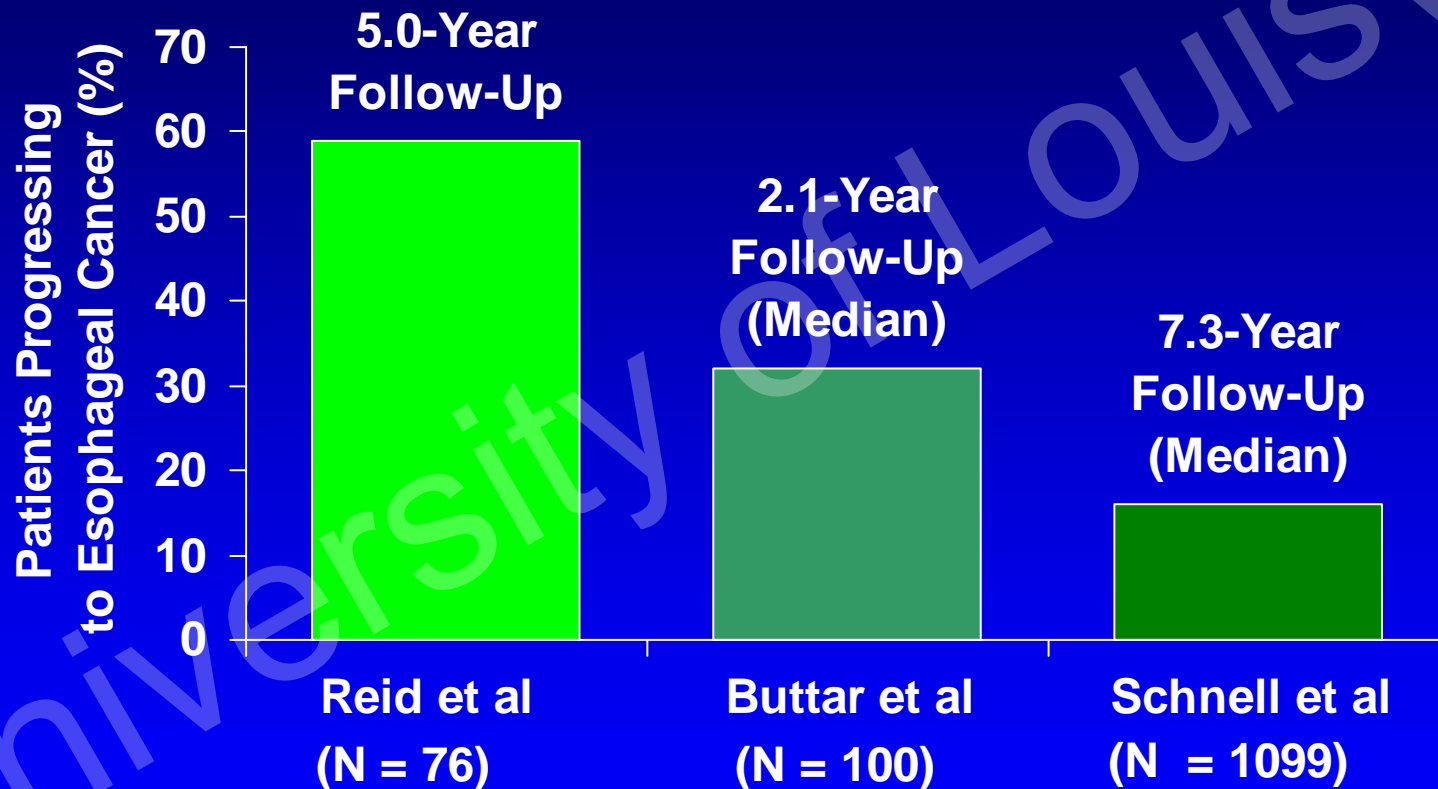
Risk of Adenocarcinoma in Focal vs. Diffuse HGD



* $P < 0.001$.

Buttar et al. *Gastroenterology*. 2001;120:1630-1639.

Progression of HGD to Cancer



Buttar et al. *Gastroenterology*. 2001;120:1630-1639.

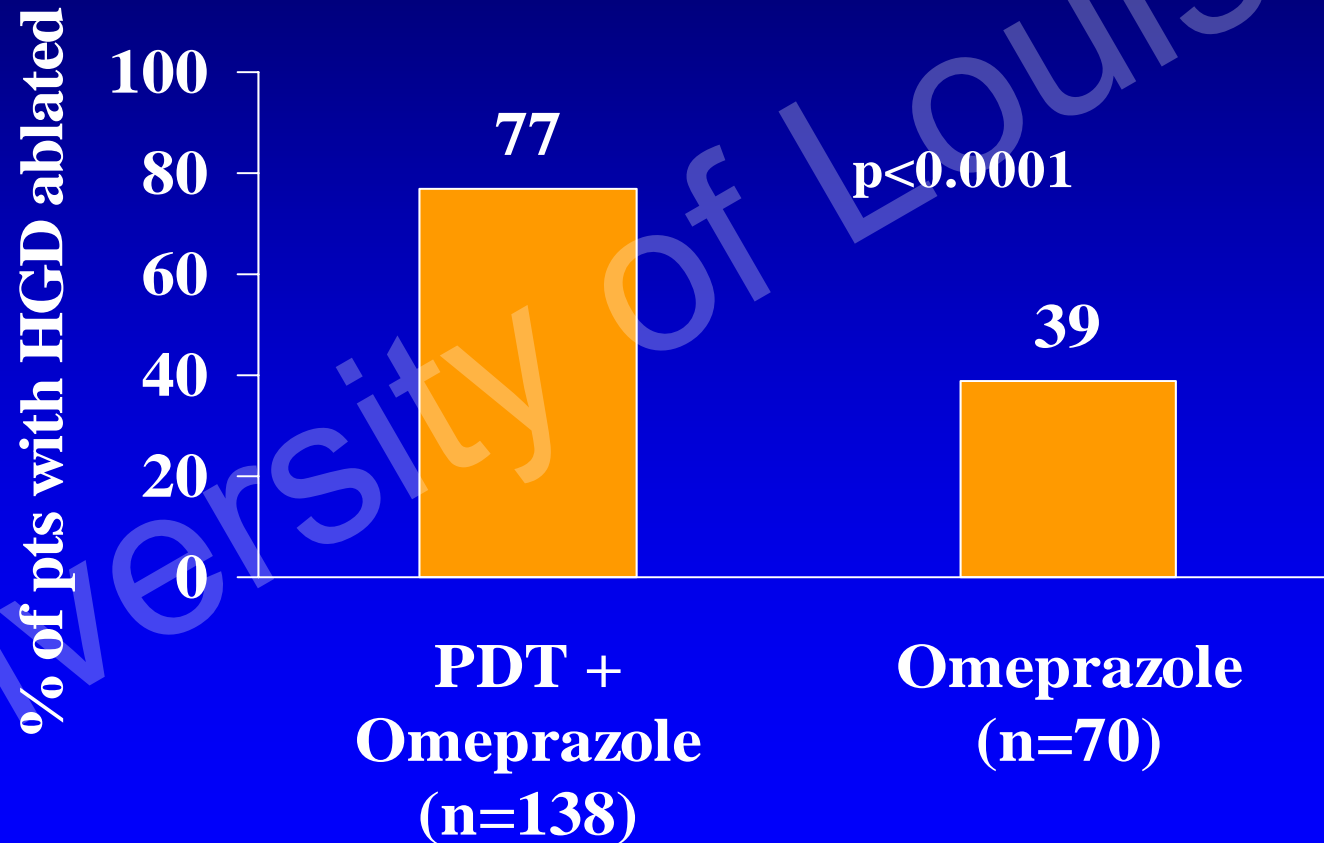
Reid et al. *Am J Gastroenterol*. 2000;95:1669-1676.

Schnell et al. *Gastroenterology*. 2001;120:1607-1619.

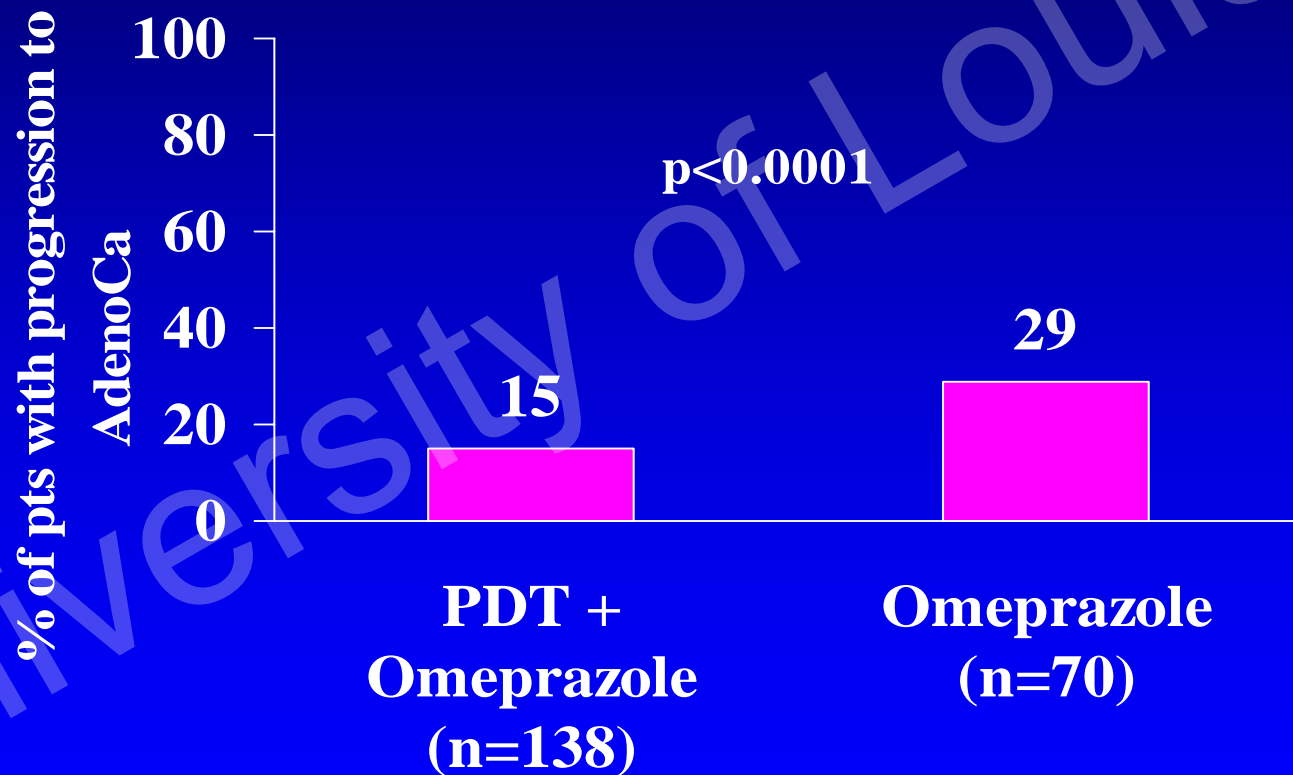
Photodynamic Therapy with Porfimer: Randomized Controlled Trial

- Pts with confirmed HGD were randomized (2:1) to
 - PDT/porfimer sodium (2 mg/kg IV) + Omeprazole 20 bid
 - Laser exposure at 630 nm wavelength within 40-50 hrs
 - Max of 3 PDT sessions at least 90 days apart
 - Single center pathologists blinded to treatment arms
 - Omeprazole 20 bid only

PDT with Porfimer Sodium: 2-Year Follow-up of RCT



PDT with Porfimer Sodium: 5-Year Follow-up of RCT



Summary

- Screening for Barrett's
 - Caucasian, male, >50 yrs old, heartburn >10 yrs
- Biopsy is inadequate due to sampling error
- Progression from intestinal metaplasia to cancer is uncommon (0.4% per patient-year)
- Expert pathologist needed to diagnose HGD