



Gruppo Italiano per lo Studio della Motilità dell'Apparato Digerente

**XII** CONGRESSO NAZIONALE **GISMAD**  
Gardone Riviera 27-28 Aprile 2007

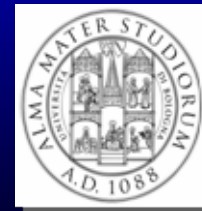
## ***GERD, DYS, IBS***

***semplice overlap o meccanismi fisiopatologici comuni ?***



1088-2007

***Vincenzo Stanghellini***  
***Department of Internal Medicine and Gastroenterology***  
***University of Bologna***



# THE IDEAL WORLD

What's  
your problem?



I've got  
heartburn and  
regurgitation

# THERE IS MORE TO GERD THAN HEARTBURN



*Andrea del Verrocchio*  
1435-1488

*“Busto di donna con mazzo di fiori”*

- $\cong$  50% of GERD patients have additional symptoms without predominant heartburn

*Locke et al, Gastroenterology 1997*

- $\cong$  25% of GERD patients do not suffer from “heartburn”

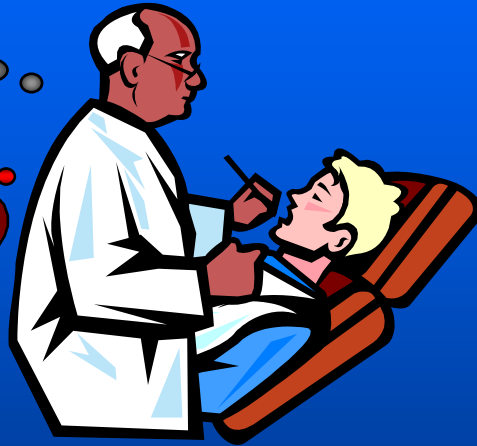
*Dent et al, Gut 1999*

... OH ! ... OH !

What's  
your problem?

Any other  
symptom?

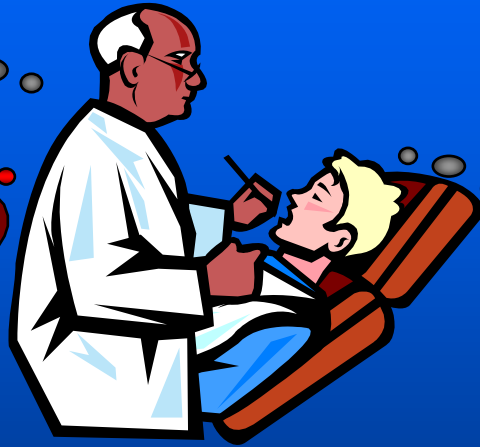
I've got  
heartburn and  
regurgitation



... OH ! ... OH !

What's  
your problem?

Any other  
symptom?



I've got  
heartburn and  
regurgitation

Chest pain, cough,  
hoarseness, sleep  
disturbances, ...

... OH ! ... OH !

What's  
your problem?

Any other  
symptom?



I've got  
heartburn and  
regurgitation

Chest pain, cough,  
hoarseness, sleep  
disturbances, ...

Epigastric pain, fullness,  
early satiety, nausea,  
vomiting, ...

# THE IDEAL WORLD

What's  
your problem?

Any other  
symptom?



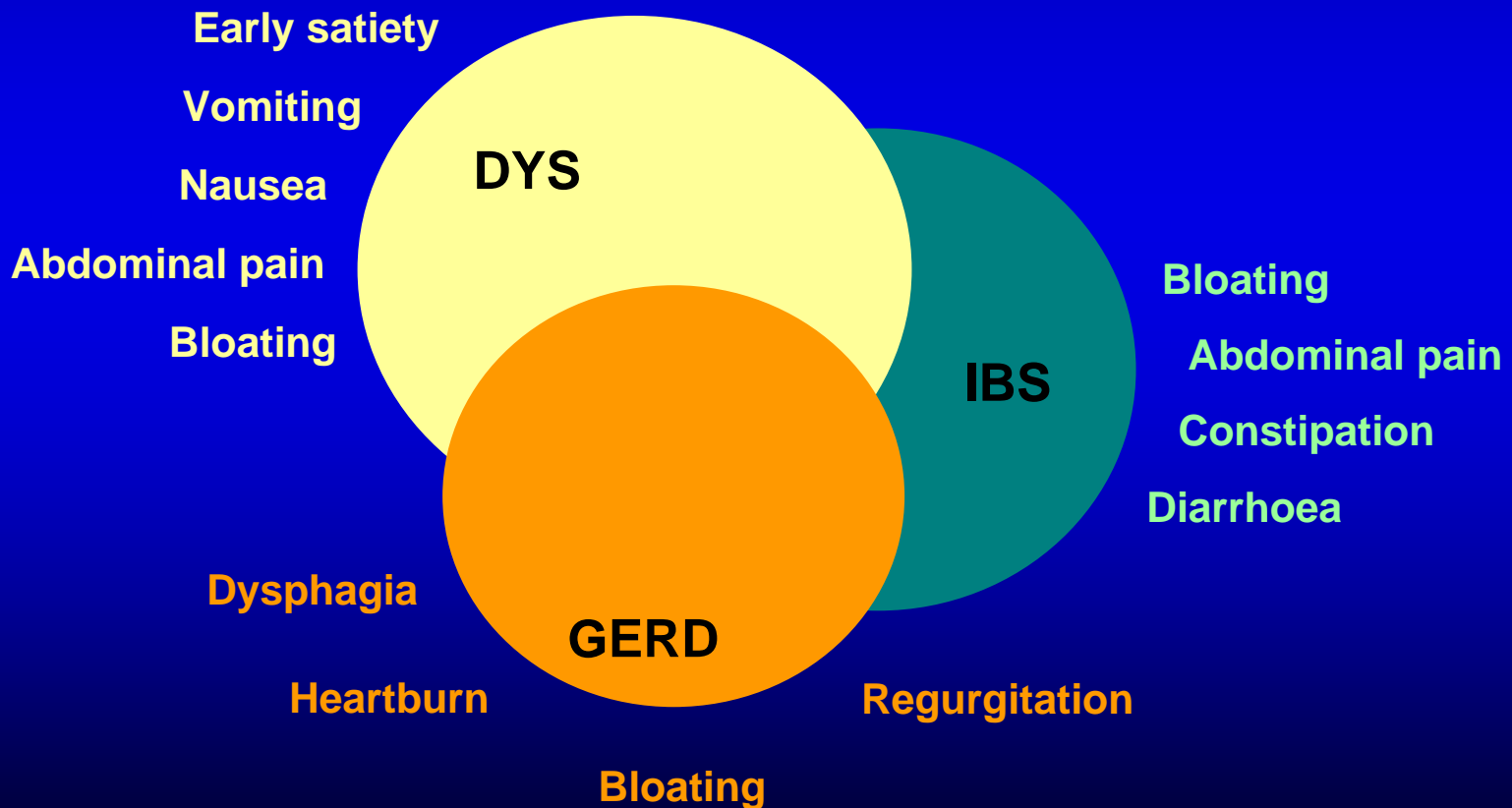
I've got  
heartburn and  
regurgitation

Chest pain, cough,  
hoarseness, sleep  
disturbances, ...

Abdominal pain,  
bloating, distension,  
flautolence, diarrhea,  
constipation, ...

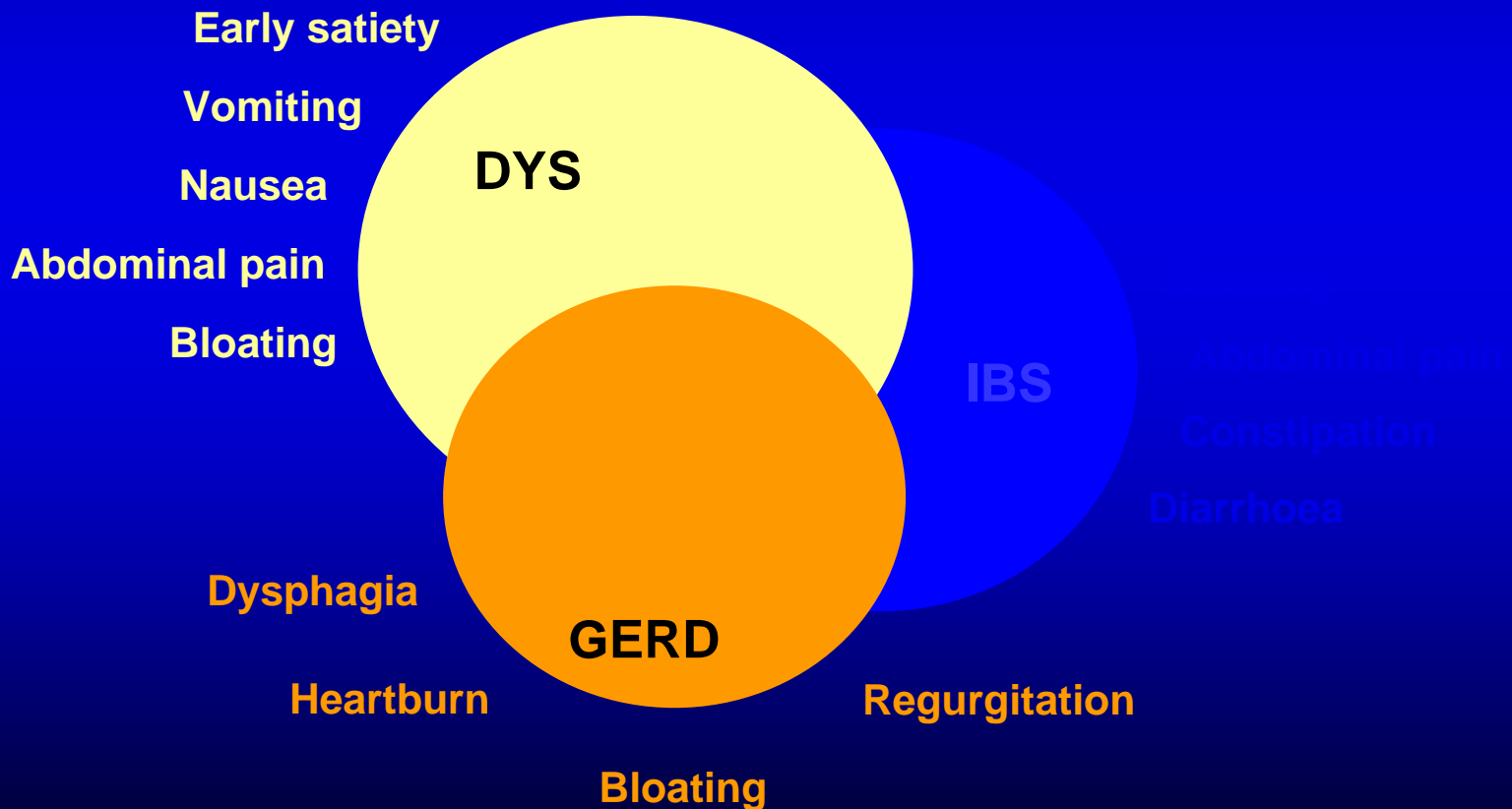
Epigastric pain, fullness,  
early satiety, nausea,  
vomiting, ...

# Overlap of Symptom Complexes and Diagnoses ... Just by Chance ?



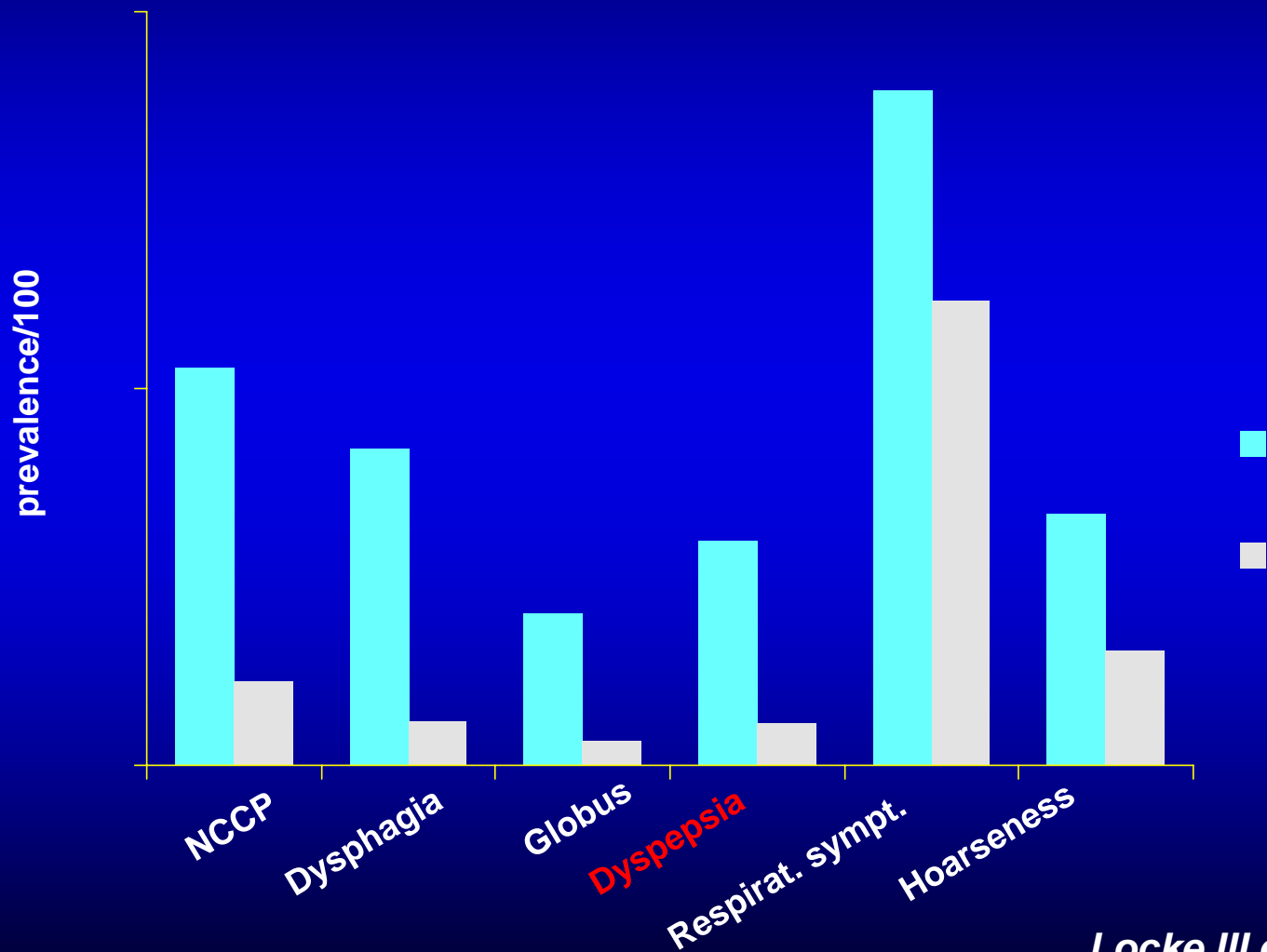
# Overlap between GERD and DYS

Just by Chance ? Wrong diagnosis? Common Mechanisms?

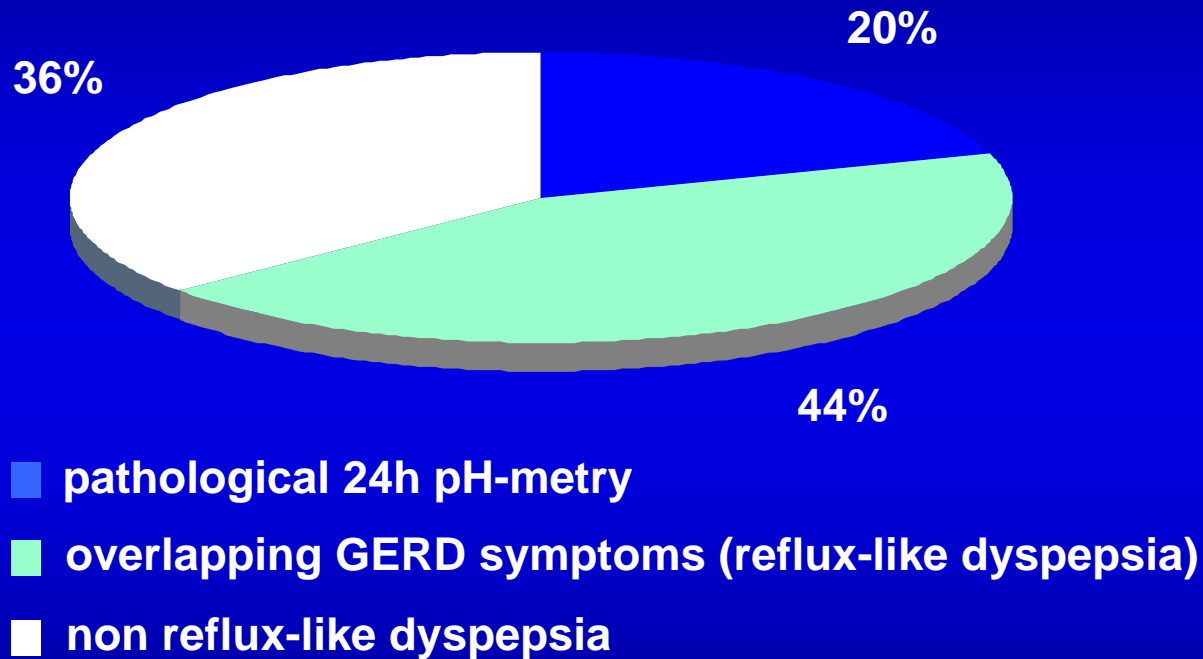


**Just by chance ?**

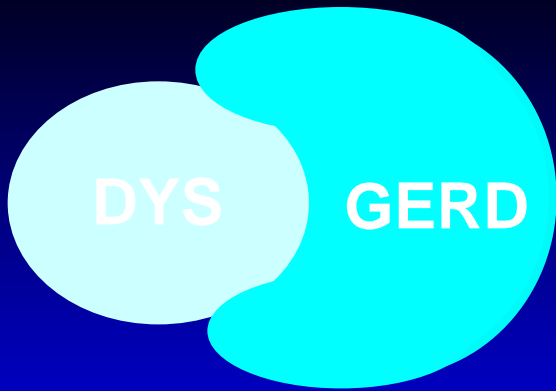
# PREVALENCE OF ATYPICAL SYMPTOMS AMONG INDIVIDUALS WITH AND WITHOUT GERD IN OLMSTED COUNTY



# GERD IN PATIENTS WITH CHRONIC DYSPEPSIA

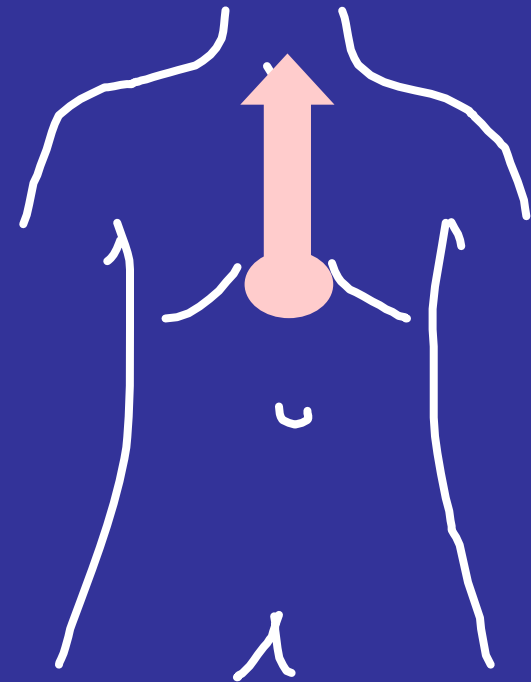


**Wrong diagnosis ?**



- Different pathophysiological mechanism
- Different response to antisecretory drugs
- Different natural history and complications

## HEARTBURN (PYROSIS)

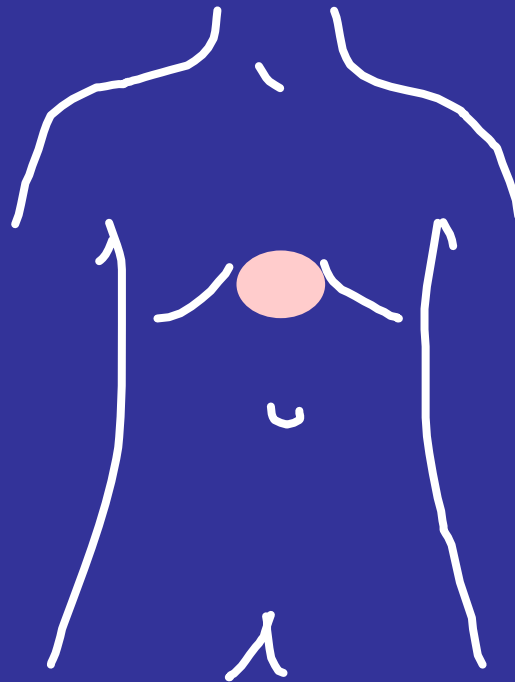


**GERD !**

DYS

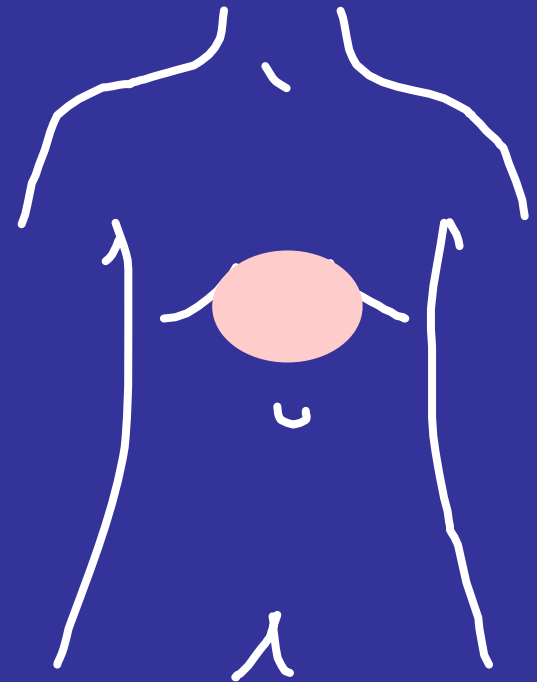
GERD

CARDIAC PAIN



GERD or DYS ?

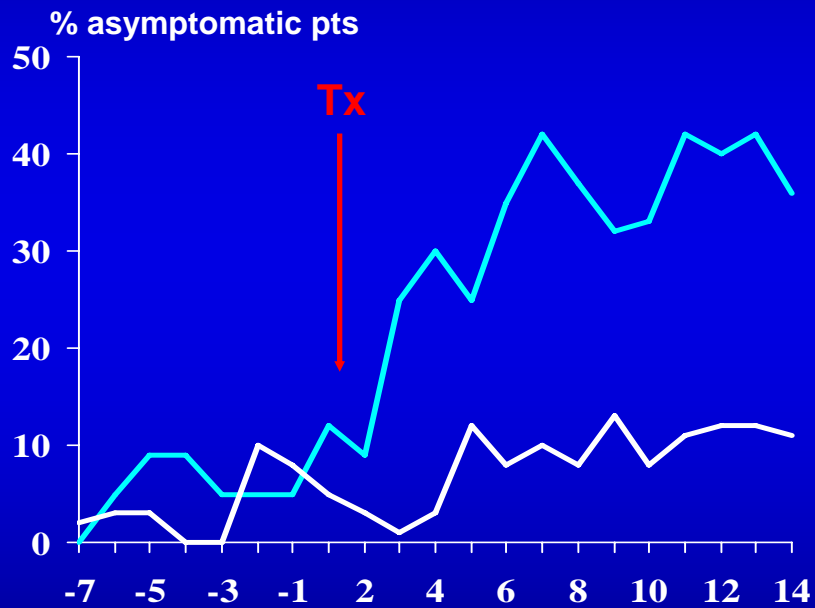
EPIGASTRIC PAIN



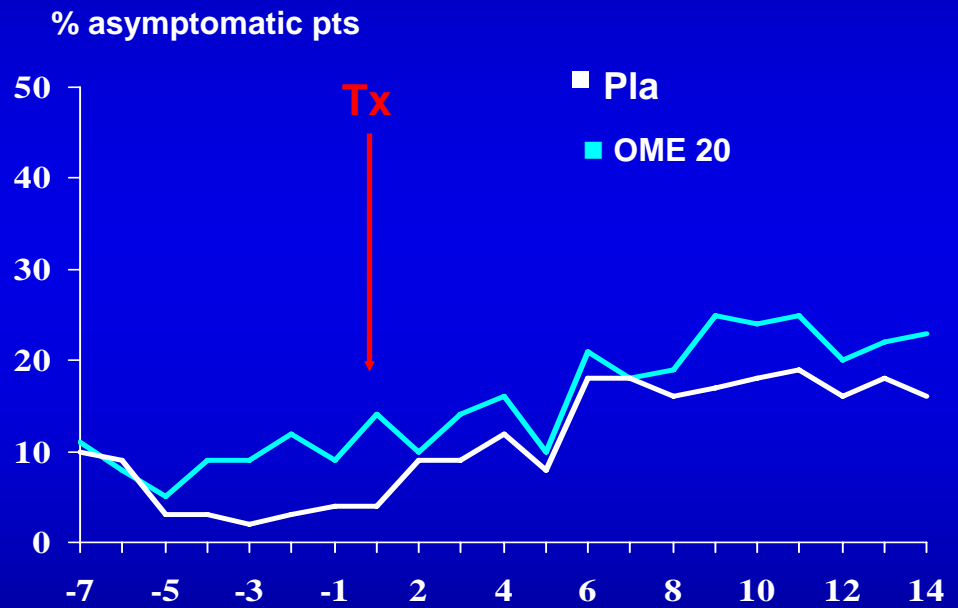
GERD or DYS ?

# EFFECT OF PPIs ON HEARTBURN DEFINED BY A WORD PICTURE

## Predominant heartburn

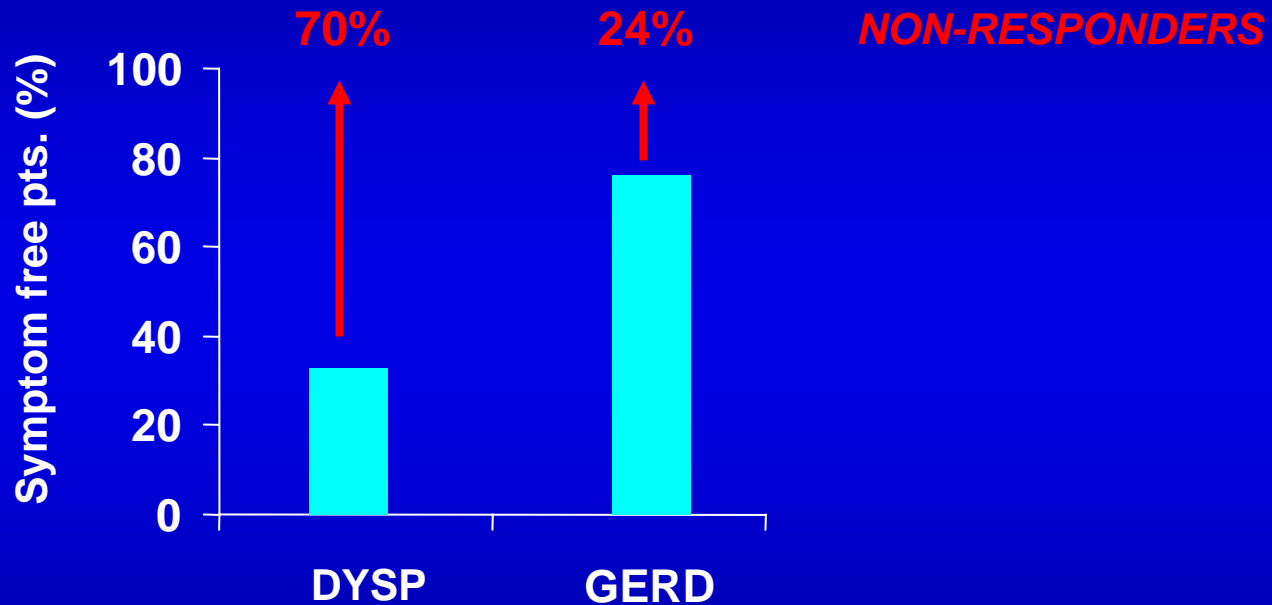


## Non predominant heartburn



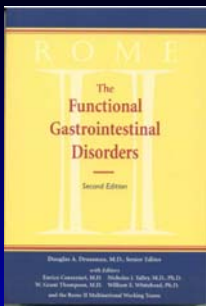
**broad indications for specific therapies may result in increased treatment failures**

# SHORT TERM EFFECT OF PPI ON UGI SYMPTOMS

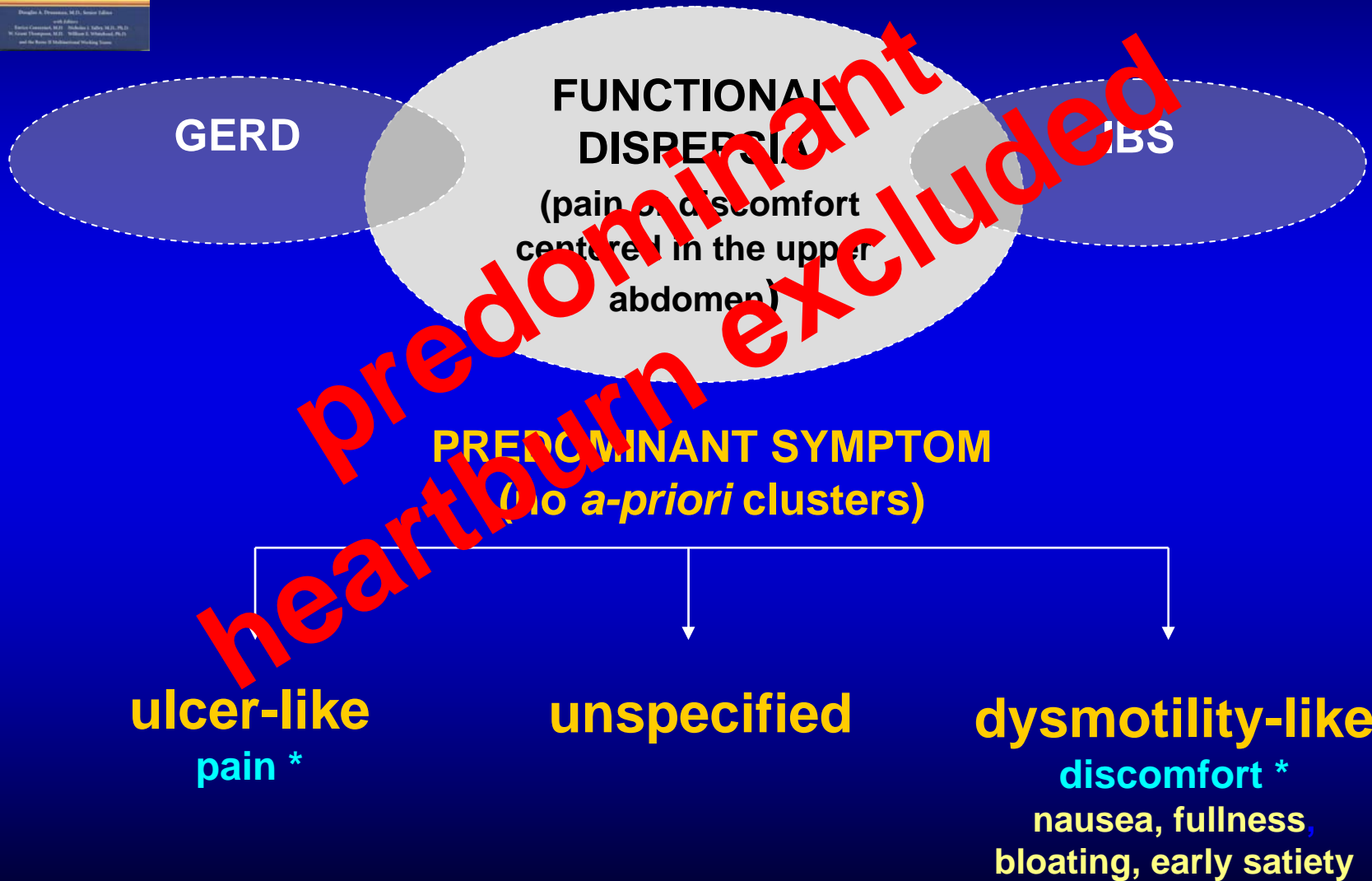


*Chiba N. et al, APT1997*

*Bolling-Sternevald et al, Scand J GE 2002*



# ROME II - *Gut* 1999



# FUNCTIONAL DYSPEPSIA / GERD

<b>Study</b>	<b>Treatment</b>	<b>Heartburn/regurgitation</b>
Hamilton, 2000	Psychotherapy	Severe 29%
Thomson, 2000	Endoscopic findings	Dominant symptom in 25% and 19%
Talley, 2001	Prokinetics	High scores during day / night
Armstrong, 2002	PPI	Most severe symptom
Malfertheiner, 2003	Hp eradication	Present in 29% - 33%
Peura, 2004	PPI	Present in 74% (??)
Madsen, 2004	PPI	>50% pathological pH monitoring
Holtmann, 2004	Prokinetics	40% moderate or severe

# FUNCTIONAL DYSPEPSIA / GERD

Study	Treatment	Heartburn/regurgitation
Hamilton, 2000	Psychotherapy	Severe 29%
Thomson, 2000	Endoscopic findings	Dominant symptom in 25% and 19%
Talley, 2001	Prokinetics	High scores during day / night
Armstrong, 2002	PPI	Most severe symptom
Malfertheiner, 2003	Hp eradication	Present in 29% - 33%
Peura, 2004	PPI	Present in 74% (??)
Madsen, 2004	PPI	>50% pathological pH monitoring
Holtmann, 2004	Prokinetics	40% moderate or severe

## **PPI-START vs H<sub>2</sub>RA-START FOR HEARTBURN-DOMINANT UNINVESTIGATED DYSPEPSIA (CADET-HR Study)**

- **Four major upper GI symptoms: heartburn, regurgitation, epigastric pain, nausea (!)**
- **PPI-start superior to H2RA-start only in the treatment of heartburn at short- but not long-term**
- **No other significant difference between the two treatments**

*Armstrong et al. APT 2005*

# **MANAGEMENT OF DYSPEPSIA WITHOUT ALARM SIGNS**

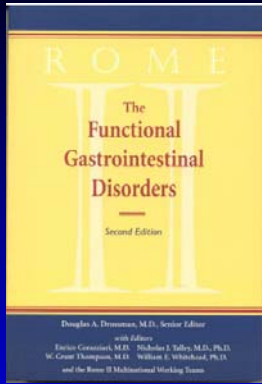
***NEW NATIONAL GUIDANCE FOR ENGLAND AND WALES (NICE)***

**... empirical management is appropriate for most patients ...**

**... providing a course of PPI and/or Hp test and treat**

**dyspepsia refers to a spectrum of upper gastrointestinal symptoms  
including epigastric pain and heartburn**

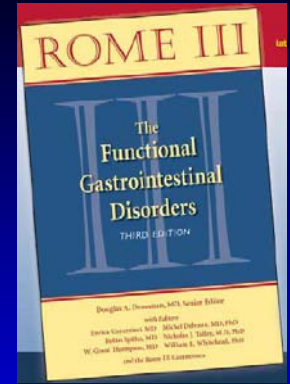
***Mason et al. APT 2005***



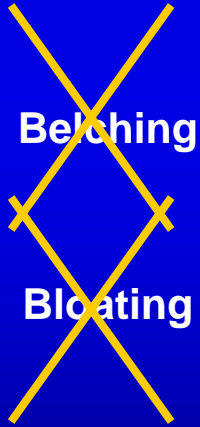
**ROME II**



**ROME III**



**Belching /  
Aerophagia**



**IBS /  
Functional Bloating**

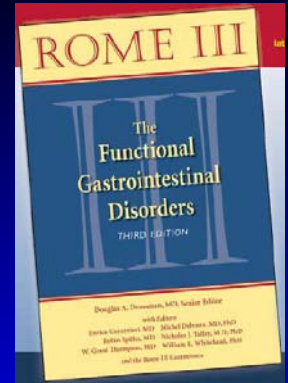
**Postprandial  
fullness**  
**Early satiety**  
**Epigastric pain**  
**Epigastric  
burning**



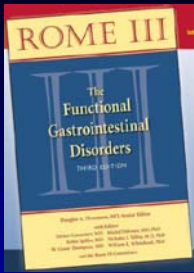
**Nausea /  
Vomiting /  
Gastroparesis**



# ROME III

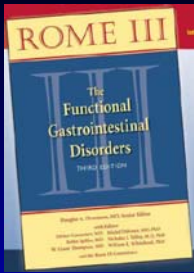


what about GERD ?



# FUNCTIONAL DYSPEPSIA DEFINITION: ROME III

- ✓ **Functional dyspepsia:  $\geq 1$  bothersome**
  - postprandial fullness, or
  - early satiety, or
  - epigastric pain, or
  - epigastric burning
  
- ✓ **No evidence of organic disease that is likely to explain the symptoms**
  
- ✓ **Overlap with GERD and IBS is common and does not exclude the diagnosis**
  
- ✓ **GERD may be accompanied by some dyspeptic symptoms. Presence of typical reflux symptoms should lead to a provisional diagnosis of GERD**



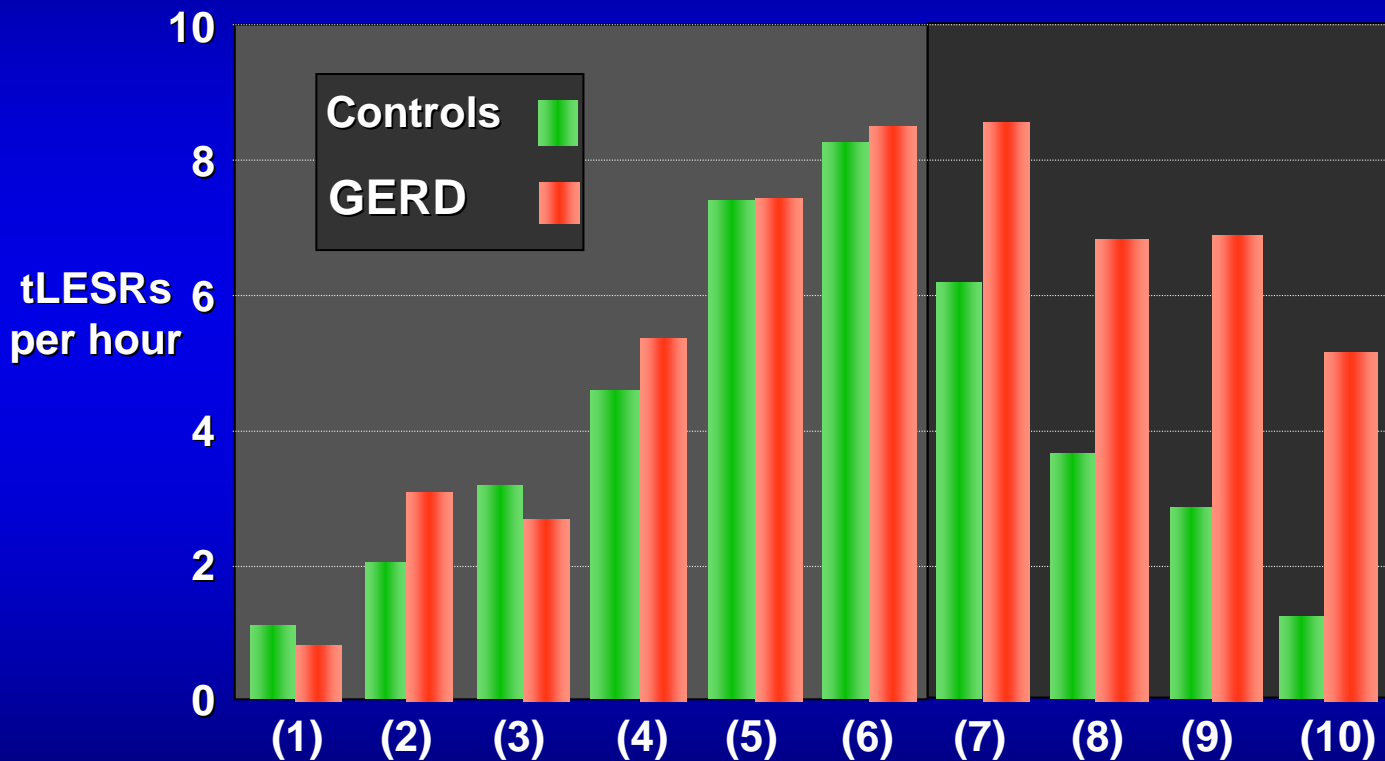
# FUNCTIONAL DYSPEPSIA DEFINITION: ROME III

- ✓ **Functional dyspepsia:  $\geq 1$  bothersome**
  - postprandial fullness, or
  - early satiety, or
  - epigastric pain, or
  - epigastric burning
  
- ✓ **No evidence of organic disease that is likely to explain the symptoms**
  
- ✓ **Overlap with GERD and IBS is common and does not exclude the diagnosis**
  
- ✓ **GERD may be accompanied by some dyspeptic symptoms. Presence of typical reflux symptoms should lead to a provisional diagnosis of GERD**

**Common mechanisms ?**

# Rate of tLESRs: Controls vs GERD Patients

## Combined manometry and pH monitoring

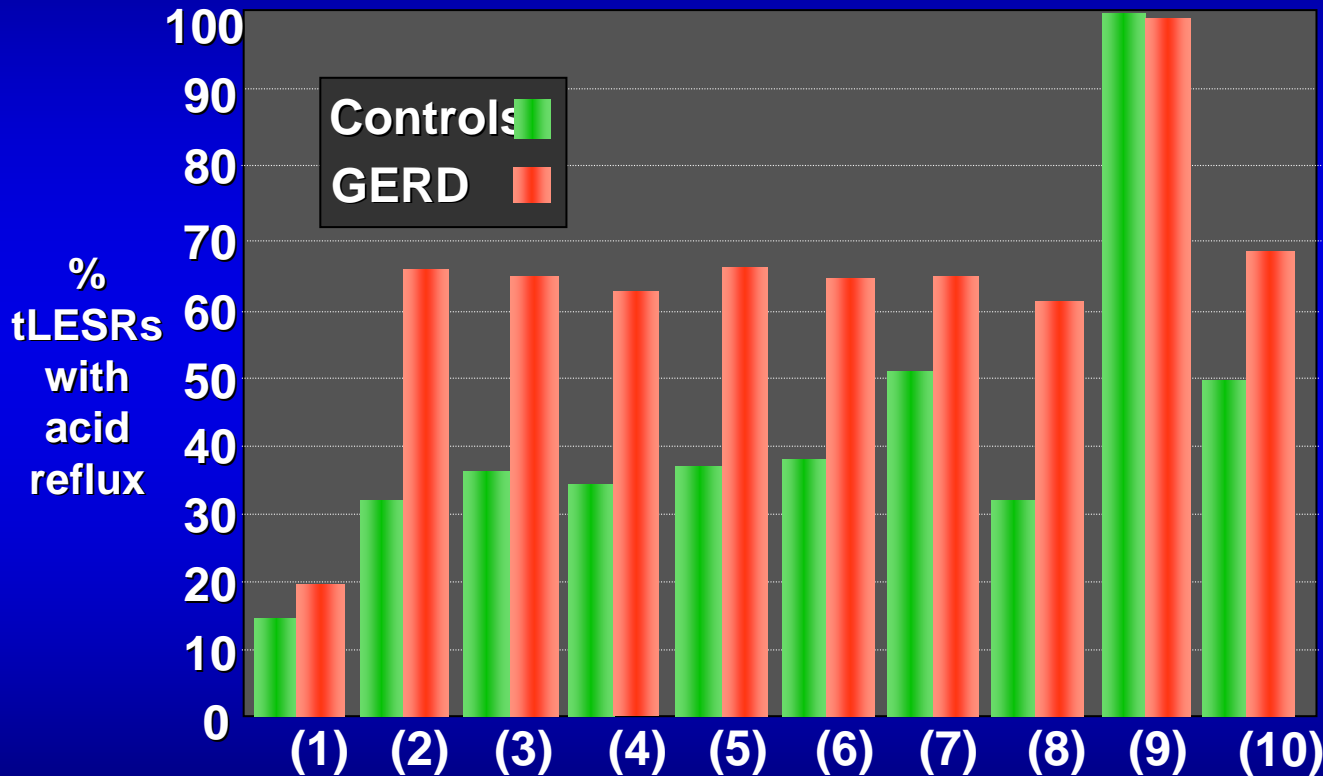


- 1) Kahrilas et al  
*Gut* 1990;31:4
- 2) Dodds et al  
*NEJM* 1982; 307:1547
- 3) Trudgill NJ, Riley SA.  
*AJG* 2001;55:2569
- 4) Schoeman  
*Gastro* 1995;108:83
- 5) Sifrim D et al.  
*AJG*2001;96:647
- 6) Mittal R et al.  
*Gastro* 1988;95:593
- 7) Holloway  
*Gut* 1997;40:449
- 8) Penagini et al  
*Gut* 1998;42:330
- 9) Penagini et al  
*Gastro* 1997;113:409
- 10)Hollowayet al  
*Dig Dis Sci* 1991;36:1034

Modified from Sifrim D and Holloway RW *AJG* 2001;96(9):2529

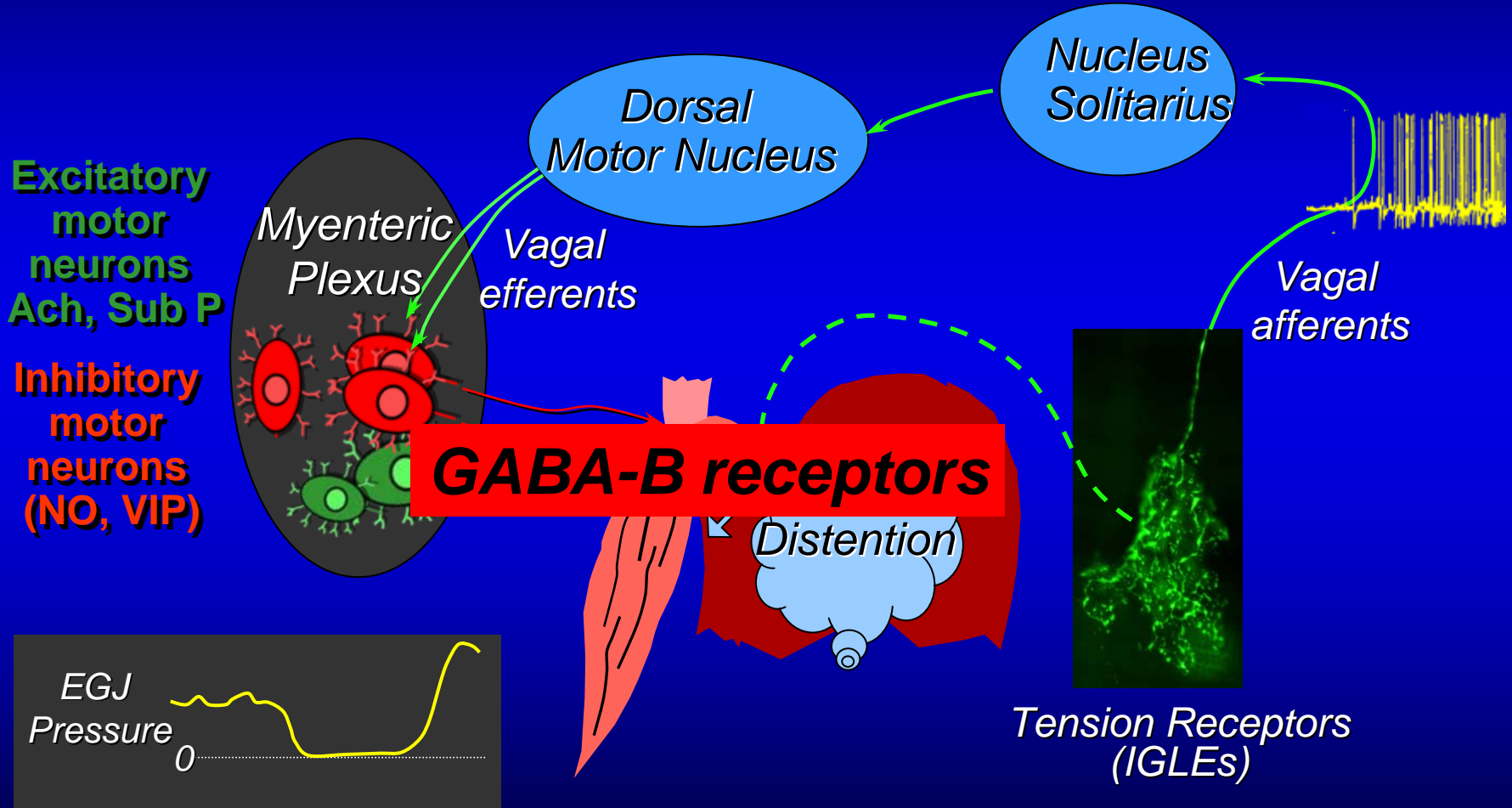
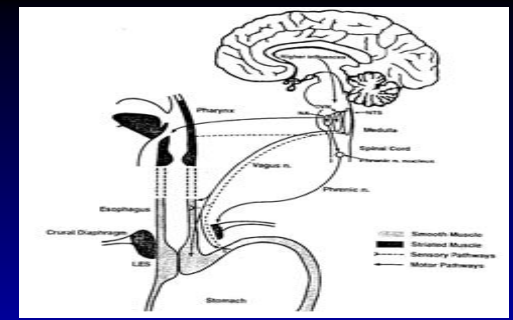
# Rate of tLESRs: Controls vs GERD Patients

## Combined manometry and pH monitoring

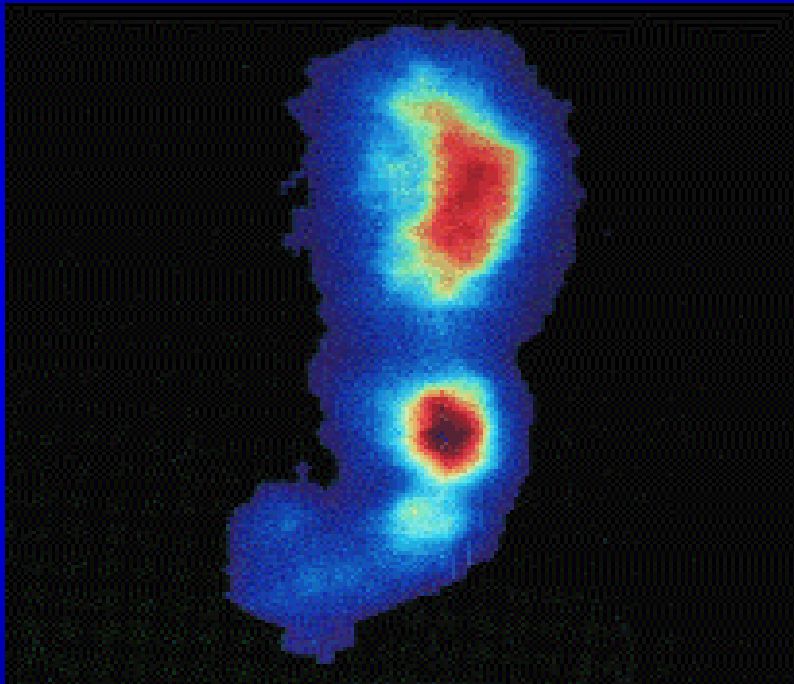


- 1) Kahrilas et al  
*Gut* 1990;31:4
- 2) Dodds et al  
*NEJM* 1982; 307:1547
- 3) Trudgill NJ, Riley SA.  
*AJG* 2001;55:2569
- 4) Schoeman  
*Gastro* 1995;108:83
- 5) Sifrim D et al.  
*AJG* 2001;96:647
- 6) Mittal R et al.  
*Gastro* 1988;95:593
- 7) Holloway  
*Gut* 1997;40:449
- 8) Penagini et al  
*Gut* 1998;42:330
- 9) Penagini et al  
*Gastro* 1997;113:409
- 10) Holloway et al *Dig Dis Sci* 1991;36:1034

# Transient LES Relaxation Neuromuscular Pathway

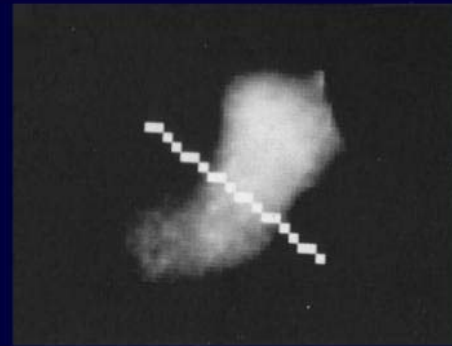


# CAN ALTERED GASTRIC FUNCTION IN DYSPEPSIA TRIGGER GERD ?



## INTRAGASTRIC DISTRIBUTION OF A RADIOLABELLED MEAL IN HEALTH AND FUNCTIONAL DYSPEPSIA (FD)

*Troncon et al, Gut 1994*



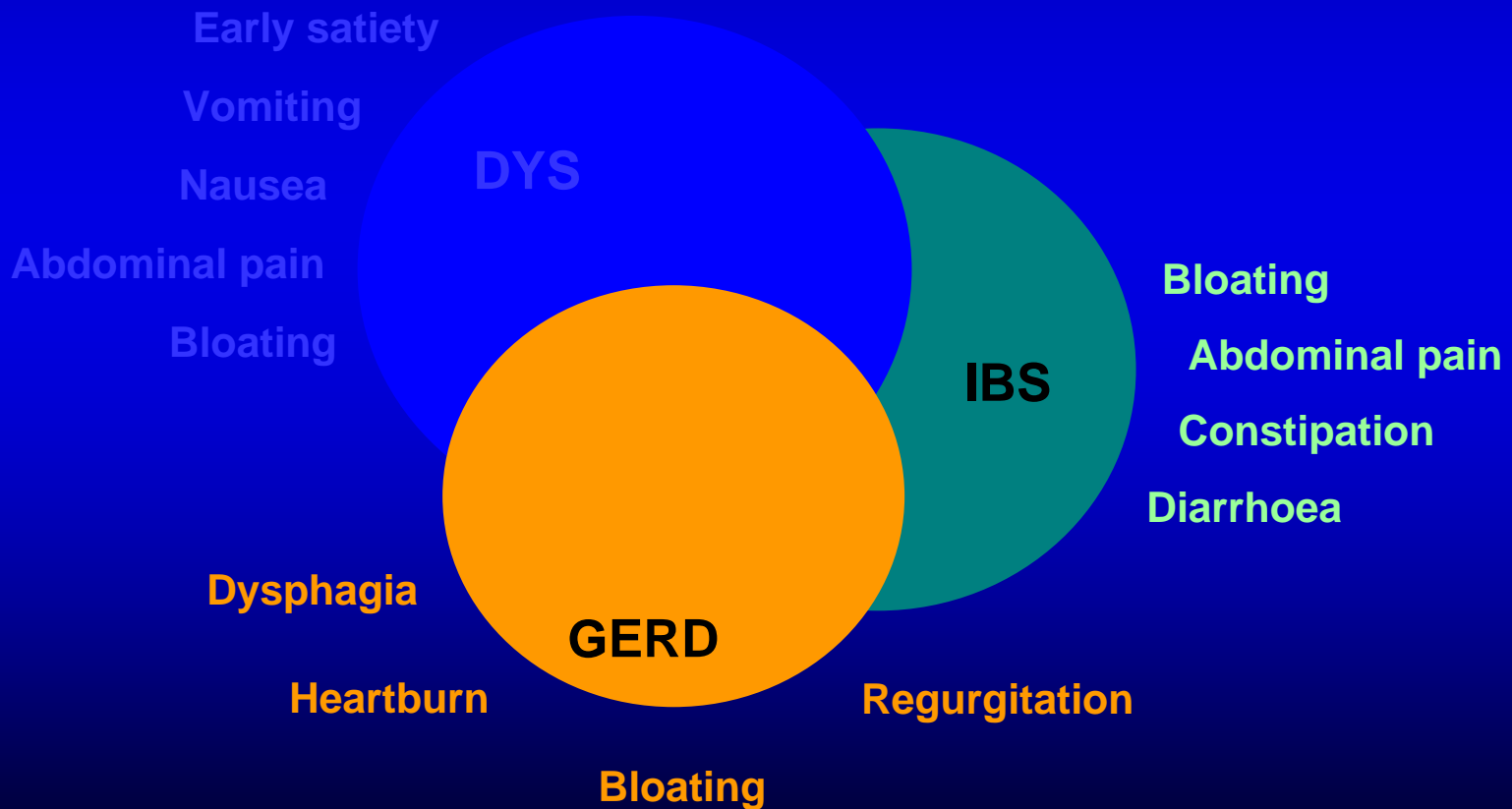
HEALTH



FD

# Overlap between GERD and IBS

Just by Chance ? Common Mechanisms?



**Just by chance ?**

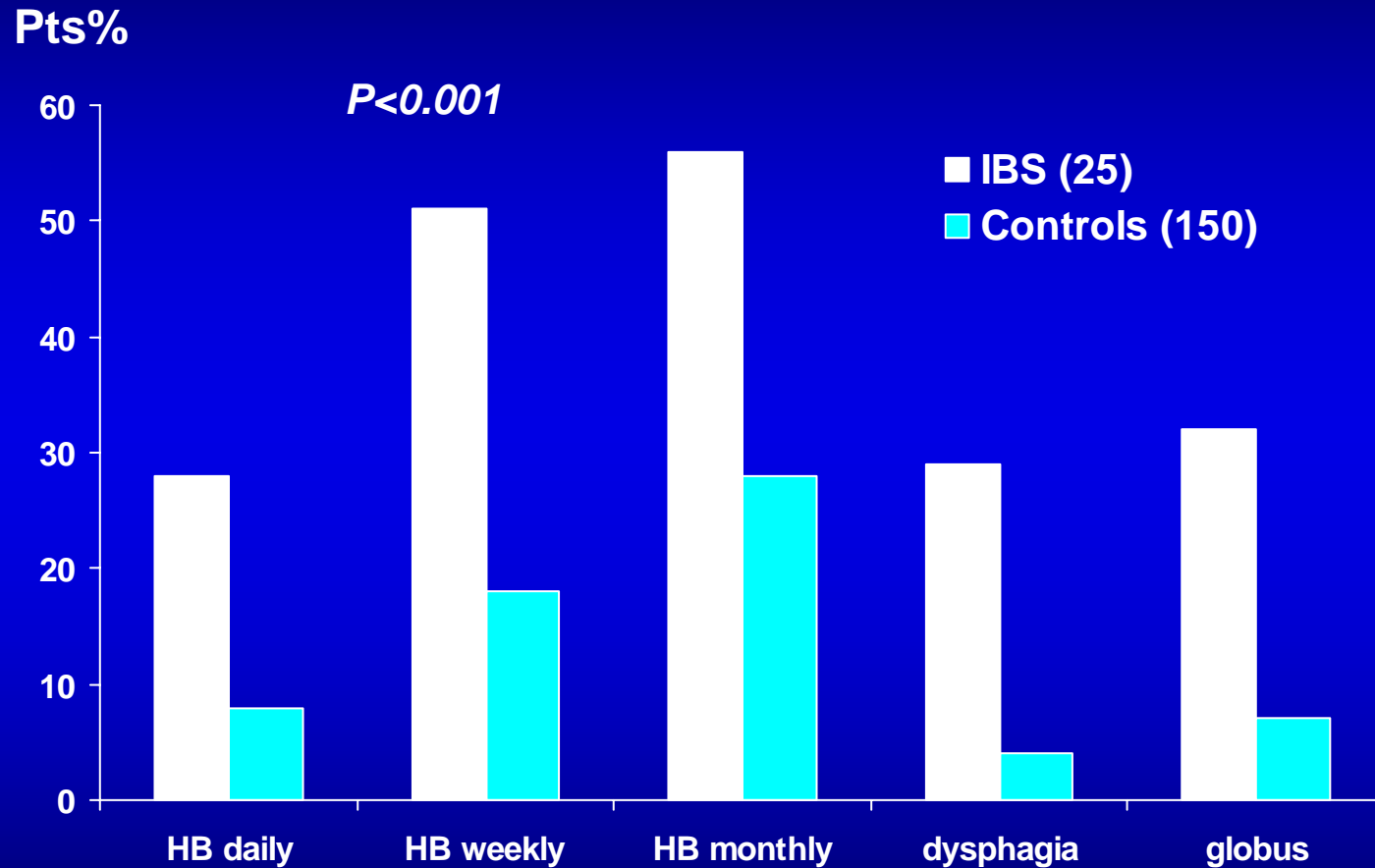
# UPPER GI SYMPTOM OVERLAP IN IBS PATIENTS

Symptoms	IBS-C	IBS-D
N° symptoms	6.67	4.62*
%		
Lower abd pain	41	24**
Upper abd pain	37	24
Bloating	75	41
Indigestion	49	36
Nausea	46	48
Early satiety	43	25
Heartburn	33	41

\* $P < 0.001$ ; \*\*  $P < 0.05$

Talley et al, AJG 2003

# ESOPHAGEAL SYMPTOMS IN IBS PATIENTS



**Common mechanisms ?**

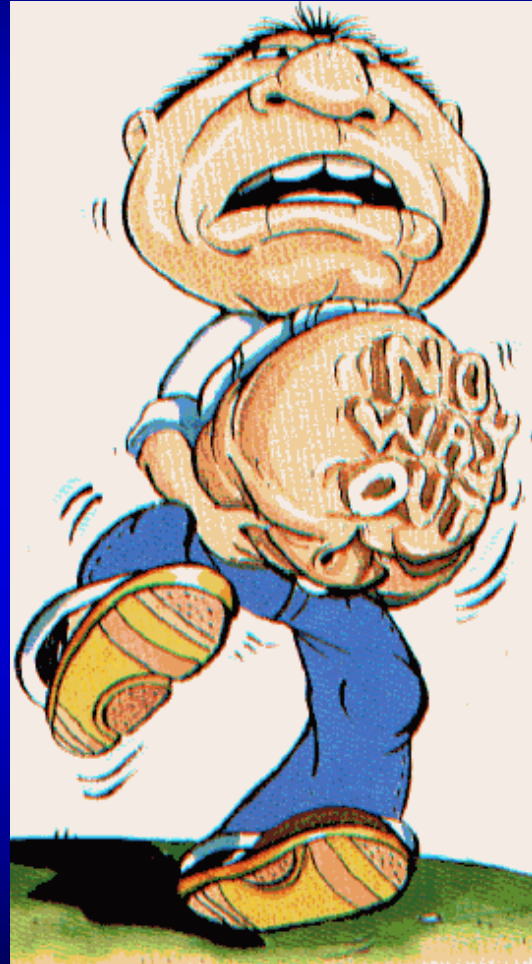
# GERD AND LES PRESSURE IN IBS PATIENTS

	IBS (25)%	Controls (150) %	p
<b>GERD</b> daily	28	7	<0.01
1/wk	52	17	<0.01
1/mo	56	26	<0.01

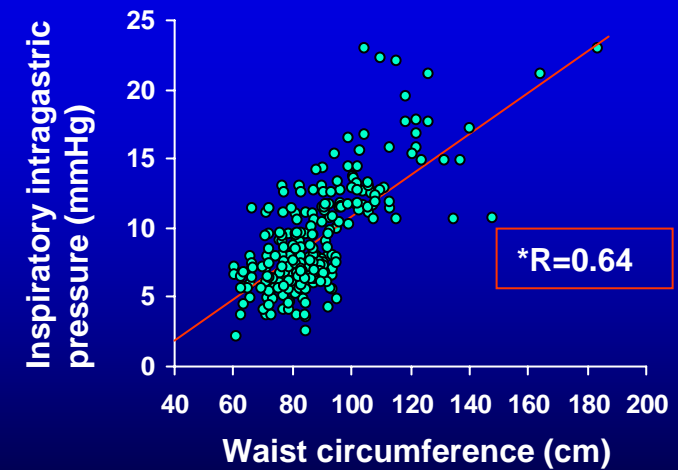
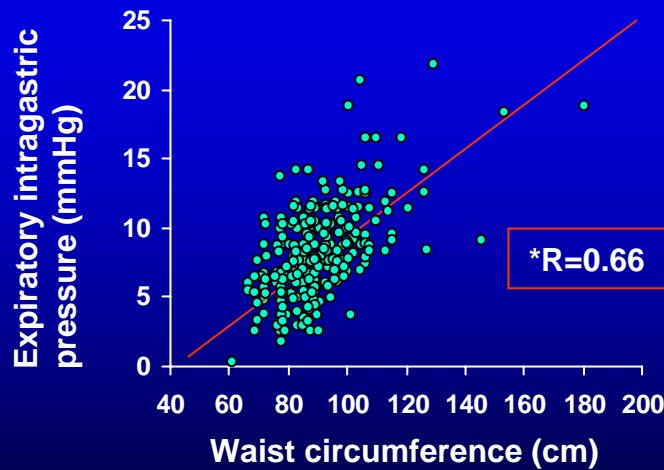
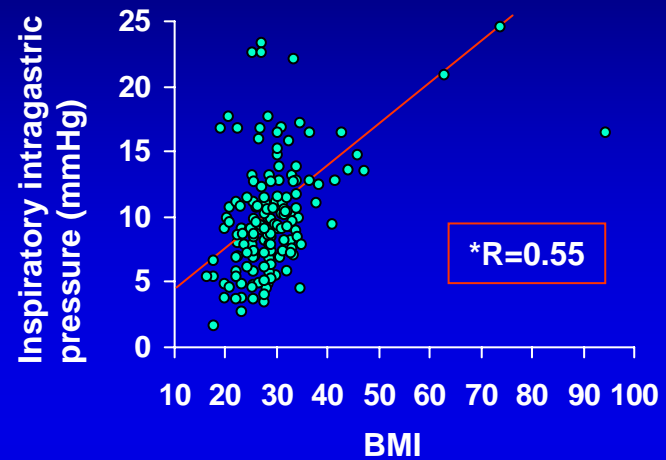
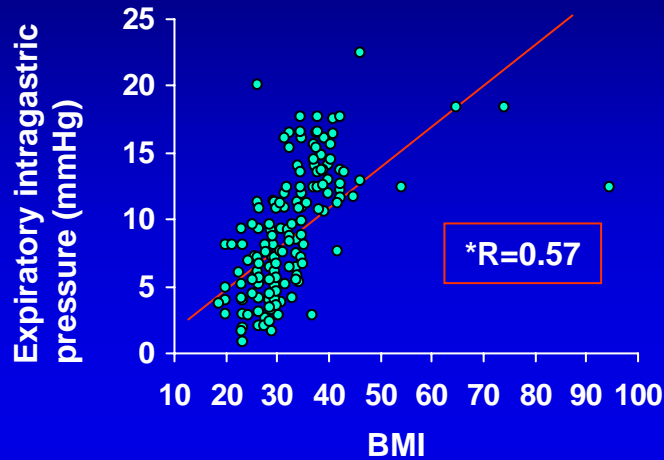
<b>mmHg</b>	N	IBS	Controls	p
All	25	14.0±5.0	19.4±5.1	<0.001
M	10	14.1±5.9	19.9±5.2	<0.05
F	15	13.9±5.0	19.0±5.1	<0.01



# GERD and overlapping IBS



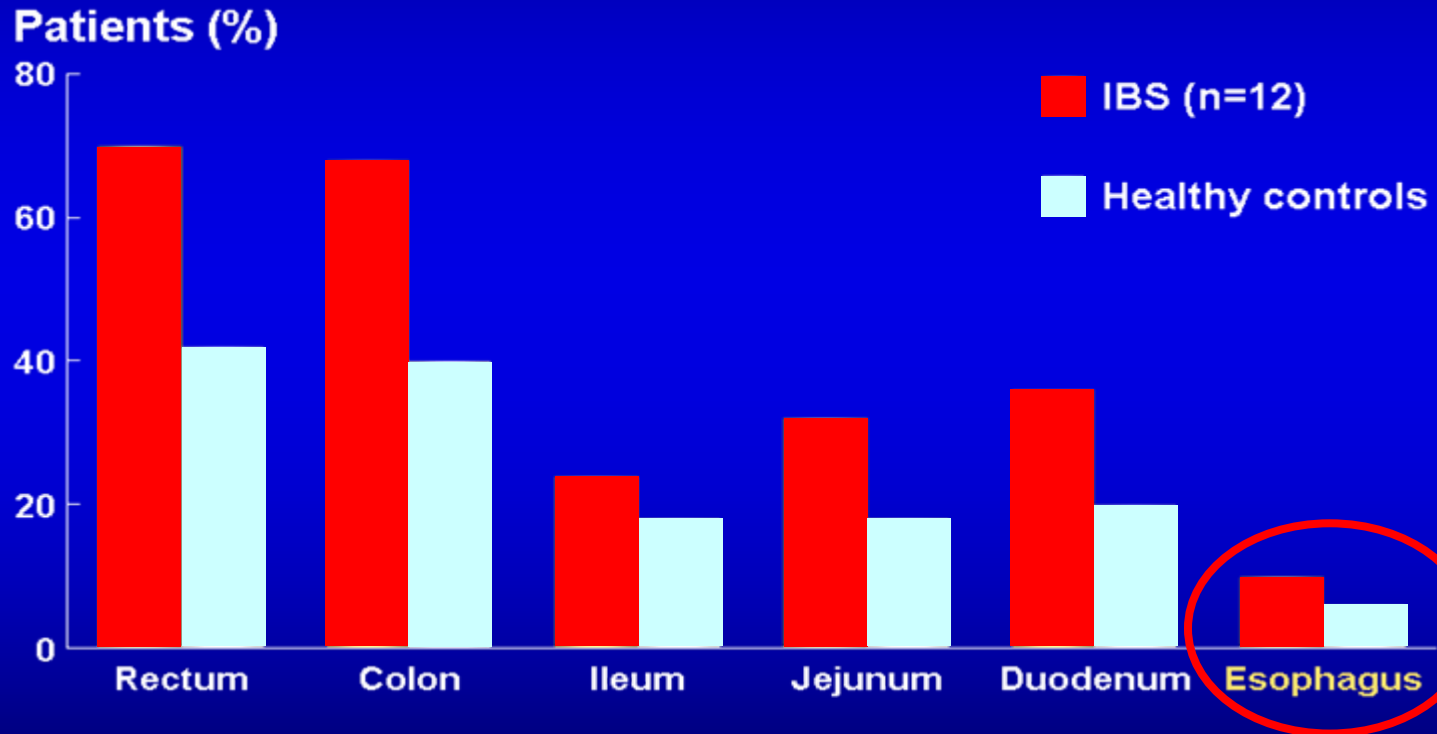
# ASSOCIATION BETWEEN INTRAGASTRIC PRESSURE AND BODY HABITUS



\*P>0.0001



# Visceral Hypersensitivity of the Whole Gut in IBS Patients



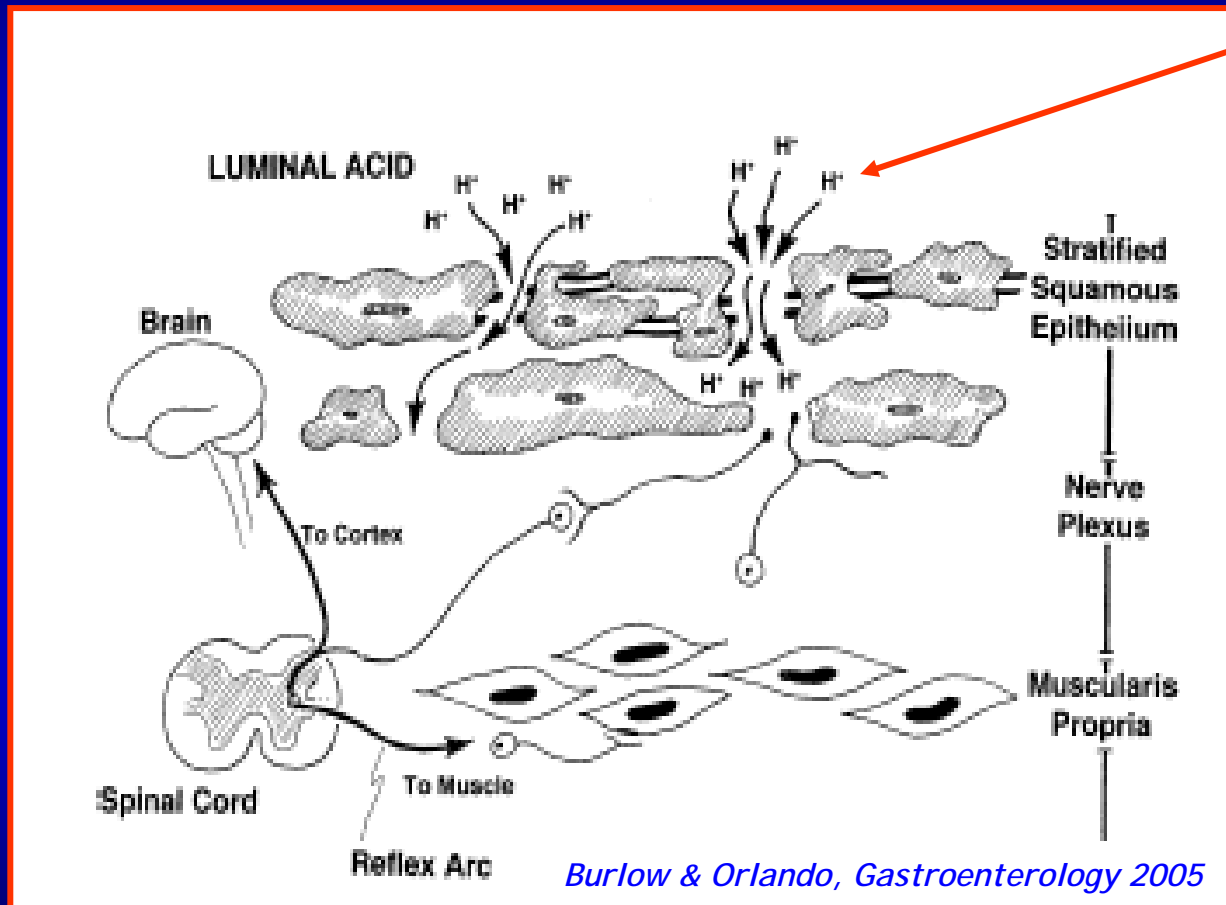






# Hypothetical pathophysiology of GERD symptoms

Abnormal  
Tissue  
Resistance

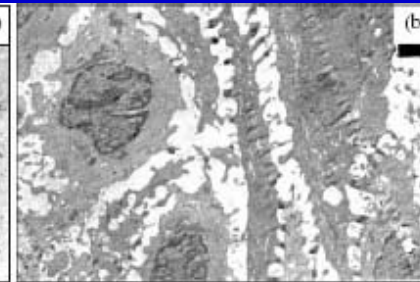
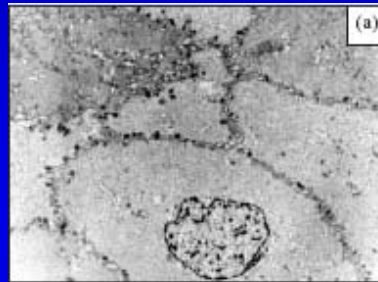


*Inappropriately increased perception or appropriately increased perception ?*

# Dilated intercellular spaces (DIS) as a marker of oesophageal damage in GERD with or without bile reflux

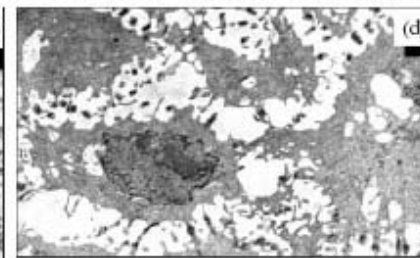
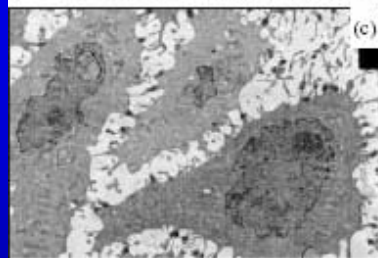
*Calabrese et al. APT 2003*

*control*



*DGE reflux*

*NERD*



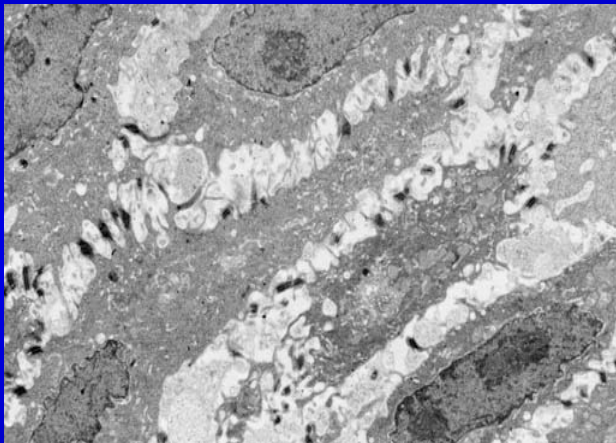
*esophagitis*

- *DIS is a sensitive marker of damage in GORD*
- *A mean DIS of 0.74  $\mu\text{m}$  provides a cut-off score for damage*
- *No correlation between DIS and acid or mixed acid exposure*

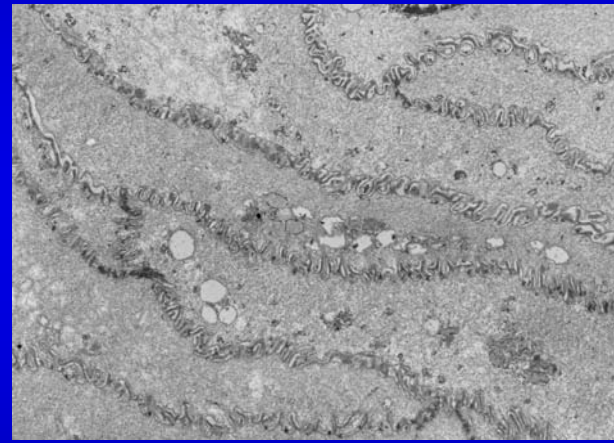
# Reversibility of GERD Ultrastructural Alterations and Relief of Symptoms After Omeprazole Therapy

*Calabrese et al. AJG 2005*

*before  
Tx*



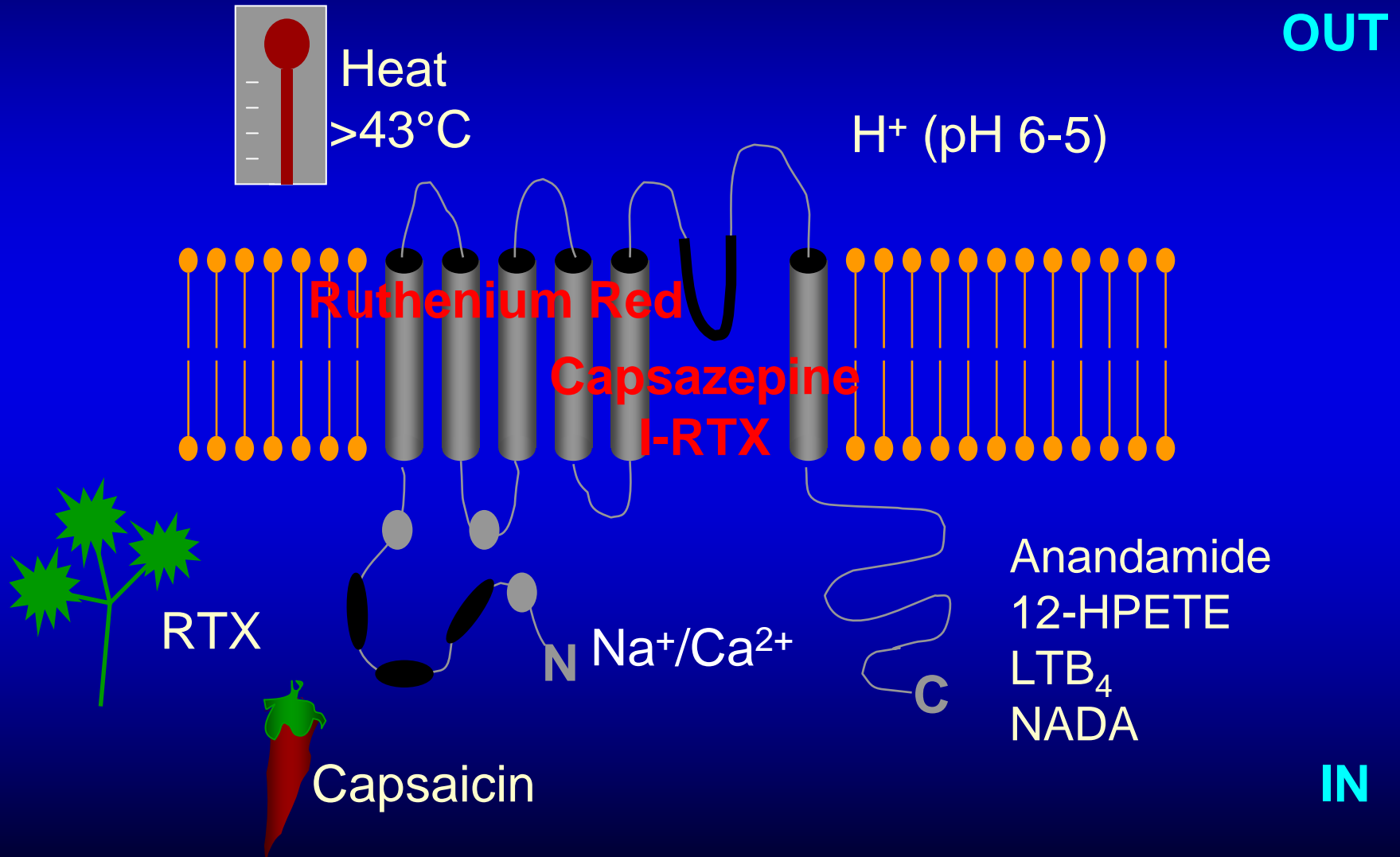
*after Tx*



- *Complete recovery of DIS on OME for 3 mos (92.1%) and 6 mos (97.4%)*
- *No significant differences of DIS in NERD and esophagitis*
- *Complete recovery of DIS associated with regression of heartburn in all cases*

**What are the sensory nerves / receptors  
potentially responsible for perception  
of esophageal “luminal” events ?**

# Vanilloid Receptor-1 (VR1 or TRPV1)



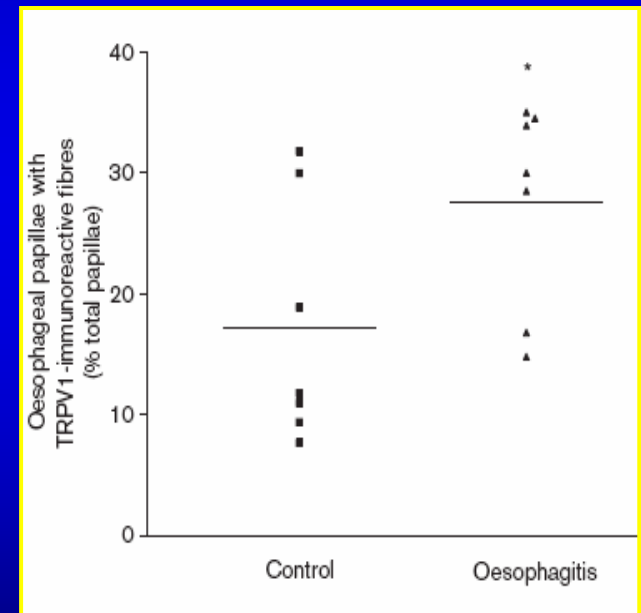
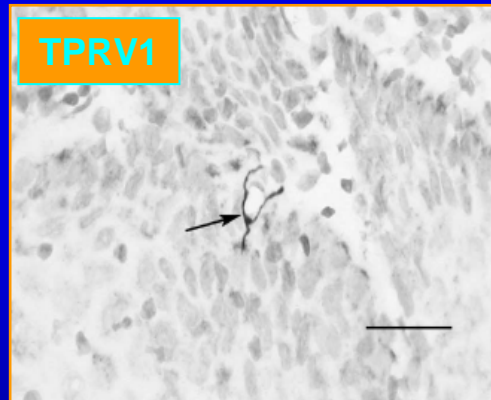
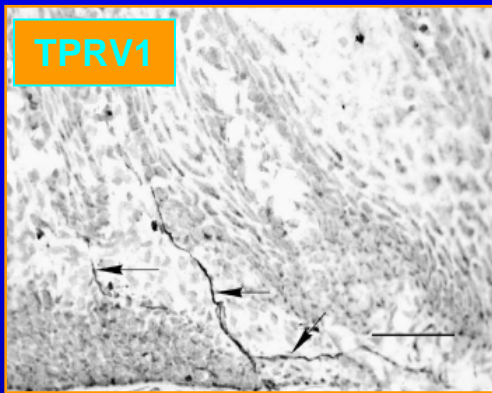


# Increased TRPV1 IR Nerves in Biopsies of Patients with Erosive Esophagitis

*Matthews et al., Eur J GH 2004*

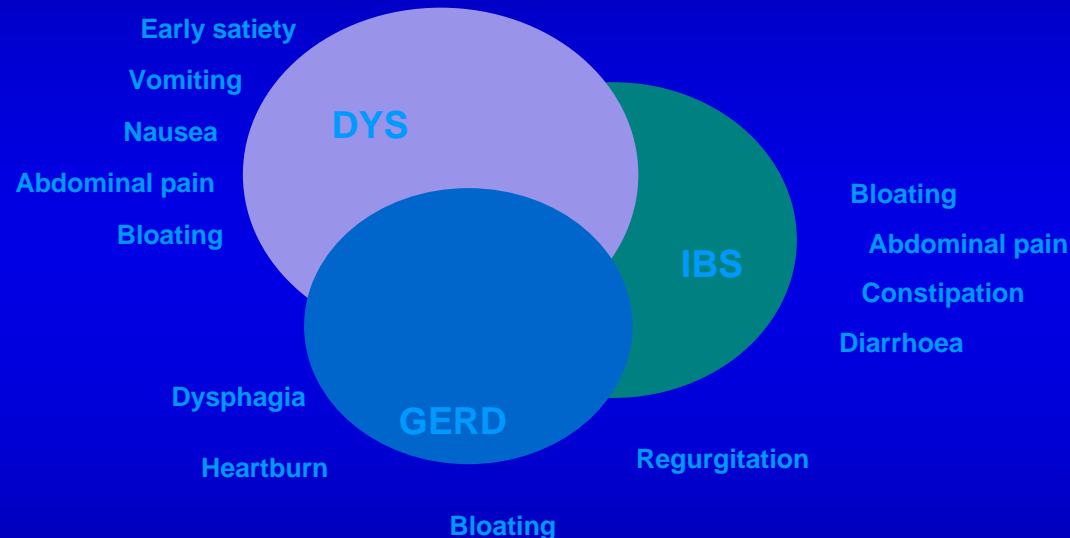
**Erosive Esophagitis**

**Control**



# Overlap of Symptom Complexes and Diagnoses

... probably not just by chance ...



- *Increased mucosal permeability, mild inflammation, abnormal neuroimmune interactions, abnormal motility, visceral hypersensitivity*
- *Direct inter-organ interference*