Helicobacter pylori and NSAID Induced Peptic Ulcer Disease

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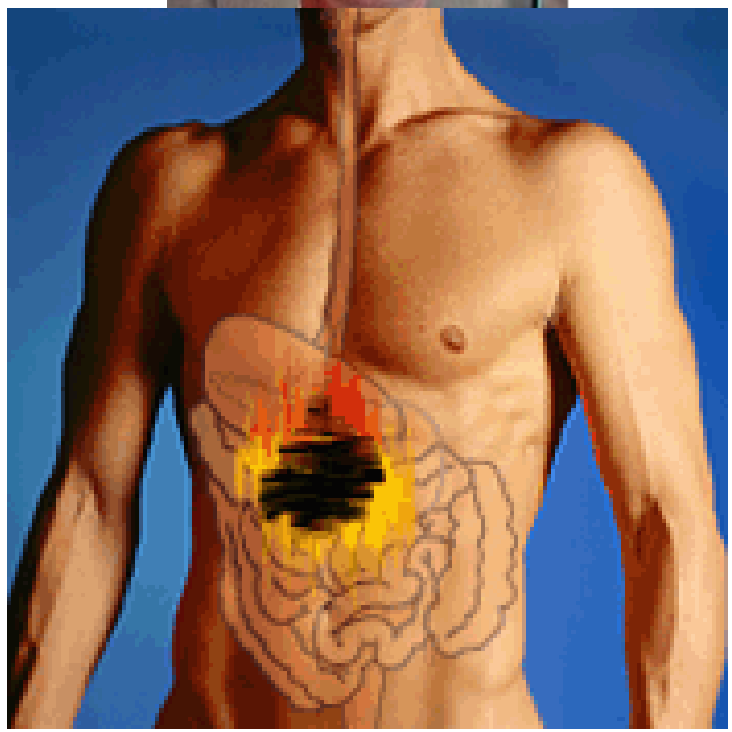
8/4/2011

Peptic Ulcer Disease

Typical Symptoms

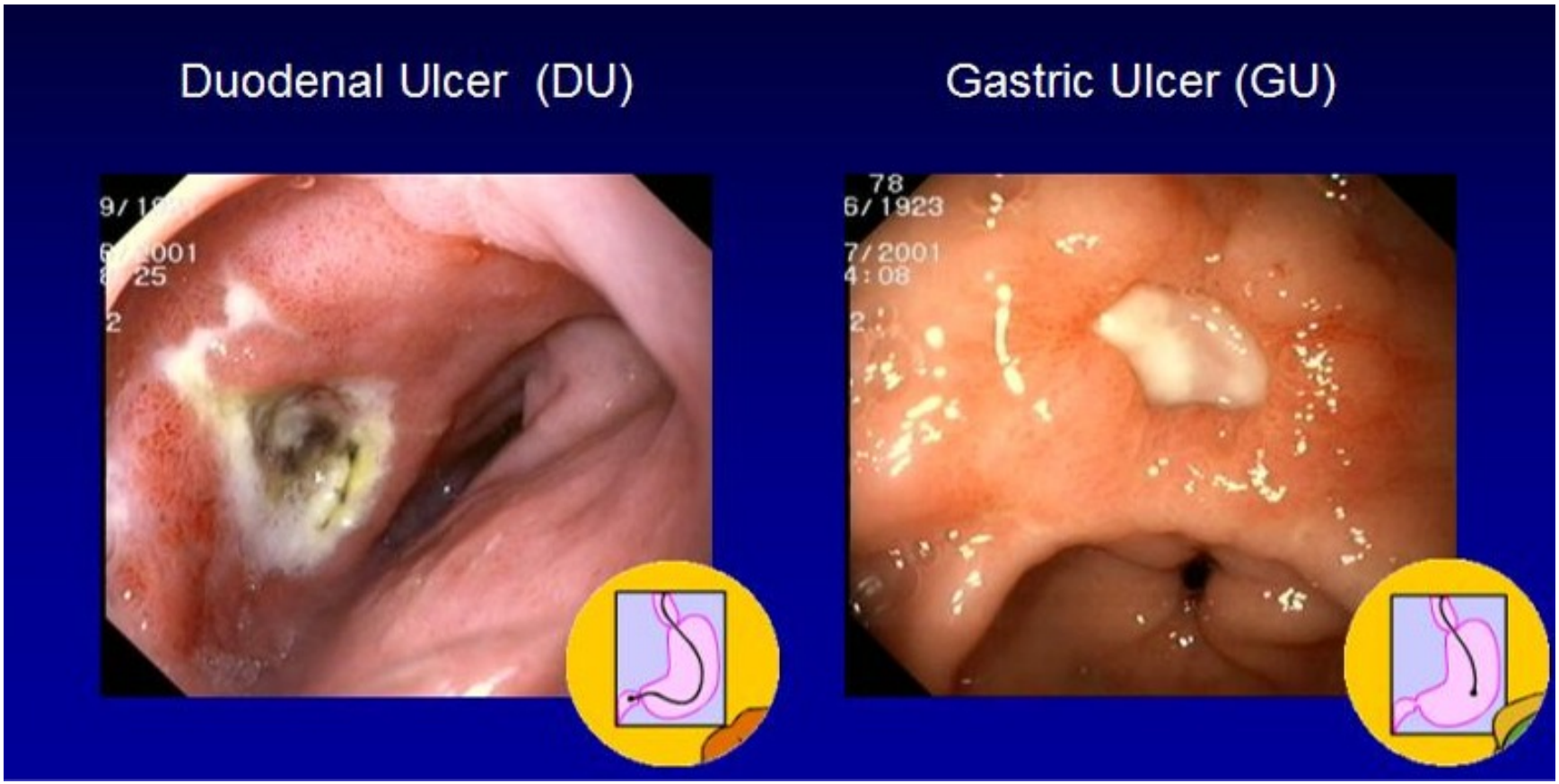
- Epigastric pain
- Nausea
- Fullness
- Bloating
- Early Satiety
- Nocturnal Pain



Alarm Symptoms

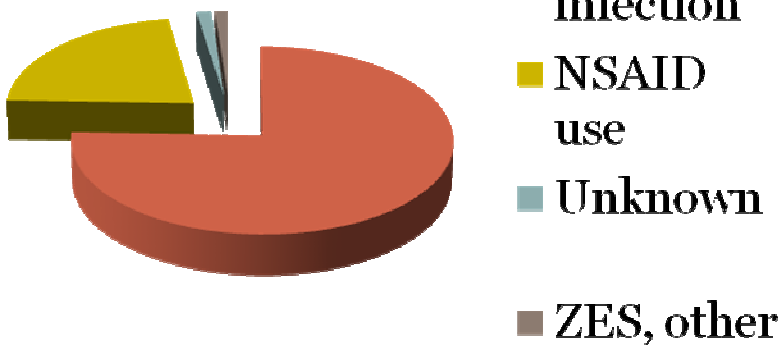
- Anemia
- Hematemesis
- Melena
- Anorexia or weight loss
- Severe upper abdominal pain

Peptic Ulcer Disease

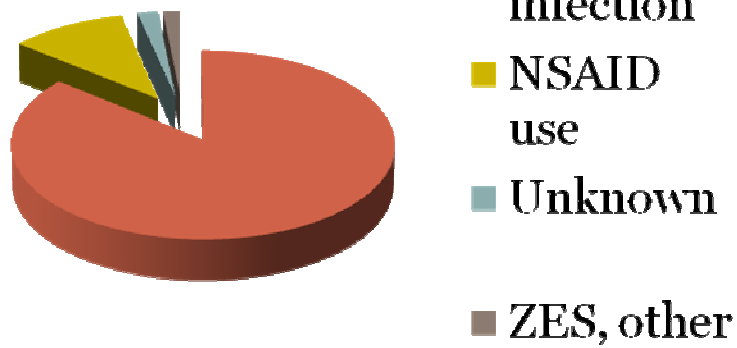


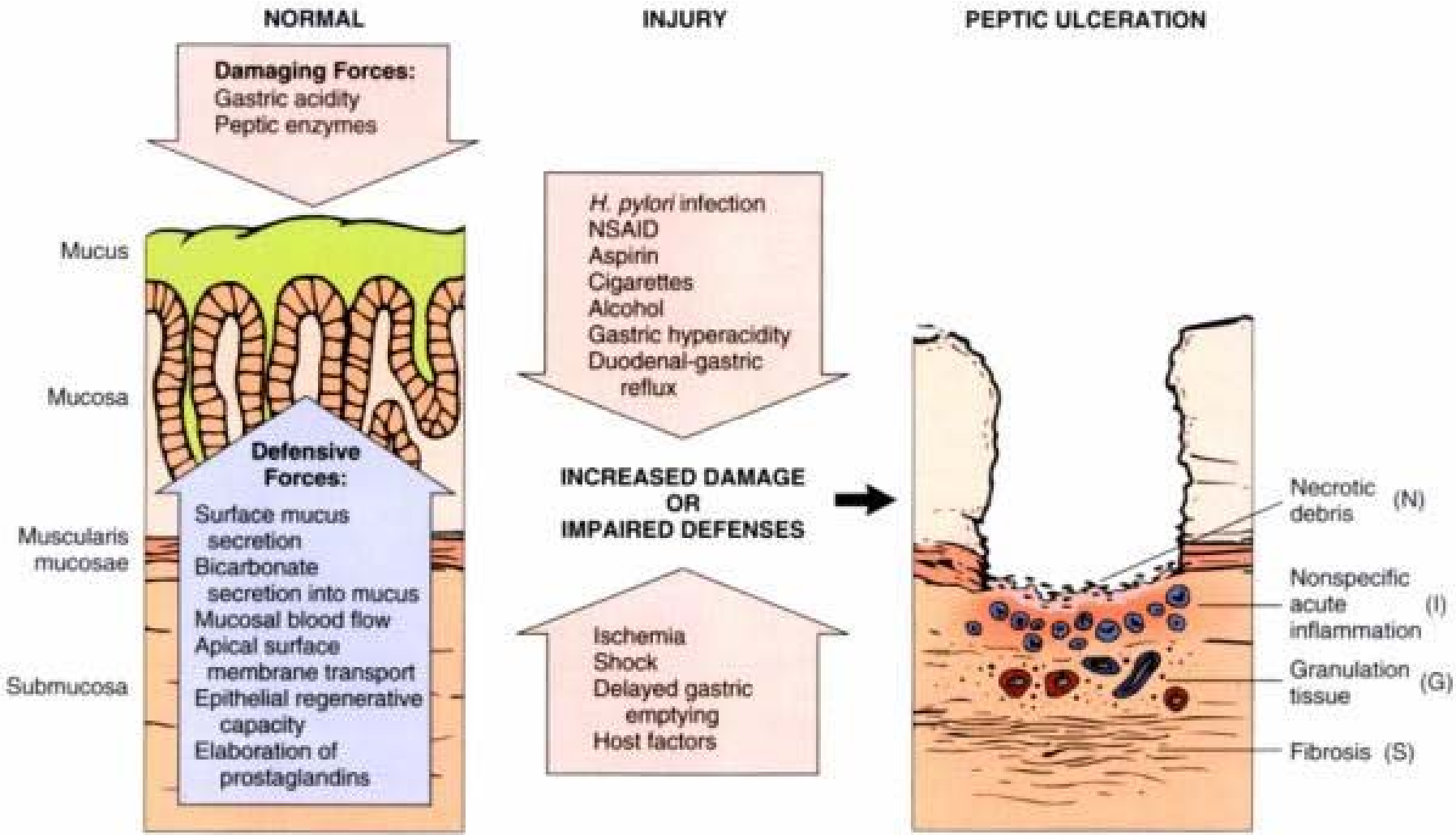
Conditions Associated with peptic ulcer disease

Gastric Ulcers



Duodenal Ulcers




NORMAL
INJURY
PEPTIC ULCERATION
Damaging Forces:
Gastric acidity
Peptic enzymes
Mucus
Mucosa
Defensive Forces:
Surface mucus secretion
Bicarbonate secretion into mucus
Mucosal blood flow
Apical surface membrane transport
Epithelial regenerative capacity
Elaboration of prostaglandins
Muscularis mucosae
Submucosa
H. pylori infection
NSAID
Aspirin
Cigarettes
Alcohol
Gastric hyperacidity
Duodenal-gastric reflux
INCREASED DAMAGE OR IMPAIRED DEFENSES
Ischemia
Shock
Delayed gastric emptying
Host factors
Necrotic debris (N)
Nonspecific acute inflammation (I)
Granulation tissue (G)
Fibrosis (S)


DAILY HAHA

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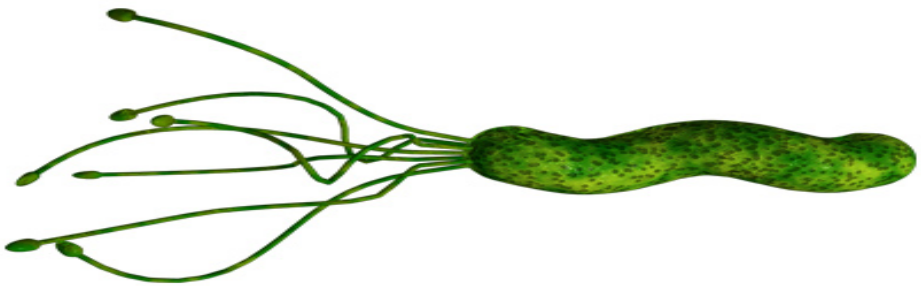
OUTBACK
STEAKHOUSE®



Barry Marshall

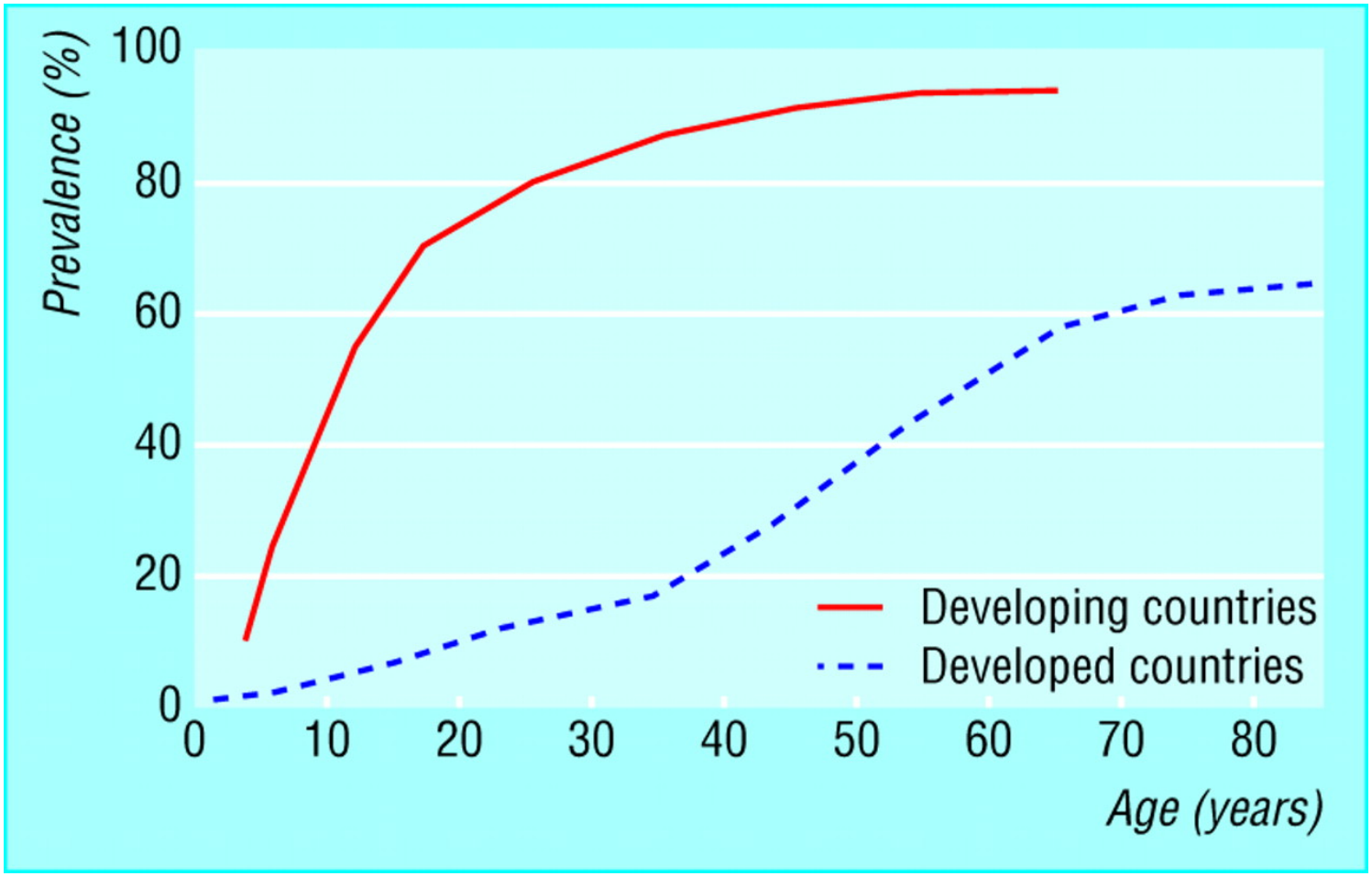
-Received Nobel Prize in Physiology in 2005 for study on relationship between H. pylori and gastritis and peptic ulcer disease

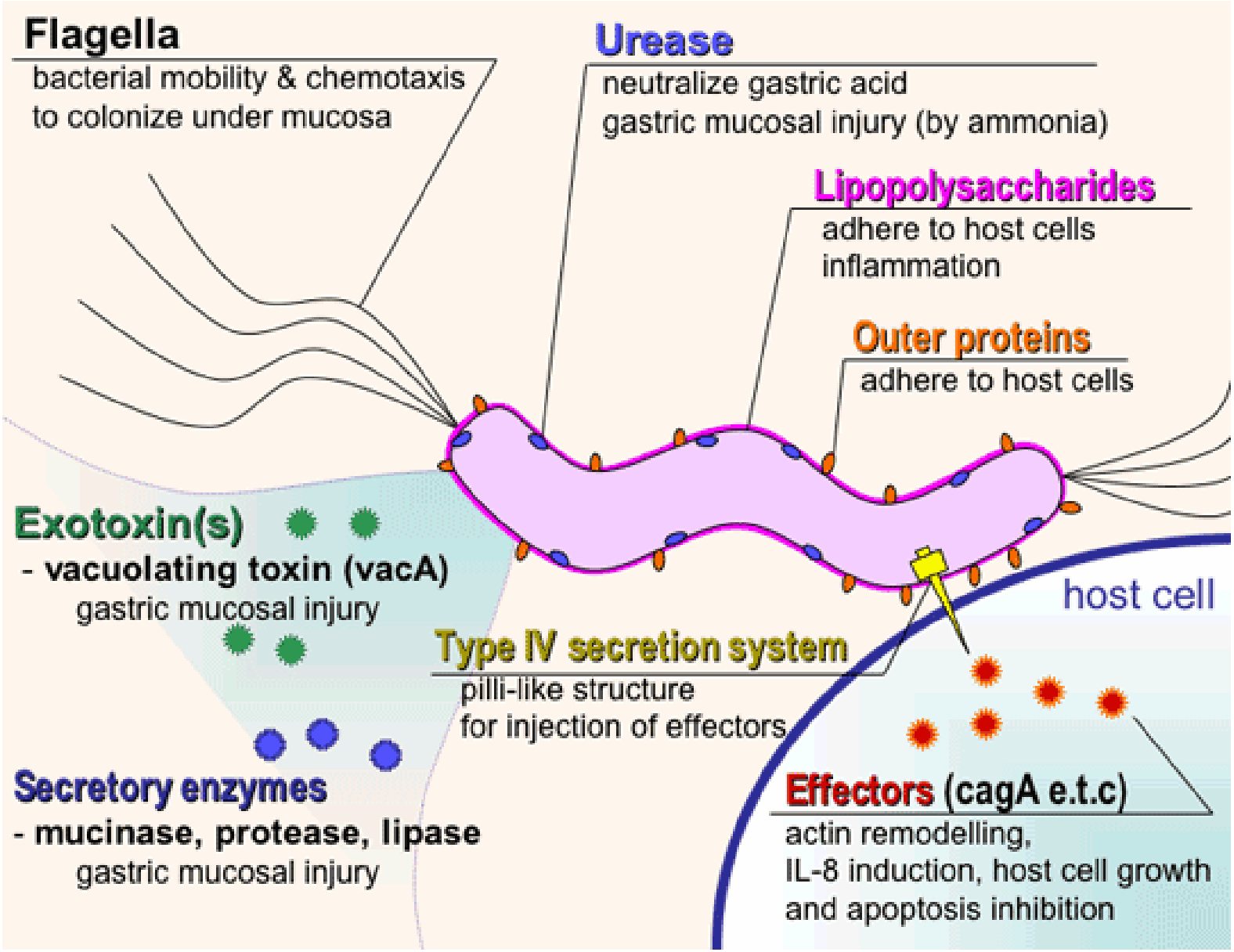
-Drank petri dish full of H. pylori bacterium and on day 5 developed abd pain and vomiting. On day 14 underwent an upper endoscopy which showed gastritis

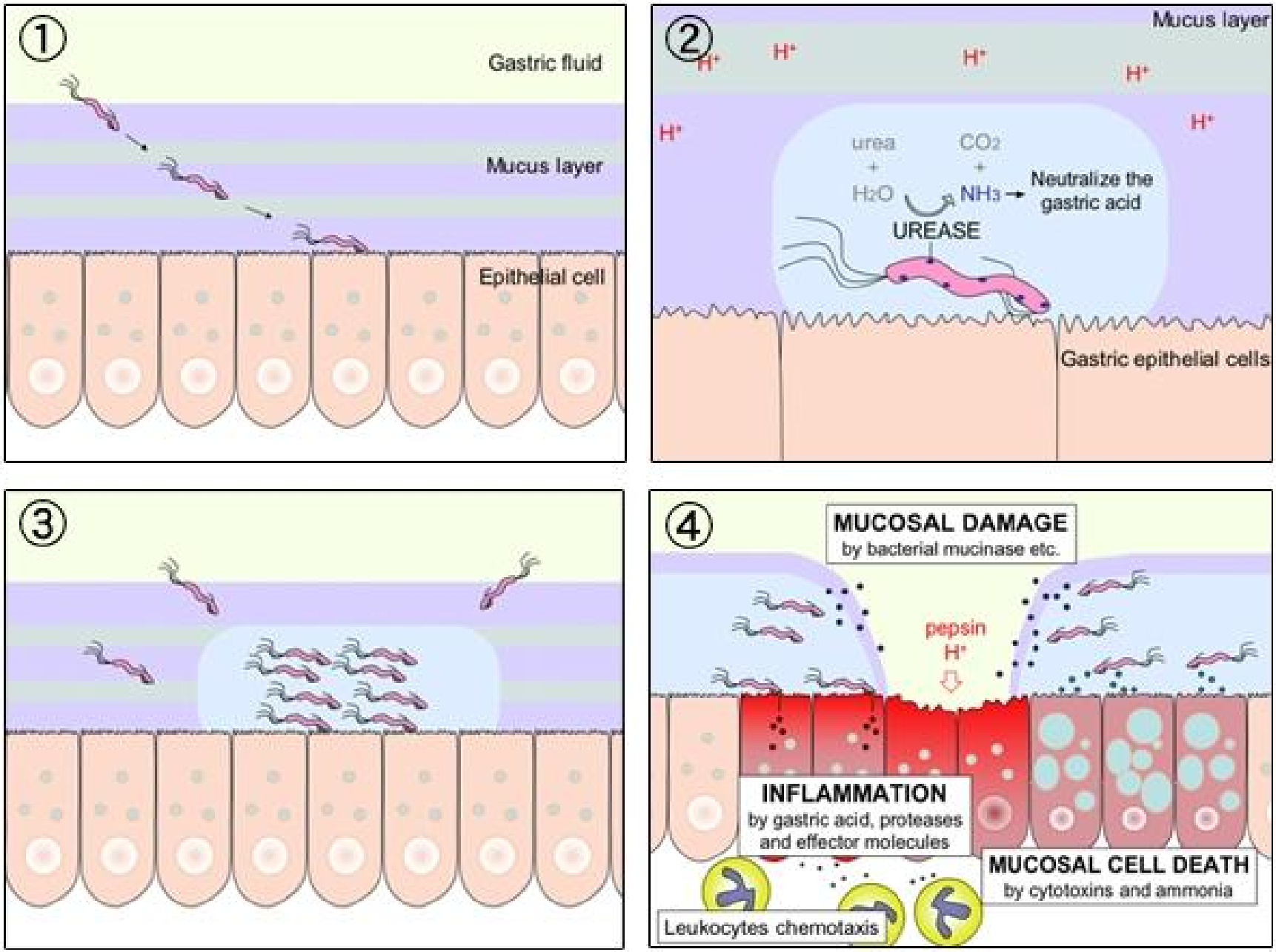
- For his pompous, arrogant approach to clinical research he was awarded a faculty position at an institution well known for similar medicine residents…

Helicobacter pylori Epidemiology

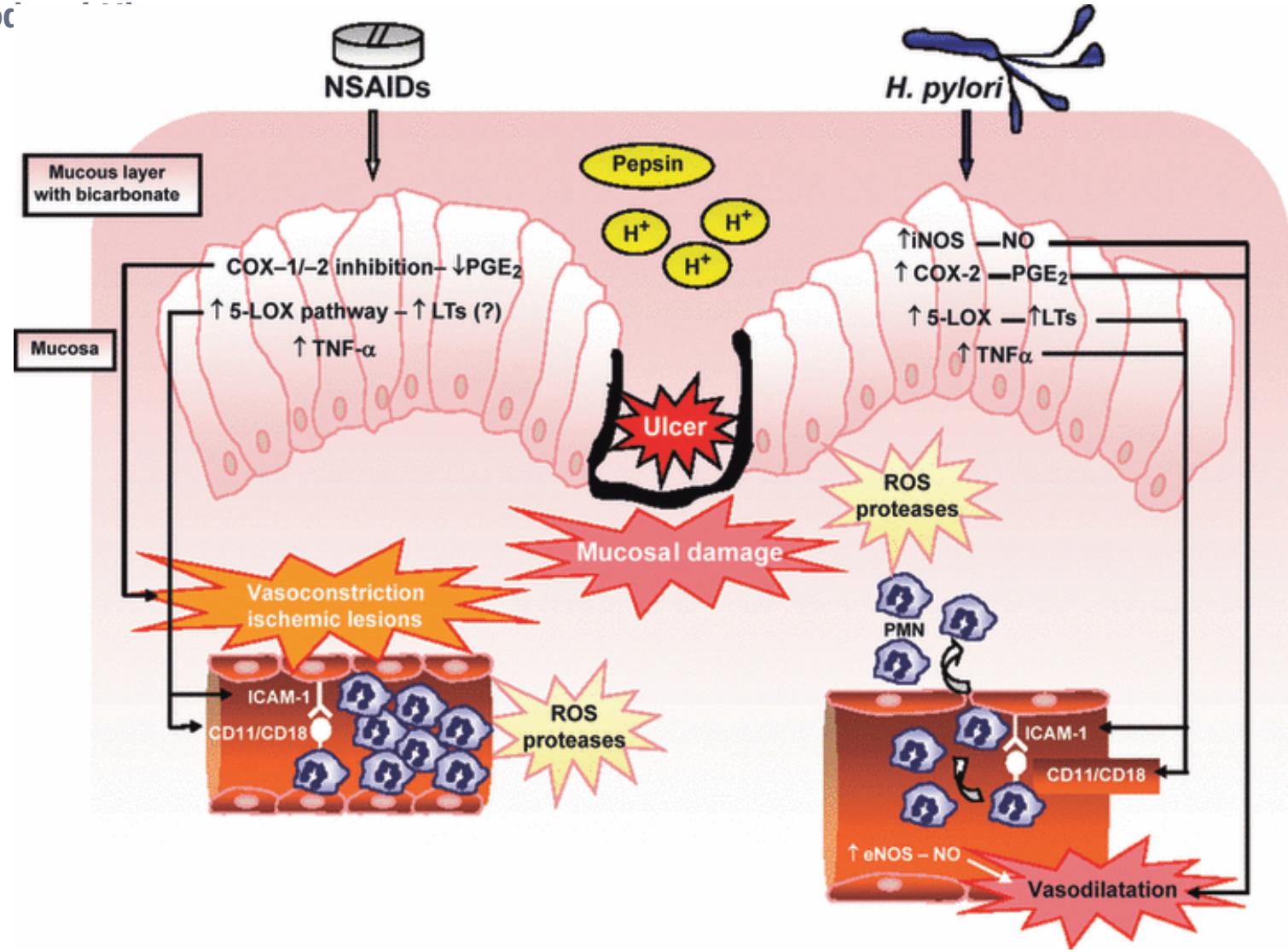
- One of the most common chronic bacterial infections in humans (>50% of world's population is infected)
- Gastric cancer is 2nd leading cause of cancer death worldwide
- Risk of infection related to housing density, crowded conditions, number of siblings, sharing a bed, lack of hot or running water
- Human is major reservoir but domestic cats can also harbor these organisms


Prevalence (%)
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
Age (years)
Developing countries
Developed countries


Flagella
bacterial mobility & chemotaxis
to colonize under mucosa
Urease
neutralize gastric acid
gastric mucosal injury (by ammonia)
Lipopolysaccharides
adhere to host cells
inflammation
Outer proteins
adhere to host cells
Exotoxin(s)
- vacuolating toxin (vacA)
gastric mucosal injury
host cell
Type IV secretion system
pilli-like structure
for injection of effectors
Secretory enzymes
- mucinase, protease, lipase
gastric mucosal injury
Effectors (cagA e.t.c)
actin remodelling,
IL-8 induction, host cell growth
and apoptosis inhibition


①
Gastric fluid
Mucus layer
Epithelial cell
②
Mucus layer
H+
urea
+
H2O
CO2
+
NH3
Neutralize the gastric acid
UREASE
Gastric epithelial cells
③
④
MUCOSAL DAMAGE
by bacterial mucinase etc.
pepsin
H+
INFLAMMATION
by gastric acid, proteases and effector molecules
MUCOSAL CELL DEATH
by cytotoxins and ammonia
Leukocytes chemotaxis

Interaction of Infection and Nonsteroidal Anti-Inflammatory Drugs in Gastric and Duod

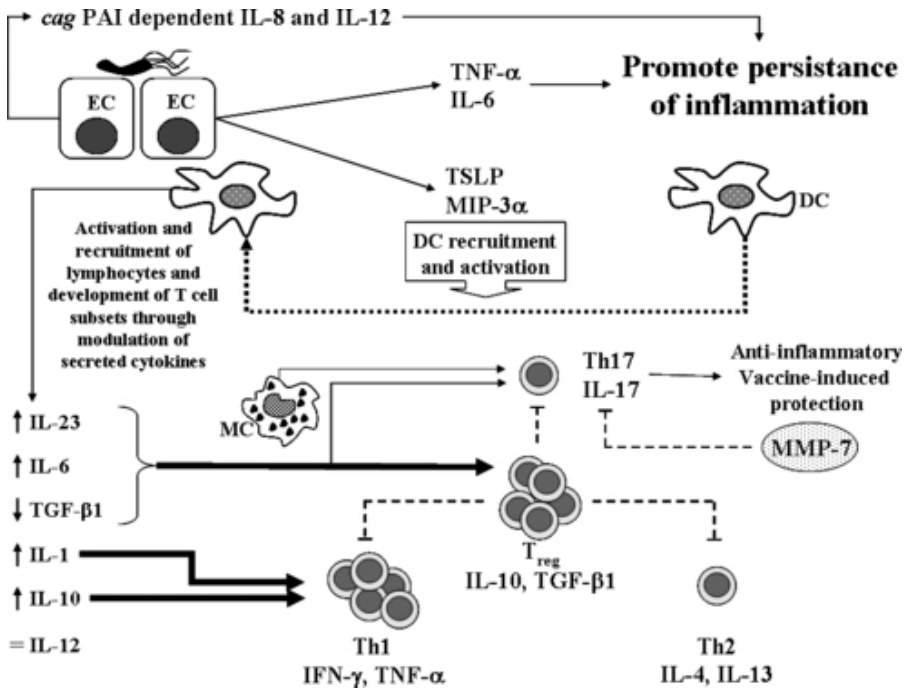


Helicobacter
Volume 15, Issue 4, pages 239-250, 16 JUL 2010 DOI: 10.1111/j.1523-5378.2010.00762.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1523-5378.2010.00762.x/full#f3

cag

- Results in more corpus inflammation
- Decrease in gastric acidity
- Increase in Proinflammatory cyotkines (IL-8, IL-1, TGF-β, TNF-α)
- Increased Gastrin
- Increased risk of Gastric cancer
- Decreased risk of GERD, Barrett's, and esophageal adenocarcinoma)

Pathogenesis of Infection



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pages 14-20, 5 NOV 2010 DOI: 10.1111/j.1523-5378.2010.00781.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1523-5378.2010.00781.x/full#f1

Consequences of Infection

Gastric

- Nothing
- Chronic active gastritis
- Peptic Ulcer Disease
- Gastric adenocarcinoma
- Lymphoma of the gastric mucosa-associated lymphoid tissue

Extragastric

- Iron deficiency anemia
- ITP
- Thyroid disease
- HTN
- SIDS
- Rosacea
- Chronic urticaria

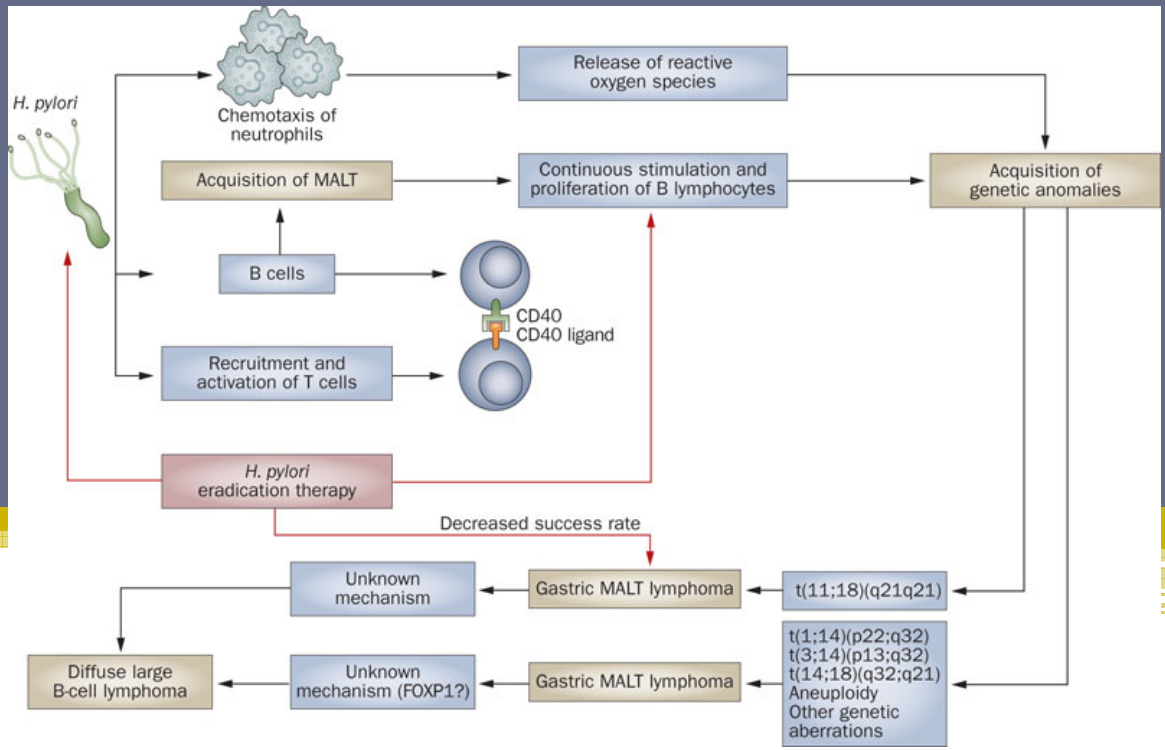
"I've had no appetite ever since I developed a bleeding ulcer!"

MALT-lymphoma

- For localized gastric MALT lymphoma, H. pylori treatment = tumor regression in 60-90% of patients
- H. pylori eradication in patients with low-grade MALT lympoma = recurrence rates of 3-13% over 5 years

- More recent study showed
  - High grade MALT lymphoma
  - H. pylori eradication = complete remission in 64%
    - Of these, relapse rate = 0% at 5 yrs

Figure 2 Hypothetical model of gastric MALT lymphoma pathogenesis



Sagaert, X. *et al.* (2010) Gastric MALT lymphoma: a model of chronic inflammation-induced tumor development
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2010.58

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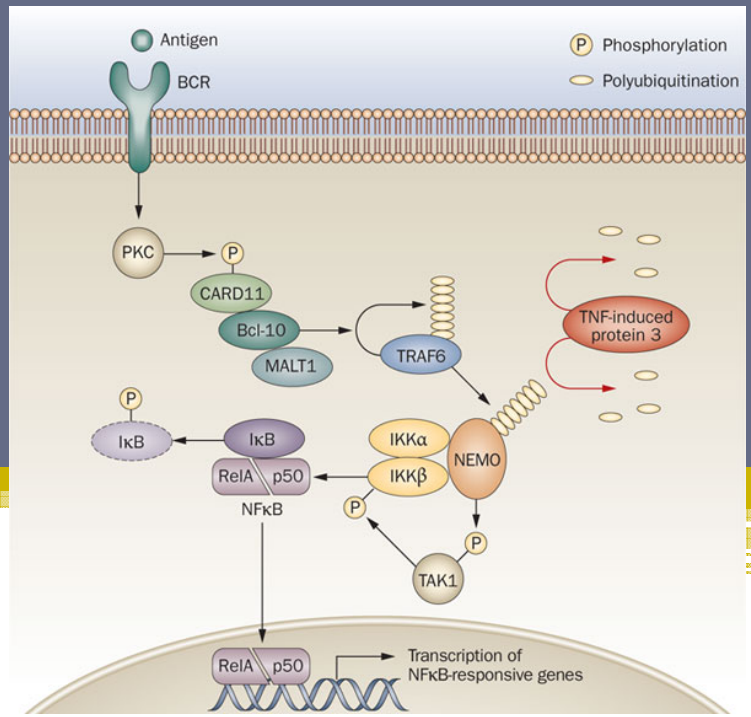
Figure 4 The canonical NFκB signaling pathway



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Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2010.58

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Who to test?

Established

- PUD
- Gastric low-grade MALT lymphoma
- Uninvestigated dyspepsia
- After endoscopic resection of early cancer
- Evaluate success of eradication therapy

Controversial

- High risk for Gastric Cancer (family hx)
- Unexplained iron deficiency anemia
- Nonulcer dyspepsia
- Chronic NSAID/ASA therapy
- Chronic antisecretory therapy
- Relatives of patients who have H. pylori infection


CHEATER
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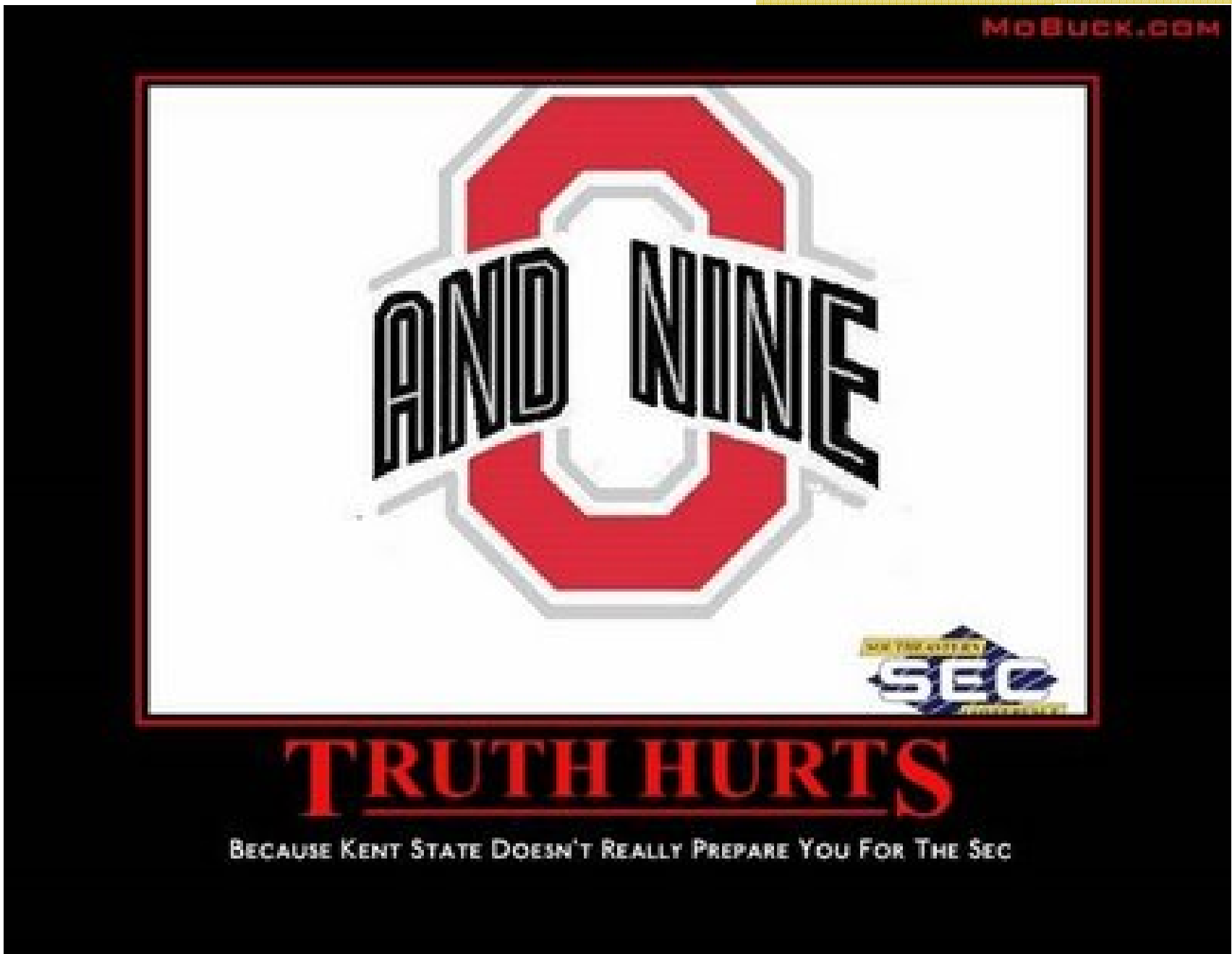
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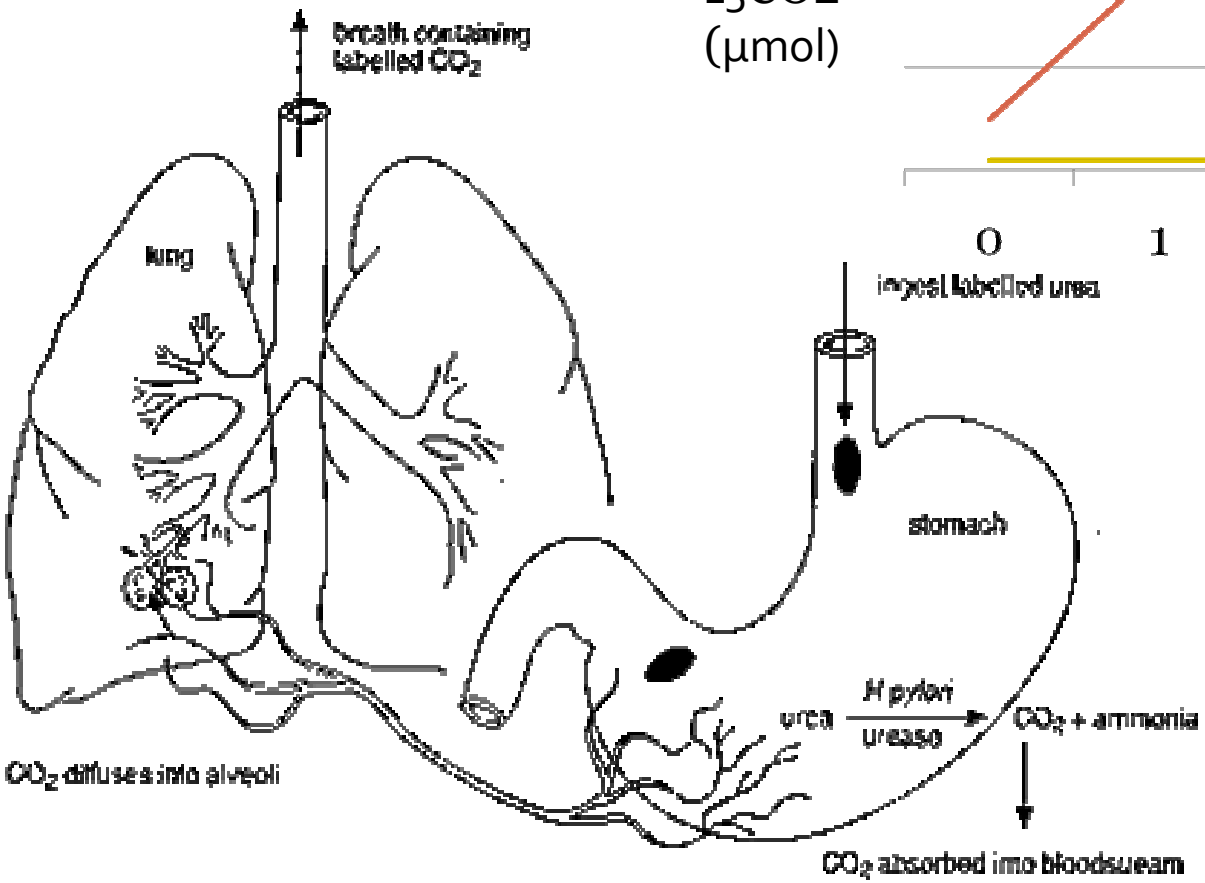
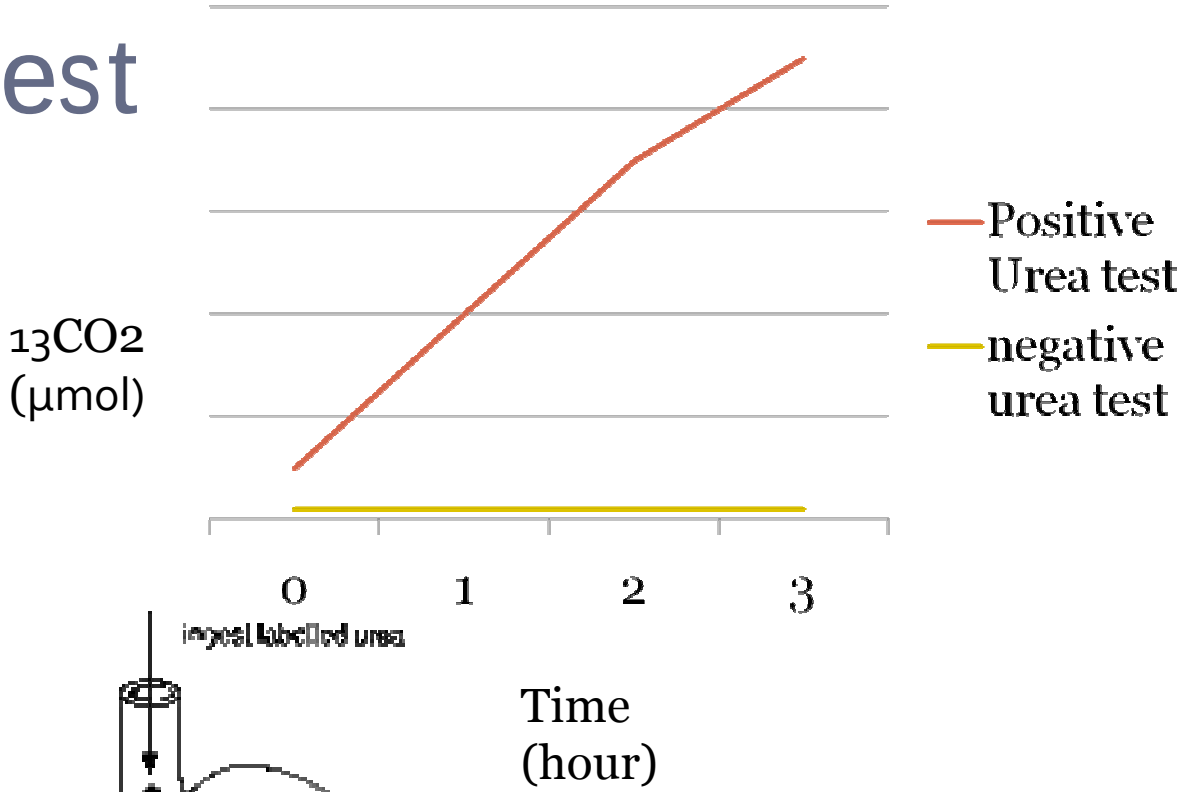
SEC
TRUTH HURTS
Because Kent State Doesn't Really Prepare You For The SEC

Non-endoscopic	Advantage	Disadvantages
Serology	Widely available, inexpensive, good NPV	Not useful after tx
Urease Breath test	Identifies active infection, accurate, useful before and after treatment	Reimburstment, availability, affected by PPI and antibiotic use
Stool Antigen	Identifies active infection, accurate, useful before and after treatment	Affected by PPI and antibiotics use
Endoscopic	**Advantages**	**Disadvantages**
Histology	Accurate, provides additional information on gastric mucosa	Expensive, observer variability, PPI and Abx
Rapid urease	Rapid results, no path cost,	PPI and Abx, requires endoscopy
Culture	100% specificity, allows antibiotic sensitivity	Expnsive, difficult, tedious
PCR	Accurate, allows detection of antibiotic resistance	Expensive, not widely available

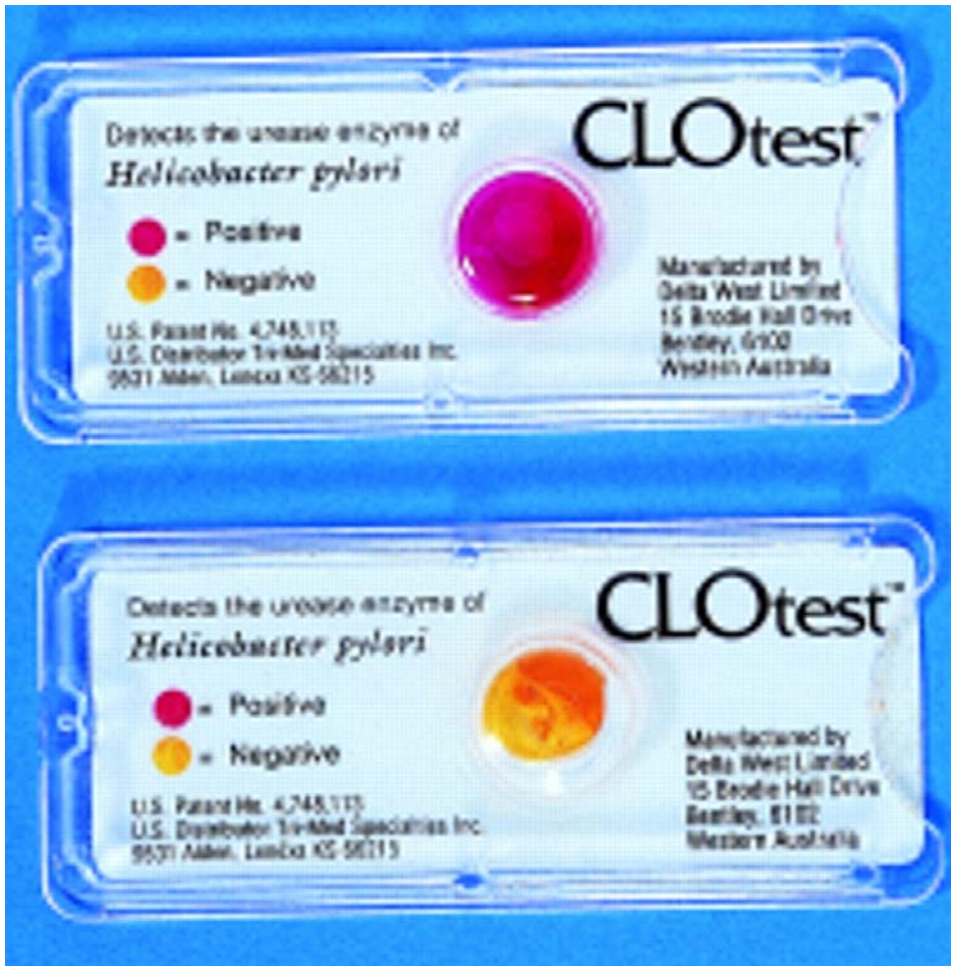
Urea breath test



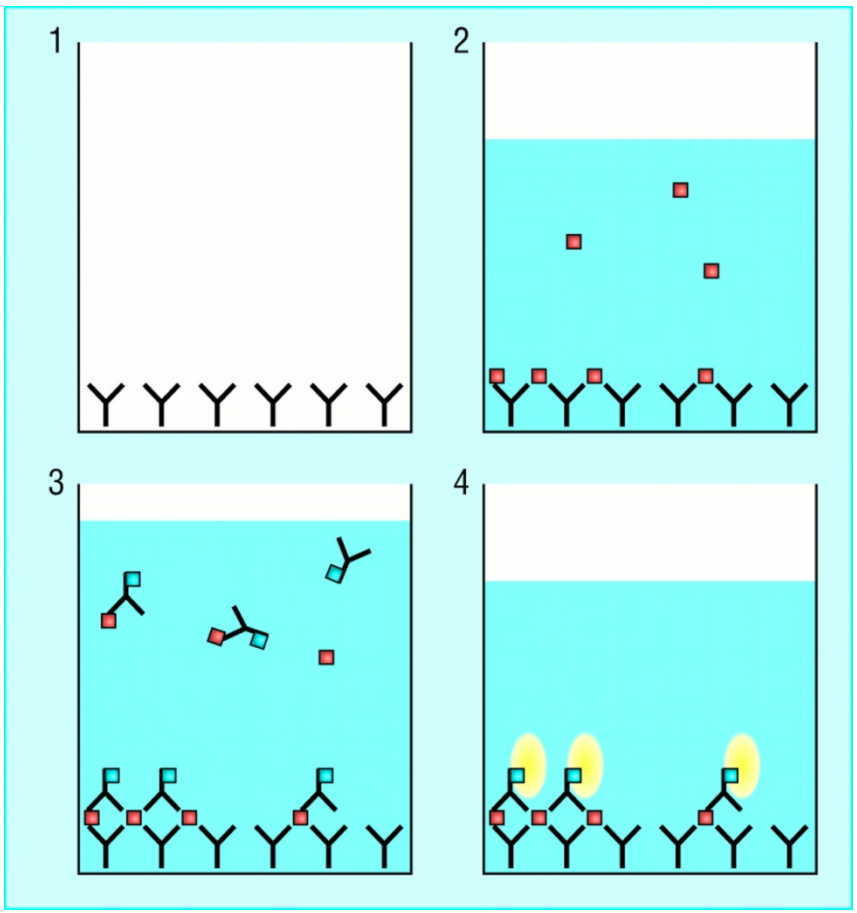


Rapid Urease Test

- Biopsy urease testing
- Less expensive then histology
- Affected by antibiotics and PPI



Fecal Antigen Testing



Principle of the fecal antigen test. Polyclonal antibody to *H pylori* is adsorbed to microwells (1). Diluted patient samples are added to the wells, and any *H pylori* in the fecal sample is bound to the adsorbed antibody (2). A second *H pylori* antibody conjugated to peroxidase is added and binds to *H pylori* (3). After unbound material is washed off, a substrate is added that reacts with bound peroxidase enzyme to produce a yellow colour (4), the intensity of which can be measured to estimate *H pylori* levels


BUGLE
INFECTION CAUSES ULCERS
CURE FOUND

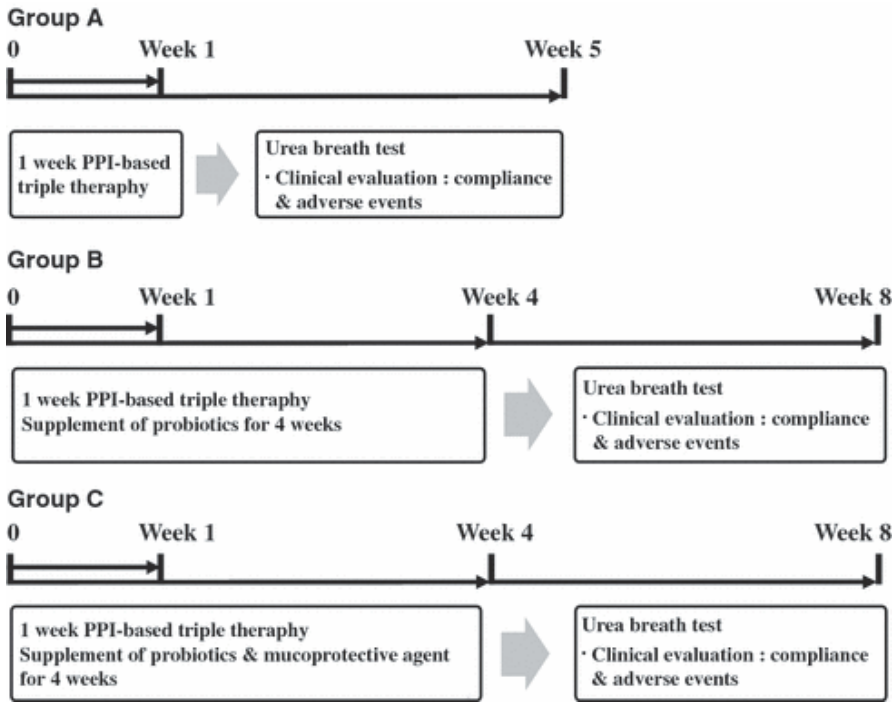
First line Treatment Regimen for H. pylori infection

Treatment Regimen	Duration	Eradication rates	Comments
PPI, Clarithromycin 500mg BID, Amoxicillin 1000mg BID	10-14 days	70-85%	
PPI, Clarithromycin 500mg BID, Metronidazole 500mg BID	10-14 days	70-85%	PCN allergic
PPI, Amoxicillin 1000mg BID then PPI, Clarithromycin 500mg BID, tinidazole 500 mg BID	5 days 5 days	90%	
Bismuth subsalicylate 525mg QID, Metronidazole 500mg QID, Tetracycline 500mg QID, PPI	10-14 days	75-90%	Inexpensive but complicated, PCN allergic or clarithromycin resistance

Rescue Treatment for persistent H. pylori infection

Regimen	Duration	Eradication rate	Comments
Bismuth subsalicylate 525mg QID, Metronidazole 500mg QID, Tetracycline 500mg QID, PPI	14 days	70%	Inexpensive but complicated, PCN allergic or clarithromycin resistance
Amoxicillin 1000mg BID, Levofloxacin 250mg BID, PPI	10-14 days	57-91%	
Amoxicillin 1000mg BID, rifabutin 150 mg BID, PPI	14 days	60-80%	Expensive, adverse hematologic events

The Effect of Probiotics and Mucoprotective Agents on PPI-Based Triple Therapy for Eradication of



Helicobacter
Volume 15, Issue 3, pages 206-213, 7 MAY 2010 DOI: 10.1111/j.1523-5378.2010.00751.x
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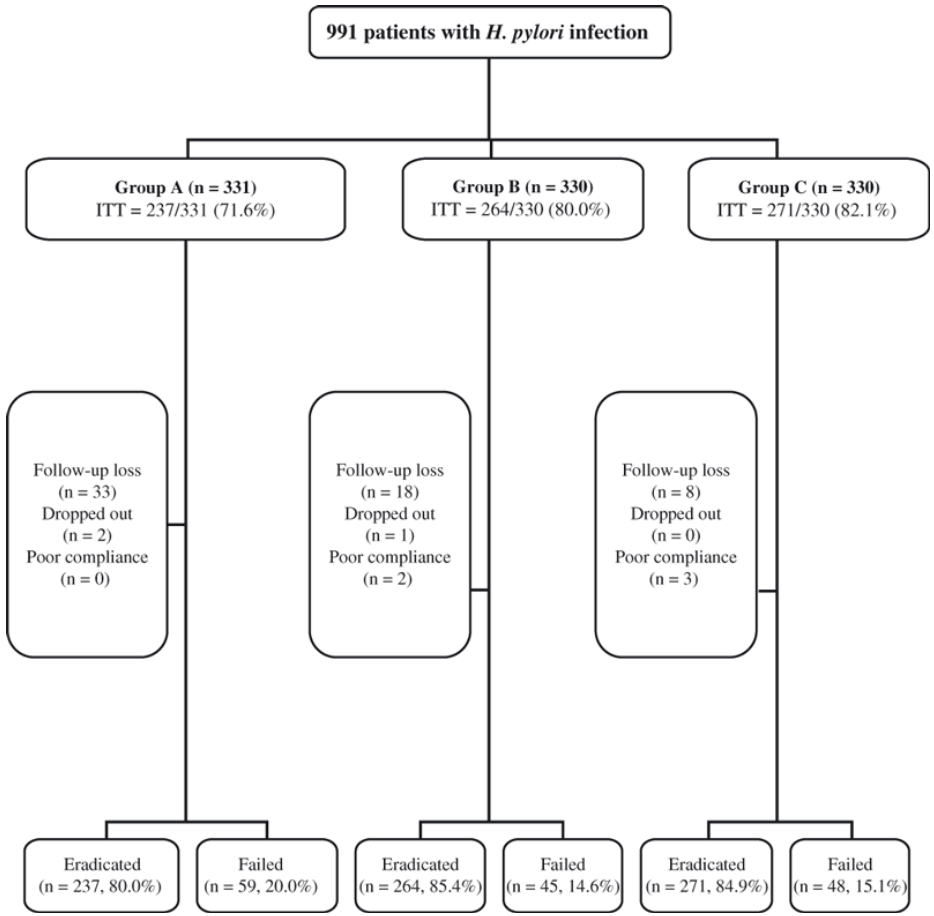

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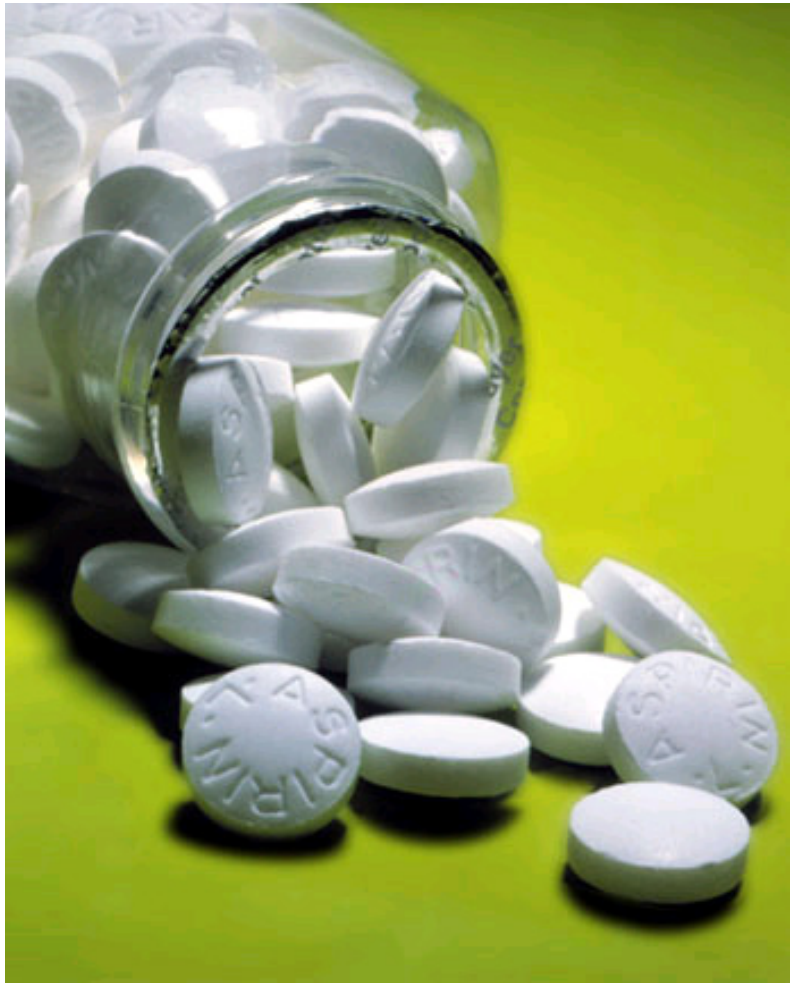
When to Confirm Eradication

- Any patient with H. pylori associated ulcer
- Individuals with persistent dyspeptia despite test and treat strategy
- Patients with H. pylori associated MALT lymphoma
- Individuals who have undergone resection of early gastric cancer

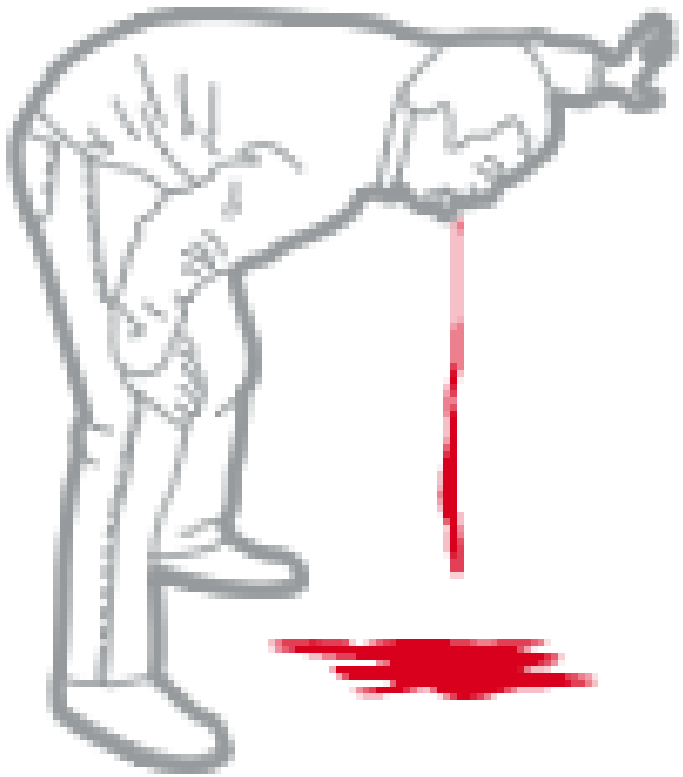

ASPIRIN


Advil
Tablets
Headache
Muscular Aches
Minor Pain of Arthritis
Menstrual Cramps
Toothache
Fever
50 PACKETS OF 2 TABLETS
KIRKLAND
IBUPROFEN
RITE AID
Naproxen Sodium

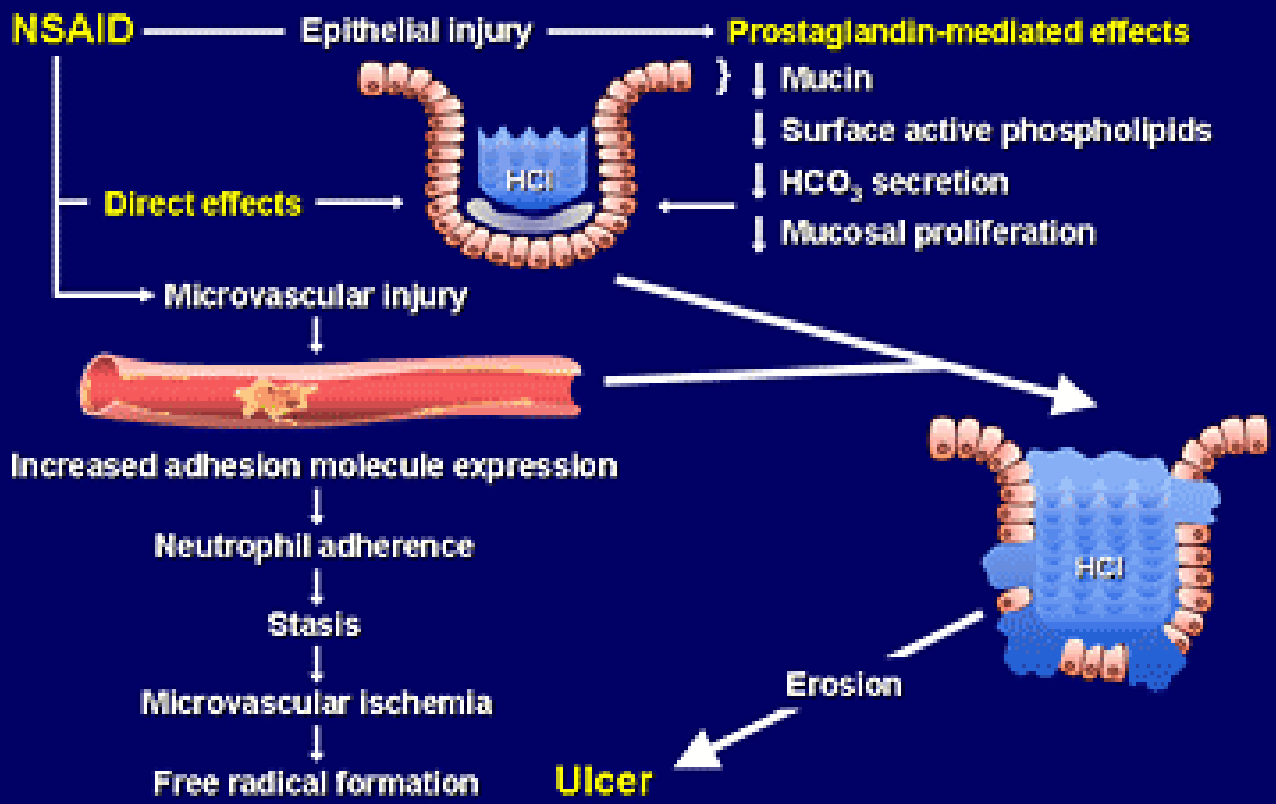
NSAIDS

Patient's perspective

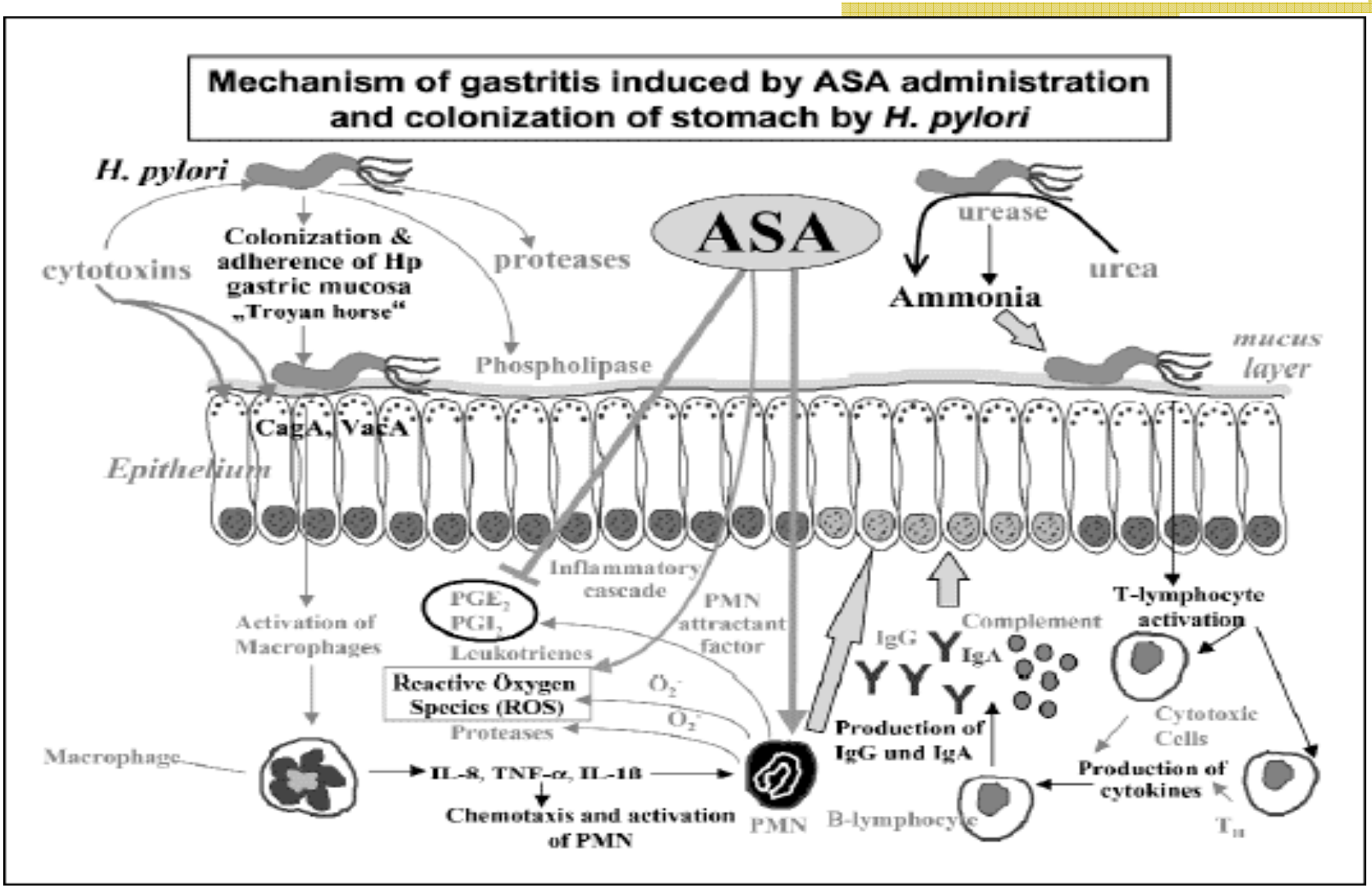
Physician's perspective



Mechanisms of NSAID-Related Ulcer Formation



Scheiman JM. *Gastroenterol Clin North Am.* 1996;25:279–298.



- *Fig. 3.* Mechanism of acute and chronic damage induced by NSAIDs such as aspirin (ASA) and *H.pylori* colonizing gastric mucosa. ASA attracts polymorphonuclear (PMN) cells and triggers production of reactive oxygen species (ROS) while inhibiting of the COX enzyme-derived prostaglandins (PGE2 and PGI2). *H.pylori* acts as a "Troyan horse" adhering to the surface epithelial cell compartment and injecting cytotoxins and ammonia responsible for the aquisition of the bacteria in acidic envinroment of the stomach and triggers the activation of neutrophils and inflammatory response mediated by proinflammatory cytokines (IL-8, TNF-alpha and IL-1ß).

T. Brzozowski et al. J Physiol Pharmacol. 2006 Sep;57 Suppl 3:67-79.

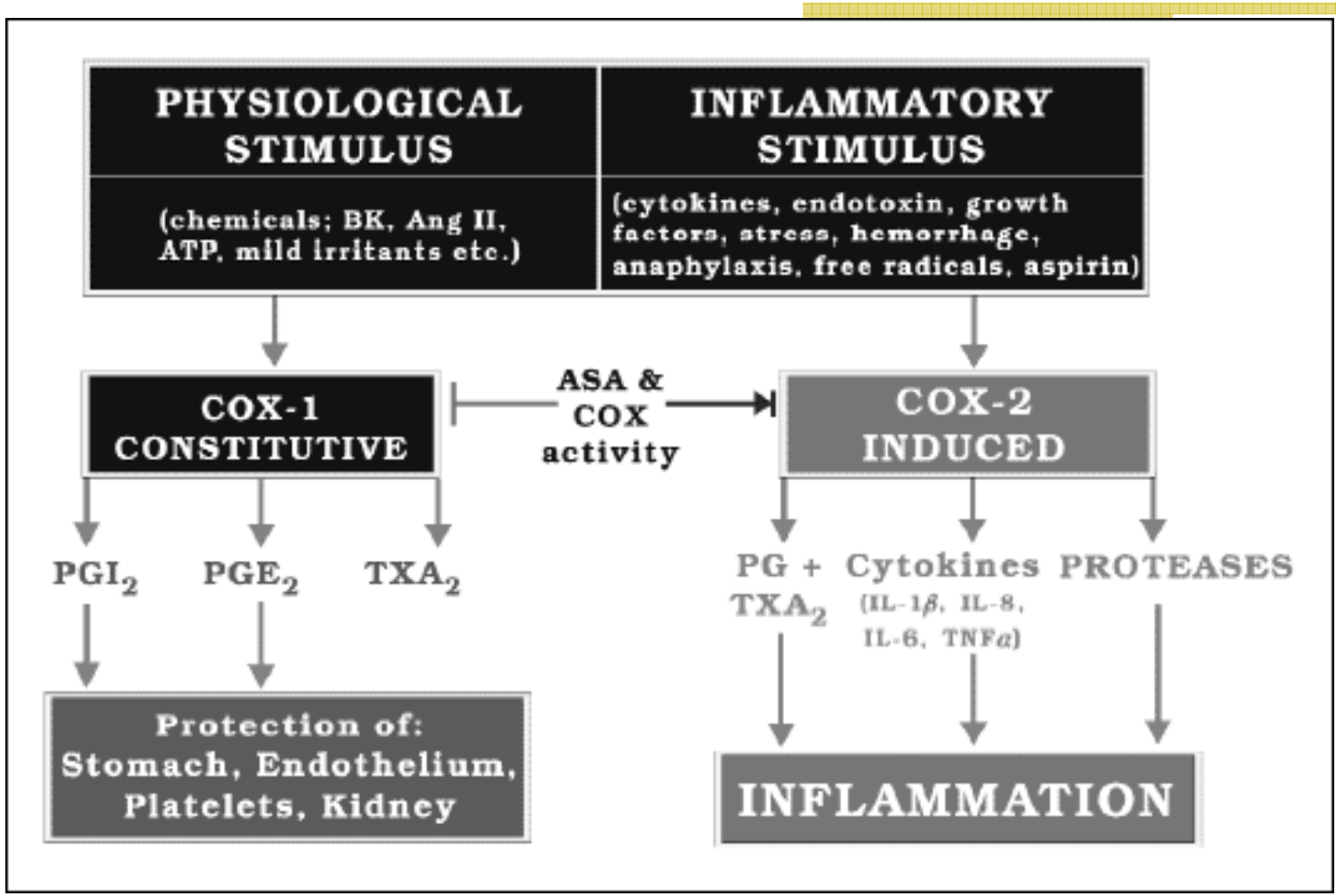


Fig. 4. Simplified demostration of contribution of COX-1 and COX-2 enzyme activities and their products such as PGs and tromboxane A2 (TXA2) to the maintenance of gastric mucosal integrity including protection (COX-1) and adverse processes (inflammation mediated by COX-2) of different organs including stomach. Physiological stimuli such as vasodilators or mild irritants were reported to influence the COX-1 activity and exert gastroprotective influence whereas various cytokines and proteases are known to stimulate COX-2 mediated proinflammatory action. Both, the COX-1 and COX-2 activities are suppressed by ASA and other NSAIDs.

T. Brzozowski et al. J Physiol Pharmacol. 2006 Sep;57 Suppl 3:67-79.

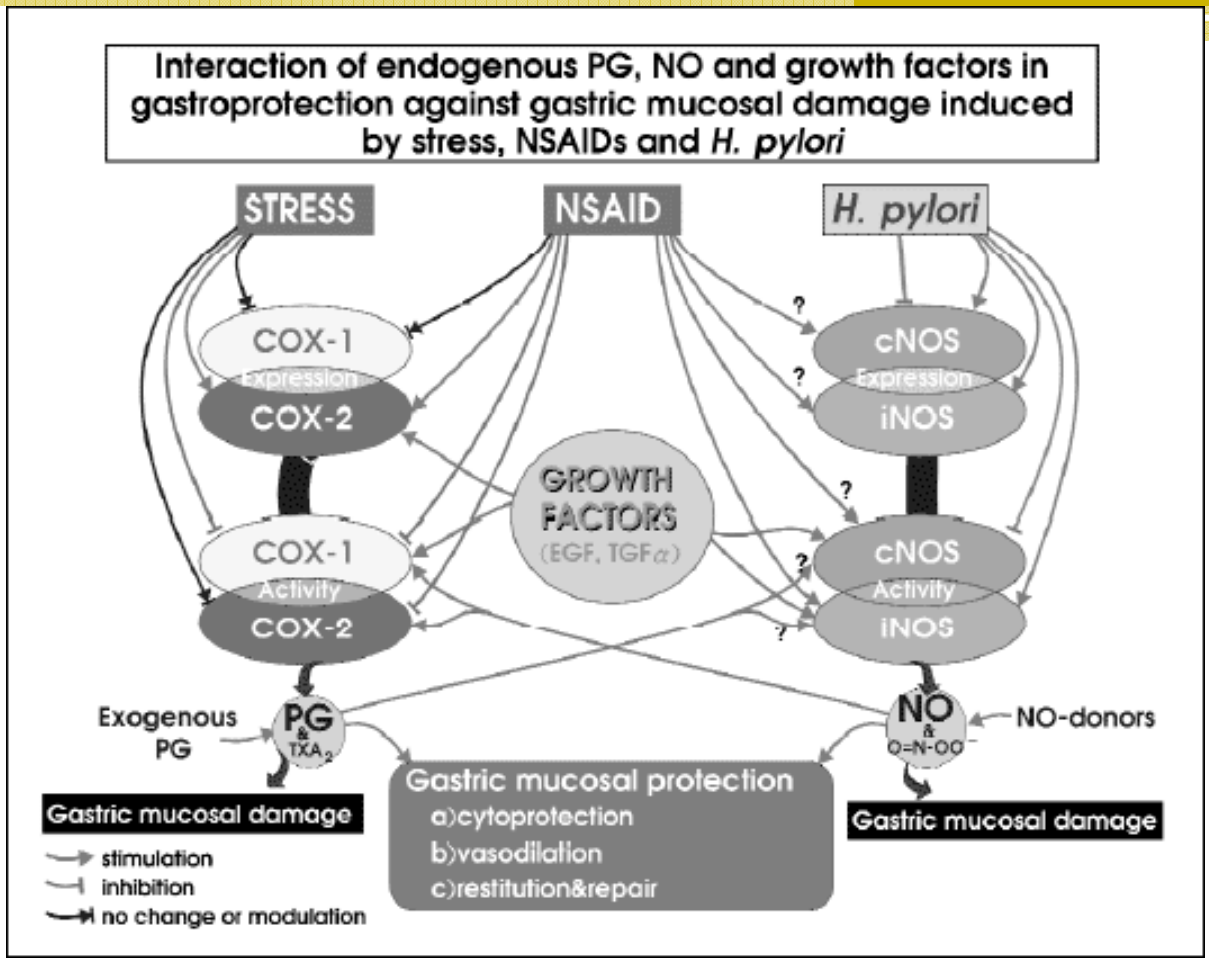


Fig. 5. Complex interactions between three independent risk factors of peptic ulcer disease such as stress, NSAIDs and *H.pylori* in the mechanism of gastric mucosal protection and ulcerogenesis. NSAIDs including ASA upregulate COX-2 expression, possibly compensating the suppression of COX-1 and COX-2 activity induced by this drug. *H.pylori* inhibits gene expression of constitutive nitric oxide (cNOS) while enhancing the expression of inducible NOS (iNOS) that may lead to overproduction of NO and excessive generation of toxic radical peroxynitrate involved in the gastric cell inflammatory response and cellular damage. Growth factors such as EGF, TGFalpha and VEGF contribute to gastroprotection by stimulation of COX and NOS enzymes expression and activities and by facilitating fast restitution process and mucosal repair of the gastric mucosa exposed to stress, or damaged by NSAIDs and *H.pylori*

T. Brzozowski et al. J Physiol Pharmacol. 2006 Sep;57 Suppl 3:67-79.

	Mechanisms	Use
H2-receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine, roxatidine)	Acid inhibition	*H pylori*-negative peptic ulcer; replaced by PPI because of inferiority in acid suppression
PPI (omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole)	Most potent acid inhibition	Standard treatment for all *H pylori*-negative peptic ulcers; prevention of NSAID or aspirin ulcers; essential component in eradication regimen; given intravenously in bleeding ulcers
Prostaglandin analogues* (misoprostol)	Increase mucosal resistance; weak acid inhibition	*H pylori*-negative gastric ulcer; prevention of NSAID ulcers
H pylori eradication regimens (PPI plus two antibiotics)	Cure of *H pylori* infection	Standard therapy in all *H pylori*-positive ulcers
Bismuth salts (subcitrate, subsalicylate)	Weak antibacterial effect; increase of mucosal prostaglandin synthesis	In quadruple therapy for *H pylori* eradication

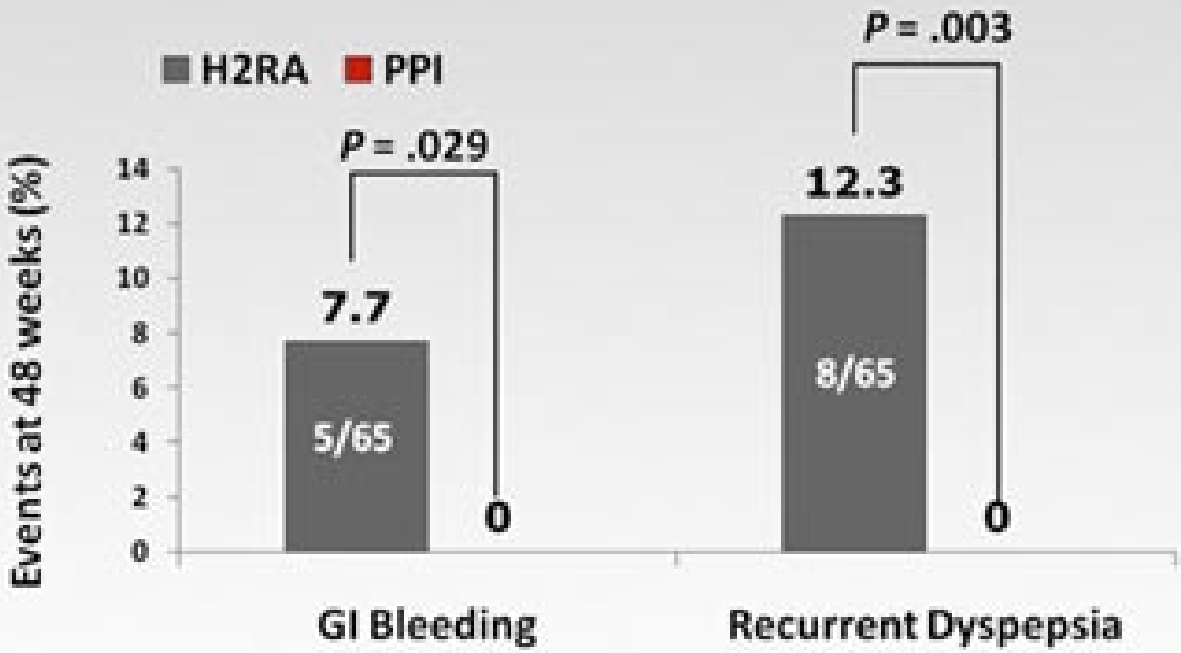
The Lancet Volume 374, Issue 9699, 24 October 2009, Pages 1449-1461

	No gastrointestinal risk factors	One or two gastrointestinal risk factors	Many gastrointestinal risk factors or previous ulcer bleed
Low cardiovascular risk (low-dose aspirin not needed)	NSAID	NSAID plus PPI or misoprostol, or COX-2 inhibitor alone	COX-2 inhibitor plus PPI or misoprostol
High cardiovascular risk (low-dose aspirin needed)	Naproxen plus PPI or misoprostol	Naproxen plus PPI or misoprostol	Avoid NSAIDs and COX-2 inhibitors if possible*

The Lancet Volume 374, Issue 9699, 24 October 2009, Pages 1449-1461

PPIs More Effective Than H2RAs

N = 130 patients with aspirin-related peptic ulcers/erosions randomly assigned to H2RA† vs PPI‡ and aspirin (80 mg)



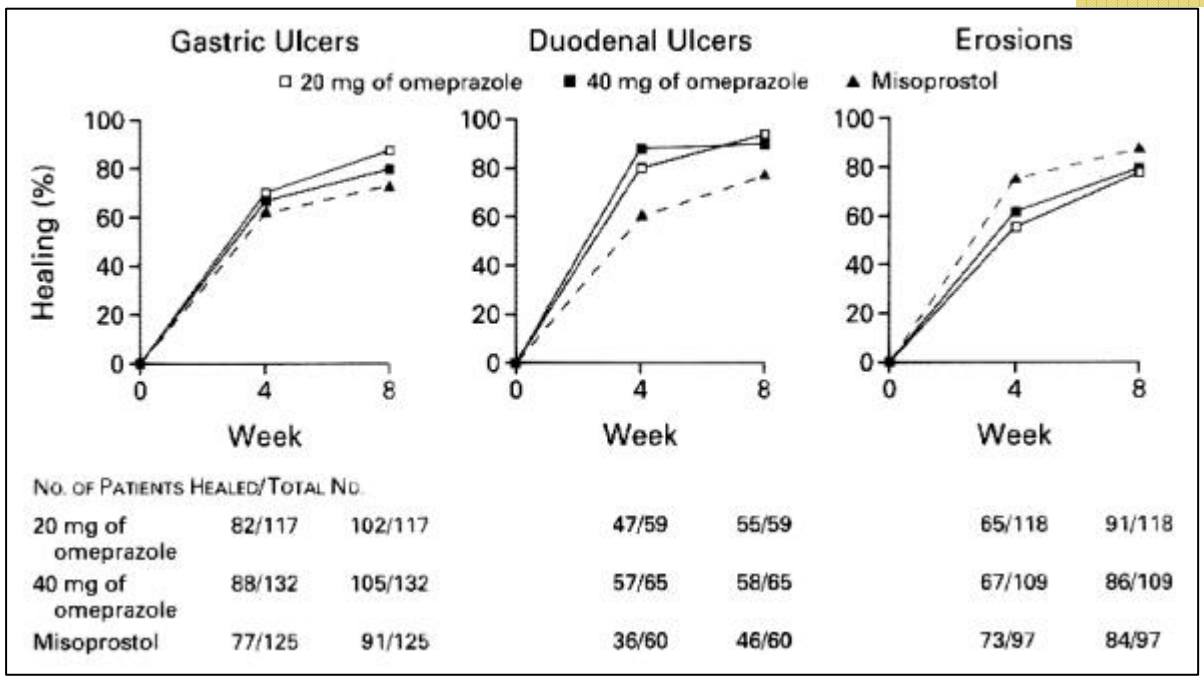
H2RA = H2 receptor antagonist

†Famotidine 40 mg twice daily

‡Pantoprazole 20 mg

Ng FH, et al. *Gastroenterology*. 2010;138:82-88.

Figure 1



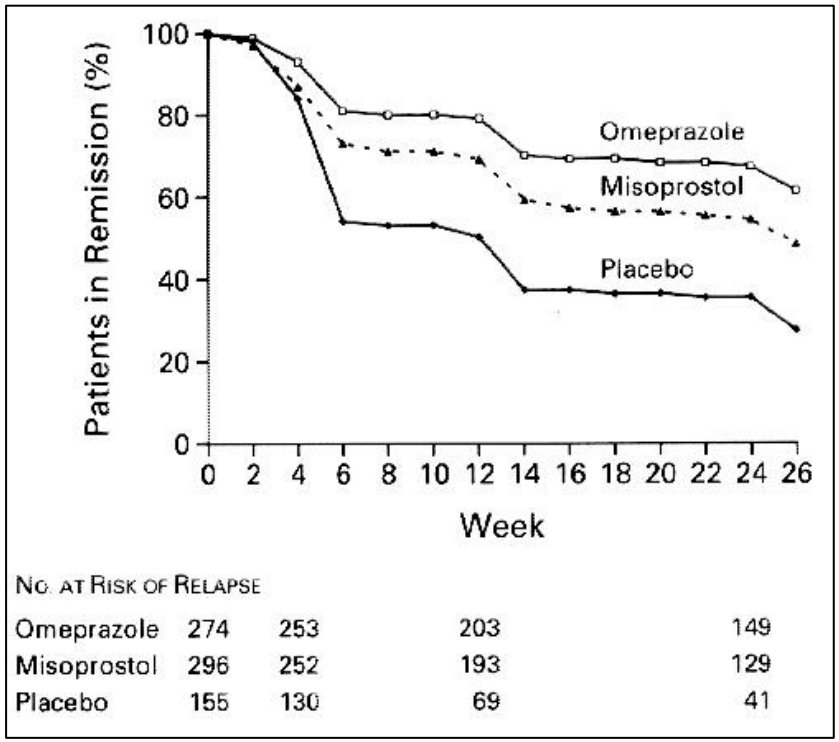
No. of Patients Healed/Total No.						
20 mg of omeprazole	82/117	102/117	47/59	55/59	65/118	91/118
40 mg of omeprazole	88/132	105/132	57/65	58/65	67/109	86/109
Misoprostol	77/125	91/125	36/60	46/60	73/97	84/97

Omeprazole Compared with Misoprostol for Ulcers Associated with Nonsteroidal Antiinflammatory Drugs.
Hawkey, Christopher; Karrasch, Jeffrey; Szczepanski, Leszek; Walker, Donald; Barkun, Alan; Swannell, Anthony; Yeomans, Neville

New England Journal of Medicine. 338(11):727-734, March 12, 1998.

Figure 1 . Cumulative Rates of Healing of Gastric Ulcers, Duodenal Ulcers, and Erosions at Four and Eight Weeks during Treatment with 20 mg of Omeprazole Daily, 40 mg of Omeprazole Daily, or 200 microg of Misoprostol Four Times Daily.

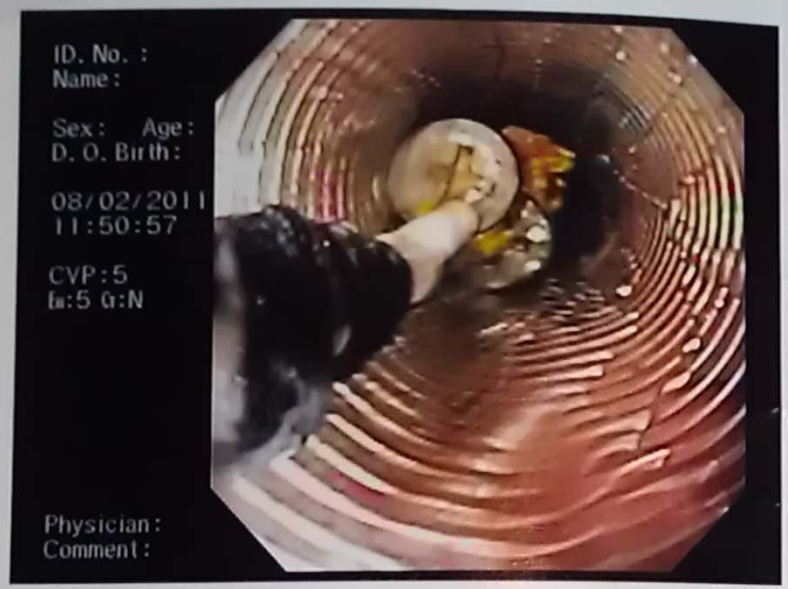
Figure 2



Omeprazole Compared with Misoprostol for Ulcers Associated with Nonsteroidal Antiinflammatory Drugs.
Hawkey, Christopher; Karrasch, Jeffrey; Szczepanski, Leszek; Walker, Donald; Barkun, Alan; Swannell, Anthony; Yeomans, Neville

New England Journal of Medicine. 338(11):727-734, March 12, 1998.

Figure 2 . Kaplan-Meier Estimates of the Rates of Remission among Patients Treated with 20 mg of Omeprazole Daily, 200 microg of Misoprostol Twice Daily, or Placebo for up to 26 Weeks. P<0.001 for the comparison of omeprazole with placebo by the log-rank test, and P = 0.001 for the comparison of omeprazole with misoprostol by the log-rank test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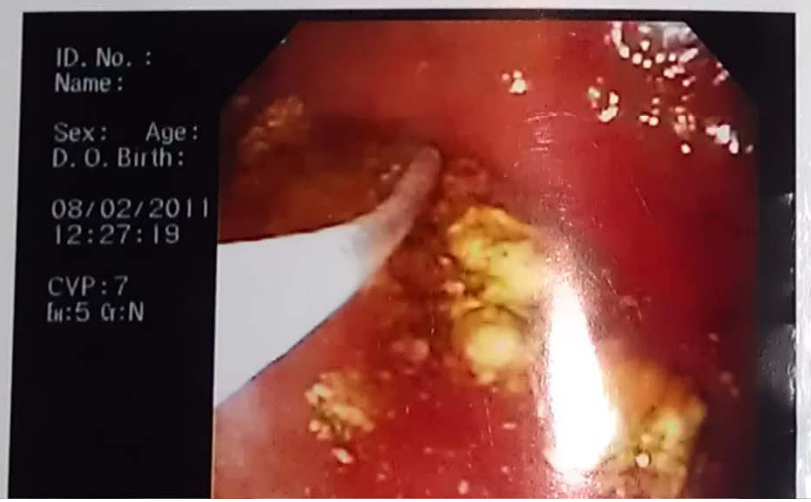
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