

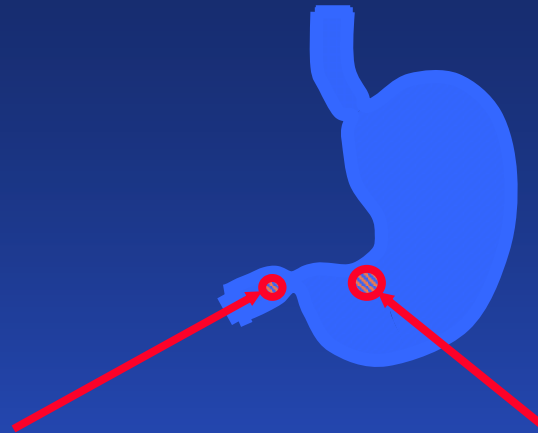
Helicobacter Connections

Barry Marshall

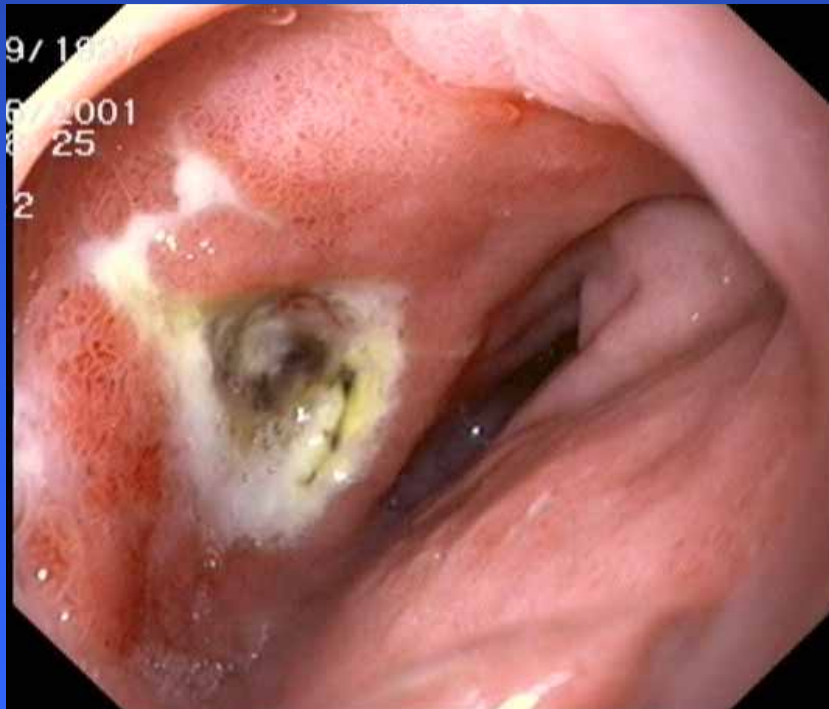
“ The greatest obstacle to knowledge is not ignorance, it is the illusion of knowledge.”

Daniel Boorstein - Historian

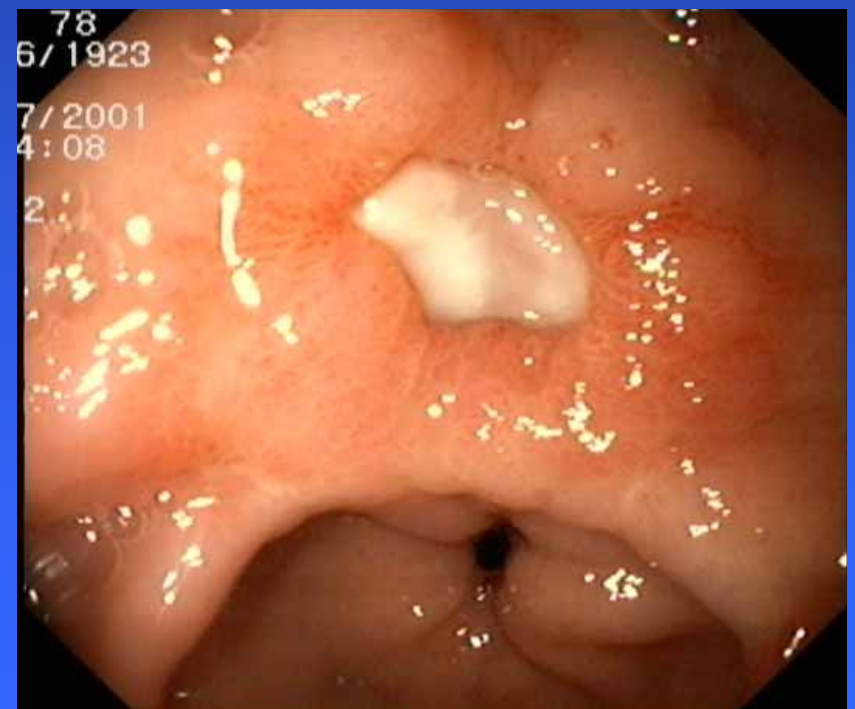
Peptic Ulcers



Duodenal Ulcer (DU)



Gastric Ulcer (GU)



SMITHKLINE'S ULCER MEDICINE "HOLY WAR"

■ SmithKline Beckman's patent on **Tagamet**, the pale green pill that cures ulcers, has been the next best thing to a license to print money. For seven delightfully profitable years, the company enjoyed a virtual monopoly. But competition was bound to rear its head sooner or later. Glaxo Holdings of Britain has brought out a drug, **Zantac**, that does the same job. A success in Europe, Zantac has just come to market in the U.S., and the competitive struggle shaping up will undoubtedly give some SmithKline executives stomach pains.

continued



Activities 1981

- Study patients with HP
 - No new information
- Take biopsies from consecutive cases
 - And from “normal” mucosa unaffected by a local lesion (away from the ulcer)
- Search the literature
- Treat one patient
- Try to culture the “CLO”
 - “Lee” method, microaerophilic

Ito, Handbook of physiology 1966.



Ito biopsied his own stomach and discovered that he was colonised with a spiral organism. This image was published in 1966 in a well known text book.

Prospective Study: 1982

- 100 Elective Patients
- Prospective consent
 - clinical data (travel, pets, drugs, teeth)
- Endoscopy
 - appearance (ulcers, oesophagitis, cancer)
- Biopsy of “normal” antral mucosa
 - Histology (blind) to JRW
 - Culture and Gram stain (blind to JP)

Results:

Bacteria were cultured from 12 patients

- Easter Thursday 1982
 - Patient 37, 70 y.o. male
 - DU, GU, artificial valve, anticoagulants
- MRSA epidemic at Royal Perth
 - Overworked microbiology technologists
 - No time to check the culture on Saturday
 - Not examined until Tuesday
 - Gram negative rods seen in pure culture
- We had been using the right methods for
 - Cultures were being discarded after 48 hours

Association of Bacteria with Endoscopic Diagnoses

Endoscopic Appearance	Total	With Bacteria	p
Gastric Ulcer	22	18 (77%)	0.0086
Duodenal Ulcer	13	13 (100%)	0.00044
All Ulcers	31	27 (87%)	0.00005
Oesophagus Abnormal	34	14 (41%)	0.996
Gastritis	42	23 (55%)	0.78
Duodenitis	17	9 (53%)	0.77
Bile in Stomach	12	7 (58%)	0.62
Normal	16	8 (50%)	0.84
Total	100	58 (58%)	

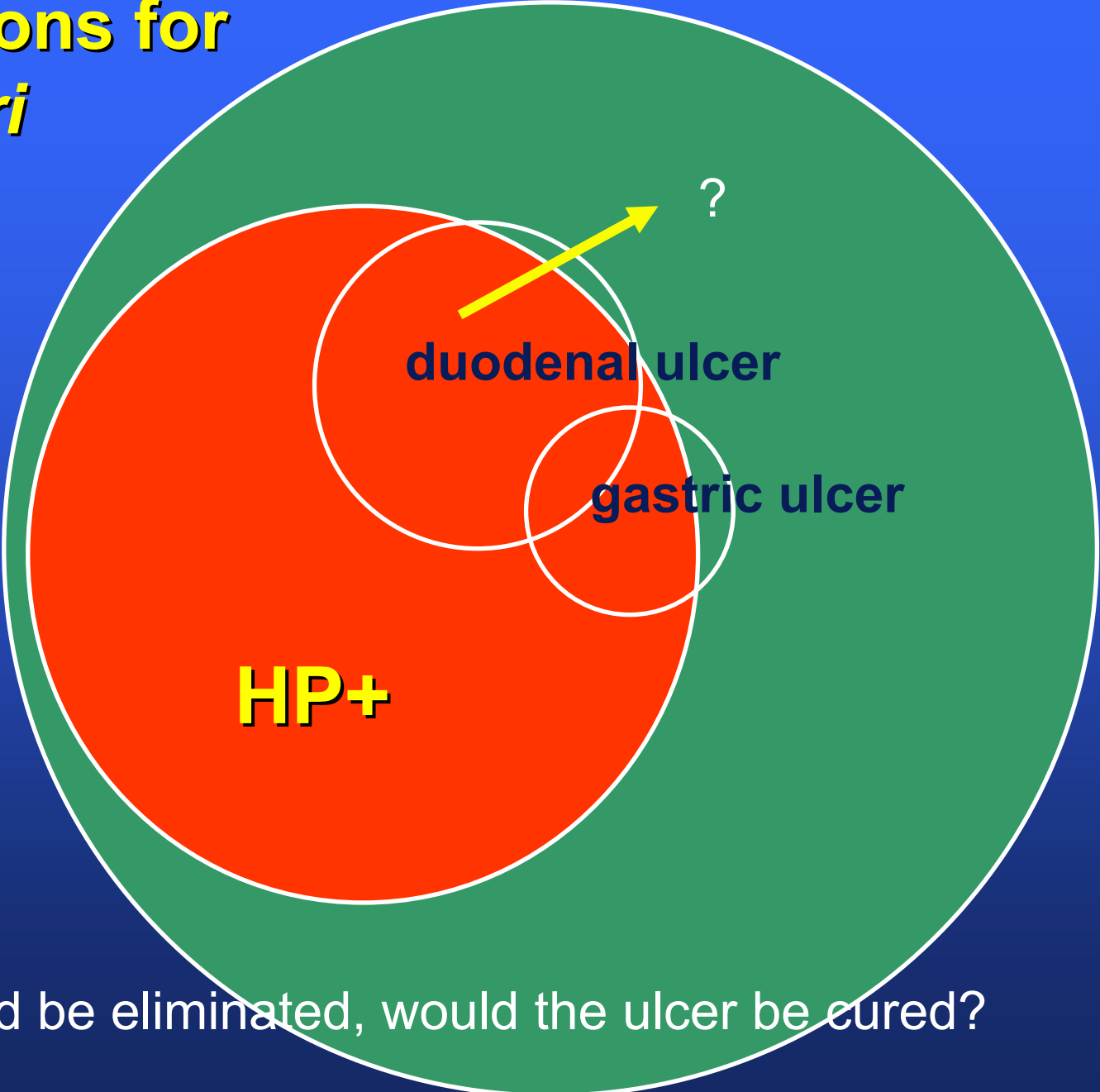
Gastritis and Duodenal Ulcer

- Magnus 1952
 - GU: gastritis in 80%
 - DU: gastritis is 100%
- NSAID's
 - Gastric ulcers with normal histology are commonly NSAID associated

Lancet Letters 1983

- A new species
- Bacteria linked to gastritis
 - “since the new bacteria are associated with gastritis as described by Warren, then they may play a role in other poorly understood gastric diseases i.e. peptic ulcer and gastric cancer.”

Disease Associations for *Helicobacter pylori*







If the bacteria could be eliminated, would the ulcer be cured?

Known Facts about Ulcer Disease

- The stomach was sterile
- Ulcers were caused by
 - Lifestyle (stress)
 - Diet, alcohol, drugs
 - Genetically determined
- Work rejected because the results were outside the current paradigm
- This was the pattern for the next 8 years

Was Hp a pathogen?

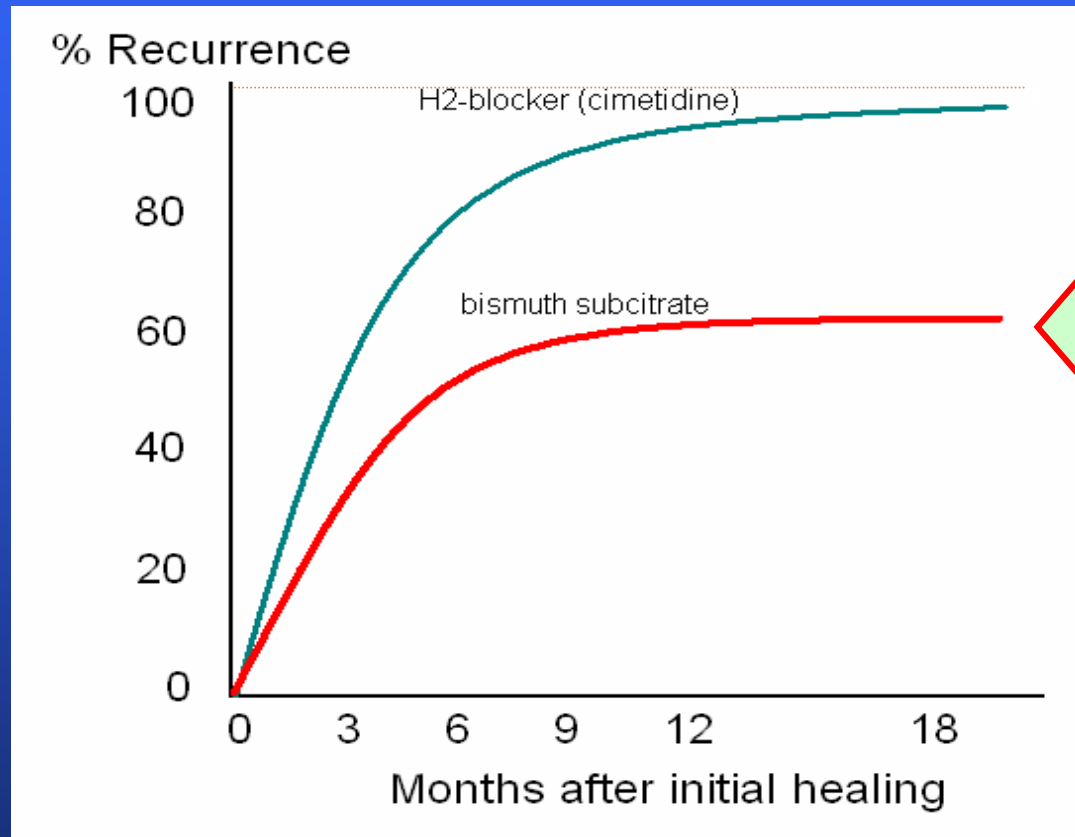
Testing the hypothesis

1. Do patients have antibodies? 
2. Do antibacterials heal gastritis? 
3. Have Koch's postulates been fulfilled?
4. What is the disease process?
 1. How does it infect? 
 2. How does it survive in the acid stomach? 

A new look at the literature:

- Heavy metals were antibacterial
 - Arsenic and Mercury for syphilis
- Bismuth had been used to treat gastric diseases for 200 years
- Bismuth was also an ulcer treatment
 - Relapse after bismuth treatment was lower
- Was bismuth killing CLO?

Hp Explains Varying Ulcer Relapse



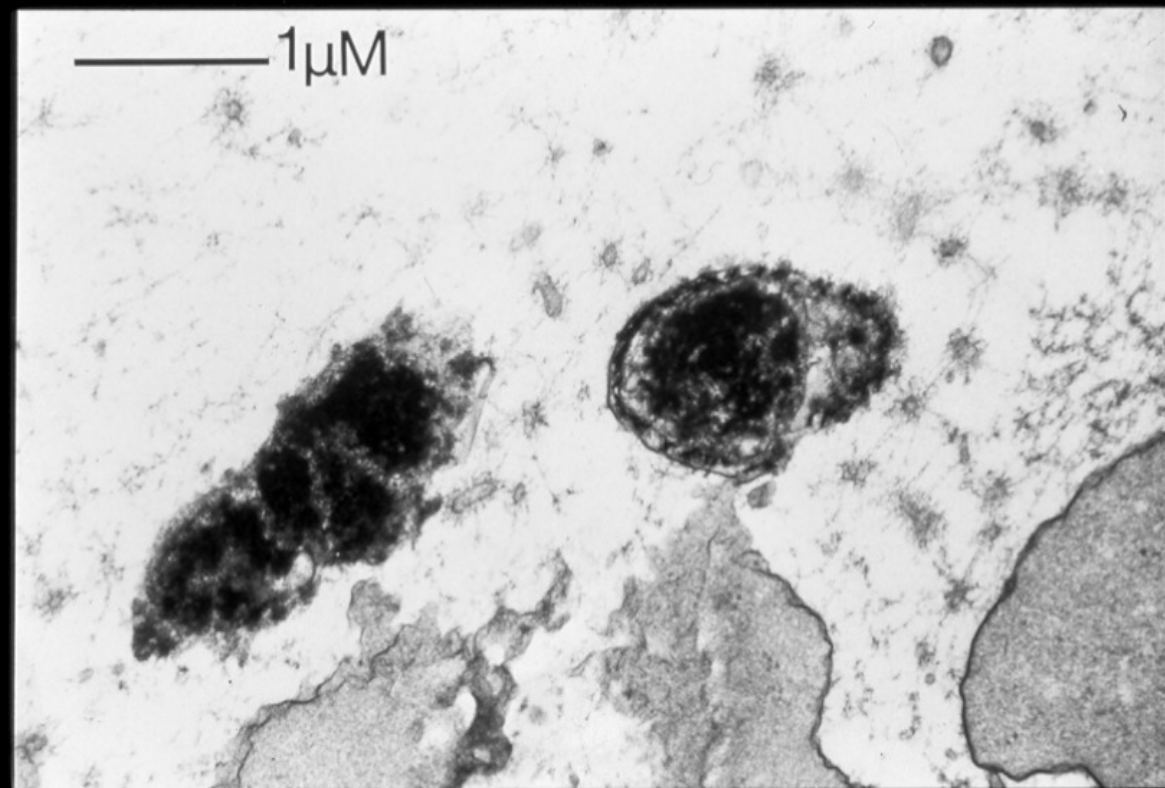
Bacterial cause explains why a heavy metal cures the disease in 40%.

Some thoughtful gastroenterologists noticed that drug therapy affected relapse rates



In-vitro

In-vivo

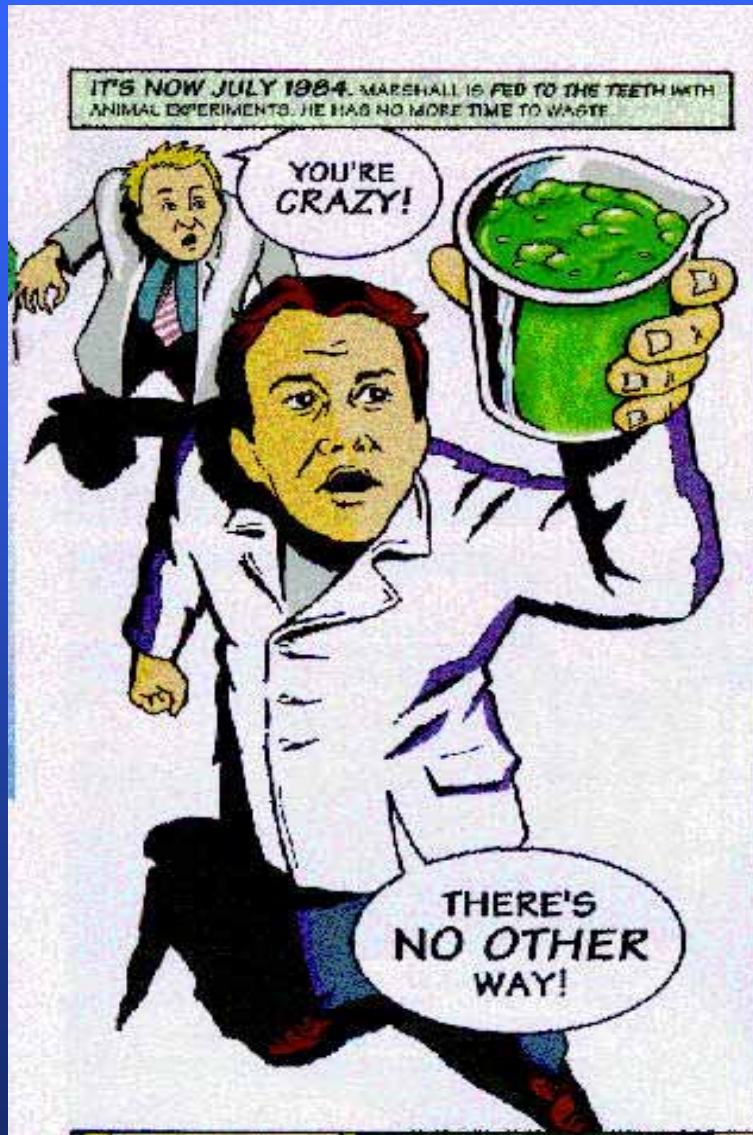


Bismuth Based Therapy Could be Used in Clinical Trials

- Placebo controlled study of ulcer patients
 - H2RA (cimetidine) vs. Antibiotic
 - » Unethical!
 - H2RA vs. Bismuth
 - » H2RA+Antibiotic
 - » Bismuth+Antibiotic
 - » H2RA alone
 - » Bismuth alone

An attempt to fulfil Koch's postulates: preliminary steps

- A red rag to a bull
 - “Dr Marshall, these changes seem very subtle..”
 - “..these commensal bacteria merely infect people with ulcers.”
- Failed attempts to infect pigs
- Serology shows 40% of population has Hp
- First treatment success
 - bismuth + metronidazole cures 75%
 - Excellent clinical responses
 - Patients
 - GP's
 - Own experience



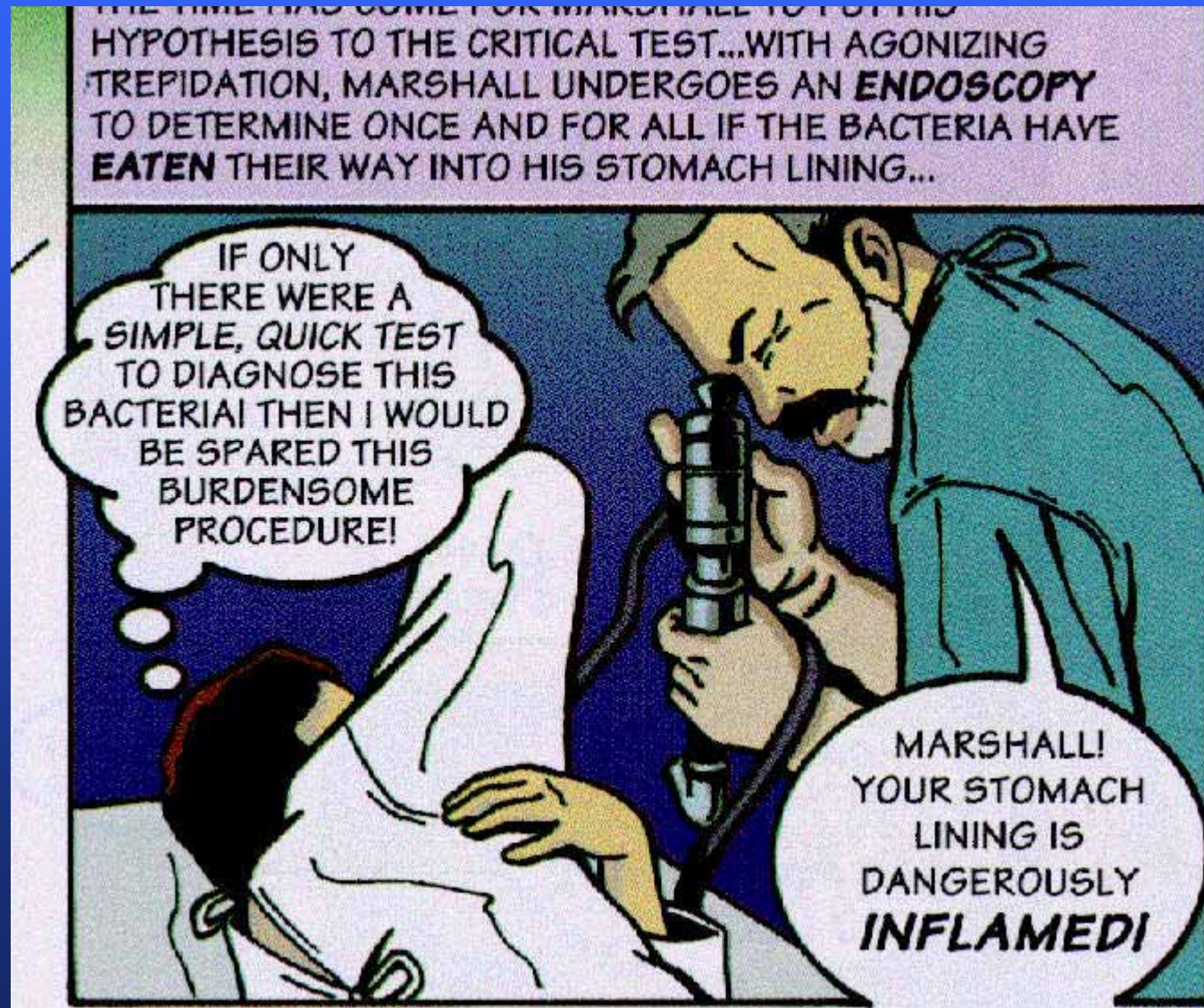
An attempt to Fulfill Koch's Postulates for *Campylobacter pyloridis*

Med J. Aust 1984

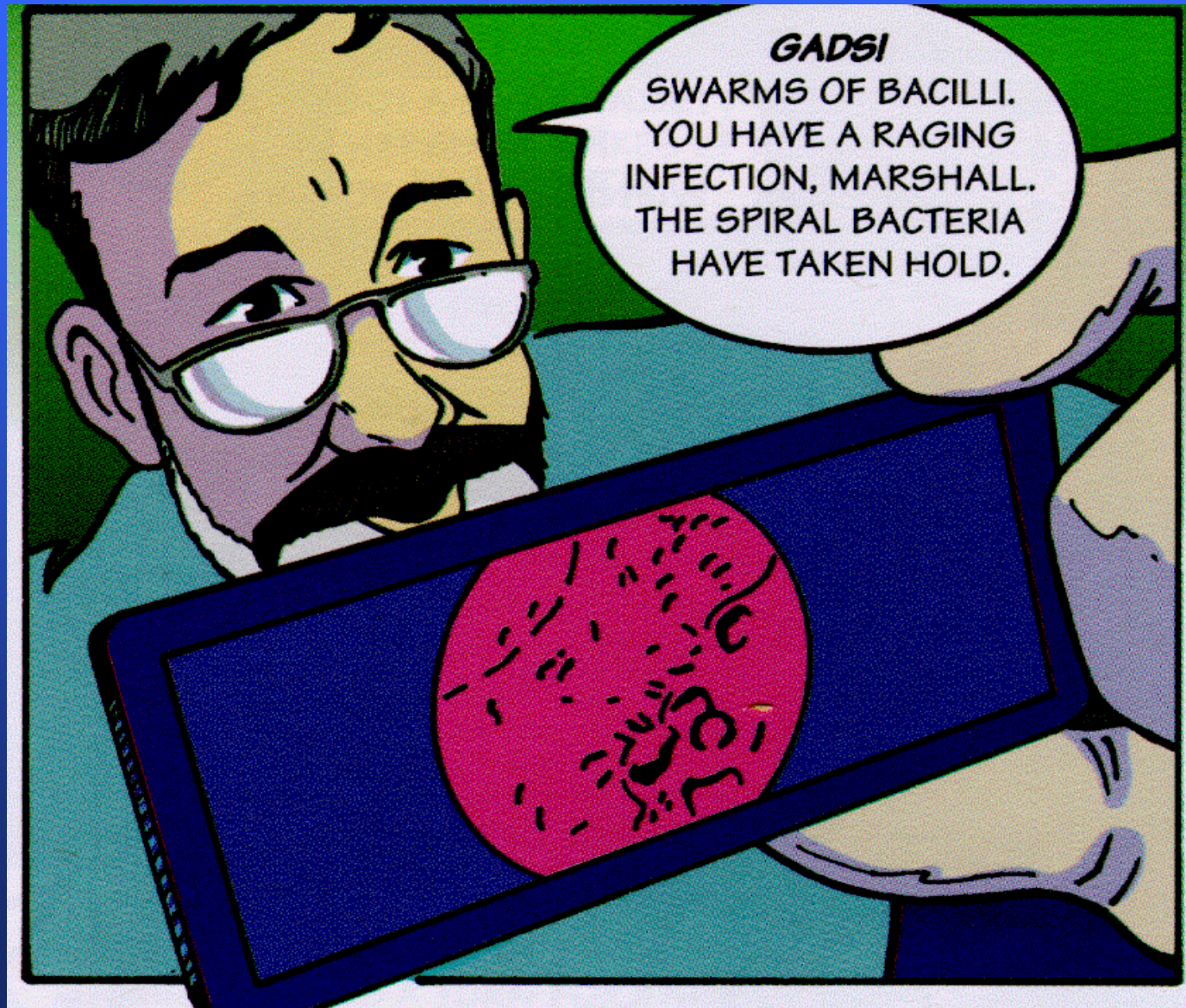
An attempt to fulfil Koch's postulates: the experiment

- Cultured a patient with gastritis
- Underwent baseline endoscopy
- Treated the patient successfully
- Drank bacteria 10^9 c.f.u.
 - d3-5 vague illness, halitosis
 - d5-8 vomiting, **no acid present!**
 - d8 – endoscopy and biopsy
- Histological gastritis
 - Hp is a pathogen

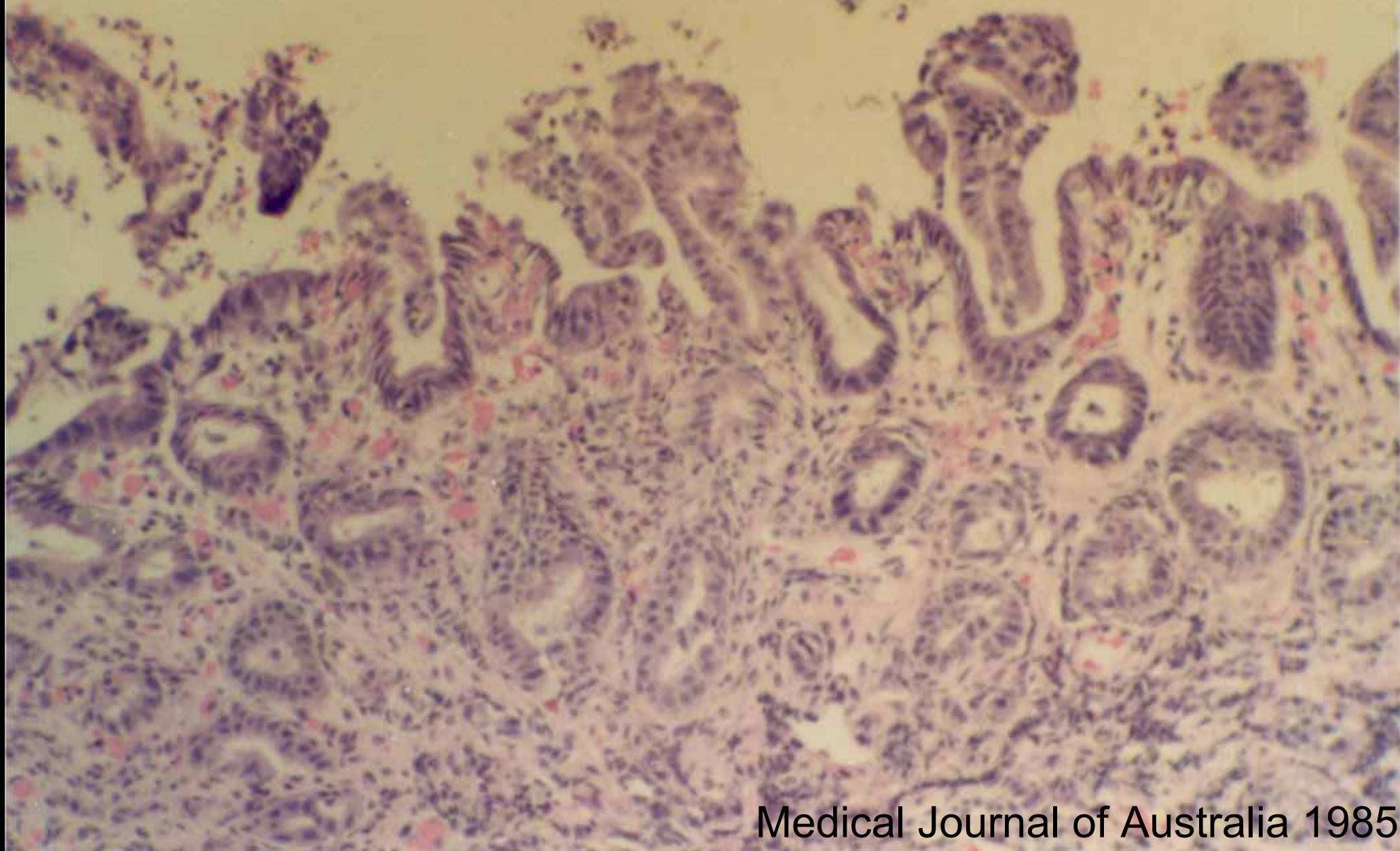
Day 8: The Infection Takes Hold



Koch's Postulates fulfilled for Gastritis



Gastric Mucosa, H&E, Day 8



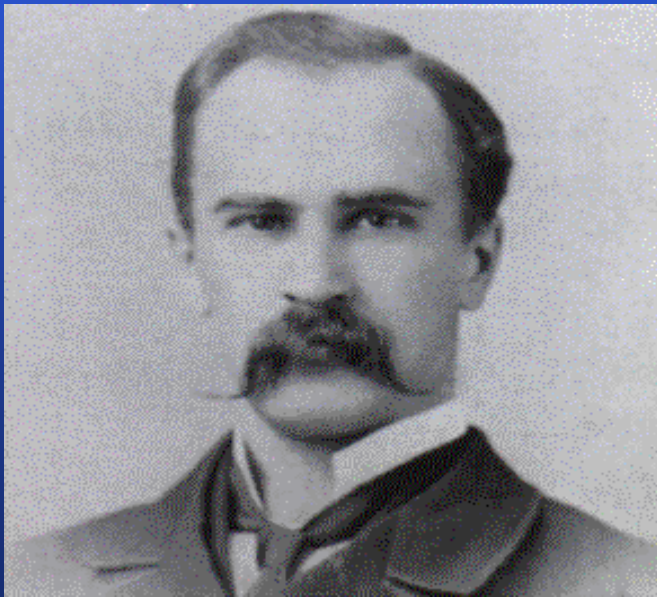
Gastric Mucosa, Silver Stain, Day 8



The Principles and Practice of Medicine

Sir William Osler & Thomas McRae 1910

Achlorhydric Gastritis in Children



“examination of the vomitus reveals as a rule, absence of hydrochloric acid and sometimes the presence of volatile fatty acids.”

Epidemic gastritis with hypochlorhydria

- The acute attack of Hp
 - In early childhood
 - Lasts a few days
 - Lifelong colonization with Hp

How does Hp survive in the stomach?

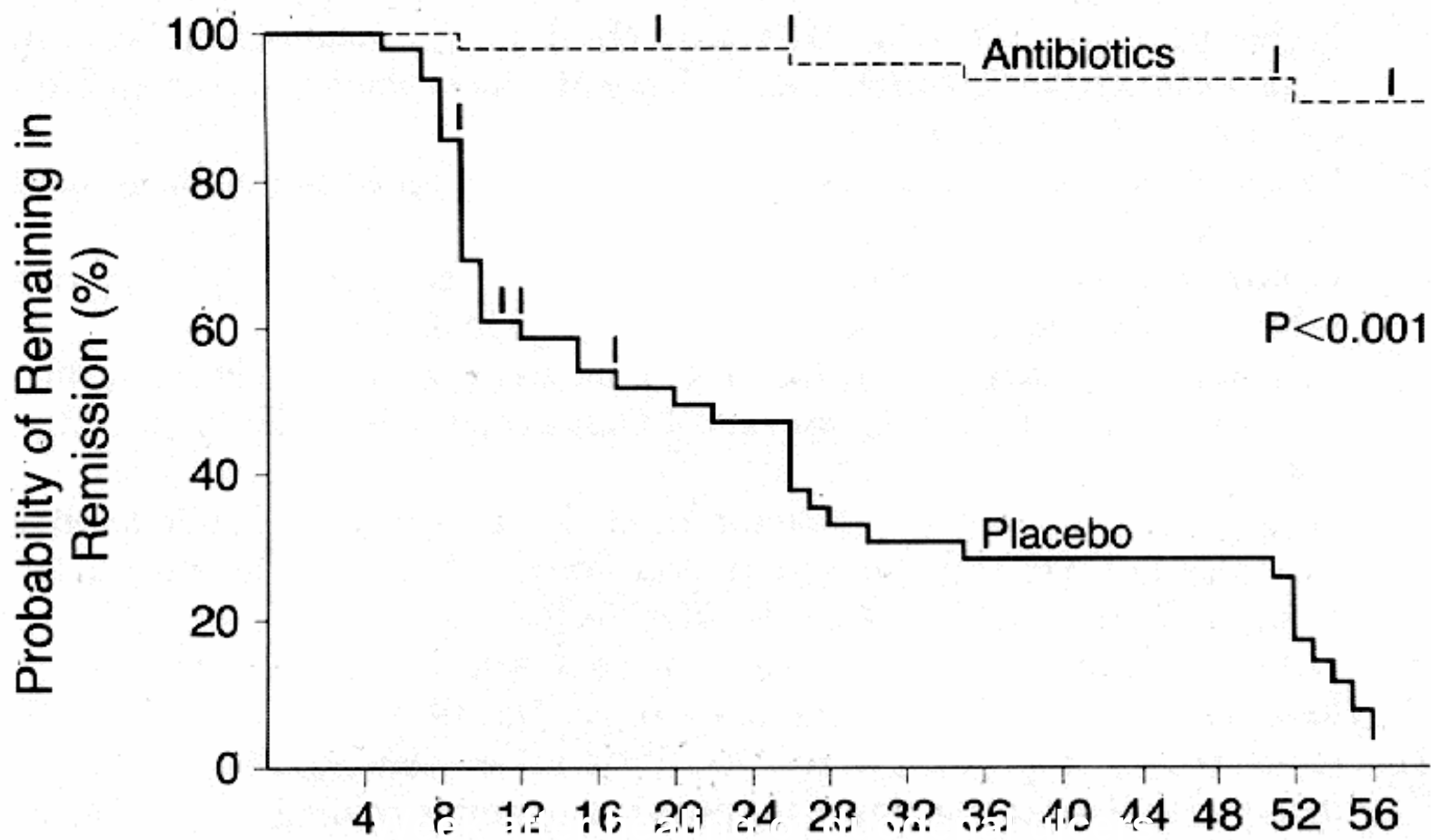
- Urease enzyme
 - Gastric urease discovered in 1926
 - Association with Hp noted in 1984
- Urea absent from gastric juice of patients with Hp
 - Hp splits urea to make ammonia and HCO_3^-
 - Hp protects itself from acid
- Biopsy Urease test
 - As accurate as Gram Stain
 - Takes a few minutes
 - Anyone can now diagnose Hp!

Implementation

- Effective therapy
 - Bismuth and antibiotic
 - PPI (Losec) with two antibiotics (1996)
- Non invasive breath test for H.pylori
 - Now GP's can treat Hp!
 - Non-invasive follow-up possible
 - Bye bye gastroenterologists!

Validation 1985-7

- Double blind study
 - 100 patients
 - H2 Blocker vs. Bismuth+antibiotic
 - Cure rate 80% vs 10%
- Replication by others
 - 1990: Rauws and Tytgat, Amsterdam
 - 1991: Graham, Houston Tx
 - 1993: Hentschel, Vienna



Acceptance

- NIH Consensus conference
 - Washington DC
 - February 1994

Postscript

Nobel Prize in Physiology or Medicine
J.Robin Warren and Barry J. Marshall

Thank You

Alfred Nobel and Helicobacter



Alfred Nobel and His Health Problems

During most of his life, Alfred Nobel suffered from poor health. He complained of indigestion, headaches and occasional spells of depression. Already as a young man, he spent several weeks at health resorts. His first stay at a spa was at Franzenbad in Bohemia in 1854. The inactivity at the health resorts made him restless and bored. He cannot have been impressed by the medical treatment offered at the spas. It consisted of baths, resting, and drinking well water. Toward the end of his life, Alfred Nobel suffered from a heart condition marked by paroxysms of intense pain (angina pectoris). The real nature of his health problems at a younger age are not clear, but one may well imagine that he was simply overworked or under serious mental stress. Often he felt **lonely** and without friends.

Urea and Urease Enzyme

