- *Helicobacter* -
THE EASE AND DIFFICULTY
OF A NEW DISCOVERY

Robin Warren
EARLY DAYS

First reports 100 years ago
– considered spirochaetes

1940 Freedburg saw curved organisms in the stomach

1954 Palmer: “Freedburg was wrong”
Acid environment kills organisms

The normal stomach is **sterile**

Bacteria seen are
- contaminant passing through
- dead, or –
- secondary to gastric lesions such as peptic ulcer
  - usually fungus or yeast in necrotic debris

Primary infection is rare
GASTRIC BIOPSIES ----- pre 1970

- Good quality biopsies were rare
- Specimens were usually **Surgical** or **Post mortem**
- Mucosa soon autolysed in digestive juice
- Helicobacter rapidly disappear
GASTRITIS ----- pre 1970

- clinical specimens were technically inadequate

- **acute** gastritis or **aplasia** with pernicious anaemia easily diagnosed but rare

- **chronic** inflammation was difficult to:
  - relate to the clinical findings
  - see, describe or classify
MAJOR BREAKTHROUGHS IN THE 1970’S

- Numerous, small well-fixed biopsies
- Histology of gastric mucosa finally seen clearly by pathologists

RICHARD WHITEHEAD - 1972

- accurately described them
- He defined “active” gastritis:
  - specific epithelial changes and leucocyte infiltration
He designed a new *classification*

- Logical, practical, descriptive

- Set out as a tree, apparently complex

  - But easy to use
<table>
<thead>
<tr>
<th>Mucosal Type</th>
<th>Grade of Gastritis</th>
<th>Metaplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyloric Body</td>
<td>Superficial</td>
<td>Pseudo-pyloric</td>
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<tr>
<td></td>
<td>Quiescent</td>
<td></td>
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<tr>
<td></td>
<td>Active</td>
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<tr>
<td></td>
<td>Mild</td>
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<td></td>
<td>Moderate</td>
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<td></td>
<td>Severe</td>
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<tr>
<td>Cardiac</td>
<td>Atrophic</td>
<td>Intestinal</td>
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<tr>
<td></td>
<td>Quiescent</td>
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</tr>
<tr>
<td></td>
<td>Active</td>
<td></td>
</tr>
<tr>
<td>Transitional Indeterminate</td>
<td></td>
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</tr>
</tbody>
</table>

Whitehead 1972
SIMPLIFICATION OF WHITEHEAD’S CLASSIFICATION

AS USED BY ME:-

- **Severity** - mild, moderate, severe
- “**Active**” or not
- **Type** of inflammation - acute or chronic
- **Other features** - atrophy, metaplasia
BACTERIAL STAINS

- I was interested in stains
- Microbiology stains clean smears
- More difficult with histology
- Tissues stain with bacterial stain
- Exceptions: Gram and Ziehl-Neelsen
- Silver used for spirochaetes and Donovan bodies in tissues
- I experimented with them successfully
A decade of well-fixed gastric biopsies

Whitehead's description & classification
  - Active gastritis
  - My interest

Bacterial stains

My other interests
  - Fine detail and drawing
  - Photography
  - Electron microscopy
HELICOBACTER AND ME – JUNE 1979

ROUTINE GASTRIC BIOPSY
- Severe active chronic gastritis
- Unusual blue line on the surface

HIGH MAGNIFICATION
- Numerous small curved bacilli
- Warthin-Starry stain showed bacteria clearly
SILVER STAIN

- Black bacilli line the pits.
- Easily seen.
Electron microscopy was of good quality
Showed bacteria resembling Campylobacter
Closely adherent to the cell surface

My colleagues were finally convinced, but not impressed
Normal epithelium
Electron microscopy
Helicobacter
Conclusion:

There is chronic gastritis with a small erosion. The quality of the surface mucus appears slightly more dense than normal in many areas, and it contains numerous bacteria in close contact with the surface epithelium. These bacteria have the morphology of Campylobacter. They appear to be actively growing and not a contaminant. I am not sure of the significance of these unusual findings, but further investigation of the patient's eating habits, gastro-intestinal function and microbiology may be worthwhile.

J. R. Warren 1979
FOLLOWUP

- I examined all gastric biopsies for the bacteria
  - Not expecting to find more

- Found them in almost half the biopsies
  - Usually associated with histological gastritis
  - Often severe and often “active”

- Reporting of the organisms became routine
  - No-one else believed they were of significance
DIFFICULTIES

DISBELIEF
- Just a secondary infection, due to the gastritis
- “If it is true, why were they not recognised before?”

LABORATORY MEDICINE
- No patient contact
- Poor biopsies for my purposes
- Taken from obvious lesions, ulcer or neoplasm
- Taken from any part of the stomach
My findings were ready for publication (summary, Lancet 1983)

Barry, gastroenterology registrar, needed a project for publication

Sent to “that pathologist who is trying to make gastritis an infection”
He agreed to a short series of gastric biopsies

Taking apparently normal antral mucosa, away from any local lesions

He was enthusiastic

Finally I had a clinician as a collaborator
MAJOR STUDY 1982

100 sequential outpatients for gastroscopy

- Formal, blind
- Detailed clinical protocol
- Biopsies for pathology and culture
- Tissue from “normal” antral mucosa
- Culture using *Campylobacter* techniques
UNEXPECTED RESULTS

HISTOLOGY UNRELATED TO:

- Symptoms except
  - Bad breath
  - Burping

- Gastroscopic findings except
  - DUODENAL ULCER
SUCCESS

BACTERIA CULTURED

New species

DUODENAL ULCER

Strongly related to the infection

We were surprised
PUBLICATIONS and PAPERS

1983 LANCET
- My summary
- Barry’s summary of our combined work

1983 BRUSSELS
- Campylobacter conference
- Barry presented our results
- Skirrow enthusiastic
1984 LANCET

- Our definitive paper presented
- Delayed by disbelieving reviewers
- Skirrow repeated our work, wrote to Lancet
- Our paper published unaltered
LATER WORK

Diagnosis

- CLOtest, serology and breath test invented or suggested by Dr Marshall

Treatment

- Barry saw Bismuth mentioned in Osler’s Textbook of Medicine
- Wondered if Denol worked by killing the bacteria
- He invented triple therapy in 1984

Proof

- Barry and Dr Arthur Morris used Koch’s postulates
- Treating duodenal ulcers with triple therapy
**EXAMPLES**

- **Initial acute gastritis**, rapidly responding to treatment
- Barry infecting himself, to fulfil Koch’s postulates

- **Chronic gastritis**, not responding to multiple courses of therapy
- Dr Arthur Morris, gave himself chronic gastritis to use Koch’s postulates

- **Duodenal ulcer due to NSAIDs**
- My wife, who also had *H pylori*. After treatment for it, she could take NSAIDs

- **Most people with *H pylori* are symptomless**
- Myself. When my wife was treated, she found I had bad breath
DU STUDY, 1986

- All treated for ulcer
- Uncertain numbers treated for *H pylori*
  - Blind study
- Repeated biopsies
  - 12 months and 7 year follow-up
- Excellent for study of *H pylori* pathology
QUANTIFICATION OF GASTRITIS

Specific features
  – Cobblestone change
  – Polymorph infiltration

Non-specific changes
  – Mucus secretion
  – Lymphoid infiltration

Each given a value 0 – 9, total of 36
QUANTIFICATION OF GASTRITIS

- Before and after treatment
- Biopsy 2 weeks after treatment
- Histogram
  - Patient numbers against pathology
  - Total change after treatment
HELICOBACTER AND GASTRITIS

H. pylori present

Patients
30

Grades of gastritis

0 5 10 15 20 25 30 35
HELICOBACTER AND GASTRITIS

H. pylori eradicated
HELICOBACTER AND GASTRITIS

H. pylori present

H. pylori eradicated
DUODENAL ULCER

- Distal gastric
- Gastric mucosa
  - Extends into duodenal cap
  - Forms proximal border of duodenal ulcers
- Other borders are duodenal
  - Usually inflamed and scarred
  - May show gastric metaplasia with *H pylori*
Pylorus
Duodenal ulcer
The importance of *H pylori* is accepted worldwide

- **Duodenal ulcer**, required treatment
- **Gastritis**, recognised aetiology, not the importance
- WHO listing as a **carcinogen**
- Related to gastric carcinoma and MALT **lymphoma**

- Possibly associated with **coronary artery disease**
- Big money: drug companies and research
- Governments considering cost of total eradication
CONCLUSION

- Gastric bacteria: known for 100 years and ignored
- Seen by me and linked to gastritis

**WITH DR BARRY MARSHALL**

- we cultured *H pylori*
- linked it to duodenal ulcer
- fulfilled Koch’s postulates for clinical disease and
- eradication cures gastritis and peptic ulcer disease