

ORIGINAL

FOOD & DRUG ADMINISTRATION CONFERENCE

JOINT MEETING OF THE
ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE (55TH)
and
GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

Holiday Inn
Grand Ballroom
Gaithersburg, MD

Thursday, October 26, 1995
8:35 a.m.

*This transcript has not been edited
or corrected, but appears as received
from the commercial transcribing
service. Accordingly the Food and
Drug Administration makes no
representation as to its accuracy.*

BETA

A Full Service Reporting Company
... There is No Substitute for Quality

(202) 638-2400

1-800-522-BETA

(703) 684-BETA

1 APPEARANCES:

2 Dr. Stephen Fredd
3 Mission Director, FDA

4 Dr. Hugo Gallo-Torres
5 Medical Officer, FDA

6 Robert Prizont John Sr
7 Medical Officer, Gastrointestinal Division, FDA

8 Dr. Loren Laine
9 GI, USC School of Medicine, Los Angeles

10 Dr. Amnon Sonnenberg
11 Professor of Medicine, University of New Mexico

12 Dr. Duane Smoot
13 Gastroenterology, Howard University

14 Dr. Kay Dunn
15 Biostatistics, Thayler College

16 Dr. Donald Parker

17 Dr. Janet Elushoff
18 Biostatistics, UCLA and Cedars

19 Dr. Allen Kaiser

20 Dr. Marian Melish

21 Dr. James Butt

22 Dr. Parvin Azimi
Infectious Diseases, Children's Hospital of
Oakland, California

Dr. Rosemarie Fisher
Professor of Medicine and GI, Yale University

Dr. Frank Judson
Infectious Diseases, University of Colorado

1 APPEARANCES (CNT'D):
2 Dr. Ermona McGoodwin
3 Dr. Barth Reller
4 Dr. Nancy Henry
5 Dr. Barbara Kirschner
6 Dr. Henry Francis
7 Dr. Joseph Bertino
8 Chung Owyang, M.D.
9 Virginia Banks-Bright, M.D.
10 Thomas Burks, Ph.D.
11 Edwin Thorpe, M.D.
12 William Craig, M.D.
13 Mary Fanning, M.D., Ph.D.
14 Robert Hopkins, M.D.
15 Division of Anti-Infective Drug Products
16 Linda Utrup, Ph.D.
17 Luigi Girardi, M.D.
18 Francis Megraud, Ph.D.
19 Dr. Mary Fanning
20 Dr. Temple, Ph.D.
21 Dr. Garry Neil
Astra Merck
22 Dr. Arthur Ciociola
Glaxo Wellcome

1 APPEARANCES (CNT'D):

2 Dr. Gail Comer

3 Dr. Barry Marshall
University of Virginia

4 Dr. Walter Petersen

5 Dr. James Freston
6 TAP Holdings, Inc.

7 Dr. J. Carl Craft
Abbott Laboratories

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

P R O C E E D I N G S

1
2 DR. JUDSON: Good morning, people. I'm
3 Frank Judson, the parent to the Anti-Infective
4 Drugs Advisory Committee and I'd like to welcome
5 you to our Joint Meeting. The meeting is being
6 hosted by the Anti-Infective Drugs Advisory
7 Committee and the Gastrointestinal Advisory
8 Committee.

9 And we will be discussing the
10 relationship between Helicobacter pylori and a
11 number of peptic ulcer diseases and the potential
12 for those.

13 Tomorrow, we will -- we put off our open
14 public hearing until tomorrow at 3:00 p.m, and
15 apparently there is one request to speak at that
16 hearing. Originally, only for today there was
17 going to be a joint meeting, but our GI colleagues
18 will be with us again tomorrow, so it will be
19 going both days.

20 There are no specific applications
21 before the committees. And both days will consist
22 of a general scientific discussion.

1 At this point, I'd like to introduce our
2 co-chair, Dr. Rosemarie Fisher, to my left.

3 And we will then, I think, given the
4 very large numbers of people sitting at the table,
5 go counterclockwise and introduce ourselves just
6 very briefly for the record.

7 Well, let's just start off at the left,
8 Dr. Fisher.

9 DR. FISHER: I'm Dr. Rosemarie Fisher
10 from Yale University, Professor of Medicine and
11 TI.

12 MS. AZIMI: Parvin Azimi, Infectious
13 Diseases, Children's Hospital of Oakland,
14 California.

15 MS. BANKS-BRIGHT: Virginia
16 Banks-Bright, Infectious Diseases, Northeast Ohio
17 University College of Medicine.

18 MS. COMER: Gail Comer, State University
19 of New York at Stonybrook, Gastroenterology.

20 MS. ELUSHOFF: Janet Elushoff,
21 Biostatistics, UCLA, and Cedars Simon.

22 DR. PARKER: Dr. Parker, Biostatistics,

1 University of Oklahoma.

2 MS. DUNN: Kay Dunn, Biostatistics,
3 Thayler College.

4 MR. SMOOT: Duane Smoot,
5 Gastroenterology, Howard University, Washington,
6 D.C.

7 DR. LAINE: Loren Laine, GI, USC School
8 of Medicine in Los Angeles.

9 MR. SENIOR: John Senior, Medical
10 Officer, Gastrointestinal Division, FDA.

11 MR. GALLO-TORRES: Hugo Gallo-Torres,
12 FDA, Medical Officer.

13 MR. FREDD: Stephen Fredd, Mission
14 Director of GI Coagulation at FDA.

15 DR. MEGRAUD: Francis Megraud,
16 University of Bordeaux, France.

17 DR. GIRARDI: Luigi Girardi. I like to
18 go by Gino, so please keep that in mind -- Medical
19 Officer, Division of Anti-Infective Drug Products,
20 FDA.

21 DR. UTRUP: Linda Utrup, Microbiologist,
22 Anti-Infectives, FDA.

1 DR. HOPKINS: Robert Hopkins, Medical
2 Officer, Anti-Infectives, FDA.

3 DR. FANNING: Mary Fanning, Director of
4 Anti-Infectives at FDA.

5 DR. CRAIG: Bill Craig, Infectious
6 Disease at the University of Wisconsin, and the VA
7 Hospital, Madison, Wisconsin.

8 MR. BIRCH: Tom Birch, Pharmacology and
9 Administration, University of Texas, Houston.

10 MR. OWYANG: Chung Owyang. I'm from the
11 University of Michigan.

12 MR. BERTINO: Joe Bertino, Department of
13 Pharmacy Services and Medicine, Health Care in
14 Cooperstown, New York.

15 MS. KIRSCHNER: Barbara Kirschner,
16 Pediatric Gastroenterologist, University of
17 Chicago.

18 MS. HENRY: Nancy Henry, Pediatric
19 Infectious Diseases, Medical in Rochester,
20 Minnesota.

21 MR. RELLER: Barth Reller, Infectious
22 Diseases and Clinical Microbiology.

1 MS. McGOODWIN: Ermona McGoodwin.

2 DR. JUDSON: Frank Judson, Infectious
3 Diseases, University of Colorado.

4 And at this point, I would like to go to
5 Ermona McGoodwin, who will read her conflict of
6 interest statements.

7 MS. McGOODWIN: The following
8 announcement addresses the issue of conflict of
9 interest with regard to this meeting and refers to
10 such at this meeting.

11 The purpose of this meeting is to have a
12 general scientific discussion of issues concerning
13 treatment of gastric ulcers.

14 Since no questions will be addressed to
15 the committee by the Agency on issues dealing with
16 a specific product, IND, NDA, or firm, it has been
17 determined that all interests in firms regulated
18 by the Center for Drug Evaluation and Research
19 which had been recorded by the participants
20 present no particular conflict of interest at this
21 meeting in evaluating the agenda.

22 However, in the event the discussions

1 involve any products or firms not on the agenda
2 for which an FDA participant has a financial
3 interest, the participants are aware they need to
4 exclude themselves from such involvement and that
5 exclusion will be noted for the record.

6 With respect to all other participants,
7 we ask, in the interest of fairness, that they
8 address the current or previous financial
9 involvement with any firm or products they may
10 wish to comment on. Thank you.

11 DR. JUDSON: And now Dr. Mary Fanning
12 has some opening remarks.

13 MS. McGOODWIN: May I just remind
14 everybody to introduce themselves as they get to a
15 microphone before they speak, since our
16 transcriptionists are off to the left.

17 Dr. Fanning.

18 DR. FANNING: Thank you very much. As
19 you noticed, there is a podium there, and I didn't
20 want to have my back to half of the audience, so
21 unfortunately, the committee members have to turn
22 around.

1 This is an exciting meeting, and that is
2 the first Joint Meeting of Infectious Diseases and
3 GI group. And I think we're forging into a new
4 relationship around a disease process that has
5 classically been treated by gastroenterologists --
6 ulcer disease -- and now has been discovered to
7 have a very strong infective component, but will
8 continue to require the therapeutic attention of
9 both disciplines.

10 So the aim of this meeting is to try to
11 bring both groups together to review the status of
12 scientific information at this point, and to have
13 a focused, general discussion around the issues in
14 this area.

15 I don't have any specific applications
16 to review. And in devising the agenda and the
17 issues that we wanted to discuss, the questions
18 that we framed were put to our medical officers,
19 were, "What answers would help you to try to make
20 some decisions around applications that you
21 anticipate, or are reviewing at the moment?"

22 The purpose of the questions is to focus

1 our discussion around some very particular issues,
2 but we anticipate that whatever discussions emerge
3 from this will not necessarily be binding as we
4 review future applications, because looking at
5 their concrete issues sometimes makes things look
6 somewhat different.

7 I would like to thank all of the experts
8 who will be speaking to us in general terms this
9 morning, and I look forward to some very lively
10 discussions around this topic.

11 One of the other components of the
12 meeting will be that we have encouraged industry
13 as well to bring forward some questions which will
14 come either come up during their presentations or
15 will be submitted during open session.

16 So, hopefully, we will have a meeting of
17 the minds again in one or two days with at least
18 some better understanding of the issues from all
19 of the disciplines and players involved in trying
20 to deal with the therapy of ulcer disease and H.
21 pylori infection.

22 Thank you.

1 DR. JUDSON: -- has revolutionized
2 concepts. And, in recognition of this, the Lasker
3 award recently went to Dr. Marshall, joining those
4 whose certain qualities and discoveries made in
5 clinical research have dramatically changed the
6 practice of medicine during the past half century.

7 This year's winner, Dr. Marshall,
8 epitomizes the power of clinical research to
9 revise the pathogenesis of treatment and,
10 ultimately, to enhance the potential for the
11 prevention of a disease.

12 I have asked, and I don't believe you
13 have gotten it -- but you will -- an article, and
14 I wanted to just point out a couple of charts in
15 that for your consideration.

16 Would you put up the first one?

17 DR. FREDD: I don't know how many of you
18 can see this, but here are a variety of
19 eradication regimens -- triple therapies, so to
20 speak -- the different eradication rates one can
21 see displayed of variability. They can range
22 anywhere from 90 percent down to around 60

1 percent, even with the same regimen.

2 But certainly there are regimens that
3 are devised and are available in the clinical
4 practice of medicine.

5 Eradication rates of Helicobacter pylori
6 -- how you view this is one of the questions that
7 you need to consider. Whether the regulatory
8 posture related to this is different from the
9 placebo -- i.e. no treatment -- or whether a
10 certain level of control, since it can be
11 achieved, should be achieved by the regimens that
12 you are going to consider.

13 The link between eradication and
14 duodenal ulcer recurrence -- and I'm afraid you
15 can't see this too well. It is in the article.

16 In the open circles at the bottom are
17 duodenal ulcer recurrences, and the dark circles
18 at the top, that is peptic ulcer occurrences in HP
19 eradicated patients, versus dark circles at the
20 top where HP was not eradicated. And the
21 difference is quite dramatically presented.

22 But then the question is, "if we can

1 eradicate, and by eradication, prevent occurrence,
2 have we done good for the patient in terms of
3 preventing complications?"

4 In this article, at least there is a
5 possibility presented that GI bleeding is much
6 less prevalent in patients who have had
7 eradication and who had less recurrence. There's
8 potential for recurrence of ulcer disease in this
9 chart. So I will get you this article if you do
10 not have it.

11 Recognizing the availability of therapy
12 and recognizing what is in the literature related
13 to the phenomenon of eradication prevention of
14 ulcer occurrence -- and the potential, from that,
15 of reducing serious complications in ulcer disease
16 -- the American College of Gastroenterology, at
17 its recent meeting in New York, promulgated
18 practice bylines.

19 And I would like to read you some of
20 these for your consideration in terms of what the
21 clinical community is doing with current therapy.

22 "Cure of HP Infection: Recommendations.

1 "Since cure of HP infections increases ulcer
2 recurrence rates and facilitates healing,
3 antibiotic therapy is appropriate for all
4 HP-infected ulcer patients.

5 "Although refinement of treatment
6 regimens is needed, the NIH Consensus Development
7 Conference firmly concluded that the cure of the
8 infection is an essential component of ulcer
9 therapy."

10 And another recommendation relates to
11 conventional ulcer therapy: "Although HP should be
12 sought and treated with antibiotics if present,
13 conventional ulcer therapy is still frequently
14 necessary to induce healing."

15 "Therefore, there is this dichotomy
16 between preventing recurrence through HP
17 eradication and, still, the need to induce healing
18 with anti-secretory drugs recognized by the
19 American College."

20 And lastly, the recommendation for
21 prevention of ulcer recurrence is that if HP is
22 present, cure of this infection is the first step

1 in preventing ulcer recurrence, since successful
2 cure of HP infection will markedly reduce the need
3 for maintenance therapy.

4 These, then, are the recent
5 recommendations of the American College of
6 Gastroenterology promulgated to the clinical
7 community, including the American Academy of
8 Family Practice, American College of Surgeons,
9 American College of Physicians, and the American
10 College of Radiology.

11 In terms of the longevity of this: If
12 ulcers are prevented for a period of time, how
13 long does that phenomenon last?

14 There are certain abstracts, some in the
15 "American Journal of Gastroenterology" in
16 September, among others, with follow-ups of 5 to
17 11 years, suggesting through these cohort studies
18 that continued decrease in peptic ulcer and
19 duodenal ulcer recurrence is provided through
20 eradication.

21 So, therefore, what is your role? What
22 is our role in FDA, since practicing physicians

1 have promulgated concepts and guidelines and since
2 drugs are in the public domain.

3 Barry Marshall, accepting his last
4 award, notes in his article in "JAMA" that no drug
5 regimen -- no drugs are yet approved by the FDA
6 for the treatment of this condition. And I think
7 that is the reason we are meeting and considering
8 these issues.

9 The power and the possibility for
10 education through appropriate approvals, labeling,
11 and promotions by the industry cannot be
12 underrated. And therefore, we in the GI division
13 will work and are anxious to work to determine
14 what regimens are approvable, what ways to
15 approach clinical trials, in terms of analyzing
16 these trials, and getting labeling written, which
17 will be informative to permit us to do our
18 educational job.

19 Thank you.

20 DR. FANNING: If I could just add that
21 it's not only professional organizations.

22 I was quite impressed to see on December

1 27, 1994, a letter from AETNA Health Plans of
2 Southern New England, to all physicians who belong
3 to this health care plan, with an algorithm for
4 the treatment of peptic ulcer disease or acid
5 peptic disorders, including an already-recommended
6 treatment for H. pylori of 2 weeks of H2
7 antagonist and tetracycline.

8 This is all for \$43, versus a two-week
9 treatment of Invectisol and Amoxicillin for \$59
10 with their recommendation.

11 So I think as we're going through this,
12 we're going to see that our recommended approvals
13 are going to be extremely significant as health
14 insurance -- HMOs, managed care organizations --
15 have already beat us to this by almost a year
16 already.

17 DR. JUDSON: I'd like the record to
18 refer that Dr. Edwin Thorpe is at the table from
19 the University of Tennessee.

20 And now, if we can go on to Dr. Bob
21 Hopkins of the FDA.

22 DR. HOPKINS: Good morning. My name is

1 Bob Hopkins and I am from the Division of
2 Anti-Infective products and I am a medical officer
3 there.

4 What I would like to do in the next 15
5 minutes is to give a brief overview as to what we
6 will be discussing over the next two days and
7 discuss what role the FDA plays in the process of
8 getting drugs designed to eradicate H. pylori
9 approved.

10 As you all know, Helicobacter pylori has
11 made the public health significant. It is
12 possibly the most prevalent bacterial infection
13 worldwide.

14 It has been associated with multiple
15 disease states, including duodenal gastric ulcers,
16 gastric cancer, and possibly even pulmonary artery
17 disease and certain growth disturbances.

18 This is a picture of a patient who is
19 suffering from extreme discomfort due to
20 Helicobacter pylori. And as you can see, there
21 are interesting pathogenic mechanisms that deal
22 with these severe symptoms.

1 The challenges that we face at the FDA
2 are really similar to the challenges that
3 clinicians face in their offices, as well as the
4 challenges that industry face in developing
5 regimens.

6 Essentially the recommendations for
7 treatment are rapidly changing. It's still "whom
8 to treat, when to treat, how long to treat and
9 what to use to treat" that we will discussing
10 today.

11 As Dr. Fredd alluded to, the NIH
12 consensus conference concluded that ulcer patients
13 with H. pylori infection require treatment with
14 antimicrobial agents in addition to anti-secretory
15 drugs on first presentation or on recurrence.

16 In addition, they stated that patients
17 with peptic ulcer disease who are on maintenance
18 therapy should be treated as well as patients who
19 have complicated ulcer disease.

20 The value of treatment of non-ulcer
21 dyspepsia patients with H. pylori infection
22 remains to be determined, and the interesting

1 relationship between infection and gastric cancers
2 require further exploration.

3 The role of the FDA is essentially
4 stated here, "To expeditiously review applications
5 and ensure that regimens are safe and effective in
6 designing clinical trials, to help craft
7 scientific-based labeled for approved regimens,
8 and finally, to reach consensus over the most
9 controversial issues through discussions with
10 academia, industry, and the public." And this is
11 the reason we are all here today.

12 The difference between designing a
13 clinical trial that may be published in the
14 literature and one that is designed to go to a
15 regulatory agency is significant. And some of the
16 differences are outlined here.

17 At the FDA, we require a factorial
18 design approach which makes sure that each
19 component of a drug regimen contributes in some
20 way to the effect of the entire regimen.

21 In addition, in the past we have
22 recommended the use of placebo controls. And also

1 we require multi-centered trials to ensure the
2 regimen's effectiveness, and we also have the
3 division of scientific investigation, which audits
4 investigators to make sure that the data is valid.

5 As you can imagine, the regulatory
6 burden, as outlined here, has caused a bit of a
7 headache in some circles.

8 Because the approach is different to the
9 design of a trial for regulatory agency versus one
10 that might have been published in the literature,
11 we have been involved, as well as other groups
12 around the world, in trying to design guidance for
13 persons interested in designing pylori clinical
14 trials.

15 The first attempt was done in
16 collaboration with the Infectious Disease Society
17 of America and the FDA, published in 1992, where
18 multiple indications were discussed about how to
19 run clinical trials for the anti-infective
20 division.

21 Subsequently, last April, in
22 Philadelphia, we distributed a "points to

1 consider" documents and the original points in the
2 document focused on H. pylori and how to design
3 clinical trials.

4 This has subsequently undergone revision
5 in June to remove some of the areas that were most
6 controversial in the area of gastroenterology.
7 And I would imagine that it will undergo many
8 revisions in the future.

9 And finally, the European H. pylori
10 study group has recently completed guidelines for
11 clinical trials in H. pylori infection. It's a
12 much more broader scope, not limited to peptic
13 ulcer disease alone. And we are waiting for the
14 soon-to-be-published manuscript to come out.

15 The issues that we will discuss in the
16 next few days are outlined here. The first three
17 issues will be discussed today and the last two
18 will be discussed tomorrow.

19 Possibly the one that is of the most
20 interest is the first one, which is choosing
21 clinical and/or microbiologic end points for
22 clinical trials.

1 The second one will be the question as
2 to whether we can use a minimal level of efficacy
3 for eradication over that matter in the other end
4 point that we might determine as plausible.

5 And finally today, we will be discussing
6 issues surrounding labeling for H.
7 pylori-associated peptic ulcer disease -- more
8 specifically, what claims we should consider.

9 And tomorrow, you will be discussing end
10 points and other clinical study designed issues
11 related to H. pylori non-ulcer conditions. And
12 non-ulcer is dyspepsia and gastric cancer.

13 And finally, we will be discussing
14 issues for resistance, not only the resistance of
15 H. pylori pretherapy or H. pylori
16 resistance-induced post-therapy, but also
17 broad-spectrum bacterial resistance as a result of
18 widespread treatment.

19 The goals of this meeting are
20 essentially to bring forth the latest developments
21 in this rapidly expanding field, to help the
22 agency and the advisory committees obtain a more

1 clear understanding of the clinical trials issues
2 and the more appropriate regulatory decisions for
3 current MBAs and the future of new drug
4 applications.

5 And finally, we would like to attempt to
6 reach consensus over some of the more
7 controversial areas of clinical trial design.

8 We have an expert list of consultants
9 today. Dr. Sonnenberg, Professor of Medicine,
10 University of New Mexico will be speaking on H.
11 pylori peptic ulcer epidemiology.

12 Dr. Duane Smoot from Howard University,
13 an Associate Professor of Medicine, will be
14 discussing pathogenesis and pathophysiology of H.
15 pylori and peptic ulcer disease.

16 And then finally, Dr. Francis Megraud
17 from the University of Bordeaux, Professor of
18 Bacteriology, will be discussing issues
19 surrounding the area of H. Pylori diagnostics for
20 clinical trials, as well as resistance.

21 And we do have Dr. Loren Laine, who will
22 not actually be giving a talk today, but is an

1 expert in clinical trial design. And so he will
2 be available for discussions.

3 Thank you very much. I will turn it
4 over to Dr. Sonnenberg from the University of New
5 Mexico, who will be talking about
6 epidemiology-based pylori and peptic ulcer
7 disease.

8 DR. SONNENBERG: Good morning. In my
9 talk on the epidemiology of H. pylori and peptic
10 ulcer disease, I will try to focus on three
11 points.

12 One is the time trends of peptic ulcer
13 disease and how it relates to H. pylori.

14 Secondly, on the geographic variation of
15 peptic ulcer disease and H. pylori-related
16 diseases.

17 And lastly, on the social and
18 socioeconomic distribution of H. pylori infection.

19 This slide shows the age-specific death
20 rates of birth cohort in Switzerland. The Y-axis
21 relates to age specific death rates per million
22 living population.

1 On the X-axis, you have the time periods
2 between 1925 and 1975. And each curve relates to
3 a different age group. Those are age 20 to 29, 30
4 to 39, 40 to 49, and so forth.

5 It is striking that peptic ulcer
6 mortality, from the onset, has declined markedly
7 throughout this century in the younger age groups.
8 The decline was not present in the middle-aged
9 ones -- that is, 50 to 70 throughout. And there
10 was actually, during the same time period, a
11 marked rise in peptic ulcer-related mortality in
12 those aged 60 and more.

13 Those time trends were always difficult
14 to explain for epidemiologists who could not
15 understand why, at the same time, the disease was
16 declining in the younger age groups and increased
17 in the older age groups.

18 Now if you take the same curve and plot
19 them, versus the period of birth rather than
20 period of death, they are spread apart and seem to
21 align to one hyperbola.

22 And this is shown more clearly in the

1 panel on the right side which calculates the
2 standardized mortality ratio, as we say, or the
3 average mortality of all those curves. And then
4 this up and down movement in ulcer-related
5 mortality becomes more clear.

6 The peak relates to those all around the
7 turn of the century -- actually, before the turn
8 of the century, around 1880. This birth cohort
9 phenomenon was originally described by Marvin
10 Sasser and his wife -- he was then the editor of
11 the "American Journal of Public Health" -- and
12 this birth cohort phenomenon remained an enigma
13 for a long time.

14 Now, it seems more clear that people
15 that were born before the turn of the century were
16 probably the ones who had run the highest risk of
17 getting infected during early childhood with H.
18 pylori, and carried this risk for the rest of
19 their life.

20 This data actually relates to the
21 duodenal ulcer. And this is now showing the birth
22 cohort phenomenon of peptic ulcer disease in

1 Switzerland, gastric ulcer in men, duodenal ulcer
2 in men, gastric ulcer in females, and duodenal
3 ulcer in females.

4 And you can see that the birth cohort
5 phenomenon relates to both sexes and both ulcer
6 diseases.

7 Initial rise to subsequent decline --
8 the peak in gastric ulcer in Switzerland was
9 around 1870, similarly in men as to women.

10 This is duodenal ulcer. You can
11 probably see it is a longer rise in duodenal ulcer
12 as compared with gastric ulcer. So the peak of
13 the curve is shifted by 10 to 20 years towards
14 more recent times.

15 It seems as if those that carried the
16 highest risk of duodenal ulcer were born 10 to 20
17 years later than those carrying the highest risk
18 of developing gastric ulcer.

19 In terms of H. pylori infection, it may
20 be that the risk of developing duodenal ulcer may
21 be associated with an infection that happens 10 to
22 20 years later than early childhood.

1 This is data from Switzerland, but
2 actually a birth cohort phenomenon can be
3 demonstrated in all Western countries. This is
4 data from Europe. This is Germany, Italy,
5 Scotland, and some other countries. Basically,
6 all European countries show the birth cohort
7 phenomenon.

8 This is the birth cohort pattern in the
9 United States. Gastric ulcer -- initial rise,
10 subsequent decline. Duodenal ulcer made a more
11 pronounced initial rise, with the shift of the
12 peak by about 10 to 20 years in the United States,
13 as in most other European countries. With
14 duodenal ulcer in females and gastric ulcer in
15 females, the initial rise was visible.

16 The other thing that I would want to
17 point out here is mortality from gastric cancer in
18 men and women in the United States.

19 We don't see the initial rise, but only
20 a decline in the risk of dying from gastric cancer
21 in the United States for consecutive birth
22 cohorts.

1 So, obviously, there is some discrepancy
2 between the patterns of duodenal ulcer, gastric
3 ulcer, and gastric cancer.

4 Yes, all three diseases show a marked
5 decline, but the initial trend or trends seem to
6 be different, and there seems to be different
7 factors that play a role in gastric ulcer because
8 H. pylori.

9 This is data that were published by --
10 from Canada. The X-axis shows the age in years,
11 and the Y-axis, the percentage of patients who
12 tested positive, serologically, for H. pylori.
13 And there is an age-related rise in H. pylori
14 seropositively, probably reflecting scores of --
15 serologic scores of infection with H. pylori
16 during early childhood. And a similar pattern was
17 reported for the U.S. population by David Brand
18 and his group.

19 By and large, in the prevalence rate of
20 H. Pylori, there's a reflection of age or
21 possibly the risk of being infected with H. pylori
22 during early childhood.

1 This is data from Finland. The X-axis
2 shows the years of birth between 1970 and 1900.
3 So it's flipped along, if you will, compared with
4 the other graphs that I've shown you.

5 This is the oldest group, and the Y-axis
6 shows the prevalence of prostritis in the Finnish
7 population. So those who were born around the
8 turn of the century had the highest prevalence
9 rate of prostritis.

10 And there was a marked decline of
11 prostritis associated with age or year of birth;
12 again, supporting the concept that the older
13 generations carry a higher risk of being infected
14 with H. pylori and developing chronic prostritis.

15 These data compilations are from England
16 and France. Francis Megraud is one of the
17 authors.

18 The X-axis shows the age in years
19 between 0 and 100. And the Y-axis, again, the
20 percent of patients who were positive for H.
21 pylori. And each curve represents a different
22 cohort.

1 Again, it is a rise in the
2 seroprevalence of H. pylori, and possibly a
3 decline for the eldest age groups -- that is,
4 those that were born before the turn of the
5 century -- again, supporting the contention that
6 the birth cohort phenomenon underlying the
7 appearance of peptic ulcer disease may relate to
8 similar birth cohort patterns of H. pylori
9 infection and the risk of being infected with H.
10 pylori during early childhood -- possibly 10 to 20
11 years later -- with respect to duodenal ulcer.

12 So duodenal ulcer may be a disease where
13 you get infected with H. pylori during adolescence
14 or early adulthood.

15 So let's forget about the summary,
16 because I can't give it anyway.

17 (Laughter)

18 I will talk now about the geographic
19 variation of peptic ulcer disease and how it
20 relates to the infection with H. pylori.

21 The upper graphs relate to gastric
22 ulcer, the lower ones to duodenal ulcer. And in

1 each panel, two different age groups were collated
2 with each other. So, in this panel, for instance,
3 the X-axis represents mortality from gastric ulcer
4 in those aged 20 to 29 correlated against those
5 aged 30 to 39.

6 And each country is represented by one
7 point. So, let's say this is Japan -- mortality
8 from gastric ulcer in Japan is high among those
9 aged 20 to 29, as well as in those aged 30 to 39.'

10 Vice versa, in the United States and in
11 Canada -- mortality from gastric ulcer is low in
12 both age groups.

13 So if you plot mortality from different
14 age groups among different countries, you find a
15 significant correlation indicating that, whatever
16 the risk factor is in different countries, it
17 affects different age groups alike. And those
18 correlations hold true if you plot 15 to 19, I
19 think, against 20 to 29, or 10 to 14 against 15 to
20 19, and so forth.

21 The correlation with respect to gastric
22 ulcer breaks up at the age of 5. If you look at

1 age groups and mortality related to gastric ulcer
2 in those aged less than 5 years, there is no
3 correlation between different age groups, but it
4 starts around the age of 5.

5 In comparison, with duodenal ulcer,
6 there is a highly significant correlation among
7 different age groups between those aged 20 to 29
8 and 30 to 39. But the correlations break off at
9 the age of 15.

10 Again, the geographic distribution
11 suggests that whatever the environmental risk
12 factors are in gastric ulcer, they become
13 effective before the age of 5 years, and duodenal
14 ulcer before the age of 15 years.

15 In light of our current knowledge
16 regarding *H. pylori*, it would suggest that
17 infection during early childhood carries the risk
18 for gastric ulcer. Infection during adolescence
19 carries more a risk for duodenal ulcer disease.

20 This is data from the EuroGas studies.
21 David Foreman was one of the authors. And what
22 they did was they plotted seroprevalence for *H.*

1 pylori against -- something else that I can't tell
2 right now.

3 Basically, it shows significant
4 correlation between mortality from gastric ulcer
5 and the seroprevalence for H. pylori among
6 different countries.

7 Each points -- each one represents a
8 different county or a different country. And
9 these correlations apply to mortality, as well as
10 incidence, in men and women, so again, supporting
11 the role of H. pylori in the geographic
12 distribution of gastric cancer.

13 We have known for quite a while that
14 gastric cancer and peptic ulcer disease showed --
15 showed marked geographic variations, always
16 indicating the role of important environmental
17 risk factors.

18 This is data from India showing that --
19 in India, for instance, there is a marked
20 variation in the occurrence in duodenal ulcer.
21 The disease seemed to foster on the eastern coast
22 and was relatively infrequent in some of the large

1 states.

2 Similar data also exists for Africa.
3 Peptic ulcer disease seemed to be relatively
4 common in Uganda and Nigeria. Gastric ulcer is
5 relatively rare in Africa.

6 Interestingly, even in countries with a
7 relatively high and uniform infection with H.
8 pylori, we find the incidence of duodenal ulcer
9 uniformly high, suggesting that in addition to H.
10 pylori, other factors might play a role in the
11 occurrence of peptic ulcer disease. This has also
12 been called the "African enigma."

13 This slide shows on the X-axis the age,
14 and on the Y-axis, the percent population testing
15 positive for H. pylori. The lower curves
16 represent Western countries. In the Western
17 countries there is a relatively slow age-related
18 rise in the occurrence of H. pylori infection.

19 In striking contradistinction with the
20 Western countries, in developing countries you see
21 a steep rise in the occurrence of H. pylori
22 infection during the first years of life, and then

1 more of a plateau subsequently, suggesting that
2 most of the relevant H. pylori infection occurs
3 during early childhood and most of the damage is
4 done by the age of 20, as more than 80 percent of
5 the population get infected with H. pylori in
6 developing countries by the age of 20.

7 It seems as if in Western countries,
8 those people with H. pylori infections carry this
9 cause of encounter with the bug during early
10 childhood -- again, relating to the birth cohort
11 phenomenon.

12 This is data from the United States
13 comparing the occurrence of gastric ulcer and
14 duodenal ulcer in different states. Each point
15 represents a different state and the size of the
16 circle relates to the different size of the
17 population. So a big circle represents, let's
18 say, New York or California, and a smaller circle
19 something like Montana or Alaska.

20 Interestingly, in the United States,
21 there is a highly significant correlation between
22 the occurrence of gastric ulcer and duodenal

1 ulcer, suggesting, again, the role of one or
2 several underlying mechanisms that are responsible
3 for the geographic distribution of both diseases
4 and that act similarly with respect to gastric
5 ulcer and duodenal ulcer.

6 Again, data from the United States.
7 This time gastric cancer is being plotted against
8 gastric ulcer. And yes, there is a significant
9 correlation between the occurrence of gastric
10 cancer and gastric ulcer, but the correlation is
11 far less significant than between both types of
12 peptic ulcer disease, suggesting that gastric
13 cancer is influenced by yet another set of risk
14 factors besides the ones that influence the
15 occurrence of peptic ulcer disease.

16 And again, with gastric cancer plotted
17 versus duodenal ulcer, it is significant, but less
18 striking as between both ulcer diseases.

19 What are the other risk factors that may
20 play a role in the occurrence of gastric cancer
21 besides H. pylori?

22 We don't know. It has been suggested

1 that salt consumption might be a risk factor for
2 the occurrence of gastric cancer. This are data
3 among different countries, worldwide distribution.

4 And on the X-axis, we have mortality
5 from gastric cancer and on the Y-axis, mortality
6 from stroke, and different points represent
7 different countries. And worldwide, there is a
8 highly significant correlation between mortality
9 from stroke and gastric cancer, suggesting that
10 possibly salt is an underlying risk factor leading
11 to hypertension and stroke on one hand, and
12 gastric diseases such as gastric cancer on the
13 other hand. Maybe Dr. Correa will speak about
14 this later.

15 This line compares gastric cancer,
16 stroke, gastric ulcer, and salt consumption among
17 different countries. Each point represents a
18 different country. Again, high death rates from
19 gastric cancer and stroke are found in countries
20 like Spain, Portugal, and Japan. Relatively low
21 mortality from gastric cancer and stroke are found
22 in countries like the U.S. and Canada. European

1 countries are somewhere in the middle.

2 And you find significant correlations
3 between gastric cancer and gastric ulcer in
4 different countries. Countries characterized by
5 high mortality from gastric cancer tend to have a
6 high mortality from gastric ulcer.

7 A typical country would, again, be
8 Japan. And interestingly, those countries with a
9 high mortality from gastric cancer tend to have a
10 high salt consumption. Those tend to be
11 fish-eating countries where salt is still used
12 widely to preserve food, specifically fish. And
13 there is a similar correlation between salt
14 consumption and stroke, salt consumption and
15 gastric ulcer.

16 So I show this slide to indicate that
17 yes, *H. pylori* is definitely a risk factor for
18 peptic ulcer disease and gastric cancer, but there
19 might be other additional environmental factors
20 that play a role in the geographic distribution of
21 those diseases.

22 I will talk lastly about the

1 socioeconomic distribution of H. pylori infection
2 factors that play a role.

3 This shows the transmission of H. pylori
4 infection in families. This is data by David
5 Graham. And his group, analyzed, let's say, a H.
6 pylori-positive index parent and then went into
7 the family and found that it would have a positive
8 index parent, 40 percent of the children were H.
9 pylori-positive, and 68 percent of the spouses
10 were H. pylori-positive.

11 On the other hand, if we had a H.
12 pylori-negative index parent, only three percent
13 of the children were H. pylori-positive and nine
14 percent of the spouses, suggesting that H. pylori
15 spreads within families.

16 This are data from Northfield and his
17 group in England, showing that living conditions
18 have a striking role in the infection rate with H.
19 pylori.

20 One was the number of children that
21 lived in the household. And the more children you
22 had in the household, the higher the risk for

1 being H. pylori-positive.

2 And other factors that played the role
3 was the availability of hot water in the house.
4 That was associated with a low risk.

5 Basically, poor standards of hygiene
6 were associated with a high risk for H. pylori --
7 again, suggesting that it spread within families.
8 And standards of hygiene played a significant role
9 in the occurrence of H. pylori.

10 We have always known that peptic ulcer
11 disease and hospitalization rates and mortality
12 from peptic ulcer disease are associated with
13 social class.

14 On the left side, we have data from the
15 United States, and on the right side, data from
16 England and Wales.

17 The red bars represent duodenal ulcer
18 and the blue bars, gastric ulcer. And high social
19 class is one. Low social class, 5. Those are in
20 between manual workers and semi-skilled workers.

21 And there is a clear-cut correlation
22 between low social status and high mortality from

1 gastric and duodenal ulcer in the United States as
2 well as in England and Wales.

3 And this correlates nicely with the
4 infection rate of H. pylori. Those are data again
5 from David Graham and his group in Easton.

6 The X-axis shows the income in thousands
7 of dollars. So this is the high income group,
8 \$80,000 family income and more. And the Y-axis
9 shows the percent infected with H. pylori as shown
10 by serology. An inverse correlation between
11 family income and H. Pylori seropositivity
12 obviously significant for whites, not obvious for
13 blacks.

14 Data from the United Kingdom -- again,
15 showing two things. One is the social
16 distribution, and secondly, the birth cohort
17 phenomenon of H. pylori factors.

18 The X-axis shows year of birth between
19 1910 and 1950. The Y-axis showing prevalence of
20 H. pylori infection, early birth cohorts, more
21 recent birth cohorts, a decline, and, more
22 interestingly, in this context, is the full line

1 representing high social classes and the broken
2 lines showing lower social classes in England,
3 again indicating that for different birth cohorts
4 alike, the risk of being infected with H. pylori
5 was higher for the lower socioeconomic classes in
6 England as separated by the Surgeon General in
7 England.

8 This slide shows that other factors
9 besides H. pylori again may play a role in the
10 development of peptic ulcer disease, and that We
11 had to keep in mind other factors like that which
12 may influence acid secretion.

13 This is data from Germany showing energy
14 expenditure in kilocalories per day and on the
15 Y-axis, duodenal ulcer prevalence. There is a
16 highly significant correlation between energy
17 expenditure and the risk of developing duodenal
18 ulcer disease.

19 This may be a reflection of multiple
20 factors that may be a reflection of energy
21 expenditure itself, possibly energy expenditure in
22 physical workloads stimulating acid secretion and

1 representing the risk factor for the development
2 of duodenal ulcer.

3 It may also represent the fact that
4 people with lower income carry a higher physical
5 workload. So it may, again, reflect the influence
6 of social class on the development of duodenal
7 ulcer disease.

8 Those are my summaries. Basically, yes,
9 there is good epidemiology evidence that H. pylori
10 plays a significant role in the development of
11 gastric ulcer, duodenal ulcer, and gastric cancer,
12 but that the temporal and geographic distribution
13 of H. pylori most likely does not explain all that
14 we see in the epidemiology of all three diseases.

15 Thank you very much.

16 DR. JUDSON: Thank you. We're running
17 just a little bit late, so I think we best go on
18 to a break.

19 If individuals have specific further
20 questions of Dr. Sonnenberg, perhaps we can pin
21 you down at break.

22 We are ready for a coffee break.

1 (Recess)

2 DR. JUDSON: Dr. Duane Smoot will
3 discuss the pathogenesis of peptic ulcer disease.

4 DR. SMOOT: Good morning. I'd like to
5 take a few minutes to go over H. pylori
6 pathogenesis.

7 There's still a lot of controversy in
8 this area. I would like to try to summarize some
9 of the major issues dealing with H. pylori and
10 peptic ulcer pathogenesis.

11 It is estimated that one in 6 persons
12 infected with H. pylori in the high-incidence
13 areas will develop a peptic ulcer.

14 H. pylori is found in over 90 percent of
15 patients generally with duodenal ulcers. Active
16 chronic gastritis, we have found, precedes the
17 formation of duodenal ulcers, and this was even
18 known prior to the discovery of H. pylori.

19 H. pylori is found in 75 to 85 percent
20 of the patients with gastric ulcers. Dr.
21 Sonnenberg has talked a lot about that earlier.

22 There is also a lot of indirect evidence

1 for the role of H. pylori in peptic ulcer
2 pathogenesis. Successful treatment of H. pylori
3 infection heals ulcers, both gastric and duodenal,
4 without acid suppression.

5 It also accelerates ulcer healing when
6 combined with acid suppression. So the use of
7 antibiotics with acid suppression appears to
8 accelerate ulcer healing.

9 And use of antibiotic significantly
10 reduces ulcer recurrences and has also been shown
11 to prevent rebleeding ulcer recurrences.

12 I'd just like to show you data from a
13 case control study that was reported in "Annals"
14 last year. There was a large cohort of over 5,000
15 Japanese-Americans in Hawaii.

16 Serology was used to determine H. pylori
17 status, and a bank stored serum on both cases and
18 the controls.

19 150 patients were seen with gastric
20 ulcers. 93 percent of these were positive for H.
21 pylori, compared to 75 percent of controls. Also
22 in this study, 92 percent of 65 patients with

1 duodenal ulcer and 78 percent of controls were H.
2 pylori-positive.

3 What they did was look for the odds
4 ratio, the risk of gastric ulcer and duodenal
5 ulcer in the cohort of the 150 patients. There is
6 a odds ratio of 3.2 for gastric ulcer in the
7 cohort. With the duodenal ulcer, there is a odds
8 ratio of 4.

9 And whether you developed a gastric or
10 duodenal ulcer, with a cohort of 215 patients,
11 there was about a three to three and a half
12 increase risk of this with being infected with H.
13 Pylori.

14 They also looked at this, since they
15 used serology, looking at the antibody levels.
16 And if you take the antibody levels and the
17 antibody levels have been shown to correlate with
18 bacterial load, so that people who have a high
19 bacterial load overall will have higher antibody
20 levels.

21 If we look at the people with the low
22 positivity, they have a two to two and a half to

1 three-fold increase of potential for ulcer.

2 If we get up into the moderate range, it
3 goes up to almost 6. And for those very high, the
4 odds ratio is almost 7 for development of duodenal
5 ulcer.

6 They also looked at this in relation to
7 gastric ulcer. And we saw the same thing, but not
8 as high a ratio, going from about 0.2 in the 95
9 percent confidence interval goes down to 1. But
10 those were moderate to higher.

11 These 95 percent confidence intervals
12 show a higher than one-fold increase risk of
13 ulcers, so that antibody levels -- possibly
14 meaning that bacterial load may also have an
15 impact on the development of the ulcer.

16 Now, look at the peptic ulcer
17 pathogenesis. I divided it into three areas. I
18 would like to take a few minutes to go over some
19 of the bacterial virulence factors that have been
20 described. Also, we have to talk about the host
21 immune response. There's a lot of debate in this
22 area. And then thirdly, go over the environmental

1 co-factors that might be involved.

2 And with the bacterial virulence
3 factors, there are several that have been
4 described and there are others that are there that
5 I won't talk about, just to try to summarize.

6 The vacuolizing cytotoxin is a 90 --
7 approximately a 90 kDa protein, which is due to
8 the vacuolation in eukaryotic cells. And this has
9 been found in vitro.

10 Studies in vivo do appoint that the
11 bacteria does make this protein and that there are
12 antibodies to this protein in vivo.

13 Strains expressing high cytotoxin
14 activity are more commonly isolated from patients
15 with peptic ulcer disease than from patients with
16 gastritis alone.

17 What has also been shown is that oral
18 administration of the cytotoxin in mice causes
19 ulceration and gastric lesions, which have
20 similarities to gastric ulcer disease in man.

21 So there is some evidence and some
22 people would believe that this strain variability

1 and possibly the presence of vacuolizing cytotoxin
2 is important for development of ulcer disease.

3 There is also a cytotoxin-associated
4 gene and protein that was found in relationship to
5 the cytotoxic protein. It is called CagA. This
6 encodes a 120-140 kDa protein which is found
7 commonly in cytotoxin strains.

8 Early studies reported CagA positivity
9 in about 60 percent of patients with gastritis, as
10 opposed to 100 percent of patients with peptic
11 ulceration.

12 More recent studies have reported that
13 at least 20 percent of duodenal ulcer patients are
14 negative for CagA. So there are people with
15 ulcers that do not have CagA, and now more recent
16 studies appear to associate CagA more strongly to
17 gastric cancer development than to peptic ulcer
18 disease.

19 Some people feel that the presence of
20 CagA, or maybe the presence of the cytotoxin, may
21 determine whether patients are infected with this
22 strain, which is more likely to cause an ulcer. They

1 may be surrogate markers and may identify patients
2 that are more likely to be treated.

3 What's also mentioned is that the
4 organism produces a proteinase and lipase which
5 reduce the viscosity of mucus and may also
6 increase the risk of back diffusion of acid and
7 then ulcer development.

8 Also of note is the urease produced by
9 H. pylori. This a high molecular rate protein
10 which is very important to the organism.

11 The urease produces ammonium from the
12 breakdown of urease. This has been shown in vitro
13 to be toxic to human gastric epithelial cells.
14 Also, in vivo animal experiments have shown
15 ammonia to be toxic.

16 Initially, urease was felt to be
17 important for production of ammonia in that it
18 neutralized the acid in the microenvironment
19 around the organism, so that it could survive in
20 the pH of the stomach, which would get down to as
21 low as two, and allow it to get below the mucus
22 layer where the pH at the gastric epithelial cell

1 is approximately about 6 to 6 and a half.

2 What we recently found is that urease
3 not only acts to protect the organism from the
4 acid initially, but is an essential colonization
5 factor, in that urease-negative H. pylori mutants
6 are unable to colonize gnotobiotic piglets,
7 regardless of the gastric acidity.

8 So, even when they inhibit the acid, we
9 are unable to colonize these animals with the
10 urease-negative mutant.

11 Now, to talk a little bit more about the
12 host response, we'll look at inflammatory
13 response, effects of H. pylori on acid secretion,
14 possible genetics susceptible related to acquiring
15 H. pylori and then also development of gastric
16 adenoplasia in the duodenum.

17 What I also need to mention is that,
18 with this host response, we can now completely
19 separate this from some of the bacterial virulence
20 factors, because a host response appears to vary
21 in relation to some of the bacterial factors. So
22 there's still a lot of debate whether it's really

1 the host response that's different or if it is a
2 strain variability that alters the host response.

3 There is induction of a strong oxidative
4 burst in neutrophils by H. pylori, but this is
5 found to be variable between H. pylori strains.

6 Now, this variability is independent of
7 cytotoxin production. Strains that induce this
8 strong oxidative reaction from neutrophils are
9 much more common in peptic ulcer disease patients.

10 So this induction of this inflammatory
11 response, it may be host mediated, but then again,
12 there are some other factors.

13 There is a correlation that has been
14 observed between the density of H. pylori
15 colonization in the interim and ulcer formation.
16 And that goes back to the other studies showing
17 that the antibody levels also correlate.

18 Strains that are CagA-positive induce a
19 much higher interleukin-8 secretion in the gastric
20 epithelial cell lines in vitro.

21 Now, interleukin-8 attracts the
22 inflammatory response. So the difference in the

1 inflammatory response and maybe even in the
2 oxidative burst may be related to interleukin-8.
3 And if that is the case, then it would also be
4 related to the CagA, which I mentioned earlier.

5 So that the host of the immune response
6 is going to be affected by the strain of H. pylori
7 that someone is infected with.

8 Let's move on to acid secretion. H.
9 pylori-infected persons, compared to normal
10 volunteers, have a lower nocturnal pH. When H.
11 pylori is successfully treated, there is a rise in
12 the nocturnal pH.

13 So indirectly, there is evidence that H.
14 pylori may be increasing the acidity and altering
15 the gastric pH.

16 Other studies have shown no difference
17 or even elevated fasting pH in H. pylori
18 volunteers without ulcer disease compared to
19 uninfected volunteers. In the non-ulcer patients,
20 there appeared to be less evidence of H. pylori
21 alteration of the acid response, but in the ulcer
22 patients, it does appear to be alteration or

1 decrease in acid. And also there is a similar
2 change in gastrin secretion, which is responsible
3 for the majority of acid secretion.

4 To look at some of the potential
5 mechanisms, investigators have postulated that
6 ammonia, the bicarbonate produced by the H.
7 pylori, may buffer the acid.

8 Most people feel that this is really
9 insufficient and is unlikely to affect the acid
10 secretion related to meals.

11 Gastric somatistatin has been found to
12 be decreased in H. pylori-positive patients. This
13 is a possible mechanism through which gastric acid
14 secretion may be increased in ulcer disease, since
15 somatostatin inhibits acid secretion. A loss of
16 this inhibitory mechanism may be associated with
17 H. pylori infection.

18 Now, on the other hand, fatty acids
19 secreted by H. pylori have been proposed as acid
20 inhibitory factors. As I mentioned, there are
21 patients that appear to have less acid when
22 infected with H. pylori.

1 This can be related to fatty acids.
2 Also, the progression of superficial gastritis to
3 atrophic gastritis is one mechanism through which
4 H. pylori may decrease acid secretion.

5 And if we do not have endoscopy data and
6 gastritis information, when you're just doing
7 serology or doing pH monitoring, it's difficult to
8 separate patients with superficial gastritis and
9 those with atrophic gastritis.

10 And as the population ages and the
11 infection progresses, there is the tendency for
12 the development of atrophic gastritis.

13 So as we look at the data on the acid
14 secretion, we also have to control for the type of
15 gastritis that is present.

16 As we mentioned, there is some evidence
17 of genetic susceptibility of persons infected.
18 Those who have blood type O are known to have an
19 increased risk of peptic ulceration, and this was
20 known even before H. pylori.

21 Studies have since reported an enhanced
22 ability of H. pylori to adhere to gastric

1 epithelial cells from patients with blood type O
2 and relate it to the surface antigens that are
3 present on the cell, and that this may increase
4 the presence of the bacteria in the stomach.

5 Also, the development of gastritis
6 metaplasia. This is one of the more important
7 issues and related to the development of duodenal
8 ulcers. The presence of gastritic metaplasia in
9 the duodenum is a prerequisite for H. pylori
10 colonization of the duodenum.

11 Duodenal gastric metaplasia occurs more
12 frequently in patients with duodenal ulcer
13 disease. And there have been several studies. It
14 will just take a minute to take a look at a couple
15 of them.

16 If we look at the frequency of gastric
17 metaplasia and inflammation in the first part of
18 the duodenum, we have patients with gastritis who
19 are H. pylori-positive. The metaplasia is present
20 in about 42 percent of these individuals, and
21 there is duodenitis present in about 77 percent.

22 If we look at people who are H.

1 pylori-negative, we only see 6 percent of these
2 with gastric metaplasia.

3 If people have a normal antral mycosa,
4 we only see a three percent. So there is
5 definitely a correlation to having H. pylori
6 infection in gastritis to having metaplasia in the
7 duodenum.

8 The risk for ulcer disease, based on
9 these factors, gastric metaplasia in the duodenum,
10 gives you a relative risk of about 6.2.

11 Having H. pylori infection in the antrum
12 would give you a relative risk of about 7 to 8.
13 And if you would have both colonization of H.
14 pylori in the duodenum when gastric metaplasia is
15 present, then you have a 50-fold increased risk of
16 developing a duodenal ulcer.

17 So it appears very critical in the
18 development of duodenal ulcer that we get gastric
19 metaplasia.

20 The gastric metaplasia has also been
21 found to be reduced after successful treatment
22 with H. pylori infection in parallel to duodenal

1 ulcer healing.

2 There are more studies ongoing to really
3 map the duodenum, follow gastric metaplasia and to
4 really lock down this hypothesis as the etiology
5 of the development of duodenal ulcers.

6 H. pylori therefore may contribute to
7 the appearance of gastric metaplasia in the
8 duodenum if it does affect acid secretion,
9 increasing the acid load, which is felt to be
10 necessary for metaplastic development.

11 Also there is still a question of the
12 susceptibility and whether certain persons having
13 increased acid loads, if that alone is enough to
14 develop metaplasia, or if there are certain
15 persons that are at risk for this.

16 Also we have noted that H.
17 pylori-infected volunteers have been found to have
18 accelerated gastric emptying of acidic meal and an
19 impaired ability to neutralize the acid in the
20 duodenal bulb. And this has been well-described
21 with duodenal ulcer disease.

22 What has recently been shown is that

1 decreased duodenal bicarbonate secretion is
2 present in ulcer patients. This has been
3 attributed with H. pylori infection, and when you
4 treat for H. pylori, you get an increase in
5 bicarbonate secretion.

6 So H. pylori may also have a primary
7 role in the mucosal protection that is related to
8 ulcer development.

9 Now, lastly, I'll just take a couple of,
10 minutes and mention some of the environmental
11 cofactors.

12 Diet and peptic ulcer disease -- there
13 has been a falling incidence of peptic ulcer
14 disease in developed countries. This has been
15 linked to increased consumption of polyunsaturated
16 fatty acids and, as I mentioned earlier, H.
17 pylori.

18 Polyunsaturated fatty acids have been
19 found to inhibit growth of H. pylori in vitro. So
20 there is a potential that diets rich in
21 polyunsaturated fatty acids will limit the
22 bacterial load. And as we mentioned before,

1 limiting the bacterial load may have some impact
2 on the risk of developing duodenal ulcer.

3 Also environmental pathogenesis, age at
4 time of infection, and duration of infection may
5 also have an impact. Dr. Sonnenberg also
6 mentioned this earlier in his talk.

7 In countries with a high incidence of
8 childhood infection, the risk of ulceration is
9 low, but the prevalence of the advanced
10 preneoplastic lesions in young adults is high.

11 And as Dr. Sonnenberg mentioned, perhaps
12 with ulcer disease, the infection needs to occur a
13 little later in childhood than we see in some of
14 these other countries.

15 The progressive inflammation of the
16 glandular epithelium of the stomach is postulated
17 to impair the acid secretion potentially below the
18 point necessary for ulceration. And maybe if the
19 infection occurs in early childhood and in
20 infants, then there would be a decreased ability
21 of the stomach to secrete acid in this early
22 developmental stage.

1 Now, just to finish off as a possible
2 hypothesis for H. pylori and ulcer formation. As
3 we mentioned, there is still the importance of
4 acid and increased duodenal acid load. This may
5 be related to increased gastrin, which has been
6 shown to be present in H. pylori-positive
7 patients. And when you treat, you do decrease the
8 gastrin.

9 The question is how H. pylori infection,
10 is causing the increase in gastrin, and this leads
11 to the increased acid load in the duodenum. And
12 as with increased acid in the esophagus, you get
13 development of gastric metaplasia in the esophagus
14 such as Barrett's esophagus.

15 We feel that similar things can happen
16 in the duodenum where we get gastric metaplasia
17 development. And as I mentioned, this is a
18 prerequisite for H. pylori being present in the
19 duodenum. And once this occurs, we have active
20 duodenitis with H. pylori, and this epithelium
21 might be more sensitive to the toxic effects of H.
22 Pylori, or certain strains or certain toxins, and

1 then we may get ulcerations.

2 Possibly, the junction between the
3 duodenal metaplasia and the normal duodenal mucosa
4 is an area where the ulcer may develop. So this
5 seems to be a very viable hypothesis for the
6 duodenal ulcer.

7 I think that's all I have right now.
8 Thank you.

9 DR. JUDSON: Thank you very much. I
10 think we'll go ahead and take time for just a few
11 questions, if there are any. And I have one
12 that's really speculative.

13 It seems that some of the features of H.
14 pylori lead to increased acid production and some
15 to decreased acid production. And that seems to
16 create a etiologic dissonance.

17 DR. SMOOT: Yes.

18 DR. JUDSON: What are the more important
19 factors and how do you explain them?

20 DR. SMOOT: Taking the patients who have
21 a history or have a duodenal ulcer, predominant
22 data shows that there is evidence of increased

1 acid related to H. pylori and that with treatment
2 of H. pylori, there is a decrease in acid, also
3 along with a decrease in gastrin.

4 So the effect on gastrin appears to be a
5 real one, and this does have an increase in the
6 acid secretion.

7 Also the importance is the selecting the
8 population, knowing that we're talking about the
9 superficial gastritis, not mixing in patients with
10 atrophic gastritis.

11 When you look at duodenal ulcer, you
12 usually are able to select against that because
13 duodenal ulcer disease is less frequent in people
14 with atrophic gastritis with a decrease in acid.

15 So if we look at that population, the
16 predominant evidence is that H. pylori does affect
17 acid secretion through possibly the somatistatin,
18 loss of somatistatin inhibition, and by increased
19 gastrin, which is stimulated.

20 And if we look at the general studies
21 where you're mixing different patients, you may
22 have some of those with atrophic gastritis or

1 something else, and there we see more conflicting
2 data.

3 DR. JUDSON: Thank you very much. Yes?

4 DR. SONNENBERG: Basically, no one knows
5 the answer to your question, but it may be that if
6 you get infected during early childhood, you
7 develop gastritis that changes into atrophic
8 gastritis in your acid secretion levels alone.

9 On the other hand, if you encounter the
10 bacterium as an adult with already high acid
11 output, the bacterium does not affect your acid
12 output. Your acid output stays high or it may
13 even increase, secondary to inhibition of
14 somatostatin and increased gastrin levels.

15 So it may, again, be an age-related
16 phenomenon, as to whether the bacterium leads to
17 low acid secretion or high acid secretion.

18 DR. FISHER: But nobody has done those
19 age-related studies on infection and acid
20 secretory capability. Is that correct?

21 DR. SONNENBERG: It's based primarily on
22 epidemiologic data showing that populations that

1 get infected with H. pylori during early
2 childhood, atrophic gastritis is very common and
3 secretion levels are relatively low.

4 In a typical population of the United
5 States, such as Native Americans, where H. pylori
6 infection is very common, acid secretion is
7 relatively low, peptic ulcer disease is rare, and
8 gastric cancer relatively common.

9 DR. FISHER: I might just ask Dr.
10 Kirschner -- who is a pediatric gastroenterologist
11 that has seen a large amount of HP-related
12 gastritis in children age group -- have you had
13 the chance to look at acid secretory status on any
14 of these people?

15 DR. KIRSCHNER: No. We haven't looked
16 at acid secretion, but among pediatric
17 gastroenterologists, gastritis is a lot more
18 commonly associated in peptic ulcer disease.

19 In fact, all these guidelines in which
20 they talk about treating H. pylori in patients
21 with ulcers are difficult for us, because most of
22 our patients have gastritis and not ulcers.

1 DR. FISHER: That is something to keep
2 in the back of the mind when we come down to some
3 thoughts about some of the studies.

4 DR. JUDSON: Thanks very much and we
5 will go on to our final speaker of the morning,
6 Dr. Megraud.

7 DR. MEGRAUD: Thank you very much, Mr.
8 President.

9 I would like to thank first the FDA, and
10 especially Dr. Hopkins, for inviting me. I must
11 say that I'm very pleased and very honored to be
12 here and to present a diagnosis.

13 So, as you can see, there are quite a
14 number of diagnostic tests which can be used, and
15 we have the experience of most of these tests
16 since I met Barry Marshall in 1983, except
17 histology, which is brought from a dedicated
18 laboratory.

19 So it is usual to separate the
20 diagnostic tests between those who are invasive --
21 we mean biopsy-based -- which includes histology
22 and CLOtests, and those which are not invasive,

1 including the breath test as well as serology.

2 And we can add, maybe now, among the new
3 tests, PCR which can be also used in a standard
4 way.

5 So I think the characteristics which are
6 important to consider, speaking about tests -- and
7 especially in the context of clinical tryouts --
8 are sensitivity, specificity, probably the
9 globality of the tests, and the possibility to do
10 retrospective analysis, and obviously the
11 possibility to measure the susceptibility of the
12 strain to anti-microbilation and to type
13 eventually.

14 The problems between sensitivity and
15 specificity are, first, that there is no gold
16 standard for H. pylori. We must define the
17 reference.

18 Second, we must distinguish between
19 tests performed at the time of the disease and
20 during the follow-up, because a load of bacteria,
21 when this treatment was not successful, is not so
22 high than before the first diagnosis.

1 And also I must say that the test must
2 be from an optimal condition and which has not
3 been always the case in studies up to now because
4 in one center, for example, you have usually one
5 laboratory which is dedicated to H. pylori and not
6 the others. And this is maybe not fair for one of
7 the techniques.

8 So, coming back to the biopsy-based
9 test, which is important, is the collection of
10 biopsy. Where usually biopsies are taken in the
11 interim two to 5 centimeters from the pylorus,
12 that it is also recommended to take biopsy from
13 the fundus, and especially when countering as a
14 treatment.

15 Also, when to take this biopsy is a
16 problem -- is a sufficient endeavor after a
17 previous treatment, especially if the previous
18 treatment contained antibiotics, PPI, or bismuth.

19 The problem with this biopsy-based test
20 is the sampling error. And I think that this work
21 illustrates very well this biopsy sampling
22 problem.

1 If it took ten biopsies from 32 patients
2 and performed different techniques on each of
3 these biopsies, you will see that the histology --
4 which is written "WS" for walk-in study -- in
5 fact, if only one biopsy is taken, it doesn't
6 perform very well because the sensitivity was only
7 80 percent.

8 But if you increase the number of biopsy
9 to 4 biopsies, you reach 95 percent.

10 It's probably why, in the system, the
11 recommendation is to take 4 biopsies. And this is
12 in order to have a very good sensitivity.

13 Indeed, if you look to culture, one
14 biopsy gives a better sensitivity, but probably
15 not enough. And the usual recommendation to take
16 only one biopsy for culturing is not good and we
17 should take probably two or even more to reach a
18 good sensitivity.

19 But you can see also that if you use two
20 techniques on the same biopsy, you obviously
21 increase tremendously the sensitivity.

22 The first test to consider, because it

1 can be performed in the endoscopy ward is the
2 rapid urease test -- and I am sure that everybody
3 here knows this test -- it is based on the fact
4 that *H. pylori* produces huge amounts of ureas and
5 dysureas, breaks down urea into ammonia and carbon
6 dioxide.

7 The ammonia raises the pH and the pH
8 indicator changes color from yellow usually to
9 red. But there are other possibilities of pH
10 indicator.

11 Concerning the sensitivity of this test,
12 if you read after one hour, as it's usually
13 performed, at least in Europe, I think the
14 sensitivity is not optimal. The sensitivity is
15 around 85 percent, but the specificity is usually
16 good, more than 95 percent.

17 With this test, you cannot perform
18 retrospective analysis, but what is possible is to
19 send by mail and to confirm, for example, by PCR.

20 I think the problem is related to this
21 rapid urease test in clinical tryouts are the
22 following:

1 At the inclusion, first, the
2 sensitivity, 85 percent. And this may be
3 introduce a selection bias if you take only those
4 who are rapid urease test positive, for example.

5 Usually, at least in Europe, this test
6 is used to select patient and to enter patients'
7 studies the same day as the endoscopy. And this
8 may be introduced as bias.

9 For followup, the sensitivity is
10 definitely not sufficient, and also there is a
11 problem that the investigator is not blind
12 anymore.

13 Going back to the other test, what is
14 required is to transport the specimen. Obviously,
15 histology is not a problem. But if you want to
16 perform a culture, this is a very big problem
17 because H. pylori is very susceptible to --
18 especially to temperature and to contact with
19 oxygen, so you must transport.

20 And if you can do it in a few hours, you
21 can just put it in saline, and maintain 4 degrees
22 Celsius. But if you cannot do that, you must use

1 either transport medium, which maintains the
2 organism viable for usually one day at 4 degrees
3 Celsius, or to freeze the biopsy and send them
4 frozen, usually in liquid nitrogen.

5 So, on this biopsies in laboratories,
6 you can perform histology and the imaging material
7 is stained. This usually allows us to see the
8 bacteria, but it's recommended to use another
9 stain like Warthin-Starry stain, for example, but
10 also you can use Giemsa stain, which has been
11 developed in the United States.

12 Histology is a very sensitive technique,
13 but the program is very much observer-dependent,
14 and we may come back on this point.

15 The specificity is usually good. It
16 allows to direct retrospective analysis and it has
17 another value which is unique. It allows to look
18 to the histology for the status of the mucosa.
19 And this may be important, especially after
20 eradication therapy.

21 It also allows us to detect another
22 bacteria sometimes found in the stomach which

1 cannot be grown on artificial medium yet.

2 It's an example of this bacteria which
3 you can see with the typical morphology. But the
4 program of this histology is the problem of
5 interpretation by the pathologists.

6 And you can see, for example, in this
7 study, the predictive value for positive test and
8 negative test among the pathologists was not
9 always very good compared to consensus diagnosis.
10 And especially this one was quite low. And this
11 is really a big problem.

12 Concerning culture, the main aspect
13 besides transportation has are the technical
14 demands. You must use fresh media. You must
15 select unknown media. You must grind the biopsy
16 and you must incubate up to ten days.

17 So, culture can be excellent in regard
18 to sensitivity. But as I said, this may be
19 impaired by the very strict transport on culture
20 conditions required.

21 The specificity is undoubtedly the best
22 because you can really identify the bacteria, but

1 I think what is probably the most important, with
2 regard to clinical trials, is that it allows the
3 determination of antimicrobial susceptibility and,
4 also interesting, the typing of the strains.

5 Just to show you, some colonies, and you
6 can identify and you can see the bacteria grow.
7 You can eventually look to pathogenic properties
8 of the bacteria. For example, you can detect the
9 CagA gene which has been mentioned previously by
10 Dr. Smoot, you see which is present in more than
11 80 percent of DU strains versus 50 percent of
12 non-DU strains.

13 You cannot perform molecular typing,
14 which can be interesting in the context of
15 clinical tryout, especially if you want to
16 differentiate if it is reinfection or relapse of
17 the same infection. For example, you see two
18 strains with the same pattern, and two strains
19 with different patterns.

20 So I would like to mention briefly the
21 possibility to use polymerase chain reaction,
22 which is a technique that is quite sensitive and

1 specific, especially if you use two sets of
2 primers. It allows retrospective analysis, but
3 allows also some possible typing, but not, today,
4 the strain's measure of susceptibility.

5 We have compared PCR to culture, for
6 example, for 537 specimens, and you can see that
7 the agreement is quite good. Those were PCR
8 negative and culture positive, where in fact, true
9 positive confirmed by all the techniques, as were
10 those with PCR positive and culture negative.

11 One of the advantages that you can also
12 get from PCR on CLOtests, biopsies put on CLOtest,
13 or other kind of test sent by mail, and the
14 correlation is quite good and you improve your
15 sensitivity.

16 So I would like now to move to the non-
17 invasive test, and especially the breath test.
18 The advantage of this test is that it will give
19 you the global view of the infection in the
20 stomach, and there is no problem of sampling
21 error.

22 With the breath test, it's very easy to

1 perform, and consists of, after consumption of the
2 test meal, to collect -- to ingest labelled urea,
3 and to collect expired air before and 30 minutes
4 after the absorption.

5 The analysis can be performed either by
6 mass spectrometry, but also by infrared
7 spectrometry, and maybe in the future by laser
8 spectrometry.

9 Just to remind you of the principle of
10 this test, again, it's made from the strong urease
11 of the bacteria, which breaks down urea. The
12 labelled CO₂ is absorbed and found again in the
13 expired air.

14 If you look to the limination of
15 labelled CO₂, you can see that you can
16 discriminate very easily the positive patient from
17 the negative patient. So, usually, we take the
18 end points 30 minutes after the ingestion.

19 This urea breath test is very good with
20 regard to sensitivity and specificity. It's quite
21 quick. It gives a global idea of the infection.
22 It allows us to spectroanalyze this and promises a

1 unique feature that it detects current infection
2 without the need of endoscopy. And this is very
3 interesting and very helpful, especially for
4 controlling the efficacy of treatment.

5 Another possibility of indirect test is
6 to use serology. Serology is sensitive, but the
7 specificities may be impaired sometimes. But you
8 can confirm by immunoglobulin. It allows us to
9 spectroanalyze this, it is also a global test, but
10 the problem, as seen in the next slides, is that
11 it doesn't allow you to differentiate between
12 positive eradicated and non-eradicated after -- 4
13 weeks after therapy.

14 This is a decrease in the level of
15 antibodies which is significant only after a few
16 months, usually 6 months. And furthermore, you
17 must test a sample before, as well as the actual
18 sample, in the same -- the same day.

19 I think, in a general way, that for
20 clinical trials there is a requirement to use
21 in-house facilities, in order to avoid
22 interlaboratory error. As you can see, this is

1 true for histology. This is also true for culture
2 and probably for PCR.

3 So coming to the comparison of these
4 different tests with regards to sensitivity. I
5 would like just to mention two studies. The first
6 is a study presented by Abbott, this year, at the
7 Edinburgh meeting, and you can see that they
8 compared culture and urea breath test to
9 histology, which was considered as a gold standard
10 in this particular study.

11 And they got sensitivity of 82 percent
12 for culture and a little bit more for urea and
13 breath test.

14 So because there are very few studies
15 comparing different tests after treatment, one
16 they took in Europe studied comparing three
17 diagnostic tests after treatment, 4 to 6 weeks
18 after the end of eradication therapy. The
19 techniques were culture, histology, and C13 test
20 performed in any case in same-house facilities.

21 So we took only the cases where the
22 three test were available -- a total of 89 -- the

1 definition of a gold standard for the presence of
2 H. pylori was treated as three positive in 27
3 cases, or two out of three -- 7 cases -- or
4 culture, because it cannot be disputed -- the
5 culture -- positive culture is a real positive
6 result.

7 And at that time, we obtained the
8 following: you can see that for culture, there
9 were 4 false negative versus gold standard. With
10 histology, two false negative and one false
11 positive, and with breath test, 5 false negative
12 versus gold standard, which gives the following
13 sensitivity rate. You can see they are, in fact,
14 very close to 90 percent. And if you combine two
15 of the three, you get the sensitivity of 99
16 percent.

17 So our conclusion would be that no
18 method is perfect, and the combination of two
19 tests is really needed today. Those are the
20 recommendations I would like to make in our
21 guidelines, which are not yet published and still
22 can be modified.

1 So we think that for clinical trials,
2 dealing with new drugs, new combination of drugs,
3 new formulation and new categories of patients
4 which includes comparative studies, is a primary
5 objective and not the true eradication rate, as
6 well as well-known treatment of ulcers.

7 In this particular case, we propose that
8 an inclusion will include tests on biopsy
9 specimen, perform histology in all cases, and add
10 at least second test.

11 The use of culture, in our opinion,
12 should be mandatory if the antibiotic regimen
13 contains an antibiotic to which H. pylori may be
14 or may become resistant.

15 Regarding follow-up, we think that it's
16 possible to test one month, or 4 to 6 weeks after
17 treatment, and again to include tests from biopsy
18 specimens, to perform histology in all cases, and,
19 again, to include culture if there is possibility
20 to see emergence of resistance. But we can use
21 other tests in other cases.

22 I must say that because of the emergence

1 of new therapies with very high eradication rates
2 -- over 90 percent -- we thought that you should
3 also add another possibility. This possibility is
4 to not to perform endoscopy 4 to 6 weeks after the
5 end of treatment, but only one breath test.

6 If this breath test is negative, we
7 would repeat with another breath test three months
8 after. And if two breath tests are negative, we
9 consider that the patient is eradicated.

10 But if one of the breath tests turns out
11 to be positive, in this case, we will recommend to
12 endoscopy the patient and to get biopsies to
13 perform the biopsy-based test that we mentioned
14 before.

15 Just to switch now to the second part of
16 my talk which concerns resistance. So, everybody
17 knows what resistance is. It's when, in fact, it
18 depends if the MIC of a given agent -- again, H.
19 pylori -- must be greater than one-fourth of the
20 concentration achieved.

21 Where is the bacteria? But, in fact,
22 usually we don't know what is the concentration of

1 the drug achieved in the stomach. And this is a
2 big problem.

3 So usually, we take the break points
4 proposed for infection, but this may or may not be
5 good. So to detect resistance, there are
6 different possibilities: agar diffusion test, disk
7 diffusion, break point method, E test.

8 What we really recommend today, as a
9 reference, is to perform agar diffusion test. But
10 this test, it may be also helpful, and especially
11 if in a particular study, similar laboratories are
12 involved. I think it's worth to perform E test
13 day by day. And after, to group the strains and
14 to perform, again, diffusion tests.

15 So this is an example of what you can
16 get with E tests and you measure the MIC.

17 So there are different kinds of
18 resistance. The resistance which is called
19 "natural" means that it concerns all the strains
20 of H. pylori. But more interesting for us is
21 "acquired" resistance which concern only
22 substrains of the species.

1 They can be so-called primary, and that
2 means that before the actual treatment. But
3 usually it's induced by treatments that the
4 patient got in the past, or exposure of the strain
5 to the drug in the past for whatever reason, or
6 secondary to the actual treatment.

7 And we can add, because of our lack of
8 knowledge in the pharmacokinetics of antibiotics
9 in the stomach, we can add, with this
10 pharmacological resistance, that it means that the
11 bacteria is susceptible in vitro, but inactive in
12 vivo.

13 Acquired resistance concerns
14 nitroimidazoles, macrolides, but also
15 fluoroquinolones and rifamycins. But I will only
16 talk about the these two first categories of
17 drugs.

18 What is striking is that with acquired
19 resistance, in fact, there is a cross-reaction
20 within a class of antibiotic. And also what we
21 can say is that the cutoff usually is not known
22 because we don't have good studies to conclude

1 that.

2 But we know that there is a high level
3 of resistance for macrolides, while there is a
4 wide range of MIC for nitroimidazoles.

5 Coming to the macrolides, you see that
6 all of them will be efficacious on *H. pylori*
7 bacteria and especially clarithromycin, which is
8 the less susceptible to the decrease in pH.

9 Resistance as a mechanism of action is
10 probably the usual mechanism, which is blockage of
11 protein synthesis by interaction with the
12 ribosomes. And the mechanism of resistance has
13 been proven to be, in fact, a mutation by the
14 group of Valsolovich and the group of David
15 Girard. So it's a mutation of the chromosome.

16 What about the frequency of this
17 resistance? This is data collected in Europe.
18 You can see that in some countries like Belgium,
19 France, Spain, there is around ten percent
20 resistance of *H. pylori* to clarithromycin. It's
21 less in other countries, and even very low, for
22 example, in Germany and Austria.

1 So this, in fact, depends on the use of
2 macrolides in the considered country. In France,
3 we used macrolides since '82 on a large scale for
4 respiratory tract infection. And in my opinion,
5 this may explain why we have rates of about 10
6 percent today.

7 The evolution of resistance to
8 clarithromycin and macrolides has been studied in
9 Belgium. And they found that before 1992, it was
10 only 1.7 percent. And now it's about 10 percent.
11 And the use of the new macrolides, in fact,
12 happened between these dates.

13 In France, we studied all the strains
14 that we had in our freezer since '85, and it turns
15 out that in the first period -- '85 to '87 --
16 there was already about 88 percent resistance,
17 which has not increased so much during these ten
18 years.

19 So we think that probably the resistance
20 happened to occur in the first year in the use of
21 macrolides and is now relatively stable.

22 But you must also look to secondary

1 resistance after a given treatment using
2 clarithromycin, and you can see. But we saw very
3 small studies that it may occur.

4 What is the consequence of
5 clarithromycin or macrolide resistance on H.
6 pylori treatment? You can see on this slide that
7 there is a marked difference between the success
8 in clarithromycin-susceptible strain versus
9 clarithromycin-resistant strain.

10 And we got the secondary resistance
11 about two-thirds of the strains which we could
12 recover after failure of treatment, where indeed
13 there was resistance.

14 But if you look to the spontaneous
15 mutation rate of resistance versus these three
16 antibiotics in vitro, you can see that, in fact,
17 the rate of mutation is relatively low for
18 macrolides, and it's much higher for
19 nitroimidazole. And this turn out to be also true
20 in vivo.

21 So the usual mechanism of action of
22 nitroimidazole concerns the oxidation of DNA,

1 strand breaks, and helix destabilization which
2 leads to the cell death, and the possible
3 mechanism of resistance would be linked to the low
4 redox potential of the strain which is not
5 sufficient to allow reduction of nitroimidazole
6 compound. And it seems that it is also
7 chromosomally mediated.

8 The rate of primary resistance is very
9 different between the developing countries, where
10 you can see it's very high -- about 80 percent --
11 versus developed countries, where the range goes
12 from about 5 to 40, 50 percent. In the US, I
13 think it varies from 20 to 30 percent.

14 This is the range that you will observe
15 in Europe, for example. We see that, again,
16 France has a high rate of resistance, about 50
17 percent. And this may be linked to the widespread
18 use of metronidazole for infection in our country,
19 but in all the countries -- and this is a wide
20 range because some countries like Austria and
21 Italy -- have very low rates of resistance.

22 Resistance was considered as an MIC of

1 greater than 8 micrograms. But maybe this is a
2 problem and we can come back to this.

3 So the rate of secondary resistance is
4 very high with metronidazole if you use single
5 drug therapy or dual therapy or triple therapy for
6 less than 7 days.

7 And what about the consequence of this
8 metronidazole resistance? You see that again
9 that's a triple -- for example, triple therapy
10 with bismuth, you see that with a
11 metronidazole-susceptible strain, you have a high
12 rate versus none if the strain is resistant.

13 And this is also true, but to a lesser
14 extent, if you use triple therapy with bismuth for
15 more than 7 days. With a susceptible strain,
16 there was a 90 percent usually of success, versus
17 a range between 18 and 60 percent if the strain is
18 resistant.

19 This is also true for the PPA, PPI
20 therapy. For example, the therapy and -- in fact,
21 if you look to the results of Basili in Italy, you
22 see that the filler was about 25 percent in

1 Metronidazole resistant strain. It was only 20
2 percent -- less than 20 percent in U.K., but it
3 was 45 percent in Ireland.

4 And following this -- the data gathered
5 in Ireland, Basili proposed the predicted
6 eradication rate of H. pylori according to the
7 rest of Metronidazole resistant presence in a
8 given country.

9 And you can see that if this rate goes
10 up to percent, the success rate would not be more
11 than 50.

12 How to prevent resistance, I think the
13 traditional way used for microbacteria and
14 tuberculosis is to use two antimicrobial agents
15 together is probably the best to do.

16 And also indirectly because if you
17 decrease your side effect, you increase your
18 compliance and probably you decrease the rate of
19 resistance because as you know, resistance can be
20 acquired with suboptimal concentration of the
21 antibiotic, which at least in vitro.

22 So in conclusion, I think that for a

1 patient monitoring, we need to culture the
2 bacteria and to -- in case of -- and this is
3 especially true for clinical tryouts, and we need
4 that the national level also to have permanent
5 flow up of this resistance issues and probably we
6 need also to have a rational attitude in the
7 future and to improve our knowledge in the demand
8 of pharmacology of antibiotics and also in the
9 clinical bacteriological correlations.

10 So because -- don't forget that today's
11 solutions are tomorrow's problems. Thank you for
12 your --

13 DR. JUDSON: Thank you very much. And
14 thank you for coming all the way from Europe.

15 Any questions of Dr. Megraud? Yes, Dr.
16 Fredd?

17 DR. FREDD: Could you tell me, in the
18 resistant strains, on re-treating those with a
19 different regimen, is one able to eradicate such
20 bacteria? And do those bacteria -- are they more
21 virulent by any measure?

22 DR. MEGRAUD: The second part of your

1 question, we look to -- the only virulence marker
2 that we had today is the so-called CagA gene. And
3 we did this correlation. And we didn't find any
4 increased presence of strain with CagA gene in
5 among those resistant to antimicrobial agents.

6 But I did not understand correctly your
7 first part.

8 DR. FREDD: Let us say, you know, you
9 develop resistant organisms. And let's say you
10 only get from an 80 percent expected eradication
11 rate down to a 50 percent eradication rate.

12 In that population in whom you are
13 unable to eradicate, by using a different regimen,
14 will there be any more difficulty eradicating such
15 organisms?

16 DR. MEGRAUD: I think the difficulty
17 will be if you keep the same regimen.

18 DR. FREDD: No. No. I agree. That's
19 obvious.

20 DR. MEGRAUD: But if you change
21 regimens, there is not much gross reaction in
22 gross -- between class of antibiotics.

1 DR. FREDD: So, clinically, it is quite
2 possible, even though you have failed to
3 eradicate, to then go on and use another regimen
4 successfully?

5 And as I understand it, there will not
6 be any more virulence to the organisms from
7 whatever we can measure -- namely CagA.

8 So, that was the answer to that
9 question. Now, in terms of the correlative study
10 that you did, which I think you correlated
11 culture, histology, and C13 urea breath test; is
12 that correct?

13 DR. MEGRAUD: Yes.

14 DR. FREDD: What was your gold standard?

15 DR. MEGRAUD: As I mentioned, the gold
16 standard was a combination.

17 Either three tests positive, or two
18 tests out of three, or culture. So it's a
19 combination of these three possibilities.

20 DR. FREDD: Okay. And the patient
21 population entered for that study?

22 DR. MEGRAUD: The patient population

1 were people with gastritis and H. pylori infection
2 which had received whatever treatment that there
3 was, you know, in the --

4 DR. FREDD: But you didn't enter a broad
5 spectrum of patients with other gastrointestinal
6 diseases?

7 DR. MEGRAUD: The main introduction was
8 to have gastritis, whatever particular cell, not
9 particular cell.

10 DR. FISHER: It was a small number of
11 patients, if I'm right, correct? It was 35
12 patients in that study?

13 DR. MEGRAUD: It was 89.

14 DR. FISHER: 89. Okay.

15 DR. JUDSON: There was another question?
16 Yes, please identify yourself.

17 MR. GALLO-TORRES: Hugo Gallo-Torres. I
18 would like to make sure that I understand your
19 recommendations for the diagnosis of HP. Predrug
20 for the initial diagnosis versus follow-up. Would
21 you explain that for us, please?

22 DR. MEGRAUD: In the special cases which

1 we are stating, we think that for entry, we need
2 to have biopsy-based tests, and we need to have at
3 least two tests, including one for histology. And
4 the other can be an another test -- for example,
5 rapid urease test or maybe PCR. Culture should be
6 required if one of the antibiotics used in the
7 original may select resistance for entry.

8 After treatment, the original
9 recommendation was to perform only the same test,
10 the same thing. That means two tests,
11 biopsy-based tests, including histology and
12 including culture, if the drugs induce resistance.

13 But because of the availability, now, of
14 a very efficient regimen, we thought we had to
15 reconsider and propose a guideline probably that
16 would be already evolved, and the evolution was
17 that we still need two tests, but it could be two
18 breath tests. One performed 4 to 6 weeks after
19 the end of treatment, the other, three months
20 after.

21 If both are negative, we consider that
22 there are two tests negative and that the patient

1 can be considered eradicated.

2 But if one of the tests -- either the
3 first or the second -- turns out to be positive,
4 in this case, the requirement is to do an
5 endoscopy and to perform biopsy-based tests,
6 including culture, especially if the antibiotic
7 used may select resistance.

8 Am I clear?

9 MR. GALLO-TORRES: Quite. Thank you.

10 DR. JUDSON: Yes, sir.

11 MR. MARSHALL: I'm Barry Marshall,
12 University of Virginia. I've got a question about
13 macrolide resistance. And you were telling us
14 that 10 to 12 percent of H. pylori in France are
15 resistant to clarithromycin.

16 Can you give us some background about
17 the history of new macrolides in Europe, because
18 my recollection is that azithromycin and some
19 others have very weak H. pylori activity, but have
20 a very high propensity for inducing macrolide
21 resistance in H. pylori.

22 And we just have, I think, azithromycin

1 approved in the US for pediatric use. And so I
2 would predict that we're going to see that happen
3 here in the US.

4 DR. MEGRAUD: I think this is an
5 interesting point, but, unfortunately, I cannot
6 give you an answer, Barry.

7 We have data concerning the susceptible
8 of H. pylori to different macrolides. This I
9 presented to you. But data concerning the
10 acquisition of resistance, according to
11 macrolides, I must say that you we don't have
12 because, it has never been studied in a proper
13 way, in my mind.

14 It's definitely possible that some
15 macrolides, especially among the new macrolides,
16 may turn out to be different, with regard to
17 selection of resistance. I think this has to be
18 studied.

19 MR. MARSHALL: I think Bergendorfer did
20 do some studies about macrolides about 7 years ago
21 when they were first looking at these macrolides
22 for H. pylori therapies. And they showed that