

ORIGINAL

FOOD & DRUG ADMINISTRATION CONFERENCE

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE (55TH)

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## P R O C E E D I N G S

1  
2 DR. JUDSON: This is the same joint  
3 meeting that began yesterday. This is the 55th  
4 Anti-Infective Drugs Advisory Committee Meeting  
5 conjoined with the first Gastrointestinal Advisory  
6 Committee. And we will continue our discussions  
7 of Helicobacter pylori and the various conditions  
8 and diseases with which it's associated.

9 Now, the topic seems to be fairly  
10 cleanly divided. Yesterday, we dealt mainly with  
11 ulcer conditions. Today we're defining what it is  
12 and what it isn't. We're dealing with all ulcer  
13 and non-ulcer conditions.

14 And I have been told by some of our FDA  
15 colleagues that this should be less controversial,  
16 because there is even less data than there was  
17 yesterday.

18 (Laughter)

19 So we shouldn't have as much to argue  
20 about. And --

21 DR. FISHER: Or the other way, if you  
22 want it.

1 DR. JUDSON: Right.

2 DR. FISHER: But some of us have planes  
3 tonight to get out of here.

4 DR. JUDSON: And with that, I would like  
5 to turn to Dr. Mary Fanning for her remarks.

6 DR. FANNING: Thank you very much.  
7 Yesterday was a very interesting day and I'm  
8 really looking forward to some of the discussions  
9 around today.

10 But before we get into the agenda, this  
11 is the time of the year when there are transitions  
12 on our committee. And rather than making these  
13 comments at 4:00 p.m., when half of you will have  
14 departed, I would like to take the opportunity now  
15 to thank three of our members who have finished  
16 their term with our committee and present them  
17 some certificates of appreciation.

18 Dr. Allen Kaiser, who has joined us  
19 today, is finishing his three-year term. And we'd  
20 like to thank you very much for your contribution  
21 to the committee and present you with our  
22 certificate.

1 Dr. Barth Reller is also ending his term  
2 with us. Barth, if you could come to get your  
3 certificate.

4 And last, but certainly not least, Frank  
5 Judson, who has done an excellent job stepping in  
6 as chairman of the Committee on very short notice  
7 and has carried us through the last couple of  
8 years, is stepping down as chair.

9 Thank you for your contribution.

10 DR. JUDSON: Thank you very much. I'll  
11 deliver my acceptance remarks at 3:30 this  
12 afternoon.

13 DR. FISHER: This morning, we won't need  
14 a conflict of interest statement by Ermona  
15 McGoodwin because yesterday's will apparently  
16 suffice.

17 And we have -- my co-chair and I have  
18 neatly divided up the rest of the session.

19 Rosemarie will take on issue number one  
20 which is mainly GI. And then we will -- I will  
21 return to issue two, which is, I suppose,  
22 microbiology and infectious diseases.

1           So, Dr. Fisher.

2           DR. FISHER: Thank you. Let me just --  
3           Dr. Kaiser was introduced as he got up to get his  
4           certificate but was not with us yesterday.  
5           Everybody else around the table, I believe, was  
6           with us yesterday. So, welcome.

7           And we have lost some people, as you'll  
8           notice, along the way. But I think we can see the  
9           screen a little bit better.

10          I just want to remind people, when we  
11          come around to the issues on this, the issue was  
12          going to be a discussion as opposed to taking a  
13          vote.

14          So I want people to be aware of at first  
15          that we're not coming to any conclusions in this  
16          discussion as to how -- you know, coming down with  
17          pronouncements about how things should be done,  
18          but being able to discuss this as they will come  
19          forward in the future.

20          So the issues, as it reads in the agenda  
21          for number one are, "What are the appropriate end  
22          points for non-ulcer HP-related conditions?" For

1 example, non-ulcer dyspepsia, gastric cancer,  
2 lymphoma.

3 And as we put up the issue in the end,  
4 it will be, "Please discuss clinical study designs  
5 appropriate for the study of non-ulcer-related  
6 conditions."

7 We're going to start with an  
8 introduction from Dr. Girardi who is going to talk  
9 about study design issues for HP-associated  
10 non-ulcer conditions.

11 Dr. Girardi?

12 DR. GIRARDI: It's nice to see Dr.  
13 Graham in the audience. What I wanted to do was  
14 briefly set up the discussion about end points for  
15 non-ulcer H. pylori conditions.

16 And as we have already mentioned, some  
17 of the non-ulcer-related conditions associated  
18 with H. pylori are dyspepsia, gastric cancer,  
19 gastric lymphoma, as well as certain non-gastric  
20 conditions such as hyperammonemia, a metabolic  
21 coronary artery disease.

22 The association with gastric cancer

1 really has been an interesting one. The primary  
2 link has mainly been through epidemiologic  
3 studies. And that's because long-term prospective  
4 studies with the development of cancer as the end  
5 point has been very difficult and can be  
6 impractical because it can take upwards of 30  
7 years or so.

8 And one has to recognize that in any  
9 potential application that arises, looking at the  
10 claim for gastric cancer would most likely require  
11 a multi-disciplinary approach because it crosses  
12 the lines of GI and ID and oncology.

13 I'm just going to briefly mention the  
14 possible design issues related to gastric cancer  
15 studies. And I know that Dr. Craft is going to  
16 elaborate more on this. So I'm not going to usurp  
17 a lot of that time.

18 It might be appropriate for gastric  
19 cancer studies to use histologic precursors as end  
20 points. However, which histologic precursors to  
21 be used I think remains open to question.

22 Examples of histologic precursors include chronic

1 gastritis, atrophy, intestinal metaplasia, or  
2 dysplasia.

3           Alternatively, one may decide to  
4 randomize only patients with certain risk factors  
5 into these trials, and these risk factors,  
6 obviously, are patients that have a strong  
7 familial predisposition toward the development of  
8 gastric cancer, other patients with specific  
9 cultural risk factors, and also patients that are  
10 in certain geographic locations that may  
11 predispose them to certain risks.

12           If we use patients with certain risk  
13 factors, it may also be appropriate to use these  
14 patients, as well as histologic precursors in  
15 these patients, as potential inclusion criteria.

16           However, we have to recognize at which  
17 point along this schema the process is still  
18 reversible, so that if one decides to treat  
19 patients with gastritis or atrophy metaplasia, the  
20 treatment will still be on time in order to  
21 prevent the progression along this line and  
22 eventually towards cancer.

1           Let me switch gears to non-ulcer  
2 dyspepsia, and I know Dr. van Zanten is going to  
3 have some comments about this.

4           The association with H. pylori in  
5 non-ulcer dyspepsia has been controversial because  
6 really definitive studies are lacking.

7           There is a pressing need for  
8 well-designed clinical trials, as evidenced by  
9 this patient who was misdiagnosed with  
10 indigestion, but who has non-ulcer dyspepsia.

11           DR. FISHER: It's those little Blue  
12 Devils, Dr. Girardi.

13           DR. GIRARDI: Well, you know that Duke  
14 has a very strong influence among all of us here.

15           I just wanted to put up certain  
16 elements, with regard to potential non-ulcer  
17 dyspepsia study design. And certainly these are  
18 open for discussion, and we would be interested in  
19 hearing more about these from our next speakers.

20           I think that a lot of people agree that  
21 in potential trials that look at non-ulcer  
22 dyspepsia, placebo controls are essential. In

1 terms of analyzing the data, some form of an  
2 intention-to-treat analysis -- looking and  
3 analyzing patients who are HP-positive and  
4 assessing certain symptoms -- would be important.

5 And also avoiding multiple comparison  
6 testing -- mainly that one should really define  
7 specifically the symptom that one is interested in  
8 looking at, because if you start looking at a  
9 variety of symptoms, this potentially could lead  
10 to a Type 1 error.

11 Both microbiologic as well as clinical  
12 end points would be important to look at. I  
13 cannot overemphasize the blinding aspects of these  
14 trials for both the investigator as well as the  
15 patient.

16 And long-term -- and by "long-term," I  
17 guess we mean one-year follow-up for symptoms --  
18 would be an important element of this study,  
19 recognizing, however, that by doing an ITT  
20 analysis, it would be difficult, given the  
21 potential number of dropouts.

22 So with those issues briefly discussed,

1 I will leave the floor open to our next speakers  
2 and look forward to an interesting discussion that  
3 will ensue from that.

4 Thank you.

5 DR. FISHER: Thank you. If there no  
6 burning questions for Dr. Girardi, we will go on  
7 to our next speaker, Dr. van Zanten, who is a  
8 consultant for TAP Holdings on HP and non-ulcer  
9 dyspepsia.

10 DR. VAN ZANTEN: First of all, I would  
11 like to thank you for allowing me to give this  
12 talk.

13 The association between H. pylori  
14 infection and non-ulcer dyspepsia is probably the  
15 most controversial. And I will show you some data  
16 which hopefully clarifies this difficult area.

17 First of all, the vital statistics, as I  
18 like to call them, of functional dyspepsia are  
19 enormous. Up to five percent of all people who  
20 come to a family physician or general practitioner  
21 come for symptoms of chronic dyspepsia.

22 The major part of all upper-GI

1 endoscopies and X-rays are done for this entity.  
2 And from a study in Sweden, up to 98 percent of  
3 patients that come through a physician's office  
4 leave that office with a prescription.

5 Now, one of the problems, of course,  
6 that we have in this area is that the tremendous  
7 overlap of other conditions, particularly reflux  
8 disease, both with esophagitis and without  
9 esophagitis, peptic ulcer disease, and also  
10 syndromes like irritable bowel syndrome.

11 And lately, there has been a lot of talk  
12 about whether it's feasible and possible, based on  
13 symptoms, to subclassify patients into dyspepsia  
14 subgroups.

15 First of all, I'd like to stress the  
16 fact that it's very important that we have a  
17 clear, accepted definition. I think what I've put  
18 on the next line is sort of accepted by most  
19 people.

20 But for example, if you critically  
21 evaluate the literature, many studies on non-ulcer  
22 dyspepsia don't make very clear what the patient

1 population was that they studied.

2 So we're talking about chronic pain or  
3 discomfort that is centered in the upper abdomen  
4 and no convincing evidence of structural  
5 abnormalities.

6 I think most people would nowadays also  
7 agree that symptomatic gastroesophageal reflux  
8 disease, either by presence of esophagitis -- in  
9 patients who don't have esophagitis but have  
10 dominant heartburn. But they probably should be  
11 excluded, and then IVS is probably another common  
12 overlay.

13 Now, what I'm going to talk about is the  
14 association between this organism and non-ulcer  
15 dyspepsia. I'll briefly review some data about  
16 the gastrophysiology, but then we'll mainly  
17 concentrate on the effect that eradication may  
18 have long-term on improvement of symptoms.

19 Now, I'd like to remind you, though --  
20 and this is some data from a small study that we  
21 presented last year at the FDA, that, by and  
22 large, non-ulcer dyspepsia is a nuisance entity.

1           If you look at the impact of chronic  
2 dyspepsia on the whole range of social activities,  
3 you can see that the impact is relatively small.

4           Now, when we look at the H-meshed  
5 studies and a lot of the early studies were not  
6 H-meshed, there does not appear to be an increase  
7 in the prevalence of *Helicobacter pylori* in  
8 patients who fulfill the criteria for chronic  
9 dyspepsia when you compare them to normal  
10 controls.

11           Also, if you look very carefully at the  
12 frequency of symptoms and the severity of  
13 symptoms, by and large, you don't find any  
14 difference in patients who fulfill the criteria of  
15 either HP-positive or HP-negative.

16           So, not surprisingly, based on symptoms,  
17 it is very difficult to tell what's going on, and  
18 certainly it's impossible to tell whether patients  
19 are infected.

20           Now, on a few data on gastric  
21 physiology. I mean, I think the data are  
22 increasingly clear that *H. pylori* is a true

1 pathogen.

2 And what you see here is a slide that  
3 was recently published from Dr. McCall's group in  
4 Scotland and he's done very elegant studies using  
5 GRP-stimulated acid secretion and gastrin response  
6 to patients that were either HP-negative, healthy  
7 volunteers that were infected but asymptomatic,  
8 NUD HP-positive patients and patients who are both  
9 infected and duodenal ulcer disease at which you  
10 can see the acid output in response to GRP  
11 stimulation, but clearly the patients that have  
12 chronic dyspepsia and are infected have an  
13 abnormal response compared to non-infected  
14 individuals.

15 And here is also shown, at least for the  
16 DU patients, that this response normalizes or goes  
17 back towards normal following successful  
18 eradication.

19 I'll show you a few other slides which  
20 look at the motility aspects of it. This is a  
21 study that was published in the Italian study in  
22 1992 in gastroenterology. When you look at

1 gastric emptying, this was only solid gastric  
2 emptying with a chicken liver, beef broth meal.

3 About 50 patients were studied and  
4 compared to healthy controls. Half of the 50 were  
5 infected with H. pylori. The other half was not  
6 infected with H. pylori.

7 And what you can see is that there is no  
8 difference between the infected overall, the  
9 average levels in the HP-infected group, compared'  
10 to the healthy controls.

11 But I'd like to point out that the range  
12 here clearly is much wider, so based on this,  
13 certainly it's possible that there may be a small  
14 subset of these HP-infected chronic dyspepsia  
15 patients who have predominant problem with delayed  
16 gastric emptying.

17 Interestingly enough, in the HP-negative  
18 group, there appeared to be a large proportion of  
19 these were young women.

20 Now, Dr. Malagelada from Spain, he has  
21 done some very interesting studies looking at  
22 gastric sensitivity. And what he does is he

1 measures simultaneously anterior duodenum  
2 mortality with a sleeve catheter. Also folds a  
3 balloon in the stomach, gradually increases the  
4 volume of the balloon and looks at -- looks at  
5 what happens at intragastric pressure.

6 And the other things what they looked at  
7 is what the perception that the patients had  
8 towards this slow increase in volume.

9 And here you can see the study -- they '  
10 studied about 50 patients. Once again, about half  
11 were H. pylori-infected. The other half were not  
12 infected. These were all patients with chronic  
13 dyspepsia and compared them to normal controls.

14 The normal controls are shown here in  
15 the squares. And you can see, if you look at the  
16 slope of the relationship between increase in  
17 gastric pressure and intragastric volume, that  
18 there is no difference in either normal  
19 individuals and those patients who have chronic  
20 dyspepsia in either infected or non-infected.

21 Now, the situation is slightly different  
22 if you look at perception -- that is, with the

1        increase in volume, patients were asked to tell  
2        what their average level of discomfort was.

3                And here you can see that clearly both  
4        the HP-infected group and non-infected group,  
5        there is no difference between the two.

6                But their perception of gastric  
7        distension is markedly different compared to  
8        non-symptomatic, asymptomatic, non-infected  
9        volunteers.

10               And this is the same story in irritable  
11        bowel syndrome, that in a lot of patients with  
12        non-ulcer dyspepsia, something is wrong with their  
13        visceral perception.

14               Finally, the same group -- this is from  
15        Malagelada -- they also did studies on anterior  
16        duodenum or filter, you know.

17               When they did the studies in the fasting  
18        state, they did not find any difference. But do  
19        you see the data on what happens two hours after  
20        meal.

21               And what this shows -- is shown here on  
22        the vertical axis is a motility index which is

1 basically a summation of the number of waves and  
2 the amplitudes of waves that occur in the anterior  
3 duodenal area.

4 And what you can see is that they did  
5 find a statistically significant difference with  
6 less motility activity in the antrum of these  
7 patients.

8 Once again, though, I'd like to stress  
9 that I'm not quite sure that even though these  
10 differences are statistically significant, what  
11 the clinical relevance offered is. And more  
12 importantly, once again, certainly there is a  
13 marked outline here, but also that the range of  
14 values in the HP-infected group seems to be much  
15 larger.

16 So, based on these studies, it's  
17 certainly possible that there may be a subgroup of  
18 patients that have a motility problem.

19 By and large, though, I don't think that  
20 this is going to be true for most patients who are  
21 infected with non-ulcer dyspepsia.

22 I am now going to focus on the most

1 important question is what happens with  
2 eradication with the symptoms of chronic  
3 dyspepsia?

4 Now first of all, it is a true pathogen.  
5 And what you see here is an early slide from a  
6 study done in Holland.

7 Just to drive home the point at issue,  
8 if you eradicate *Helicobacter pylori*, you do get  
9 healing improvement of the gastritis.

10 And what you can see here on the  
11 vertical axis is basically the severity of  
12 histologic gastritis. And it's followed up in  
13 patients before, before and after treatment. And  
14 they're followed-up for about 12 months.

15 And what you can see in the patients in  
16 whom eradication was successful, that there was a  
17 marked histologic improvement, whereas in patients  
18 in whom only suppression of the organism occurred,  
19 patients very quickly returned back to baseline.

20 The other important thing -- and this  
21 may be relevant when we talk about that it's  
22 necessary to measure long-term follow-up up to a

1 year -- you can see that it certainly takes up to  
2 at least six months in these patients for the  
3 histology to return completely to normal.

4 And in most of the late responses though  
5 is it takes much longer for the lymphocytes to  
6 disappear from the stomach than the neutrophils.

7 Now how do we use symptoms in clinical  
8 practice? First of all, we use them to classify  
9 syndromes like dyspepsia. Secondly, we try to  
10 subdivide it, no reflux versus peptic ulcer  
11 disease versus other entities.

12 Based on severity of symptoms, we might  
13 try to predict as the more severe patient symptoms  
14 are, the more likely, for example in esophagitis,  
15 it is that they're going to require maintenance  
16 therapy.

17 But in the area of non-ulcer dyspepsia  
18 where we want to determine whether treatment is  
19 efficacious, we want to use symptoms as an  
20 evaluative function, that is to really prove  
21 whether treatment has been beneficial.

22 Because in non-ulcer dyspepsia, of

1 course, no hard outcome measures are available  
2 such as an ulcer or healing esophagitis.

3 I can't review the whole area, but I'm  
4 just going to show you two early studies that were  
5 published in this area to highlight some of the  
6 problems that existing studies have.

7 Most of the early studies only looked at  
8 clearance so controls are not all that relevant  
9 anymore.

10 But here is a study published in Gutt,  
11 50 patients were randomized, and what you can see  
12 here is they used a global assessment and a  
13 four-part scale for these symptoms.

14 But if you look at that four-point  
15 scale -- present, absent, improved, and  
16 disappeared -- it clearly doesn't make much sense  
17 because symptoms can be improved and still be  
18 present. And it's very unclear from the paper to  
19 determine what they mean by symptom improvement.

20 Another study -- this is a Belgian  
21 study -- again, an early study that only looked at  
22 clearance. But they used these six symptoms and

1 added them all up and measured on a zero to four  
2 point scale to a summary support of it.

3 Just to ask -- and the paper doesn't  
4 make this clear -- but how is epigastric pain  
5 different from an ulcer pain, and how does this  
6 differ from dyspepsia? It's very, very difficult  
7 to tell.

8 And these studies, incidentally, they  
9 did not show much difference immediately following  
10 treatment.

11 So one of the problems that we have is  
12 that there is really a lack of consensus on  
13 outcome measures in non-ulcer dyspepsia trials.  
14 And recently we have looked at all the non-ulcer  
15 dyspepsia trials that were placebo controls over  
16 the last ten years. And some of the data were  
17 actually quite surprising.

18 For example, only three of these studies  
19 had made any prior attempt to the studies to  
20 validate outcome measures.

21 Also, a lot of the studies used what I  
22 think are probably suboptimal scales like, as I

1 already mentioned, non-ulcer dyspepsia is a  
2 nuisance entity.

3 If you use a scale from zero to four,  
4 one would say overall severity of pain, I think  
5 it's very unlikely that patients are going to rank  
6 either on zero or on the four point end of the  
7 scale which basically leaves you only with a  
8 two-point scale to determine whether there's any  
9 -- any differences.

10 Furthermore, but of course, a lot of  
11 these studies were done in the pre-H. pylori era,  
12 it's also surprising how few studies in fact have  
13 looked at longer follow-up in these patients.

14 Now, when we look at sort of quality of  
15 life measures, there's a whole range of sort of  
16 generic measures, general health status measures  
17 available. And they're certainly very good to  
18 assess the overall health of a population. But I  
19 think they're clearly not going to be very useful  
20 if you look at the impact that non-ulcer dyspepsia  
21 may have on patient symptoms.

22 And it's not only in the area non-ulcer

1 dyspepsia, but more and more disease specific  
2 quality of life measures have been developed and  
3 are being developed to study particular disease  
4 entities.

5 And the advantage of it is that that  
6 focuses a lot more on the problems of the  
7 patients. They are also more responsible for  
8 this. They're more able to detect what are  
9 changes taking place following the treatment.

10 So if you'll look at, let's say, quality  
11 of life or symptom assessment measurement, what  
12 are the requirements that these measurements have  
13 before you can use them in clinical trials?

14 First of all, they should be valid as  
15 they clearly should test the range of symptoms  
16 that are important for the population.

17 Secondly, in patients in whom the health  
18 status, the overall health status doesn't change,  
19 if you repeat the measurement after a certain  
20 interval, you should find, more or less, the same  
21 results.

22 And finally, following treatment,

1 assuming that that treatment was effective, you  
2 should be able to pick up that a change in health  
3 status, hopefully an improvement, did take place.

4 Now not much has been done in this area  
5 so far because a few groups out there who focused  
6 on them, and again, my only highlight.

7 One, this is from Myron's group in  
8 Sweden. What they looked at, they developed a  
9 non-ulcer dyspepsia pain score, and they only  
10 looked at the severity of epigastric pain. So it  
11 was singled out co-measure.

12 And they looked at three dimensions of  
13 this pain: the duration, the intensity, and how  
14 patients behave towards the pain.

15 Now, they never published anything on  
16 behavioral aspects of it, so basically they looked  
17 only at duration and intensity.

18 And they did a study prior to a clinical  
19 trial where they compared a visual analog scale  
20 with a certain point like in scale which was  
21 self-recorded that showed that these were  
22 reasonable outcome measures and that there were

1 not much differences between the fast scale and  
2 the seven point interval scale.

3 So they used this in one of the most  
4 quoted trials in non-ulcer dyspepsia published in  
5 1987 in New England where they randomized of the  
6 59 patients, the placebo and antacid and  
7 cimetidine.

8 Now in their earlier study they had  
9 shown that pain and duration were two different  
10 aspects of the epigastric pain and they calculate  
11 the so-called pain index.

12 Now how duration there was defined was  
13 not totally clear in the sense if you, let's say,  
14 have a severity of pain of three -- you had that  
15 for four hours, as opposed to six hours. Now the  
16 change in pain index was not completely clear, but  
17 by and large, and they only assessed epigastric  
18 pain.

19 And the results are shown on these  
20 slides and basically convincingly, they showed  
21 that between these three treatments, there was no  
22 important clinical differences.

1           So I think this trial really drives home  
2 the message that I think it is possible to  
3 validate outcome measures in this area.

4           Now, for a long time when I looked at  
5 this trial, I was not certain whether you used a  
6 single outcome measure such as epigastric pain,  
7 whether that was sufficient, but I must say,  
8 having digested this now for a couple of years, I  
9 come more and more around to maybe it is important  
10 to go back to the single outcome measure to avoid  
11 this problem of multiple comparisons.

12           Now, whether epigastric pain is the one  
13 we should pick, I don't know, but it's probably  
14 not a bad one.

15           Now, when I showed you the active, I  
16 also showed you the AJ. Once again, it was a  
17 small study. We tried to validate outcome  
18 measures in a slightly different way. We took a  
19 range of common GI symptoms and measured those  
20 initially on a five-point scale, late on a seven  
21 point scale.

22           And we showed that you could use this as

1 outcome measures; that is, we showed that the  
2 symptoms were important for the non-ulcer  
3 dyspepsia group. We showed, and I'll show you the  
4 data, if you administer this questionnaire with a  
5 one imprint, that the results are reasonably  
6 reproducible, although not perfect.

7 And using a correlation with the global  
8 assessment following treatment, and this was a  
9 non-randomized study, I should say, we showed that  
10 you could pick up a change in the overall health  
11 status.

12 And here I show you that on a slide from  
13 the study -- a study of about 55 patients, 20 were  
14 HP-negative and 30 were HP-positive. It would  
15 show us these were the most common symptoms. And  
16 we ranked them in this study on a five-point  
17 scale. We later switched to a seven-point scale  
18 because we felt we would be able to pick up  
19 smaller differences.

20 Now if you'll look at the Streamer  
21 correlation coefficient, it's a coefficient  
22 between time one and time two.

1 I should add that after time one, and  
2 endoscopy took place so reassurance for a negative  
3 endoscopy may have an effect.

4 This is what all studies have shown.  
5 You can see most of the symptoms in most groups  
6 show a tendency towards improvement. So this is  
7 the reason that the Streamer correlations are not  
8 perfect, but I think in the area of non-ulcer  
9 dyspepsia, I doubt whether you'll get a follow-up  
10 there.

11 Now we also showed following a  
12 treatment. This was a former treatment. It was  
13 non-randomized. The following treatment, an  
14 improvement did take place in these patients and  
15 this correlated with an improvement in overall  
16 global assessments.

17 So what the P showed, it's a  
18 non-randomized trial. It only tells you a little  
19 bit about the magnitude of change that these  
20 symptoms were able to pick up.

21 So I think this is just another way of  
22 looking it out. To me it shows that it is

1 feasible, using these strategies, to come up with  
2 better data outcome measures.

3 So we did a small study when patients  
4 with non-ulcer dyspepsia and compared triple  
5 therapy to placebo. And this is only one of the  
6 surprisingly, the very few studies for a true  
7 placebo which is -- and tried to look at the  
8 course of whether there is a sustained improvement  
9 in the severity of symptoms.

10 There was a tied in exclusion criteria  
11 self-serving was a select population to which more  
12 severe symptoms were -- symptoms had to be present  
13 for at least three months and two-thirds of the  
14 patients had symptoms in effect for more than a  
15 year.

16 It needed to be, of course, HP-infected  
17 and they had to be symptomatic at the time of  
18 enrollment for which we required the minimums for.

19 We used a whole range of exclusion  
20 criteria: Heartburn, as a dominant symptom,  
21 esophagitis, pre-dyspeptic ulcers and also we  
22 wanted to avoid overlap with irritable bowel

1 syndrome.

2 So whether for clinical practice we  
3 should go to a highly selected patient with really  
4 stringent criteria in a way that may be ideal as  
5 far as the study design as to whether the  
6 generalized ability of such a study will apply  
7 when physicians enter or patients enter  
8 physicians' offices. I don't know.

9 So you could also argue to be a lot more  
10 liberal in your inclusion criteria and only  
11 exclude, let's say, peptic ulcer disease and  
12 esophagitis.

13 But in this study, we chose to have all  
14 exclusion criteria.

15 Patients were randomized for day  
16 treatment with Bismuth subcalicilate or  
17 Amoxycillin or identical looking placebo. But we  
18 had difficulty when we got from Proctor & Gamble  
19 who partially forwarded this study for formulation  
20 of placebo of Pepto-Bismol. Very difficult to  
21 make, but by and large, I would say, it did work  
22 in the sense that patients did not -- could not

1 tell whether they had been on the active treatment  
2 or the placebo.

3 But clearly where we now have treatments  
4 available that don't include compounds that darken  
5 the stool, they might be easier with regard to the  
6 promo blinding.

7 All symptoms and global assessments were  
8 measured on seven-point scales. Like all scales,  
9 these are integral scales and you see the example  
10 that was used for epigastric pain. And we use a  
11 whole range of outcome measures. These are the  
12 esophageal -- the GI symptoms that I already  
13 mentioned. And we use two global assessments.

14 One was an overall global assessment of  
15 quality of life. And the second one, we've  
16 checked and I'm glad for the way we do. We also  
17 assess the global assessment of the overall  
18 severity of the dyspepsia because we have this  
19 feeling that since this is a nuisance condition,  
20 that hopefully patients would be able to  
21 distinguish these symptoms of dyspepsia from their  
22 overall quality of life. And I think by and

1 large, that was successful.

2 I'll just show you a few of the results.  
3 We entered 53 patients. Four patients have  
4 dropped out of the study so this is, in fact, not  
5 an intent to treat analysis, but given that the  
6 numbers are so few, it really didn't make any  
7 difference.

8 But here I show you just a few of the  
9 outcome results. So overall severity of dyspepsia  
10 symptoms, epigastric pain, which I think most  
11 people in this area argue is the cardinal symptom,  
12 pain or discomfort in the epigastric region to  
13 support an ulcer dyspepsia. And this is the  
14 overall global assessment.

15 So eradication was very successful, 96  
16 percent, and only one patient in the placebo was  
17 eradicated.

18 Now what you can see is that there is a  
19 marked improvement in both groups from zero and  
20 six weeks, that is just four weeks after treatment  
21 was finished, but that there was no or very little  
22 improvement when we went another six months.

1           So there is an improvement but it's an  
2 improvement regardless of whether Helicobacter  
3 pylori was eradicated. And as you can see, the  
4 overall global assessment doesn't appear to change  
5 all that much.

6           Now there is a problem with multiple  
7 comparisons in this area clearly, but these were  
8 the main outcome measures that we had picked.  
9 When we looked at all the other individual  
10 symptoms, no important differences were found for  
11 the duration of the study.

12           Now many people argue that -- certainly  
13 the people in the pain literature -- that it's  
14 almost impossible to measure pain. So if you  
15 think about pain, you may think of several  
16 dimensions; that it's a weighted average of the  
17 global severity, is a weighted average of  
18 intensity, frequency and duration.

19           So we also looked to -- we asked  
20 patients questions about frequency and duration of  
21 their symptoms, and again, I only show you  
22 epigastric pain. That's for the number of days

1 per week that they had symptoms, the number of  
2 episodes per day, and the duration of these  
3 episodes.

4 And one again, you can see the active  
5 and placebo group, no significant differences  
6 occurred.

7 Now -- so if you argue that, let's say,  
8 frequency and duration is a different dimension  
9 than overall severity, it might make sense to,  
10 apart from overall severity, measure these  
11 entities.

12 So this is just one slide that looks at  
13 that in a little bit more detail where we  
14 correlated the overall severity of epigastric pain  
15 to measures of frequency and duration. And you  
16 see that correlations vary.

17 What it is, as a lot to an overall  
18 expectation of a study, I must say, I don't know.  
19 But based on these data, you could argue that it  
20 might be a good idea to, in addition to measuring  
21 overall severity, look at things like number of  
22 episodes per day or number of days per week.

1           Now, not surprisingly, if you will look  
2           at the correlation between histologic parameters  
3           such as inflammation, the correlation is, in fact,  
4           lousy. So I don't think anybody will be surprised  
5           at that result.

6           But certainly you couldn't take  
7           histologic improvement as a substitute end point  
8           in these studies, although we didn't do it either.  
9           We drew biases from the interim ability.

10          There is very few studies done that have  
11          really biopsied all the regions of the stomach  
12          very, very carefully. And I think the study needs  
13          to be done, but I doubt how practical that is  
14          going to be in the future.

15          So we concluded from this study, but  
16          it's a small study. I think it should be seen  
17          more in the sense that I think it is possible to  
18          do group studies that are in this area. But we  
19          clearly need a lot bigger studies with longer  
20          follow-up.

21          And the study that has driven home the  
22          message that it's going to be important, although

1 I don't think it proved it, to look at the  
2 long-term follow-up, is this study from Dr.  
3 Almorán's group in Dublin.

4 They started off with a cohort of  
5 patients, patients, of which 83 were evaluated for  
6 filter criteria from an ulcer dyspepsia. And they  
7 randomized them two to the three treatment arms  
8 that you see.

9 And they assessed their symptoms four  
10 weeks after treatment and repeated endoscopy and  
11 then followed these patients up for one year.

12 They used outcome measures. It's not  
13 the same as we use, but it is fairly similar as  
14 far as in -- as far as content. The range of  
15 these symptoms and added them up.

16 And here you can see the results  
17 immediately after treatment; that is, four weeks  
18 after treatment was finished.

19 You can see that in all treatment  
20 groups, there is a marked improvement in the  
21 overall severity of symptoms. But once again, in  
22 the bottom part of the slide, the results are

1 shown as to those patients that were successfully  
2 cured of their infection in the effect that there  
3 were no differences.

4 So once again they showed, at least in  
5 the short-term, that symptom reimprovement is  
6 irrespective of whether or not you eradicated the  
7 H. pylori infection.

8 But they followed these patients up to  
9 one year later and showed in the data were  
10 interesting. What they showed is that those  
11 patients who had a persistent infection, in fact,  
12 their symptoms came back up, became more severe.  
13 Whereas the group of patients that stayed cured of  
14 their infection, their symptoms stayed low.

15 They have 13 patients who were  
16 reinfected -- probably some of these were patients  
17 who, in fact, were not successfully eradicated --  
18 but the other outcome measurement I looked at as  
19 additional treatment is how many prescriptions and  
20 how many office visits were there in these groups.

21 And you see that there is a dramatic  
22 difference between the patients that were infected

1 with the Helicobacter compared to patients that  
2 were not infected.

3 So clearly this study has raised a  
4 question. And since we know it takes a long time  
5 for the gastritis to heal, that we have to follow  
6 them up long-term.

7 The problem with this study, though, is  
8 that both the patients and the physicians knew in  
9 six weeks whether or not they were infected. So  
10 this was an unblinded study. And therefore, I  
11 think although I think the point is well made, I  
12 don't think the data here, although interesting  
13 proof that they, in fact, are direct, but I think  
14 that certainly now everybody, since this study,  
15 has come out with ways that we have to do studies  
16 with a follow-up of at least six months,  
17 preferably one year.

18 Now the question then is, should we look  
19 at improvement on symptoms? This is what the  
20 large majority of patients come to see us with, or  
21 should we look at cure of the infection and  
22 healing of the gastritis?

1                   And I think in practical terms, the  
2 biggest shift that has taken place over the last  
3 five years is that more and more people really  
4 regard this infection as true pathogens. And  
5 there is no advantage to having H. pylori in the  
6 stomach that we're aware of.

7                   So I'd like to finish with two slides.  
8 The GI community certainly doesn't practice what  
9 it preaches. This is a study that Dave Foreman  
10 published in *Gott's* where they polled  
11 gastroenterologists going to the British Society  
12 of Gastroenterology Meeting. I think it was about  
13 300 individuals.

14                   And surprisingly -- this was done about  
15 -- patients whereas two-thirds of the individuals,  
16 even though they did not believe that there was  
17 proof that they played a role in ulcer dyspepsia,  
18 in fact, stated to the patients who fulfilled  
19 these criteria -- and I think if I see what is  
20 going on in the GI community at large, I would say  
21 a large proportion of us do, in fact, treat these  
22 patients. And I think what is driving that is the

1 underlying believe that chronic gastritis is  
2 potentially harmful.

3 So I would like to summarize with my  
4 favorite slides on ulcer dyspepsia. I think at  
5 the moment we really don't know what -- what to do  
6 with patients with chronic dyspepsia with regard  
7 to treatment for their symptoms. Measures such as  
8 overall severity of dyspepsia symptoms and a  
9 careful assessment of some of the other individual  
10 symptoms is a way of doing better studies in this  
11 area.

12 And I'd like to leave it at that.

13 DR. FISHER: Thank you, Dr. van Zanten.  
14 Anybody have any burning questions right now  
15 before we get to the discussion at the end? Dr.  
16 Laine?

17 DR. LAINE: Well, just a comment on the  
18 Almorán study. Although I mean I agree, it  
19 certainly raises important questions.

20 I have a whole lot of problems with that  
21 study. First of all, it wasn't a randomized  
22 study. It was "sequentially allocated," so it's

1 non-randomized, which is a major problem.

2 You know, obviously they had a lot of  
3 loss of follow-up and I had great difficulty with  
4 the fact that they took those 13 patients who  
5 actually presumably were infected all along  
6 because the Irish group has a very high rate of  
7 initially finding them not there and then actually  
8 showing that it's a recrudescence rather than  
9 reinfection.

10 And that group still had a very low  
11 dyspepsia score in bringing up that question on  
12 bias as well, in terms of they were told they were  
13 negative.

14 So to me, although it certainly raises  
15 interesting questions, I really thought their  
16 conclusions were over-broad and much too strong  
17 based on their study results.

18 DR. FISHER: Dr. Francis?

19 DR. FRANCIS: In the evaluation of the  
20 symptomology, I realized that cell phenotyping may  
21 not be helpful in evaluating the disease.

22 Have you looked at using a sabakine

1           secretion as an assessment of inflammation and  
2           presence of disease?

3                         DR. VAN ZANTEN:  No.  We haven't done  
4           it.  And these, of course, are difficult and very  
5           expensive.

6                         But I think -- I mean it certainly needs  
7           to be done but for the large scale trials, the  
8           other thing is, the more you do to this patient  
9           group of non-ulcer dyspepsia, the more difficult  
10          the studies are.

11                        And I can tell you from my experience,  
12          there is an incredible knowledge out there on H.  
13          pylori infected people.  Once they know they have  
14          an infection in the stomach, it's "not good."

15                        It's really quite hard to convince them  
16          that they should go through a true placebo which  
17          is what we would like in the non-ulcer dyspepsia  
18          trials.

19                        But it's increasingly difficult.

20                        DR. FISHER:  Dr. Kirschner?

21                        DR. KIRSCHNER:  You know, as you know in  
22          kids with H. pylori infection, we often find

1        nodular gastritis.

2                    You define non-ulcer dyspepsia as no  
3        structural abnormalities.    Would nodular gastritis  
4        be a non-structural abnormality?

5                    And if you look at those kinds of groups  
6        separately, is there any greater effect on therapy  
7        of those?

8                    DR. VAN ZANTEN:    Well, I think the  
9        nodular hyperplasia in kids has been well  
10       recognized, even in the pre-H. pylori era.    So it  
11       seems to be a typical immunological response in  
12       children.

13                    The largest studies -- but again, the  
14        studies are not very good in association with  
15        chronic abdominal pain which is a common  
16        presenting symptom to pediatric  
17        gastroenterologists or pediatricians in general.

18                    There doesn't appear to be any  
19        correlation in whether or not the patients are  
20        infected, but I think in that sense, most  
21        pediatricians would simply -- would not regard it  
22        as a structural and nodular, although I can't

1 speak for them.

2 But if they do studies, I think it would  
3 certainly be worthwhile that they look at this  
4 group separate from patients with H. pylori  
5 infection without that response.

6 DR. FISHER: Barbara, let me ask you  
7 since you're a pediatric gastroenterologist.

8 In the pediatric GI circles, is it  
9 considered a structural abnormality or --

10 DR. KIRSCHNER: I don't know that we've  
11 ever addressed this issue. But in my mind, when  
12 we talk about something like non-ulcer dyspepsia  
13 which is a very vague term, it would be to the  
14 exclusion of something that is more specific.

15 And actually, we very rarely see nodular  
16 gastritis except in face of H. pylori. So that if  
17 we saw that, it would be -- it's almost a  
18 different category. It would be under nodular  
19 gastritis as opposed to dyspepsia.

20 DR. VAN ZANTEN: Even in adults, we see  
21 it about one -- actually up to perhaps one-third  
22 of the time in people with H. pylori infection of

1 -- and healthy volunteers, at least that we've  
2 studied.

3 So at least in adults, we generally were  
4 not considered as anything else outside of kind of  
5 the normal --

6 DR. JUDSON: Is this histologically or  
7 endoscopically?

8 DR. VAN ZANTEN: Endoscopically. When  
9 we just looked at the group of volunteers, and the  
10 Germans have done this a different way, we found  
11 that nodularity had about a 30 percent  
12 sensitivity, but a specificity of over 90 percent,  
13 at least in healthy volunteers.

14 This wasn't ulcer patients, and there  
15 may be differences.

16 DR. FISHER: I think it's something that  
17 has come up several times, including in past  
18 discussions in the GI group advisory committee  
19 about the difference of HP infection in children  
20 and what they manifest as.

21 And Barbara has raised it a couple of  
22 times in people talking about not seeing DU's as

1 much, but seeing nodular gastritis.

2 And perhaps that's a hint to the  
3 pediatric GI society even to do something in the  
4 way of looking at that population and seeing if  
5 that's really true. And there has to be some  
6 separate sort of recommendations or analysis of  
7 study in that population.

8 As we talk often within our groups, we  
9 don't have good recommendations or studies in  
10 pediatric groups, as far as controlled randomized  
11 studies for FDA approval or recommendations for  
12 regimen or drugs.

13 So maybe this is something that needs to  
14 be looked at a little bit more.

15 Dr. Bertino?

16 DR. BERTINO: I think I understood from  
17 your presentation that pain was probably your main  
18 outcome variable.

19 DR. VAN ZANTEN: Well, we looked at the  
20 overall severity of dyspepsia symptoms and FDA  
21 should find those -- sort of put our hat on, so to  
22 speak, when we measured the whole range of

1 symptoms and many aspects of pain and those --

2 But what I'm saying is, the initial way  
3 I thought about that Myron study, you know, a  
4 couple of years ago, I said, "Well, you know, have  
5 they really proven that epigastric pain is a  
6 sufficient measure for the overall severity of  
7 dyspepsia symptoms?"

8 I think it's actually quite a good  
9 measure. My hunch is that an overall severity  
10 might be dyspepsia symptoms, whichever way you  
11 define it. It's probably you capture a little bit  
12 more the whole complex of it because, I mean, this  
13 is a mine field, if you want to study.

14 So I think that you surely could make a  
15 case for measuring a whole range of symptoms and  
16 in the large trials we need today because it's  
17 going to be very, very important.

18 Because I would hang my hat on a single  
19 outcome measure preferably.

20 Yes?

21 DR. BERTINO: I guess I was saying from  
22 a patient standpoint, pain would probably be one

1 of the most important --

2 DR. VAN ZANTEN: It would -- I mean in  
3 an ulcer dyspepsia, but it's pain or discomfort.  
4 But it really isn't -- you're really asking  
5 carefree about just the burping and belching and  
6 all this kind of thing. It's -- it can be -- it  
7 can be very subtle.

8 Some patients -- people may say, "Well,  
9 it's not really pain." Well, is it discomfort?

10 Well, I guess you could call it, but I  
11 have -- I mean it's not a --

12 DR. BERTINO: I guess I had a method --

13 DR. FISHER: How about -- I mean how  
14 about a visual analog scale of 100 on a nuisance  
15 score. Well, you know, I mean --

16 DR. VAN ZANTEN: Yes. I have done that.  
17 I mean we prefer the Liker scales because it's a  
18 little bit easier to understand for patients in  
19 the other -- at least in studies on chronic  
20 obstructive lung disease that consists of heart  
21 failure.

22 It is easier for us to understand --

1 well, let's say a two point improvement is on a  
2 seven point Liker scale. And our minds then say a  
3 50 on a visual analog scale.

4 And I want to make one other comment  
5 that I didn't mention this.

6 Of course, the million dollar question  
7 in this area is, what is the minimum -- if you use  
8 seven-point Liker scale, for example, what is the  
9 minimal difference that you think is clinically  
10 relevant?

11 And again, in the chronic obstructive  
12 lung disease, but it's probably a more severe  
13 disease than congestive heart failure, on an  
14 overall assessment, they use sort of in the range  
15 of 1.5 on a scale of seven.

16 DR. FISHER: Let's have three quick  
17 comments. Dr. Gallo-Torres, Dr. Marshall and  
18 myself, and then we'll go on and get more in to  
19 the discussion later.

20 Hugo?

21 DR. GALLO-TORRES: Will someone please  
22 characterize the nodular gastritis a little bit

1 more.

2 Where is it located? The antrum, the  
3 fundus? Is it accompanied by duodenitis? What do  
4 we see?

5 DR. FISHER: Dr. Kirschner?

6 DR. KIRSCHNER: Well, it's usually --  
7 and I agree that it's very sensitive. Not all  
8 children have it. It probably is 30 or 40  
9 percent.

10 But when we see it, and it's certainly  
11 more than a nuisance. I mean it's got to be  
12 endoscoped because they're very symptomatic.

13 So I have to response a little bit to  
14 the triviality of the symptoms because it can be  
15 quite significant.

16 But, in fact, it's mostly antral. And  
17 it's highly variable. And the longer it goes  
18 untreated, the more extensive it may become.

19 And usually you see a lot of lymphoid  
20 aggregates in the stomach like lymphoid follicles,  
21 and that's what these look like, lymphoid nodule  
22 or hyperplasia.

1           You can also have gastritis and  
2 inflammation as well. In fact, you can have acute  
3 inflammation. Very often you do.

4           But it's -- endoscopically, it's very  
5 characteristic when it's there.

6           DR. FISHER: Dr. Gallo-Torres?

7           DR. GALLO-TORRES: Does it go away  
8 continuously in any manner, in any way? Does one  
9 know? Anyone know? Do you see it --

10          DR. KIRSCHNER: Well, this is obviously  
11 something that needs to be built into studies. I  
12 mean the only way you would serially endoscope an  
13 untreated child who has come to you symptomatic --  
14 I mean it just isn't, as far as I know, not done  
15 --

16          DR. GALLO-TORRES: So we don't know?

17          DR. KIRSCHNER: -- in any large number.

18          DR. FISHER: Dr. Marshall?

19          DR. MARSHALL: Regarding non-ulcer  
20 dyspepsia studies, remember most of the patients  
21 in the study haven't got all symptoms. So if I go  
22 into your study and you ask me about five

1 different symptoms, three of those symptoms start  
2 off at zero.

3 So random variation that I get in  
4 symptom that I don't have can only be worse.

5 So I don't agree that you should include  
6 a symptom for burping.

7 On my questionnaire, if I didn't come to  
8 you with burping -- I came to you with nausea and  
9 I would say that my scoring should be related to '  
10 nausea and maybe the pain that I had.

11 So finally it comes around to this thing  
12 again. I think the global scoring in the studies  
13 is probably much better than having seven  
14 different things you're asking every single  
15 patient when three of them are only going to  
16 contribute noise into the statistics.

17 And I haven't seen any intelligent  
18 statistical discussion on these kinds of points  
19 with non-ulcer dyspepsia. And I think we've got a  
20 long way to go before we really know how to  
21 analyze them.

22 And it seems to me like stock market

1 type analysis is the way to do this. You go to  
2 trend and you're going to see a shift in the  
3 baseline.

4 DR. VAN ZANTEN: Well, that's certainly  
5 an interesting comment although I'm glad you say  
6 you agree with that of global assessment.

7 The other question that Dr. Graham has  
8 proposed, he said well maybe it's -- you only look  
9 at the number of pain free days that they're  
10 really well.

11 And I think it's the same thing as an  
12 irritable bowel syndrome. This type of patient --  
13 I think there will be a subset of patients who  
14 always will be somewhat symptomatic.

15 So I think you only look at complete  
16 disappearance of symptoms, although an interesting  
17 measure, I don't know whether it would be  
18 applicable to these groups.

19 DR. MARSHALL: My question would be, if  
20 you have let's say no burping, would you agree  
21 that you need to have at least epigastric pain and  
22 discomfort?

1 DR. FISHER: That was a yes, nod of the  
2 head, for the record.

3 DR. VAN ZANTEN: Because that's what  
4 most people would argue.

5 DR. FISHER: Okay. I just have one  
6 quick question on the data you showed us on your  
7 study, although granted small numbers.

8 There seem to be a difference in some of  
9 the baseline numbers and the numbers may have been  
10 too small to say anything statistically.

11 But if you then looked at change from  
12 baseline in those groups, as opposed to just  
13 numbers difference, was there any difference in  
14 that?

15 Okay. All right. Thank you very much,  
16 Dr. Van Zanten.

17 Let's go on now. Dr. Webb, I guess,  
18 from Glaxo Wellcome is going to introduce our next  
19 speaker or two speakers?

20 DR. WEBB: Yes. Thank you, Rosemarie.  
21 It's my pleasure to introduce today to you

22 Dr. Plato Correa, who is from the

1 University of Louisville -- excuse me --  
2 Louisiana, and he's a Professor of Pathology -- my  
3 geographic shift.

4 And also to follow Dr. Correa's talk, we  
5 have invited Dr. Barry Marshall to also comment on  
6 the connection between H. pylori infection,  
7 gastritis and gastric cancer.

8 Three points to consider during these  
9 talks: One is, H. pylori pathogen that is in any'  
10 way worthy of treatment. Does it cause a disease?  
11 Is H. pylori gastritis a disease that warrants  
12 treatment?

13 Number two, is H. pylori a antigen in  
14 the sense of stimulating gastric lymphoma?

15 And number three, is it indeed a  
16 carcinogen and what is the evidence that would  
17 support that concept?

18 I was pleased to see Dr. van Zanten  
19 begin to move the discussion away from symptomatic  
20 end points towards the more objectively measured  
21 end points such as the gastritis scores and the  
22 other inflammatory markers that are seen in this

1 entity.

2 I think there are a number of precedents  
3 in medicine where inflammation occurs in a  
4 asymptomatic fashion, yet can lead, over the  
5 long-term, to carcinoma or adenoma carcinoma.

6 A good example might be chronic  
7 cervicitis, for instance, leading to cervical  
8 cancer.

9 Another one would be for hepatologists,  
10 hepatitis-B leading to hepatoma.

11 Gastroenterologists all know that  
12 patients with quiescent ulcer and colitis on  
13 biopsy can still have significant inflammation  
14 develop dyspepsia in those biopsies, even when  
15 they're asymptomatic.

16 So I think what we're hoping to show  
17 today is that strictly dealing with symptoms may  
18 not be a fruitful endeavor; that we need to look  
19 for objective end points and objective  
20 measurements of improvement in designing these  
21 clinical trials to make your case that this is  
22 indeed pathogenic and carcinogenic.

1 DR. CORREA: Good morning. I appreciate  
2 the opportunity to address you today.

3 I'm going to do two things: One is to  
4 explain or show what we pathologists think this  
5 bacteria do to the stomach.

6 And second, try to speculate a little  
7 bit about the potential role of the carcinogen and  
8 explain the chain of events that leads to the  
9 carcinogenic end point.

10 Okay. This is the Helicobacter pylori.  
11 It's, as you know, a spiral bacteria. It's  
12 especially suited to live where it's niche is,  
13 which is in the gastric mucus overlying the  
14 mucosa.

15 Of course, it's propelled by this very  
16 strong flagelli which make it possible for it to  
17 move around.

18 And the other thing it has, of course,  
19 is urea. It is very potent that helps the  
20 bacteria live in this acid environment which is  
21 hostile to almost all other bacteria.

22 So this is all the structural

1 photograph. This is the gastric epithelial cell  
2 at the bottom showing the microvilli. And these  
3 are the bacteria floating next to the surface of  
4 the epithelium.

5 It produces damages to the epithelium in  
6 that it makes the microvilli coarse and blunt, and  
7 also produce liposomes and damage to the mucus  
8 epithelium.

9 The bacteria sort of lives on the urea  
10 that has leaked in between the epithelial cells.  
11 And with this potent urea stomach gas, it's  
12 capable of breaking it down into a cloud of  
13 ammonia that neutralizes the environment and mucus  
14 in the vicinity of the bacteria and therefore  
15 makes it possible for the bacteria to live where  
16 other bacterias cannot live in a pH of 1.

17 So the bacteria lives outside the body  
18 in a way, but produces damage into the body.

19 The main defense that's mounted by the  
20 organism is the PML, the polymorphonuclear  
21 leukocytes that are coming out of the stroma and  
22 get into the lumen of the gland and fibrocitize

1 all damage to the cell by the toxins that it  
2 produces.

3 But before they can get to the point  
4 where the bacteria is, the polymorphonuclear  
5 leukocytes will have to travel quite a long  
6 distance. And many of them become degenerated in  
7 the way.

8 Sometimes the infection is massive, as  
9 you can see. This is a working starry stain.  
10 It's showing the positive stained bacteria in the  
11 immediate vicinity and in between the cells, but  
12 not really penetrating in the cell. But the  
13 infection can be very massive.

14 The -- from the pathology standpoint,  
15 there are two main lesions that are produced by  
16 the bacteria. The one -- one is the damage to the  
17 mucus. This is a urea stain showing that each of  
18 the cellular elements at the surface or follicular  
19 cells have a very tall column of neutral mucin  
20 which makes the cell resistant to the environment  
21 and it's practically the main defense that the  
22 cell has.

1           This is a normal structure, but when you  
2           have an infection of Helicobacter, this is what  
3           happens. The mucus becomes very damaged and  
4           discharged and it's very clear. This has been  
5           seen and documented by pathologists all over the  
6           world. And this comes back very clearly when you  
7           eliminate the bacteria.

8           The second -- and this is an HNE slide  
9           showing the circus of a cell in which the  
10          epithelial cells have lost the mucus which is this  
11          column that should be here. And of course, this  
12          makes the epithelium vulnerable to the acid in the  
13          lumen and produces microerosions.

14          The second thing, of course, the  
15          bacteria is the inflammation which is -- has two  
16          components, the lymphocytes and plasma cells  
17          called MALT or mucosa-associated lymphoid tissue,  
18          which is especially a tissue that comes through  
19          the stomach and is not present normally.

20          Then the other is the polymorphonuclear  
21          leukocytes which you will see here in this slide.  
22          They are very abundant, not only in the stroma,

1 but also in the glands and coming out into the  
2 lumen.

3 So these are the -- these are the two --  
4 practically all patients infected with  
5 Helicobacter have some degree of inflammation.

6 There were some reports at the beginning  
7 that this could be presence of bacteria without  
8 inflammation. What happens is that sometimes you  
9 only have biopsies that does not have  
10 inflammation, but the inflammation is nearby.

11 But when you document the cases, well,  
12 everybody who is infected have some degree of  
13 inflammation.

14 The inflammation into the stomach or in  
15 the stomach can follow several ways. One is this  
16 in which there is a dense infiltrate or  
17 lymphocytes going all the way from the surface of  
18 the mucosa to the muscular mucosa in between the  
19 glands, but no loss of glands. This is the lesion  
20 that's more -- that's practically all is found in  
21 patients with duodenal ulcer and is the new  
22 nomenclature I use is the non-atrophic gastritis

1 and a very common name for this is diffuse  
2 enterogastritis.

3 Now in some cases, and this leads to a  
4 very large accumulations of lymphoid tissue that  
5 you see here, and this is I think what we're  
6 referring to earlier today, nodular gastritis,  
7 also called follicular gastritis. This is the  
8 type of gastritis seen in practically always in  
9 children that are infected with *Helicobacter*  
10 *pylori*.

11 This patient do have a few  
12 polymorphonuclear leukocytes, but for some reason,  
13 the infiltrate by PMNs is much less.

14 In my experience, this is due to  
15 *Helicobacter* infection. Whenever we see this in  
16 children, if the children are treated, the  
17 infection clears up. The inflammation goes away.

18 It's also rather frequent in young women  
19 to have this nodular gastritis and we have  
20 conducted studies in Columbia and this was clear  
21 practically completely with *Helicobacter*  
22 treatment. And all of these patients were

1 infected.

2 Now what happens when you clear the  
3 Helicobacter infection, this is what happens to  
4 the polymorphonuclear infiltrate. In a question  
5 of a month or so, it goes down to very little.  
6 And in two months or so, you don't find any.

7 This is a number of stale and blinded  
8 pathologists looking at biopsies and classifying  
9 the infiltrate as zero, mild, moderate or severe.  
10 Those people who did not clear the infection with  
11 the therapy just didn't change anything.

12 The question for lymphocytes is a little  
13 bit different. It takes a longer time to take.  
14 And although many patients go down to zero, some  
15 patients even two years after have some  
16 lymphocytic infiltrate for some reason. But -- so  
17 it stays around.

18 But you can develop, and there are very  
19 good analog scales, and sort of protocols to  
20 follow in grading gastritis. And it's very useful  
21 to do it.

22 Now the second thing that the gastritis

1 and the Helicobacter does is to produce loss of  
2 glands. This is a biopsy from the stomach and  
3 this is the muscular mucosa down here. And these  
4 are a few remaining anterior glands.

5 But all of this empty space full of  
6 fibrous tissue is where the muscle glands were  
7 there. So for some reason Helicobacter pylori  
8 produces loss of glands in some individuals. And  
9 this is what we call multifollicular atrophic  
10 gastritis, unfortunately after much arguing, the  
11 pathologists, we have come to agree on the name of  
12 multifollicular atrophic gastritis for this  
13 entity.

14 We have conducted a case control study  
15 in New Orleans where the relative risk for atrophy  
16 was about five so that there is no question in our  
17 mind of Helicobacter infection. Each one of the  
18 causes, or at least a cause of atrophy of the  
19 gastric mucosa.

20 Now this atrophy goes on to produce what  
21 we call intestinal metaplasia. This is the normal  
22 stomach. On your right is the normal glands. But

1 all of these focus have been replaced. There are  
2 no more normal glands. They are atrophic, they  
3 are lost, they are gone, and they are replaced by  
4 these epithelium, which has two cells.

5 So this is the intestinal metaplasia.  
6 It's a consequence -- follow of atrophic  
7 gastritis.

8 And then this is a specimen dissected  
9 for stomach cancer. This is a big ulcer here is  
10 the carcinoma of the stomach.

11 This stomach has been stained for  
12 alkaline phosphatase, which is one of the end  
13 sign. It's normally in the intestine. If you  
14 come forward -- those of you who can see the  
15 duodenum here, it's normally deeply stained with  
16 red because it's full of alkaline phosphatase.

17 The point here is that this carcinoma  
18 arose right in the insure angularis where the --  
19 where the metaplasia is more frequent because each  
20 of these red spots represent an area of  
21 metaplasia, represent an area where the gastric  
22 mucosa has been replaced by intestinal mucosa and

1 produce these enzymes.

2 So it's the experience of practically  
3 everybody that most of these carcinomas arise in  
4 areas where there has been intense intestinal  
5 metaplasia.

6 The exception to this is the so-called  
7 diffuse carcinomas which are -- may be a different  
8 entity. But most of the carcinomas are of this  
9 type.

10 So the -- the relationship between  
11 Helicobacter pylori and carcinoma was suspected by  
12 many case control studies before. But the real  
13 best evidence came when three cohort studies were  
14 published. They were the ones in Hawaii where  
15 they were following the Japanese migrants from  
16 anywhere from ten to 20 years.

17 There were the Kaiser-Permanente cohort  
18 in California, and there was a big cohort of  
19 British workers.

20 And what they did was when they -- these  
21 persons were entering the cohort, blood was taken  
22 and serum was frozen and kept in a freezer. And

1 ten or 15, sometimes 20 years later, they went on  
2 and found who developed cancer of the stomach.  
3 They retrieved the frozen serum and retrieved a  
4 number of serum from patients who did not develop  
5 the disease.

6 And there is no question that in all of  
7 the three very different populations, the risk of  
8 cancer of the stomach increased anywhere from 2.8  
9 to 3.6, if the person had been infected.

10 The meta analysis of this data has been  
11 done and there is a lineal relationship. The  
12 longer the cyst has been -- the infection has been  
13 present, the risk is becoming higher.

14 So there are many other pieces of  
15 evidence sort of concluding the same thing.

16 So then I'm going to try to follow what  
17 is -- what we think happens to the stomach before  
18 it develops stomach cancer.

19 And the first thing that happens is that  
20 the normal mucosa becomes inflamed as with  
21 gastritis. Some of those patients as we saw go  
22 into atrophy.

1           When there is atrophy, then the pH of  
2 the gastric cavity goes up because there is less  
3 production of acid, and then bacteria -- and I  
4 wrote bacteria probably from the stomach -- many  
5 of them have cases that convert in nitrate that  
6 almost every diet has, into nitrite, which is a  
7 very active molecule and is very capable of  
8 producing nitrous compounds.

9           Most of the -- many of the nitrous  
10 compounds are mutagens. And what is hypothesized  
11 is that because of these mutagens, then there is a  
12 sequence of mutation that takes place.

13           Up to this point, there is no mutation.  
14 They're just more or less glands. But from this  
15 point, the glands that are living in the mucosa  
16 are of different lineage and therefore we think  
17 they are mutations.

18           So in this chain of events, where does  
19 *Helicobacter pylori* fit?

20           The first one, of course, is that  
21 *Helicobacter* produces inflammation. I don't think  
22 there is much argument today about the main cause

1 of gastritis. The overriding cause of gastritis  
2 is the infection of Helicobacter.

3 Dr. Marshall found the -- here because  
4 he was one of the guinea pigs that showed that up.  
5 But lately there has been many, many evidence of  
6 that.

7 The best evidence is that when you treat  
8 the Helicobacter with an antibiotic and you clear  
9 the Helicobacter, the inflammation goes away.

10 The second thing that this inflammation  
11 does is very interesting. It increases the rate  
12 of replication of the epithelium. And this shown  
13 here with this antigen which is the PCNA,  
14 polynuclear antigen, which stains one of the  
15 sightings, which are only produced during the  
16 S-phase of the cycle. In other words, this is  
17 actively synthesizing DNA.

18 And when the patient is infected with  
19 Helicobacter, the proliferation index here is  
20 about 20.

21 When you clear the patient with  
22 antibiotics, it goes back to less than 415, which

1 is what you find in the normal mucosa.

2 If the patient does not clear the  
3 infection, then the proliferation index stays  
4 there.

5 So I think there is a general agreement  
6 in the scientific community that increasing the  
7 rate of proliferation upsets -- increases the rate  
8 of cancer because it can be -- any carcinogen that  
9 may be exposed then is potentiated by this.

10 And also there is this question of  
11 autonomous mutation that may be -- may be sort of  
12 internalized by the proliferation.

13 But there is no question in many studies  
14 that increasing the rate of proliferation in  
15 almost any carcinogenic experiment increases the  
16 yield of carcinoma.

17 Then in the second stage, after you have  
18 atrophic gastritis in pH, the bacteria produces  
19 nitrogen compounds in the stomach. But this is  
20 blocked by ascorbic acid which is a very good  
21 antioxidant.

22 And what happens with the infection of

1 Helicobacter is followed, when the patient is  
2 infected with Helicobacter, the gastric juice  
3 ascorbic acid is very low. When the patient is  
4 not infected, it is very high.

5 So this -- there's a lot of work going  
6 on at the present of what it's meaning, but there  
7 is no question that there is an interference by  
8 the bacteria with the normal function of the  
9 stomach which is to produce -- to have an adequate  
10 amount of ascorbic acid in the gastric -- in the  
11 gastric cavity.

12 Now this last -- last portion of the  
13 chain of events, there's sequential mutations.  
14 You may have a luminal carcinogen as we discussed,  
15 but you may also have the presence of these  
16 inflammatory cells which produce nitric oxide and  
17 high free radicals.

18 There are well known mutagens that will  
19 be ammunition in other changes in the DNA that  
20 produce mutations.

21 And what happens in the stomach is  
22 illustrated in this slide. This is a gland in the

1 mucosa of the stomach. And this stain with PCNA  
2 show all of the cells are actively replicating.

3 The bacteria located at the center of  
4 the gland. The PMN's come from the blood level --  
5 vessels in the stroma, and they travel to the  
6 gland through all the tissues, separating and  
7 getting in between the cell, therefore becoming in  
8 intimate contact with the cells that are actively  
9 dividing.

10 And we know very well that these cells  
11 are releasing nitric oxide in hydro free radicals.  
12 So there is at least the theoretical background  
13 for a carcinogenesis effect of Helicobacter pylori  
14 in three different points of the chain of  
15 causation.

16 Now this is the last slide and then it  
17 tries to do some speculation on the paths of  
18 infection.

19 And about half of the world is infected  
20 with Helicobacter pylori. Now -- so most of the  
21 people, of course, are not going to the doctor,  
22 even though they have the infection. So this big

1 component of the infected population do not go to  
2 the doctor. Whether they have symptoms or not, is  
3 arguable.

4 There was a study in Italy that went to  
5 the blood bank, found people who were infected,  
6 and then scoped them and found ulcers and many  
7 other diseases. And we don't really know if there  
8 was some kind of selection in that study, but some  
9 investigators believed that what happened here is  
10 that the strains of bacteria that are not so  
11 virulent have -- lack some of the virulence genes.  
12 But this is still being investigated.

13 I don't think we have come to a  
14 conclusion there yet. Nobody really can tell what  
15 kind of strains of bacteria are infecting these  
16 people who are not going to the doctor, and  
17 therefore you are not finding them.

18 But the others who have symptoms and go  
19 to the doctors have one or two pathways. They all  
20 have inflammation in the stomach. And part of  
21 that inflammation is the MALT, the lymphocytic  
22 plasmolytic cells, and part of the inflammation is

1 the PMN's.

2 And practically, they are mixed, but in  
3 some of them, the inflammation is mostly  
4 lymphocytic and plasmolytic and most of them go to  
5 develop diffuse antral gastritis. And some of  
6 them develop a duodenal ulcer.

7 But the ulcer comes and goes and the  
8 gastritis stays. So the real disease is the  
9 gastritis. The ulcer is a by-product of the  
10 inflammation or something that's associated, that  
11 comes and goes and -- but the entity, the  
12 nosologic entity is the gastritis.

13 A few of them may go on to lymphoma.  
14 I'm not going to say much about that. It's a very  
15 rare event.

16 But the PMN infiltration, when it is  
17 very massive, it does lead to atrophy and then it  
18 has been shown that some of the strains that have  
19 some of the genes that are more virulent attract  
20 many more PMN's and there's more damage to the  
21 mucosa in there. All of those patients develop  
22 atrophic gastritis metaplasia.

1           Again, some of them develop gastric  
2           ulcers that comes and goes and a few of them will  
3           go to dyspepsia or carcinoma.

4           So this is a theoretical sort of sketch  
5           or hypothesis of how things go, mostly  
6           illustrating the very complex pathways that can be  
7           followed by the infection with Helicobacter.

8           I think I'll stop here. Thank you.

9           DR. FISHER: Thank you, Dr. Correa. Any  
10          questions specifically? Yes?

11          DR. PRIZONT: Atrophic gastritis is  
12          usually associated with hypochlorhydria or  
13          achlorhydria.

14          Hypochlorhydria and achlorhydria in the  
15          stomach is associated with colonization of floral  
16          type bacteria. And that's nothing new. We knew  
17          that for over 25 years.

18          When you administer antibiotics, you may  
19          not only eradicate H. pylori, but you may  
20          eradicate the colonic type bacteria as well, which  
21          are known to produce pro-mutagens.

22          Have you -- has anybody tested the

1 difference between the patients with colonization  
2 of floral type of bacteria in those who have only  
3 H. pylori colonization in the gastric mucosa in  
4 terms of the production of these pro-mutagens and  
5 that sort of thing which may lead to gastric  
6 cancer.

7 DR. CORREA: That's right. Yeah. There  
8 since have been studies in patients with  
9 intestinal metaplasia who do have the two flora  
10 there, the Helicobacter and the anidoli bacteria.

11 And the patients with DHE, the  
12 non-atrophic gastritis, we don't really know. I  
13 don't know of any good study that shows that they  
14 are the only bacteria present besides the  
15 Helicobacter.

16 But it is true that the antibiotic would  
17 probably take care of both floras and how that  
18 influences the outcome is not really well known.

19 DR. FISHER: Dr. Butt?

20 DR. BUTT: I have two questions. One,  
21 is there any evidence that any of the genetic  
22 material from H. pylori is incorporated into any

1 of these malignancies?

2 DR. CORREA: Not that I know. There is  
3 -- there is no mutagen or any part of the bacteria  
4 that's carcinogenic.

5 It seems to be -- the hypothesis again  
6 is that it may induce carcinoma by other means.

7 We don't know exactly how many -- what  
8 proportion. The only two studies that I know  
9 relevant to that question are -- were done in  
10 Yugoslavia.

11 The first study, they classified  
12 patients with metaplasia or without metaplasia and  
13 followed them for over ten years. And the risk of  
14 cancer in the metaplasia was ten times that of the  
15 risk of the non-metaplasia.

16 Then there was a follow-up of that  
17 cohort in which they studied the so-called type  
18 three or colonic or incomplete metaplasia in one  
19 that produced sulfomucins, which is a marker of  
20 more advanced metaplasia. And the risk of  
21 patients with that type of metaplasia, compared to  
22 those with metaplasia in general, was 5.7.

1                   So we were -- it is a marker, but it is  
2 a better marker if you can subclassify the  
3 metaplasia and identify the more dangerous  
4 portion.

5                   DR. FISHER: But do you know actually  
6 what the percentage was, as opposed to the  
7 relative risk? I mean the relative risk could be  
8 one in non-metaplasia and ten in the metaplasia  
9 out of a thousand patients, and I think that's  
10 what Dr. Butt --

11                   DR. BUTT: Yeah.

12                   DR. FISHER: -- is asking, is the  
13 percentage.

14                   DR. BUTT: There was a report by Basil  
15 Morton in 1956 that only about three percent of  
16 patients with intestinal metaplasia in resected  
17 specimens had associated carcinoma. But that was  
18 just a --

19                   DR. FISHER: Dr. Azimi?

20                   DR. AZIMI: Do you -- two brief  
21 questions. Number one, do you have any  
22 information on tissue pathology on people who are

1 asymptomatic but do have Helicobacter pylori?

2 Do you have any tissue information on  
3 the histology?

4 DR. CORREA: Yeah. Every book --

5 DR. AZIMI: And number two is, do you  
6 have any information about this organism residing  
7 in any other areas of the mucosa of the  
8 gastrointestinal tract, and if so, is there  
9 pathological information on that?

10 DR. CORREA: Right. The first question,  
11 everybody who is infected and has a good  
12 representation of the stomach in the microscope  
13 has an inflammation. This inflammation may be of  
14 different types and degrees, but no pathologists  
15 really believe that you have bacteria without  
16 inflammation.

17 The second -- the second -- the niche of  
18 the bacteria depends on gastritis epithelium for  
19 some reason that we don't really know. It lives  
20 where this epithelium is present, in the normal  
21 vermicular neutral mutant producing glands.

22 For instance, you have it in mucosal

1           reticulum. You have it in rectal metaplasia or  
2           gastric type. You have it in esophageal  
3           metaplasia or gastric type.

4                     But where there is no gastric mucosa,  
5           nobody has found it except the dental plaque. But  
6           whether that's a viable organism, the dental  
7           plaque, is still debatable.

8                     But by PCR, you can find in the dental  
9           plaque occasionally.

10                    DR. FISHER: Dr. Gallo-Torres and then  
11           Dr. Judson.

12                    DR. GALLO-TORRES: Very nice  
13           presentation.

14                    DR. CORREA: Thank you.

15                    DR. GALLO-TORRES: You show a very  
16           dramatic, very convincing effect on mucus,  
17           quantitative. Some areas are completely denude of  
18           the mucus.

19                    Do we know either it's also an effect on  
20           the mucus composition?

21                    Is this a quantitative as well as a  
22           qualitative effect?

1 DR. CORREA: Yes. The changes are the  
2 mucus are very interesting and have been studied  
3 with some detail.

4 The first thing that happens is the loss  
5 of the neutral mucin. When the metaplasia takes  
6 place, that neutral mucin is replaced by acid  
7 mucin. And the acid mucin in the so-called small  
8 intestinal are complete metaplasia and the early  
9 phases of metaplasia resembles the small  
10 intestinal sealomucin.

11 But when it goes on and becomes closer  
12 to the dysplasia, then you begin to see sulfated  
13 mucins.

14 So it's a very clear change in mucin.  
15 And mucin is a very complex set of molecules.

16 There is the blood group antigens are  
17 represented there, and they seem to play a role in  
18 susceptibility to carcinoma.

19 DR. FISHER: Go ahead. Dr. Judson?

20 DR. JUDSON: I think you've already  
21 answered the question partly, but as this  
22 committee and subsequent committees consider their

1 role for antibiotic treatment, there are two  
2 things that I think are really crucial to our  
3 deliberations.

4 I gather that there is unanimity that  
5 this organism does not have a long-term colonizing  
6 non-pathogenic colonizing role.

7 Is that true that it's only found in the  
8 presence of inflammation?

9 DR. CORREA: That's my perception. Yes'.

10 DR. JUDSON: And the next part of that  
11 is and I think we discussed this yesterday is  
12 that, once eradicated, reinfection rates are very  
13 low.

14 DR. CORREA: That depends on which  
15 population you are in.

16 DR. JUDSON: Developed countries.

17 DR. CORREA: In developed countries, in  
18 Holland and in Australia, I think the reinfection  
19 is very low.

20 In Colombia, my experience is different.  
21 We don't really know why, if it's reinfection or  
22 resistance of the bacteria of whatever. It's not

1 known.

2 DR. JUDSON: Thank you.

3 DR. FISHER: Just on follow-up to that,  
4 we asked this a little bit yesterday.

5 With reinfection or recrudescence in the  
6 countries where it does happen, people have talked  
7 about, at least short-term, that there does seem  
8 to be a recurrence of ulcer disease.

9 Do we know what happens with the  
10 gastritis with the reinfection or recrudescence?

11 DR. CORREA: In our limited experience,  
12 they come back with gastritis. It's always there.

13 You can cure the gastritis and the  
14 metaplasia sort of stays there for a while or  
15 maybe forever. I don't know.

16 But when there is the presence of  
17 bacteria, there's again inflammation.

18 DR. FISHER: So there is documentation  
19 that you can have complete recovery of mucosa  
20 reinfection and reoccurrence of gastritis, at  
21 least?

22 So that would answer part of your thing

1 about colonization, as well as the reappearance of  
2 the organism -- actually evidence of reinfection,  
3 or is it colonization and do we know that in any  
4 large studies?

5 DR. CORREA: No. No.

6 DR. FISHER: Okay.

7 DR. CORREA: Total, but not any  
8 systematic study.

9 DR. FISHER: Okay. Dr. Butt, one quick  
10 question and then I want to get on to Dr.  
11 Marshall.

12 DR. BUTT: Another question. Patients  
13 have been followed-up with Billroth IIs have had  
14 resection for ulcer disease have -- there have  
15 been some concern that they may develop carcinoma.

16 And a great number of these, of course,  
17 you would expect were infected with H. pylori.

18 In the United States, the evidence has  
19 not really been forthcoming, at least none that  
20 I've seen that indicate that surveillance in these  
21 patients really turns up useful -- is not a useful  
22 technique to pick up early carcinoma.

1                   And yet many of these patients are  
2 infected with H. pylori because they have had  
3 resection for ulcer disease.

4                   Do you have any comments on the question  
5 of stump carcinoma and the relation of H. pylori  
6 to carcinoma in these patients?

7                   DR. CORREA: I think that the majority  
8 of papers show an association between the Billroth  
9 II after ten or 15 years. Not the first ten  
10 years.

11                   So those carcinomas are -- most of them  
12 are in the stomach and they have a very peculiar  
13 morphology.

14                   They have a precursor which is very well  
15 known. It's called narcissistic polyposa. And if  
16 I had one of those, I would be under surveillance.

17                   I think that the role of Helicobacter  
18 there is not very well known. The role of reflux  
19 bile, many people believe is very strong.

20                   DR. LAINE: Let me just comment that  
21 actually H. pylori prevalence markedly decreases  
22 after those surgeries it's felt because of

1 duodenal contents or bile being bad for the bug.

2 DR. FISHER: Okay. Dr. Marshall, go  
3 ahead, and then you can --

4 DR. LAINE: Just a question for Dr.  
5 Correa. Have you treated your own infection yet?

6 DR. CORREA: Unsuccessfully.

7 DR. FISHER: Okay. Let's go on to Dr.  
8 Marshall.

9 DR. MARSHALL: I only have five slides '  
10 so we won't keep you very long here.

11 Last week, I gave a talk to a group of  
12 gastroenterologists discussing the management of  
13 dyspepsia.

14 Could we have the lights off in the  
15 front rather than in the back?

16 DR. FISHER: Barry, you can pick the  
17 mike out of the thing if you're more comfortable  
18 than leaning down with it.

19 DR. MARSHALL: Let me have those little  
20 spotlights off down here, if possible. Just dim  
21 the lights.

22 Well, in 1986, I'll just show you the

1 dyspepsia flow chart in patients with dyspepsia  
2 would attend. And we would ask the question, "Has  
3 endoscopy been done in the past two weeks."

4 And if the answer was no, well, of  
5 course, we would do the endoscopy. And if the  
6 answer was yes, the algorithm would be to wait 14  
7 days and then ask the question again. And so --

8 I just thought I'd put that in because  
9 it seemed that we were all getting very serious  
10 here and I thought a few people were going to  
11 sleep.

12 Well, anyway, 1996, I think that's going  
13 to be different. And we might not even have any  
14 endoscopy on this algorithm as we replace it with  
15 non-invasive studies for H. pylori.

16 This is some data. I just wanted to try  
17 and put some balance into the gastric cancer issue  
18 because I think it is an important thing in there.

19 There is a lot of very good  
20 epidemiological data showing a link, but not every  
21 study does show the link with gastric cancer.

22 And rather than us swinging the pendulum

1 all one way and then being very disappointed when  
2 someone shows up these studies which contradict  
3 their ideas about H. pylori and gastric cancer, I  
4 just thought it would be wise to just show a  
5 little more valence.

6 These are -- there are several studies  
7 which show very weak associations between H.  
8 pylori and gastric cancer. The ones that David  
9 Foreman and everybody puts most of their weight on  
10 are these well-controlled case control studies.

11 And here you see the -- on the orange  
12 bar, we have the percentage of cancer cases  
13 infected with H. pylori. And the red bar shows  
14 the percentage of nested case controls that are  
15 associated with H. pylori. And the blue bar shows  
16 the relative risk. And then there's another  
17 number here, a dark blue bar, which shows the  
18 number of years of follow-up.

19 And several things come out here is that  
20 a lot of the relative risks aren't particularly  
21 great. So that if you looked at a country with a  
22 large cancer risk and said that your chance of

1 getting cancer in the next year is one in a  
2 thousand, and if we don't treat your H. pylori,  
3 it's going to be 2.8 in a thousand, well most  
4 people wouldn't lose a lot of sleep over that.

5 So why don't you get particularly  
6 excited about making sure I treat every patient  
7 now, and I think it -- you could look at each  
8 patient individually and say maybe two or three  
9 years we're going to know a lot more about  
10 treatment and have very simple uncomplicated ways  
11 of managing H. pylori infection.

12 The point to make here is that in  
13 studies that have shown the highest risk, I've got  
14 the longest follow-up between the initial serum  
15 and then the follow-up serum. So that it does  
16 appear that, for instance, in this Hawaiian study  
17 by Numera, et al., they had 13 years average  
18 follow-up on their cases. And they got a six fold  
19 increase in the odds ratio.

20 Here's a 14 year study, the California  
21 Kaiser-Permanente study with a 3.6 fold on  
22 average.

1           The other thing to notice is that in  
2 these studies, because the original serum was  
3 taken in the 60's, the control group had a very  
4 high prevalence of H. pylori. These are 45 year  
5 old men in California in 1968. And you'll see 68  
6 percent had H. pylori.

7           If you went out to California now and  
8 got 45 year old mainly Caucasian males, you'd  
9 probably only be about 25 percent infected. So  
10 you might not get the same -- you may see an  
11 increased risk if you could repeat that study  
12 today.

13           Here's a study -- case control study in  
14 China which doesn't show any increase in the H.  
15 pylori -- increase in the risk in the H. pylori  
16 group. And you'll see the infected is slightly  
17 less.

18           Here's another one in Taiwan. Very  
19 slightly increased on it's ratio, 1.6. And I  
20 think that included one, so that there wasn't  
21 really a significant -- but the follow-up was only  
22 three years in that study. But there was a large

1 amount of -- large number of patients.

2 So I'm just saying that not all the  
3 studies support the data.

4 Now unfortunately in this -- when this  
5 was printed last night, these bars here turned to  
6 purple and we can't see them. But in -- this is a  
7 case study in Japanese with gastric cancer. And  
8 there's a blue bar -- a purple bar here that shows  
9 very little difference between the cancer cases  
10 and the H. pylori infection rate. And you see  
11 that the cancer cases were about 80 percent  
12 regardless of the age.

13 So if you have gastric cancer in Japan  
14 and you're aged 20 to 29, the infection rate is 80  
15 percent. If you're aged 60 to 69, you still got  
16 80 percent.

17 But in the nested case controls in the  
18 60 to 69, it was like 75 to 80 percent here, but  
19 this bar was only about 30 percent in the 20 to 29  
20 year old group. So that we see the major  
21 difference between the H. pylori infection rate in  
22 the cancer patients versus the control group in

1 the younger patients.

2 Now the yellow line is the relative risk  
3 and they could see a relative risk for gastric  
4 cancer 20 fold in these 20 to 29 year-olds  
5 infected with H. pylori and it was lesser in the  
6 older ones.

7 So in young people, it appears that the  
8 relative risk of getting gastric cancer from H.  
9 pylori is much higher. But on the other hand,  
10 gastric cancer in that age group is pretty low  
11 anyway.

12 But it is evidenced that H. pylori is  
13 important, particularly in young gastric cancers.

14 In 1972, a document of Ken Kumura, who's  
15 now an H. pylori enthusiast in Japan, he looked at  
16 570 Japanese stomachs and he matched these  
17 stomachs. And he showed that almost all people in  
18 Japan at that time had gastritis. And he showed  
19 that atrophic gastritis expanded approximately  
20 with age and so that it would sort of move up the  
21 stomach from the pyloric and lesser curve area.

22 And so that if you looked at the young

1 people, it would stop here. The 40 years old  
2 would be there, and by 60, you wouldn't really  
3 have any normal gastric mucosa on your lesser  
4 curve, and most of the antrum might have some  
5 atrophic gastritis.

6 In those days, he said that this was --  
7 must have been a normal process which occurred  
8 with aging. And there is some new data coming out  
9 of Japan now which suggests that almost all  
10 intestinal metaplasia is actually related to H.  
11 pylori infection.

12 You'll see other data will argue with  
13 this, but it looks as if in Japan, you have to  
14 have intestinal metaplasia or at least most of  
15 your gastric cancers occur in stomachs with  
16 intestinal metaplasia.

17 And then nearly all the intestinal  
18 metaplasia seems to be related to H. pylori. So  
19 this is just more evidence that the precursory  
20 agent to the gastric cancer is substantially  
21 caused by H. pylori, at least in Japanese.

22 This final slide just shows some data

1 from Zang, et al. And somebody gave me this  
2 slide. But it looks at the association between  
3 gastric juice vitamin C and CagA. And CagA is the  
4 marker for H. pylori cytotoxin and other genes.  
5 This is cytotoxin associated gene A.

6 And if you have CagA, usually you have  
7 an increased degree of inflammation. An increased  
8 degree of H. pylori colonization and  
9 predisposition towards duodenal ulcer.

10 But I looked at ascorbic acid  
11 concentrations in gastric juice, and you'll see  
12 here that if you have these H. pylori-negative  
13 group and then CagA-negative with gastritis and  
14 CagA-positive with gastritis.

15 So as the -- as you had a more virulent  
16 H. pylori and perhaps more inflammation in your  
17 gastritis mucosa, you ended up with less vitamin C  
18 which is just one thing people have pulled out as  
19 a possible link between cancer and H. pylori.

20 And again, it may be one of the reasons  
21 why we see this which is the final slide. Just  
22 showing the cancer rate in all different --

1 various different countries. This is by the world  
2 health organization. And we've got lung cancer,  
3 liver cancer and stomach cancer. Green is the  
4 liver, red is the stomach, yellow is the lung.

5 And you'll see that some countries with  
6 a very high -- well, let me just take Japan for a  
7 start and you'll see that stomach cancer is more  
8 than 80 percent 100,000 per annum. And so, you  
9 know, Japan is leading the world in stomach cancer's  
10 stakes.

11 Number two in Japan is lung cancer and  
12 then liver cancer.

13 If you look at another country with a  
14 lot of H. pylori, west Asia, and I think this is  
15 actually the middle east, some Arabian countries  
16 around that area, you'll see that they have a lot  
17 of lung cancer, not so much stomach cancer.

18 If you look at India, you got lung  
19 cancer winning again here.

20 Southeast Asia, about 70 percent of the  
21 population with H. pylori, and you see stomach  
22 cancer less than lung or liver.