

1 well the micrograms per mil is of course the
2 aspect of synergy that we measure in vitro has to
3 have a direct relevance to the clinical situation.

4 And the key issue as raised by Dr.
5 Francis Megraud yesterday is what are the
6 clinically achievable levels of the antimicrobial
7 agents at the site of infection including the data
8 that Abbott presented over the last few years
9 clearly shows that this is an achievable level at
10 the site of infection.

11 Just to round off on synergy here where
12 we have a Metronidazole resistant strain, it's
13 again isolated from the normally susceptible
14 strain. We have to use very high -- relatively
15 high concentrations of Metronidazole.

16 But again, both agents on their own do
17 not give total kill. And the two together, we get
18 complete wipeout of even a Metronidazole resistant
19 strain.

20 Now the first suggestion in the
21 literature that the addition of Bismuth could
22 actually prevent the development to resistance was

1 put forward in a paper by Goodwin and Marshall and
2 others in 1988, published in the Journal of
3 Clinical Pathology, where they were looking at
4 therapeutic elements of Cimetidine plus
5 Tinidazole, in comparison with colloidal Bismuth
6 subcitrate and Conitizole.

7 And what they found was that the
8 increased -- they found generally that this
9 therapeutic element of Bismuth plus Tinidazole was
10 certainly more effective than Cimetidine plus
11 Tinidazole.

12 But in terms of modern therapy and
13 co-therapy with Bismuth, the data from NOACH, from
14 Titkat's group in Amsterdam is absolutely crucial
15 in clinical evidence pointing to the fact that
16 Bismuth may actually prevent the development of
17 resistance in *Helicobacter pylori*.

18 What they did from their studies, they
19 found that when they used Clarithromycin on its
20 own with no acid suppression, only two of 19
21 patients had eradication of the organism, 11
22 percent, which is one of the lowest values yet

1 seen with Clarithromycin on its own.

2 In the 17 patients in which there was no
3 eradication, nine of these organisms, 53 percent,
4 became resistant because they established that in
5 the 19 organisms at the beginning, none were
6 resistant to Clarithromycin. So 53 percent of
7 those not eradicated became resistant to
8 Clarithromycin.

9 Though in contrast, when they added
10 colloidal Bismuth subcitrate to the Clarithromycin
11 arm, yes, indeed as one would expect from
12 synergistic activity, they found the increased
13 activities under eradication.

14 But more importantly in terms of effect
15 of Bismuth on the effect of resistance, none of
16 the 16 strains that were not eradicated, the first
17 in "failures," none of those 16 strains became
18 resistance to Clarithromycin.

19 Now we've instituted some experiments
20 within a research laboratory in London where we've
21 taken two strains of clinical isolates of
22 *Helicobacter pylori* and we've subcultured them

1 with and without Ranitidine Bismuth Citrate at
2 doses roughly a half of the MIC. And this is a
3 concentration of Ranitidine Bismuth Citrate that
4 does not markedly diminish the growth rate of the
5 organism.

6 And at various times through 22
7 subcultures, we subcultured every three or four
8 days on agar plates containing the Ranitidine
9 Bismuth Citrate. We looked for the actual numbers
10 of organisms within the population. This is a
11 population analysis of cells that were resistant
12 or susceptible to Metronidazole, Erythromycin or
13 the reference compound, the ammonia galaxide
14 Streptomycin which is not used clinically.

15 Now I shall not show you the data with
16 Streptomycin because we didn't find that
17 Ranitidine Bismuth Citrate had an effect on the
18 frequency of resistance acquisition.

19 However, as shown here, we found a
20 drastic and significant difference with Ranitidine
21 Bismuth Citrate affecting the resistance to
22 Metronidazole and indeed to Clarithromycin.

1 If we focus on this particular strain
2 here, first of all, what we establish from five
3 separate individual observations during those 22
4 subcultures, the average frequency of occurrence
5 of a resistant organism within the population was
6 roughly one in 20 million bacteria.

7 In contrast, when the organisms have
8 been precultured with Ranitidine Bismuth Citrate,
9 the frequency of occurrence dropped by a factor of
10 17, a highly statistically significant difference
11 down to one in roughly three billion bacteria.

12 Now the relevance of these numbers
13 become crucial in terms of some recent
14 observations by Martin Blazer which either have
15 been published or about to be published in the
16 Journal of Theoretical Biology whereby from a
17 basis of his own studies and work published from
18 England a couple of years ago now, they've
19 estimated that the number of *Helicobacter pylori*
20 in a colonized stomach, the entire stomach ranges
21 between ten to the power of seven to ten to the
22 power of ten. So in other words, ten million up

1 to ten billion bacteria.

2 So in other words, if you have only got
3 -- only got ten million bacteria in your stomach,
4 you could perhaps have the chance of having one
5 organism within those ten million that is
6 resistant naturally to Metronidazole.

7 However, if you have ten million
8 bacteria, maybe in the presence of Ranitidine
9 Bismuth Citrate, you do not have sufficient
10 numbers to generate that spontaneous resistant
11 mutant.

12 Now in the case of this other strain, we
13 found that roughly one in 20,000 organisms was
14 expressing resistance, but indeed that dropped by
15 a factor of five when pregrown with Ranitidine
16 Bismuth Citrate.

17 The results with Clarithromycin, we
18 found an eight-fold decrease in this particular
19 strain and a numerical difference with this
20 strain. But, of course, that was not
21 statistically significant.

22 So I'd just like to summarize and

1 conclude that Ranitidine Bismuth Citrate has a
2 true antagonist activity, although I haven't shown
3 that. And it's my personal belief that this is
4 responsible for the potentiation by acid
5 suppression of an antimicrobial agent.

6 The Ranitidine Bismuth Citrate has anti
7 H. pylori activity, which I have demonstrated by
8 the in vitro and in vivo. Of great interest and
9 importance is the synergistic activity with
10 Clarithromycin and other agents, and really of
11 major interest is that Bismuth affects the
12 reduction and the emergence of the frequency of
13 resistance in Helicobacter pylori.

14 I would like to thank you for your
15 attention.

16 DR. JUDSON: Thank you very much. And I
17 think we can open the discussion to any technical
18 questions that people want to get in that are
19 pretty well focused of these preceding speakers.

20 And then we'll go on to a discussion of
21 issue number two in these specific subquestions.
22 So if there are no specific --

1 Yes, Dr. Craig?

2 DR. CRAIG: Does anybody have any
3 population distribution by MIC's for these
4 organisms for Metronidazole, Clarithromycin and
5 also for let's say Amoxicillin so that we know
6 whether we're talking about a single population or
7 where are we dealing with?

8 I'm a little unclear as to what the
9 population distribution of MIC's is.

10 DR. WILLIAMSON: I'd just like to
11 comment very quickly, of course.

12 When you culture so-called resistant
13 organism from a biopsy sample, you will find
14 you're essentially dealing with a population of
15 bacteria.

16 To my knowledge, no one outside of our
17 company has looked to the actual numbers of
18 organisms within a population expressing
19 resistance. And the only way of doing that is by
20 doing total viable counts compared with the number
21 of organisms that you recover on a selective
22 agent.

1 As far as I'm aware, that's some of the
2 first phase that has been presented.

3 DR. JUDSON: Yes.

4 DR. TANAKA: Ken Tanaka, Abbott
5 Laboratories. We do have and have accumulated a
6 significant amount of information on population
7 distributions as Dr. Craig asked, and we don't
8 have it here.

9 DR. CRAIG: What does it look like?

10 DR. TANAKA: Clarithromycin distributes
11 to two distinct populations --

12 DR. CRAIG: Far apart?

13 DR. TANAKA: Far apart.

14 DR. CRAIG: Yeah.

15 DR. TANAKA: Amoxycillin. More or less
16 there is a single population with perhaps a tail.
17 Metronidazole is a single very broad population.

18 DR. JUDSON: Yes, Dr. Kaiser.

19 DR. KAISER: Just a typical question.
20 Nobody has any information that resistant
21 organisms are less virulent, less associated with
22 gastritis?

1 DR. FISHER: Could you repeat the
2 question, Dr. Kaiser. We didn't hear you.

3 DR. KAISER: A little louder. How's
4 this?

5 DR. JUDSON: Good.

6 DR. KAISER: Any data that the resistant
7 Helicobacter are less virulent as if some other
8 vacuoles is present?

9 SPEAKER: That question was asked of Dr.
10 Megraud yesterday I think and I don't think there
11 is any data.

12 DR. JUDSON: Somebody attempting to
13 answer that?

14 DR. GRAHAM: And if you look at cites
15 where cancer and ulcers are very prevalent --

16 DR. JUDSON: Dr. Graham?

17 DR. GRAHAM: -- like Colombia. I mean
18 we found in Colombia 100 percent resistant, for
19 instance, to Metronidazole. And their disease is
20 worse. So I don't think that anywhere we've
21 looked for disease associations, you can't predict
22 disease or recurrence of disease based upon

1 susceptibility of the antibiotics that we've
2 talked about.

3 DR. KAISER: Thank you.

4 DR. GRAHAM: One different issue,
5 though, and that is that when we're talking about
6 MIC's, you really don't know what the bacteria has
7 seen. Because remember, they're in the stomach
8 outside of the body and the antibiotic is put in
9 the stomach.

10 And we do an experiment, for example,
11 where we gave seven milligrams of Furazolidone
12 seven times a day or 49 milligrams total because
13 we calculate that was hundreds fold more than the
14 MIC. And we showed that we could suppress the
15 criteria.

16 So when we're doing these and asking,
17 you know, why does an occasional Clarithromycin
18 resistant organism be killed with Clarithromycin,
19 it may well be that the topical antibiotic in that
20 patient was a critical element.

21 And this makes all of the in vitro, in
22 vivo data interesting and we'll have to do the

1 correlations to ask, what are the real cutoff
2 values that really give us the clinical
3 correlations?

4 DR. JUDSON: I have, regarding that,
5 I've been making an assumption that may not be
6 correct. And that is that any of the Bismuth
7 effect, the heavy metal effect, toxic effect on
8 bacterias is going to be topical, whereas the
9 majority of the antibiotics effect is going to be
10 systemic through absorption, blood flow and, you
11 know, reexcretion diffusion.

12 Is that not correct? Usually we don't
13 think of taking a long-term established infection
14 that seems to be fairly deep in the tissues here
15 all the way down to the stroma, in some cases, and
16 treating with by putting antibiotics on the
17 surface.

18 DR. GRAHAM: We obviously don't know,
19 but you may not need both, some to kill what's on
20 the surface and some different to kill deep
21 because we don't really know the sanctuaries where
22 it grows from.

1 But this bug has challenged all of our
2 preconceived notions in gastroenterology and it's
3 going to do some damage to the ID guys also.

4 DR. JUDSON: So you think the analogy to
5 treating a deeper seated cellulitis by putting
6 antibiotics on the skin would not be completely
7 accurate?

8 DR. GRAHAM: Yeah. I say all bets are
9 off until we get some data.

10 DR. LAINE: But it is interesting that
11 there is the Japanese study where they basically
12 just put balloons in the stomach and put some
13 agents topically. And within an hour or two get
14 -- are able to cure the infection, eradicate the
15 organism.

16 Although if you give Amoxycillin, for
17 instance, you can also get eradication of
18 organisms. So it's confusing.

19 DR. JUDSON: I'm just amazed that for a
20 slow-growing organism like this, it appears to
21 achieve reasonable penetration that you could use
22 a topical antibiotic that may only be at effective

1 concentrations for a couple of hours before or
2 even less before it goes on down the GI tract and
3 is absorbed. That's surprising to me. But --

4 DR. WILLIAMSON: I think I would like to
5 make a comment that certainly if you do have a
6 topically acting agent, it certainly needs to be
7 rapidly sital against the organism because of
8 various situations.

9 I'd just like to add to Dr. Laine's
10 comments, in those Japanese studies, they did use
11 approach litigation to make sure that the
12 integrity of mucus was somewhat reduced.

13 The comment would be though that Bismuth
14 is certainly is going to be acting topically or
15 indeed locally in the stomach. Agents such as
16 Clarithromycin might well be working systemically
17 by passive or active diffusion back from the
18 mucosa.

19 But in the case of freely soluable
20 antibiotics, which Amoxycillin is one, that it
21 could be easily be working either topically or
22 systemically. And it's remarkably difficult to

1 try and analyze which route is necessary.

2 DR. GRAHAM: We must remember too, each
3 time we eat, the mucus on the surface layer of the
4 stomach are shed. So this bacteria is really
5 living in a very inhospitable area, even for
6 itself.

7 DR. VAN ZANTEN: I want to go on about
8 the Bismuth and the working topical.

9 For some of the compounds, there is
10 evidence that you actually do get mucosal levels
11 particularly for colloidal Bismuth subcitrate. So
12 I think Metronidazole and topical is not correct.

13 DR. JUDSON: What do you think the
14 penetration is then? What is the evidence for it?

15 DR. VAN ZANTEN: Well, there's some
16 papers from where a group -- I think in 1992 in
17 gastroenterology, would have done very careful end
18 studies and shown that colloidal Bismuth
19 subcitrate, small particles penetrate between
20 cells at quite deep levels in the mucosa, whereas
21 for Bismuth subsalicylate, that seems to be
22 largely confirmed through the mucus layer.

1 So I don't know about the root being
2 Bismuth citrate. But I think it may just be
3 higher levels, deeper than you think.

4 DR. JUDSON: Okay. Thank you. Dr.
5 Williamson, and then we'll have to go on to --

6 DR. WILLIAMSON: Yes. I'd just like to
7 make a very brief comment about that.

8 Yes, indeed, various sorts of Bismuth
9 can penetrate through mucus, and indeed they can
10 penetrate between the gaps between the cells in
11 the mucosa.

12 However, the extent of absorption of
13 Bismuth is so small that the amount that's in
14 circulation is absolutely totally insufficient to
15 be working systemically.

16 DR. JUDSON: Thank you. Dr. Henry?

17 DR. HENRY: I just had a question.
18 We're hearing a lot about Metronidazole resistance
19 and Clarithromycin resistance. And since there
20 are no NCCLS guidelines defining resistance or how
21 to even do the microbiology, is there some sort of
22 standardization that's gone on among the people --

1 the GI people studying Helicobacter pylori, and
2 can one lab or one group of researchers who have
3 demonstrated resistance to these organisms have
4 their results reproduced in someone else's
5 laboratory?

6 Sort of open to anyone who can at least
7 tell me how the definition of resistance to these
8 drugs was determined, and is there standardization
9 among those studying Helicobacter pylori?

10 DR. JUDSON: Part of that may relate to
11 the questions coming up, or at least people will
12 be able to express their thoughts about how we
13 best grow this organism and measure resistance.

14 Did you have an answer to Dr. Henry?

15 DR. TANAKA: I'd like to address it some
16 way. Ken Tanaka, Abbott Labs.

17 In the Abbott trials, standardization
18 was not undertaken in their regular sense for they
19 were more concerned about the ability to throw the
20 organisms than were more contested, you know, in a
21 standardized manner.

22 We have done comparisons to compare

1 different media for susceptibility testing at the
2 outset of the trials and for most, I assume we've
3 been more or less at the starting point of current
4 NCCLS guidelines as they pertain to other
5 organisms.

6 As a result of the trials, and we could
7 go backwards, redefined new susceptibility break
8 points specific for H. pylori if they differ.

9 DR. FISHER: But TAP, Glaxo Wellcome and
10 Abbott have not exchanged resistance strains and
11 seeing if they have been resistant in their own
12 laboratory facilities.

13 I think that's what you were asking, Dr.
14 Henry. Is that it?

15 DR. WILLIAMSON: I would be gladly
16 willing to supply Abbott with Clarithromycin
17 resistant strains.

18 DR. TANAKA: We've been involved with
19 Dr. Graham's lab and some of the European sites.
20 And we can, in fact, reproduce almost -- generally
21 reproduce the results of relative susceptibility
22 or resistance or sensitivity and lack of

1 sensitivity, if you will.

2 There have been instances where we could
3 not avidly produce results from the clinical
4 laboratories.

5 DR. JUDSON: Thank you. That's
6 reassuring. Now we will go on to attempt to
7 answer for the FDA really five fairly discreet
8 answers, which I think I can put into a binder and
9 reform if they're not already.

10 However, the overall charge is
11 incredibly daunting.

12 How well approval of anti HP regimens
13 affect resistance patterns of HP and other
14 pathogenic bacteria?

15 I think we're going to fall short of --

16 DR. FISHER: Can we give you a "who
17 knows" answer?

18 DR. JUDSON: Answering that in general.
19 Also I will say that several of these questions
20 are really are quite technical. Therefore many of
21 the panel members may choose to simply pass on
22 these and I think that's probably appropriate.

1 I wanted to just perhaps abuse the
2 position of the Chair just for a second to give a
3 little perspective of my own on antimicrobial
4 resistance as it relates to this particular
5 problem and raise a couple of issues.

6 And my experience is probably most
7 connected to sexually-transmitted agents over the
8 last 22 years or so. But I do think that we often
9 have to drop back from the specific organism and
10 the specific disease that we're intending to treat
11 and try to view things in an overall population or
12 even environmental context.

13 I think increasingly, if you were to put
14 on line a new factory that was putting sulfur
15 dioxide into the air or chlorinated hydrocarbons,
16 that there would have to be some sort of statement
17 as to how that's going to affect the overall
18 balance of air pollution and health to humans.

19 I think to the extent that we're
20 contemplating new uses for new and old
21 antibiotics, antimicrobial agents that are going
22 to be potentially for very highly prevalent

1 infections, that the FDA probably has to come to
2 grips a little bit with this new indication may
3 result in a population-based exposure of hundreds
4 of pounds, thousands of pounds, and that the
5 exposure to this new use or to these new agents is
6 probably going to include most of the bacteria
7 that inhibit the mucosal surfaces of large numbers
8 of the population.

9 Now the other perspective I was thinking
10 of or part of it is that we're now four to five
11 decades into the modern antimicrobial era so that
12 -- and H. pylori has presumably been with us much
13 longer than that.

14 So in a sense, some of these experiments
15 have already been conducted and that is if H.
16 pylori has a propensity to become resistant with
17 its self-inhibitory exposure to say Amoxicillin or
18 Tetracycline, gosh, I mean millions and millions
19 of people over decades have had this exposure.

20 So I think our pre-exposure or our pre-
21 treatment susceptibility testing will probably
22 tell us a lot about what we need to know about

1 those levels of resistance.

2 Now the other thing that we often do is
3 that we tend to focus again on the -- or a little
4 disease that we're treating. For me, it's been
5 gonorrhea or chlamydia. And we somehow assume
6 that the CDC's recommended treatment guidelines or
7 FDA's recommended use will determine the --
8 largely the exposure of those agents to
9 antimicrobial agents, and therefore, the
10 likelihood of resistance.

11 Well, I think when we think about it,
12 that's just clearly not true. And most of the
13 exposure, past and future, of H. pylori to these
14 antimicrobial agents will probably not be in the
15 context of specific treatment of H. pylori.

16 And whether it be urinary tract
17 infections, sinusitis -- I was thinking about the
18 resistance levels to Metronidazole. I mean that
19 is the drug of choice for two of the most common
20 conditions of women at -- who would also be at
21 high risk use for H. pylori, that is, bacterial
22 vaginitis and trichomoniasis, the most common

1 sexually-transmitted infestation or infection in
2 the world.

3 And therefore probably it isn't
4 surprising that one of the studies mentioned
5 showed that levels of Metronidazole resistance,
6 pre-exposure, was perhaps higher in women than
7 they are in men.

8 Tetracycline I see is good news. In the
9 winter months, we find as many as ten percent of
10 our general population in STD clinics ranging from
11 15 to 40 years of age were taking Tetracycline.
12 They tend to be younger.

13 But the use and abuse of that agent is
14 just absolutely legion. We treat anybody who
15 comes into an STD clinic and has GC, chlamydia,
16 NGU, PID, exposure to any of those things, with
17 ten days of Tetracycline.

18 I don't doubt that after these
19 deliberations that many of these people are also
20 carrying on their chronic H. pylori gastritis.

21 In terms of surveillance, since this
22 issue is really -- and I want to make sure we're

1 clear on this. We're talking about after
2 approval. You're not asking for how these studies
3 should be conducted, right? Okay.

4 So an example of how one might try to
5 track on what the FDA may actually require,
6 tracking on antimicrobial resistance over time is
7 a -- a potential model is a gynecological
8 surveillance project. There you have huge numbers
9 of infections, a great capacity, great genetic
10 resilience or capacity for developing resistance.

11 So the CDC has set up a program which
12 samples a very small number of patients relative
13 to the whole from different places all over the
14 country.

15 So it is -- the data is timely. It's
16 sufficient sample size. It is representative and
17 it is therefore generalizable.

18 So what FDA may want to consider is not,
19 for instance, saying that the standard of
20 treatment is that anybody who is going to be
21 treated for H. pylori should have pre and
22 post-culture or diagnostic tests and that the

1 organism needs to be isolated to determine
2 susceptibility.

3 But there would be some sort of
4 surveillance if this becomes a very commonly used
5 therapy where a small subsample size around the
6 country is viewed from time to time to keep a
7 check on where we are.

8 And if resistance begins to emerge very
9 quickly, we'll know that.

10 For instance, we just used the gyneco
11 isolates surveillance project to pick up the first
12 cases of Quinolone medium to high level
13 resistance.

14 So I think that's a very good model.
15 That's really my last point except for, I guess,
16 Bismuth. I think the heavy metal approach is in
17 some ways taking us back 50 years, but it gets a
18 pretty permanent mechanism of survival, and
19 therefore resistance may not be lower -- may not
20 emerge very readily to that type of approach.

21 It reminded me, just in closing, of this
22 Charlie Brown cartoon many microbiologists saw

1 about 20 years ago where I think Linus is jumping
2 around on the ground and being asked, "What are
3 you doing?"

4 And he's saying that there isn't a
5 bacteria, and he's stopping. He says, "There
6 isn't a bacteria in the world that's developed a
7 resistance to being stomped on."

8 So if we got back to very affirmative
9 approaches, we may avoid some of that.

10 So let's then go on to take on our first
11 question. And this can be answered in -- yes --
12 further discussion.

13 MS. UTRUP: Yes. I would just like to
14 clarify what the first question means. It really
15 means --

16 DR. JUDSON: You were --

17 MS. UTRUP: Well, a lot of people was.

18 DR. JUDSON: Okay.

19 MS. UTRUP: The question is whether we
20 want to do -- require susceptibility testing in
21 clinical trials for the patients that are entering
22 in the H. pylori clinical trials preimposed era.

1 DR. JUDSON: Okay. So this isn't after
2 approval then?

3 MS. UTRUP: No.

4 DR. JUDSON: Okay.

5 MS. UTRUP: It's now. It's clinical
6 trials.

7 DR. JUDSON: Okay. And --

8 MS. UTRUP: So that's 1A.

9 DR. JUDSON: Okay. So let's turn our
10 thinking back to the clinical trials. And with
11 that, I think I'd like to just call the question
12 and try to keep us on track. And I guess the
13 chairs can answer -- answer that.

14 So Dr. Reller?

15 DR. RELER: Yes or no and no
16 discussion. Clinical trials. Which question?

17 DR. FISHER: Yeah. You're asking 1A,
18 basically. Should we require susceptibility,
19 correct? Should we require susceptibility testing
20 preimposed therapy to determine baseline resistant
21 patterns and to determine if induction of
22 resistance occurs with regimens studied in

1 clinical trials?

2 So start out, in clinical trials --

3 DR. KAISER: I'll vote yes.

4 DR. JUDSON: Or do you want to --

5 DR. KAISER: I'll vote yes. That's easy
6 because Barth takes a while to make up his mind.

7 DR. FISHER: We'll come back to Dr.

8 Reller. Once he does though, it's going to be as
9 clear and as precise as you will get.

10 Dr. Henry?

11 DR. HENRY: The answer is yes.

12 DR. JUDSON: Dr. Kirschner.

13 DR. KIRSCHNER: I'm going to pass, but
14 it would seem to me that maybe certain centers
15 could do this and not all.

16 DR. JUDSON: Okay. Dr. Francis?

17 DR. FRANCIS: I vote no. I could
18 understand the pre-test and susceptibility
19 testing, but I think the post-therapy I think can
20 be better addressed with the surveillance system
21 you talk about and perhaps looking at people who
22 fail symptomatically, that it makes sense then to

1 look at susceptibility.

2 DR. JUDSON: Well, this I think would be
3 in an opportunity to tell up front whether a
4 proposed new regimen would lead to the induction
5 of resistance. And you will be able to tell post
6 from pre.

7 DR. FRANCIS: The difference between
8 genotypic and phenotypic results on this?

9 DR. JUDSON: It will tell whether there'
10 is a genetic propensity for induction or selection
11 of resistance.

12 DR. FRANCIS: I'll abstain then.

13 DR. MELISH: I vote yes.

14 DR. ELUSHOFF: I'm going to pass on
15 this, but I wanted to make a brief comment on
16 something that there hasn't been a space for.

17 In terms of testing whether HP is
18 present or not, some proposals have been made that
19 you might use test A and B, pre-therapy, and test
20 C and B, post-therapy and something else further
21 out.

22 From a statistical point of view, I

1 would like to see the same test being done at each
2 point in time.

3 DR. JUDSON: I appreciate -- I think
4 that standardization obviously is a major
5 challenge for these studies. And we'll leave that
6 to the FDA.

7 Dr. Craig.

8 DR. CRAIG: I would say yes, although I
9 would call it baseline activity, not necessarily '
10 resistance because I think it's only for
11 Clarithromycin that we have evidence that
12 resistant organism results from less response.

13 I'm not sure that we have any data on
14 that with Metronidazole.

15 DR. JUDSON: I think I'll need a little
16 guidance on what's permissible here.

17 Dr. Megraud was kind enough to leave his
18 answers with us. He is no longer sitting at the
19 end of the table.

20 Shall I go ahead and express his
21 answers? Dr. Megraud votes yes for weak. Let's
22 see. Where do we pick up down here?

1 DR. FISHER: Dr. Laine. Dr. Laine.

2 DR. JUDSON: Dr. Laine?

3 DR. LAINE: Like most, I don't know that
4 I have a background, but I'll vote anyway.
5 Actually I think -- I think maybe a limited yes.
6 I don't think you need to do it in every single
7 patient in every single clinical trial.

8 But I think valuable information to
9 gather, kind of like Dr. Kirschner said. And I
10 don't think you need to do it with every
11 antibiotic.

12 But there should be no reason, I think,
13 with Amoxycillin and Tetracycline and things like
14 that right now.

15 DR. JUDSON: Dr. Sonnenberg?

16 DR. SONNENBERG: Similar answer as Dr.
17 Laine. I would say a limited no, though.

18 DR. PARKER: I want to express my
19 support for your standardization. The same thing
20 also just from a purely statistical point of view.
21 I don't know how to do the other one.

22 And also I think the idea of gathering

1 this information in clinical trials is a good one.
2 So I'm voting yes. Let's do this, at least for a
3 while and see what's happening.

4 DR. JUDSON: There's great danger of
5 multiple, non-comparative methodologies entering
6 into this process.

7 Dr. Kaiser has voted yes. Dr. Butt?

8 DR. BUTT: Yes.

9 DR. JUDSON: Dr. Azimi?

10 DR. AZIMI: My answer is yes.

11 DR. FISHER: I'm going to put a limited
12 yes because perhaps knowledge based on the same
13 way that Dr. Laine and Dr. Kirschner did.

14 DR. JUDSON: I vote yes and Dr. Reller?

15 DR. RELER: Everything is hinging on
16 this.

17 DR. FISHER: It's his last leaving.
18 Give him a good chance.

19 DR. RELER: On principle, I mean
20 everyone would say yes. But it seems to me this
21 is premature and doesn't necessarily get at the
22 most important issue at this stage. And I'll tell

1 you why I'm concerned.

2 Bismuth seems to be an important
3 component of many of the successful regimens for
4 eradication of H. pylori which is actually the
5 only clear measurable end point for any of the
6 things we've discussed that we're going after.

7 And for H. pylori resistance to Bismuth,
8 whatever the mechanism of action, has not been
9 described. And there certainly aren't any
10 susceptibility methods that are recognized --
11 generally accepted, at least in NCCLS-types, maybe
12 not necessarily a correlation with resistance as
13 it's been described and clinical efficacy.

14 Amoxicillin we've not heard resistance
15 described. And Tetracycline, it's low.

16 What concerns me more is the issue
17 having to do with approval of multi-drug regimens
18 and I think the need for both safety and efficacy
19 would show that each compound would add something.

20 And when a part of the success seems to
21 be the coupling of a non-antimicrobial or a
22 Bismuth compound, one or the other, with one, two

1 other antimicrobials, that one has that component
2 that would go into the overall success.

3 So what seems to me to be more important
4 are trials that delineate the additive efficacy
5 because to really establish the break points that
6 are reliable and predictive of failure or a high
7 correlation with that or success, the NCCLS takes
8 into consideration multiple things, only some of
9 which have been discussed here.

10 One is population distribution. The
11 other is pharmacodynamics which we have not heard
12 any discussion of with these agents, the clinical
13 trials results and in terms of whether or not
14 there's response to the patients.

15 So it would seem to me that a design
16 where one early on is going to be having
17 endoscopy, that a firm would want to have the
18 organism that's isolated and for the failures to
19 have the organism so that over time, one would
20 have the paired isolates to be able to, as the
21 NCCLS bakes these things and then come up with
22 some reasonable criteria to look objectively and

1 see if there is any correlation. Because if there
2 is no correlation, then susceptibility tests
3 become unnecessary and, at least in concurrent
4 terms and for everyday practices where we
5 eventually want to go with this. And that's why
6 the NCCLS voted not to do susceptibility testing
7 routinely with anaerobic organisms because it
8 became clear that there were so many other factors
9 going on that it wasn't a practical utility and
10 most diagnostic labs don't do it.

11 So I would -- I think it's way
12 premature. I mean the only time I would consider
13 susceptibility testing is in the context of
14 clinical trials. It's way too early for anything
15 else.

16 And in that context, I'm more interested
17 in whether a combination is shown to be
18 efficacious in the eradication and then have the
19 organisms to then have -- the components of the
20 data base, you would need to establish reasonable
21 interpretative criteria for whether or not the
22 organism is susceptible or resistance.

1 But to try to beforehand apply that, we
2 don't have the data base to do that. And
3 consequently, it's a know the way we usually think
4 about it, but I think the organism should be saved
5 so that when the clinical results are available,
6 one can in the failures go back and look and see
7 if there is any correlation.

8 DR. JUDSON: Thank you. That's actually
9 how I was interpreting the question, too. At the'
10 very least in clinical trials, there should be the
11 effort to isolate and preserve these strains. And
12 it may well be that things will be sorted out
13 later in terms of prevalence and mechanisms of
14 resistance than interactions. So multiple drugs.

15 Dr. Craig.

16 DR. CRAIG: I would just -- I find it
17 very difficult to correlate where you're only
18 looking at your failures without also looking at
19 your successes to see what the organism was like
20 at the beginning.

21 So I think -- I agree you learn a lot
22 from failures, probably more than you do from

1 successes. But I think you still need to have
2 some data on your successes to correlate them.

3 DR. RELLER: Bill, thanks. What I'm
4 really trying to say is I do not think the
5 susceptibility testing should be a factor in the
6 entry of patients in the trials.

7 DR. JUDSON: Oh, I don't either. Well

8 --

9 DR. FISHER: We're not asking for that.'

10 DR. JUDSON: It's just -- yeah, it's
11 just saying to determine resistance, not to
12 determine eligibility.

13 DR. RELLER: I understand. The
14 information needs to be -- until you've got the
15 strains and have the clinical data, you cannot
16 establish, you know, the break -- you know, the
17 break points. So that basically the entry and
18 analysis has nothing to do with the break points.
19 It's after the fact that it basically would be a
20 help to establish whether there's any relationship
21 that you get out of the trial, but has nothing to
22 do with interpreting the results of the trials, is

1 what I'm trying to say.

2 DR. JUDSON: I agree with that.

3 DR. CRAIG: That's the way I thought it
4 should be to determine baseline activity. Because
5 as soon as you say, "resistance," then you start
6 getting in the ethical questions of can you enter
7 somebody in if they're starting with a resistant
8 organism.

9 I don't think we know right now what's
10 resistant and what's not. So that's why I would
11 have used the term up there to determine baseline
12 activity because I think that is useful where we
13 are right now.

14 But I would agree that I don't think
15 that you would use that as a justification for
16 entry into the study.

17 DR. JUDSON: Okay. I think we're
18 reasonably clear on that now.

19 And the -- moving on to the next
20 question, there seems to be -- this is which MIC's
21 susceptibility testing methodology. We're given a
22 choice of three here, although this comes up in

1 the next one.

2 It should be considered the method of
3 choice when testing H. pylori isolates in clinical
4 trials.

5 Maybe we can speed this up in one way.
6 I saw no support for a disk at this point. And if
7 we can -- if anybody feels otherwise right now
8 that the disk should emerge as a -- as the
9 preferred methodology, please say so. Otherwise
10 we'll get disk off the table.

11 Any? Okay. Let's come back then to
12 agar dilution versus broth dilution versus E test.
13 And again, it's only probably people who have
14 worked with these methods in laboratories who were
15 really be informed enough I think to vote.

16 Dr. Megraud votes in favor of agar
17 dilution with E test as a second choice.

18 Dr. Reller. We're counting on you
19 again.

20 DR. RELLER: The NC -- the NCCLS people
21 -- CCLS people cannot pass on this.

22 I think to say we endorse one method or

1 another is premature. For example, a current
2 issue of great concern to the NCCLS and of
3 national concern, although it's a limited problem
4 in some areas, is the accurate determination of
5 extended beta-lactamase activities in ecoli,
6 clepsiella and other commonly occurring enteric
7 Gram-negative rods in clinical infections.

8 Now the methodology for detecting that
9 resistance at first pass is by some of these
10 techniques other than disk diffusion. But the
11 committee currently is saying, "Okay. Those
12 techniques delineate what is described and
13 associated with clinical failure and so on, but
14 how can we modify the disk diffusion test which
15 practically is what everybody uses -- or not
16 everybody -- that is commonly used. Let me put it
17 another way, to modify that to be able to
18 accurately detect this mechanism or resistance.

19 And I could imagine the same evolution.
20 I mean the disk test here has gigantic zones. But
21 it's -- but there are not enough data to say that
22 it's, you know, good or no good, I mean.

1 So consequently, I think we should just
2 steer clear of this whole area. What we want to
3 do is have good clinical trials with patient
4 outcome measuring an objective end point and then
5 to have the strains available to make the
6 correlations with all of the components that go
7 in, and then it's a matter of adapting the
8 different techniques to give the same answer.

9 I mean in the end, one would like to
10 juggle the system such that no matter how you did
11 it, if you could do it all by that technique, one
12 would come up with the same answer.

13 So I don't think that we should vote on,
14 you know, individual methodologies because it's
15 premature to either include or exclude any of them
16 with the data that we have available.

17 DR. JUDSON: Actually I now see that
18 almost none of this question has to do with after
19 approval. And we -- I think the real question is
20 do we have anything to offer the FDA or the
21 companies in terms of recommendations for
22 susceptibility testing methodology?

1 And in lieu of that, the FDA is going to
2 have to work it out or the companies are going to
3 have to use everything until we sort out if any
4 one emerges as a superior technology. That's --
5 we can say we don't know.

6 DR. RELER: I would encourage, and I'm
7 sure there's discussion that's taking place and
8 dialogue back and forth. I hope there is.

9 There's a well demonstrated, you know,
10 format mechanism for addressing these new issues
11 as they come up. I mean there's a working group
12 on an extended beta-lactamase testing. There's
13 the expansion of anti-viral testing with NCCLS and
14 so on.

15 And it would seem to me it would be a
16 wonderful opportunity for the scientific expertise
17 within industry, as well as government and those
18 academic centers, research institutes, holding
19 companies, et cetera that has worked in this area
20 to get their people in the context of a working
21 group with NCCLS to come up with the technique or
22 repertoire of techniques that would facilitate

1 clinical trials.

2 DR. JUDSON: Okay. I think that may be
3 a good way to just close on this. We don't have a
4 yes or a no or a name. We're saying that the data
5 at this point is insufficient for even the experts
6 in the area to make a choice.

7 Now Dr. Utrup, I think you have already
8 stated your preference for E-strip, right, or did
9 you?

10 MS. UTRUP: No, I did not.

11 DR. JUDSON: Okay. Do you have a
12 preference? If any of the experts in this area
13 would like to state a preference, please feel free
14 to do so. I, over the years, with organisms like
15 this,

16 Have been most comfortable with agar
17 dilution because of the tremendous experience and
18 reproducibility of that. But I don't know that
19 it's going to be appropriate for this.

20 Dr. Williamson?

21 DR. WILLIAMSON: Certainly everything at
22 Glaxo Wellcome, we only use agar dilution for the

1 principal reason that when you try and grow
2 Helicobacter pylori in microturnative plates, it
3 actually doesn't grow that well. And we find
4 different susceptibility data from the agar
5 dilution.

6 DR. JUDSON: Dr. Craig.

7 DR. CRAIG: Yeah. I think agar dilution
8 from a point of view of being able to do large
9 numbers at one time is, you know, a very nice
10 technique.

11 Obviously, though, for the clinical
12 laboratory, if anything is ever going to get to
13 that stage, that's where the E test I think
14 becomes something valuable.

15 So again, I would be more like our
16 French colleague in terms of favoring the --

17 DR. JUDSON: Further trials.

18 DR. CRAIG: -- dilution and then also
19 the -- test.

20 MS. UTRUP: Would you also favor what
21 Dr. Megraud said in that the clinical
22 investigators at the site do an E test and then

1 send the isolate strips then to a laboratory and
2 have them check by agar dilution?

3 DR. CRAIG: I'd like to see more data on
4 how helpful that is.

5 DR. JUDSON: Yeah, I think that's -- it
6 would be repetitious. You're still going to have
7 to end up deciding what your gold standard is

8 MS. UTRUP: They suggest that agar
9 dilution will eventually -- well, that's their
10 opinion.

11 DR. JUDSON: Okay. All right. We've --

12 SPEAKER: Dr. Judson, could I just make
13 one comment?

14 DR. JUDSON: Yes.

15 SPEAKER: I think that this will never
16 come up after the clinical trials because I don't
17 think that anybody is ever going to culture
18 *Helicobacter pylori* and rarely do susceptibility
19 tests.

20 I think no one could argue with agar
21 dilution as the gold standard, but in fact, if you
22 look at the European papers on E test, that

1 actually is quite nice.

2 So I think either of that --

3 DR. JUDSON: Were you the one who
4 suggested --

5 SPEAKER: -- would be acceptable. Yes.

6 DR. JUDSON: Okay. I'm sorry. I
7 attributed that to the wrong person.

8 Okay. We've discussed the disk
9 diffusion and there's consensus that that isn't
10 ready to go.

11 Then we're on to D. If susceptibility
12 testing of H. pylori in clinical trials
13 demonstrates that certain antimicrobial -- a
14 certain antimicrobial agent has a distinct modal
15 population, should susceptibility break point
16 criteria be established, even though testing
17 methods are not standardized?

18 Dr. Reller? We'll come back to you.

19 Dr. Craig?

20 DR. CRAIG: I'll start off. I would say
21 yes, if you can also demonstrate that clinically
22 that makes a difference. It may be that you've

1 got the two populations, but still a drug is so
2 good and so active at the site that clinically,
3 that doesn't make any difference with a standard
4 dose of therapy.

5 But if it did, yes. I think that then
6 you would have some at least data to establish
7 break point.

8 DR. JUDSON: Dr. Reller?

9 DR. RELER: I don't think any one
10 criterion is enough to have the best predictive
11 value in in vitro susceptibility testing. I mean
12 what we want ultimately is the highest possible
13 correlation with the end point that we're looking
14 for. In this case, it's eradication of H. pylori.

15 Because no matter how much manipulation
16 and fiddling around, I mean one cannot duplicate
17 in a plastic tray the complex milieu we've heard
18 described in the gastric mucosa.

19 What one can do is take what is known
20 about in vitro susceptibility testing and look at
21 it critically in a way that gives one the best
22 predictor of activity or lack thereof.

1 And the bimodal distribution is an
2 important issue that is, Dr. Craig said, it's not
3 the only issue that goes into break point criteria
4 that stand the test of time.

5 DR. JUDSON: Also I think that when
6 you're dealing with chronic populations subjected
7 to lots of environmental pressures over many years
8 and numbers exceeding billions of organisms that
9 you probably got a heterogenous -- quite a
10 heterogenous population.

11 What I worry about here is that we
12 culture it and then we sample a couple of colonies
13 and we end up with a very unrepresentative measure
14 of resistance. That is something that will have
15 to be dealt with, too, in these studies.

16 We've done that many times with
17 gonorrhoea. We've had mixed populations and we
18 didn't realize it because of our very approach.

19 Any other comments on this from the
20 experts?

21 DR. RELLER: I would vote yes, in
22 general.

1 DR. JUDSON: Anyone else have a burning
2 comment?

3 Then the final question, for multi-drug
4 regimens, should synergy testing be recommended
5 for clinical studies or as you have implied, this
6 isn't quite ready for prime time. But --

7 The next thing, Pepto-Bismol with
8 Omeprazole and Clarithromycin.

9 DR. CRAIG: I would vote no. My -- one'
10 of my favorite titles of an article is Dr.
11 Moellering, who has studied this issue so well.
12 And one of his papers was Synergy, an Elusive
13 Concept. And it is elusive. And no.

14 DR. JUDSON: Dr. Megraud also votes no
15 saying because combinations are never truly
16 synergistic or antagonistic in vitro.

17 Dr. Craig? Anybody else along the way?

18 DR. CRAIG: Yeah. I would also vote no.
19 I mean I don't think we have very -- I mean there
20 are only a few situations with other antibiotics
21 where we are -- have been able to show that
22 demonstrating synergy in vitro applies to the in

1 vivo situation.

2 So that again, I would want to see a lot
3 more clinical data supporting the test, if
4 somebody wanted to do it, and be able to clearly
5 show that the synergy was very predictive of what
6 you're going to see, then it might be helpful.

7 But based on what we have right now and
8 what we know before, I wouldn't require it.

9 DR. JUDSON: And we were discussing
10 earlier and I was asking Dr. Fisher to reassure me
11 of my understanding, it's even more complicated
12 here because the activity of so many of these
13 antimicrobial agents depends upon their PKA and
14 the microenvironment and the extent to which
15 they're rediffused and to microenvironment of
16 varying pH's.

17 And here we are using at the same time
18 acid suppressive agents which may be variably
19 affected -- effective in different individuals and
20 it could well be that a treatment success or
21 failure depends not on the antibiotic and not just
22 on the pre-treatment isolate, but on the extent of

1 which the Ranitidine or Metronidazole effectively
2 reduced or increased pH at the time that the
3 antimicrobial agent was being applied.

4 It is incredibly problematic I think at
5 this point.

6 Yes.

7 DR. ELUSHOFF: I thought this question
8 applied to the actual clinical study in that you
9 would test the individuals who tested on not only
10 the multi-drug but the individual ones and the
11 combinations of two and that sort of thing?

12 DR. JUDSON: Well, we were thinking -- I
13 believe we were thinking of microbiology synergy
14 in the laboratory, antimicrobial synergy.

15 DR. ELUSHOFF: It says, "clinical
16 studies." I don't know what they intended.

17 DR. HOPKINS: I think the question
18 refers to in vitro testing. However, we do --
19 would recommend, you know, clinical, you know,
20 business and testing.

21 DR. JUDSON: But you're right. Clinical
22 synergy is going to be different than in vitro

1 synergy and even more difficult.

2 Yes, Dr. --

3 DR. CRAIG: I would say if anybody is
4 going to look at it, specifically it should be
5 done like -- they were -- was done with Bismuth
6 where you're looking at the eradication of the
7 organism, not just the synergy for growth
8 inhibition, since the goal of the therapy is to
9 eradicate the organism.

10 DR. JUDSON: Do you have a comment, Dr.
11 Melish?

12 DR. MELISH: I would vote no for E, that
13 I don't believe the synergy testing should be
14 recommended for the clinical studies. I thought
15 that you were voting.

16 And for the reasons that Dr. Reller and
17 Dr. Craig have mentioned, I think it's
18 interesting if someone wants to do these kinds of
19 microbiologic studies on isolates they get from
20 the patients, but I don't see any reason to
21 require it, and I think it would probably be
22 misleading.

1 DR. JUDSON: Okay. Any other votes?

2 Dr. Fisher?

3 DR. FISHER: I would vote no on that, as
4 well.

5 DR. RELLER: Frank, one analogy that may
6 be of interest. It depends why are we using
7 multiple drugs here.

8 Part of the reason is that they work
9 better because of suspected, you know, inactivity'
10 of one of the other agents.

11 I mean with M-tuberculosis, we always
12 used multiple drugs. But nobody does synergy
13 testing of the components of an anti-tuberculosis
14 regimen, that is anti M-tuberculosis.

15 I will say that the susceptibility basis
16 behind multiple drug treatment of TB seems
17 relatively straightforward now compared to this.

18 DR. JUDSON: We can do it in a
19 laboratory. We know rates of mutation. We're not
20 mixing in other drugs that activity
21 physiologically, completely differently.

22 I never saw that as simple before until

1 the last few days.

2 DR. AZIMI: Dr. Judson?

3 DR. JUDSON: Yes, Dr. --

4 DR. AZIMI: I'd like to make a comment
5 about all of these.

6 I really firmly believe -- in agreement
7 with the statement that was made that in treating
8 patients, these sorts of tests are not going to
9 done; that the organism -- that there is going to
10 be a screening test for H. pylori. And if that's
11 positive, the patient is going to be treated. And
12 people are not going to be doing susceptibilities.

13 And for that reason, I feel like any
14 information that we can get from clinical trial is
15 going to be all that we're going to have.

16 So I feel like even though many of these
17 may not be applicable to treatment, I think it
18 will give us information.

19 It's not only as interesting, but we can
20 interpret it after we have the results of these
21 information. So there is nothing wrong with doing
22 a lot of these things, including synergy, during

1 the clinical trial because that's the only time
2 we're going to have access to any of this
3 information.

4 DR. JUDSON: Well, let's --

5 DR. AZIMI: It's not going to come
6 afterwards.

7 DR. JUDSON: That's an interesting
8 point. Good point.

9 DR. KAISER: Frank, just a comment about
10 compliance of patients in medication -- in taking
11 different regimens.

12 This may have been discussed yesterday,
13 but -- and I don't know the FDA guidelines
14 regarding intention to treat requirements for drug
15 studies across the board.

16 But it seems that we have some problems
17 in compliance which have been demonstrated in
18 previous published trials. They had some
19 insistence upon intention to treat protocols be
20 important in evaluating this particular therapy
21 for this particular agent.

22 DR. JUDSON: I also think myself about

1 the compliance issue, that we, in fact, don't know
2 what compliance is for most regimens, especially
3 those that go on towards two weeks. So that isn't
4 anything that's going to easily resolved here or
5 elsewhere.

6 The best we'll do is in these studies,
7 we'll come up with an efficacy rate.

8 The use effectiveness studies will
9 probably have to come later when people are not
10 being paid to comply or otherwise induced to
11 comply with the regimens.

12 DR. KAISER: Well, I can envision
13 regimens that are double-blind and -- so both
14 investigator and patients are blinded to the
15 therapy where this could be looked at.

16 And my concern is that you could give
17 Clorox to patients that eradicate the organism,
18 but compliance will be poor. And the volume
19 reported was success rates that would a little
20 good.

21 So I -- somewhere in all of this, that
22 has to be factored in. And I don't know if this

1 is the drug and the germ to start with or not.
2 But it seems to be an important consideration.

3 DR. JUDSON: Well, I hope here that
4 maybe the interest of the pharmaceutical companies
5 coincides with our desires to understand
6 compliance because one would hope that they
7 wouldn't be attempting to study regimens that they
8 know have 50 percent vomiting rates or whatever,
9 or were the gastritis induced by the antimicrobial
10 agents worse than the original H. pylori. So
11 that's up to them.

12 Okay. I think we've concluded with
13 issue number two and we now have scheduled an open
14 public hearing. And there is but a single
15 request, and that is Dr. Graham. And you now have
16 the floor. And you have the pressure everybody in
17 this audience who is worried about departing
18 flights and --

19 DR. GRAHAM: The -- I'm going to be
20 brief.

21 DR. JUDSON: We're counting on it.

22 DR. GRAHAM: It was interesting to

1 listen to the previous discussion about the use of
2 antibiotics, though, and I think antibiotics were
3 given for fever.

4 I saw an advertisement yesterday, a
5 cartoon, that said, "If you think you need
6 antibiotics, just eat some beef." So it's a
7 bigger problem than we want to admit.

8 I want to bring us back to the patient
9 and if I can figure this thing out.

10 Let's talk about the disease that the
11 gastroenterologists used to take care of when it
12 existed: Peptic ulcer disease.

13 Now remember again that one in six
14 people with the *Helicobacter pylori* infection
15 develop a peptic ulcer. And of those, ten to 20
16 percent will have a life-threatening complication
17 of ulcer disease.

18 Everybody that has it essentially
19 experiences morbidity such as pain and inability
20 to sleep, lost days from work, you have to take
21 medicines and go see doctors and get tests, et
22 cetera.

1 So it's not a trivial disease. It's
2 only thought to be trivial by academic physicians
3 who don't see the patients. So no one wants their
4 ulcer disease. And find the most grateful
5 patients will tell you they really didn't
6 recognize how much of this disability they had
7 until they got rid of it.

8 So our goal to treat this infection is
9 to cure the infection, which of course, cures the
10 ulcer disease and at least prevents ulcer disease
11 from recurrence if it was caused by that. And
12 there are unfortunately more than one cause of
13 ulcer. And it prevents ulcer complications.

14 The gastritis, of course, heals but it
15 may not return to normal, depending about how bad
16 it was. And I understand yesterday, you talked
17 about the expectations, and we want to cure 100
18 percent. But as we all know, we're not at that
19 stage yet.

20 Now what are bad things that happen?
21 Well, the first thing we learn that different,
22 seemingly identical, protocols gave different

1 results. And somebody in one place would get a 90
2 percent cure rate and somebody else in another
3 place would get a 20 percent cure rate. And this
4 is just not what you'd expect with an infectious
5 disease.

6 You expect if someone treats a urinary
7 tract infection with a susceptible organism in
8 Moscow and in Ohio, they get the same results, and
9 at least similar results.

10 And we're getting these remarkably
11 different results with some therapies and we
12 really don't know why. And it's interesting, when
13 we start looking at those in durations and
14 formulations, we really haven't come up with
15 answers.

16 So this is a new approach and it's
17 gotten more surprises for us in the future.

18 What does the failure to cure mean? So
19 if you put a patient in a study and he fails, it
20 means to the patient that they still have that
21 disease and they're going to need to be retreated.
22 They need more tests and more drugs and more lost

1 time from work and more pain. And they have other
2 risks, continued risks for major life-threatening
3 complications from their underlying disease.

4 It's Dr. Elushoff's data from the past,
5 it's about two and a half percent per year will
6 have a life-threatening complications. And if
7 they have never had one before, that doubles if
8 they'd had one before, and it goes up to about one
9 percent per month if they have had a recent
10 gastrointestinal bleed.

11 And so the patient who fails not only
12 have -- fails therapy, but has tremendous risk,
13 and in fact, may die because of the disease that
14 we didn't cure. So we can't just put them in the
15 category of failure.

16 So this has, I think, a major impact
17 upon the way the FDA has looked at drugs in the
18 past, and I think we have to look at this disease
19 in a different way. And just the outcome for an
20 individual patient with failed therapy is probably
21 not that much different for a syphilis patient.

22 So if we took a therapy -- I've got here

1 the newest therapy which is a macrolide, a PPI, a
2 new drug, Helacomycin, and we say that is one of
3 the options. And the FDA would in the old days
4 say, "There's seven options. Let's look at them
5 all."

6 And the factors that one must consider
7 to decide, I think what ones you've wanted to test
8 would be the cure rate, whether there was a
9 propensity to develop resistance or whether there'
10 was a propensity for other organisms to develop a
11 resistance, and of course, side effects. And
12 let's look at some of those briefly.

13 Here I've listed those seven where they
14 were given me of a cure with no side effects and
15 no resistance at best and no cure, lots of side
16 effects and development of resistance that's
17 worse. And you can list only probably the first
18 four would be even acceptable, and most of those
19 are not very acceptable.

20 Now we know what's going to fail before
21 we start therapy in most instances. We know, for
22 example, that we're not going to cure anybody with

1 an H2 blocker or proton pump inhibitor or a
2 sucrofater with -- really with Bismuth, we might
3 cure 10 percent or with all of the antimicrobials
4 tested today.

5 So we know that monotherapies with those
6 are destined to leave our ulcer patients with
7 their disease.

8 If we took it too currently, what were
9 called good protocols, that would be the mark or
10 the Metronidazole, Omeprazole, Clarithromycin or
11 the traditional triple therapy Bismuth,
12 Metronidazole, Tetracycline, it would be rapidly
13 apparently when you look at the previous criteria
14 that it would be inappropriate to look at any of
15 those subgroups because we could assure with any
16 of the subgroups that would have a low cure rate
17 with Clarithromycin and Metronidazole a high
18 frequency of development of resistance and that
19 those are predicted beforehand saying that those
20 would not be intelligent things to do, at least
21 from the patients' perspective.

22 If we looked at Omeprazole,

1 Clarithromycin the same way, we can know that we
2 can have low cure rates or high resistance rates
3 for both or when we use them as monotherapies.

4 So therefore the patients, when they got
5 these therapies and got those individual ones,
6 many patients may have suffered either now or in
7 the future, and the answer is, "The FDA made me do
8 it," which is really not true. The drug companies
9 did it without fighting that battles with the FDA'.

10 But Dr. Fredd can take credit for it up
11 until now, but the ID side has to take credit for
12 it in the future.

13 Now what does it mean to that patient
14 who had failed? Let us say the patient was on one
15 of those studies and received either
16 Clarithromycin or the PPI. Now the patient gets
17 more endoscopies. He got two at least with the
18 study that was known to be low cure rate
19 associated with sedation and risk and lost time
20 from work, et cetera. They took the experimental
21 drug that they would know that probably wasn't
22 going to benefit them but may have untoward

BETA REPORTING

(202) 638-2400

1-800-522-2382

(703) 684-2382

1 events, and then they end up with the infection
2 that's not cured and need a retreatment, possible
3 a development of resistance HP, but the possible
4 development of other resistant organisms in their
5 body which may come to haunt them later on in
6 their lives. So there's no benefit for the
7 patient to have gotten into that study.

8 So I think if you're going to require
9 that, you need to put a sentence like this or
10 sentences like this in the consent form.

11 It says, "If I randomized to receive
12 either Omeprazole or Clarithromycin alone, I
13 understand that the rate of cure will be either
14 low or extremely low and that I may develop a
15 strain of H. pylori that is resistant to the
16 antibiotic used.

17 "Development of resistance may make
18 eventual cure of my infection difficult or
19 impossible. Additionally, there may -- is a
20 possibility that I may transmit the resistant
21 organism to others."

22 DR. JUDSON: Where do we sign up for

1 this?

2 DR. GRAHAM: I mean they should have put
3 this in -- "I refuse to be part of some of these
4 trials because I thought that they were not
5 necessarily to the patients' benefit."

6 So how do we tell if we're going to do
7 these studies actually up front?

8 One way, of course, is just -- see if
9 the organism is resistant in vitro, and you
10 wouldn't want to test that.

11 But as a monotherapy, you can ask
12 whether it's resistant in the laboratory? Can we
13 make it resistant or we can test isolates in the
14 community and see if there are any resistant. And
15 that would be hard to find, for example, with
16 Clarithromycin because it's about three percent
17 and it means, statistically if you tested 20 or
18 30, you may not pick it up.

19 I'm almost finished. So I think that we
20 should start with what we've learned and we don't
21 test the predictable failures. We need to look
22 for the resistance both in vitro and in vivo, and

1 we could also get some idea how it works by
2 looking at how, on patients, it was used before.

3 For example, a patient has pneumonia and
4 they use this antibiotic initially for pneumonia.
5 If they have serum available, they can ask whether
6 that patient was infected, and then they can just
7 do a breath test.

8 Now it asks whether that patient has
9 been cured. So you're doing an H. pylori
10 treatment on patients. Every time you're treating
11 them for something else, it's no need to throw
12 that data away on a prospective way.

13 And otherwise you can do a pilot study
14 in a small number of patients, but they shouldn't
15 have peptic ulcer disease because the peptic ulcer
16 disease patients have failed. Remember they have
17 all these bad things that can happen to them or
18 the asymptomatics. At least we don't know that
19 they're at high risk for these other problems.

20 And this slide shows the 95 in yellow
21 and the percent confidence limits for failures.
22 If you just look at ten patients, so you have one

1 failure, two failures, three failures, four
2 failures, five failures, six failures, et cetera
3 and it's easy to see if ten patients, if you have
4 four or more -- if you have less than four or more
5 successors that there's no need to even consider
6 that.

7 Now in a lot of therapies we looked at
8 that looked very good in vitro, and when we tested
9 them, their cure rates were zero. And it doesn't
10 take 50 or 100 patients to prove zero.

11 The last step, I'm going to just briefly
12 -- I understand there were some questions about
13 the breath test and I'll just show the data that
14 we have. And when we did our initial study
15 recently to ask what the cutoff value was, we did
16 60 infected and 60 uninfected, three doses of C-13
17 urea, 125 and 250 milligrams.

18 And it turned out that with a cutoff
19 value of .4, we got 100 percent specificity and
20 sensitivity.

21 And that was used in the subsequent
22 clinical trials. And you saw some of this data

1 yesterday from Abbott. When you look at a study,
2 the pre-therapy, where almost everyone's infected
3 and you have almost no true negatives, it's hard
4 to analyze the positive and negative predictive
5 values.

6 It's much easier later when about half
7 are infected and half are uninfected like in a
8 general population.

9 Here we get 92 percent, if you like
10 accuracy. Here, it goes up, and here, it's in the
11 90 plus percent sensitivity and specificity.

12 And then in Los Angeles, they've
13 recently done a similar study with 141 patients
14 and were presented recently at the American
15 College of Gastroenterology with similar
16 sensitivities and specificities.

17 So the test in everybody's hands and all
18 forms, words, it's hard to screw it up unless the
19 person administering it screws it up or the
20 patient takes some kind of antimicrobial before
21 they get it.

22 And with that, I'll stop.

1 DR. JUDSON: Thank you very much. I
2 have just a couple of concluding comments.

3 For those of you who want to recycle,
4 there's a box at the door before you exit. And
5 then finally, I'd like to take this opportunity to
6 thank for their many contributions my Co-Chair,
7 Dr. Fisher, who's about to depart, the committee
8 members, guests, consultants and in particular,
9 the FDA for their typically excellent preparation.

10 Thank you very much. We're adjourned.

11 (Whereupon, the hearing was
12 adjourned at 3:00 p.m.)

13 * * * * *