ORIGINAL

UNITED STATES OF AMERICA
BEFORE THE FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

In the Matter of:	:	
Enrofloxacin for Poultry: Withdrawal of Approval of Bayer Corporation's New Animal Drug Application (NADA) 140-828 (Baytril)	:	FDA DOCKET NO. 00N-1571

Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland

Thursday, May 1, 2003

THE HEARING in the above-entitled matter commenced at 9:30 a.m., pursuant to notice.

BEFORE:

DANIEL J. DAVIDSON, Administrative Law Judge

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00N-1571

~~FR 4~~
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C O N T E N T S

P R O C E E D I N G S

JUDGE DAVIDSON: Good morning. Let us come to order. We may all be seated.

Any preliminary matters?

Mr. Krauss?

MR. KRAUSS: Gregory Krauss. I'm here on behalf of the corporation.

Just to let Your Honor know, yesterday we did play the track from -- the exhibit for Dr. Angulo, and I asked him whether it sounded like his voice and he agreed that it did sound like his voice.

JUDGE DAVIDSON: Did he then give you the same explanation he gave us several times yesterday, or was that over with, too?

MR. KRAUSS: That's all there was to it, Your Honor, in the conference room based on the agreement of counsel --

JUDGE DAVIDSON: That's fine.

MR. KRAUSS: The impact of that Your Honor is we would like to call Dr. Angulo because his -- and recross on this limited issue because -- if it's his voice what he says on the tape is a prior inconsistent

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statement with his testimony, and we are entitled to impeach him on that.

What he said in the scientific ~~norms~~ NARMS meeting which he testified he was attending in his capacity as the branch chief for FoodNet and NARMS is inconsistent with his testimony with respect to the representativeness of the campylobacter sampling ~~scan~~ scheme.

JUDGE DAVIDSON: Do you have a comment?

MR. SPILLER: First I would like to join in Mr. Krauss' recitation that the conversation yesterday indicated that Dr. Angulo did confirm that sounded like his voice.

Whether it requires any additional testimony, I don't think so. I think Your Honor's order yesterday was that the witness was excused subject to that listening to that tape and the answer to that question, which has been accomplished.

Certainly if there were any contention that that is a prior inconsistent statement I believe it is not and I believe the witness has explained that.

But if it were a prior inconsistent statement the allegation of inconsistency has been more than

adequately dealt with already by questions and answers by this witness yesterday already on the record.

MR. KRAUSS: Your Honor, may I?

JUDGE DAVIDSON: A response to a response? I don't think so.

The way I see it, the fact that the witness was excused doesn't mean that -- he's here in the room, and I could recall him if I want to.

But even though you didn't use the words yesterday it was fairly clear, Mr. Krauss, that you were driving towards a prior inconsistent statement. Anybody who's following this case at all would have known that's why you're asking those questions about that particular statement.

The witness explained several times how that came about. I don't know if you're old enough to remember Judge Henry Friendly, but one of my favorite quotes is from the first case I handled when I came to the Food and Drug Administration back in 1975. It was a remand from the court Judge Friendly sat on, and it was remanded because the judge that the FDA had borrowed to handle the first part of that -- right in

the middle of the hearing -- wouldn't allow a particular person to cross-examine the star witness for the government.

Judge Friendly said "You can't do that." He said "Even though what most trial lawyers had learned through sad experience, the dreams of confounding expert witnesses on cross examination usually are dreams, indeed."

So I'm satisfied that the record adequately reflects the fact that your position is this is a prior inconsistent statement. It's in the record -- you probably -- they may have moved to strike it. It's not stricken.

The witness has been asked more than once if he remembered. First he said he didn't recall. Then he said yes it refers to his recollection -- these may not have been his exact words but he then went on to explain why he believed that wasn't inconsistent -- even though neither one of you used those terms.

So I'm satisfied the record adequately covers that, and we don't have to go into it anymore.

MR. KRAUSS: Thank you, Your Honor.

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MR. SPILLER: Thank you.

JUDGE DAVIDSON: Ready for the next witness?

MS. ZUCKERMAN: Yes, Your Honor.

The Center for Veterinary Medicine calls Dr. Kirk Smith.

Your Honor, may I approach the witness?

JUDGE DAVIDSON: Certainly.

Dr. Smith, raise your right hand, please.

Whereupon,

KIRK SMITH

was called as a witness and, having been first duly sworn, was examined and testified as follows:

JUDGE DAVIDSON: Please be seated and give your name and address to the reporter and then await Ms. Zuckerman.

THE WITNESS: My name is Kirk Edward Smith. My address is 164 Green Briar Drive, Lino ~~Greenbriar Drive, Lionel~~ Lakes, Minnesota 55014.

MS. ZUCKERMAN: I am handing the witness Exhibit 1473.

DIRECT EXAMINATION

BY MS. ZUCKERMAN:

Q Dr. Smith, do you recognize this?

A I do.

Q Would you please identify it?

A It's my written direct testimony in this matter.

Q Would you please turn to page 21.

Is that a copy of your signature?

A It is.

Q Thank you.

MS. ZUCKERMAN: This witness is ready for cross examination.

JUDGE DAVIDSON: Please proceed.

Mr. Nicholas?

MR. NICHOLAS: Thank you, Your Honor.

My name is Robert Nicholas and I represent Bayer Corporation in this matter, and I'm going to be conducting cross examination.

CROSS EXAMINATION

BY MR. NICHOLAS:

Q I want to ask a question before we begin with

respect to your testimony. Is there anything in your testimony that you believe is inaccurate or you'd like to correct at this time before we begin cross examination?

A No, sir.

Q Thank you.

Dr. Smith, you are a doctor of veterinary medicine and have an M.S. in veterinary preventive medicine, a Ph.D. in veterinary parasitology, that's correct?

A That's correct.

Q You currently work at the Minnesota Department of Health, which you joined I believe in 1998?

A Correct.

Q And from 1996 to 1998 you were at the Centers for Disease Control?

A Correct.

Q You're not a medical doctor, that's correct?

A That's correct.

Q And you do not have advanced degrees in human medical microbiology or in epidemiology, do you?

A Well, the master's in veterinary preventive

medicine should be considered a degree in epidemiology.

Q You're not a poultry veterinarian?

A That's correct.

Q In the c.v. that was presented attached to your testimony you stated that you served as a reviewer for several peer reviewed scientific journals, correct?

A Correct.

Q Would you generally describe to me -- your role as a reviewer of medical journals -- veterinary journals?

A Sure. In the review process you usually get sent an article to review by the editor or an assistant editor of the journal and usually they have objective criteria -- how do you rate this journal, should it be published -

Q I'm sorry, how do you rate this journal or this article?

A Sorry -- how you rate the article -- thank you.

And then you go through the paper and critique it and list out and explain areas that you think need improvement.

Q Do you generally get the protocol for the study when you're reviewing the study?

A The protocol -- that's one of the things you critique -- the protocols should be adequately described in the methods section of the paper such that anybody could repeat the study.

Q But you don't physically receive a copy of something entitled protocol?

A That's correct.

Q You don't know when the protocol was originally put together, you don't know what amendments there might have been to the protocol -- what you received is the journal article?

A That's correct.

Q I assume from that statement that you don't receive a copy of the raw data -- if it was a case -- an article -- involving isolation of campylobacter or prolonged resistance to campylobacter, you would not receive duplicates of the isolates, you would not receive the data sheets -- basically you receive the article when you act as a jurist?

A That's correct.

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Q If you could just generally tell me how much time one spends reviewing an article of five or six pages -- seven or eight pages?

A When I do it I spend probably several hours, four or five hours.

Q Would it be fair to say you were a relatively young reviewer in terms of your experience with respect to epidemiology and medical matters -- human medical matters?

A "Fairly young" is a subjective term but -- I agree.

Q How long have you been a ~~review~~ reviewer of these kinds of journals? Particularly epidemiology studies.

A Ten years. About 10 years.

Q So you were reviewing these kinds of articles subsequent to going to CDC and you were reviewing them before you went --

A Even before.

Q When you're reviewing these kinds of articles, since you don't have the raw data, you don't have the protocol, you have just what's in the article, you don't know what statistical techniques might have been

considered by the author other than those that are presented in the analysis, is that correct?

A The methods section should say, and they always in my experience, say what statistical methods were used to achieve the results.

Q But you don't know whether in fact they've used alternative statistical techniques to determine what analytical technique might in their view best fit the data or confirm or deny their conclusions?

A I suppose that's technically true although you should have your statistical methods laid out before you do the analysis of the study.

Q Did you have a protocol in your study in this -- I'm sorry.

Let me identify for the record G-589, which is entitled "Quinolone-resistant Campylobacter Jejuni Infections in Minnesota 1992 -- 1998" and let me provide you with a copy of that. I have a clean copy without my notes on it this time.

Dr. Smith, did you have a protocol for that study? A written protocol?

A The protocol is described in the methods

section of the paper.

Q In your testimony I believe you said you started that study in 1996, is that correct?

A That's correct.

Q Did you have a protocol prior to commencing that study? A written protocol, a ~~former~~ formal protocol, that had been reviewed and had set forth in it the plan of data collection, the analysis that was to be conducted, the statistical techniques.

My question is, when you began that study did you have such a protocol?

A We did not have a formal written protocol. The study design was discussed and the questionnaire would be the formal tool that was used. But there was not a formal written protocol as you described it.

Q Would you consider it generally good scientific practice to have a formal written protocol that described data collection methods and analytical techniques that you used in this study, the hypothesis that was you were trying to test in that study -- had all of those defined up front in a document?

A I would describe that as good, yes.

Q With respect to that particular article which was in the New England Journal of Medicine -- that is a peer reviewed journal, correct?

A Correct.

Q And so your article was subject to peer review as I understand it -- and you did not provide, did you, the protocol to the researchers other than what's in the paper. You did not provide the questionnaire, you did not provide your statistical analysis -- you provided no data to the reviewers other than what was in the paper?

MS. ZUCKERMAN: Objection, Your Honor. That's a compound question.

MR. NICHOLAS: Your Honor, I can ask these serially. I'm trying to speed up the process. If the witness wants to respond individually that's fine.

JUDGE DAVIDSON: All right, well, ask it again.

You don't have to break it up for each one of them but -- too much -- you've just got too much in there.

Also, to the extent that you haven't already

covered it -- if you do have it --

MR. NICHOLAS: Well, I do have it with respect to the --

JUDGE DAVIDSON: Excuse me.

MR. NICHOLAS: I'm sorry, Your Honor.

JUDGE DAVIDSON: You didn't have a written protocol. I don't believe he could furnish it to anybody.

MR. NICHOLAS: That's correct, Your Honor.

JUDGE DAVIDSON: And yet you asked him "you didn't furnish a written protocol," which is an unnecessary question.

MR. NICHOLAS: Sorry, Your Honor.

JUDGE DAVIDSON: So you'll have to do each one in serialized form. But you can break it down so it's a little easier for the witness to answer.

MR. NICHOLAS: I will rephrase the question for Dr. Smith.

BY MR. NICHOLAS:

Q Did you provide data other than the written article to the reviewers of the article?

A No.

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Q Thank you.

Now, as I understand it, in January 2001 you were contacted by Nathan Beaver, who is an attorney who works at McDermott, Will and ~~Embry~~ Emery, requesting the raw data and the questionnaire to your study, do you recall that?

A I don't know if that's the exact time -- I talked with Mr. Beaver -- many times. But he did request those items.

Q As I understand it, you informed Mr. Beaver that if he wanted any of those materials he had to file a request under the Minnesota Data Practices Act, is that correct?

MS. ZUCKERMAN: Objection, Your Honor. This is beyond the scope of the witness' testimony.

MR. NICHOLAS: Your Honor?

JUDGE DAVIDSON: Go ahead.

MR. NICHOLAS: What we're going to demonstrate, Your Honor, is that we attempted to get all of the underlying data from the State of Minnesota in order to conduct our analysis of these data. These data are represented under various witnesses'

testimony.

The question of the credibility of these data and the conclusions drawn is what's directly before the Court at this moment. We want to lay the foundation for how they got the information and what information he got and what information he did not get, Your Honor.

JUDGE DAVIDSON: My question is did you get the information they received?

MR. NICHOLAS: We didn't get it all, Your Honor.

JUDGE DAVIDSON: If you didn't get it, then that is what you put on the record what you didn't get. And I have to draw my conclusions of what impact that has on the -- conclusions -- drawn by the various witnesses and various studies.

If you did get it then you had it.

MR. NICHOLAS: That's correct.

JUDGE DAVIDSON: And what are we doing here now?

MR. NICHOLAS: I'm just trying to establish what we did get from the witness so we have a common ground to go forward. And then what we did not get from

the witness Your Honor.

I can rephrase and ask him just about what we did not receive. I'm happy to do that if that would please the Court.

JUDGE DAVIDSON: Have you indicated for the record what you did receive in the past?

MR. NICHOLAS: I'm not sure, Your Honor. There are some documents in the record that -- discuss back and forth but I'm not quite clear on that at this point.

JUDGE DAVIDSON: I don't think that it's appropriate for you to get it from this witness in this kind of form. Go ahead with what you were going to do -- ask him about what you didn't get -- but what you did get -- if you haven't put it in the record already, you may ask for permission to do so later.

BY MR. NICHOLAS:

Q Dr. Smith, do you recall whether Mr. Beaver requested the duplicates of the isolates from you?

A No, sir.

Q Did you provide them?

A No.

Q Do you recall that in Mr. Beaver's request that he specified that the isolates were going to be used in part, were needed in part, in order to do genetic typing of the isolates and otherwise to examine them with respect to the filing of the NOOH, by FDA concerning the attempt to remove the withdrawal of the approval for fluoroquinolones in poultry and enrofloxacin?

A I don't recall that specifically.

Q If I showed you a letter that you were copied on that was the appeal filed with the commission -- would that refresh your recollection?

MS. ZUCKERMAN: Objection, Your Honor. It is not even clear whether this witness is responsible for requests at the State of Minnesota. Again this seems to be far beyond the scope of his testimony.

JUDGE DAVIDSON: Where are you going, Mr. Nicholas?

MR. NICHOLAS: Dr. Smith was involved in all of these discussions Your Honor. He advised Mr. Beaver that he could not -- release them. He filed an appeal. Dr. Smith was copied on the appeal. These documents are

in fact in the record. Mr. Smith is well aware of these facts Your Honor.

JUDGE DAVIDSON: But what are you doing now?

MR. NICHOLAS: I'm -- trying to attempt to establish Your Honor is that the isolates were not provided to Bayer Corporation and in fact it was explained that these isolates were requested specifically in part to be able to respond --

JUDGE DAVIDSON: Why don't you just ask him if he knows whether -- they were in fact furnished and we can move on.

MR. NICHOLAS: Okay. Thank you Your Honor.

BY MR. NICHOLAS:

Q Mr. Smith, do you know in fact whether the isolates were provided by the State of Minnesota to McDermott, Will & Emery?

A I know that they were not provided.

Q Now Mr. Smith -- Dr. Smith, rather -- I'd like turn to your testimony if I may, on page 2 line 25 -- 29. You state that there are several reports -- this is by 1996 -- several reports had been published in the scientific literature indicating that fluoroquinolone

resistance among human isolates of campylobacter was rising in Europe.

And you said some of these reports indicated that animals were the driving force. Could you identify those reports, please? What reports you were relying on? There's no citation for this paragraph --

A Right.

Q -- so I'd like to establish what scientific reports you were relying on when you made this statement.

A On page 21 of my testimony there's a reference number four that I use as a chapter that I wrote on microbial resistance in campylobacter. And those studies are cited within that chapter. There are studies from the Netherlands, Spain, the United Kingdom.

Q What is the date of that chapter?

A It was written -- or published 2000. May 2000.

Q The studies that were specifically identified -- I'm sorry, would you repeat those again, please?

A There were studies from the Netherlands --

Q And so then --

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A -- with a primary author, and from the United Kingdom, studies of various authors, ~~Pyddie~~ Piddock, ~~Gunn~~ Gaunt, and ~~Thruolphal~~ Threlfall, and then Spain --

Q Could I ask you -- does ~~Thruolphal~~ Threlfall involve salmonella or campylobacter?

A Well, both.

Q You did not have a written protocol when you commenced the study. Was there ever a written protocol for this study or amendments to a written protocol?

A Not as you described it.

Q When you decided to conduct the study reflected in the New England Journal of Medicine article at G-589, you began that in 1996 -- the beginning of 1996 I believe you testified -- at that point you were looking and collecting human isolates of campylobacter, is that correct?

A Correct. But that process was independent of the study. We did in the study.

Q I think you have described this study as -- you conducted a case comparison study of patients with ciprofloxacin resistant campylobacter jejuni, during 1996 and 1997 -- domestic chicken was evaluated as a

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potential source of quinolone resistance, is that correct?

A Correct.

Q But in your testimony you basically state the purpose ~~Pro-crit~~ as broader, I believe.

So if you turn to page 4 of your testimony, line 36 -- I believe it says "to define clues as how, where and why people become infected with quinolone-resistant campylobacter jejuni we evaluated Minnesota residents" and so forth and so on.

Further in that paragraph on line -- 40, to paraphrase, you interviewed patients with a standardized questionnaire that contained questions about various antibiotic use, illness clues -- and you concluded by saying "anything that might have yielded clues as to what was the source of their infection and why campylobacter they acquired was resistant to quinolones." Is that correct?

A Yes.

Q So that the purpose of this study was really to look broadly -- not just in poultry -- was to look broadly as to what were the risk factors for acquiring

campylobacter jejuni infections for Minnesota residents whose isolates had been collected in 1996-7, is that correct?

A I would qualify that a little bit. The purpose was to look at those factors for quinolone-resistant campylobacter.

Q The study as you described it involved 130 patients with quinolone-resistant jejuni infections in 260 matched controls with quinolone-sensitive infections.

As you did this study was there prospective as you got control -- sorry -- as you found a case you went and looked for controls? Or was it retrospective? You had your cases and then went out to look for the controls?

A For 1996 cases there was retrospective. In 1997 we enrolled cases and controls as they occurred.

Q Tell me if you would how you matched controls in 1994 -- for cases in 1996 when did you begin to match controls?

A I'm sorry could you repeat your question? I thought you mentioned 1994?

Q No, I was talking about the period of time in your study, 1996 to 1997.

A And your question was?

Q My question was, was this a prospective study or a retrospective study?

A It was, as I described, in 1996.

The case control study began early in 1997. We went retrospectively and enrolled cases and controls for 1996 and then continued the study throughout 1997.

Q So for the cases that you found in 1996 you were interviewing controls you identified in 1997, do I understand this correctly?

A That's technically correct, yes.

Q Could you tell us, please how you determined these campylobacter jejuni were resistant to nalidixic acid?

A Sure. It was our laboratory that did that. Every campylobacter isolate that was submitted to our laboratory gets screened for nalidixic acid by a diffusion test. If it's positive it gets a standardized diffusion test.

Q How did you determine that these organisms

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were in fact campylobacter jejuni?

A Our laboratory has -- it was standard methodology to identify campylobacter to species -- that was done by our laboratory.

Q Do you know what tests were used, the standard tests that were used to speciate?

A I know some of them. There are a variety of biochemical tests and one key test is a ~~separate~~ hippurate hydrolysis test.

Q Did you look at the difference between the various campylobacter using nalidixic acid susceptibility test?

A That test was performed but was not used to identify the campylobacter isolates to species.

Q In 1996 were the isolates sent by clinical laboratories around the state to the Minnesota Department of Health?

A Yes.

Q So they would have been speciated before they arrived at the Minnesota Department of Health?

A That's incorrect. None of our laboratories in Minnesota identified campylobacter species -- only the

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genus
~~genes~~.

Q So they would just identify the ~~genes~~ genus?

A Correct.

Q You used a particular questionnaire in your study. Did the form of that questionnaire or did any of the questions change over time?

A Yes. We used a different questionnaire in 1997 than we did in 1996.

Q What were the principal differences?

A We dropped some questions from 1996 when we realized they were mostly food consumption questions, food handling questions -- that we recognized were not going to be useful for our purposes because for 1996 the people didn't have a very good recollection of what they ate or how they handled food during the week before their illness.

So we found them not to be useful so we didn't ask them in 1997.

Q So there's a different database in 1996 versus 1997 -- were there differences in the databases between 1996 and 1997 -- based on the differences on the questionnaire that was submitted?

A The -- database in 1997 would simply be a subset of the database in 1996. It just was -- 1997 didn't have a certain number of variables that were included in 1996.

Q Is any of this described in the New England Journal of Medicine article?

By this I mean, the difference in questionnaires between '96 and '97 or the fact that the study was performed retrospectively from 1996 and prospectively from 1997?

A The first part of your question I can say no. The change in the questionnaire was not. I'd have to check on the second part of your question.

The answer to the second part of your question would be no as well.

Q Can you tell me more specifically what questions were dropped from the questionnaire between 1996 and 1997?

A Yes, the questions as such was "were chicken or beef or pork handled in your household during the week before the cases onset of illness."

Q When you say they were dropped -- is it fair

to say that the differences between the 1996 and 1997 -- questionnaire were deletions in 1997.

Were there any additions in 1997 -- between 1996 and 1997?

MS. ZUCKERMAN: Objection, Your Honor. It is not clear that this is at all relevant, what questions were dropped from the study. Moreover, it seems to be well beyond the scope of Dr. Smith's direct testimony.

JUDGE DAVIDSON: All right. I'll let this one question go and then we can move on.

BY MR. NICHOLAS:

Q The question was were there any deletions -- and were there any additions to the questionnaire in 1996.

A I do not believe there were any additions.

MR. NICHOLAS: The whole purposes -- one of the main purposes of the witness' testimony both written and direct on the article he submitted was certain conclusions with respect to risk factors for fluoroquinolone-resistant campylobacter," whether in fact poultry is a significant risk factor, whether there is an extended duration of illness when one has a

resistant versus a susceptible infection.

All of those data are generated using these questionnaires during this particular study. So I believe what's identified -- what's asked about in the questionnaire -- are critical issues to understand in both this study and the conclusions drawn by the witness.

MS. ZUCKERMAN: The testimony and Dr. Smith's paper speak for themselves.

Mr. Nicholas just mentioned that he is interested in what questions were in the questionnaire and what was testified to by the witness. So why he's talking about questions that were dropped appear to be irrelevant to the statement that he just made.

JUDGE DAVIDSON: I understand why he's after it. I'm just having a problem because most of the evidence in this proceeding from both sides deals with studies and papers that represented, some were juried, some were not, and the conclusions that the experts or the scientists or the lawyers drew from those papers -- and I don't get a chance to see any of the raw data -- I have to rely on the fact that the experts have made

their conclusions.

Now, if you can get something from this witness that allows you to get the material you can get -- which I doubt -- then you're in fruitful territory. Otherwise we are in what is irrelevant material. Because I have to rely on the experts and published studies just like everyone else does.

And if the material is not there I have to take that into consideration as to how much weight I give the evidence.

But you're trying -- it seems to me, to get things that aren't there. You've already had the witness explain that there are certain material and underlying data that was not furnished along with the study and you asked Mr. Beaver or Bayer asked for it and didn't get the material they wanted, now it seems that you're going after the differences between the questionnaire that was issued or given -- to see if there might be some other basis for determining that maybe there's a little less weight or no weight should be given to this.

In other words, it's getting pretty far afield

considering the fact that I have to deal with all of this material anyhow and you could -- we could be here till November talking about the things that aren't in the data that's presented as evidence in this proceeding.

MR. NICHOLAS: I understand, Your Honor.

If I might, what we did not get from the state of Minnesota, with the isolates, duplicates of the isolates themselves -- we did get the questionnaires.

JUDGE DAVIDSON: Then you have them.

MR. NICHOLAS: We do, Your Honor. I'm trying to establish the differences between the two questionnaires and the significance that has.

JUDGE DAVIDSON: But it isn't in his testimony. You have the questionnaires. You have the differences. You have an obligation to, if you think there's something there, to put that on the record. You're trying to get cross examination from a witness who didn't testify to that particular aspect. All right?

MR. NICHOLAS: Thank you.

JUDGE DAVIDSON: Move on.

BY MR. NICHOLAS:

Q Did either of the questionnaires ask whether bottled water --

MS. ZUCKERMAN: Objection, Your Honor.

JUDGE DAVIDSON: Is that considered moving on?

MR. NICHOLAS: I'm sorry, Your Honor.

JUDGE DAVIDSON: You have the questionnaires, right?

MR. NICHOLAS: That's correct.

JUDGE DAVIDSON: Well, if you have points to make about the differences between them, put it in your brief.

BY MR. NICHOLAS:

Q Dr. Smith, I'd like to focus your attention on Exhibit 589 table one on page 528 -- entitled "Potential risk factors from infection of quinolone-resistant campylobacter jejuni as compared with quinolone-sensitive campylobacter jejuni among Minnesota residents 1996 to 1997."

How many people were involved in this study that are represented on the chart -- how many isolates?

A 390.

Q This is the chart that you prepared as a result of the study that we've previously described, is that correct?

A Correct.

Q I see drinking water, contact with pets, all of these, as risk factors, including foreign travel -- 75 percent, I believe -- as risk factors.

MS. ZUCKERMAN: Objection, Your Honor. The table says right here "potential risk factors." The table speaks for itself, and for the record, I just wanted to clarify that.

JUDGE DAVIDSON: I don't think Mr. Nicholas meant to mischaracterize --

MR. NICHOLAS: Well, I read the title as "potential," I believe.

JUDGE DAVIDSON: Sorry, but the last question you didn't use "potential" in your words, so that's what she's objecting to.

MR. NICHOLAS: I'm sorry, Your Honor.

JUDGE DAVIDSON: I don't think you're trying to mischaracterize the material, so I'll overrule the objection.

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BY MR. NICHOLAS:

Q Just to be clear, then, I don't see chicken on this list as a potential risk factor, is that correct?

A That's correct.

Q Thank you.

There's an additional part of the study described in G-589 and also in the testimony that deals with genetic typing of campylobacter isolates, is that correct?

A Correct.

Q My understanding is generally one uses various genetic techniques to try to identify relationships perhaps between different species -- different clones of subspecies of microorganisms -- maybe you could tell me the definition?

A That's correct. We identify relationships between different strains of a particular species of bacteria.

Q In your study you used a technique called ~~TCR~~ PCR RFLP, is that correct?

A Correct.

Q That was a -- technique that was widely used

at that time for these kinds of purposes?

A Correct.

Q But since that time there have been a number of other molecular-genetic techniques that have would it be fair to say can tell you more about the genetic structure of the individual organisms so that there are more points of comparison?

A I'm not sure I would say they can tell you more. Different subtyping methods tell you different things. Not necessarily that one tells you more than the other.

Q If I wanted to sequence a particular organism and looked at every genetic structure there I could do that.

In my view that would tell me more than if I looked at one particular region of the particular organism, wouldn't it?

A That would tell you more, but it would be less useful for epidemiologic purposes.

Q That wasn't my question.

My question was would it tell you more about the genetic structure of that organism?

A That's technically correct.

Q Thank you.

Would you agree that, if I told you Dr. Besser said the molecular subtyping cannot be interpreted independent of an epidemiological analysis --

MS. ZUCKERMAN: Objection, Your Honor.

JUDGE DAVIDSON: I will allow this one.

MR. NICHOLAS: Your Honor, I have the testimony --

JUDGE DAVIDSON: I understand. Go ahead.

MR. NICHOLAS: Thank you.

JUDGE DAVIDSON: If the witness has a problem with it he can ask to see it. If he understands what you said, he can answer the question.

THE WITNESS: Yes. When you are evaluating subtyping methods for bacteria it's best to have epidemiologic evaluations with that to see how useful it is.

BY MR. NICHOLAS:

Q Would you agree, again, with Dr. Besser and Dr. Tenover if they said the molecular subtyping serves to strengthen statistical associations that may already

be present by removing from consideration cases less likely to be associated? By "already present" they're talking about the epidemiology.

A Could I see that statement, please?

MR. NICHOLAS: I'm going to give the witness a copy of Dr. Besser's testimony, which is G-1455, and Dr. Tenover's testimony, which is 1476.

MS. ZUCKERMAN: Your Honor, would it be possible for Mr. Nicholas to identify the parts to these exhibits?

MR. NICHOLAS: I'm going to do that.

BY MR. NICHOLAS:

Q For Dr. Besser, which is G-1455, if you look at page 6, line 28 to 30, and if you would start by line 27, it says "DNA fingerprinting cannot be interpreted independently of an epidemiological analysis. In this context DNA fingerprinting serves to strengthen statistical associations that may already be present by removal from consideration cases less likely to be associated."

Would you disagree with that or would you agree with it?

A I agree with that.

Q Thank you.

If you would turn to Dr. Tenover's testimony and look at page 4, line 10 to 12, please:

"The goal of strain typing is to provide laboratory evidence that the epidemiologically related isolates collected during an outbreak of disease are also genetically related and thus represent the same strain. This information is helpful to the understanding and control of the spread of infection disease."

Do you agree with that statement?

A I agree that it is a goal of strain typing, yes.

Q If you would look at Dr. Besser's testimony, again, page 7 -- that's G-1455 -- page 7, line 1 to 3.

A I'm sorry, what page?

Q Page 7, line 1 to 3. "These analyses" -- and the section actually begins on the preceding page; he's talking about various techniques with DNA fingerprinting -- "in these analyses not the DNA fingerprinting that provides the proof. DNA

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fingerprinting works by facilitating recognition of clusters of disease, not providing causes of illness."

Do you agree with that statement?

A Yes.

Q When did you add the ~~fore-typing~~ pfa typing analysis to your study that began in 1996?

A In 1997.

Q At what point in 1997?

A In the fall.

Q Isn't it correct that you began collecting isolates in September 1997? And you collected them until November 1997, early November?

A Retail chicken isolates.

Q Retail chicken isolates? That's ~~great~~ correct.

When did you make the decision to do this in terms of January 1997, July 1997?

A The decision to collect chicken products?

Q That's correct.

A I don't recall the month.

Q Do you recall whether it was before the summer began?

A I don't recall specifically. Probably was

during the summer at some point, but I can't recall specifically.

Q Had you done interim analyses of the data in mid-'96 or late '96 or early '97 to see where the data were going?

A Yes, we did do interim analysis.

Q Did any of those analyses show that chicken was a potential source of fluoroquinolone-resistant campylobacter in humans?

A To us they did because we had observed domestically acquired resistant cases.

Q Was there anything in the analysis of the domestically acquired cases that pointed to fluoroquinolone-resistant campylobacter as coming from poultry?

A No.

Q Thank you.

JUDGE DAVIDSON: He can explain.

If you want to say more, go ahead.

THE WITNESS: Thank you, Your Honor.

What you have to understand is that this study was not designed necessarily to identify specific food

vehicles for campylobacter because our cases were quinolone-resistant campylobacter infections -- but our control group was also campylobacter infections. They were just quinolone-sensitive campylobacter infections.

So if both groups came predominantly through the same food vehicle, we would expect in fact not to find a difference implicating that food vehicle in one group.

BY MR. NICHOLAS:

Q Let me see if I understand this. As I understood you undertook this study ~~to~~ as a case comparison study with patients with ciprofloxacin-resistant campylobacter jejuni, domestic chicken was evaluated as a potential source of quinolone resistance?

So you did that, but you didn't expect to find a particular food source, or if you found a particular food source -- I'm not quite -- if you could explain that?

A Sure. We didn't know what we would find. We wanted to ask good questions. But as it turned out, a very high proportion of quinolone-resistant cases and

quinolone-sensitive cases had consumed chicken.

Q You say you didn't know what you would find and as I understand your testimony you basically say -- on page 2 at line 25 you begin to speak about "these reports in the scientific literature associating resistance in human isolates in campylobacter was increasing. Some of these reports propose that fluoroquinolones in animals were the driving force."

Later on, in the following paragraph at line 33, you begin "Therefore we at the Minnesota Department of Health felt compelled to evaluate the issue and to see whether there was resistance."

So you felt compelled to do this, you believe from the European studies that animal sources in poultry was a source and yet you didn't expect to find -- you weren't looking at chicken as a source?

MS. ZUCKERMAN: Objection, Your Honor. Mr. Nicholas is mischaracterizing Dr. Smith's testimony.

JUDGE DAVIDSON: Overruled.

If you have a problem with the question, just state the problem, and we can ask it in different ways or break it down.

THE WITNESS: Thank you, Your Honor.

Our thought process was -- you're right. The European studies and authors suggested that veterinary use of fluoroquinolones, especially in poultry, played a primary role in the increasing human resistance there.

So we knew there was a possibility that that could be happening here as well. But we didn't assume that -- it was only when we observed domestically acquired cases of fluoroquinolone-resistant campylobacter in humans that we then considered poultry as a possible source. That is why we collected the retail chicken samples.

BY MR. NICHOLAS:

Q Just so I understand. Three-quarters of the period of time into the study or more, you decided to collect the isolates? The study began in 1996. You started collection in September 1997?

A That's correct.

Q You a moment ago were talking about domestically acquired -- in your study a very significant portion of people had listed foreign travel

on your questionnaire. I believe the percentage was 75 percent?

A That's correct.

Q So the risk factors for acquiring a fluoroquinolone-resistant campylobacter infection could be different in a foreign country -- outside the U.S. -- than they are in the United States, is that correct?

A Correct.

Q And one of the things you might do is a study looking at that, but you don't know without conducting an analysis of some sort what those risk factors might be in another country, is that correct?

A Correct.

Q Not only could the epidemiology -- in other words, the potential risk factors, causative factors -- be different in different countries, could there be different strains of campylobacter in different countries?

A Yes.

Q Could there be different medical practices in different countries both with respect to diagnosis, treatment, treatment guidelines, availability of

doctors?

MS. ZUCKERMAN: Objection, Your Honor. Again, it's beyond the scope of Dr. Smith's testimony. He's not testifying to medical practices in different countries.

MR. NICHOLAS: Your Honor --

JUDGE DAVIDSON: I'm listening.

MR. NICHOLAS: I'm sorry -- one of the questions very clearly here -- Dr. Smith has made representations about the duration of illness between resistant organisms and susceptible organisms, comparing, in part, infections acquired abroad with infections domestically acquired. So what he knows about European data or other foreign data is perfectly relevant to the background of his testimony.

JUDGE DAVIDSON: I'm not so sure.

MR. NICHOLAS: It's a foreign-acquired infection.

JUDGE DAVIDSON: I understand, but, boy, the details you're going into -- I'll allow it, but let's see if you can't shorten this somehow, because you're just -- I know what you're after. I know what you're

trying to do. But you can't get everything from this witness. He didn't do those studies.

MR. NICHOLAS: But he did this study, Your Honor.

JUDGE DAVIDSON: Right, and he responded -- and he gave you the authority and that's -- what I have in all the material.

Ask the question -- answer it. You may answer.

Do you remember the question?

THE WITNESS: I do not.

JUDGE DAVIDSON: Okay.

BY MR. NICHOLAS:

Q What information do you have on medical practices, diagnostic practices, treatment practices, availability of medical services, use of anti-diorrheals, and other factors that might affect the duration of illness with respect to fluoroquinolone or quinolone-resistant campylobacter infections that would be acquired outside the United States?

MS. ZUCKERMAN: Your Honor, again, I object.

JUDGE DAVIDSON: I understand; but I

already -- what information do you have, that was the question?

THE WITNESS: Well, all of the infections in my study were diagnosed and the ones that were treated were treated in this country. So in that respect we have good information.

BY MR. NICHOLAS:

Q Do you have any information other than that about what goes on in foreign countries? These infection were acquired abroad; do you know about treatment practices or conditions of medical care in other countries?

A Not specifically.

Q Returning to your genetic analysis, as I -- please correct me if I am not characterizing this properly -- you found using the RFLP PCR technique --

JUDGE DAVIDSON: Is this from his paper?

MR. NICHOLAS: I'm sorry, Your Honor?

JUDGE DAVIDSON: Is this from his study or from his testimony?

MR. NICHOLAS: This is from his paper, Your Honor.

JUDGE DAVIDSON: If you give reference to that then we can all check to see what you're talking about before you ask the question.

MR. NICHOLAS: It's from testimony on page 13, line 41 to 45.

JUDGE DAVIDSON: You just said it was from the study. Now you're saying it's from the testimony. That's what I have to know. I can't follow along if I don't know what to look at.

MR. NICHOLAS: Sorry, Your Honor.

BY MR. NICHOLAS:

Q As I said, page 13, line 41 to 45.

Looking just at the 1997 patients, 12 of the 13 patients had domestically acquired resistant C-jejuni and a subtype that is also found in quinolone-resistant strains acquired from chickens." Is that correct?

A Yes.

Q Could all of the forms come from one chicken?

A Could you rephrase?

Q Could all of the isolates in common between poultry sources and human sources come from one --

chicken source?

MS. ZUCKERMAN: Objection, Your Honor. That doesn't seem to make sense. One chicken? One bird? The same bird?

JUDGE DAVIDSON: He's asking the questions. Overruled.

BY MR. NICHOLAS:

Q If the witness doesn't understand it --

A Very unlikely.

JUDGE DAVIDSON: He answered.

BY MR. NICHOLAS:

Q In the 1996 to 1997 data, if you combine them I believe your testimony is that six of the seven had identical DNA fingerprint strains found -- that's in the line before that?

JUDGE DAVIDSON: I don't follow you.

MR. NICHOLAS: Starting on line 38 on page 13.

THE WITNESS: Correct.

BY MR. NICHOLAS:

Q Now when you say "identical DNA fingerprinting," my understanding is that your technique looked at one genetic region for a gene, and

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that's the sole genetic analysis you did or your laboratory did to look at the comparisons between the strains, is that correct?

A That's correct. We looked at the fingerprint of the ~~flagellum~~ flagellin gene.

Q That's not the fingerprint of your particular organism, that's a small portion of the organism, is that correct?

A That's correct.

Q As I understand it you only did molecular typing with this technique of poultry isolates, is that correct? So you didn't compare human isolates of campylobacteriosis that were resistant to water-borne infections -- isolates -- taken from water -- from sheep, from lamb, from cattle, from horses, from domestic pets -- from any other potential source of fluoroquinolone-resistant, quinolone-resistant campylobacter?

A We compared human isolates to the retail chicken isolates.

Q Isn't it true that common source roots of infection cannot be ruled out for populations with

overlapping campylobacter genotypes?

A Sorry, I don't understand your question.

Q Let's turn to -- look at your testimony, page 14 lines, 20 to 21. What I'm saying is, if organisms have a common source infection you can't rule out that each of these organisms has acquired the infection from a third source.

I will phrase it a different way. If two organisms share a subtype in common, there are several possibilities. The first organism could -- person -- could have gotten the organism in this case. The chicken could have gotten the organism from the person, or, alternatively, either could have acquired it from a third source, or they both could have acquired it from the same third source, is that not correct?

A It depends on your definition of "possible." I mean, anything's possible.

Q Let's talk reality. You looked at only campylobacter isolates in poultry. And campylobacter isolates from humans, correct?

A Correct.

Q So if there were a common third source you

would not have been able to find that in your study. Is that correct?

A I guess that's technically correct.

Q Your epidemiology didn't find that. When you did your epidemiology on fluoroquinone-resistant campylobacter infections in 1996 and 1997, the Minnesota residents, the risk factors did not identify poultry as a risk factor. In your genetic analysis you're saying there's an association between campylobacter from poultry and humans based upon six isolates or 13 isolates? Is that correct?

A You have a multi-tiered question there.

First -- as I explained earlier, the epidemiology did not identify consumption -- or handling of chicken as a risk factor for quinolone-resistant campylobacter infections primarily because our control group were also campylobacter patients. If both groups come from chicken we would not identify chicken as a risk factor for either group using this study design.

That was the first part of your question. Could you repeat the second part of your question?

Q The second part -- I'll rephrase:

Is it not true that molecular subtyping might not identify specifically where a bacterium comes from, the origin -- but only what type it is? If you were to take an organism and subtype it without knowing that it was isolated from a person or from a chicken or from a cow, all it could tell you is about the subtype. It wouldn't tell you about the source of animal?

A I would say that's not strictly true. There are cases if we detect a subtype from a -- particular subtype from a human case of campylobacter or salmonella or whatever, in some instances we do feel that we know what species that the subtype comes from.

Q Particularly in outbreak investigations?

A In outbreak investigations, but also sometimes with sporadic cases.

Q How many subtypes of campylobacter have you identified in poultry?

A From poultry? I think it was about a dozen. That's in my testimony. There are subtypes from 13 positive chicken products, samples of 13 chicken products.

427	13	is the transcript	as the transcript
427	18-19	merely an audible	nearly inaudible
431	20	MR. NICHOLAS	MR. SPILLER
433	1	899	A-99
448	17	medium	median
449	22	resistance	resistant
457	13	Karl Mollbach	Kare Molbak
457	15	Mollbach	Molbak
460	19	apriority	*a priori*
461	2	apriority	*a priori*
462	10	apriority	*a priori*
462	12	apriority	*a priori*
463	5	apriority	*a priori*
463	8	multi-variant	multivariate
465	12	multi-variant	multivariate
465	13-14	multi-variant	multivariate
465	15	aggression	regression
465	16	variants	variance
466	3	multi-varied	multivariate
467	2	multi-varied	multivariate
467	7-8	multi-variant	multivariate
467	10	apriority	*a priori*
475	5	Ms. Zuckerman	Judge Davidson
475	9	Ms. Zuckerman	Judge Davidson
484	3	norms	NARMS
484	7	scan.	scheme.
487	17	Greenbriar Drive, Lionel	Green Briar Drive, Lino
492	12	review	reviewer
494	6	former	formal
494	18	methods analytical	methods and analytical
497	4	Embry,	Emery,
503	2	Pyddic, Gunn,	Piddock, Gaunt,
503	3	Thruolphal,	Threlfall,
503	4	Thruolphal	Threlfall
504	5	Pro crit	purpose
507	8	separate	hippurate
508	1	genes.	genus.
508	2	genes?	genus?
516	19	TCR	PCR
521	5	flore-typing	fla typing
521	14	great.	correct.
523	11	to	as
532	5	flagellum	flagellin
536	2	flaw	fla
536	5	flaw-typing	fla typing

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Q Is it true that diverse and distinct campylobacter strains may share the same ~~flaw~~ f/a types?

A I would say that's correct.

Q Back in 1997 when you were doing these techniques, was ~~flaw-typing~~ f/a typing generally standardized?

A I believe so.

Q What standard would you reference for that?

A There's a ~~Nachompkin~~ Nachamkin paper that described the process.

Q So you would have been following in the ~~Nachompkin~~ Nachamkin process?

A Yes. That would be a better question for my laboratory people.

Q Isn't it true that campylobacter jejuni strains undergo a recombination within the ~~flaw~~ f/a gene?

MS. ZUCKERMAN: Objection Your Honor. This is beyond the scope of the witness' testimony.

JUDGE DAVIDSON: First of all, what was the last word you used? Bar gene?

MR. NICHOLAS: ~~Flaw~~ F/a gene -- ~~F-L-A-W~~ F-L-A.

JUDGE DAVIDSON: ~~Flaw~~ F/a gene? Okay. You can answer the question.

He's an expert. He can answer if he can. If not, he can handle it.

THE WITNESS: I don't know that for a fact.

BY MR. NICHOLAS:

Q Thank you Dr. Smith. In your testimony on page 14, lines 8 to 12 -- and I believe also on 16 to 18 -- I'm sorry, 8 to 12 -- you state that "patients with domestically acquired quinolone-resistant C-jejuni infections were 15 times more likely to have a C-jejuni subtype that was also found among quinolone-resistant C-jejuni isolates from domestic chicken products collected in 1997 than patients with domestically acquired quinolone-insensitive infections."

JUDGE DAVIDSON: Where's 1997?

MR. NICHOLAS: Let me find that -- well, let me ask the question.

BY MR. NICHOLAS:

Q Is this analysis based on the 1997 data or the 1996-1997 data?

A 1997 data.

Q With respect to this statement and with respect to this statement and with respect to 1997

data, is it true that the link here refers to a causal link?

A Essentially what we're saying is that this is evidence that retail chicken products were the source of domestically acquired infections in humans in Minnesota.

Q But wouldn't you consider it a causal link in -- because it's there proves that the chickens were the source?

A This is one piece that has to be considered with everything else.

Q Is it true that the 15-fold factor indicates that the resistant strains of C-P are more likely -- that's campylobacter -- than sensitive strains to be found in multiple species? Including at least chickens and humans?

A No. I wouldn't say that.

Q Is it true that the 15-fold factor indicates that chickens are an unlikely source of non-resistant C-jejuni detection in humans?

A When combined with all the other evidence, yes.

Q But not by itself?

MS. ZUCKERMAN: Asked and answered.

JUDGE DAVIDSON: He's already said it's a factor. You asked him the whole. Forgetting your asking him the causal question, he said it's a factor to be considered. Now you're asking parts of the same question and you're getting the same answer, and I don't know why you keep going.

MR. NICHOLAS: Thank you, Your Honor.

BY MR. NICHOLAS:

Q On page 14, lines 12 to 16, you also state that "Patients with domestically acquired resistant C-jejuni infections were 22.3 times more likely to have a C-jejuni subtype that was also found among resistant C-jejuni isolates from domestic chicken products than patients with foreign travel-associated quinolone-sensitive C-jejuni isolates. This link is statistically significant."

Is it true that 22.3-fold factor indicates that resistant campylobacter from the U.S. are more likely to colonize those domestic chickens and domestically exposed humans than the resistant C-P

strains --

A I wouldn't say that.

Q You wouldn't?

A No.

Q Does the fact that domestic bacteria are more likely than foreign bacteria to be found in domestic chickens and domestic human cases provide evidence that domestic chickens are a source of domestic human campylobacteriosis?

A I would agree with that.

Q On page 14, lines 22 to 25, you state "When a large number of subtypes are generated by subtyping methods two isolates that share an identical subtype are more likely to be related to a common source than if the method used a smaller number of subtypes," is that correct?

A Yes.

JUDGE DAVIDSON: I'm sorry for interrupting you so much, but we can all read the testimony. Your reading the testimony and your saying "is that what it says?," it's -- I understand, but refer him to the testimony -- if you insist on reading it read it, but

you don't have to ask him if that's what it says. Because we all see that.

MR. NICHOLAS: Okay. I will refrain from reading the testimony, Your Honor. I'm sorry.

JUDGE DAVIDSON: Thank you.

BY MR. NICHOLAS:

Q Considering a subtyping method, method A generates 100 subtypes is a hypothetical -- 100 subtypes but with all samples in the data set fall into just one of those subtypes, so you have 100 subtypes but all samples in the data set fall into one of those subtypes.

Let's compare that to a second method that generates only 10 subtypes with 10 percent of the samples in the data set falling into each one. If two isolates share the same subtype in method A, would that make them more likely that they have a common source than if they share the same subtype in method B -- the second method?

A I would think so. That's a broad generalization, but --

Q You would think so?

A Yes.

Q Thank you.

Is it not the discriminatory ability of the method and not the number of subtypes that is the most important factor in the subtyping methodology?

A They're related. Discriminatory ability directly relates to the number of subtypes, the number of subtypes, the amount of variability that's picked up --

Q So the less discriminatory, the more subtypes you're going to find or the fewer subtypes you're going to find? The less discriminatory the technique the more subtypes you're going to find or the fewer subtypes you're going to find?

A I would say that the more discriminating it is the more subtypes you find.

Q I'd like you to turn to page 10, line 31 in your testimony, please. With respect to the statement that runs from line 31 through line 34, I'd like to ask you some questions, if I might.

Is it true that the median duration of the illness is only one way to compare the distributions of

illness durations between fluoroquinolone-resistant and fluoroquinolone-susceptible campylobacter?

A That's correct.

Q Did you do other analyses in your study? Did you look at the mean?

A Yes. We looked, and the measurement of the mean was not an appropriate test for the provided data.

Q Why was that?

A Because the variances of the populations differ, so therefore you should use the median as the measure.

Q Are you familiar with a test for shift in distribution in duration called the Cole-Morgrove-Smirnoff test?

A Very vaguely.

Q Did you use that test in this case -- and on these data?

A No. No.

Q It is true that a statistically significant difference in the duration of illness is found in foreign travel cases are left in the analysis. That's your testimony, basically, isn't it?

A Yes.

Q And when you analyzed the data involving both domestic and foreign-travel acquired illness you found a difference in the duration of illness?

A That's correct. "Do not separate out foreign travel from domestic."

Q Isn't it true that cases with recent foreign travel are significantly more likely to have fluoroquinolone resistance than domestically acquired cases?

A That's true.

Q Isn't it true that cases with foreign travel only have longer duration diarrhea on average than cases without foreign travel, in your study?

A No. Because when you say "different" you should mean "statistically significantly different," and that was not the case.

Q So there is a difference? It's just not statistically significant?

A When it's not statistically different you shouldn't say they're different.

Q Okay.

Isn't it true that statistically significant association between fluoroquinolone resistance and longer duration of diarrhea disappears when only domestically acquired cases are considered?

A That's correct.

Q I have trouble figuring out in your study, so I'd like you to help me if you would. In the 1997 analysis how many patients were included when you looked at the duration of illness domestically acquired for quinolone-resistant campylobacter infections?

A I don't remember specifically. There were 18 domestically acquired cases.

Q How many foreign travel-associated cases?

A I don't remember specifically. I think the total -- sample size of people who met the criteria that I used was about 94 case patients.

Q With respect to the patients that were included in the 1997 analysis, the duration of illness comparison between resistant and non-resistant infections included both domestic and foreign -- were any of those patients included that had responses on the questionnaire that did not provide information

during that duration of illness?

A No. If they did not provide a duration of illness they were excluded.

Q So no patients with missing values or unclear values were included in that analysis.

A For duration of illness.

Q On page 10 lines 35 to 37, look at that, please.

When you say "not as effective in treating patients," you mean the duration of diarrhea was longer for the fluoroquinolone-treated patients with resistant infections versus the sensitive infections?

A Yes.

Q Is it untrue that fluoroquinolone-resistant campylobacter infections can also have a longer duration of diarrhea than untreated fluoroquinolone-sensitive infections?

A Yes, it's possible, but it didn't show up in my study.

Q In your data set is it not true that fluoroquinolone resistance is associated with shorter duration of illness among people who have recently

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eaten chicken?

A No.

Q Does your data set contain one or more variables recording the specific reasons for the length of illness of each patient, such as treatment values for specific strains of campylobacter involved?

A Well, we can die of variables on treatment failure. But there are variables on different, you know, the ~~flawed~~ f/a types of the campylobacter, whether or not they're resistant -- if that's what you're asking.

Q Well, I'm talking about the human samples, because I'm talking about patients. So the question is what variables do you have in interactions?

A Duration of diarrhea. It's the one --

Q Was clinical failure of Ciprofloxacin treatment demonstrated in all the cases with resistant isolates?

A Well, the cases that were appropriate. I mean, it's not inappropriate to include patients in that analysis if they had taken fluoroquinolones before their culture, for example.

Q Let me rephrase the question. With respect to

the isolates from resistant patients, did you document clinical failures in treatment with Ciprofloxacin?

A Yes. I mean, we've just been talking about it.

Q From the medical records, you documented that there was treatment failure?

A Well, to the extent that's included in my testimony that we documented the longer duration of diarrhea.

JUDGE DAVIDSON: Excuse me. Are we having a problem? It seems that every question is taking an awful -- after an answer, it takes, you know, 20 to 30 seconds before you ask the next question. Now I want to give you as much time as you need, but I'd like the record to reflect that you're taking this time. So if you're going to take more than five or six seconds to ask the next question, just indicate you'd like time, and then I can divert my attention elsewhere.

MR. NICHOLAS: What I'm really trying to do is cut down on --

JUDGE DAVIDSON: I thought that's what it was, but I'd still like the record to show what's going on

here.

MR. NICHOLAS: I need another minute, Your Honor.

JUDGE DAVIDSON: Certainly.

BY MR. NICHOLAS:

Q Dr. Smith, if you would turn to page 7 of your testimony, line 12. If you'd look at that, please.

Now this testimony relates to the period from 1992 to 1998. Were there any changes in the isolation procedures between those years in the isolation of campylobacter?

A Not that I'm aware of.

Q Were there any changes that don't affect -- did not adjust to the effects of changes in criteria used to submit and select isolates for testing? Were there any changes during that period of time in the criteria used to submit and select isolates for testing?

MS. ZUCKERMAN: Objection, Your Honor. It sounded like there were two questions in there and I heard the word "change," I think, three or four times.

MR. NICHOLAS: I'll rephrase the question,

Your Honor.

JUDGE DAVIDSON: All right, ask it again.

BY MR. NICHOLAS:

Q Between 1992 and 1998, were the changes in the criteria used to submit and select isolates for testing in Minnesota, with respect to the isolates that --

MS. ZUCKERMAN: Objection, Your Honor. Asked and answered.

MR. NICHOLAS: Your Honor, these are changes in criteria to submit the isolates for testing. The previous --

JUDGE DAVIDSON: This is submission and the other was --

MR. NICHOLAS: Isolation procedures.

JUDGE DAVIDSON: All right. I'll let him answer.

THE WITNESS: Don't know that I'd characterize it as a change in criteria, but in 1994 -- we'd always received isolates because we're a reference laboratory -- in 1994, we began requesting that laboratories send us all campylobacter isolates. In 1995, it was made official under our reporting rules

that clinical laboratories must send all campylobacter isolates associated with cases of clinical illness in humans to us.

BY MR. NICHOLAS:

Q Thank you. Have you done an analysis to determine, or do you know whether the -- how the population of Minnesota compares to the population of the United States generally?

A I do not do that specifically.

Q So you don't know specifically whether the Minnesota results or experiences from your data are generalizable to the United States as a whole do you?

A I guess that's strictly correct.

Q Okay, thank you, Dr. Smith.

MR. NICHOLAS: Your Honor, I need another minute, please.

JUDGE DAVIDSON: Okay.

MS. ZUCKERMAN: Your Honor, may I approach the witness to give him a little water?

JUDGE DAVIDSON: Sure.

MS. ZUCKERMAN: Thank you.

THE WITNESS: Thank you.

JUDGE DAVIDSON: Mr. Nicholas, the witness has been on the stand for about an hour and a half. If you're having some problem deciding what you want to ask next, maybe we could take a short recess. The witness has been drinking a lot of water and probably needs a recess.

All right, now we'll be back at 20 minutes to 11:00 promptly, and I'm not leaving, so you don't have to get excited.

We'll go off the record.

(A brief recess was taken.)

JUDGE DAVIDSON: Everybody's refreshed and ready to go, so we can go through this lickety-split now, right, Mr. Nicholas?

MR. NICHOLAS: Yes, Your Honor, I've thought out -- I've revised my questions, and you'll be pleased to know I just have a few more questions.

JUDGE DAVIDSON: Well, I'm glad to hear that. That's not like the two you had the other day, was it?

MR. NICHOLAS: It certainly wasn't like the witness' testimony yesterday.

JUDGE DAVIDSON: You're not kidding. Let's

go.

MR. NICHOLAS: Thank you, Your Honor.

BY MR. NICHOLAS:

Q With respect to your study, Dr. Smith, the study that's referenced in the New England Journal of Medicine article, G-589, I believe it is, did you quantify the statistical power of your study to detect associations between higher chicken consumption and the higher risk of FQ -- fluoroquinolone-resistant campylobacter?

A I'm sorry if the question is not clear to me. I didn't get what you meant about power.

Q Well, as I understand various statistical techniques have more power -- define various things -- the size of the study -- the -- you talked about the power of the study.

So did you quantify the statistical power of your study to detect associations of higher chicken consumption and higher risk for fluoroquinolone-resistant campylobacter?

A No, we did not.

Q Does the determination of statistical

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significance sometimes depend upon the specific statistical technique used?

A That's true.

Q Does a finding of longer duration of diarrhea in one group compared to another depend on the specific statistical technique used to compare them?

A True. That's why you must use the appropriate test.

Q Thank you.

MR. NICHOLAS: I have no further questions, Your Honor.

JUDGE DAVIDSON: Okay. Ready?

MS. ZUCKERMAN: I am. Pursuant to our agreement, though, we'd like to switch tables.

JUDGE DAVIDSON: All right. We'll go off the record for a short time while we switch tables.

MS. ZUCKERMAN: Thank you.

(A brief recess was taken.)

Judge Davidson

~~MS. ZUCKERMAN~~: Back on the record.

REDIRECT EXAMINATION

BY MS. ZUCKERMAN:

Q Dr. Smith, if you know, is it common to

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receive a request for isolates that were used in a study of the type -- let me rephrase that, please. Is it common to receive isolates pursuant to an ~~FOR~~ FOI request?

A Not common.

Q Is it likely that if one were to receive an ~~FOR~~ FOI request for isolates, that a laboratory would be able to produce such isolates?

MR. NICHOLAS: Objection, Your Honor. If the counsel would qualify that for the State of Minnesota as opposed to generally, we'd understand more about what the witness' response --

MS. ZUCKERMAN: That's fine.

JUDGE DAVIDSON: Okay. Limit it to Minnesota.

MR. NICHOLAS: Unless the witness has other knowledge.

THE WITNESS: Could you ask it again, please?

BY MS. ZUCKERMAN:

Q Sure. If Minnesota were -- if you know -- if Minnesota were to receive an ~~FOR~~ FOI request for isolates, is it likely that any laboratory would be able to actually provide such isolates?

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A Most laboratories wouldn't; ours would.

MS. ZUCKERMAN: I need one moment, Your Honor.

JUDGE DAVIDSON: Certainly.

BY MS. ZUCKERMAN:

Q Dr. Smith, I want to follow up on a question that Mr. Nicholas asked regarding using the ~~FLAG~~ FLA as the fingerprint, as the DNA fingerprint.

He had asked you whether only a small portion of the organism was typed in that method; and, as I understand, your answer was yes. Could you explain whether it is appropriate to use only a small portion of the DNA gene -- of the DNA in this type of sequencing?

A Yes, it is very appropriate for epidemiologic purposes. What you want is a subtyping method somewhere in the middle, something that provides considerable variability, but yet every single isolate is not different.

Subtyping could range all the way from, you know, you can call campylobacter ~~to doing~~ jejuni a subtype -- to the opposite end of the spectrum. If you were to do the whole DNA sequence of each bacteria, every one

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would be different.

If you took a bacterium and did a DNA sequence and it splits into two bacteria, the DNA sequence of those two bacteria would be different, but yet they're still the same strain. And that's not at all what you want. You don't want that level of detail for epidemiologic purposes; you want something in the middle, such as --

Q Mr. Nicholas asked you about the ability to identify a common third source of resistant infection. Are you able to state whether it is likely that any common third source would have been responsible for the correlation ~~and~~ in molecular subtyping between the human isolates and the chicken isolates?

A Sure. In my opinion, it's not likely at all that there's a common third source. You have to kind of use common sense and go by what's logical -- that resistant campylobacter is on the chicken and people are eating the chicken. So that's by far -- that's the most likely explanation.

You don't necessarily need to be looking for some proposed third source when a direct link is

available.

Q I'd like to now ask you a question regarding the analysis in your paper, and in your testimony, about the duration of diarrhea from the 1997 study.

MR. NICHOLAS: What page are you looking at?

MS. ZUCKERMAN: The --

MR. NICHOLAS: What are you referring to in terms of the witness' statement?

JUDGE DAVIDSON: All right, whoa, whoa.

MR. NICHOLAS: I'm sorry, Your Honor.

JUDGE DAVIDSON: If you have an objection, you can state it. Don't --

MR. NICHOLAS: I object, Your Honor.

JUDGE DAVIDSON: -- don't ask counsel questions.

MR. NICHOLAS: I'm not sure what statement the counsel is asking the witness --

JUDGE DAVIDSON: Well, if she asks a question and it's not clear, then you can object on that basis; but let her ask the question first.

BY MS. ZUCKERMAN:

Q Would you please explain why you did not

remove those individuals with foreign travel from your analysis of duration of diarrhea?

A Sure. Because it was not indicated to remove people with foreign travel. When you looked at foreign travel, again, it was not statistically significantly associated with duration of diarrhea in my study, and therefore, it should not have been excluded.

MS. ZUCKERMAN: One more moment, Your Honor, please?

JUDGE DAVIDSON: Certainly.

MS. ZUCKERMAN: Your Honor, may I take a few minutes to -- for counsel?

JUDGE DAVIDSON: All right. Off the record.

(A brief recess was taken.)

MS. ZUCKERMAN: Thank you, Your Honor, for the time; that allowed me to eliminate a number of questions.

JUDGE DAVIDSON: Okay, good. Very --

MS. ZUCKERMAN: And I have one last one, one final question.

JUDGE DAVIDSON: Okay.

BY MS. ZUCKERMAN:

Q Dr. Smith, did the New England Journal of Medicine indicate that a lack of a formal written protocol had any scientific -- any impact -- I'm sorry, let me start over.

Did the New England Journal of Medicine indicate that the lack of a formal written protocol had any impact on the scientific merit or validity of the submission of your study for publication?

A No.

MS. ZUCKERMAN: Thank you. No further questions.

MR. NICHOLAS: Your Honor, I just have one question.

JUDGE DAVIDSON: Okay.

RECROSS-EXAMINATION

BY MR. NICHOLAS:

Q Dr. Smith, do you know whether the New England Journal of Medicine knew whether you had or didn't have a formal written protocol?

A No, I do not know whether they knew that.

MR. NICHOLAS: I have no further questions.

MS. ZUCKERMAN: No further questions, Your Honor.

JUDGE DAVIDSON: All right. Do we have anything we have to consider? Everybody keeping track of my exhibits?

MR. NICHOLAS: Yes, Your Honor.

JUDGE DAVIDSON: I want to know about one in particular. I think you -- Mr. Krauss, you put one in and then you sort of took it out. I don't know where it stands. Was that number B-1929, or --

MR. KRAUSS: Your Honor, we'll clear that up tomorrow morning.

JUDGE DAVIDSON: That's fine with me, as long as we know where we stand. Now tomorrow you're also presenting me with your positions on the seconal study?

MR. NICHOLAS: That's correct, Your Honor.

JUDGE DAVIDSON: Okay. What else can I tell you? I'm not -- here, I guess. I'll have lots to say when we -- but right now, I'll let you worry about it.

All right, I'll ask. What are your -- Dr. Kassenborg tomorrow?

MR. NICHOLAS: That's correct, Your Honor.

JUDGE DAVIDSON: Now do we have to start at 8:30 so we can finish at a reasonable hour, or you don't know because you don't know how the doctor is going to answer the questions? Is that it?

MR. KRAUSS: We do not need to start at 8:30.

MR. NICHOLAS: Well, at least not our side.

JUDGE DAVIDSON: All right. Well, we'll start at 9:00 o'clock again tomorrow. We're adjourned until 9:00 a.m., tomorrow.

MR. NICHOLAS: Thank you, Your Honor.

(Whereupon, the hearing was adjourned, to reconvene Friday, May 2, 2003 at 9:00 a.m.)

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