UNITED STATES
COURT OF FEDERAL CLAIMS

THERESA CEDILLO AND MICHAEL CEDILLO, AS PARENTS AND NATURAL GUARDIANS OF MICHELLE CEDILLO,	)	
Petitioners,	)	
v.	)	Docket No.: 98-916V
SECRETARY OF HEALTH AND HUMAN SERVICES,	)	
Respondent.	)	

Pages: 2072 through 2277

Place: Washington, D.C.

Date: June 21, 2007

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IN THE UNITED STATES COURT OF FEDERAL CLAIMS

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SECRETARY OF HEALTH AND HUMAN SERVICES,	)	
Respondent.	)	

Ceremonial Courtroom
National Courts Building
717 Madison Place NW
Washington, D.C.

Thursday,
June 21, 2007

The parties met, pursuant to notice of the Court, at 9:02 a.m.

BEFORE: HONORABLE GEORGE L. HASTINGS, JR.
HONORABLE PATRICIA CAMPBELL-SMITH
HONORABLE DENISE VOWELL
Special Masters

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C O N T E N T S

WITNESSES:	DIRECT	CROSS	REDIRECT	RECROSS	VOIR DIRE
For the Respondent:					
Stephen B. Hanauer	2076	2144	--	--	--
	--	2197	2198	2199	--
Christine McCusker	2202	2246	--	--	--
	--	2271	2274	2275	--

P R O C E E D I N G S

(9:02 a.m.)

SPECIAL MASTER HASTINGS: Good morning to all those in the courtroom and at home. We're going to be starting with the testimony of Dr. Hanauer in just a minute.

I first want to let you folks know that are listening in about a special procedure tomorrow morning. Tomorrow morning we are going to be starting the phone conference call a bit late. We are going to be taking some brief testimony from one witness presented by Respondent, Dr. Chadwick, by telephonic conference call from England.

That necessitates unfortunately that we are not going to be able to put that particular testimony over the telephonic conference call. That's not because this testimony is going to be secret in any way. It will be done here in the public courtroom. It will be transcribed.

I'm not sure whether it will also be on the internet audio download, but it's not because it's not public. It's for the very simple reason that we have only one telephone line available in this courtroom, and when it's coming with the testimony coming in we will not be able to do the telephonic conference call.

We will be starting the telephonic conference call tomorrow morning probably sometime around 9:30. As soon as that one witness is done the second witness for the day will be available through the telephonic conference call. We apologize for that, and you can set your schedule for tomorrow accordingly.

With that, Mr. Matanoski, who will be doing the examination of Dr. Hanauer?

MR. MATANOSKI: Ms. Ricciardella will be.

SPECIAL MASTER HASTINGS: Okay. Ms. Ricciardella?

MS. RICCIARDELLA: Thank you.

SPECIAL MASTER HASTINGS: Dr. Hanauer, could you raise your right hand, please?

Whereupon,

STEPHEN B. HANAUER

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

SPECIAL MASTER HASTINGS: Okay. Ms. Ricciardella, please go ahead.

MS. RICCIARDELLA: Thank you.

DIRECT EXAMINATION

BY MS. RICCIARDELLA:

Q Good morning, Doctor. Would you please

identify yourself for the Court?

A Stephen B. Hanauer.

Q And what is your current academic appointment?

A I am Professor of Medicine in Clinical Pharmacology and Chief of the section of Gastroenterology, Hepatology and Nutrition at the University of Chicago.

Q And would you briefly describe your educational background for us?

A I went to the University of Michigan undergraduate, to the University of Illinois for medical school. I did my training in internal medicine and fellowship in gastroenterology at the University of Chicago, and I remained at the same institution.

Q Would you please describe your fellowship in gastroenterology at the University of Chicago?

A When I did my fellowship between 1980 and 1982 it was a two-year fellowship. It's currently a three-year fellowship.

This entailed specialty training in digestive diseases, which required rotation through endoscopic procedures, rotation through nutrition service, rotation through liver service, a lot of

times rotating through inflammatory bowel disease, which is a major component of our institution's practice, and also I spent several months training in pediatric gastroenterology.

Q And do you hold any board certifications?

A I'm board certified in internal medicine and in gastroenterology.

Q Doctor, would you briefly highlight some of the honors you've received in your career?

A Well, I've risen through the ranks of academic medicine at my institution. I am now a tenured professor and actually a chaired Professor of Medicine at our institution.

Within different societies I've won the awards for clinical research and clinical care from the American Gastroenterologic Association. I was the inaugural chair of the Crohn's & Colitis Foundation's Clinical Alliance, which was a group of institutions collaborating in research related to Crohn's disease and ulcerative colitis.

I'm a fellow of the American College of Gastroenterology. I've served on the boards. I'm currently on the board of trustees of the American College of Gastroenterology. I've served on the governing board of the American Gastroenterologic

Association and chaired the section of Inflammation, Immunology and Inflammatory Bowel Disease of the American Gastroenterologic Association for six years, and I chaired the Clinical Practice section in the American Gastroenterologic Association for four years.

I've chaired the International Organization for Inflammatory Bowel Disease. I've served on the FDA Advisory Panel for Gastrointestinal Drugs and then chaired that panel as well. Some of the things I've done.

Q Do you hold any teaching positions in your specialty?

A Yes. Again, I'm Chief and Professor of Medicine at the University of Chicago, so we are constantly teaching trainees in gastroenterology, internal medicine and medical students.

Q And what do you teach?

A I teach gastroenterology, and my special focus within the field of gastroenterology is inflammatory bowel disease.

Q And do you also give lectures to professional groups or organizations concerning inflammatory bowel disease?

A Yes. I lecture frequently.

Q How often?

A Probably once a week I'm invited to speak at a university or a GI society. I also have been giving the annual lectures on updates of inflammatory bowel disease to the American College of Gastroenterology at their annual meetings for the past years.

Also at the American Gastroenterologic Association meetings, as part of their postgraduate courses I've given lectures on inflammatory bowel disease.

Q Now, your CV mentions that you are a member of the Crohn's & Colitis Foundation of America. Is that correct?

A Yes. I've held various positions with the Crohn's & Colitis Foundation since about 1983 or 1985.

Q Are you currently on the Research Initiatives Committee?

A Correct.

Q What does that committee do?

A The Research Initiatives Committee is looking for novel projects that are not necessarily mainstream, looking for cause or new treatments of ulcerative colitis or Crohn's disease, so trying to stimulate research where there is speculation regarding new hypotheses.

Q Has the Research Committee of the Crohn's &

Colitis Foundation of America ever received a research grant request to research the relationship between measles virus and Crohn's disease?

A The Research Initiative Committee has not, and I actually spoke directly with the head of research from the Crohn's & Colitis Foundation to see if historically there had been any grant applications to this organization which spends several million dollars a year in research on Crohn's disease, and they have not received any grant application.

Q Had they received any grant applications to research a possible relationship between Crohn's disease and autism?

A No.

Q Doctor, I'd like to go over your experience as a gastroenterologist.

I believe you stated you're currently a full Professor of Medicine in Clinical Pharmacology at the University of Chicago School of Medicine. Is that correct?

A That's correct.

Q And how long have you been a full professor?

A I think about 15 years.

Q And along with being a full professor at the University of Chicago School of Medicine, what other

positions have you held throughout your career?

A Well, I mentioned several in the awards. Within the institution I've served on numerous institutional committees, and I also am co-director of research in inflammatory bowel disease at our center.

As I mentioned, I've held positions with national and international organizations that have been focusing on gastroenterology -- the American College of Gastroenterology, the American Gastroenterologic Association -- and also specialty societies within that that are focused on inflammatory bowel disease such as the International Organization for Inflammatory Bowel Disease.

Q Do you currently have a clinical practice?

A Yes. I'm actually the busiest clinician within my section of gastroenterology. I see more patients than anyone else in my section and probably more than anyone else in the Department of Medicine.

Q And as part of your clinical practice do you conduct endoscopies?

A Yes, I do.

Q Approximately how many times per week?

A I perform at least 12 or so colonoscopies a week.

Q Have you ever diagnosed a patient with an

inflammatory bowel disease?

A I frequently diagnose patients with inflammatory bowel disease, and I frequently undiagnose patients who are referred with a suspected diagnosis of inflammatory bowel disease who don't have it.

Q How many persons with inflammatory bowel disease are you currently following as patients?

A Well, we have a database at our institution regarding patients with ulcerative colitis and Crohn's, and over the past year we've seen 6,000 patients.

Q Doctor, you've published over 280 articles related to GI issues and specifically inflammatory bowel disease. Is that correct?

A I don't think it's 280 related to inflammatory bowel disease, but that's about the sum of my peer reviewed publications.

Q In addition, you've published over 70 book chapters. Is that correct?

A I think so, yes.

Q And you currently serve on the editorial board of approximately nine GI-related medical journals. Is that correct?

A Yes.

Q And your CV states that you're the editor in chief of the *Inflammatory Bowel Disease Monitor*. Is that correct?

A Yes.

Q What is that?

A The *Inflammatory Bowel Disease Monitor* is a newsletter essentially that goes out to physicians in the U.S. and Europe related to recent advances in inflammatory bowel disease, again ulcerative colitis or Crohn's disease.

Q And you're the section editor of *Gastroenterology and Hepatology*. Is that correct?

A For inflammatory bowel disease, yes.

Q And what does it mean to be a section editor?

A I solicit and review articles to be submitted for that journal related to IBD.

Q And you're also the section editor of the *Inflammatory Bowel Disease Journal*. Is that correct?

A I'm one of the section editors, yes.

Q Are you a reviewer for any journals?

A I'm a reviewer for numerous journals.

Q Doctor, I believe you briefly touched on it, but you currently are conducting research into inflammatory bowel disease. Is that correct?

A Yes. Through my career I've focused on clinical research, which is primarily patient-related research, as to the epidemiology and potential cause and certainly therapies for both ulcerative colitis and Crohn's disease.

Q Your CV mentions that you're co-director of the Inflammation Bowel Disease Research Center. What is that?

A Within our institution we have a group of individuals, both basic researchers, translational researchers who work between basic and clinic research, and clinical researchers looking at potential causes of Crohn's disease and ulcerative colitis from a basic research mechanism, looking at some of the risks involved with the disease.

For instance, why is cancer more common in patients with ulcerative colitis or Crohn's disease, and certainly looking at novel therapies for these diseases.

Q Have you ever received funding from a pharmaceutical company for your research?

A A lot of our research is funded by pharmaceuticals related to drug development and also some aspects of the disease.

For instance, support for studies related to

the quality of life, new diagnostic techniques. Many of these are supported by pharma.

Q Doctor, have you ever testified as an expert witness in a legal case before?

A Yes.

Q Approximately how many times?

A I've testified probably 50 times in medical malpractice cases, a few times in toxic tort cases.

Q And do you testify for the plaintiff or the defendant?

A In medical malpractice I testify for both sides.

Q And have you ever consulted for a pharmaceutical manufacturer in a legal case?

A Yes. I am currently consulting with Roche related to Accutane.

Q Doctor, turning to the facts of this case, did you review the medical records pertaining to Michelle Cedillo's GI issues?

A I've reviewed many of the medical records. I don't believe I've reviewed 100 percent, but I certainly reviewed those related to her endoscopic and GI evaluations.

Q And did you review the expert report submitted by Dr. Arthur Krigsman in this case?

A Yes, ma'am.

Q And did you review the medical literature that was submitted with Dr. Krigsman's report?

A Yes, and expanded that medical literature with my own searches on PubMed and Google Scholar related to possible associations of measles, measles virus, measles vaccine and specifically related to intestinal inflammation, what has been described as autistic enteropathy, autism and inflammatory diseases, so I expanded the search beyond Dr. Krigsman.

Q Did you also review the trial testimony of Dr. Krigsman?

A Yes.

Q And did you review the copies of the slide presentation that Dr. Krigsman presented during his trial testimony?

A Yes.

Q And did you review the pathology slides from Michelle Cedillo's January 2002 upper and lower endoscopy?

A Yes, I did.

Q And did a pathologist at the University of Chicago also review those biopsy slides?

A Yes. I reviewed the biopsy slides with Dr.

John Hart from our section of Gastrointestinal Pathology.

Q And did you review sections of the capsule wireless imaging, also known as the PillCam, taken of Michelle on June 6, 2006?

A Yes. I reviewed both the images presented to the Court, as well as the original disk.

Q Doctor, in your opinion is there any evidence in the record which shows that Michelle Cedillo has chronic bowel inflammation?

A No.

Q Before we get to the basis for your opinion, I'd like to talk about inflammatory bowel disease. What is inflammatory bowel disease?

A Inflammatory bowel disease encompasses a spectrum of inflammatory disorders of the digestive tract, and depending on the location within the digestive tract the nature of these diseases are quite different, so anything that produces inflammation of the digestive tract would be an inflammatory bowel disease.

The most common are infections such as salmonella or shigella or the Norwalk agent that produces viral diarrhea or rotavirus, a virus that affects children. Acute infections are the most

common types of inflammation.

We have inflammation in the intestine that may be related to injury such as radiation. We have types of inflammatory bowel disease that are related to medication, in particular nonsteroidal anti-inflammatory drugs that are aspirin-like agents.

But there are two types of chronic inflammatory disease of the intestines that we really describe as chronic and idiopathic, meaning we don't know the cause of these diseases, and those encompass Crohn's disease and ulcerative colitis. Those are the main forms of chronic inflammatory bowel disease.

There's another form that's called microscopic or collagenous colitis that's a relatively newly recognized form of pathologic inflammation in the setting of a normal endoscopic examination, and that would be another type of chronic inflammatory disease.

Q Now, is inflammatory bowel disease the same thing as irritable bowel syndrome?

A Absolutely not. The hallmark of inflammatory bowel disease is inflammation. Irritable bowel syndrome is a group of disorders, a group of symptomatic disorders, that affect the digestive tract that are related to increased motility or pressures

within the digestive tract and also an increased perception of that motility within the digestive tract.

Q And what are the symptoms of irritable bowel syndrome?

A Irritable bowel syndrome has symptoms of abdominal pain with diarrhea or constipation, but most often with alternating diarrhea and constipation.

Q Doctor, you touched on the different inflammatory bowel diseases, but what are the various inflammatory bowel diseases?

A Again, we should probably limit the discussion to the chronic inflammatory diseases, which are ulcerative colitis and Crohn's disease. Frankly, having read Dr. Krigsman's testimony, he did a pretty good job of defining.

Ulcerative colitis is a diffuse, continuous, superficial inflammation. By superficial we mean it only goes through the inner lining, affects the inner lining of the large intestine or what we call the colon.

Ulcerative colitis begins always at the anal verge, at the very bottom of the colon, and can affect a more proximal extent of the colon in individual patients, but once any portion of that colon is

affected everything downstream to the bottom is affected in the same manner in a very superficial inflammatory process.

The ulcerative colitis, if you look at it through a scope, it looks like someone took sandpaper and rubbed the lining of the colon so it looks granular. It looks exactly like underneath a scab.

If you have a scab, underneath it is this granular, oozy tissue. The large intestine doesn't make a scab because it's a mucous membrane. It's always moist, so that granular tissue is what looks like ulcerative colitis. In ulcerative colitis, only the large intestine is affected.

In Crohn's disease, the pattern of inflammation is different. In Crohn's disease, rather than a continuous pattern of inflammation Crohn's disease is more focal or patchy inflammation that can affect not only the large intestine, but can affect any portion of the digestive tract from the mouth all the way down to the rear end.

The pattern of inflammation, the focal pattern, is also deeper so in Crohn's disease the inflammation goes through all of the layers of the intestinal wall and can actually affect an adjacent organ, which we would call a fistula if the

inflammation actually burrows through.

So the symptoms or the findings are going to depend on what the disease is and also how severe it is in any particular portion of the digestive tract.

Q Is there a subcategory called indeterminate colitis?

A Yes. Indeterminate colitis refers to patients who have such severe ulceration of their large intestine, of their colon, that you can't separate the pattern between ulcerative colitis and Crohn's disease.

It doesn't refer to any minor condition. I would call a minor condition nonspecific, but indeterminate colitis is really a specific condition where the inflammation and ulceration is so severe that you can't separate between the pattern of ulcerative colitis and Crohn's disease.

Q Doctor, this is probably self-explanatory, but itis. What does itis mean?

A In medicine when we refer to itis it means inflammation. Colitis is inflammation of the colon. Ileitis would be inflammation of the ileum. The term enterocolitis, entero refers to the small intestine, colon to the large intestine, so enterocolitis would refer to inflammation in both the small and large

intestines.

Again, those are nonspecific terms. They're very general. There are many types of colitis. There are many types of enteritis. There are many types of enterocolitis.

Q Doctor, is there any evidence that viral infections cause inflammatory bowel disease?

A No.

Q The last page of your report states that, "Viral enterocolitis are self-limited." Would you please explain what you mean by that?

A Well, this is pretty common. When one of us has a stomach virus, stomach flu, it lasts 24 to 72 hours. That would be typically what's known as a Norwalk agent. That's what causes the diarrhea and vomiting on cruise ships.

Rotavirus is the most common cause of diarrhea in children throughout the world, and this is a viral infection that causes kids to have diarrhea. It usually lasts three to seven days and then it's gone. There is no chronic viral inflammatory bowel disease.

Q So in your report when you state that, "These do not include chronic symptoms," could you just expound on what you mean by that?

A When the intestine is confronted with a bacteria or a virus it develops acute inflammation to get rid of it. That's the way our body gets rid of pathogens or invading organisms.

Once that organism is eradicated, the intestine goes back into its normal physiologic amount of chronic inflammatory cells that line the normal intestine.

Q Doctor, are you aware of any evidence of measles virus causing inflammatory bowel disease?

A Outside of the Royal 3 group, no.

Q Doctor, what are the neurological complications of inflammatory bowel disease?

A There are no specific neurologic complications of inflammatory bowel disease. In other words, ulcerative colitis or Crohn's disease inflammation do not affect the brain or the nerves.

On the other hand, there are secondary consequences, so someone with Crohn's disease, for instance, does not absorb Vitamin B12. If you have a Vitamin B12 deficiency that can cause neurologic conditions, particularly a tingling or numbness in the fingers or toes known as a peripheral neuropathy.

In addition, if you do an MRI of individuals with inflammatory bowel disease you find nonspecific

changes in up to 30 percent of patients in the brain that is not associated with any symptoms or any specific patterns of neurologic illness.

Q Doctor, what is gastrointestinal reflux disease?

A In contrast to inflammatory disease of the intestines, gastroesophageal reflux is caustic, an acid-related injury to the lower esophagus from acid pushing up into the esophagus, which then erodes the lining of the esophagus and causes ulcerations due to that caustic or acid injury.

Q Is it an immunologic injury?

A No. It's a caustic injury due to acid, just as if you'd put acid on your hand you would have an ulcer and irritation from that.

Q Is it evidence of inflammation?

A No. There's no active inflammation aside from the healing components of the ulcer. The injury in acid reflux is due to acid.

Q Doctor, how is inflammatory bowel disease diagnosed?

A Inflammatory bowel disease is diagnosed by, first of all, having a suspicion that an individual's symptoms, which would typically be diarrhea, weight loss, fever, rectal bleeding or abdominal pain, would

be due to inflammation.

So you're looking for inflammatory symptoms, which again are fever, weight loss, bleeding, diarrhea, diarrhea that has inflammatory cells within it, that would lead one to suspect that there's chronic inflammation.

Then the diagnosis is made by a combination of endoscopic examinations, looking at the tissue, biopsies from the tissue, or if the tissue can't be reached with an x-ray of an area that may represent inflammation based on different forms of x-rays or CT scans.

Q You mentioned endoscopies, the necessity of having an upper and lower endoscopy. What is an upper endoscopy?

A An upper endoscopy is a tube that's passed through the mouth, down the esophagus, into the stomach and into the first part of the small intestine.

Q And what is a lower endoscopy?

A A lower endoscopy, typically a colonoscopy, is a similar tube that's passed up the other direction into the rectum that can examine the entire large intestine and frequently get into the bottom part of the small intestine that's known as the terminal,

meaning the end of the ileum.

Q Doctor, what is meant by the term histopathology?

A Histopathology is a microscopic examination of tissue that's obtained either with biopsies or at surgery.

Q Is it the same thing as pathology?

A Essentially, yes, but pathology you could see gross pathology with just taking the organ, looking at it. The histopathology refers to a microscopic examination.

Q And what is the purpose of sending a tissue biopsy for a histopathologic analysis?

A Well, different types of inflammation, different types of inflammatory bowel disease, have different types of microscopic or histologic inflammation, so even though a growth or a visible lesion may have several different differential diagnoses to it the examination under the microscope can clarify and help to classify the exact type of inflammation.

Q Doctor, would you diagnose inflammatory bowel disease in a patient if the histopathology showed no inflammation?

A Not unless there were absolutely

pathognomonic features in areas where you could not biopsy.

Q And what does that mean?

A In other words, if a patient had absolutely typical x-ray appearance of Crohn's disease in an area that was not accessible we might make that presumptive diagnosis, but that is extraordinarily rare.

Virtually 99 percent of patients with ulcerative colitis or Crohn's disease have lesions that are accessible to endoscopy.

Q Doctor, what if you saw evidence of possible inflammation during endoscopy, but the tissue diagnosis at pathology found no inflammation? Would you conclude nonetheless that the patient at IBD?

A Absolutely not. You can make the appearance of the intestine look different according to how traumatic the examination is, so if there's a lot of rubbing of the scope along the lining of the intestine it will look as though you've rubbed the skin hard and it will be red. It may be granular. You may actually wipe off some of the cells. So the examination itself can cause lesions that may or may not look like inflammation.

There are other lesions, and we'll get to that in our further discussions, that may look like

inflammatory lesions, but are not inflammatory and are indeed, for instance, traumatic.

Q Doctor, if you saw evidence of possible inflammation during endoscopy but the tissue diagnosis comes back from pathology as negative or unremarkable, does that mean that the patient's inflammation falls into the category of indeterminate colitis?

A No. Again, indeterminate colitis applies to such severe ulceration that you can't distinguish it, but you can't have an itis without inflammation so you can't have any kind of colitis unless there is active inflammation.

Q Doctor, what percentage of your patients with inflammatory bowel disease have normal pathological findings?

A None, but let me extend that a little bit. Essentially none do, but if you go to an area of the intestinal tract that's not affected by the disease that will appear normal.

Q Sure.

A But areas that appear abnormal, to find no pathologic correlation to the endoscopic appearance is not seen.

Q Doctor, I know you have a slide here to describe briefly how the digestive tract functions.

That's not the digestive tract. There we go.

Would you briefly describe how the digestive tract functions?

A Yes. This is important because we need to understand the different symptoms that a patient may have and actual pathology.

Just to say it outright, diarrhea may be due to inflammation, but there are many other causes of diarrhea aside from inflammation. Understanding a bit about how this tract works helps us understand I think some of the symptoms and what was going on in this patient.

The digestive tract is actually a tube through the body. It's open at the top, and it's open on the bottom. Actually anything that's in that tube is outside of our body, and the function of the digestive tract, besides giving pleasure on both ends, actually has two functions. One is that the digestive tract is actually our immunologic eye to the world.

More of our environment is sampled through our intestinal tract than the rest of the body. Most of the foreign material we sample is actually through the digestive tract, so there is more lymphoid tissue or immune tissue in the gut than any other portion, so the number one function is the immune function of the

gut.

The second, of course, is digestion and absorption of nutrients, and in order to digest nutrients and absorb nutrients the intestinal tract is divided into several functional segments. It's one long tube. The first portion is actually the mouth, and the mouth is important because the saliva lubricates food, starts to mix it with digestive enzymes that come from our salivary glands.

Then the esophagus is the long tube that goes from the mouth to the stomach. The esophagus is mainly a transport tube. Once the food hits the stomach the stomach acts like a holding tank or a reservoir, and the stomach mixes the food with digestive enzymes and acid that break the food down from big particles into microscopic particles.

As food primarily is a liquid exits out of the stomach into the small intestine, the role of the small intestine, first of all, is to mix that liquid with enzymes from the pancreas and from the gallbladder and liver that further break down the liquid into microscopic particles that are absorbed along the length of 20 feet, the 20 foot length of the small intestine.

About one quart a day empties from the small

intestine into the large intestine, which is known as the colon. The job of the colon is really waste management. The job of the colon is to take the excess water out of that quart and to package stool for convenient elimination.

We like to say the colon is often considered a social organ. You can live without a colon. You may not be happy, but you can live without a colon quite normally.

Now, about a quart of undigested food, food that's not digested, and the sloughing off of our normal cells because our digestive tract turns over every week -- the lining of the digestive tract regenerates every week -- so that quart enters into the large intestine.

The large intestine churns around through its motility and as the liquid is in contact with the lining the liquid is absorbed, and as the material moves down the colon it is more or less packaged.

Finally, a packaged bolus or fecal bolus reaches the rectum, the bottom of the large intestine, the bottom of the colon, and what happens is that stretches the rectum. When the rectum is stretched, we feel like we have to have a bowel movement.

At the same time, there is an unconscious,

an autonomic, relaxation of the lower sphincter, of the anal sphincter at our butt, and this is what maintains our continence and prevents us from losing control.

There are two muscles, an internal sphincter, which is under autonomic or unconscious control, and an external sphincter, which is under conscious control. When a bolus of stool reaches the rectum it stretches. We have the urge to defecate, but we don't defecate until we sit down on the toilet and consciously relax our external sphincter and press down and push that bolus out.

Now, the liquidity or solidness, the two extremes of stool, are going to depend on several factors. One of the factors is how long this material is in contact with the colon. If things are rushing through the large intestine, not much of the fluid is going to be absorbed and it's going to come out as loose stool.

The longer it's in the colon the more water is going to be absorbed and the more and more compact that stool is going to be and the more solid it's going to be.

Now, what also can happen is that in individuals who are so constipated that they have a

large bolus of fecal material in the rectum, it is stretching the rectum. That leads to a relaxation of that inner sphincter, and we can't consciously control that forever so what happens is the liquid stool actually goes around that formed stool and can actually cause diarrhea in the presence of constipation.

That's not an uncommon thing, particularly in children who have chronic constipation or mental disorders who are unable to evacuate for one reason or another.

The liquidity of the stool, whether or not you have diarrhea or hard stools, is going to depend on the motility of the intestine. It's going to depend on what you eat. If we eat prunes, prunes actually have a laxative effect and actually will cause more frequent bowel movements.

If we eat no fiber, on the other hand, or an Atkins-like diet where there's no fiber to hold in water we can actually be constipated, so there are many aspects, many things that can affect the motility of the colon, the liquidity of the stool, outside of inflammation.

Now, the way inflammation causes diarrhea is that the inflammation can either secrete fluid --

again think of that oozy scar. It's oozing tissues out. That would be one reason, but also if the inflammation impairs the intestine from absorbing nutrients those nutrients actually go into the large intestine and hold water in and can produce diarrhea.

The perfect example is when you take Milk of Magnesia. It's a laxative. The magnesium in that is a particle that holds in water and loosens the stool. That can be seen in different foods as well.

So the presence or absence of diarrhea can be due to motility. It can be due to foods. It can be due to other medications. It can be due to inflammation.

Q Doctor, if the patient presented to you with GI symptoms of diarrhea, constipation and abdominal pain would you assume that that person had an inflammatory bowel disease?

A The only conditions that produce diarrhea alternating with constipation is what's known as irritable bowel syndrome. Inflammatory disease produces a chronic persistent diarrhea with inflammation in the stool.

Q Now, are fluctuations in bowel movements necessarily caused by inflammation of the bowel?

A Absolutely not. As I just stated,

fluctuations in bowel movement could be due to fluctuations in motility in the intestines.

For instance, when we scare an animal they defecate. That's come into our common vernacular. We're known as we get scared blankless. That's common.

When performers go on stage or attorneys have to go on trial they frequently get butterflies in their stomach, and they get more frequent bowel movements due to the nervous energy and the connection between the brain and the intestine that can affect the motility of the intestine, so there are many things that can affect it.

Q Can diet affect the motility of the intestine?

A Absolutely. The more fruits and vegetables that we eat that have more fiber, the more looser the bowel movements are going to be.

Again, if we're eating foods that have laxative properties like prunes you're going to have liquid diarrhea. On the other hand, if you're eating foods without fiber you're going to have less frequent bowel movements.

Q Can food allergies also cause diarrhea and constipation?

A Absolutely. Both food allergies, which are immunologic reactions to food, and also food intolerances, which are sensitivities.

For instance, people who will go out and eat hot, spicy food will often have increased bowel movements because the spices act as stimulators to the nerves of the intestine and can increase the motility of that, but foods that can also have laxative properties can affect the liquidity of the stool as well.

Another example are foods like milk and the milk sugar, lactose. Many individuals are unable to digest that sugar and that sugar acts as an osmotic particle, meaning it holds water in and can make the stool more liquid.

Q Now, Doctor, your report on page 1 states that worsening diarrhea and constipation are not associated with enterocolitis or inflammatory bowel disease. Could you briefly explain what you mean?

A Again, inflammatory bowel disease entails inflammation of the intestine which is chronic, unless it's treated, and patients with inflammatory bowel disease that are progressive have progressive diarrhea. They don't get constipation.

The only thing that produces alternating

diarrhea and constipation, as I've said, is irritable bowel syndrome, which is not associated with the inflammation.

Q Now, is the symptom of persistent diarrhea sufficient to conclude that that person has inflammatory bowel disease?

A Not at all. Thirty percent of patients who have irritable bowel syndrome have a diarrhea predominant form.

Q I'd like to turn specifically to the facts of this case. Now, Michelle has had five endoscopies. Is that correct?

A Yes.

Q And have you reviewed the medical records pertaining to each of those five endoscopies?

A Yes.

Q Her first endoscopy was on June 10, 2000, and that was an upper endoscopy, correct?

A Yes.

Q And before we look at those records, Petitioners' Exhibit 44 at 58 describes her GI symptoms that she was having before the endoscopy. I'll read those aloud.

"Her usual pattern is that of two to seven mushy stools each day containing visible mucous of a

variable size, including smears, although there was a recent three-day period without any bowel movement. No blood in the stool is reported.

"The patient additionally has frequent bloating of the upper abdomen associated with excessive flatus and sleeps poorly, often waking up at night and appearing upset.

"She has a history of frequent regurgitation associated with the constipation up until one year ago, and although she no longer vomits she gags easily and appears to ruminate associated with coughing and taps at her upper chest."

Doctor, is this description sufficient to indicate inflammation of the bowel?

A No. The alternation between loose bowel movements and constipation associated with symptoms of gastroesophageal reflux have no specificity or even insinuation of inflammatory bowel disease.

Let me just comment on the mucous. The mucous. Irritable bowel syndrome used to be called mucous colitis, which is an inappropriate term because there is no itis in it, but mucousy stools are primarily associated with irritable bowel syndrome.

The intestine is a mucous membrane. The lining cells of the colon produce mucous, which

actually serves as a kind of lubricant and a protective barrier against that lining.

Q Doctor, turning to the postprocedure diagnosis following Michelle's June 10, 2000, endoscopy -- I'm referring to Petitioners' Exhibit 44 at 65 -- the postprocedure diagnosis is erosive esophagitis. What is that?

A Erosive esophagitis is related to the reflux, the movement up, of acid from the stomach, which is normal in the stomach, into the esophagus.

Under normal situations the esophagus is protected against acid by the propulsive motility and the sphincter muscle between the esophagus and the stomach, and if that sphincter muscle is loose or if there's increased abdominal pressure the acid from the stomach can come up into the esophagus in inappropriate amounts and produce injury to the lining of the esophagus.

That's known as erosive esophagitis or gastroesophageal reflux with esophagitis.

Q Also known as GERD, the acronym GERD?

A Yes. Gastroesophageal reflux disease.

Q Is that an indication of inflammation?

A It's an indication of acid injury. Actually the inflammation is part of the healing in that

situation, but it's not an inflammatory injury. It's a caustic acid injury.

Q And the other postprocedure diagnosis is gastritis. What is gastritis?

A Well, again using our terminology, gastritis is inflammation of the lining of the stomach.

There are many different types of gastritis. You can have gastritis, as is alluded here, related to a bacterial infection called helicobacter that can also be associated with gastric and duodenal ulcers, but there are many things that can cause gastritis.

Again, different foods. Allergic reactions can cause gastritis. Certainly many different medications, including nonsteroidal anti-inflammatory drugs can do this. Other bacteria and viruses can cause gastritis.

I will also mention that there is a specific form of gastritis that's called a multifocal gastritis that has been associated with Crohn's disease identified by a pediatrician, but the histologic examination in this patient did not show that particular pattern.

Q What is the role of acid damage to the lining of the stomach in causing gastritis?

A Well, acid can produce inflammation in the

stomach under several situations. One is if there's too much acid produced it can cause ulcers, but usually if there's some other component in the stomach to cause the injury -- for injury, if there's a helicobacter infection of the lining in the intestine it can make it more susceptible to acid damage.

Again, most frequently in our society it's aspirin-related medicines that actually erode or prevent the lining of the intestine from healing similar to what Dr. Krigsman said in his deposition. It can produce gastritis and also ulcers.

Q Okay. Now, the record does not contain a report on pathology following this June 10, 2000, upper endoscopy. However, we do have evidence in the record as to what the pathological diagnosis was. I'm referring to Petitioners' Exhibit 44 at 31.

It states that following biopsy the histologic evidence was gastroesophageal reflux disease or GERD, correct?

A Correct.

Q And in addition to focal gastric enteroinflammation was prominent eosinophils. What are eosinophils?

A Eosinophils are one of the types of white blood cells that are most commonly associated with

allergic reaction.

You'll see eosinophils in patients who have allergic asthma or allergic sinus or nose problems, sinusitis or rhinitis, and in patients who have allergic reactions, and they may be very subtle or mild, to foods or to medicines can have increased amounts of eosinophils in the lining of their digestive tract, anywhere actually from the esophagus down into the colon.

Q Are they indicative of inflammatory bowel disease?

A No, they're not specific in any way for inflammatory bowel disease. They're more indicative of an allergic type reaction or exposure, for instance, to parasites, but we don't have any evidence of a parasitic infection in Michelle.

Q Now, Michelle was put on Prilosec following her June 2000 endoscopy. What is Prilosec?

A Prilosec is a medication that stops the stomach from producing acid or greatly reduces acid production from the stomach, and without the acid there's no longer injury to the esophagus and under usual situations the esophageal ulcers then heal.

Q And that's what happened in this case? She had a follow-up endoscopy on December 11, 2000, and

the postprocedure diagnosis, which is found at Petitioners' Exhibit 44 at 42, states: "Resolved erosive esophagitis." Does that mean that her GERD had resolved?

A The gross lesions, the visible lesions -- when I say gross I mean visible, although they might be gross as well -- are gone.

Q And the pathology report following the December 11, 2000, endoscopy, which is found at Petitioners' Exhibit 44 at 43 through 44 -- we'll blow that up for you, Doctor. How do you interpret that pathology report?

A There's been some confusion I think in testimony previously at least with Dr. Krigsman between the term indeterminate and the term nonspecific.

Nonspecific means that there are many different explanations for the findings, so nonspecific gastritis means that, as I said, it could be due to acid injury. It could be due to infection. It could be due to trauma. It could be due to other medication. It could be due to, as I said, other infection.

Q So would this pathology report, Doctor, indicate at all to you any inflammatory bowel process

at work?

A No, and specifically this is not a multifocal gastropathy or inflammation of the stomach that's been associated in children with Crohn's disease.

Q Now, she had her next endoscopy, an upper and lower endoscopy, so the first time she had a colonoscopy was January 31, 2002.

The postprocedure diagnosis is found at Petitioners' Exhibit 44 at 13 through 14. We'll look at page 14. We'll blow that up. The postprocedure diagnosis was, "Lymphonodular hyperplasia of the colon." What is that?

A I started by describing the digestive tract as an immune organ, and the way that the immune tissue is organized throughout the digestive tract is actually in two different ways.

There is an underlying continuous layer of chronic inflammatory cells along the lining of the intestine, as we'll see in a few minutes, but also the intestinal tract, in order to process foreign material, is also organized into lymphoid aggregates or little, small, microscopic lymph nodes essentially that line the entire digestive tract.

If those appear enlarged we call that

hyperplasia, so lymphonodular hyperplasia would be an apparent enlargement of the lymphoid tissue in whatever organ you're describing.

Q Is it a normal finding in children?

A Yes, it certainly can be a normal finding in children and even increased in children with constipation.

Q Is it evidence of chronic inflammation?

A Absolutely not. This is normal lymphoid tissue. It's just larger.

Q Can lymphonodular hyperplasia be associated with constipation?

A Yes, it can be associated with constipation. It's thought that because of prolonged contact with stool in patients who are constipated, and the majority of stool is actually bacteria, that may lead to a more increased need to process more bacteria, but it's not pathologic. It's not disease. It's normal tissue.

Q Now, Doctor, the results of that January 2002 endoscopy also stated that, "The terminal ileal mucosa appeared normal without signs of inflammation and only mild nodularity." Is this a significant finding?

A It's a normal finding.

Q And, Doctor, the pathology report following the January 2002 upper endoscopy is found at Petitioners' Exhibit 44 at 17. We'll pull that up on the screen.

I note they use the word unremarkable. What does an unremarkable finding on pathology mean?

A Normal.

Q No inflammation?

A Correct. Inflammation would be remarkable.

Q Did you review the slides of tissue taken from this January 31, 2002, endoscopy?

A I reviewed the slides from the small intestine and large intestine, yes.

Q And what did you find?

A That these were normal tissue.

Q Okay. And I believe you alluded earlier that a pathologist at the University of Chicago also reviewed those slides?

A Yes. I reviewed it with our head of GI Pathology, Dr. John Hart, so we looked at the tissue together. I did not prejudice him as to what the reasons for looking at the tissue was. I said what do you think of this tissue.

Q And what did he find?

A He felt that it was absolutely normal, as

have all the other pathologists who have reviewed it.

Q Doctor, I know you have a couple slides you want to show as to what a normal tissue looks like. We'll put those up on the screen. What are we looking at in Slide 2?

A Okay. We are looking at a biopsy of the lining of the colon. The colon has those crypts, which look like the test tubes that are going down.

Those crypts are actually the absorptive component of the colon, and at the top layer you can see that these crypts are comprised of a single layer of cells, and then underneath that single layer of cells are inflammatory cells, but these are not inflammation.

These are chronic inflammatory cells that are constantly sampling the environment. They're sitting there. They're not activated. They're not acute inflammation as we'll see in other examples.

You can actually tell what part of the world an individual is from by the amount of these chronic inflammatory cells between these glands. If you're from a third world country where there's a lot of dysentery and bacterial infection we'll see more of those cells. If you're in a very clean environment, a first world country, there will actually be less.

This is probably a biopsy with a normal amount of these cells that are inflammatory cells, but this is not inflammation. This is normal cells.

The next slide --

Q Slide 3. What are we looking at?

A Okay. The next slide is an example of how the immune tissue of the intestine is organized into these aggregates.

So in the previous slide you saw all these test tubes that were aligned together, but intermittently along the intestine are these small aggregates of lymphoid tissue, which would be called lymphoid aggregates, lymphoid nodules. If there's a big aggregate in the small intestine it's called a Peyer's patch.

Now, the lining cells of this are somewhat different. Instead of having those same absorptive cells these cells actually have what's called an M cell, which is a very thinned out cell overlying these lymphoid cells, the lymphocytes, which is able to sample then the environment and tell the lymphocytes whether this is a harmful feature or if it's something that's absolutely normal.

And so that area on top of this aggregate is actually very thin, and if that thin cell is eroded we

would call that an aphthous ulcer, which is an erosion that overlies a lymphoid aggregate anywhere through our digestive tract from our mouth again all the way down to the small intestine, so the simplest form of an aphthous ulcer is the cold sore that we know about that can affect most of us on our lips or gums would be an example of a small ulceration over a lymphoid aggregate.

These are again organized in different parts of the intestine, most prevalent at the junction between the large and small intestine, in order to sample the intestinal environment.

Q The next slide, Doctor, is a photograph of the tissue slide of Michelle Cedillo graciously provided to us by Dr. Michael Gershon. What are we looking at?

A These are cells actually. This is a biopsy of the small intestine. We see the same lining cells. Now, what's happened here is the colon -- you guys look at me for a second. Thank you.

The colon, the crypts, the absorptive cells, are layered down as you saw in the first microscopic slide. In the small intestine, which needs to absorb nutrients, they're out. They reach into the lining, and those are called villi.

What you're seeing here is a biopsy that's cut off. It biopsied those villi, so you cut off the tips of these circumcised villi, but we can see enough into these that you have normal appearing lining cells -- there's no disruption, there's no ulceration; you wouldn't see those cells there -- and a normal amount of lymphocytes or chronic inflammatory cells underneath it.

What you do not see are any acute inflammatory cells. You do not see pus cells or what are known as granulocytes, neutrophils or polymorphonuclear leukocytes. They're all the same type of cell that mean acute inflammation.

This is the normal amount of chronic inflammatory cells in the small intestine and no evidence of ulceration or aphthous ulceration or underling ulceration.

Q I believe the next slide is a photograph of Michelle's tissue slide from her colon. What are we looking at here? I'm referring to Slide 5.

A Again, these are two slightly different views. Now, remember, as I just showed you, the colon has like test tubes so on the right side they've cut across the test tube like this and so you're seeing the test tubes head on.

These are normal appearing glands. They are not disrupted in any way, and there is a normal amount of chronic lymphocytes between these cells. They are well organized.

In patients who have ulcerative colitis or Crohn's disease these crypts are disorganized. They're irregular in shape, and that's a hallmark of chronic inflammation is what's known as chronic architectural damage. These crypts are perfectly aligned.

On the other slide on the left it's cut a little bit more at an angle so you're seeing a different view of these slides, but again there is no disruption of the lining, the epithelial lining. There's no ulceration. There's no increase in amount of chronic inflammatory cells, and there are no acute inflammatory cells.

Specifically in inflammatory disease, bowel disease, you would be looking for acute inflammatory cells invading and disrupting those crypts, and that would be known as cryptitis, but we don't see any of this. These are normal.

Q Thank you.

A It's what we would see in anybody.

SPECIAL MASTER HASTINGS: Before you go on,

can you spell a couple terms for us? The crypt? How do you spell that?

THE WITNESS: C-R-Y-P-T.

SPECIAL MASTER HASTINGS: All right. And villi?

THE WITNESS: Villi. Villi are the projection of the small intestinal lining into the intestine.

SPECIAL MASTER HASTINGS: You told us what they are. How do you spell that word?

THE WITNESS: V-I-L-L-I.

SPECIAL MASTER HASTINGS: Okay. Go ahead.

THE WITNESS: Or if you're talking about them in the aggregate you might talk about villis changes.

MS. RICCIARDELLA: Thank you.

BY MS. RICCIARDELLA:

Q Doctor, if this had been your patient and you received the same postprocedure report and the pathology report, would you conclude that the patient had an inflammatory bowel disease?

A Let me just again say that these are just representative biopsies. We've looked at multiple biopsies, and she had multiple biopsies of the intestine. This is just one high power view of a

single specimen.

If you looked at this in aggregate there would be many different microscopic views. In none of them was there any evidence of active inflammation.

Q Okay.

A And, no, I would not have diagnosed this patient with any form of inflammatory bowel disease. These biopsies of the small intestine and of the colon are normal.

Q Even if the patient's clinical presentation was having watery, acidic, mucous-like stools every day?

A Again, watery, mucous, acidic have nothing to do with inflammation, and certainly the biopsies bear out that there was no active inflammation.

Q Okay. Thank you. Michelle had her fourth endoscopy, an upper and lower endoscopy, on September 25, 2003, the one performed by Dr. Krigsman.

His findings, his postprocedure report, is found at Petitioners' Exhibit 28 at 454 through 456. We'll look specifically at page 455. He says that the upper endoscopy findings he found esophageal streaking nodularity. What is that?

A I'm not certain what he means, but some streaking or bumpiness would certainly be consistent

with someone who's had esophagitis that's been treated and it doesn't heal perfectly normally. It looks a little bit abnormal.

There's no specificity to that description. It doesn't fit any pattern of anything.

Q Is it evidence of inflammation?

A Absolutely not in and of itself without biopsy evidence of inflammation.

Q He also found on upper endoscopy two distinct enteral inflammatory mucosal swellings. What does that mean?

A Honestly I don't know. Those are not common terminologies used. It's a description of what he saw in the lining, but it has no pathologic correlation to anything that I know of.

Q Now, his findings following the colonoscopy are also found on page 455 of Petitioners' Exhibit 28, and he found again the lymphonodular hyperplasia. That's what we were just discussing, correct?

A Yes.

Q And he says he also found following this colonoscopy multiple sigmoidal aphthous ulceration. You touched a little bit on what aphthous ulcerations are, but could you describe and explain what exactly those are?

A Yes. Aphthous ulcers in the intestine are usually pinpoint, barely visible erosions over a lymphoid aggregate that can be due to trauma, medications, the bowel preparation itself, infection or part of the normal intestinal lining.

Again, an aphthous ulcer is no different than a canker sore that occurs in the mouth. Those are called aphthous ulcers as well, and they can come and go in healthy individuals or they can be present in patients who have these hyperplastic or grossly enlarged lymphoid aggregates, but in and of themselves they have no specificity whatsoever.

Dr. Krigsman in his testimony describes aphthous ulcers in the setting of Crohn's disease, and certainly aphthous ulcers can be the first sign of Crohn's disease, but by no means are they specific for Crohn's disease.

Again, we all have aphthous ulcers in our mouths coming and going, and this does not mean we have Crohn's disease.

Q Are they specific that there's an inflammatory bowel process at work?

A Absolutely not. They can be due to the preparation that you give to cleanse the bowel. They can be due to minor injury.

Some of us get these sores in our mouths from brushing our teeth or from toothpaste. Just minor traumatic injuries can induce this both in the mouth and also in the intestine.

Q And can it be considered a normal finding?

A It certainly can be found in individuals with no disease whatsoever. We don't know the history of them.

Most of these come and go and in children can be present at different times associated with these enlarged lymph nodes in the small intestine, depending on whether there's traumatic injury.

Again, if there's constipated stool rubbing against a lymphoid aggregate you're going to get an aphthous ulcer there.

Q Can you conclude that there's inflammation just by looking and seeing an aphthous ulcer, or would you like a biopsy and a histopathologic confirmation?

A Well, an aphthous ulcer, as we said, doesn't mean inflammation in and of itself. It can be a traumatic injury, just like acid reflux can be due to caustic injury.

So without other tissue diagnosis of inflammation either adjacent to that ulcer or some other tissue, it doesn't have any specific meaning

whatsoever.

Q Now, your report states that aphthous ulcers can be due to bowel preparation for colonoscopy. I believe that's what you just testified about, correct?

A Yes.

Q And your report also states that aphthous ulcers can be related to the use of anti-inflammatory medication. What do you mean by that?

A Well, just as Dr. Krigsman mentioned that aspirin-related medicines that we've called nonsteroidal anti-inflammatory drugs, which includes aspirin, Advil, ibuprofen, Motrin, Aleve, Vioxx, Celebrex, these medications prevent the lining of the intestine from coming together and regenerating and so it's frequent in patients who are taking those medications to have either the microscopic ulcerations or what we call mucosal breaks in the lining of the intestine; not only in the stomach, but also in the small intestine and in the colon.

Q Was Michelle taking nonsteroidal anti-inflammatory drugs?

A Her medical records say she was taking Advil frequently and often on a continuous basis, so yes. That's ibuprofen, and that's certainly been associated with these same findings.

Q Doctor, the pathology report following this September 2003 endoscopy is found at Petitioners Exhibit 28 at 407 through 408, which we'll put up on the screen. We're looking at page 407.

Do you see anything in this pathology report? Are there any significant pathological findings found in this report?

A No, and I should mention particularly that these were interpreted by Dr. Noam Harpaz at Mt. Sinai Hospital in New York, who is one of the world authorities on inflammatory bowel disease and probably trained Dr. Krigsman in pathology when he was at Mt. Sinai for his fellowship, but these were interpreted as essentially normal.

Q The report carries on through page 408, which we'll pull up. Do you see anything in the report on page 408 of any significance?

A No. They were all within normal limits, meaning there was no active inflammation.

I have not seen any biopsy of her small intestine or her colon either in the reports or the biopsies that I reviewed from 2002 that had any evidence of microscopic inflammation.

Q Doctor, if this had been your patient would you say that she had colitis?

A There's no itis.

Q Would you say that she had some form of indeterminate colitis?

A There is no itis or enteritis.

Q What if in addition the patient may also have had the comorbid condition of arthritis? Would that have made a difference?

A There's still no itis here, but patients with arthritis can develop some lymphoid hyperplasia and aphthous ulcers in their intestines.

Whether it's related to the arthritis or that they frequently take these anti-inflammatory medicines for the arthritis is yet to be really elucidated.

Q What if in addition the patient may have had uveitis?

A Uveitis is again often associated with different forms of arthritis. Again, patients are often taking medication for that so you may or may not see them, but there's no specific intestinal correlation to uveitis to my knowledge.

Q What if in addition to the arthritis and uveitis the patient also had elevated C-reactive protein? Would that have made a difference?

A Well, Michelle actually had evidence of an

inflammatory arthritis. We've seen the joints and the evidence of her eye inflammation.

Those in and of themselves would raise the C-reactive protein in the sedimentation rate. You don't need to invoke anything gastrointestinal.

Q What if a patient also had an elevated platelet count?

A Again, elevated platelet counts are associated with inflammation anywhere. She had active inflammation in her joints and in her eye.

Q What if the patient had an anti-OmpC finding?

A OmpC is a serologic finding that's been associated with disease of the small intestine. It's been tested in patients with Crohn's disease of the small intestine and has been found to be elevated in about 60 percent of patients who have Crohn's disease of the small intestine.

It's also been found to be elevated in patients who have other diseases of the small intestine, and the problem is it's never been tested in a population of patients with arthritis or patients who are talking anti-inflammatory drugs that make the intestine leaky to what OmpC is. It's a protein from a bacteria.

So we don't know what OmpC would look like in patients with arthritis or those taking a nonsteroidal drug. It is not what we call a pathognomonic, meaning a virtual feature, of Crohn's disease. It's an association that may or may not be present in Crohn's disease.

Although the lab reports say 95 percent sensitivity or specificity, that's compared to the normal population. It's not compared to patients with arthritis or those taking anti-inflammatory medicine. We don't know what this looks like in that group of patients.

Q Would you prescribe an anti-inflammatory medicine regardless anyway?

A There are several different types of anti-inflammatory medicines, and that's an excellent question.

The ones that we are talking about that produce injury to the lining of the intestine anywhere are called the nonsteroidal anti-inflammatory medicines. Those are the aspirin-like medicines that we've been discussing that I already mentioned -- Advil, ibuprofen, Aleve, Vioxx, Celebrex.

The other types are called steroid. That would be cortisone or its derivative such as

Prednisone. Now, those actually treat the acid inflammation present anywhere in the body and do not cause these lesions in the small intestine or colon or stomach.

So when I say anti-inflammatories causing injury, I will be more specific and call them nonsteroidal anti-inflammatory drugs or we call them NSAIDs, nonsteroidal anti-inflammatory drugs.

Q If a patient with this presentation were receiving and taking anti-inflammatory medication and that person's abdominal pain and the GI symptoms improved, would you conclude that the patient must have had inflammatory bowel disease?

A Absolutely not. These are nonspecific. One of the interesting things is that patients who develop perforating ulcers from taking aspirin or aspirin-like medicine often have no pain. The ulcer is present, but the effects are to block the pain reception from that.

Q Doctor, the last endoscopy Michelle has had took place on June 8, 2006. She had another upper and lower endoscopy.

The postprocedure report of the upper endoscopy is found at Petitioners' Exhibit 59 at 20. We'll blow that up. It says, "Normal examination."

What does that mean?

A Normal examination.

Q Okay. And the postprocedure report of the colonoscopy is found at Petitioners' Exhibit 49 at 23. I'll bring that up on the screen.

A And I should mention one other thing. It also said, "Rule out gastritis." The reason it says rule out is that gastritis itis is a pathologic diagnosis. It's not an endoscopic diagnosis.

You can have the appearance of gastritis with or without actual inflammation, so if you traumatize the stomach rubbing it it will look like it's gastritis, but there won't be any significant pathology.

Q Now, the postprocedure report following the colonoscopy on June 8, 2006, says, "One active ulcer seen in the transverse colon." Again, to you what is this indicative of?

A It's completely nonspecific and may be a normal finding. A single aphthous ulcer means nothing.

Q And looking at the sigmoid colon it says, "Absent ulcer." Is that a typo for aphthous ulcer?

A I don't know.

Q Have you ever heard of an absent ulcer?

A I think that she had many absent ulcers. I'm not certain how many aphthous ulcers she had, but they are described.

Q Now, the pathology report following this June 8, 2006, endoscopy is found at Petitioners' Exhibit 49 at 82 through 83. We'll pull that up.

What do you conclude from this pathology report? It says, "No pathologic diagnosis."

A All of the biopsies of the small intestine and of the -- let me see if this one actually has the small bowel. Can we move down on that one?

Q It might continue onto page 83.

A But certainly the colonic biopsies were all normal, and I don't see a biopsy of the small intestine in this.

Q Okay. Now, in addition to the upper and lower endoscopy, Michelle also had a wireless capsule imaging taken of her, what's known as a PillCam.

Now, we don't have the report of those findings in the record. However, Dr. Krigsman in his written report and in his oral testimony here last week said he saw multiple aphthous lesions and erosions in Michelle's small bowel, and he presented photographs, selected photographs of the aphthous lesions that he said he found.

Do you agree, Doctor, that this is evidence of chronic inflammation?

A Not necessarily at all. First of all, 15 percent of normal individuals will have aphthous lesions in their small intestine.

Patients taking nonsteroidal anti-inflammatory drugs have a high likelihood of having these aphthous lesions and mucosal breaks or erosion throughout their small intestine and often in their colon as well.

Q Let's take a look at one of the slides that Dr. Krigsman presented to the Court last week. I'm referring to page 18 of Dr. Krigsman's slides.

I realize the resolution on this image is not as clear as the slide from the direct presentation he presented, but from Slide 18 he said this was evidence of ulcerations. What are we looking at?

A What you're looking at is, first of all, you're looking at a lot of bubbles, but this slightly pink here, the more salmon colored tissue, are probably what we would call mucosal breaks. They're very shallow erosion.

Let me just say the difference between an ulcer and an erosion is depth, so something that is very, very shallow is just like an erosion, like you

rub off the surface layer. If it's deeper and has visible depth we call that an ulcer. These are little erosions that are seen.

Also keep in mind that this pill camera is a little capsule sized pill that is right up against the lining, so we are talking about something that is millimeters away, as Dr. Krigsman reported, so these are minute, pin-size head breaks in the lining of the small intestine.

Q Okay. And again, page 19 of his slide presentation?

A Again, on the right you see mainly bubbles with those little areas of eroded tissue.

You can't see that these are aphthous ulcers, but you can see that the color is a little bit different showing that there's been some break in the epithelial barrier. This is most likely due to the nonsteroidal drugs that she was taking.

Q Now, you have a slide, Doctor, do you not, of what a colitis lesion looks like?

A What Crohn's disease looks like.

Q Excuse me. Crohn's disease.

A Yes.

Q Yes.

A So as Dr. Krigsman said, these aphthous

ulcers may be the first presenting lesions of Crohn's disease, but they don't stay that way. They enlarge.

Now, this is an endoscopic view. We're not right up against it. We're looking down the tube here so we're several centimeters away.

These lesions are 10, 50 times the size of what we saw in the capsule study. We're now actually looking further away, and you can see these punched out ulcers, irregularly shaped ulcers and also in contrast to what Dr. Krigsman said you can see these areas of redness in between those ulcers.

Now, that's Crohn's disease in that area. That biopsy will show active inflammation, but you don't see an aphthous ulcer there. Aphthae -- aphthous ulcers -- can evolve into these punched out ulcers in Crohn's disease, but you don't need an aphthous ulcer to have evidence of Crohn's disease.

This is an example of Crohn's disease in the large intestine and colon. This is very different from the tiny pinpoint aphthae that someone is talking about.

SPECIAL MASTER HASTINGS: To be clear, Doctor, this --

THE WITNESS: This is not Michelle.

SPECIAL MASTER HASTINGS: This is not

Michelle. This is some other person.

THE WITNESS: This is what Crohn's disease looks like.

SPECIAL MASTER VOWELL: Dr. Hanauer, it would be very helpful to me if you could use a pointer and show us on that picture what it is that you just described.

THE WITNESS: How do I do that?

SPECIAL MASTER VOWELL: Someone should have a laser pointer in this courtroom.

THE WITNESS: Okay. Can I stand up? No, I can't.

SPECIAL MASTER HASTINGS: Right behind you.

THE WITNESS: Sorry. You actually do not see normal tissue here. This red tissue is inflamed, but not yet ulcerated.

These white patches are excavations. These are ulcers of Crohn's disease that we call either punched out or linear, but between them you don't see any aphthous ulcers like you saw in Dr. Krigsman's. You may or may not have these aphthae.

I wouldn't be surprised if it started as an aphthous ulcer, but this is an ulcer of Crohn's disease. The aphthous ulcers are not specific for anything.

I think we have just a couple others to show you.

BY MS. RICCIARDELLA:

Q That for the record was page 8 of Dr. Hanauer's slide presentation. And page 9? What are we looking at on page 9?

A Okay. This is again the colon. This part of the colon up here is actually pretty normal. It's pink. It's not red, but it's right adjacent to a shallow linear ulcer and then a very deep what we would call a bear claw ulcer.

One of the features, ulcerative colitis looks like you rubbed the colon with sandpaper. Crohn's it looks like you take a rake and pick at it or a deep ulceration, so this is a colonic ulcer.

Adjacent to it are areas of heaped up tissue. That's swelling around it, around that ulceration. This is quite visible. You don't need to be up against it to see this. This is seen from several inches away.

Then I think the next one is an example of an ulceration in the small intestine. Again, you're probably now several inches away. You can see the deep, punched out ulcer here, another linear ulceration.

This would be pretty mild Crohn's disease, frankly, of the small intestine, yet you can still see these visible punched out or linear ulcers.

Q Doctor, in your review of Michelle's records has there been any biopsy diagnosis of Crohn's disease?

A No, there's not been any biopsy diagnosis of either enteritis or colitis of any kind.

Q Among your patients with Crohn's disease, Doctor, how many have normal findings on pathology?

A If you biopsy within the area of the disease, the answer would be none.

Q Doctor, assume it's true that as of June 2006 Michelle does indeed have Crohn's disease. Does that mean that she has had a chronic inflammatory process at work in her bowel all these years?

A No, by no means. In fact, if she indeed had these aphthous ulcers years ago one would have anticipated that they would have extended into some other visible or microscopic feature of Crohn's disease over the years that she's been scoped and/or treated.

Q Dr. Krigsman, when he was here last week, showed the Court a photo of a diarrhea-filled diaper that he said is typical of the stool that Michelle

produces. Did you look at that photo?

A Yes.

Q And is that the type of diarrhea indicative of an inflammatory bowel?

A It's not indicative of anything. It's a loose poop.

Q What else could be causing that type of diarrhea?

A Anything that could cause diarrhea from a bowel preparation to overflow incontinence in someone who is constipated.

In inflammatory bowel disease the stool has evidence of inflammation, which are white blood cells or blood, and to my knowledge she's never had any evidence of inflammatory cells in her stool or blood in her stool.

Q If she had blood in her stool would that be evidence of inflammation?

A Not necessarily. It just means that something -- that a blood vessel is leaking, and that could be due to trauma. It could be due to hemorrhoids. It could be due to fissures.

Certainly constipated kids and adults when they pass a bulky stool that stretches and causes a crack in the anal canal can have blood from that,

which would be a fissure and hemorrhoids.

Bleeding per se does not mean inflammation. Pus cells in the stool -- not mucous, but pus cells -- are sign of inflammation.

Q Doctor, does the GI community accept as reliable the diagnosis of autistic enterocolitis?

A To my knowledge, it's not in any of the gastrointestinal textbooks. It's certainly not in our descriptions of inflammatory bowel disease in any of the text related to inflammatory bowel disease that I'm aware of.

Q Doctor, in your review of the medical records and in your review of Dr. Krigsman's testimony, Michelle certainly has significant GI symptoms, does she not?

A Absolutely.

Q And are they deserving of careful care and treatment?

A Absolutely.

MS. RICCIARDELLA: Thank you. I have no further questions.

SPECIAL MASTER HASTINGS: All right. Why don't we take our morning break? It's about 10:35. We'll come back at 10:50.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: All right. We're back from morning break, and we're now going to have cross-examination of Dr. Hanauer.

Ms. Chin-Caplan, please go ahead.

MS. CHIN-CAPLAN: Thank you, Special Master.

CROSS-EXAMINATION

BY MS. CHIN-CAPLAN:

Q Dr. Hanauer, I just want to be absolutely certain about what you're saying. Are you saying that Michelle Cedillo has no GI disease?

A No.

Q Then what are you saying? Everything is normal according to you.

A Her biopsies of her intestines are normal. I'm saying that there is no evidence of inflammatory bowel disease.

Q Inflammatory bowel disease, but you acknowledge that she has bowel symptoms?

A I certainly acknowledge that she has bowel symptoms.

Q Doctor, if we go back to Michelle's history initially, you're aware that she developed diarrhea approximately 14 days after an MMR immunization?

A I'm aware of those reports.

Q And you're aware that the diarrhea persisted

for about perhaps 30 weeks or so?

A I'm not certain of the exact length of that.

Q But it did not resolve immediately. Is that true?

A I haven't seen the specific records of that interval, but I would not contest that.

Q Okay.

A But I've not seen the records, and I can't agree with it.

Q Okay. Doctor, are you aware that one of the adverse effects after a measles vaccine can be diarrhea?

A I'm aware that that has been reported after measles vaccination. Whether causation or some other cause of diarrhea, to my understanding, has not been established.

Q Okay. But you acknowledge that it has been reported?

A I certainly acknowledge that it has been reported consistent with what happens in the general population.

Q Okay. So in your opinion, the diarrhea that Michelle had approximately two weeks after her immunization, would that be related to her immunization?

A I do not know.

Q Okay. You have no opinion?

A I think there are many reasons she may have had diarrhea two weeks after her immunization that have nothing to do with the immunization.

Q And what would they be?

A She could have had a food intolerance. She could have had another infection. It could have been her first symptoms of irritability.

There are many explanations. As we said, diarrhea is not a specific symptom for anything.

Q Is there any documentation in the record at that particular time after the immunization of any food intolerances?

A Not to my knowledge.

Q You mentioned another infection. Are you referring to a GI infection?

A Any kinds of infections in children can cause diarrhea. Many kids who have ear infections can get diarrhea associated with that.

Or, the antibiotic that she was administered for the infection, presumed infection, that she had after the vaccination. She did get an antibiotic. That could have caused diarrhea.

Q Usually with infections and antibiotics once

the infection resolves and the antibiotic ends the diarrhea goes away, doesn't it?

A That aspect of the diarrhea goes away, but many people, in particular those who have had irritable bowels, have persisting symptoms after some inciting stimulus.

Q Persisting symptoms for how long?

A They can be for years or even longer, but her diarrhea did not persist. She then developed constipation.

Q So it's your opinion that after a dose of antibiotics you can have weeks of diarrhea?

A Certainly.

Q And you consider that normal?

A No, I wouldn't consider that normal. I would say it's often related to the antibiotics.

We know there are many people who get antibiotics get diarrhea from it. They may develop changes in their bacterial flora and have continued diarrhea for a period of time.

Q And when you indicate they have a change in their flora, it's related to the antibiotic administration, isn't it?

A Yes.

Q And once that ends, the flora returns back

to its normality, doesn't it, as a rule?

A Usually it does, but often there are other strains, such as clostridium difficile, that may produce, that may overgrow and cause persistent symptoms.

Q Doctor, isn't the clostridium difficile related to the use of antibiotics?

A It may or may not be. Usually it is related to antibiotics, but it can be associated with just exposure to C. difficile. It could be related to other underlying illnesses, and it can be related to other therapy, other medication.

Q Any indication in the medical record that she had C. difficile?

A I don't have any evidence that she was tested in those weeks.

Q Is there any evidence in the medical records that she had C. difficile at that point in time?

A To my knowledge, nobody looked for it.

Q Doctor, you're not a pediatric gastroenterologist, correct?

A Yes.

SPECIAL MASTER HASTINGS: Before we go on, Ms. Chin-Caplan, what was the term you were asking him about. C?

MS. CHIN-CAPLAN: Difficile, D-I-F-F-I-C-I-L-E. It's a bacteria.

SPECIAL MASTER HASTINGS: All right. And it's capital C?

MS. CHIN-CAPLAN: Capital C period for clostridium difficile.

SPECIAL MASTER HASTINGS: All right. Go ahead.

MS. CHIN-CAPLAN: Thank you.

BY MS. CHIN-CAPLAN:

Q Doctor, would it be fair to state that children are not little adults?

A In certain aspects, children are not little adults. In many aspects they are.

Q With respect to the GI tract, are children's GI tracts the GI tract of little adults?

A In 99 percent of the aspects, and of course it depends on what age you're talking about. Neonates have slightly different digestive -- the lining of the intestine is more absorptive in neonates, but the closer the kids get to adulthood the more mature the digestive tract is. Within several years, the digestive tract is essentially the same.

Just like kids can have enlarged lymph nodes from a variety of things, lymphoid hyperplasia is seen

much more commonly in kids than it is in adults.

Q So with respect to a five-year-old child, would her GI tract be comparable to that of an adult?

A In almost all aspects aside from the increased presence of this lymphoid hyperplasia that is common in children. Otherwise the digestive tract would look both endoscopically and microscopically the same as an adult.

Q So if they're essentially the same at five years old as that of an adult, why do we have the field of pediatric gastroenterology?

A Some of the disease that affect children are different from those that affect adults, and there are some developmental abnormalities in kids that are not seen in adults of the digestive tract but for, and in children who do have chronic intestinal disease some of the complications related to growth are different than adults.

So pediatric gastroenterologists primarily will focus the difference between a pediatric and an adult gastroenterologist in one, the set of diseases in young kids may be somewhat different, but also the focus on growth and nutrition is very important for pediatrics and less focused of adult gastroenterologists.

Q So there are differences?
A In what?
Q There are differences in the treatment of children as opposed to those in adults with GI problems?
A The medical therapies for the diseases are the same, although you need in children to focus on nutrition to allow growth.
Q Well, didn't you also indicate that there are certain disorders that are prevalent in the pediatric population that are not seen in the adult population?
A Congenital disorders, yes.
Q So no others?
A That's the main issue. The main issues I think as I told you are developmental or congenital disorders in kids and the complications of the diseases related to growth and nutrition.
Q Now, Doctor, let's get back to Michelle's history. We know that she had an MMR immunization and approximately two weeks later she development diarrhea which persisted for number of weeks. You would agree with that?
A Yes.
Q And then it developed into constipation for

a period of time. Is that true?

A Yes.

Q And then it reverted back to diarrhea. Is that true?

A I think it alternated between diarrhea and constipation.

Q Okay. And by the time she was five years old she was worked up for her diarrhea, correct?

A Yes, and also was having constipation at that time as well.

Q So she was having GI symptoms?

A No question.

Q GI symptoms apparently were unrelated to anything such as food, correct?

A I did not say that.

Q Okay. Do you recall whether any of her physicians looked for the common causes of GI problems?

A They looked for common causes, yes.

Q And did they find any?

A There were questions of whether she had food sensitivities or not, she changed her diet from cow's milk off and on, so there were foods that she was sensitive to, yes.

Q Even when the foods were changed and

everything did the symptoms abate?

A Her symptoms continued to alternate between diarrhea and constipation. One may or may not have been predominant for any period of time.

Q But she continued to have GI symptoms?

A No question that this patient had GI symptoms.

Q And it was perfectly normal then for a pediatric gastroenterologist to take her in for a diagnostic work up, correct?

A To work up which aspect?

Q Her GI symptoms.

A It would be normal to work up those symptoms.

Q Right. And at the first upper endoscopy an ulcer was noticed, correct?

A An esophageal ulcer was noticed.

Q Right. And they ordered treatment for that, correct?

A Yes.

Q And after the treatment they did another upper GI. Is that true?

A Yes.

Q That essentially showed a healed ulcer?

A Yes.

Q Did her symptoms go ahead?

A Her reflux symptoms improved.

Q Did her other GI symptoms go away?

A No. There would be no reason why treating an esophageal ulcer would impact on other symptoms, although please note that when some of her medicines for the ulcer were increased, the Prilosec, that she got more diarrhea, which is a known consequence of that class of medicines.

Q So you think that the diarrhea might have been related to drugs at that point? Is that it?

A No, I don't think that it was solely related to drugs. I think there are many things as I described that can cause diarrhea, and they don't need to be in isolation, they can be in composite, and in children like this they can vary according to changes in the diet and changes in medication.

Q Okay. So they had already made an attempt to change her diet earlier and the symptoms persisted. They found an abnormality on upper endoscopy, they treated it and the symptoms still persisted, correct?

A You're lumping everything together. Her reflux symptoms improved for that. She had varying lower abdominal symptoms through her course.

Q Okay. So her lower abdominal symptoms

persisted, correct?

A In varying forms.

Q Yes. And, Doctor, you reviewed the medical records. When those lower abdominal symptoms persisted it led to a weight loss of approximately 25 pounds, didn't it?

A I don't know that the symptoms led to a weight loss. I will not contest that she lost 25 pounds, but this young lady has obviously complex issues related not only to her digestive tract but to other organs and her growth and behavior.

Q Well, Doctor, how does one lose 25 pounds?

A Most often by not eating.

Q Would the persistence of diarrhea also lead to the loss of weight?

A In this young lady absolutely not.

Q It didn't?

A No.

Q Well, Doctor, you know that she was hospitalized in 2003, correct?

A Yes.

Q And do you recall what the reason for that 2003 hospitalization was?

A Yes.

Q What was it?

A I don't remember the exact terms, but weight loss and continuing gut symptoms, different digestive symptoms, at that time.

Q And wasn't one of the causes also dehydration?

A Yes.

Q So how does one get dehydrated, Doctor?

A Well, you're trying to imply that the diarrhea causes weight loss, and I do not accept that in this individual. The weight loss in this individual was from reducing her dietary intake, which is common in this group of patients.

Q But would you accept that the dehydration was related to the diarrhea?

A No. It was related to not drinking enough to compensate for her bowel activity, whatever it was, at the different times.

Q So the diarrhea had absolutely nothing to do with this hospitalization?

A No.

Q So are you aware that during this hospitalization because Michelle was unable to eat that she eventually had a feeding tube put in?

A When you say unable to eat I would interpret that somewhat differently. She was not eating enough.

Whether she was able to eat or refusing to eat is a different issue, and I can't account for that. I don't know.

Q But a feeding tube was put in, wasn't it?

A Yes.

Q Because she was malnourished, correct?

A Yes.

Q Doctor, they started her very slowly initially, didn't they?

A Yes.

Q And they had to gradually increase the rate of her feeding tube?

A Which is what's routinely done.

Q Yes. That's because the GI tract becomes somewhat intolerant to foods when it hasn't had any for a while. Isn't that true?

A No, that's not the case. If you give a full amount of feeding right away you're going to overcome the normal ability of the intestine to absorb, so our intestines, like most of our organs, are able to adapt, and the way to do that is to start slowly and to advance gradually.

Q So it doesn't cause diarrhea?

A So it doesn't worsen the diarrhea. Certainly.

Q That she already had?

A She had other symptoms as well including constipation at that time.

Q So, Doctor, let's bring us forward now. We've had an MMR immunization, we've had diarrhea two weeks afterwards, and that diarrhea persisted for a while. You would agree with that. We have an upper GI which shows an ulcer and which subsequently heals, but the diarrhea persists.

Then we have a hospitalization for a 25 pound weight loss for malnutrition and dehydration, and you're not attributing that hospitalization to the diarrhea at all?

A No. Not in isolation. Put it that way.

Q Well, let's put it all together then.

A She wasn't eating enough.

Q She wasn't eating enough, but the diarrhea had nothing to do with this?

A The diarrhea in small ways increased her fluid losses, but the majority of time she's been able to compensate for that by increasing her intake either via feeding tubes or orally.

Q So earlier, Doctor, she had been able to eat orally. Now, she was not able to eat orally, correct?

A No. She was not eating.

Q She was not eating. And she required a tube feeding to sustain her choleric status, correct?

A Yes.

Q So she was eating earlier in her life, and then at eight years old when she was hospitalized she was no longer eating and required tube feedings, correct?

A Yes.

Q Would you consider that a deterioration in her GI status?

A No.

Q You wouldn't. Now, you've reviewed the medical records, correct?

A Yes.

Q And are you aware that there was a positive measles gut biopsy obtained at approximately age three?

A I'm aware of that in the records.

Q Okay. And do you assign any significance to the positive gut biopsy in her GI symptoms?

A No.

Q No. They're just isolated?

A No. I don't know the validity of those findings.

Q Well, assume it's valid.

A Okay.

Q If it's valid would you attribute her GI symptoms to the positive gut biopsy?

A No.

MR. MATANOSKI: Just a minute. For clarification, Your Honor, there was a misstatement of fact in terms of the record, and if you're going to pose a hypothetical that's based on this record even if we're supposed to assume a fact I think it ought to be a fact that's reflected in this record. The fact that was misstated for the hypothetical goes back to a couple of questions previously when Ms. Chin-Caplan said are you aware of a positive measles virus biopsy at age three.

As I recall, the biopsy was taken much later in Michelle Cedillo's life, and in fact would be after these hospitalizations that she's talking about right now.

MS. CHIN-CAPLAN: I stand corrected, Special Master. It was in 2002.

SPECIAL MASTER HASTINGS: All right. Go ahead.

BY MS. CHIN-CAPLAN:

Q Now, Doctor, we know that there's a positive measles gut biopsy in 2002, correct?

A No.
Q You don't know?
A I know that on the record that a lab reported it as positive, but as I said I do not know the validity of that lab or report.
Q Okay. And, Doctor, the hospitalization for malnutrition, and weight loss and where the feeding tube was inserted was in 2003?
A Yes, I believe so.
Q Okay. So, Doctor, knowing that this biopsy had taken place in 2002 and had yielded positive measles virus RNA in the gut would you sitting there associate her gut symptoms to the measles virus that was recovered in her gut tissue?
A Absolutely not.
Q Doctor, would you associate any symptoms with the positive gut biopsy?
A I'm not aware of any symptoms associated with an intestinal biopsy for measles.
Q Doctor, it's a virus, right?
A It's a virus.
Q And do viruses cause GI symptoms?
A Some viruses can cause acute GI symptoms. I'm not aware of any virus that causes chronic symptoms. By the way, the biopsy that you're talking

about did not demonstrate full viruses. It if it was valid showed RNA from viruses, which does not mean that these are replicating active viruses.

Q And you were not here for the testimony of Dr. Kennedy, were you?

A No, I was not, and I've not read that testimony.

Q Okay. Now, Doctor, you write. You're an author of papers, correct?

A Yes.

Q Okay. Did you write an article entitled *Inflammatory Bowel Disease: Epidemiology, Pathogenesis and Therapeutic Opportunities*?

A Yes.

Q That was published in *Inflammatory Bowel Disease* in 2006?

A Yes.

MS. CHIN-CAPLAN: Okay. And, Doctor, we're going to try and show you this. I'm sorry. It's on page 9.

SPECIAL MASTER HASTINGS: Are you about to show something?

MS. CHIN-CAPLAN: Yes.

SPECIAL MASTER HASTINGS: What is it? Is it something that's in the record?

MS. CHIN-CAPLAN: No, it's not, Special Master.

SPECIAL MASTER HASTINGS: All right. Do you have any copies of it? It's a medical journal article?

MS. CHIN-CAPLAN: Yes. It's an abstract, Special Master. We don't have copies, we're just going to show it on the screen.

SPECIAL MASTER HASTINGS: All right. While we're waiting for you let me take care of another housekeeping item. Dr. Hanauer talked about a series of slides that were numbered, and we've now been given paper copies of those slides. Let's mark that set of slides as Respondent's Trial Exhibit No. 14. I'm sorry, 15. Let's mark it as Respondent's Trial Exhibit No. 15.

Go ahead then, Ms. Chin-Caplan.

BY MS. CHIN-CAPLAN:

Q Okay. So, Doctor, this is an abstract from *Inflammatory Bowel Disease*. Is this your article?

A Yes.

Q And it talks about ulcers, colitis and Crohn's Disease, correct?

A Yes.

Q And you talk about who it occurs in,

correct?

A Okay.

Q Okay. You indicate that environmental factors can play a role, correct?

A Yes.

Q Okay. You say that there's clearly an established genetic link between certain NOD2 variants and Crohn's Disease. Is that it?

A Yes.

Q Regardless of the underlying genetic predisposition a growing body of data implicates a dysfunctional mucosal immune response to commensal bacteria in the pathogenesis of IBD, especially Crohn's Disease. Possible triggers include a chronic inflammatory response precipitated by infection with a particular pathogen or virus or a defective mucosal barrier. Have I read that correctly?

A Yes.

Q So viruses can initiate an inflammatory process you say?

A We know that's stated that viruses can cause an inflammatory process in the intestine.

Q And can it lead to the development of a chronic inflammatory bowel process?

A We don't know that yet.

Q Okay. Well, isn't that what your article said?

A No.

Q Let me read it again. It says possible triggers include a chronic inflammatory response precipitated by infection with a particular pathogen or virus or a defective mucosal barrier.

A Yes. We are continuing to look for the cause of Crohn's Disease and ulcerative colitis, and we are focusing on microorganisms such as viruses, bacteria, and thus far we have not identified any that have been associated with the development of Crohn's Disease.

Q Doesn't this article indicate however that a chronic inflammatory response can be triggered by an infection or a virus?

A That is the hypothesis that we are currently working on.

Q So you acknowledge that there's some evidence to support this?

A To support what?

Q The fact that a chronic inflammatory response can be triggered by an infection or a virus?

A We know some situations where that is the case, but we do not know of any virus or bacteria that

leads to a chronic inflammatory response in patients with the ulcerative colitis.

Q Now, Doctor, would you agree that a person has symptoms for a very long time before Crohn's Disease or ulcerative colitis is diagnosed?

A They may or may not.

Q Right. Doctor, would you agree as you indicated that Crohn's Disease can start with the beginning of aphthous ulcers?

A Can start, yes.

Q Yes. And that's what Dr. Krigsman said during the case, correct?

A Dr. Krigsman described the aphthous ulcer as the initial lesion of Crohn's Disease.

Q Right. And do you disagree with that?

A I think that it can be one of the initial lesions of Crohn's Disease that evolves into the ulcers that I showed on my slide. They don't stay constant as aphthous ulcers that come and go through the tract.

Q Correct. So they would progress, yes?

A Yes.

Q Into the classic presentation that you would see of crypts, correct?

A I don't know what you mean.

Q Well, what are the classic pathological findings that you see in Crohn's Disease?

A Focal acute inflammation with or without granulomas.

Q So you don't see projecting villi and crypts at all?

A Projecting villi is normal, crypts are normal.

Q Okay. And, Doctor, would you agree that sometimes it's just hard to be able to tell where one process begins and another one ends?

A I don't know what you're talking about.

Q Well, would the inflammatory bowel disease be on a spectrum?

A That doesn't imply beginning and ending to me. I don't know what you're asking.

Q Okay. Can you have very mild symptoms of inflammatory bowel disease with mild findings and at the other end you would have Crohn's Disease and ulcerative colitis?

A That's not what I was speaking to.

Q Well, I'm asking your opinion.

A You can have mild Crohn's Disease or mild ulcerative colitis. Symptoms of irritable bowel do not progress to Crohn's Disease.

Q So you're saying that the more generalized type of colitis that occur can never progress to Crohn's Disease?

A I have no idea what you're talking about in generalized colitis. No meaning to me.

Q Okay. So, Doctor, did you author an article on *Update on Etiology, Pathogenesis and Diagnosis of Ulcerative Colitis*?

A Yes.

Q And it was published in *The National Clinical Practical Gastroenterology and Hepatology*? Is that the journal?

A Yes.

Q And that was published in 2004?

A Yes.

Q And, Doctor, in the next to the last sentence did you say in particular it's difficult to discriminate ulcerative colitis from other forms of colitis including Crohn's Disease, and there seems to be a growing overlap of pathophysiologic processes between ulcerative colitis and postinfectious irritable bowel syndrome? Did you write that?

A Yes.

Q Patients who remain indeterminate between ulcerative colitis and Crohn's Disease also continue

to be a diagnostic challenge. Is that true?

A Definitely.

Q Okay. Was it true when you wrote it?

A Yes.

Q And is it true today?

A Yes.

Q So, Doctor, continuing back with Michelle's history here --

SPECIAL MASTER HASTINGS: Before we go on you've now cited two abstracts of Dr. Hanauer. Can you file those, one as I think we're up to Petitioners' Exhibit 10.

MR. SHOEMAKER: Your Honor, if we could file all of this thing as one exhibit? There are 10 pages.

SPECIAL MASTER HASTINGS: Well, we need to make a reference to them. Just say Petitioners' Trial Exhibit. Use the word trial since you already have other exhibits.

MR. SHOEMAKER: The first thing referred to is page 9 of that exhibit.

SPECIAL MASTER HASTINGS: All right. Listen for a second, would you? I have a list here of nine items that we've already referred to throughout the trial as Petitioners' Exhibits 1 through 9. Trial exhibits. Petitioners' Trial Exhibits 1 through 9.

If you want to file all of those on one CD, fine, but label it CD of Petitioners' Trial Exhibits 1 through whatever number we get to.

All I'm saying is we're going to add these two abstracts as Petitioners' Trial Exhibit 10 and Petitioners' Trial Exhibit 11. We've already referred to these. That will make it easier for us to get back to them if we need them.

Go ahead, Ms. Chin-Caplan.

MS. CHIN-CAPLAN: Thank you, Special Master.

BY MS. CHIN-CAPLAN:

Q So, Doctor, we're up to 2003 with Michelle's history now. You know that shortly after this hospitalization she went to see Dr. Krigsman?

A Yes.

Q And you know that Dr. Krigsman did an upper and lower endoscopy, correct?

A Yes.

Q Do you recall what his findings were?

A I believe we've already looked at those, but yes.

Q Do you recall that his colonoscopy revealed an aphthous ulcer in the sigmoid colon?

A Yes.

Q And this is the first documentation of an

aphthous ulcer in Michelle. Is that true?

A The previous colonoscopy had shown some lymphoid hyperplasia in the same area, but I believe this is the first description of an aphthous ulcer.

Q Okay. Doctor, while she was there an OmpC was also drawn. Is that true?

A Yes.

Q What is an OmpC?

A OmpC stands for the outer membrane pore, that's the Omp. It is a bacterial protein that is found in normal bacteria that live in the intestine, and in patients with Crohn's Disease and other small intestinal diseases there has been an increased amount of that found in the serum compared to normal individuals, healthy individuals.

Q So it's a blood test that could potentially indicate the presence of Crohn's Disease?

A It is a blood test that may or may not represent an increased leakiness of the small intestine.

Q Okay. And was Michelle's OmpC positive?

A Yes.

Q Okay. So we're now somewhere into late 2003, correct?

A Yes.

Q At this point Michelle was continuing to have diarrhea, she had a colonoscopy that revealed the presence of an aphthous ulcer, a positive OmpC and she had a feeding tube because she was unable to maintain her calories for nutrition. Is that true?

A Yes.

Q Doctor, in your mind does the constellation of those signs and symptoms, would they constitute inflammatory bowel disease at all?

A Absolutely not. She had no evidence of inflammation on biopsies of her small or large intestines.

Q So you're basing your opinion solely on the presence of tissue of pathology?

A No. You're basing your question solely on an aphthous ulcer and a serologic test that is not pathognomonic.

Q Plus the diarrhea, correct? I said that.

A The diarrhea was not an inflammatory diarrhea.

Q And that's your opinion?

A There's no evidence that there were fecal leukocytes, blood or malabsorption.

Q Okay. So, Doctor, let's continue on. So now Michelle is presently being fed by tube, and she's

now developing other symptoms. She's developing eye problems as well as arthritis. In your field are there extraintestinal manifestations of inflammatory bowel disease?

A Definitely there are.

Q Would those be arthritis and eye conditions?

A Those are several of the possible associations.

Q Okay. Let's continue on. She has another endoscopy done by Dr. Ursea at Phoenix Children's, and do you know what the result of that endoscopy is?

A Which one are we talking about now?

Q The last one.

A The 2006?

Q Yes.

A Yes.

Q It's Petitioners' Exhibit 49, page 23.

A Is that the 2006?

Q That's the 2006.

A Thank you.

Q So, Doctor, do you know the result of this endoscopy?

A Yes.

Q What was it?

A The small intestine and the colon were

normal.

Q Was there an aphthous ulcer seen in the transverse colon?

A Yes.

Q You've indicated that when you see those things it could be related to insertion of the tube. It's like a canker sore you said, right?

A Can be like a canker sore, can be trauma. They come and go. They're really of no significance in and of themselves.

Q Okay. So she had a canker sore in 2003 earlier, she's got a canker sore now in 2006 and she had a capsule endoscopy, a PillCam, done, didn't she?

A Yes.

Q You recall from reading Dr. Krigsman's testimony that he saw multiple aphthous ulcers?

A Yes.

Q Would you consider that to be a normal finding?

A No. Excuse me. Let me retract that. Fifteen percent of normal individuals have aphthous ulcers or mucosal break similar to what we're seeing on capsule endoscopy. My belief is that hers were related to the Advil that she had been taking, which is a common association.

Q Okay. So it's not related to her bowel prep this time?

A I think that she may have been on Advil at other times as well. I never attributed it to the bowel prep, I'm saying that it can be related to bowel prep. I don't know why she had an aphthous ulcer, but I do know that an aphthous ulcer in the absence of any microscopic evidence of inflammation means nothing.

Q Okay. So as you indicated on page 2 of your opinion, the next to the last paragraph, you're talking about IBD and you say that aphthous ulcers may be typical of Crohn's Disease, IBD, but are in no means specific. They can be seen in normal individuals after exposure to bowel preparations for colonoscopy or related to the use of anti-inflammatory medications. Is that what you said?

A Yes.

Q Okay. Doctor, we know that Michelle did not receive any bowel prep in her 2006 colonoscopy, don't we?

A I don't remember. I was unable to find how she was prepared or not.

Q Well, if you look at page 23 of Petitioners' Exhibit 49 about a third of the way down the column it says colon prep, doesn't it?

A I don't have that.

Q Let me show you. Doctor, to be perfectly clear, again, this is page 23 of Petitioners' Exhibit 49. At the top it says Phoenix Children's Hospital, flexible sigmoidoscopy report. Then it says colon preps?

A Yes.

Q And does it say used none for colon preps?

A Yes.

Q Is that an indication that Michelle Cedillo did not receive any colon preps?

A Probably not, but according to their records.

Q So is it fair to state that the record indicates that she received no colon preps?

A Yes.

Q So the aphthous ulcer in this instance can't be related to the colon prep, right?

A It may or may not be with others, but it doesn't appear -- if she had no preparation it's unlikely that the single aphthous ulcer that was seen was due to a bowel prep if none were given.

Q Thank you, Doctor. So now, Doctor, we're here at 2006. Michelle has had diarrhea alternating with constipation returning to diarrhea since she was

about a year and a half old. She's had multiple endoscopies, an upper GI which revealed the gastric ulcer and she's had a lower GI.

A I don't believe it showed a gastric ulcer.

Q An esophageal ulcer, wasn't it?

A Yes.

Q Yes. So an esophageal ulcer at the junction of the esophagus and the stomach, wasn't it?

A This is where ulcers related to gastric reflux occur.

Q Okay. So she has a GE junction ulcer. She had a lower GI colonoscopy done, an aphthous ulcer is seen there, she's got a positive OmpC, she has another colonoscopy done which reveals an aphthous ulcer in a different part of the colon, she has a PillCam done that shows multiple aphthous ulcers in the small bowel, and your opinion is that she has no inflammatory bowel disease?

A She does not have inflammatory bowel disease.

Q Okay. Doctor, you know that she's currently under treatment at UCLA?

A Yes.

Q And do you know Dr. Ziring?

A Yes.

Q And are you aware that Dr. Ziring has ordered Humira for the treatment of Michelle's bowel disease?

A Just from the testimony that I've read. I have not reviewed any of those records.

Q Okay. Would you have any reason to doubt that Humira has been ordered?

A I do not doubt that Humira has been ordered.

Q And Humira is a brand new treatment for inflammatory bowel disease. Is that true?

A Humira is an old treatment for arthritis.

Q But a new one for inflammatory bowel disease, yes?

A It's recently been approved for the treatment of Crohn's Disease.

Q Okay. Thank you. Now, Doctor, you had indicated earlier that you've testified approximately 50 times. Is that it?

A Yes.

Q You've done it in medical malpractice cases and toxic tort cases. Is that what you said?

A Yes.

Q Out of that 50 times were they all medical malpractice cases?

A The vast majority were.

Q How many times did you testify for plaintiffs?

A I need clarification, please. When you say testify do you mean in Court or deposition? My 50 was inclusive of both.

Q In Court.

A In Court I've only testified under 10 times.

Q For plaintiffs?

A Total.

Q So out of that 10 times how many times did you testify for plaintiffs?

A A few. Just a couple.

Q One to two?

A Yes.

Q Okay. Now, you also testified that you work as an expert in toxic tort cases?

A Yes.

Q And can you just tell us what your work involved in the toxic tort cases?

A It had to do with one of the chemical companies in California clearing up their land and individuals in the area who developed inflammatory bowel disease that they associated with the environment.

Q Did you testify for plaintiffs there?

A No.
Q You testified for the chemical companies?
A Yes.
Q And how many times?
A One.
Q Was it one environmental toxic tort case?
A Yes.
Q Okay. Doctor, you lecture, correct?
A Yes.
Q Are you aware that on the web when one types in your name you come up with site that's on Medscape that says evidence and experience the art of managing inflammatory bowel disease?
A I have not.
Q Let me show you this. It's up there on the screen. It's copyrighted by the University of Chicago Pritzker School of Medicine. Is that where you practice?
A Yes.
Q Did you have input into this?
A In the segment that I participated in.
Q So you knew that this was on the site?
A I'm not aware of all the Google references for me.
Q Okay. Doctor, if you go to the very top at

the very top it says that these educational activities certified by accredited providers were not prepared by Medscape editors but are made available to our site as a service to our audience. Authors are routinely instructed by the provider to disclose significant financial relationships and mention of investigational drugs and unimproved indications. Is that true? I've read that correctly?

A Unapproved.

Q Unapproved. Yes. I read that correctly, right?

A Yes.

Q And, Doctor, you're on this site, correct?

A Yes.

Q What is your disclosure at this site?

A That disclosure was that I am a consultant and lecturer for Centocor.

Q And what is Centocor?

A Centocor is a pharmaceutical company that makes a drug called Infliximab or Remicade.

Q Remicade. That's the drug that's used for inflammatory bowel disease, isn't it?

A Yes.

Q You're a consultant to them?

A Yes.

Q And you lecture on their behalf?

A I've been paid to give continuing medical education lectures through them, yes.

Q Okay. So you're one of the experts that they've tapped to lecture on the efficaciousness of Remicade to other GI physicians. Is that it?

A That's one of the aspects that I lecture on. I also talk about the risks.

Q I'm glad you do, Doctor. Now, Doctor, you've appeared at the American College of Gastroenterology's Seventieth Annual Scientific Meeting. Is that true?

A I presume. I presume you're going to show me that I did.

MS. CHIN-CAPLAN: Yes, I am.

SPECIAL MASTER HASTINGS: Well, before we go on then, the excerpt from that web page that you just showed, why don't you make that Petitioners' Trial Exhibit 12. Now you're showing something further?

MS. CHIN-CAPLAN: Yes, Special Master.

SPECIAL MASTER HASTINGS: Or is this the same?

BY MS. CHIN-CAPLAN:

Q On the next page, Doctor, are you listed there?

A Yes.

SPECIAL MASTER HASTINGS: So this is just the next page of the document you just showed a minute ago?

MS. CHIN-CAPLAN: Yes.

SPECIAL MASTER HASTINGS: Okay. All right.

BY MS. CHIN-CAPLAN:

Q Doctor, on your disclosure this time it says that you've received grants for clinical research from Abbott Labs, correct?

A Yes.

Q Asahi, USB Pharma or Celltech, Centocor, Elan, Genentech, Otsuka, Protein Design Labs, Prometheus, Targicept, Therakos. You've also served as a consultant to Abbott Labs, Amgen, Asahi, USB Pharma or Celltech, Centocor, Elan, Genentech, GlaxoSmithKline, Novartus, Otsuka, Protein Design Labs, Targicept, Teva and Therakos, and that you've served on the speakers bureaus of USB Pharma, which is Celltech, and Centocor. Have I read that correctly?

A Yes.

Q Doctor, these are all pharmaceutical companies?

A Yes.

Q When you say you received grants for

clinical research what did you receive from Abbott Labs?

A I don't receive anything. These are grants to the institutions. We do clinical trials with these drugs to help them lead to FDA approval in the right patient population, so because of my experience over the years I'm one of the primary investigators for most of the new drugs that are being developed for ulcerative colitis or Crohn's Disease.

I consult with the pharmaceutical industry as to how to design, and perform and evaluate these trials to help them get FDA approval. That's been successful thus far with Remicade for Centocor, Humira for Abbott and the others are in process.

Q So the grant is provided to your hospital or the medical school. Is that it?

A They're provided to the medical school to pay our support staff to do the clinical trials on these patients or with these patients.

Q Are you the principal investigator?

A In most of those, not all of those.

SPECIAL MASTER HASTINGS: Are you done going over that --

MS. CHIN-CAPLAN: I am, Special Master.

SPECIAL MASTER HASTINGS: Let's put that

last one back on. I'm a little confused. Prior to that you had showed something from the Medscape website?

MS. CHIN-CAPLAN: Yes, Special Master. It's identified where it's posted.

SPECIAL MASTER HASTINGS: All right. We were going to mark that as Petitioners' Trial Exhibit No. 12. That's taken from the Medscape website. Is that correct?

MS. CHIN-CAPLAN: That's correct, Special Master.

SPECIAL MASTER HASTINGS: And then the last thing that you just showed and went over that noted the list of drugs, is that from a separate --

MS. CHIN-CAPLAN: It looks like it's from Medscape as well, Special Master, and it's a summary.

SPECIAL MASTER HASTINGS: All right. But it's a separate place on the Medscape website?

MS. CHIN-CAPLAN: Yes.

SPECIAL MASTER HASTINGS: Okay. Mark that then as Petitioners' Trial Exhibit 13. We have 12 and 13.

MR. SHOEMAKER: Your Honor, if I may, Exhibits 10, 11, 12 and 13, we can file it as the same document with different page numbers if you'd like and

refer to the page numbers or we can do it this way.

SPECIAL MASTER HASTINGS: Well, we've already discussed them as 10, 11, 12 and 13, and they're from different places. Indulge me on that one, Mr. Shoemaker.

MR. SHOEMAKER: Yes, sir.

SPECIAL MASTER HASTINGS: On that last one, Ms. Chin-Caplan, you have at least one paper copy of it?

MS. CHIN-CAPLAN: Yes, Special Master.

SPECIAL MASTER HASTINGS: You can make a copy, but before you have lunch give a paper copy of that last one to the reporter so that list of drugs -- otherwise we'll never get that.

MS. CHIN-CAPLAN: Okay.

SPECIAL MASTER HASTINGS: All right. So go ahead.

BY MS. CHIN-CAPLAN:

Q Doctor, what date was the *Evidence and Experience: The Art of Managing Inflammatory Bowel Disease* posted?

A I don't know when it was posted.

Q Do you know the date that this occurred?

A I don't recall the exact date.

Q Okay. Would the copyright date help at all?

A The copyright says 2002, but I don't remember the specific date of this presentation or document.

Q Okay. Doctor, when we go to what has been labeled as Petitioners' Exhibit 14 --

MS. CHIN-CAPLAN: Special Master, is that what --

SPECIAL MASTER HASTINGS: The last one with the list of drugs?

MS. CHIN-CAPLAN: Yes.

SPECIAL MASTER HASTINGS: Was 13.

MS. CHIN-CAPLAN: Thirteen. Okay.

BY MS. CHIN-CAPLAN:

Q Doctor, when we go to this document what is the date on this document?

A I can't read it.

Q Above the author does it say copyrighted?

A I'm sorry. I'm unable. Now it says 2005.

Q So, Doctor, in the period of three years you went from consulting to one drug manufacturer to all those that are listed on this page. Is that true?

A No, that is not true. The conflicts of interest or the potential conflicts of interest relate to the topic of the discussion, okay? So in the first example the topic may have specifically been related

to Infliximab, one compound. In a subsequent I'm talking about the entire spectrum of therapeutic options. I'm going to list every potential conflict.

So it really depends upon the topic. If I'm talking about constipation, for instance, I don't have any conflicts because I don't work with any pharmaceuticals related to that issue, as an example. The conflicts of interest pertain to the medical education at hand and are not ubiquitous.

Q So you have no standard practice on conflicts of interest?

A I do have a standard practice that applies to the content.

Q So depending on the content will depend on which drug company you indicate you disclose as potential conflicts of interest?

A Yes.

MS. CHIN-CAPLAN: Okay. If I could just have a moment, Special Master?

SPECIAL MASTER HASTINGS: Sure.

BY MS. CHIN-CAPLAN:

Q So, Doctor, do you know whether that practice of disclosing just the particular medication that you would be lecturing on is standard?

A I don't think that there is a single

standard except that it pertains to the content of the educational material.

Q Okay. So if you look at this page, which is page 2 of Petitioners' Exhibit 12, Dr. Sandborn --

SPECIAL MASTER HASTINGS: Or is it 13? Is it 12 or 13?

MS. CHIN-CAPLAN: It's 12.

SPECIAL MASTER HASTINGS: Twelve. I'm sorry. Go ahead.

MS. CHIN-CAPLAN: Dr. Sandborn disclosed every single company he consulted to, didn't he?

THE WITNESS: I don't know that this is inclusive.

BY MS. CHIN-CAPLAN:

Q Okay. But it appears that he has disclosed many companies. Is that true?

A It appears that he has disclosed many companies.

MS. CHIN-CAPLAN: Okay. Thank you, Doctor.

SPECIAL MASTER HASTINGS: Nothing further for this witness? I'm sorry.

MS. CHIN-CAPLAN: No, Special Master, not from Petitioners.

SPECIAL MASTER HASTINGS: Okay. Any questions for this witness? Go ahead.

SPECIAL MASTER VOWELL: Dr. Hanauer, just so I understand your testimony, and this particular pertains to some of the testimony on cross-examination, if you have 1,000 people with irritable bowel syndrome and another 1,000 without is there any difference in those two groups in terms of who may ultimately develop irritable bowel disease?

THE WITNESS: You mean inflammatory?

SPECIAL MASTER VOWELL: Inflammatory bowel disease. I'm sorry. Inflammatory bowel disease. Thank you.

THE WITNESS: There is no predisposition of patients with irritable bowel syndrome to develop inflammatory bowel disease. It's unrelated, so it would be the same as the general population. Similarly or the converse is also the case. If up to 30 percent of our population have symptoms at one time or another of irritable bowel it's going to be the same.

Patients with inflammatory disease can have irritable bowel symptoms as well. Irritable bowel does not lead to inflammatory bowel disease.

SPECIAL MASTER VOWELL: And is your testimony that Michelle has irritable bowel syndrome not an inflammatory bowel disease?

THE WITNESS: My testimony is that there is no pathologic evidence that Michelle has inflammatory bowel disease. Her symptoms are consistent with irritable bowel syndrome, and there is no specific symptom, there is no finding in her examinations that are pathognomonic or even pathologic confirmation. The young girl has had multiple biopsies on multiple occasions of purportedly abnormal bowel that was normal.

SPECIAL MASTER VOWELL: For you to say someone has inflammatory bowel disease you have to find inflammation?

THE WITNESS: You can't say inflammatory without inflammation. That would be inflammatory.

SPECIAL MASTER VOWELL: That would be a histopathological finding of inflammation?

THE WITNESS: Yes. The scopes identifying minor lesions are not accurate at predicting the pathologic lesions, they are often over interpreted.

SPECIAL MASTER VOWELL: Thank you.

SPECIAL MASTER CAMPBELL-SMITH: I did have one question, Special Master.

SPECIAL MASTER HASTINGS: Please go ahead.

SPECIAL MASTER CAMPBELL-SMITH: You made several references, Dr. Hanauer, to inflammatory is

that there can be evidence in stool or diarrhea of inflammation because clearly you're an expert here. You mentioned blood with one of them. When you said this you apparently looked at the diaper from Michelle. I just want to be clear I understand.

Are you indicating that there can be some visual indicators? Obviously, there will be other tests that you would run, but visual indicators from examining stool or diarrhea in particular that an expert could determine absent blood that this was the result of something inflammatory or not?

THE WITNESS: Absent blood the only way you could tell what's causing the diarrhea if it's from inflammation would be simply looking at a drop under the microscope for pus cells, and there were not any documented at any point in her course.

SPECIAL MASTER CAMPBELL-SMITH: I thought it needed to be at the microscopic level, but I wanted to be clear when you said there could be stool that had evidence of inflammation.

THE WITNESS: This is a very easy thing. You just take a drop of the stool, you look under a microscope and you look for white blood cells. It's not a difficult test. It's something that anyone at the bedside could do, and all of the labs do it when

they are looking for parasites. The labs look for a term called fecal, meaning in the stool, leukocytes, white blood cells.

She never had any fecal disrupt in the stool samples.

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

SPECIAL MASTER HASTINGS: And, Doctor, if I understand you correctly having looked at the record they did look for that on a number of occasions?

THE WITNESS: They did ova and parasite examinations, and in most laboratories if there are fecal leukocytes because they need to be separated from parasites under the microscope they would be reported.

SPECIAL MASTER HASTINGS: All right. Now, Mr. Shoemaker, can you help me? Can you put back on the screen what we marked as Petitioners' Trial Exhibit 11, the second Hanauer abstract? This was the one with the mention of irritable bowel syndrome.

MR. SHOEMAKER: Page 8.

SPECIAL MASTER HASTINGS: Right. Okay. You've got it on the screen here. Thank you. I wanted you to clarify your answer to Ms. Chin-Caplan's question about that. In the abstract here you stated that there seems to be a growing overlap of

pathophysiologic processes between ulcerative colitis and postinfectious irritable bowel syndrome.

THE WITNESS: I'd be happy to clarify that.

SPECIAL MASTER HASTINGS: Could you, please?

THE WITNESS: Absolutely. There is a small subgroup of patients who develop diarrhea predominant irritable bowel syndrome after an episode of something like a traveler's diarrhea, and some of those patients have evidence of increased bacteria in their small intestine and very mild inflammatory changes. That group of patients responds to an antibiotic. It's a very small group.

That does not apply to this patient who presented initially with diarrhea, then constipation and had this mix back and forth, and, and, and, and had no inflammation on biopsy. So this doesn't apply to a syndrome where there is extra inflammation.

SPECIAL MASTER HASTINGS: All right. Now, let me also ask you, you stated earlier I think that you reviewed the records of Michelle Cedillo with respect to her GI symptoms. Are there places in those medical records where her treating physicians mentioned Crohn's Disease, a diagnosis of Crohn's Disease?

THE WITNESS: Only Dr. Krigsman. Until Dr.

Krigsman.

SPECIAL MASTER HASTINGS: Okay.

THE WITNESS: Now after that it's very interesting because sometimes these diagnoses get carried over. So if you actually read some of the subsequent rheumatologists' reports it's in their report that she has Crohn's Disease. Well, that's based on Dr. Krigsman, it's not based on his independent review of the biopsy material, which was all normal. So you know some of these insinuations get carried out any level of review.

SPECIAL MASTER HASTINGS: Well, I guess you're already answering the question that I was going to ask you. I just ask that he be given a copy of Exhibit 28, page 590 to 592. So if counsel have a copy of that in front of them?

THE WITNESS: Yes.

SPECIAL MASTER HASTINGS: I'm going to get my electronic copy in front of me. If you'll bear with me a minute? Doctor, as I read that, there's a three-page report there at 590 to 592 from Dr., if you look at the third page, S-Z-E-R is the last name?

THE WITNESS: Yes.

SPECIAL MASTER HASTINGS: And I couldn't tell what the specialty of that doctor was from that

document. But if you can, let me know. Okay. It is in pediatric rheumatology. That's what I was hoping it was. All right. Bear with me just a minute.

I'm going to have you look at the top of page 590. This electronic version of large records like this is a little difficult to work with, but I'm getting myself to the top of page 590 in just a minute. You'll see in the second or third line at the top of page 590, there's a mention of Crohn's Disease.

THE WITNESS: I think there's an erroneous statement that she has biopsy-proven Crohn's Disease.

SPECIAL MASTER HASTINGS: That's what I wanted to ask you about.

THE WITNESS: Again, this is how diagnoses get handed down without any re-check or evidence review of primary data. But that's an obviously wrong statement, because the Court has not seen any evidence of biopsy-proven inflammation of the small or large intestine.

SPECIAL MASTER HASTINGS: So in your knowledge of the medical records, your study, you don't see anything to support that statement that there's biopsy-proven Crohn's Disease?

THE WITNESS: I haven't seen, nor had Plaintiff's counsel provided, any biopsies that showed

a diagnosis of Crohn's Disease.

SPECIAL MASTER HASTINGS: All right. That's all I had then. Is there any redirect for this witness then?

MS. RICCIARDELLA: No, Your Honor; but I'd really just like to clarify the record. Mr. Case pointed out that I misspoke when I was talking about the date of 2006, upper and lower endoscopy. I referred to it as Petitioner's Exhibit 59. It's 49.

SPECIAL MASTER HASTINGS: All right. Thank you. All right. Anything further for this witness?

MS. CHIN-CAPLAN: I have just one other item.

SPECIAL MASTER HASTINGS: Go ahead.

FURTHER CROSS-EXAMINATION

BY MS. CHIN-CAPLAN:

Q Doctor, I'd like to show you, it looks like the prescription from Dr. Ziring. Is that true?

A Yes.

Q Could you just read what's on the prescription into the record, please?

A Adalumimab 40 milligram syringe, one starter pack (Crohn's Disease), four syringes, sub-que on week zero; two syringes, sub-que on week two; then Adalumimab, 40 milligram, sub-que on week four and

every two weeks; Valium, two milligrams, two tabs, PO one prior to Humira injection.

Q Who is that signed by?

A Dr. Ziring.

Q And where is Dr. Ziring located?

A The Mattel Children's Hospital at ULCA.

MS. CHIN-CAPLAN: Thank you. I have no further questions.

SPECIAL MASTER HASTINGS: Is that from the medical records?

MS. CHIN-CAPLAN: But this is a prescription, Special Master, that Mrs. Cedillo has.

SPECIAL MASTER HASTINGS: All right.

MS. CHIN-CAPLAN: It's not listed as an exhibit. Should we make it an exhibit?

SPECIAL MASTER HASTINGS: Why don't you?

MS. CHIN-CAPLAN: And this one is --

SPECIAL MASTER HASTINGS: That would be number 14, Petitioner's Trial Exhibit 14.

MS. CHIN-CAPLAN: Thank you, Special Master.

MS. RICCIARDELLA: May I proceed?

SPECIAL MASTER HASTINGS: Yes, go ahead.

REDIRECT EXAMINATION

BY MS. RICCIARDELLA:

Q Dr. Hanauer, seeing that prescription that

was just read to you today, does that cause you to change your opinion in any way as to this child?

A No, the primary reason that this child was getting the Remicade and then the Adalumimab or Humira was for her inflammatory arthritis, which is an approved indication of the drug.

MS. CHIN-CAPLAN: I have one last question, Special Master.

SPECIAL MASTER HASTINGS: Go ahead.

RECROSS-EXAMINATION

BY MS. CHIN-CAPLAN:

Q Dr. Ziring, is he a rheumatologist?

A No.

Q Is he a pediatric gastroenterologist?

A Yes.

Q Are you saying that a pediatric gastroenterologist would order medication for rheumatoid arthritis?

A Absolutely.

Q Oh, he would?

A Yes.

Q And do you routinely order medications outside your specialty area?

A It didn't say it was outside his specialty in patients who have been continually followed for

arthritis, and these medicines were started by a rheumatologist, and continued by the treating physician. So if Dr. Ziring is treating her for the inflammatory arthritis, there's no reason he couldn't continue the Humira.

Q Doctor, are you saying that Dr. Ziring, at UCLA, a pediatric gastroenterologist, is ordering Humira to treat Michelle Cedillo's rheumatological condition?

A I do not know. You might ask Dr. Ziring.

MS. CHIN-CAPLAN: Thank you, Doctor.

SPECIAL MASTER HASTINGS: All right. If there's nothing further for this witness, why don't we take our lunch break at this time, and we'll come back in the afternoon with Dr. McCusker, all right? We'll start back at 1:00.

(Witness excused.)

(Whereupon, at 12:05 p.m., the hearing in the above-entitled matter recessed, to reconvene this same day, June 21, 2007, at 1:00 p.m.)

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A F T E R N O O N S E S S I O N

(1:05 p.m.)

SPECIAL MASTER HASTINGS: All right. We are ready to start the afternoon activities here. We have Dr. McCusker at the witness table, and Ms. Babcock will question for the Respondent. Dr. McCusker, could you first raise your right hand for me?

Whereupon,

CHRISTINE MCCUSKER

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

SPECIAL MASTER HASTINGS: Okay. Please go ahead, Ms. Babcock.

MS. BABCOCK: I'll start by saying that we do have a short Power Point. I'm not sure what trial exhibit we're up to.

SPECIAL MASTER HASTINGS: Do we have copies?

MS. BABCOCK: They're being handed out as we speak.

SPECIAL MASTER HASTINGS: Okay. Great. I think this will be Respondent's Exhibit 16, according to my count.

MS. BABCOCK: Okay. Trial Exhibit 16.

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DIRECT EXAMINATION

BY MS. BABCOCK:

Q Good afternoon.

A Good afternoon.

Q Could you please state your name for the record?

A Christine McCusker.

Q And what is your profession?

A I'm a pediatric immunologist.

Q Could you briefly describe your collegiate and medical education?

A I have a BSC in microbiology and immunology from the University of Toronto. I have a Master's Degree in molecular virology from McMaster University. I have three years of a PhD thesis degree in immunogenetics, also from McMaster.

I have my MD degree from McMaster University. I then went on to do a residency in pediatrics, a clinical fellowship in allergy and clinical immunology, and then two years of a post-doctoral research fellowship in immunology at the Meakins-Christie Laboratories, McGill University.

Q And are you board certified?

A I am board certified in pediatrics in the American Board of Pediatrics. I have a Royal College

certification, the Royal College of Physicians and Surgeons of Canada certification in pediatrics and allergy and immunology as well as the Collège des Médecins du Quebec certification for pediatrics and allergy and immunology. So those would be the Canadian equivalent of the American boards.

Q Are you an examiner for any licensing boards?

A I'm an examiner for the Royal College of Physicians and Surgeons of Canada for the qualifying exams for allergy and clinical immunology.

Q Do you hold teaching positions at McGill?

A Yes, I'm an Assistant Professor at McGill University, and I have teaching responsibilities that extend from teaching basic undergraduate immunology courses, teaching medical student immunology courses, as well as teaching both post-graduate grad student courses and resident courses in immunology.

Q Do you hold laboratory positions, as well?

A Yes, I have both a clinical laboratory responsibility and a research laboratory responsibility. I am a principal investigator of a research laboratory at the Meakins-Christie Laboratories of McGill University, where my research interests are in understanding the developmental

immune system from infancy through to essentially adolescence; and trying to understand how the immune system sets itself up and is regulated throughout that period of time, particularly early in life.

In my clinical laboratory responsibilities, I'm the Clinical Director of the Immunology Laboratory at the Montreal Children's Hospital, where I'm responsible for the organization, running, quality assurance of clinical immunological testing; as well as with two of my colleagues with the signing and interpretation of lab results, which will then be sent out to the ordering physicians.

Q Is that immunology lab also a National Reference Center?

A Yes, our laboratory runs tests that are specific for the diagnosis of primary immunodeficiency, and in that capacity, we have developed and have accredited certain immunological testing for the diagnosis of specific humoral immunodeficiencies.

As well, we are the Reference Center for several different providences in Canada, including Quebec, Nova Scotia, and the other maritime provinces.

Q Now what is the division between your research and clinical work?

A I'm officially 50 percent research and 50 percent clinical.

Q And about how much of the latter is clinical lab?

A Approximately of that 50 percent, it you called that 100 percent, it would about 30 percent of my clinical time is spent in running and managing the clinical lab.

Q About how many patients do you see in a month?

A Somewhere on the order of 200, on an average month.

Q Are the majority of these adults or children?

A They are almost exclusively children. I rarely see adults.

Q Do you see children in a general pediatric capacity, as well?

A Yes, my clinical time in actual seeing of patients is divided into clinical week, where we see patients who are being evaluated for primary immunodeficiency; a clinic where we see patients who are being evaluated for allergies and allergic problems; and then I do what's called the walk-in clinic or a drop-in clinic for minor pediatric

emergencies once a week.

Then I do two to three emergency room shifts a month, where I am often in charge of the emergency room at the Montreal Children's Hospital. In that capacity, I can see anything from very minor problems to acute resuscitations in patients who require significant medical attention.

Q Have you published in the field of pediatric immunology?

A Yes, I have.

Q About how many times have you testified in a legal proceeding?

A This will be my third time.

Q Now in the course of your current practice, as you just described, do you see children who have recently received an MMR vaccine?

A Yes.

Q Is fever a common occurrence after MMR?

A I wouldn't say that fever is a common occurrence. Fever does occur.

Q Even a high fever?

A More rarely, but it certainly can occur.

Q And does fever typically have long-term clinical ramifications?

A In the context of MMR, not in my experience.

Q Now moving back to pediatric immunology, I wanted to start by taking a historical look at what was theorized about autism and immunity. When you discussed Dr. Gupta's evaluation in your report, you mentioned there was a time when autism was thought to be related to immune dysfunction. What was the genesis of this theory?

A That theory was initially put forth by an investigator by the name of Stubb, who started looking at immune responses in children with autism. He initially started with a case report and then a case series, to determine whether or not some of the effects that you were seeing in autism were related to the immune system.

Since that time, there have been several studies that have tried to evaluate immunity in autism, and up until the present time, the studies have been somewhat inconsistent in their findings.

Q Let me be clear, the study was published in --

A The first publication was in 1976.

Q In the 1970s -- would you say that that theory or that hypothesis is generally accepted today?

A No.

Q Now getting back to Dr. Gupta's report, I

want to go through it in some detail. It's obviously been a topic of conversation. Generally, when making conclusions about immune function, is a single evaluation sufficient?

A As a general rule, no -- the immune system is not a static organ. It doesn't stay the same throughout your entire life. It changes as you age. It changes as you develop. It changes with the environment that you're exposed to in any given time and on any given day.

So as a general rule, in our practice, when we're evaluating patients for primary immunodeficiency, we see several patients a week who come to us for that problem. We will start with an initial screen of the immune system, and any abnormalities that are detected are always followed with a repeated test to see if it's consistent over time.

Q Now can you talk in general about these evaluations are done?

A Yes, sure; when we're asked to evaluate a child's immune system, basically, we have to use the tools that we have at hand. It would be nice to be able to be thorough and complete, but we are not able in the clinical laboratory, to fully evaluate a

child's immune system as you would in an ideal world.

Q What we have at our disposal is the capability to examine essentially the adaptive immune response. We have some specialized testing for children who appear to have problems with the innate immune response. But for the most part, our focus is on the adaptive immune response.

So essentially, what we're looking at is the T cells and the B cells; and we want to know, those P cells, are they present? Do they look normal as one would expect, and do they function normally?

So in order to do that, we have to look into two ways. One, we look at their numbers, and we do that by a method known as flow cytometry, where we take the lymphocytes of a patient and we run them through the flow cytometer, and we look to see how many lymphocytes they have, what is the distribution of the lymphocyte, the T cells, the B cells, the different T cell subsets. We can do B cell subsets now, as well as the NK cells.

Then we move on to look at the functioning of the immune system. So the functioning, we have two options for that. To look at the TH1 arm or the cell mediated arm of the immune system, primarily what we can do is, we can look at whether or not the cells can

activate in the presence of a stimulus that's appropriate. So we take the cells, we put them in a petri disk, and we try to stimulate them, and then we look to see if they stimulate.

In order to look at the other side, at the other arm, the humeral arm, we look to see if the T cells and the B cells were able to communicate. Because if they were able to communicate, then the B cells were able to be told to produce an antibody. So if you have antibodies to stimuli that you know the child has had, then you know that that arm of the immune system is in tact. So we can do that as our initial screen.

Then if we find an abnormality, we will generally begin to do finer and finer testing, all the way to genetic testing, to determine where the problem is.

Q Now when evaluating a child's immune system, is it important to use age specific values?

A Absolutely; there is absolutely no question.

Q Is the immune system of a child the same as an immune system of an adult?

A No, it is not.

Q Slide 2 here also is from Dr. Ward's report yesterday.

A Basically, what you can see in this slide is that the numbers of immune cells -- and these are just absolute values -- changed significantly over time. Unless you are going to specifically examine the patient at the age appropriate time, you really don't have any idea of what is normal and abnormal.

Q Now in her expert report and testimony last week, Dr. Byers stated that it is standard practice to use adult values to assess a child's immune system. Do you agree?

A I do not.

Q And to be clear, do you evaluate immune results like these on a regular basis?

A Yes.

Q When you test in your own lab, do you use age adjustment measurements?

A Yes, we do.

Q Is this practice widely accepted in the pediatric immunology community?

A Yes, it is. It's considered standard of care.

Q Now although Dr. Byers made this assertion, she also used normal values from several of your filed papers in her Power Point presentation. Did you review these slides in her testimony about them?

A Yes, I did.

Q Do you agree with the ranges that she proposed?

A She put the adult ranges on her slides.

Q She put the adult ranges?

A Yes.

Q Okay. Now she seemed to make a point in her slides about stating that the values you used were from foreign laboratories?

A Yes.

Q Is this correct? This is Slide 3.

A Could you move on to Slide 3? What you can see in Slide 3, and what the blue arrows are highlighting, are the values that are reported in my report for the T and B cell enumerations and their normal ranges. This report comes from the study of Shearer, et al, which is also filed. I'm not sure what exhibit.

Q It's Defendant's Exhibit C at Tab 4.

A Okay. And Shearer is a large study in the United States which looked at 807 children to define the normal ranges based on age. In this particular study, three of the participating centers were from California, including UCSF.

Q Now would a pediatric immunologist at the

University of California Irvine use different normal pediatric values than a pediatric immunologist in Montreal, Quebec?

A No.

Q Does it matter that Michelle's testing was done in 1997, and you have the benefit of more recent normal values?

A It really does not. This is Slide 4. What Slide 4 shows you is the normal pediatric ranges that were available as of 1992. They are the ranges that actually we still use as our initial screen today, although we tend to move on to the Shearer paper for the final finite testing. The reason is that in this particular study of Hanan, et al, they had a relatively small number of patients per group, and the Shearer paper had a much larger patient population from which to draw. So they were able to achieve more accurate ranges.

Again, this moves back to the concept of the pediatric immune system. Because it can vary from day to day, the more patients that you have of that age group, the more you are able to capture what is a normal range on a normal every day variance. So the Shearer paper is probably more accurate, based on numbers. But this is what was available in 1992, and

it really isn't significantly different from Shearer. I just chose the more accurate numbers.

When you're talking about this particular analysis, what you're using, as I mentioned before, is a flow cytometer. So the question is, was flow cytometry in 1997 significantly different from flow cytometry in 2007 or 2003, when Shearer did the work?

There have been changes and upgrades to the machine. Certainly, they work much faster than they did in 1997.

But the principles are identical. Because most of these studies, or all of the studies and all of the work, is done in accredited labs, they have to maintain a certain consistency in their results, particularly for these kind of studies, because they have vast reaching effects; not just for the diagnosis of immunodeficiency.

But these results are used for the diagnosis of cancers. They are used for the diagnosis of problems post-transplant. They are used for many different reasons in medicine. So it isn't just to evaluate immune systems, because immunologists just like to do that. It really has broad-reaching effects. Nephrologists use it. Hematologists use it. Oncologists use it.

So I thought I'd take a second and just kind of explain what flow cytometry is, so that you can understand where the consistency is. Basically, a flow cytometer is a machine. You take a patient's sample, and you drop it, drop by drop, through the machine. The drops have been treated in such a way that you ensure that only a single cell from the patient passes through the reader at any given time.

So it's a very thin drop that drops down from the retainer. It drops through past the reader. What is the reader? It's actually a laser.

So when the cell drops into the reader, the laser hits it. That laser hitting it causes the laser to scatter. That scattering gives us a lot of information. It tells us the size of the cell, and it tells us how much stuff is inside the cell; the granularity of the cell.

Using that information alone, we can differentiate the different populations of white blood cells. We can say that granular cells tend to be things like neutrophils, macrophages, those kind of cells.

The less granular cells, they are smaller and less granular. Those are the lymphocytes. So you can then gate. It's called gating, where you circle

that lymphocyte population, and you can study it further.

So how do I say how many lymphocytes are T cells? Well, T cells are defined. They are differentiated from one another on the basis of certain surface markers. Flow cytometry takes advantage of that, and there have antibodies that have been made in the laboratory to these specific surface markers.

So there's an anti-CD3 antibody. There's anti-CD4 antibody. There's an anti-CD8 antibody, Anti-CD-19, CD-20, antibody. There's lots and lots of different ones.

In fact, one of the things that has improved in the last 10 years is the capability to type cells has expanded dramatically by flow cytometry. But using the antibodies that were available in 1997, these antibodies are then coated with a tag.

The cells are put in the presence of these antibodies, and any cells, for example, that are CD-4 -- if this is an anti-CD4 antibody, we'll bind it. So that when it passes through the reader and it gets hit by the light, it will glow a different color. So it will change color, and it will glow for example. Depending on the tag you use, it will glow green.

The receiver actually can detect -- oh, that's a cell that scattered this way, so as a lymphocyte and glowed green and, as such, is a CD4 positive T cell. So it's very simple in that sense. The concept of a flow cytometer -- it's beautiful technology, but it hasn't significantly changed. They've gotten faster. The anti-bodies may have gotten a little bit easier to use. But the reality is, if there's a tag on the antibody, that antibody has that receptor and, therefore, is counted as a CD-4.

Q So is it fair to say that it's still your opinion that the values you used in your report are the values that should have been applied to Michelle Cedillo's immunological evaluation?

A Yes.

Q Now let's move on to Dr. Gupta's actual testing. What were serum immunoglobulin and antibody response results?

A Can we have the next slide?

Q No, it's not on a slide.

A Oh, okay. So in terms of her immune work-up, the serum immunoglobulin levels; that is, the IgM, IgG, IgA, and IgE total levels were all within normal limits. In addition, she made antibodies to the

components of the vaccine she had received, including diphtheria, tetanus. Rubella, polio, pneumococcus.

Finally, with respect to the measles virus, she had detectable measles IgG antibodies, but no detectable IgM antibody, which would be interested as being a child who has seen and cleared the measles virus.

Q Now there's the next slide.

A Okay. Sorry.

Q I wanted to talk about testing for T and B cell enumeratings. What were the findings?

A Well, I think it's clear from my slide here, that essentially, if you apply the normal ranges that are appropriate for a three year old child, her T and B enumerations all fall within the normal range.

Q Now this chart has something called percents and absolute numbers. What's the distinction?

A When you're looking at the flow cytometer, basically what the flow cytometer captures is a certain number of cells that run past the reader; run past the laser. If you call the total number of cells that are red 100 percent; and then you calculate, or the machine calculate how many of those glowed green, then you know that her CD4 count was 38 percent.

But that gives you a percentage. It doesn't

actually tell you what an absolute number is. In order to convert that to an absolute number, you need to know how many cells were in the pool to start with.

So you need to have an evaluation of your total lymphocyte count. Then once you have an evaluation of the total lymphocyte count, what you do is, you can calculate, while 38 percent and there were 150,0009 in me, the lymphocyte pool. Therefore, this is the total lymphocyte count that is represented by the CD four count.

Now why is that important? Well, to use only percentages can sometimes run you into trouble. Because if a patient has an extremely low level of lymphocytes, as lymphogenic, which happens under certain conditions, then your relative percentages become less valid, and you really need the absolute number in order to determine where the decrease in the T cell or the B cell population is occurring.

Q In particular, can I draw you attention to CD4/CD8.

A Yes.

Q Is that value normal?

A It is for me.

Q Now what are proliferation studies. That's next, Slide 6. Proliferation studies are a little bit

more variable from laboratory to laboratory. These can get much more difficult to interpret. In fact, you really have to be very careful when you're interpreting proliferation studies. The reason is, unlike the flow cytometry, where basically, if the cell is present, it's going to glow and you're going to see it.

So your error range is fairly narrow. These are called in vitro studies. Basically, you're doing something to the sample, and asking for a response.

The problem with biological assay systems such as this, is that there are many places in the ANSI to introduce error. So, for example, what is a proliferation? We take the patients lymphocytes. We put them in a petri dish, and in that petri dish with some growth factors and media to keep the cells happy, we put a factor that will stimulate the cells.

What you see in this slide are the factors, the mitigens, which are fighting human gluten, and Con Conavolie and Polk mitogen. Why do we use those? Because they are known to activate T cells and B cells, in some instances, to divide.

If you have an extremely sick B cell or T cell, even under this aggressive stimulus, it will not divide. So an absence of T cell proliferation is

important diagnostically for when you're diagnosing SKID. When you're looking at post-bone marrow transplant, and you want to see if any of those cells are healthy, in a patient population. But basically, how do you know that the cells are dividing? Well, what you do is, you put into the culture media a marker, and we use Tritium (Tritiated thymidine) which is incorporated into the cell when it divides. Then the cell will glow in a reader, which means relatively simple. But lot to lot differences in the thymidine can make a big difference in your absolute values that you see when you're looking at the results.

So for example, in our laboratory, and it's standard for the pediatric laboratories that I have encountered, we always controlled patients on the same day with a known normal. Why; because that means if the tech sneezed into the dish, it doesn't happen.

But let's say it could. Or if the temperature of the room was too high, or the carbon dioxide content of the incubator was too low, the cells are not going to be as happy. These are very fragile cells in culture. So if they're not happy, they're not going to proliferate as efficiency.

Well, if your test case doesn't proliferate

efficiency, they you're left with a question. Is it because it just didn't proliferate efficiently and there's a primary problem; or is it because the tritium wasn't as robust as the last lot? The only way that you're going to know that is if you control it with a normal control.

Now unfortunately for the case of Michelle Cedillo, I was not provided with a control value that was run on the same date.

Q It's not available in the transcripts?

A I'm sorry, by transcripts, you mean not available in the medical records?

Q Medical records, sorry.

A Okay.

Q It is any interpretation that you want to make on the prolipher studies, you really have to put into that interpretation in the codill that you're not sure what the sensitivity of the assay on that day required,

Having said that, I did find in the Stern paper, which is the Stern 2005 paper. Do you know which one that I did find normal ranges, or at least ranges? Because on that paper, they compared autistic children, proliferation assays to normal controls run on the same day.

So if you look at that paper, you can see that's what is presented here as the autistic children's range, and the normal children's range.

MS. BABCOCK: Just to be clear, really, if you look at those ranges, then the results of Michelle Cedillo fall within the normal range.

BY MS. BABCOCK:.

Q Just to be clear, it's Exhibit C, Tab 7. So essentially, given the results that I have available to me, it would appear to me that her T cells were able to be stimulated.

A T & B cells were able to be stimulated up to a reasonable level, in this assay. Again, it's qualified by several different methodological issues.

Q Okay. Now you alluded to this earlier. When would proliferation studies cause you concern in a child?

A We were particularly worried about proliferation assays when they are severely depressed. When you do not get proliferation much above the background levels.

And these tests for Michelle Cedillo, they are considerable or robust. I mean, I suppose I could imagine that if her unestimulated is not given, it might be somewhere in the higher range. But even if

you put it in the higher range, you would say that those were perfectly acceptable responses to the mitigens, because they proliferated well?

Q Now moving on to the immunoglobulin subclasses, what were Michelle's test results?

A Her subclasses.

Q Yes.

A She had a normal for range IgG1, IgG3, and IgG4. Her IgG2 was mildly elevated compared to normal ranges.

Q Now what is the clinical significance of a mild IgG2 elevation?

A There has not been any defined clinical significance in the extent literature for humans of an elevated IgG2. There are some case reports or case series that suggest that specific IgG2 antibodies can be elevated. Don told you these.

Q Now are you aware of any literature where they looked at autistic children in IgG2 levels?

A Yes, there was the paper by Trajkovski, et al, 2004 --

Q It's Exhibit C, Tab 11, at Tab 11.

A -- where they looked at immunoglobulin subclass levels in patients with autism, compared with their neurologically siblings, and found that there

were changes in IgG-1 and IgG-4 levels, and no changes in IgG-2 levels.

So it's really difficult to know what the significance of that is. In fact, these kind of studies haven't been replicated, so it's also very hard to know what they mean in general.

Q Overall, what conclusions can you reach based on the immune evaluation of Michelle Cedillo?

A Well, as I said in my report, my opinion, I would evaluate this child, if this was the lab reports that I was to sign out as an entirely immune response.

Q And even though he may have used adult values, did Dr. Gupta come to a similar conclusion?

A Yes, he did.

Q So would you agree or disagree with Dr. Byers's conclusion regarding Michelle Cedillo's immune evaluation?

A I disagree with it.

Q Now moving on to the subject. They called one TH1 and the other TH2. It's obviously been discussed by several experts in reports and testimony. I wanted to start by talking about the background of this principle. When was the theory developed? This is slide seven.

A The first report of cloning of TH1 and TH2

cells was in 1986 Mosmenek, et al. In that study, what they were able to do was, they were able to stimulate T cells in culture and clone out, meaning finding a piece of the population that they were able to isolate away from the other T cells, that would produce either the cytokine uniform on Gamma, or the cytokine on aisle 4.

Because they were able to clone these two cytokines away from these other and find these populations of T cells that would only secret one or the other of their cytokines. They called one, TH1; and the other, TH2.

Since they had known, up until that time, that interferon gamma was important for activation of macrophages, and was important for the driving of cell mediated immune response, the TH1 side of the immune response was considered to be cell mediated.

Because aisle 4 was important in the activation of B cells and, therefore, the formulation of antibodies, they separated the two into TH2 being the humoral arm of the immune system.

Now although this paradigm has been very useful in helping us try to understand immunoregulation, it had subsequently been found to have several flaws. The first of the main flaws in

this particular paradigm is that when these things were first defined, they were defined in mice and they were defined in inbred mice.

The inbred mouse has a much "simpler" type of immune system. You can say it under several different immune threats, and look to see what happens. It seems to separate much more directly into TH1 or TH2, than what the human studies were showing.

So probably about five or six years ago, or maybe a little longer, about 1999, people started to think, well, that paradigm where it's TH1 or TH2, and the two don't crosstalk, and if you have TH1, TH2 goes down. If you have TH2, TH1 goes down. seem to be fast for aisle four, at least in the human population.

There were studies that began to look at what the immune system did in fact. And believe it or not, rather than simplifying things, things just got more complicated because like everything in MMLG, if you find an effect, you define a cell.

So they defined a new cell type and they called it the T regulatory cell type. Since that time, there has been an extensive amount of active research on T regulatory cells and dendritic cells, T regulatory cell interactions. In fact, that's one of the things that my lab does at the Meakins-Christie.

So I have a lot to say about it, but I won't.

The T helper cell subsets have now been -- this is probably a little bit out of order now, sorry -- have now been defined as TH1, TH2, T regulatory cells. There's a TH3 cell that has been defined, and there is now a TH-17 cell that has been defined.

TH-17, not because it would have been easier to call it TH4, but because the cytokine that defines it, is called aisle 17. So they decided to just follow the Interleukin, instead of calling TH4, to bring it down the pathway. I know it just adds confusion, but immunologists are crazy -- nice, but crazy.

Q And is this the illustration of what you just said?

A Yes, so this is the illustration of what we currently understand is the choices that a naive T cell has to make, once it sees its antigen.

SPECIAL MASTER HASTINGS: Now we have slide 10.

MS. BABCOCK: Yes, we're going to skip. We're going to go back to eight and nine in a moment.

THE WITNESS: I jumped ahead. I got excited.

BY MS. BABCOCK:

Q So it's safe to say, our THT are mutually exclusive, based on our current understanding.

A In fact, there have been many studies now that suggest that once antigen T cell interactions -- yes, an individual naive T cell makes a decision, and it will go towards one of these pathways. But there are many different clones that are being activated at any different time.

Those T cell energy in presenting cell interactions are unique to the T cell, and they don't pay attention to what their neighbors are doing. So it is clear that both TH1, TH2, and T-regulatory responses occur in concert.

Now as the immune response progresses, one tends to predominate; the one that is probably considered to be most necessary for removing the threat. But all of them occur, and as the immune response begins to wain, as the body begins to combat the infection, and the antigen drops -- in fact low antigen levels promote the formation of T regulatory cells.

So basically, when you have a high threat, you're going to go for your affecter cells, which are your TH1 or your TF-2. Because they're the ones that are going to be able to activate the set of toxic

cells. Toxic -- that's a good cell to get when you're infected with a virus.

They are the ones that are going to be able to activate your B cells in the TH-2 arm, to protect antibodies so that you can combat the bacteria and the extra cellular pathogens.

But as that threat is coming down, you really want to be able to turn that response down. So as antigen level drops, the regulatory cells start to increase; and those cells are responsible for just calming down the response and shutting everything off.

Q We can go back to Slide 8 here. How is TH2 cytokine-induced antibody induced in humans?

A Well, TH2 is characterized by the initial production of aisle 4 and subsequent production of aisle 13; aisle 5 is among other cytokines that have been shown important.

But what the importance of this slide is, it is to show you that, in fact, if you are driving towards TH2 with a significant amount of cytokines, so that you would consider this to be a TH-2 predominant response, then the type of immunoglobulins that you are going to see are IgG1, IgG3, IgG4, in IgE production. This is taken from a study in humans. The animals with data; the subclass is very slight in

mice. But this is what is found in humans in a TH-2 response.

Q And were these values measured in Michelle Cedillo?

A Yes, they were.

Q And what were the results?

Q They were all normal.

A And I believe Slide 9 is just the summary there. Now what happens with respect to TH1 and TH2 when the vaccine enters the immune system, and now we're skipping to slide 11?

A Sorry; I realize that this is a bit of a complicated slide. But it sort of talks about the things that I've already mentioned. In the center, the orange cell there, that's the naive T cell. So that's the cell, that once it sees it's antigen, it has to make a decision. It sees its antigen in the decision that it has made is dependent upon the antigen presenting sales.

So these guys here are depicted in green, and the T cell itself, and what's happening in the environment. So if there is a dangerous excel, for example, who has seen an antigen that it believes to be a threat -- and how does the dangerous excel know that? Because there are these innate receptors found

on the antigen-presenting cells that have been called "pamps" or "toll light receptors"; and these receptors, certain repeating structures that are found on viruses and bacteria that make them viruses and bacteria; not mammalian, not human.

So the immune system says, well, wait a minute, this didn't come from me. They can bind into these receptors, and they can tell the andrigic cell. You have picked up something that is dangerous. It's sort of the danger theory of immunity. That danmeric cell will process that antigen and present it to the T cell.

But at the same time it presents it to the T cell, it expresses other receptors. But basically, these receptors talk to the T cell at the same time the T cell sees the antigen; and they say, you know, when I've seen this danger signal before, or illusionarily, when this danger signal came, this one really needs a TH1 response. So why don't you start producing a lot of interfering gamma, and activate the TH-1 cells?

On the other side, let's say it's a bacterial cell wall product, the lipopolysaccharide being a classic example of that, that will bind into its total like receptor TLR4, and the dendritic cell

will be induced or the macrophage will be induced by the TLR4 engagement of the receptor, to tell the T cell, you know what, this is an extra cellular pathogen.

It's okay if some T cells what to make some immediate responses. But our focus should really be making of antibodies, because that's what is going to protect us. I mean, that's how we now think; that the innate system is able to help mould and craft an immune response that is appropriate for the antigen for the invading organism to protect us from it. Does that answer your question?

Q More or less. Is it clear up top? Now Dr. Byers asserts that Michelle had evidence of a dysregulated immune system at the time of her MMI vaccine. Do you agree?

A No.

Q Does she also state that the presence of a fever was the sign of an immune dysregulation in Michelle Cedillo?

A Yes, she does state that.

Q Did Michelle have any evidence of immune suppression at the time of her testing in 1997?

A No, she did not.

Q Now Dr. Byers cited to a paper by Agrawall

to postulate that Thimerosal was affecting the dendritic cells.

A That's correct.

Q And did you read that paper?

Q Yes, I have.

A What was the immunologic effect on dendritic cell that Agrawall observed?

Q When he treated the human dendritic cells with Thimerosal, in the presence of the stimulus LPS, he found that there was down regulation, decreased production of the cytokines TNF alpha, IL-6, and IL-12 subcomponent P-70. He also found and up regulation of aisle 13 and aisle 5. Okay. So a down regulation of aisle 6?

A That's correct.

Q And just a small point of clarification. I think Dr. Byers said that dendritic cells secrete LPS?

A Yes, she did. I'm thinking she may have made a mistaken; because LPS is found in bacterial cell walls, and so dendritic cells do not secret it.

Q Now what is one of the major effects of aisle six?

A Well, aisle six was first defined, along with aisle 1, as a component of a substance that way back in the early days of immunology was found as

indigenous pyrogen, because it is one of the major cytokines involved in promotion of fever.

Q So if aisle 6 is down regulated, would someone be able to produce a fever?

A If aisle 6 is down regulated, one would anticipate a blunted fever response.

SPECIAL MASTER HASTINGS: Blunted?

THE WITNESS: Blunted -- I can't tell you that it would be absolutely abrogated, because there is aisle 1 still available. Although aisle 6 and aisle 1 are intimately associated in their regulation. So you might also postulate that aisle one would be down regulated. But based on what he showed, you would anticipate a blunted fever response.

SPECIAL MASTER HASTINGS: And what do you mean by a blunted fever response; less fever?

MS. MCCUSKER: Less fever.

BY MS. BABCOCK:

Q Now there's also been a lot of discussion of cytokines, and this is probably a topic that we could be here for hours on, and we will not. But could you just briefly describe the role of cytokines in the immune system?

A Sure, cytokines are small proteins that are released by different cells. The interleukins were

originally defined as cytokines that were released by leukocytes, and they were primarily thought to be used to allow for communication from one leucocyte to another.

They can be divided into several different ways. One of the divisions that is commonly used is that they're divided into pro-inflammatory and anti-inflammatory cytokines. Another division is that they are divided into short-acting, or those cytokines that act over very short distances, and those cytokines that can act over longer distances.

So they can be divided into several different categories, although there is a current move afoot to try and categorize them much better, based on their structure and function. But that's still a few years away.

Q Another small point of clarification, is nitric oxide a cytokine?

A No, it is not.

Q Now which immune responses are cytokines involved in?

A Cytokines are involved in all immune responses.

Q Do they play a role in any other systems?

A Sure, cytokines are used in the CNS system,

to allow for communication between leukocytes at the CNS and the glial cells, astrocytes, other cells of the CNS.

They're great tools for communication. They are secreted by other cells; not just cells of the immune system. They are secreted by astrocytes. They are secreted by smooth muscle cells of the airways. They are secreted by epithelial cells of the airways.

So we now know that they are used as communication tools by more than just the immune system. Although there are some that are very specific for the immune system.

Q And do cytokines act locally or systemically?

A Well, probably we would classify the vast majority of cytokines as acting over a short distance, very much locally. Those are the ones that are primarily responsible for activation of one cell type by another cell type.

Because essentially, you want to regulate that activation very tightly. You want that T cell that has already recognized its antigen. I'm a cell for polio virus. I've seen polio virus, and now I want to activate that B cell that recognizes polio virus. I don't want to activate this B cell over

here, that recognizes CAT, because that's not going to help me.

So those cytokines act over very short distances. Some cytokines, the more pro-inflammatory, the cytokines that are responsible for turning up inflammation, those ones tend to act over a slightly longer distance, and why is that?

Well because if I get a cut on my arm, I have to call in cells from everywhere to fight that infection. I don't want to be relying on just the local area cells. I want to be calling them in from everywhere.

So the only way I can do that is to create a gradient to release my cytokine, and it can shoot out its signal over a longer distance, so the cells can be called into the area that is at risk.

The other cytokines that will act ever longer distances are things like aisle 1 and aisle 6, because you want those to be acting on the hypothalamus, which is your fever center, because you want to turn up temperature. Why do you want to turn up temperature? Because microbes, bacteria and viruses really don't like high temperatures. They don't replicate well at high temperatures.

And so it will slow down their replication

if you have a fever. It slows down the replication and allows the immune system a little bit more time to rally the troops, get everybody to the right place and eliminate the infection.

Q Now Dr. Byers discussed some of the black box warnings for some of the cytokines. If you're administering cytokines therapeutically, what type of doses are we talking about?

A You're talking about what would be considered supernormal doses. You're talking about high doses administered systemically. You're not talking about what would happen in the lymph node when IL2 is released, for example, which would be small doses of IL2 in a confined space.

Q So these are not levels that would be naturally produced by the body?

A No.

Q I would like to also clarify some of the terminology that's been used. Does the pediatric immunology community recognize the term selected immune dysfunction?

A I have never heard that term.

Q It also seems that TH2 is being used interchangeably with immuno suppression. Does that make sense?

A No, it does not.

Q What is a clinical example of someone with TH2 skewing?

A A classic example of TH2 skewing is: 30% of our population, and those people would have allergies.

So when you see a patient who sneezes in the middle of rag-weed season, or in the middle of tree season, that's a person who's immune system is skewed a little bit too far to the TH2 side, and produces the anti-body known IgE, which is the only available bio-marker that's easily assessed in patients for this "TH2 skewing."

Q Is there any clinical evidence that Michelle Cedillo had TH2 skewing?

A No, there is not. Her IgE levels were normal.

Q If someone were significantly immuno suppressed what would you expect to see?

A I would expect to see a significant increased frequency of recurrent infections.

Q Is there any evidence that Michelle Cedillo had an abnormal, or an increased, frequency of recurrent infections -- in the time before her MMR vaccine?

A No.

Q in the time before her MMR vaccine?

A I'm sorry.

Q That's okay. Now, if the theory is that thimerosal had a sufficient immuno suppressant affect on an immune system as to allow the persistence of the measles virus, what would you expect to see clinically?

A If the thimerosal were persistent, and if that effect was clinically relevant, then it should not just affect the ability of the body to fight measles, and it should affect the ability of the body to fight infection.

So if you can't fight infection, your infections are going to be more frequent. There is going to be more clinically apparent, and they are going to last longer.

Q Now, is there any evidence that Michelle had an abnormal number of infections after her MMR immunization?

A No.

Q Can you think of an example where the immune system has been altered in some way physiologically, or otherwise, where you could see the effects of T-cell depression?

A Well, there are several examples. But one

of the ones that comes to my mind, and that we see frequently in the immune-deficiency clinic, is the disease known as the DiGeorge Syndrome.

What the George Syndrome is: It is a genetic disease. Because of a deletion on Chromosome 22, the way the body forms of the major organs of the immune system, the thymus, is aberrant. Because of when this gene dilution, gene mutation takes affect during the development of the fetus, you can have wide spectrum of clinical disease.

So you have these children who were born, and they are born with what's known as congenitally athymic. They do not have a thymus at all. Those children are unable to mature T-cells. So they have zero, no T-cells, and they present very early in life as severe combined immune-deficiency.

Without intervention, either bone marrow or thymic transplant, they will die very early. But then the vast majority -- that's actually relatively rare. But the vast majority of children with DiGeorge Syndrome actually have a spectrum of immune-deficiency. Because although the thymus doesn't form completely normally, it does form.

What we have found from studying patients with DiGeorge is that the T-cells do not form as

quickly, or as robustly, as in a child who has a perfectly normal thymus.

So their T-cell numbers when you look at them, when you do those T- and B-cell enumerations, they tend to have low T-cell numbers because their thymus cannot handle the processing of the T-cells appropriately.

In addition, when you do your proliferation, they tend to have a slightly decreased prolix compared to normal. I would look at those prolixes and I would say: slightly depressed T-cell proliferations to mitogens, consider congenital thymic dysplasia, meaning considered DiGeorge in your diagnosis.

When they have looked at studies -- now, DiGeorge, genetically, has been elucidated relatively recently, from a medical point-of-view, in the last ten years. So there have been many, many patients who have had DiGeorge Syndrome who were not defined; and there are other congenital effects associated with DiGeorge. It is not just the thymus that can be problematic.

There are lots of children, who because of the other problems we've identified, or suspected, as having DiGeorge Syndrome that never came to our clinic, and these children received their full

vaccinations.

Interestingly, there has not been a reported case of persistent viral infection, as a result of a live viral vaccination, in a patient with DiGeorge.

Now our recommendations are: If we know a patient has DiGeorge, that we wait until we're sure that their immune system can handle the vaccine before we give it. But there have been many, many, many children, and there is actually a large international study going on right now trying to collect the numbers of these patients who have received their vaccinations, and have had no untoward affect as a result of it because it gives us a lot of information.

It tells us that, even with depressed T-cell numbers and decreased proliferations, these children are able to cope with the vaccine strain and clear it. And they can do it with measles, mumps and rubella, and they can do it with the varicella vaccine.

Q So, overall, based on your medical experience, and your review of the medical records and testimony, what is your opinion as to Michelle Cedillo's immune functioning?

A In my opinion, Michelle Cedillo had a normal immune system at the age of three.

Q And you hold this opinion to a reasonable

degree of medical certainty?

A Yes, I do.

MS. BABCOCK: No further questions.

SPECIAL MASTER HASTINGS: Let me follow-up and ask a question before we have cross. You said: A normal immune function at the age of three.

THE WITNESS: That's correct.

SPECIAL MASTER HASTINGS: What about an earlier age?

THE WITNESS: There was no evidence of immune dysregulation in my opinion before the age of three. But if you're asking me to evaluate her immune system, the only objective evaluation that I have was at age three, which was normal.

Clinically, in my opinion, she did not have any evidence of an immune abnormality prior to that.

SPECIAL MASTER HASTINGS: You said at the age of three because that's when Dr. Gupta did his work-up.

THE WITNESS: That's correct.

SPECIAL MASTER HASTINGS: But you're also saying that: throughout the medical records you looked at, you didn't see any clinical evidence of immune dysfunction at any other time?

THE WITNESS: No, I did not.

SPECIAL MASTER HASTINGS: All right. Any cross for this witness? Ms. Chin-Caplan?

CROSS-EXAMINATION

BY MS. CHIN-CAPLAN:

Q Good afternoon, Doctor.

A Good afternoon.

Q You're from McGill?

A Yes, I am.

Q Do you know Dr. Ward and Dr. Fombonne?

A Yes, I do.

Q Have you worked with them?

A I've worked with -- well, no, truthfully, I know who they are. Dr. Ward is an adult microbiologist, so I don't interact with him clinically. I know him professionally; and Dr. Fombonne, I've had some interaction with when he did his study of the immune responses in autistic children because it was done in my lab.

It was done as a research study, but using the services of our lab, so I had some interaction in that sense, but, other than that, no.

Q Was your name on that study?

A Nope. No, it was not, sorry.

Q But it was done in your lab?

A It was done in my clinical lab. It was --

it was incepted and run by Dr. Fombonne and Dr. Bruce Maser, who is my colleague. but it was not my inception, so my name was not on the paper.

Q Okay. Do you know what Dr. Fombonne's role in this study was?

A I think Dr. Fombonne will be testifying. You can ask him.

Q Okay, I shall do that. Doctor, if you take a look at Respondent's Exhibit Z, which contains your opinion, under Tab 7, is this the study that you're referring to, Stern's study?

A Can I have that? Yes.

Q Dr. Fombonne is listed on this, correct?

A That's correct.

Q And this study was done in 2005?

A It was published in 2005. It was actually done in patients who were accrued in the immunodeficiency clinic between 1996 and 1998. It says it in the abstract.

Q Do you notice any conflict-of-interest declarations on this article?

A I will look at the back. Okay, except for the fellowship. I don't see any, no.

Q Okay, thank you. Doctor, you were speaking of Michelle's immune status, and we we're looking

primarily at Dr. Gupta's records, is that true?

A That's correct.

Q And that would be Petitioners' Exhibit 3, correct?

A Yes.

Q I would ask you to take a look at page 12.

A Yes.

Q This is the lymphocyte subsets, is that true?

A That's correct.

Q And there is an indication that the normal range is that for an adult, is that correct?

A That's correct.

Q Okay. Doctor, does it indicate that the ratio of CD4/CD8 which is the helper-suppressor ratio, is 2.24?

A That's what it says, yes.

Q And the normal range for this laboratory, for the adults in laboratory?

A Right.

Q Was .82 to 2.02?

A That's correct.

Q Okay. Doctor, for the CD20s, which is the total B-cell count, Michelle's was 21%, correct?

A That's correct.

Q An absolute number 670?

A Yes.

Q Yes. And the normal range for this laboratory was a high of 16.8% cells.

A The normal range for the adults in this laboratory was 16.8 cells.

Q And the high range for this laboratory, for the absolute numbers, was 4.11?

A For the adults, yes?

Q Yes. And the last one would be for the CD3/CD6 genes. Was that the normal range for this laboratory?

A For the adults, yes, you were correct.

Q If you go to page 13, Doctor.

A Yes.

Q These lymphocytes transformation mitigens, do you see any abnormalities here for this laboratory?

A Well, again, there is no standardization for normal ranges, or lymphocyte proliferations, nothing is accepted either by the council that accredits laboratories, or by the WHO, and it is laboratory-specific.

You must always control it with a controlled sample, so it's difficult to know the validity of that normal range.

Q Okay.

A In addition, it appears, although again it's difficult to evaluate appropriately, that there are differences between pediatrics and adults. I realize that a lot of adult doctors see children as little adults, but they're really not.

Q I tried to say that today.

A They're very different.

Q According to this laboratory, though, do they have a normal range listed?

A They do, but it's for their adults, so you can't really use it to evaluate. And I think, although I am not Dr. Gupta, and I can't tell you what he was thinking, I would think that, given that his opinion was that her immune system was and I quote "essentially normal," if he felt that her ranges were outside the norm for pediatrics, he would have commented on it.

Certainly that's what I would do in my laboratory, and I assume he is as creditable a physician.

Q Doctor, the question before you was: Are there normal ranges listed for this laboratory?

A Yes, there are.

Q For Con A and pulp wheat mitogens, are they

within the normal range?

A Not for the adult normal range, no, they are not.

Q Okay. Doctor, let's go to page 14. These are the lymphocyte transformation antigens. Am I correct?

A Uh-huh.

Q For the mumps virus, is Michelle's range within the normal range for this laboratory?

A For the adults, no.

Q And for C albertans, is it within the normal range for this laboratory?

A Again, it is not in the normal range for the adults of this laboratory.

Q Okay. For the PPD,is it within the normal range for this laboratory?

A No, not for the adults.

Q But for the tetanus toxoid is it?

A The tetanus toxoid is within the normal range for the adults. I thin, you should, though, make a small note: The PPD, to my knowledge, Michelle Cedillo never received a BCG vaccination, neither did she have tuberculosis.

So one would not expect her to proliferate to PPD, regardless of what the normal range is. And

it is quite normal, in patients who have never been exposed to TB, to have no proliferation under those circumstances, or not above baseline.

So, again, that's part of the problem with trying to evaluate these patients based on "normal ranges" because it does depend on what they have seen in their lives.

Q Doctor, I'm going to put up a slide. This is the one that was in Dr. Byers' presentation.

SPECIAL MASTER HASTINGS: Just for the record, it was Slide 6 of Dr. Byers, it looks like. Go ahead.

MS. CHIN-CAPLAN: Okay.

BY MS. CHIN-CAPLAN:

Q Doctor, as you can see, the UCI, which would be the UC Irvine Laboratory, is all in blue, am I correct?

A That's correct.

Q Okay. You have indicated that it's not proper to use adult values for pediatric patients. Is that true?

A That's correct.

Q You actually cited in your reports several authors, correct?

A That's correct.

Q Okay. And, Doctor --

A It's interesting to know that she calls the Shearer Report a foreign laboratory, since it was not only American but three of the labs were Californian.

A I think she used that to mean that it's not UCI, that's to distinguish it from the laboratory that treated her.

A Okay.

Q So, Doctor, if you would like to look at the articles that you submitted that's more than fine. For Hannet, the CD4s/CD8s and the ratio CD4s/CD8s is in green?

A That's correct.

Q And that would be what you consider to be the normal range, correct?

A That is what was available in 1992 for a normal range.

Q Okay. But for the CD/20 --

A Could you wait one second?

Q Sure.

A Do we have that article?

SPECIAL MASTER HASTINGS: What article are you looking for, Doctor?

THE WITNESS: I have it here. It's the Hannet article. I just want to check what the numbers

are here. Go ahead, I'm on the same page.

BY MS. CHIN-CAPLAN:

Q So, have we cited this correctly?

A Yes.

Q So, for the CD20 count, though, you went to Shearer, is that it?

A Yes.

Q And for Shearer, you used the CD4/CD8, the CD4s and CD8s ratio, correct?

A That's correct.

Q Along with the CD20?

A Uh-huh.

Q But then for Gasperronni, you had different values for CD4 and CD 8, didn't you?

A I didn't quote Gasperroni in the values.

Q Did you quote it in your --

A I'm sorry, I misunderstand your question. I used, for my evaluation as a T-B cell numeration, the Shearer report for CD4/CD8, and the CD19 that was available in the Shearer reports.

Q Okay. So you're saying that the basis for the normal values is based in the Shearer report?

A That's correct.

Q Okay.

A And if you look at my slide, that comes from

Shearer.

Q Okay.

A I've highlighted it.

Q Okay. If we just go to the T-cell function test, Doctor.

A Sure, where's that.

Q Slide 7 from Dr. Byers' presentation. For the T-cell function test, you used Stern for the normal, is that it?

A That's the only one that provided a normal range. So, as I've explained, there's a significant problem with trying to find normal ranges; and most studies will not provide a normal range. For proliferation assays, they will always compare to control. So you are limited by what is available in --

Q In the literature.

A -- in the literature. I'm a little surprised that mumps was 1.3, when it's listed here as 112.97, though. So there are some errors here, or is she --

Q Mumps was 1.2, 1,097 --

A Oh, she's just changed the units?

Q Yes.

A Sorry.

Q Okay.

A But she didn't change the units for PPD. It's inconsistently changed, so that's how I guess how my confusion comes, you're right.

Q Doctor, just go to the next slide, which was Slide 8. You had to go to Trajkovski to find the normal ranges for the immunoglobulin subclasses, correct?

A Well, there are actually several different publications for normal ranges of immunoglobulin subclasses.

In fact, what I'm trying to look for was the most relevant articles. And because this article actually spoke about normals versus children with autism, I choose those normal ranges because it seemed to correlate with the population that we were trying to look at here.

But it doesn't -- those normal ranges are not outside norms for H-matched controls. I used Trajkovski's study because it did provide normal ranges; and because if seemed to be reasonable to use that as a look to see whether or not it fit with even the autistic ranges.

Q Uh-huh.

SPECIAL MASTER HASTINGS: I will note that

Ms. Chin-Caplan referred to this as Slide 8. It's Slide 8 of Dr. Byers's presentation.

BY MS. CHIN-CAPLAN:

Q Now, Doctor, if you go to page 15 of Petitioners' Exhibit 3, which was Dr. Gupta's record.

A I have that, hang on one sec.

Q If you look at this.

A Which page, I'm sorry?

Q Fifteen.

A Fifteen, yes.

Q If you look at this lab result, is there an indication that for this lab, IgG2 and IgG4 were elevated?

A Yes, there is an indication on this page.

Q Okay.

A But these are not age-specific ranges.

Q Okay.

A Again, particularly with immunoglobulin subclasses, their formation if developmental. So you see changes in the development -- the formation of subclasses based on age.

So, when I choose the Trajkovski range, I was choosing based on age because it is given for age in that paper.

Q Okay. If you assumed that these elevations

are proper, are they of any significance to you at all?

A Not really, in truth. It's really -- I looked in the literature for a clinically relevant disease associated with an elevation in IgG2 subclasses, and was largely unable to find anything.

I found an increase in IgG2 subclass specific antibodies associated with certain infections, particularly, as I mentioned before, the periodontal diseases. But I was unable to find a significant clinical relevance to IgG2 elevations.

And with respect to IgG4, isolated IgG4, I haven't heard of anything that is associated clinically, although it is elevated when -- in allergic individuals when the IgG is elevated.

Q What about the combination of the two being elevated, the IgG2 and --

A I looked for that in the literature. I didn't really find anything in humans. Were you able to find something?

Q Well, have you seen anything that indicates that this would mean a skewing of TH2?

A No, not in humans. IgG2 is not associated in humans. It is in mice, but not in humans.

Q Okay. Doctor, when we go to your report,

Exhibit C, Tab 11, page 748, that very last paragraph.

A Sorry, I'm looking in the wrong place.

SPECIAL MASTER HASTINGS: What page?

MS. CHIN-CAPLAN: Page 748.

SPECIAL MASTER HASTINGS: Okay, now which tab again?

MS. CHIN-CAPLAN: Tab 11.

SPECIAL MASTER HASTINGS: Okay, thank you.

MS. CHIN-CAPLAN: You're welcome.

SPECIAL MASTER HASTINGS: Go ahead.

BY MS. CHIN-CAPLAN:

Q It says: increased serum concentration of IgGs in autism, may point towards an underlying auto-immune disorder, and/or enhanced susceptibility to infections, resulting in chronic viral infections; whereas, the IgG subclass skewing may reflect different cytosine- dependent influences on autoimmune B-cells and their products.

Have I read that correctly?

A You have.

Q Do you agree with that?

A No.

Q No?

A I haven't found any evidence in the literature that would support that subclass changes

are related to autoimmunity.

Q Okay. But this article says it?

A This article postulates it.

Q The one that you cited in support of what your opinion.

A The one that I cited to give you, yes, to give you normal ranges for H.

Q Okay. Now, Doctor, you said that you based your opinion primarily on the Shearer article that listed the different normative values for pediatrics?

A Yes.

Q And Doctor Shearer is contained at Respondent's Exhibit Z, Tab 4.

If we go to page 978, which is the discussion, if you go to the right-hand column for the sentence that begins: In addition, the range of co-efficients for laboratory variables could be larger than the range of co-efficients for age groups, indicating that the difference between the results of two different laboratories, analyzing the same blood, could be larger than the biggest difference between the age groups.

Have I read that correctly?

A That's correct, yes.

Q So, Doctor, does that sentence indicate that

you shouldn't compare one lab's values to another lab's values?

A It's the recommendation that you stick to your own validated lab values.

What generally happens is in accredited laboratories, you've given reference samples. And the reference samples are given a certain value, and you ensure what your variance is over that reference sample. But the reference samples are based on the published ranges.

Q But they are recommending that you not use one lab value and compare it to another person's lab value. They are recommending that you try and keep repeated assays within the same laboratory. That's what it says.

A Okay. Therefore, a pediatric study should use the same laboratory for following a patient's results.

MS. CHIN-CAPLAN: Okay. I don't have any further questions, Special Master.

SPECIAL MASTER HASTINGS: All right.

SPECIAL MASTER CAMPBELL-SMITH: Doctor McCusker, I just wanted it to be clear because we heard a couple of terms that have been used.

Immune dysfunction, immune abnormality,

immune deficient are all synonymous, but distinguishable from immune suppression?

THE WITNESS: I wold not use all three of those as synonymous.

SPECIAL MASTER CAMPBELL-SMITH: Okay, why don't you --

THE WITNESS: So immune --

SPECIAL MASTER CAMPBELL-SMITH: Dysfunction.

THE WITNESS: Immune dysfunction is one of those very nebulous terms that is used when you cannot make a definition of anything.

You kind of say: Well, there's a dysfunction. And sometimes that's used when you have a patient, for example, when we have a patient who's had multiple infections. Clearly, there is something that is not completely right with this child, but all of our immune parameters are normal.

Essentially, what we're finding now, as our technology gets better and better, that we're able, in these kids, to go back when a new immunodeficiency is defined and say: Ah, that's where the child's problem is.

So, because we don't fully understand the way an immune -- all of the defects that are possible in children, in terms of the functioning of their

immune systems, sometimes that word is used as kind of: I think there's something going on here, but I can't put my finger on it.

Immune -- what was the second one you used?

SPECIAL MASTER CAMPBELL-SMITH: Abnormality.

THE WITNESS: Immune abnormality would be used to define a objective laboratory abnormality.

SPECIAL MASTER CAMPBELL-SMITH: The same with deficient, immune deficient.

THE WITNESS: Immune deficient would be used to bring together the objective laboratory abnormality with the clinical abnormality.

So, for example, a patient with the DiGeorge Syndrome might be immune deficient because his T-cell numbers are low, and clinically, he may have more susceptibility to getting a couple more colds every year.

He's not truly in danger; he's not worrisome. But there is something there in his immune system that is a little bit more profound than his friend down the block with DiGeorge Syndrome, whose immune system functions perfectly normally.

They are used in slightly different ways to convey, I suppose, in a sense, the association with the clinical and the laboratory findings.

SPECIAL MASTER CAMPBELL-SMITH: And each of those references is distinct from immuno suppression?

THE WITNESS: Classically, immuno suppression has been used when we use medications to suppress the immune system. That's often how it is used at least clinically.

So, if I give a patient corticosteroids, I know I'm going to be immuno suppressing them because I know I will be interfering with the ability of their immune system to function normally.

If I give one of the humanized monoclonal antibodies, those specifically knock out or are designed to knock out or interfere with the function of a specific area of the immune system. Those patients for that area will be immunodeficient or immuno suppressed.

SPECIAL MASTER CAMPBELL-SMITH: Thank you. I did have one more question. When you talked about the DiGeorge kids, you've indicated that if you know that you've got a DiGeorge kid, before you would administer an attenuated vaccine, you would wait to see how they handled colds, infection?

THE WITNESS: Well, DiGeorge is a very interesting disease. But basically children that do have thymuses as opposed to the truly athymic

DiGeorges, they're called complete DiGeorge, and they have no thymus and they will never have T-cells that function properly.

Those that have either a vestigial thymus or a partially formed thymus or an immature thymus, they will be able to form T-cells, but their ability to form T-cells is delayed relative to their peers.

In truth, they never truly reach, the vast majority, not all, some do, reach normal levels of T-cell numbers. So, their T and B-cell numerations, will always be slightly below normal.

Because we don't know where on the spectrum an individual child is, are they sort of pretty close to complete DiGeorge, but not quite there; or are they really -- they have a normal, fully functioning thymus. Because we don't know that, and because vaccines are things that you use to prevent disease, but because herd immunity will protect a given individual child, the risk-versus-benefits under those circumstances, don't fall on vaccinating these kids because we just don't know where on the spectrum they are.

But, things being what they are, many, many children with DiGeorge have been vaccinated; and we have immune parameters that tell us what their immune

systems look like, and their immune systems are still depressed. Yet, they are able to functionally combat and clear the live viral vaccines.

So, you know, it's one of those things where, if I know something, to actively give a virus is not, I think, in the child's best interest. But if it's already been done, we can study it. We can look at it, and we'd say: Wow, look, even with these low T-cells, and this depressed function, this child was able to clear this. Don't let it happen again.

SPECIAL MASTER HASTINGS: All right. I have a question for you, Dr. McCusker.

Dr. Byers, in the slides that you just went over a few minutes ago with Ms. Chin-Caplan, her testimony was that: Because of great variances in laboratories, and I'm summarizing her testimony to mean better to use the normal ranges from the UC Irvine Laboratory, even though they included adults, than to use a pediatric range from some other laboratory.

How do you respond to that?

THE WITNESS: Well, in truth, that would definitely not be considered, in my opinion, standard-of-care.

It's not that they included adults, they're

adult ranges. Adults' immune systems are very different from children. If you took a neonate, a newborn child, and you applied adult ranges, all neonates would have an abnormal immune system. That is clearly not the case.

In that situation, yes, there are some variations that can occur between laboratories. There are always ranges of error. But when you have, for example, as in the Shearer report, 807 children, you are able to get a decent range that is at least better than an adult range for a two-year old. Because they do not reflect the child's immune system at all.

SPECIAL MASTER HASTINGS: So, in your opinion, the best would be a normal range for children in the laboratory in question, that would be the best, if you had such a thing.

THE WITNESS: In truth: Ideally, the best is an accredited laboratory that performs regular Q&A. And if their ranges do not match the ranges that are supplied by the accreditation service, whether -- in the U. S. it's the FDA; or, in Canada, we have our own laboratory accreditation services.

If they don't match, you figure out what's wrong with your lab. But, ideally, you have a lab where you can check it. You can take a blind sample,

you can check it, and make sure that you're right. That's ideal.

The best thing, I guess, would be ranges for age from that laboratory. Although, in truth, when you look at 807 patients and you know what the ranges are, that's a very good indication of what is within normal. Because, again, we're talking about small variations. We're not talking about this child having sky-high CD4s, or unbelievably depressed CD8s. We're talking about a small variation, which, in my mind, even at the best, would not be considered clinically relevant.

However, the ideal world, make your lab run properly, accredit it properly, and do the proper quality assurance to ensure that your range is fit with what is published and what is acceptable.

If that doesn't work, then, I guess, you have to go about making your own ranges. but that would be more difficult because it's got to be population based.

SPECIAL MASTER HASTINGS: All right.

SPECIAL MASTER VOWELL: That was the question for me. Let's assume for a moment that the normal values in Michelle's work-ups were children. Let's assume that.

THE WITNESS: Uh-huh.

SPECIAL MASTER VOWELL: And Dr. Gupta is obviously an immunologist, or he's the director of the immunology laboratory at UC Irvine. Would he have said, given then, that many of her laboratory values are out of range, would he have said what he did.

Let me rephrase this: Would a competent immunologist have said: Oh, this is nothing to worry about?

You quoted him directly, what essentially he said.

THE WITNESS: Let me just take one quick look at the ranges before I answer that question.

SPECIAL MASTER CAMPBELL-SMITH: Okay.

THE WITNESS: Because I don't want to give you the wrong information. That would be Tab 3.

SPECIAL MASTER CAMPBELL-SMITH: I'm sorry, I don't have his statement here.

THE WITNESS: No, I have it here. The only reason -- I just want to look.

I mean, truthfully, when I looked at those values, given that I sign these things out all the time, I looked and said: Oh, that's normal, and I didn't -- and then I went and started reading the reports; and then had to figure out where the

"abnormalities" were coming from.

So my feeling is that: If I saw these numbers, I would say this is a normal child's immune system, even given the ranges. And I would expect that anyone who has had any experience in quality assurance for flow cytometry would do the same.

I don't know if that helps you.

SPECIAL MASTER CAMPBELL-SMITH: So it doesn't matter whether they apply the adult ranges to the child ranges in --

THE WITNESS: It's always a bad thing to apply the adult ranges.

SPECIAL MASTER CAMPBELL-SMITH: Yes.

THE WITNESS: And I realize that there are variances between labs, but all the labs use the published ranges. We all do quality assurance.

SPECIAL MASTER HASTINGS: If I understand what you just said: You're presuming that Dr. Gupta did what you did. Just look at the numbers, and say that looks normal, that looks normal, that looks normal without ever looking over to the right to the adult range because he already knew what the pediatric range was?

THE WITNESS: I can't speak for Dr. Gupta, but that's what I did.

SPECIAL MASTER HASTINGS: All right.

THE WITNESS: I know that he has a robust clinical lab, so he probably signs these things out as regularly as I do, probably more regularly, a bigger catch material. I was not surprised by his evaluation of her immune system. His conclusion, sorry.

SPECIAL MASTER HASTINGS: Okay. Any redirect for this witness?

MS. BABCOCK: No.

SPECIAL MASTER HASTINGS: Anything further based on our questions?

MS. CHIN-CAPLAN: Just a few questions.

FURTHER CROSS-EXAMINATION

BY MS. CHIN-CAPLAN:

Q Dr. McCusker, are you aware that Dr. Gupta has actually published an article about TH1 and TH2 cytokines in CD4/CD8 T-cells in autism?

A I have a memory of that article, but I don't have it here at my fingertips.

Q Let me refer you to Fujinami, Respondent's Exhibit R, Attachment 22.

A Yes?

Q Doctor, in this article, does he indicate that there is a skewing of TH1, TH2 cytokines in

autistic children?

A You will have to give me a minute to read it.

Q All right, go ahead.

A What he concludes -- I mean you have to realize this was done in 1998.

So what they looked at in this study was -- they looked at the percentage of cells that were positive for IL4, CD4 positive, IL4 cell.

And the percentage of interferon gamma-producing cells and showed that there was a -- I'm sorry. Let me just -- if I could just scan a research article. I'm sorry.

What they found was that there was more IL4-producing cells compared with interferon gamma-producing cells.

SPECIAL MASTER CAMPBELL-SMITH: And IL4 is a TH2?

THE WITNESS: IL4 is a TH-2 cytokine. Although they had a small population of 20 patients, and their P value only just reached statistical significance.

So you would actually, probably suggest that this is more of a trend because it barely reached significance in this population.

SPECIAL MASTER CAMPBELL-SMITH: Okay.

THE WITNESS: I just need to see one thing.

SPECIAL MASTER CAMPBELL-SMITH: Okay.

(Pause.)

THE WITNESS: Yes, they didn't look at any of the other cytokines associated with TH2. And they didn't look at any of the intercellular cytokines that you'd find with TH2.

So, a preponderance of IL4 is there, but it's not huge.

SPECIAL MASTER CAMPBELL-SMITH: Okay. And Michelle was seen in 1997, was that it?

THE WITNESS: Uh-huh.

SPECIAL MASTER CAMPBELL-SMITH: And this article was written in 1998?

THE WITNESS: No, it was published in 1998. If you look at when -- oh, they don't do it. Oh, here. It was received November 1997.

SPECIAL MASTER CAMPBELL-SMITH: Okay. Thank you, Doctor.

THE WITNESS: So, in fact, I guess one would hypothesize that he would have been able to assess the IL4 for capacity for Michelle at that time, but did not.

SPECIAL MASTER CAMPBELL-SMITH: Thank you,

Doctor.

SPECIAL MASTER HASTINGS: Nothing further?

SPECIAL MASTER CAMPBELL-SMITH: Nothing further.

SPECIAL MASTER HASTINGS: Nothing further for this witness?

MS. BABCOCK: Just briefly.

SPECIAL MASTER HASTINGS: Okay.

REDIRECT EXAMINATION

BY MS. BABCOCK:

Q So, as Ms. Chin-Caplan just asked you, Dr. Gupta published on the topic of TH2 skewing?

A Yes.

Q So we can assume this is something that he would have recognized in evaluating an immunological evaluation on a child?

A I would have expected so if he felt it was important.

Q And Dr. Gupta's conclusions about Michelle was that she was normal?

A That's correct.

MS. BABCOCK: I have no further questions.

MS. CHIN-CAPLAN: Just one briefly.

SPECIAL MASTER HASTINGS: All right.

RECROSS-EXAMINATION

BY MS. CHIN-CAPLAN:

Q Doctor, the terminology that Dr. Gupta used was almost normal, didn't he?

A Yes.

MS. CHIN-CAPLAN: Thank you.

(Witness excused.)

SPECIAL MASTER HASTINGS: All right. So does that conclude the witnesses for today?

MR. MATANOSKI: Yes, sir, it does.

SPECIAL MASTER HASTINGS: All right. We are going to conclude for the day now.

Just, especially for those listening in, let me remind you, as I said earlier today, that we are going to be starting with the phone conference a bit late tomorrow. We are going to be taking one witness who will not be available via phone conferencing, although the testimony of that witness will be available on the transcript.

So tomorrow morning, we will be starting the conference call at 9:30 a.m., or some time shortly thereafter.

So we are adjourned for today.

MR. MATANOSKI: Thank you, sir.

(Whereupon, at 2:48 p.m., the hearing in the above-entitled matter was adjourned, to reconvene Friday, June 22, 2007, at 9:30 a.m.)

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REPORTER'S CERTIFICATE

DOCKET NO.: 98-916V

CASE TITLE: Theresa Cedillo v. HHS

HEARING DATE: June 21, 2007

LOCATION: Washington, D.C.

I hereby certify that the proceedings and evidence are contained fully and accurately on the tapes and notes reported by me at the hearing in the above case before the Office of Special Masters.

Date: June 21, 2007

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