**Improving Digestive Health**

- So let's get on with what is a fantastic 24th Mini Med School program.

It's frankly accidental that this time everybody in the lineup is from the Department of Medicine. This isn't about my department or Dr. Rice's or Dr. Mentor's. This is about really multidisciplinary care but today we're going with the gut and it's really my pleasure to introduce one of my closest colleagues here in the Department of Medicine. The division head for Gastroenterology and Hepatology which is one division of the Department of Medicine, Dr. Michael Lucey. Dr. Lucey, his distinguished career is described on the sheet, did I mention there's a tear off at the bottom? The sheet that describes the speakers and he is a world-renowned international expert on Hepatology and liver transplants, so please join me in welcoming our emcee for tonight, Dr. Michael Lucey.

(applause)

- Thank you very much Rick and thank all of you for coming.

It's impossible to start without acknowledging that it's a sad moment. Partings are such sweet sorrow to see Rick leaving, but it's extraordinary to see this meeting because I was involved in one of the very early ones when there were about 100 people and I really did think 100 was a great attendance. And coming over here today I was wondering why has it grown such as it has? It's clearly a testament to the leadership from the Dean's office, from the Dean, from the mini Deans, including Rick. But I think there's another reason as well because I think it has captured one of the essential experiences of the medical student. Now medical students have many and varied experiences recorded in lots of books and movies but perhaps one that is not recorded enough or acknowledged enough is the sense of delight that you get when you're at a lecture or in a teaching experience and learn something new and exciting, something that opens a vista to you that you hadn't seen before and it really does happen. And it can change your life actually. And so I think that that's the reason why the hundred has grown to 200, and 400 and 600. The early people have come back and everyone has come back more and more because you're getting one of those experiences that has carried us as people who've been to medical school-- I went to medical school in 1970-- and has carried us forward because we have experienced that delight and have kept looking for it ever since. So I hope today that you're going to get another opportunity for that experience. We have four great speakers. We're are going to start with Rich Halberg. Rich is an associate professor of medicine and he's a director of the Biomedical Research Model Services. He received his PhD in biochemistry from Michigan State University and he then did his postdoctoral work here in the University of Wisconsin with Bill Dove, and then set up a very successful laboratory of his own in our division, the division of gastroenterology and hepatology.

There's an arc to today's talks and it starts with something that goes against one of the observations of Alexander Pope, he said, "The proper study of mankind is man." But Rich is going to show you that it's equally proper to study mice. Why we can learn from our animal friends. So with that introduction I'd like to give you Rich Halberg.

(applause)

- Thank you Dr. Lucey.

So, if I want you guys to think back to maybe first grade when they came around and they said, "What do you want to do when you grow up?"

When they asked me that question I never one time said, I want to build a better mouse, that was not an answer. I think I said something about, I wanted to detassel corn because my older brother was detasseling corn and making lots of money, so I thought that was really cool. So why did I spend the last 20 years of my life trying to build a better mouse? The answer is on the next slide.

So colon cancer is the second leading cause of cancer death in the United States and in this year alone 150,000 people will be diagnosed with colon cancer. And those patients are all treated the same way. They get surgery and then usually surgery's followed by chemotherapy, and the chemotherapy one of the drugs that we use is called, 5 Fluorouracil, it was a drug that was developed here at the UW in the 1950s and it's still being used. And for some of these patients they're very fortunate. That drug works, and it works really well. We cure them. The big problem, we have two problems. Half the people aren't cured and the other problem is we don't know who will be cured and who won't be cured, and I think if I give you a simple analogy I can explain why there is that different between those that'll be cured and those that won't be cured. So I want everybody to imagine their favorite car.

Do you got an image in your mind of your favorite car?

I bet you that car has tires, bumpers, doors, windshield so on and so forth. But when I think about my favorite car, I think of about a 1965 Ford Mustang, red one.

'65 is the year I was born so that's why I picked that year. If I talk to my mom, my mom talks about a Caddy. She loves Cadillacs. If I talk to my dad he thinks Model A's with rumble seats are the best thing ever. And when I talk to my wife she says, "Rich, I want a yellow Volkswagen Beetle." Guess what she owns? Yes, a yellow Volkswagen Beetle.

(laughing)

So we know that there's cars, there's many makes and models of cars. That's absolutely true for cancers too. We thought about cancer, colon cancer as being one thing, but what we realize now is colon cancer isn't one thing. Just like cars, there's many makes and models. And if we just imagine in this particular example here, we call 'em instead of makes and models, we call 'em subtypes. There's four different subtypes: red, green, blue and yellow. And it gets even more complex than that because these subtypes can be mixed together, and so you can get all kinds of mixes. And so that's why probably some people respond to therapy and some people don't. Some of these mixtures will respond to these therapies that we currently have, while other ones do not. So Dr. Page, a couple months ago, came up to me and he said, Rich can you summarize 20 years worth of work, over 50 publications, three book chapters, in two slides? I said, absolutely not. I could do it in 200, so we got a lot of slides to go through, just be still.

(laughing)

So, no we only have two slides to go through. So in my lab what we try to do is we try to model the complexity of these human tumors as Dr. Lucey already indicated with the laboratory mouse. And so what we've been able to do is we've been able to do just that. So our mice develop red tumors,

green tumors, and the tumors that are mixtures of both red and green cells. Now, for many, many, many years, over 100 years, people have been saying that every cancer, each cancer comes from a single rogue cell. In fact a prominent scientist believed this so firmly that he wrote a book called, The One Renegade Cell. The fact that in our mice that we get these tumors that are mixtures says this book is wrong, okay? So that's the claim to fame for my laboratory, that we've proven something we thought was true for 100 years isn't accurate. You might imagine though prominent scientists don't like you throwing their books around though and saying they're wrong.

So why do we care? Why do we care whether or not a cell, a tumor's made of a single cell or if it came from multiple cells, why do we care? I think we care, is shown here on this next slide. So this is my only data slide so just stay with me on this data slide. It's pretty easy, pretty straightforward. So I already told you and showed you on the previous slide that our mice get red cancers, green cancers and cancers that are mixtures of red and green cells.

So we use the colors, the red and the green-- they actually come from squids, that's where those fluorescent proteins come from-- just to tell the difference between the tumors. Are they made up of one color or the other or are there mixtures, that's all we use those for. But the more important thing is that the green cancers are different at the molecular level than the red cancers. That means that the green cancers have things that we can target with experimental drugs. And so there was a new experimental drug that was developed that was for these green cancers and we treated our mice with these drugs.

And what we found when we treated 'em, no effect on red, no surprise right? What do you think happened with the green ones? Did we get more or less?

Who thinks more? Who thinks less? Hey, you win!

(laughing)

Yeah, we saw significantly less. It went from 50 to 20%. What do you think happened when we looked at the mixed ones? The ones that had some cells that this drug's going to work on and some cells it shouldn't work on. Do you think they responded to therapy or not? Who says no? Who says yes?

The no's have it. They did not respond to therapy. So that's why these studies in the animal models are so important because they inform us on personalized medicine. That you have to target all the cells that are within a tumor and so just knowing what alterations may be in a tumor isn't enough. You actually have to know what the structure of the tumor is. And for any drug, any experimental drug to move from the bench to the bedside it has to go through these studies in which we show pre-clinically with our animal models that the drug actually is effective. So in this case if a patient had a tumor that looked like these green cancers then they would likely benefit from this drug. If they have something that's mixed they would not. Now scientists are great at trying to reduce things down to just one thing at a time. We're reductionist by nature and that's essentially what I've done here. I've talked about the complexity of the tumor and how that potentially affects response to therapy. What we know though is it's a lot more complex than that, and the complexity comes in that you're different than I am, and you eat different foods than I do. So not only do we have to think about the complexity of the tumors, but we got to think about who are the patients that we're treating, what types of food do they eat, what pathogens have they been exposed to. And so Dr. Saftar's going to talk a little bit about the bacteria that live normally in our gut and how that affects our overall wellbeing.

And Dr. Caldera is going to talk about how when we're vaccinated against some of these pathogens how our immune system, whether it's functioning really well or not, affects how well that vaccine's going to protect us from those pathogens.

So in my two-slide summary of my 20 years of work

(laughing)

I'm hoping that you got this. That colon cancer is a leading cause of cancer death. That colon cancer isn't just one thing, but there's actually a collection of cancers. And that those collections can actually be mixtures because they can be derived from multiple rogue cells rather than just a single rogue cell. And because of this complexity they're going to be difficult to treat. So one cure isn't going to treat everyone. So when we think about personalized medicine we have to think about treating all the cells within the tumor and not just a single population of cells. And that whether or not these drugs are going to be effective or not could be affected by who we are, our own genetics, as well as what we eat.

And moving forward what we do is we continue to use these animal models to test these experimental drugs. So I think my laboratory this year alone has tested three different experimental drugs for colon cancer. And what we need is we need animal models that are very accurate because it cost millions of dollars and it takes years and years to move a drug from the bench into the clinic. And so if our animal models are accurate and they show that a drug's going to work and it actually works in a clinic, that's a win. And our animal models, our innovative animal models are much better models than what has been out there.

The UW is a fabulous place to work. I feel extremely fortunate to be part of the Department of Medicine, as well as the cancer center. I've had the great fortune to work with many, many people some of which are listed on this slide, not everybody, there's just not enough room. Used to be when I started my lab I could do it, but I can't do it any longer. And the work in my laboratory's mostly been funded by the National Cancer Institute,

The American Cancer Society, The American Association of Cancer Researchers. And I just got a grant from NASA about two years ago so believe it or not they want me to study cancers in astronauts using my mouse model, okay. But I've also been very fortunate that Dr. Lucey decided to take a chance on a farmer from Illinois, so I appreciate that Dr. Lucey. And there's these guys that every year in June I go up and visit and they ride motorcycles through the woods at a very incredibly fast speed and their handlebars barely fit between these trees. I don't know how they do it, but they raise money for my laboratory. I really appreciate that. This is the Wisconsin Dual Sports Riders and I also am pretty lucky that I have friends and family that have donated to my laboratory believing in the work that we do. So thank you, and I guess we'll answer questions at the end.- Thank you very much Rich. That was great and we're going to move along as you've got a little foreshadowing there of what the next talk is. It's going to be given to us by Nasia Safdar Nasia is an associate professor of medicine and she's also got some other important titles. She's the vice chair for research in the Department of Medicine and the ACOS for research at the William Middleton Memorial Veterans Affairs Hospital. And she is an infectious diseases expert and she's going to speak to us about the interaction between the world of microorganisms the gut and our health. So thank you very much Nasia.

(applause)

- Good evening everyone. It's lovely to be here talking to you today about the gut microbiome. I want to thank Dr. Lucey, Page, Rice, Minter and Dean Golden for inviting me to speak to you today. The objectives of my session will be to review the role of the gut bacteria both in health as well as we'll take a case example of an intestinal infection, C. difficile to examine the impact of what happens when there are changes in the gut microbiome or gut bacteria and to illustrate how that imbalance can profoundly affect our health in ways that we couldn't even fathom a decade ago.

We are more bacterial than we are human.

We are more bacterial than we are human. I think that's worth chewing on for a little bit, don't you think? It's a very humbling realization. Just to get the terminology out of the way, when you read the literature on gut bacteria, as you might be prompted to do so after today's session, if you've have nothing else to do and you're really at a loose end, microbiome just refers to the collection of genes that are present in the genomes of bacteria. And microbiota refers to the actual bacteria themselves. In essence a human body is really a multi species consortium of human cells, bacterial cells, human genes, and bacterial genes.

Why is this important? Well surely all these bacteria that are present in our system and even though today we're focusing on the gut we have bacteria literally everywhere that you can imagine. The skin, the nose, any other orifice you care to name, there's bacteria there. So there's a state of symbiosis that exists between us and the gut bacteria and if there's any imbalance in the normal harmonious relationship that exists that's what causes us to feel ill. The gut bacteria really has just one role and that is to defend us from the insults that we get exposed to. It's role sometimes may be to defend us from ourselves. So say the donut you had this morning. Some of your good bacteria probably groaned when they saw it coming their way. Some of the bad bacteria probably felt really good about the sugars that they could get from it.

So the multitudes within us guide how we live our lives and even though we're going to focus mostly on the bacteria, there are of course viruses, fungi and other types of organisms in the intestine. I think it's instructive to point out that most of the bacteria that are in our intestine are actually in the colon. So that's where if we were to intervene in any way to manipulate the gut bacteria that's really where we would need to intervene. But the entire intestinal tract is host to a whole bunch of organisms. The majority of these are anaerobic. This is important only because they're very difficult to culture. So for many decades using conventional microbiology techniques people weren't able to figure out exactly how many organisms were there in the intestine. It's only been in the last couple of decades that we have PCR techniques and other molecular methods to be able to determine what actually exists and now that we know what exists we can figure out what it does. The number of bacterial cells in your body are 10 times greater than the number of human cells. I can't say this enough it seems. So how do we figure out what the role is of these gut bacteria? Well, there's three distinct lines of inquiry. The most fundamental is to determine what's there and that's where the field started with these culture independent methods and using PCR and other sophisticated approaches we're now able to get a pretty good handle on what the structure is of organisms in the intestinal tract. The next step is to figure out what's the function. If they're there, what kind of role are they playing, and how important is that role for health and disease? And that's the new areas of transcriptomics and proteomics and metabolomics that is determining the function of these organisms. The holy grail of everything will of course be to determine what does manipulation of this gut bacteria look like and how can we change the course of disease by doing something as seemingly fundamental as changing the composition and the function of the bacteria that exist within us? We are a ways away from that but the field is moving at an astonishing speed.

This list of conditions associated with imbalance in the gut bacteria has probably gotten longer in the five minutes that I started talking. Literally it seems every day that there's a new condition that is associated with it and this is by no means an exhaustive list but obesity, diabetes, metabolic syndrome, cancer, something as disperate as allergies and bowel diseases such as inflammatory bowel disease that Dr. Caldera will talk about in a little bit and Metabolic Syndrome that Dr. Rice will talk about in a little bit. It all boils down to this imbalance. So there are some bacteria, just to go with this analogy here, that are good in this instance and some that aren't and the relative abundance of one versus the other will determine whether you are healthy or whether you're ill.

The gut bacteria is also very flexible throughout our lifespan. We start out as a child with a lot of modification that happens from the time that one is born to a baby and a toddler. And just to orient people to this slide, if you look at the colors most of the gut bacteria are really go into these two groups. They're called firmicutes and bacteroidetes. The light blue and the pink is what most of the gut bacteria should look like. And you can see that in the healthy adult population here that's what most of it is. There's a little smattering of other colors but those are the two predominant ones. However, that's not the case in individuals of obese, and that's not the case in people who are malnourished. This red here is very alarming because it suggests that there's new populations of bacteria that are not beneficial to the host that have now taken over some of the beneficial bacteria that should be there instead. This is also the case with advancing age, although for the most part, it's only after the age of 100 that these changes really occur dramatically. But any condition that you can think of will affect this balance that exists and that's what we think accounts for the symptomatology of that condition in part. Now everything is multifactorial and very complex but the gut bacteria certainly shouldn't be discounted. They seem to play a key role. So as an example, we're going to take the case of clostridium difficile infection commonly called C. diff. It's almost always in the press as it has grown to be a very common healthcare associative infection. What does it look like? It's an anaerobic bacteria. It forms a spore which is in part why it's so difficult to contain. The reason that it got its name, Difficile, is that it was very difficult to culture. It needs special microbiologic media

and so most places find it difficult to culture.

And this spore is the reason that it's difficult to eradicate from health care institutions because the spore is resistant to virtually any disinfectant that you can think of. The only thing that works for it is a high concentration of bleach and even that it can find ways to get around. So there's one pathogen we really want to try and prevent in healthcare institutions, it's clostridium difficile. Having said that the current state of affairs is that there are still about 500,000 cases a year. About 30,000 deaths. There's a 30% recurrence rate, which is very problematic, because you can get away, you can be treated for the first episode of C. diff but if 30% recurrence rate means that you're going down into this vicious cycle of second episode, third episode and so on. It's a severe diarrheal illness that has a major impact on quality of life and suffering. Some of my patients in clinic tell me that they have had to completely change their lifestyle ever since they got C. diff. They no longer go to see their grandkids. They no longer go to eat out. They're always trying to make sure that there's a rest room close by. These things are not trivial especially when you think about the fact that the incidence is highest in those over the age of 65 years. Those individuals are getting somewhat frail and might find it difficult to now handle their lives with C. diff.

So what role does the gut bacteria play in the manifestations of C. diff? This slide shows us, let me just orient you here to this. So this is a study where they took some control patients who were healthy. Some patients who had had an initial episode of C. difficile such as the one episode and then others that had had multiple episodes. So if you look at the colors here the green and the red are what's normal. So in the control populations asides from this minor smattering here the vast majority of bacteria are either in the green or in the red group. This remains the case with the first episode of C. diff. So even though you've had C. diff this hasn't altered the bacteria to a great extent. But look what happens to the group with recurrent disease. In this individual for example, the entire green has been replaced with this purple group which again is not something you want to see and it's not advantageous to the host at all. Same thing with this patient here where most of the beneficial bacteria have been replaced by this abnormal imbalance. And it is that imbalance that must be cured if we are to treat the symptoms of C. difficile effectively. Well, this gives us an idea for therapeutic manipulation, doesn't it? How can we get back to a healthy gut bacteria?

Well fecal microbiota transplantation or taking healthy stool from a donor and putting it into the intestine of somebody with C. difficile is now a therapy that has really taken the whole field by storm because nothing else seems to really work very well and this does seem to work well. I don't necessarily recommend that people try it at home.

(laughing)

But you'd be surprised how many people have. You know, desperate times call for desperate measures. But this is basically what it looks like. And if you do the at home equivalent, this is all you need.

(laughing)

All of these items are readily available. Don't forget the Lysol, it's really kind of critical to the whole approach.

And who are the donors? There's a wide variety of them.

We also have an oral form of fecal microbiotic transplantation that comes like this. Unlike any other medication where you have to take one pill or two, if you're undergoing this procedure you have to take 30 capsules of this. But the most important question I think is does it work and how well does it work? This is an example of how well fecal microbiota transplantation work. If you look at the control treatment here which is what's considered usual care. So for most people with C. diff they'll get oral Vancomycin, which is an antibiotic. Oral Vancomycin works about 30% of the time which is a very dismal cure rate for recurrent C. difficile infection. However, when you do infusion of donor feces, and in this case they did it via a nasogastric tube in a form of a slurry. But no matter which route you take it works about 81 to 94% of the time. Those are astounding cure rates and there's no other antibiotic that comes even close. So I think that's part of the reason why patients are willing to go the route of fecal microbiota transplantation because it relieves the symptoms associated with C. diff. In your spare time you might want to consider being a donor for fecal microbiota transplantation. What else are you going to be doing in the evenings? You might as well proceed with that.

The criteria to be donor though for a fecal microbiota transplantation are very, very strict. Only about 2% of people that apply to be a donor actually get selected to be a donor, because you have to be free not only of all chronic and infectious conditions, but a whole host of other things that one is tested for. This is our way, the field's way of making sure that even if we have to do this procedure for patients that it in the safest possible way and we're not inadvertently transmitting something that we shouldn't be transmitting. In the future we hope that there will be precision fecal microbiota transplantation where you can get the benefits without the mess, so to speak. There's also a bunch of other reasons why fecal microbiota transplantation should be employed for treatment of C. difficile. There's no production shortage.

(laughing)

And there's no addiction potential.

(laughing)

Thank you very much for your time and we'll be taking questions at the end.

(applause)

- Thank you very much Nasia. We're going to continue our move to another clinical indication of the interaction between the gut microbial world and human health. We're now going to look at inflammatory bowel disease. Our speaker is Freddy Caldera. Freddy received his medical degree from Des Moines University and then his medical residency and G.I. fellowship at the University of Kentucky and since then has been here as an assistant professor in our division with a special interest in Inflammatory Bowel Disease and he's going to talk to us today about Inflammatory Bowel Disease, building better therapies.

(applause)

- So I want to thank the organizers for allowing me to talk today on a topic that's very dear to my heart which is treatment of patients with Inflammatory Bowel Disease. I'm actually a little jealous of Dr. Halberg. I didn't know we could bring props. I would've brought a scope from the DHC, but I think Dr. Lucey might have had a talk with me afterwards for taking it.

(laughter)

So over the next eight to 10 minutes I'll be talking about what is Inflammatory Bowel Disease, how we treat it and how we can keep patients safe with treatment.

And some of you in this room or the additional two rooms or maybe at four o'clock in the morning might actually have Inflammatory Bowel Disease or have a loved one, whether it be a child, a grandchild or a friend that's afflicted with Inflammatory Bowel Disease because at times having Inflammatory Bowel Disease can be like, untreated, can be like having C. diff all the time, where it can control your life. But Inflammatory Bowel Disease it's a group of intestinal disorders. So even going back to Dr. Halberg's talk you know there's more than one but for the most part it's a condition where our own immune system causes inflammation in the intestine. The two main types that many of you and what we'll definitely talk about today is ulcerative colitis and Crohn's Disease. It's a chronic condition that can cause inflammation that's incurable. It's autoimmune just like other autoimmune conditions like rheumatoid arthritis, but nowadays it's a very treatable condition.

You might be asking yourself, well I've never heard of inflammatory bowel disease, is this really common? So it affects about three to four million Americans with 70,000 new cases each year. So that means one in 200 people. You might actually be surprised. You might actually know someone who has inflammatory bowel disease but probably has never said anything because you know, talking about diarrhea, about bleeding or having an accident are not really socially acceptable conversations.

But even if you don't know someone you might actually know someone in the future because we're actually seeing more cases of inflammatory bowel disease now in all the industrialized nations and what's really interesting is we're actually seeing it in parts of the world where we never saw it before. So where it's being seen more in the Middle East, in Asian countries, and in Latin America. We didn't see that in the past.

You might be saying, well what is really inflammation? So, our immune system, so the part of our body that keeps us healthy, you know, has a very basic way to deal with an insult. So we all have had a splinter. And at times that splinter gets really irritated, and gets red, and it's not infected. It's just your own body responding to that insult. And what it does, it causes inflammation. So these are white blood cells that go to this area, make it warm, they can cause pain.

So just like if you have an infection in your hand you could see that this is very inflamed compared to that. And the same thing can happen with someone with inflammatory bowel disease. Where their intestine gets inflamed.

And after learning that we're actually more bacteria walking around in human bodies you might be saying, well why doesn't everybody get inflammatory bowel disease? And so basic research actually asks that question. Why doesn't everybody? And we know that there's 163 genes associated with inflammatory bowel disease but we know that most people with those genes don't get it. So it's a disturbance in the microbiome, you know. Is it we live in a very clean environment? Is it changes in our diet? Is it changes in the environment or pollution? We actually don't know. But we know once this immune response happens

you have the state of inflammation. And once that happens you can't go back.

So we have two types. We have ulcerative colitis. So as you can see in red this is the large intestine or colon so if any of you here had a colonoscopy that's the part of the intestine we look at and depending on the amount of inflammation in the colon, it can lead to bleeding, diarrhea, to the point where some of my patients, they're like, looking bathroom, after bathroom, after bathroom. And they can have periods of abdominal pain, they can have incontinence.

And as you can see in this picture, you don't need to go to medical school to say one looks better than the other.

This is the picture of someone with ulcerative colitis. This is one of my patients where they were newly diagnosed, they're in their 20s, they just got into college. And at first they didn't want to go seek care because they were worried why they were bleeding and they had lost about 20 pounds.

And we got his colon to look like this which is a normal colon. So you can definitely see how this can afflict someone.

And some of the complications that these people can suffer is they can develop anemia, they have an increased risk for colon cancer. This is a picture right here of colon cancer in a patient with ulcerative colitis. And they can even develop a perforation or ruptured bowel.

While Crohn's disease is a condition that can affect anywhere in the intestine. So it can go from the mouth, all the way to the anus and depending on where you have inflammation it can cause either abdominal pain, diarrhea, it can make it feel like someone has an ulcer if it's only in the stomach. And it can also lead to complications. It can lead to a blockage where someone might also need emergent surgery. It could lead to colon cancer in patients who have inflammation of their colon. It could lead to an abscess so a pocket of infection or narrowing. You might be thinking, wow this is really depressing. This sounds like a horrible disease. And while it can be a very bad disease and in the 1960s or the 80s there wasn't much to treat it, you know. So this would've been a way shorter Mini Medical School one. But most people would have surgery, might need Prednisone, but nowadays most patients are actually treated with immuno-suppressants. And these medicines that decrease the activity of the immune system have actually transformed the field. And actually not only are the medicines we have now, but medicines that are in the pipeline, have really transformed it to the point where you saw that colon where it went from inflamed to not inflamed. Where we're actually changing how the disease is behaving. So the majority of patients I see in clinic can lead a normal life, you know, whether they're a physician, whether they're a CEO whether they're a nurse or a policeman. For the most part they lead a normal life. Where I usually have 'em come in when they're healthy also and then they're like well, do I still have to see you? I feel fine, why do I have to come in? But that's the goal. The goal is we want to keep that patient safe and we want to keep him in remission and feeling well.

But being well and staying well comes with a price. That price is there's a risk for infection. So one of the most common complications of all the treatments we have, because they're altering the immune system, is there's a risk for infection. But many of these infections are actually preventable.

So for anyone in the room, so there are not many vaccines we give to adults. Obviously everyone if they've watched the news in the past nine months has heard that the flu was very bad this year. So that's why everybody should get a flu shot. You know, everyone in this room should also get a booster shot for pertussis or whooping cough. A vaccine for pneumonia. There's actually a new shingles vaccine that now the age actually went down to 50. And this really doesn't change for patients with inflammatory bowel disease and it's actually of extreme importance, because we said, infection is the most common complication they can have. And actually that's what our work at UW has focused on is trying to prevent these infections so we're not trading one complication for another. So some of our research has shown, which has been aided by philanthropy, that patients with inflammatory bowel disease don't respond to the regular flu vaccine. So we did a study where we gave them a high dose influenza vaccine which is the influenza vaccine for anyone above age 65 and we showed we had better protection. We did a study where we checked their titers to pertussis and we found that they have lower protection to healthy people. So because of that we're recommending they should get pertussis vaccine every 10 years. And we just finished a study where we did in people 35 to 49 and we found that someone with inflammatory bowel disease whether they're on medicines that suppress their immune system or not actually had the same risks for shingles as someone in their 50s. So that's going to follow a study where we're going to try and vaccinate people under 50 with the new shingles vaccine. So some of these common complications you know we can prevent. That's where we want to improve the quality of care we give these people.

But in summary if you've not heard anything at all if you meet someone or you heard someone that is dealing with inflammatory bowel disease, at least let them know that there are treatment options because it has severely changed and we can give someone back their normal life. So there are two conditions called Crohn's and ulcerative colitis that can have bad complications but nowadays we can treat it to the point where they almost don't know they have it.

So, thank you.

(applause)

- Thank you very much Freddy.

If you're reliving the medical school experience, another very common and repeated experience was, are we nearly at the end yet? But you are nearly at the end. Even when it's been a great set of lectures the end is something that's welcome when it's in sight and so we have a closing talk. It's from Dr. John Rice. John received his medical degree from the University of Nebraska and he did his medical residency and G.I. fellowship at Northwestern University in Chicago. He then came here and is our assistant professor in the Department of Medicine. He's also the section chief of the section of hepatology in the division of gastroenterology and hepatology and he is going to talk to us about, what is the big deal about fatty liver.

(applause)

- Thank you Michael. Thank you to our mini Deans here and thank you for the opportunity to speak. I'm going to spend some time tonight talking about fatty liver disease. Some of you may be familiar with it, some of you may not. But we're going to kind of give you the lowdown here about fatty liver and why we care about it. Why I care about it from a liver perspective. So the objectives are relatively simple here. We're going to talk about what is fatty liver disease and something called the metabolic syndrome. Why do we care? So if somebody has fatty liver why do we care about that? And then the most important thing of course is how do we treat it? So what do we mean by fatty liver? Okay, so what fatty liver is is the accumulation of triglycerides or fat droplets in the hepatocytes or the cells of the liver. So your body is made up of cells. The liver cells are called hepatocytes and in fatty liver the hepatocytes get fat deposits in them. If you look at the picture associated with this slide here the top picture is a normal liver. The bottom picture is a liver that has fat droplets and you can see the clear areas there as fat deposition of the liver. So when we see somebody with fatty liver there are two principle causes of fatty liver. The first one is alcohol, okay? So people who drink alcohol particularly to excess, it causes fat accumulation in the liver. And then there's not alcohol. A cleverly named non-alcoholic fatty liver disease also called, NAFLD as the term we'll use for it. Okay, and NAFLD is closely related to something called the metabolic syndrome. That's the fatty liver I'm going to be talking about tonight is the non-alcoholic version.

So what is the metabolic syndrome? The metabolic syndrome is a condition that's associated most commonly with obesity. Obesity's defined as a body mass index which is a ratio of your height to your weight of greater than 30. And when that sort of condition happens when obesity happens it puts you at risk for other things happening. That includes the elevation of blood pressure or hypertension, cholesterol problems, so an elevation of bad cholesterol and a lowering of good cholesterol. And then something called, insulin resistance. Insulin is a key hormone in your body that's involved in blood sugar regulation. When somebody becomes obese their body can become resistant to the effects of insulin which leads to elevated blood sugars which is diabetes. But also along with those core pieces of the metabolic syndrome we see people get fatty liver, we see people develop heart disease, kidney disease and then sleep apnea. So it's a systemic problem. It goes along with the prevalence of obesity and as you can see the rising rate of obesity is concerning because we're seeing more and more people with the metabolic syndrome. Many people have probably seen this map. This is the map of obesity prevalence in the United States through the years. And as you can see here back in, I think it was 1985 when this started, you see that there was a lot of whites and blues. That's a very low, or light blues. That's a very low prevalence of obesity. As we move up into the 2000s it just gets worse and worse, and worse, and worse, and worse. Colorado held out for a long time, but even they are getting more and more obese. So obesity is a major public health crisis.

And obesity is a major cause of fatty liver. But why do we care? Why do I care about fatty liver when I see it? Well, fat deposition of liver can lead to inflammation. Freddy talked a little bit about inflammation is basically a wound healing or an inflammatory response to an insult. When that happens as a response to fatty liver scarring of the liver can develop and over the course of time, often times many, many years that process of inflammation and scarring and inflammation and scarring, and inflammation and scarring leads to cirrhosis of the liver. So the first thing I always hear when I tell somebody they have cirrhosis is, but I don't drink. Yeah, I believe you. It's that most of these people who have fatty liver related to obesity. And then cirrhosis sets in and all sorts of complications can develop. The scary thing is that whole process of developing cirrhosis is oftentimes asymptomatic.

We've talked a lot about the microbiome tonight and this also plays a role in obesity and fatty liver. Dr. Saftar mentioned the role of the microbiome in the development of obesity. We also see importances in the microbiome in the development of fatty liver and fatty liver and inflammation, okay, so it's a vicious cycle. It's a situation where dietary changes can lead to alterations in the microbiome which can then promote fatty liver and fatty liver and inflammation and eventually cirrhosis.

But it's important to point out that it's not just liver disease.

People with NASH, which is fatty liver and inflammation, are three to four times more likely to die than people without NASH. But the most common reason they die is heart disease. Okay, so it's a systemic illness. It's not just liver disease, but you can't forget about the liver disease. This is a graph that shows the number of liver transplant wait list editions on one side, and the number of obese Americans on another. And they're linearly correlated. Meaning that as more and more Americans become obese the number of people who need liver transplants for fatty liver disease goes up.

And unfortunately there's a cancer risk with this as well. Liver cancer or cancer that originates in the liver

almost occurs exclusively in cirrhosis, okay? NASH is the most common reason that people are developing liver cancer nowadays. So we're seeing more and more of this liver cancer and cirrhosis related to fatty liver.

It's interesting because the world of liver disease has changed quite a bit in just my short career. Many of you are familiar with Hepatitis C. For those of you not familiar with Hepatitis C, you may see cryptic ads on the TV that suggest you might have Hepatitis C, okay? Well the reason that happens is that Hepatitis C is very prevalent among baby boomers. They are the most prevalent population in the United States, okay? There's a lot of reasons that that happened most of it was a lack of public health awareness to be perfectly honest with you. For years, and years, and years, and years the most common reason we transplanted people in the United States was Hepatitis C. About five years ago the first direct acting antiviral medications for Hepatis C were introduced and in this short amount of time multiple drugs have come out in the market and almost everybody who has Hepatitis C can be cured at this point with drugs. 12 weeks, all pills, pretty easy to take and 99% of people will get rid of their Hepatitis C, okay? So those of you born between 1945 and 1965 the recommendation of the CDC is to be tested, one time, for Hepatitis C because again, it's usually an asymptomatic infection until something bad happens to you. But as these drugs have come on the market the number of people who need a liver transplant from Hepatitis C is plummeting, okay? And last year, or 2015 I should say, Hepatitis C no longer became the leading indication for transplant. But as you can see here in the dashed line, the big dashes, fatty liver disease is now passing it. So we're seeing the sunset in some ways of one disease and in some ways the dawn of another.

Okay, so that's fatty liver. We know it's getting more common, it's more prevalent, it rises with obesity, how do we treat it? What would you do if told you that I had a great treatment for you? Here's what it does. It lowers weight, it builds muscle mass, it improves bone strength, it improves mood, it lowers blood pressure, it lowers cholesterol.

This sounds pretty good right? It treats fatty liver, what is it?

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[Audience]

Exercise.

- Hey!

(laughing)

Diet and exercise, okay? That is really the cornerstone treatment for fatty liver disease.

Weight loss via dietary restriction and regular exercise can lead to improvement of liver blood tests. So one of the ways we measure if the liver looks like it's inflamed or injured is to just simple blood work. The liver will release things into the blood that we can measure. We know that if people who have fatty liver lose weight, their liver tests can normalize. People who have biopsies, so they have biopsies before they lose weight and then biopsies after they lose weight, tough to sign people up for those kind of studies but you can see improvement in the liver inflammation and resolution of the fat. In addition you can see improvements in everything else. Lower blood pressure, better cholesterol,

better sensitivity to insulin.

There's a lot of dietary fads out there. You know, intermittent fasting, keto, all that sort of stuff. To be honest with fatty liver there's been no optimal diet that's been studied. What's clear though is if they lose weight and get some regular exercise you can improve fatty liver. The real challenge I have to say about that though is that because fatty liver is usually an asymptomatic process until cirrhosis or liver cancer develops. It can be a challenge to get people to really buy into what you're telling them, because what I'm telling them is even though you feel fine now for the most part this process is going on in your body and might actually kill you at some point. Medications, there are no FDA approved medication for fatty liver. There's stuff in trials, there's stuff they're investigating. I don't know if they'll be effective or not but it's also when you think about the sheer number of people, I think at one point they said there were four million Americans with Hepatitis C. Think about fatty liver, 30% of the population, way more than that. So, right now there are no FDA approved medications. What about weight loss surgery? So you guys are probably familiar with the term, gastric bypass. So weight loss surgery has been studied in people with fatty liver and obesity and the results have been mixed. It's clear that people who undergo gastric bypass or their weight loss surgery or procedure lose weight, most of them will lose weight as long as they stick to the diet. And it's definite that some people with fatty liver will see the fat resolve in the liver. They'll see the inflammation decrease. Interesting though some people have seen a worsening of the scarring in that process. So we're not quite sure why that happens, okay. So the role of weight loss surgery in the treatment of fatty liver is still being explored but it's definitely an option for people who really aren't losing weight by any other means.

Liver transplantation. So this is sort of the final pathway. If you develop cirrhosis and you start getting complications from that. For many patients with liver cancer this is the only option that's life saving, okay? So as I mentioned before we're seeing more and more people who need liver transplants because of fatty liver disease. One of the things that really attracted me to the study of liver disease and the practice of liver disease is it really is a team sport.

We have an enormous team at UW who participate in liver transplants and these are just some of the members of it. It really is a sport where everybody gets together and works in a collaborative fashion to try to help people manage their end stage liver disease or their liver cancer and then manage themselves after transplant. It's really one of the most attractive parts of the process.

We have a very robust transplant program at UW. So the comprehensive UW transplant program which was established in 1966, one of the first programs in the country, is the sixth largest program in the country. So in terms of solid organ transplants, kidney, liver, heart, lung, it is the sixth largest program in the country. We've served patients from every state and 10 different countries. We started doing liver transplants here in 1984 and have completed over 2500 liver transplants at UW.

Last year was the most number of transplants from a liver standpoint we've ever done. We did 125 liver transplants.

We're a multidisciplinary team as mentioned before. We have five surgeons, seven hepatologists, or liver specialists. 14 nurse coordinators and many social workers, addiction counselors, administrative staff, who all help keep the liver transplant team up and running. We offer different donors. So most are deceased donors so people who've been generous enough to donate their organs as part of their last wishes. We also do live donors, occasionally we do pediatric transplants and then multi organ options such as liver, kidneys. We've done our first heart and liver transplant simultaneously this year. So a different number of options there.

And part of maintaining a solid and state of the art transplant program is through groundbreaking research. Studying transplant, making it better, improving quality and that's through generous donations from donors we're able to do that.

So, to sum up did we talk about in my short little time here? Fatty liver disease or also called NAFLD is most often a consequence of obesity. And as a result of the obesity epidemic in the United States fatty liver is becoming much more common in the United States. Fatty liver is a leading cause of liver cirrhosis and liver cancer. The treatment is still weight loss through diet and exercise and it can lead to improvement or resolution of fatty liver. And fatty liver is a leading indication for liver transplantation. Thank you.

(applause)

- Thank you very much John, thank you to all four speakers. Thank you to all of you for paying such good attention. We've heard four great talks and listening to them two things occurred to me. One was the span from bench to bedside starting with Rich Halberg showing that changes that really can affect the wellbeing of patients start at basic science research. And then through Nasia's talk, through Freddy and from what you've heard even from John, the range of changes that are related to this important aspect of health, the microbiome and the gut. And the final thing I would say is I think all of the talks emphasize the value of research, all of them have looked forward as well as look back, and we will not improve the health of patients in the future without continuing that commitment to improving health by working from the bench to the bedside. So with that brief summary I'm going to hand over to one of our mini Deans, or maybe both our mini Deans.

- Dr. Halberg I'm aware that you are at a whole different level of expertise and you do colonoscopy on mice. Can you give us a little bit of insight on how that happens?

- So you actually want to come see me if you need your colonoscopy, my scope's only this long.

(laughing)

And it's only that big around.

So unfortunately I can't tell you too much though.

So yeah, we do colonoscopy on the mice. I showed you the red and green fluorescent proteins. We can actually see the tumors in living breathing mice and see how they respond to therapies. So in some cases, not an example I showed tonight, we can actually see the green cells melt away from a tumor while the red cells persist.

So it's a very powerful tool. The beauty of it is that because we can do colonoscopy on the mice and we can see the response in real time, the number of mice that we need to use goes way, way down. And so we're very contentious of the animals that we use for our research.

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[Dr. Page]

Thank you Dr. Halberg.

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[Dr. Rice]

I have several questions here about probiotics in the human biome so, Nasia?- So probiotics seem very attractive because if we know there's an imbalance in the gut bacteria can replacing it with one or two different species of bacteria restore the balance that we seek? The problem is I think two-fold, one is that we don't know enough about which probiotic to use, is it sufficient for example overdose on yogurt once in a while, will that get us what we need? Probably not. And the other is that given the millions of bacteria that exist in our intestine I think it's a little simplistic to think that taking a few million probiotics will restore imbalance that there is. They probably don't hurt the vast majority of the time but whether they help or not I think remains to be determined.

- You know, I have quite a few on probiotics as well, but here's one that's not exactly and perhaps this would be for Dr. Caldera. Are there fecal treatments for inflammatory bowel disease?- So not yet, I've actually had more than a couple patients who whether their inflammatory bowel disease was pretty severe that they tried fecal transplant at home. But to date there's no definitive either fecal transplant or probiotics have been shown to work for a lot of people.-

[Dr. Rice]

Okay, I understand that drugs to treat Crohn's disease are expensive and often not covered by insurance. Is the hope that the cost of the treatment will be decreasing in the near future?- So not all drugs are expensive. The ones you see on TV are expensive.

But honestly, very rarely does cost become an issue in limiting me in treating someone in my clinic. Actually the majority of the time regardless of the insurance it might take maybe an hour phone call with me doing a peer review, but we usually get the medicine that's needed.- Thank you. I have two questions actually. One is Dr. Page, will you ask my niece in Burlington to call, email, text more often?

(laughing)

We'll talk later.

I like that.

Dr. Rice, this is really serious. Should we opt out or opt in for organ transplantation?- Well we always say you can't take 'em with you so you might as well leave 'em here. But you know obviously in the United States it is a completely voluntary donor pool, meaning that people have to opt in. In some countries actually it's an opt out, meaning that you have to say I do not want to be an organ donor. I would encourage anybody to be an organ donor. There are way more people on the wait list for all organ types, then there are organs available and it truly is a life-changing event for somebody to get an organ transplant.

You're talking about people who are suffering mightily from end stage disease and it really does restore quantity, and quality of life, so I'd encourage anybody to be an organ donor.

- Okay, this is for Dr. Halberg. What percentage of drugs that are effective in mice transition to be helpful in humans?

- That's a challenging question. There's been in the animal models that we've used in the past there's been over 300 drugs that have been tested. I'd say about 10% of them have made it on to being shown to be effective in the clinic. But those models aren't as effective as our new models, so I think we'll get better as time goes on.- Maybe I'll have Dr. Lucey comment on this because you all may not know this but the University of Wisconsin was a pioneer in offering both the endoscopic colonoscopy and virtual colonoscopy. And the question is-- first of all Michael you might comment on virtual colonoscopy-- and also the question was, how does the prep for that or perhaps routine colonoscopy affect the microbiome?- Well, I can answer the second question first because I don't know.

(laughing)

It clearly can't like it because it's cleaning out the colon but one of the aspects of this which I think was eluded to by Nasia is that the microbiome is a dynamic thing. It's not a fixed thing. So at all times there are pressures on it to increase in one direction or another according to the composition of it. In a healthy person one presumes, but I've no data on this, that after having colon prep for a colonoscopy you restore the microbiome that you had before, that would be what one would anticipate. The prep for virtual colonoscopy is virtually the same as the prep for standard colonoscopy.

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[Dr. Page]

Thank you.

- Okay, here we go. How quickly should a meal pass through your gut or your body? What causes bowel movements almost immediately after every meal?

- Well I can answer the second part. That's a reflex, so any of you who have

seen a baby being fed at the breast and you hear a squirting sound coming out the other end, that's not the milk coming in at the top coming out at the other end. That's a gastrocolic reflex. So the gut is contracting in response to feeding.

I forget the first part was how long does it take. Anywhere from a few hours to a few weeks. It depends on who you are.

(laughing)

- Thank you. This might actually go to any of you. Just asking about prevention for the problems we've discussed today. Any further advice and specifically does organic food play any role in digestive health?- So I will tell you what I tell most of my patients even with inflammatory bowel disease, because you could Google all kinds of things of treatment of inflammatory bowel disease. I definitely think a healthy diet, a diverse diet, where there's actually a study in the microbiome showing that you want to diverse microbiome is probably more worthwhile than getting supplements where we don't know what's really needed. So getting your fair share of fruits and vegetables, fruits, fish, all the things that kind of Dr. Rice said, that's what I would suggest. As far as organic, I don't know. Depends how much you want to pay.

(laughing)

- The non-MD can add one thing. So there was an eloquent mouse study that was recently done showing there is no perfect diet for any particular mouse model. So what they did is the tried four different diets and they had four different strains of mice and they showed none worked perfectly for all four strains of mice. So as we talked about in my talk the differences between each one of us and what we eat. What may be best for me, may not be best for you.- So how can there be such a thing as live liver donor? You take a piece of the liver out and put it in and then it regenerates in the donor?

- That's a good question. The liver is made up of two lobes, the left and the right and it has tremendous regenerative capacity. That doesn't mean that the blood vessels and the bile ducts and none of the plumbing of the liver regenerates but the liver will grow to whatever size a person needs. So the way a live donor liver transplant works is if somebody has compatible anatomy and can give enough liver to the recipient and keep enough liver of their own, you can remove half the liver and transplant it into somebody else. Six, eight weeks later they'll both have enough liver for what they need. It'll be way bigger than when they planted it in. A healthy liver has the ability to hypertrophy or grow to accommodate the needs of the person.- Thank you. Dr. Caldera, we saw the fact that the risk of shingles goes up and the recommendations for shingle vaccination apply to at least a few of us in the room.

But what if someone's had shingles before. Do they need a shingles vaccine?- You definitely should. Shingles, remember it's chicken pox that everyone probably in this room had. Nowadays most people when Dean Golden was talking about they probably got the chicken pox vaccine. So chicken pox virus kind of stays around, and once you get shingles, it can still come back and visit you and anyone whose had shingles knows they don't want it to come back. So you should definitely get it.

- Exactly, okay this is for Nasia. Is it true that a potential side effect of fecal transplant is negative psychological conditions can be brought out such as depression, bipolar disease, and anxiety?

- You know that's interesting. I think you get sort of the bad with the good. So depending upon your donor, it's possible that you could be subject to some of the same experiences that the donor was feeling, which is why this criteria for picking a donor is so strict and medical students are popularly believed to be a really good choice for a donor for this very reason. This is before the first year of med school. After that they probably get too stressed to really serve as good donors.

(laughing)

So there is at least one case report in the literature where somebody who was lean before they got the stool transplant became obese after it and blamed it on the donor who gave them the stool, so anything's possible.- I guess this might be Freddy. What is the role of heredity in developing Crohn's disease?- So it's not completely, so we said it's one in 200 people in the U.S. will get inflammatory bowel disease. So if you have a first-degree relative, or the question I get always is, will my child have inflammatory bowel disease. So that only increases to 10 to 15 in 200.

So genetic plays a role, but it's not the only thing where most of my patients don't have a family member with inflammatory bowel disease.-

[Dr. Rice]

How does sugar affect gut health?-

[Dr. Page]

Dr. Safdar?- So what you eat really depends on what the bacteria like to see for growth and development. So as an example some bacteria that are present in our gut will produce enzymes that will influence our ability to digest certain things and sugar plays a role because those bacteria I'll call them the bad bacteria in this instance use those sugars to go through their own metabolic pathways and multiply to the extent that it is no longer beneficial to the human. That's a very sort of simplistic way of displaying it but that's the reason why a high sugar diet for example people that take that have a very completely different composition of gut bacteria than those that eat a very diverse vegetable, fruit, Mediterranean kind of diet. This has been the subject of intense interest to try and prevent C. Difficile using natural methods such as diet manipulation and broccoli is one thing that seems to work really well for C. diff prevention, surprisingly.

- Thank you, perhaps for Dr. Rice.

How do you know if you have non-alcoholic fatty liver disease if it's asymptomatic and a further question specifically says, is there a specialized blood test to tell one if they have fatty liver disease?- So the answer to those actually both is really it's no. You don't really know. So up to 30% of the population has fatty liver disease and to be honest if you have type 2 diabetes, the odds are better than average that you probably do have fatty liver disease. There is no specific blood test that's used to diagnose fatty liver disease. Often times the blood test will show mild elevations in liver tests, so this is the substances released into the blood, but not 100% of the time.

An ultrasound of the liver will usually show fat deposition of the liver. That's usually fairly obvious on an ultrasound. So it's usually a clinical diagnosis based on risk factors. So again, type 2 diabetes, obesity, cholesterol problems, maybe blood tests that show some mildly elevated liver tests and then an ultrasound usually will show fat deposition of the liver.- So if colon cancer is the second leading cause of cancer death why is the time between colonoscopies being lengthened?- Well it's not being lengthened for everybody.

It gets back to one of the other themes of today which is individualized medicine. So not everybody has the same set of risks. So if you have one colonoscopy which is done with a good preparation and by a competent individual and it shows no polyps, your risk, and if you have no family members who have colon cancer, then your risk drops down compared to the person who is found to have polyps or has a first-degree relative with colon cancer.

It's an individualized approach to the practice of medicine because determining the risk based on individual characteristics.

- I can just add to that. So my lab just got funding. What we did is using our mouse models, we actually followed the tumors in the mice. They start out as a benign state and then they become dangerous, malignant. And we're able to identify a signature that predicted whether or not that tumor was going to progress or not. We're now going back and looking at human polyps to see if we can use that signature to predict was that person at higher risk to develop a cancer or not. And then that will dictate how we do our screening. Those polyps that are removed by Dr. Lucey and colleagues, can we tell who is at higher risk and who needs to have screening more often? Who's at lower risk and needs screening less often so.- Great, thank you and we have time for just one more question and this might apply to any or all of you. How would stress affect the digestive system and the diseases that we've discussed this evening? We'll start with Dr. Lucey.- So stress does affect the digestive system and this has been studied and it's a difficult thing to study because it's difficult to mimic what is a real stress. But I'll just tell you one study that looked at bowel motility, so just to show that stress and the gut function are affected and it was using a simple pressure gauge that you swallowed and then gave a read out. And the stress that was most affective in changing the natural sequence of bowel motility was driving in traffic.

(laughing)

And that was a good stress because it wasn't outside the range of normal behavior. So stress does make a difference.

The brain and the gut are closely linked. The gut has more nervous tissue than the spinal cord, so it's no surprise that your gut does respond to stress.

- Let's have a final round of applause for our speakers. Thank you.

(applause)