

NATIONAL PRESS CLUB

**THE GENETICS AND PUBLIC POLICY CENTER'S
GENETICS PERSPECTIVES ON POLICY SEMINAR**

**“DO THESE GENES MAKE ME LOOK FAT?
GENETICS, ENVIRONMENT, AND OBESITY”**

**TUESDAY, DECEMBER 5, 2006
2:00 P.M.**

**THE NATIONAL PRESS CLUB
WASHINGTON, D.C.**

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JOAN SCOTT,
DEPUTY DIRECTOR, GENETICS AND PUBLIC POLICY CENTER**

**PANELISTS:
SALLY SQUIRES,
HEALTH AND DIET COLUMNIST, THE WASHINGTON POST**

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*Transcript by:
Federal News Service
Washington, D.C.*

JOAN SCOTT: – (In progress) -- The format today will be is that we have asked each of our speakers to talk about their particular content area for about 10 minutes – seven to 10 minutes – and then we will have a panel discussion amongst all of us. And then we will open it up for questions and comments from the floor.

So unless there are any other housekeeping things that I need to take care of, I will go ahead with our introductions. And I will start with our first speaker, who will be Dr. Bruce Blumberg, who received his Ph.D. at the University of California-Los Angeles, and is currently associate professor in the Department of Development and Cell Biology at the University of California-Irvine.

Dr. Blumberg has pages and pages and pages and pages of articles that he's published and speaking engagements, but I have to say, buried deep down in his C.V., it warmed the to the cockles of heart to see that his really important speaking engagement was that he was the keynote speaker at the "Ask a Scientist" night at a high school nearby where he lives. And, for three years in a row, he has hosted girl day at U.C.-Irvine, which promotes women going into sciences. So he is promoting the next generation of scientists.

So we've asked Dr. Blumberg to talk about his work in the area of looking at the environmental triggers or environmental contributors to obesity. We're all familiar with the idea that increased caloric intake and decreased physical activity are given as the primary environmental causes of obesity in Western society, but his lab is looking at some other potential environmental contributors and he'll be talking about that.

Our second speaker is Dr. Michael Christman, who will talk about what is happening in the area of genetic research to identify those genes or those variants in those genes that might have a role in causing obesity. He received Ph.D. at University of California-Berkeley and he's currently professor and chair of the Genetics and Genomics Department at Boston University. He was the principal investigator of the team that just reported the findings in "Science" last April of a common variant that may be associated with obesity that may be in as many as 10 percent of the general population, and I believe he'll be talking about that work.

And he also has ties to our community – our academic community – here in D.C. He's collaborating with researchers at Howard University to examine the role that genes may play in health problems that are prevalent in African-Americans.

And then our third speaker will be Sally Squires, who needs no introduction to a D.C. audience, certainly. She is an award-winning journalist for the Washington Post, where she writes the nationally syndicated "Lean Plate Club" column on good health and nutrition, which reaches more than five million readers. And she's also the host of the

popular weekly “Lean Plate Club” online chat, which is where she just scurried over from. And she writes a weekly email newsletter that reaches 250,000 individuals. And this year, she published a book, “The Secrets of the Lean Plate Club.”

And in case you didn’t catch this morning’s Washington Post, we are on week three of the holiday challenge, which was to have lean protein as part of your breakfast to help stave off those hunger pangs later on in the day. So in case you didn’t read it, I have informed you.

With that, I will turn the podium over to our first speaker, Dr. Blumberg.

BRUCE BLUMBERG: Thank you very much, Joan. It’s a great pleasure to be here. I’d like to thank Kathy and Joan and the staff of the Center for this invitation. This is not the kind of audience that I normally speak to, so it’s an especial pleasure.

What I want to talk to you about today is the work that’s happened in my laboratory and from several other laboratories that establishes a connection between chemicals and the environment and this ongoing epidemic of obesity. Although I’m sure you’re aware of it, let me summarize: the obesity epidemic is, in fact, an epidemic in the Western world. In the United States alone, 60 million people would be categorized as clinically obese; that is, 30 percent above the ideal weight that actuaries compute for their size and build.

Obesity accounts for 8 percent of the health care costs in Western countries. That’s really quite a significant amount. And in the U.S. last year, that worked out to about \$75 billion, so it’s one of the largest single costs that we have.

Most of that has to do with obesity being associated with what’s been loosely defined as metabolic syndrome. Metabolic syndrome is a spectrum of disorders that includes central obesity, so fat around the abdomen. Atherogenic dyslipidemia, that is: high triglycerides, high bad cholesterol, low good cholesterol, high blood pressure, insulin resistance, the tendency to have blood clots. So, all in all, this gives you a predisposition to type 2 diabetes, which is rampant, and also cardiovascular disease. And as you well know, type 2 diabetes has become an epidemic that the Department of Public Health in New York City has taken control of, which is rather controversial.

The hormonal control of weight is a very complex topic and I’m not going to go into any great detail, but you can divide it into two parts. There is the hormonal control of appetite and metabolism that occur mostly through the neuroendocrine system: when you eat there are a variety of hormones that are produced in response to eating – leptin, ghrelin, insulin – and the balance of these determines whether you feel full when you’ve eaten or whether you continue to eat even though your stomach may be distended. There are disorders where people do that.

And then the second thing is the hormonal control of the fat cell itself. And we’ll talk about it more, but this is primarily regulated by several hormone receptors. And

there's one in particular, a receptor that we'll talk about, called PPAR gamma for peroxisome proliferator-activated receptor gamma, which you can consider the master regulator of fat cell development. When you activate this receptor, cells that are susceptible will become fat cells.

So how does obesity occur? Despite the fact that we have really unprecedented public awareness of the problem, Americans are getting fatter and fatter all the time and the prevailing wisdom is that we're all fat because we eat too much and we exercise too little. And although that this is certainly one of the most important factors, I think that it's starting to become apparent that that's not the only factor. Other factors that have been associated with obesity are chronic stress, inadequate sleep, and there's this model out there called the maladaptive thrifty gene model.

The model goes like this: that evolution has conferred us with a set of genes that enable us to use limited calories very effectively. Back in our caveman days when calories were not abundant, individuals with the ability to use the calories they were able to get most effectively would have an advantage. And those genes, by that idea, should be propagated in the population. But now, when, at least in the Western world, calories are not limiting, the ability to use excess calories more effectively is not a good thing.

There's also data to suggest that things that happen when the embryo is developing have some impact on later obesity. The most clear-cut example is maternal smoking, so it's been clearly documented that the children of mother who smoke while they're pregnant have lower birth weight and higher tendency to obesity later in life. No one knows what the mechanism of that is, but it's an actual fact.

And in 2002, Baillie-Hamilton proposed that perhaps there's a connection between the increased prevalence of a variety of industrial chemicals and obesity. And in kind of a crude way, you can graph the use of chemicals after the Second World War with the incidence of obesity and by and large there's an association between those two. Now, whether that's a causal link or not remains to be established, but that was the idea.

This leads us into the concept of endocrine disrupting chemicals, which, as members of the press, I'm sure you're aware of. An endocrine disrupter is a compound that mimics or blocks the activity of hormones like estrogen and testosterone, either directly or indirectly. In doing so they disturb development, physiology, and the maintenance of balance in your body, and that maintenance of balance is called homeostasis. Endocrine disrupters typically are persistent pollutants that we get through diet and through water, and many of them act through this class of genes we're going to talk about in a minute called nuclear hormone receptors. You're all familiar with environmental estrogens and with feminized male fish in the Potomac and elsewhere that can largely be associated with increasing the amount of environmental estrogens.

So what are these nuclear receptors that I talked about? Nuclear receptors are a group of proteins, and we call these ligand-modulated transcription factors. What that means is that these are proteins that directly turn genes on or turn genes off depending on

whether or not the hormone is bound. Everyone in the audience is familiar with hormone receptors, the estrogen receptor, the testosterone receptor. These are members of this family and they're widely distributed throughout the body and they work at very, very low levels of hormone, so that's one of the key factors.

This is actually a large family of genes. In humans, there are 48 and you've heard of many of these over here. What you probably haven't heard about or you might not have heard about are genes called orphan receptors. Probably about 15 years ago now when we were first cloning the genes that encoded these receptors, we found that there were lots of molecules which looked like receptors, but for which we didn't know what the hormones were, and those we called orphan receptors. Much of the progress that's happened in the last 15 years has been with the adopting of these orphans. There's a variety of genes in this group now and some of them are ones that are going to be of interest to us.

The ones that are primarily targets of environmental chemicals are the testosterone receptor, the estrogen receptor and the thyroid hormone receptor. What I'm going to you about today is a story that concerns the estrogen receptor and two of these former orphans, the so-called retinoid X receptor and the peroxisome proliferator-activated receptors. The names aren't important, but what is important is the function that these genes have in our physiology.

So the natural outgrowth of the Baillie-Hamilton model is that there may be compounds, which we named obesogens, which are chemicals that inappropriately tell the body to accumulate fat: either to make more fat cells, make bigger fat cells, or eat more. And there's a variety of data out there – and I won't go through all the data, just other than to highlight them – that suggest there are such compounds. Retha Newbold and her colleagues at NIEHS have shown that early postnatal exposure to environmental estrogens can increase weight later.

These are things like Bisphenol A, which is a component of plastic; a famous compound DES and genestine. Exposure early after birth makes animals that are fat later. It's well known that these type 2 diabetes drugs called thiazolidinediones, when you give them to patients of any age, those people get fatter. The reason they do is because they activate this receptor called PPAR gamma. There's data to show in cells at least that another kind of component of plastics called phthalates can cause fat cells to differentiate in the tissue culture dish. We don't know yet whether that has any effect in the animal.

What I'm going to tell you about now are our recent results that show a class of compounds called organotins cause fat cells to develop both in the tissue culture dish and in live animals. These are very interesting compounds, although they're probably the most famous endocrine disrupting compound that you've never heard of. I'm sure everyone's heard about DDT. Tributyltin is an extremely important endocrine disrupting compound because it's the single example that we're currently aware of a compound that causes effects at the concentration that you find it in the environment. The effect that it

causes is called imposex, which is the imposition of male sex on female mollusks, so what happens is these mollusks get very large penises and that makes them sterile.

In vertebrates, these compounds also have effects. It's a little bit more complex, but the one that caught our attention was that they cause sex reversal in fishes to a limited extent. So it makes female fish into male fish, so that's what got us interested in this problem originally. How are we exposed to such compounds? We're exposed through marine ship paints – these were originally used, painted on the bottom of ocean going ships, so that various kinds of barnacles and things didn't attach. But there are other uses, it's not just that you get them from seafood, its used are fungicide, as a wood preservative, and probably the most important route of exposure that we have is their use as heat stabilizers in the manufacture of plastics, PVC plastic, which is used for food wraps and for water pipes. These compounds are accumulated from the environment at a very great rate. You see the numbers here from invertebrates and fishes. Basically if there's any in the water, it will be accumulated thousands of fold into living tissue.

So how do these compounds cause endocrine disruption? Well, the simple idea is that it alters sex determination typically female to male. Sex determination requires sex steroids at critical times in development, sex steroids act through these hormone receptors I've just told you about, so the simple idea was that perhaps tributyltin is acting through a hormone receptor to reprogram sexual development. So we expected to see some effect on steroid receptors. And in fact that's not what we found. What we found is that tributyltin worked through these two receptors RXR, and PPAR gamma and it activated them very well. I won't go into this at any great detail, but if anyone's interested I can talk more about it later.

This receptor RXR is very important because it works as a partner for all these other hormonal signaling pathways. You know about the thyroid hormone receptor which regulates basal metabolism, you know about the vitamin D receptor which regulates how calcium is used in the body. There's also this whole group of receptors here that are involved in the metabolism of fat and energy balance. So the argument is that inappropriate activation of this half is likely to cause wide-ranging disturbances in the body's ability to maintain homeostasis.

So to skip through lots of data and just show the key points: what happens when we treat animals with tributyltin? So here's a liver of a mouse that was exposed in utero while was still developing with tributyltin, and it's stained with a dye that stains fat red, so you see there's not any red here because these animals when they're born have almost no fat. With the tributyltin exposed animals you can see they have quite a lot of fat when they're born. If you follow these animals with time, you can see that although they start out with a little bit more fat for the first couple of months, the tributyltin exposed animals are a little bit smaller, and that's the same thing that you see with the prenatal smoking animals and with the perinatal environmental estrogen animals. If you continue to follow these animals, what you see is after six months and then nine months that the TBT animals are about 10 to 15 percent heavier. Now these animals were only exposed during

development, and they were not exposed any more after that. So these animals had normal diet, normal access to exercise, and yet they're significantly fatter later.

That's all the data I'm going to show you. I'm just going to jump to the conclusions now, and what we'd like argue from these data is that this class of compounds called organotins are very potent regulators of these two key receptors, RXR and PPAR gamma, that control whether or not cells become fat cells, and that it does this in living animals and fishes, frogs and mice, and by implication humans as well.

Then the real question is: is exposure to organotins or other environmental chemicals a contributing factor for obesity? Well, I would argue that the data show that neonatal exposure permanently alters the adult phenotype. These animals were exposed while they were developing and then left alone, and yet they became fat. And we know from other experiments I didn't show you and also from human data, from people being treated with these diabetes drugs, that exposure later in life can rapidly induce genes that form fat. So the real question is: are humans exposed to sufficient levels of these compounds for concern? Is this a laboratory curiosity or is this something that we should be concerned about in the public?

Well, one of the main points to consider is that PVC plastic is up to 3 percent by weight organotins. Now, of course, most of that stays in the plastic, but some of it leaches out, and that means that we're all exposed to different levels. It's a prevalent contaminant in dietary sources; the Centers for Disease Control maintains this toxic substances in its disease registry, and it's present in parts-per-billion levels in seafood.

There's only a single study of which I'm aware in humans, and that study showed that in 32 random people that were examined, the average level in the blood was 27 nanomolar. So 27 nanomolar is just a number, but the fact is in our experiments, the concentration at which we get 50 percent activation of the receptors is 20 nanomolar. That means that at least in this one limited sample that was examined, the concentration of organotins in the blood is at a level sufficient to activate these receptors, and we already know that if you activate these receptors, you make animals fat.

The question then remains: is the environment making us fat? I would argue that – and as you'll hear from Dr. Christman – obesity is a very complex disease. It's not something that has a single cause or a single treatment. There are many risk factors, and I would argue that exposure to these chemicals, which can cause the differentiation of fat cells, is an underappreciated risk factor that we perhaps ought to consider a little bit more. The ones that we know about these days are organotins, and of course environmental estrogens.

So that's the thought I'd like to leave you with, and just point out for a second the people who did this work; this is primarily the work of Felix Grün, is a senior person in the lab, and he had a lot of help from Zamaneh, who was an undergraduate at the time. I can't thank our Japanese collaborators enough: this is Jun Kanno from the National

Institute of Health Sciences in Tokyo, which is approximately the equivalent of NIHS and Taisen Iguchi and Hajime Watanabe. I'll stop there.

MS. SCOTT: Thank you. (Applause.)

MICHAEL CHRISTMAN: I just want to thank Joan and Kathy for inviting me today. It's a pleasure to talk to you, and the message I want to convey is that I think it's kind of underappreciated that genetic factors are a very major contributor to obesity as well as many other complex diseases, but we're talking here principally about obesity.

And I think the right way to think about this issue for complex diseases is that there's a distribution of possible risks. If this is someone with a low risk of disease and this is someone with a very high risk of disease or obesity, and this is a number of people that have that risk. There's some variation in the population in your likelihood of getting this disease, and the working definition of a complex disease is that it's partly genetically determined, and roughly speaking probably half of this variance is explained by genetic differences, and half of it or so is environmentally determined. That's the definition of a complex disease as opposed to, say, a simple single gene or Mendelian disease, where if you have the gene, you've got the disease – like cystic fibrosis or hemophilia. This isn't the case with complex things like obesity, so probably the genetic part, which is half of it, consists of maybe 10, maybe 12 – we don't know – genes, each contributing a small amount, and that's why they've been kind of hard to find, because the effect of any one gene is relatively modest.

Historically we have not known what these genes are, and it's fair to say to date that we don't know what most of them are, but we are beginning to find some of them. What's changed everything is the sequencing of the human genome and the mapping of human genetic variation by various projects: the Sequencing Project, the HapMap Project, the SNIP Consortium, et cetera. We have all the tools and technology advances now to do much, much bigger studies, and you need these bigger studies if you're going to find these genes that have relatively modest effects. One of the surprising things from sequencing the genome and mapping variation is that people are surprisingly closely related. I think probably everybody's heard that we differ about one in a thousand base pairs or so from the person next to you – 0.1 percent or so you would vary from the person next to you, but a more profound thing is if we compare these two people and we say: these people differ at these sites every one in a thousand, what about a third person? And then the striking thing is that person varies at the exact same sites.

Now, why is that? There are a couple of possible explanations for that. One is that the same sites change again and again. That's not the answer. The other is that we're all extremely closely related, maybe more closely than people thought. Humans are eight times more closely related to each other than orangutans are to each other. The reason is, because the population of the world today is all derived from a group of probably about 10,000 individuals that left Africa 60–70,000 years ago and spread rapidly throughout the whole world and have given rise to the current day population. I

have a colleague from New Zealand who asked me to point out that people have made it down here now as well. (Laughter.)

So we're all very closely related and that's good news for the genetics because what that means is that historically, these kinds of studies where you look in families for a given trait – say obesity – in a small family, have not worked to find these genes that cause 5 percent of the obesity variance because the studies are too small, and the effects are too small and are masked. But now with the realization that people are really closely related, what we can do is much larger studies of genetic variation in two different groups, a so-called case/control study where the case here might be obese people, and control people of normal body weight. So now we can ask in which group are given genetic variations more common, and the implication is that near that genetic variation is a gene that is likely to influence obesity.

These kinds of studies are also enabled by technology developments. This is a picture of the Affymetrix 100,000 SNP gene chips, or something you can hold in your hand can map 100,000 – actually 500,000, even 1 million now – sites of variation in a genome by just washing some DNA from your blood over this chip and it takes a couple of days. One can use these to map variation in those case/control groups and find genes that correlate with obesity.

This is a blow-up of what this might look like; it's called a microarray gene chip. Each little tiny square which there will be thousand on each of these individuals larger squares contains the DNA sequence corresponding to one of your 20 or 30,000 genes and sites of variation. What we did in a study recently is to map these sites of variation in about 1,500 individuals, and then we line up those patterns of variation just indicated by colors here. Now, we noticed that there's no particular pattern in people who are not obese in this area of the genome, but in people who are obese, you can see that everybody seems to have this. And the implication is that in this region of the genome there's likely to be a gene variant that's associated with obesity.

We did a scan just completely typing all the genetic variants in about 1,500 people at 100,000 variations per person, in people of different sizes, and obesity is really among the most heritable of traits; that is, among the most genetically determined of complex traits.

I should maybe back up and say that complex traits are the things that cause everyday diseases in people. Cancer is a complex disease, heart disease, in addition to obesity. While the effects are small of any one gene, it's very important to understand because the population effects of complex diseases are enormous. It has a huge impact on public health. Rare single gene disorders are certainly tragic for the individual, things like cystic fibrosis or hemophilia, but they aren't a big public health issue actually because they're so rare. They're incredibly rare.

What genomics does is open up the world of complex, everyday type diseases to study. What we did was to do a scan on the Framingham Heart Study population – it's a

study, it's been going on since 1948. It's designed to study those things that are present in everyday people. In 1948, two-thirds of the adult population of Framingham were enrolled in the study; they were not enrolled because of anything, because they were obese, or because they had a heart condition. And the data are measured again and again – this just shows you the actual data on the distribution of body mass index. If you had any doubts about whether people get heavier as they age you can see it here because these are different exams that the people returned for later as the years went by. So it's very good data.

We plugged this in, mapping all our variation and taking the family structure into account and looked for variants that are associated, and what we found was, I think, the first very common gene that predisposes to obesity.

It turns out that at a particular site in the genome on chromosome 2, if you inherited a C-containing chromosome from both your mother and your father, here's your body mass index at different ages. If you inherited a G-containing chromosome from mother and father or a G from one and a C from the other, you're down here. But the remarkable thing, and this is manifest in men and women – the remarkable thing is this: 10 percent of the world's population is CC. So this is very, very common, it modestly elevates your risk of obesity, but because so many people in the world have this – and we know this from other studies that we've done and studies that others have done, so we took this initial finding and looked in many more populations as well, and we showed that this was true in African-Americans and it was true in children, from an obesity study in Germany, and we published this in *Science* earlier this year. And there are lots other genes that have turned up as well. But this is clearly an ancient variant because the association is found in African-Americans, and that means that this variant arose prior to human migration out of Africa. I think most genetic variation in the population that causes diseases is going to be like that.

So what pathway is it? Well, I won't go through this in any detail, but it's been well studied: the gene that we think is causing this is called INSIG2. We haven't actually 100 percent proven that, but this is a key regulator of fat metabolism in mammals. It's expressed in liver and fat. The simple idea is that perhaps if you have this variant, you're better at taking up or storing fat than other people. This shows the pathways that are affected are the so-called SREBP pathway for the synthesis of cholesterol and the synthesis of fat in the lipid. This is a study from the Nobel Prize winning work of Brown and Goldstein.

Probably when we were hunter-gatherers 60 or 70,000 years ago, this variant didn't make any difference. Probably it was neutral in the early evolution, but now that we sit around on the couch and eat potato chips and we play with PlayStations and not on the playground, now it's causing some trouble. Today's environment is really probably what's bringing out the trait that existed long ago.

One recent and unpublished finding of ours is that there is a skinny gene also. Three percent of people of Western European ancestry have a lower body mass index

than average if you have this particular variant. And we've replicated that in an African-American cohort. The skinny variant turns out to also be in this pathway at a different step in the lipid/cholesterol synthesis pathway.

That suggests that this biochemical pathway in the liver may be very important in body mass index. We believe in open access for these genomic studies. I think that that's important, and there was a little blurb just recently in "Science" about a website that we've released that contains over 200 different associations from our Framingham Study. That site has gotten now 300,000 hits in about a little more than a month from researchers around the world, because it's important to reproduce these studies, and as Joan mentioned, we're doing the first African-American genome scan with Charles Rotimi here at Howard University.

Why are we doing this? What will it do for us? Well, you hear a lot about diagnosis and how we'll be able to find genes, say, for type 2 diabetes, which is better if it's found early, so that sugar doesn't do the damage to your organs. The effects of any one variant, though, are small, and I think the utility of this diagnostic aspect of this will be limited. The big payoff, I think, if there's going to be a big payoff, is here in treatment. By understanding the biochemical pathways that affect obesity or whatever in the human body, pharmaceutical companies can then go in and make more intelligent drugs. They can say: hey, I think that pathway probably affects body mass index in people. That's not the way it's done now. Now they find a drug that works in the mouse, and so they decide to try it on people, and it doesn't work a lot of the times, so the high cost of drugs is in part due to this failure. I think from genomics the good news is that we'll hopefully have better and cheaper drugs in the future. I think the diagnostic aspect will be a little bit limited. Thanks. (Applause.)

MS. SCOTT: Thank you very much, Dr. Christman.

We've asked Sally to come here today because if anybody is aware of how these issues get reported in the media and what individuals are needing to know, it's Sally.

MS. SQUIRES: I'm delighted to be here today, and I think I have one of the best jobs in Washington, frankly, and I've been here for a long time so I've grown into the job, I guess is what you can say. But I get to take the news from scientists like these you've just heard, and I've been scribbling madly, so is hope I will be calling them both.

You've probably heard and seen that newspapers are struggling a little bit these days and so is the nightly news, so while we're hemorrhaging readers and viewers in other places, we have found that topics – and I'd love to tell that we planned this all out, but it didn't work this way, we've kind of stumbled on it – the topics that are important in terms of what you eat, and how you move – we find that readers and viewers and listeners only want to know more.

We started the Lean Plate Club in 2005. It was July. Are most of you from Washington? Show hands here. Yes. Okay. So you know it's kind of hot, it's kind

muggy, people leave – there isn't much going on. We started the Lean Plate Club at about that time and started a web chat at the same time, and we figured no one would notice. We really thought, well, this is the kiss of death, and the executive producer of washingtonpost.com was so convinced that this was going to be such a wonderful success, that she gave us an eight-week try out, and that was it, and said, 'we'll reevaluate, and see where we'd go from there.'

That was in 2001 in July, and here we are five years later. This is our sixth holiday challenge, and I did bring you materials, and I hope you'll all join us, and I'll tell you about that in a minute. But we find that readers and viewers and listeners want to know more and more about this. They are confused. They are perplexed. They are frustrated. They think – they hear one time that something is good for them, and the next time that it's not, and I did rush here after hosting the Lean Club web chat, which is on Tuesdays, and among the questions is got today there was one from someone who said, well, I used to eat like the boys, I could keep up with them. I could just eat whatever I wanted, and now that I'm 30 that suddenly I can't do that anymore, and I don't know what I should eat and I'm not sure what to do. So her question, and I guess it was a her, because she was saying she used to keep up with the boys, so I'm assuming this is a woman, and she said that her question was: well, if I substituted margarine for butter, would I help to reduce calories? And I thought, wow, we've got a lot of work ahead of us here.

There's so much confusion. People do not understand what a whole grain is, they don't understand the power of fruit and vegetables, and I sometimes think that I will be accused of being in the pocket of the fruit and vegetable industry because literally every week I say: okay, if you're going to pig out, pig out first on the fruits and vegetables that aren't fried or have added sugar, and then go for the other stuff. Because we know from studies at Penn State and elsewhere that high volume foods that are loaded with water and fiber and have some complex carbohydrates really can fill people up better.

It's really been this evolution, and the whole idea behind the Lean Plate Club is to take the knowledge that you're hearing up here, because of where we are. In Washington we have access to the National Institutes of Health, to the U.S. Department of Agriculture, to Health and Human Services, to the Food and Drug Administration, to a lot of information that consumers don't know is out there, and we rely on that as well as really stellar academic institutions, including places like Johns Hopkins, and Georgetown and other spots that are well known to get the latest information that we can give to the consumers and to get rid of the nutritional fog and the physical activity fog. And there is a lot. I mean, people really, really are confused. And sometimes in that confusion they're throwing up their hands and they're saying: well, what does it matter, why don't I just do what I want because the scientists don't know and it's constantly changing, so why don't I just do what I want?

The same thing is true of physical activity. When I first came to Washington, I remember coming to this National Press Club. I came during the Reagan administration which shows you how far back it was, and I remember coming and thinking: wow, the

National Press Club, isn't this cool, and we used to come to press conferences here. Well, these days I don't ever have to leave my desk. Not only don't we go to press conferences because they are now televised, but I can get everything I need pretty much through the web, which is fantastic. The good news is that you can get access to it so quickly, but the bad news is – and I've even talked to scientists who say they're now wearing pedometers, and they're shocked when they find that if they're lucky, they get 1,000 steps, 1,500 steps a day, which is way, way sedentary. If you know anything about pedometers, you at least want to be in that 7,000 step range, and a conference that I was at earlier this year sponsored by the CDC on physical activity – an international conference on physical activity – there was a lot of talk about whether or not the 30 minutes a day and then the 60 to 90 minutes a day of activity that we're advising people who want to lose weight – 30 minutes a day for just the average Joe and Jane – that that has been set up for people who are active in the rest of their lives, and increasingly none of us are. It's shocking how little activity we can get. And I heard a lot of buzz in Atlanta that we're with physical activity where we were with nutrition about 20 years ago, which I think it's very, very interesting. So we're likely to see lots of steps toward taking more steps, and how we can figure that out.

Let me tell you just briefly about what we're doing with the Holiday Challenge, and we see the Lean Plate Club as really an interesting mixture – like the editor who let me run with this has just left the Post, and I'm thrilled that the new editors who are taking over as just as happy with this exercise because we really see this as a combination of journalism, of public health, and of public service. We have access: we can take that skeptical look at studies, or at the latest government guidelines, the dietary guidelines or whatever comes out, but by same token we have the opportunity and the means to get this message out repeatedly to lots of people in lots of different ways. And that's exactly what we're doing.

So while newspapers are starting to decline, and the nightly news – I don't know if you know that the average viewer of the nightly news is now 60 and older – that these new mediums are coming up that are quite interesting and of course there's the internet. We've experimented with some social networking around the Lean Plate Club. We had to do something last year called Frappr and if you want to see it, you can go to www.frappr.com/leanplateclub. It's these are Lean Plate Club members who just wanted to talk to each other about what they were trying to do on the Holiday Challenge.

The Holiday Challenge is based on a study that was published by Jack and Susan Yanovski at the National Institute of Health. It was published in the "New England Journal of Medicine" in 2000, and it looked at National Institute's of Health employees and followed them during the holiday season. It turned out that healthy weight people only put on about nine-tenths of a pound. Not such a big deal; they took it off in the spring. But overweight people, and whether they get overweight from the estrogens in the environment or the genes that mom and dad had, from choosing the wrong parents, I don't know, but overweight and obese people put on an average of five pounds, and they did not take that weight off in the spring.

It's very easy to do the numbers and see how rapidly this can add up, so we decided – because one of the other philosophies of the Lean Plane Club is not to talk about diets. That is the last thing we're about, and I had a lot of run-ins early on with the Atkins people and other proponents that have seen different cycles. We're not about diets; we're about adding healthy habits. So for the Lean Plate Club Challenge, we are challenging participants simply maintain their weight from Thanksgiving to New Year's. And we know that if we do that, they'll be a step ahead of the curve.

Each week we are offering a food activity and a physical activity to help people stay this line. And we're delivering news – I don't know if you've heard, but in New York City the plan to ban transfats from restaurants passed or has been adopted today. So one of the things we'll be talking about next week are the healthy fats that you can add to your life, and you probably know that canola oil has recently gotten the health claim from the Food and Drug Administration as being heart healthy, so it can sit side by side with olive oil. Those are the kinds of practical advice that we're trying to deliver to people.

We're also delivering magnets, and this year we're also playing with the new technology: we've got video blogs, or vlogs for those in the know, and we've given video cameras to three Lean Plate Club members: one is a teacher in Vienna, Virginia; one is a single employee in Baltimore; and one is a dad and father of two, and we're following their vlogs as they go through with the Holiday Challenge. I hope you'll join us too. It's never too late to join: that's another tenet of the Lean Plate Club. It's been a lot of fun, and I also hope – I know some of you are scientists, and if you do have story ideas particularly related to nutrition and physical activity, I would love to hear about them, I read all my emails so you can email me, and I'll give you my private one which is squiress@washpost.com. I would love to hear about story ideas that you have because we think this is a real growth area. We know consumers are interested in this, and we think we are poised to the place where we can really help a lot in conveying the knowledge that you're hearing up here.

So thank you very much. (Applause.)

MS. SCOTT: Well, thank you very much. What I'm going to do now is we're just going to have a couple of questions and then we're going to open it up to the group at large. We will be wrapping up at around 3:30. Let me start by asking – sort of following up on what Sally was just talking about that people are confused and they're looking for information, but how do you make sense of what we're hearing?

We've just heard that obesity is one of the most inheritable traits, and then is the environment making us fat? So how are people supposed to think about those two things, and how does that translate into a day-to-day sort of activity? I'm going to ask our scientists, from their perspective, how do you try and deliver that information?

DR. CHRISTMAN: Well, I would say, I think of genetics as sort of determining your range of weight, a high and a low point, and that's going to vary from person to

person. And then your behavior is what determines where you fall in that range. So they're both important, and there can also be interactions between the genes and environment. For example, the gene that I talked about probably had no effect in the environment of early human history. In today's environment it has an effect. So there's genetics, there's environment, and there's interactions between the two also.

DR. BLUMBERG: I think that's a very good point, and one of the things we should keep in mind with the observation that obesity is inheritable is that it's not just the genes, it's the behavior. It's the behavior, it's the way that people live, it's what they learn from their parents and in the home environment that they carry forward that also certainly has a big impact on the final outcome.

MS. SCOTT: Sally, in your experience, do you think people are able to differentiate between those?

MS. SQUIRES: Well, I think what often comes up, particularly in web chats or emails that I get from readers is, 'my family's fat, and I've been fat my whole life, maybe I just can't do anything about it.' You probably know about the National Weight Control Registry, which is a group of several thousand successful losers. It's been done by Jim Hill at the University of Colorado, and also Rina Wing at Brown University, and these are people who have lost at least 30 pounds and kept it off for at least a year, and often they're higher weight losses of 50 or 60 pounds and kept it off for 5 years, and they're very interesting to study because how they've done it and what do they do – they're free living. And so we've used that as an opportunity to look at our successful losers.

And it's absolutely true, I'm sure we're going to find lots of things that contribute to obesity, but even if we come up with a fantastic drug, odds are you're still going to have to eat smart and move more to really make it work effectively, is my bet. So I think we try to tell people: in terms of genes, sure you might have family members who are quite overweight, but you can still help moderate that by your own behavior.

MS. SCOTT: Let's talk about that sort of issue of control and how much control people think that they may have over their weight. Does identifying a particular genetic variant that may contribute to the risk of obesity, or identifying a specific environmental cause that we may have been exposed to when we were in fetal development – how does that help us to take some of the onus off ourselves? Is it a motivating factor? How might people use that information or not?

MS. SQUIRES: Well, I would suspect – I'm old enough to remember when we used to say people were big boned, remember? Yes. (Laughter.) We had the metropolitan weight tables and everyone said, 'oh, I'm in that big boned category.' It used to be it was glandular condition that we've heard. I think throughout the time that I can remember, there have always been reasons that you could attribute to. And clearly science will teach us whether or not those things are true, but what else can you do to shape your – I'm sure there are those of us in this room who are more susceptible to alcohol, or more susceptible to cigarettes, so there's going to be variability.

DR. CHRISTMAN: I think it's a double-edged sword. It can be enabling, I suppose, to some people to know that genetics is a major contributor to their obesity. On the other hand, if you are in the obese range, then you can't change your genetics, so all you can do is exercise and change your life style, eat better, and it's all the more important if you're in those high weight ranges. With every step up in your body mass index over 25, there's an increased risk of early death. So it's a serious thing, but I think that genetics – I think it's more appropriate to think of it as sort of a medical condition like heart disease. Heart disease is also environment and genes, but if someone has heart disease, they're usually not blamed for it.

MS. SCOTT: We're going to open it up for questions. If you could wait until you get the microphone, we have our roving mike.

Q: Hi. Will Saletan from Slate magazine. I recently was writing about gastric bypass surgery, and I went and looked at the websites, and I was dismayed – just dismayed and maybe it's just the truth. Just about every one of these websites, and they're all offering that surgery – sometimes offering other kinds of weight loss – they're all saying, diets don't work, diets don't work. If you are in this category of significantly obese, morbidly obese, all the studies show that yes, you'll lose the weight, but you'll get it back. Almost nobody – and the message that I took away as a reader was, there's no point in even trying this.

First of all, can you tell me, as far as you know, do the data bear that out? And secondly, to the extent that the data do correspond to that, how should we look at that? How should we look at dieting? How should we look at the surgery? Because what they're telling you is that if the odds are so low that you're going to succeed with the non-surgical options and that the medical risk from the obesity is so great, you'd better go straight to the surgery.

DR. BLUMBERG: I don't know so much about the gastric bypass surgery, but I think everyone here knows how difficult it is to control your weight. So it's hard to get enough activity. It's hard always to make the best food choices; a lot of times people just take the easy way out. And depending on your genetic make up, and perhaps other factors, you're going to fit within a certain range.

Now, with regard to the surgery, I know two people in fact who had that surgery, and both of them lost a lot of weight and they're both drifting back up. So I don't know how permanent that actually is.

MS. SQUIRES: I was intrigued when Al Roker, who did – I think he was outted actually by a tabloid when he underwent gastric bypass surgery, and in recent years I've noticed that he's been kind of looking rounder, and I was curious, and so that started me on a column about gastric bypass, and in fact there are ways to eat around gastric bypass, and the majority – I shouldn't say majority, it's been a little while since I reported this, but a significant number of people are able to bypass the bypass, and so if you don't

change those habits, again, you might have the surgical intervention, but you don't – if you slip back and all the same things apply, just like heart disease that if you have high blood cholesterol, and you get a blockage and you do angioplasty or bypass, if you go back to eating and doing all the things you did before, odds are that you're going to develop more problems.

So I think the gastric bypass websites may play off the fact that it is hard sometimes to lose weight, but it's also very clear that people who stick with it and really – they may not reach the perfect weight that they want, but they can reach a healthier weight, and we know from the Diabetes Prevention Program that even 7 percent weight loss among a group poised to get diabetes can have a significant medical benefit. You guys – would you agree?

DR. CHRISTMAN: I would agree that even modest weight loss can be beneficial, but I would agree with the first part of what you were saying: that the data are reasonably clear that in general diets don't work, and that's obvious there are lots of exceptions to that general rule, but that's the way it's perceived, certainly by pharmaceutical companies.

MS. SCOTT: Actually, that raises a good question particularly about that skinny gene and that pathway. Wouldn't that be an obvious target for a pharmaceutical drug intervention, to have a skinny pill?

DR. CHRISTMAN: It is. And I think the payoff from the genomic studies is defining those pathways, so potentially via drug intervention you could influence body weight in people, and that's not the way drug discovery is normally done. And so there are companies, Novartis notably, and others that are targeting that pathway with drugs now. Whether those drugs will work, I think, is another question, so this sort of validated target paradigm as it's often referred to is intriguing. I like it, but I'm not sure it will prove to be correct. Time will tell. These drugs also, even if you have the issue of long term toxicity with all these drugs. That pathway in particular is a key aspect of metabolism.

Q: Hi, my name is Sherry Marts and I'm with the Society for Women's Health Research. I'm a ringer here. I'm not a reporter. I'm actually a scientist by training. And this may be a complete blind alley, but I'm just curious: I recently heard a talk by Roy Wise from the National Institute on Drug Abuse and he and Nora Volkow, who is the director of that institute, published a paper fairly recently comparing overeating to drug addiction and essentially arguing the possibility that food – and avoiding the whole question of whether it's possible to be addicted to food – but that essentially overeating can affect the same systems in the brain that drug abuse does, which is essentially the dopamine system and the pleasure centers and all that.

And I'm just curious as to whether either the genes that you're looking at or the environmental – the endocrinal disruptors you're looking at could possibly interact with that system as well and have an effect on behavior where essentially the behavior that is

causing harm is so desirable from a pleasure standpoint that it can't be overcome or stopped, the habits can't be changed.

DR. CHRISTMAN: I think that's definitely a point of view that's reasonable. I showed a slide illustrating that there's a very complex control of how your body decides to eat, when it knows it's full, when your body will have cravings for more of a certain kind of food. We've all had those cravings, and that's hormonally controlled, so you could certainly make that connection that in a way it's like an addiction.

DR. BLUMBERG: I think it's clear that the circuitry in the brain can be a big determinant of eating behavior. But the discovery of the hormone leptin 12 years ago or so – leptin is a hormone that's made by fat cells and tells your brain to stop, that you're satiated, to stop eating. So you can imagine perturbations in neural circuitry affecting eating behavior just like it could affect addictive behavior. Whether there will be common genetic variants that are in those pathways is not known.

MS. SQUIRES: We also know one of the things that is reported in today's health sections is that the hunger hormone ghrelin if you eat more proteins seems to – in some recent studies, seems to help drop levels of ghrelin in some people. And so there may be different ways to moderate some of these things.

Q: So, Sally, you talked about sort of individual behavioral changes and sort of at the individual level, and Bruce, you talked about more really what would have implications for environmental regulation in the long term and sort of what kinds of environmental pollutants we might regulate or avoid in our own lives and allow to be out there. I was interested, Mike, in your discussion talking about the ability to have the diagnostics for the variant that contributes only modestly to obesity or any complex disease, and you're sort of – the word's not quite pessimism, but sort of lack of enthusiasm for the utility of those diagnostics in and of themselves.

So then we're sort of looking at what do we do when the diagnostics are available and we have the test for the skinny gene, and the fat gene and the super fat gene, and the time lag between having those variants in hand and either having an individual modifier, an environmental modifier, or a pharmaceutical modifier that we can effectively use to sort of avert those negative consequences. How do we handle the interim period with all that information?

DR. CHRISTMAN: Well, I think that's a very interesting area. I think a standard for genetic testing ought to be that if you're going to have a test for something there ought to be some effective intervention. Now, when things have modest effects, a lot of these complex traits will increase your risk 30 percent above normal for obesity or whatever – 50 percent. Then it becomes a very difficult question of how – does that really – is it warranted, is the cost warranted? Will insurers pay for it? But in my opinion, for most of the risks that are out there, they're almost all going to be small. If they were a huge risk for individual variance, we'd already have found those genes.

And so we know they're not really there. So all the effects are pretty modest, so I think the value of the diagnostic testing is limited.

There is kind of a danger area, though, of potential for abuse of that system, because studies show that people want to be tested. They don't care that there's nothing you can do. They're curious and they want to be tested.

Q.: So there's a market place.

DR. CHRISTMAN: There's a market.

Q: It's actually a response to this last question. So would you not consider in terms of the value of predictive or diagnostic genetics in this area – would you consider something like a drug targeted to specific genetic profile in terms of you have mutation here, but not here in this gene, and this drug, but not that drug might be better for you? In terms of the value beyond merely identifying knowledge drug pathways.

DR. CHRISTMAN: Yes, oh, yes. Certainly. I think there's potential for that: genetic profiles determining which drug might be more effective for a given individual. And also I think an even more important area that can be applied now and is being applied now, is to identify genetic profiles that would predict an adverse event.

It's being done now for Vioxx. Why do some people get heart attacks from Vioxx? One can develop a genetic profile even if you don't know what the genes are – and so the pharmaceutical companies are trying to develop tests like that, but equally valid would be the first thing you suggested.

Q: Dave Kaufman, from the Genetics and Public Policy Center. Given the difficulties that we might encounter doing prognostic testing and seeing the prevalence of the estrogen disruptors, do you all think there might be a bigger – I mean, we've talked about what individuals can do, diets, stomach stapling, but from a public health perspective do you think that there's maybe more bang for the buck in, say, assuming that we find the estrogen disruptors are significant, is our public health dollar better maybe spent abating these disruptors than testing for genes?

MS. SCOTT: Can I add something? Would that also mean that if you knew, if you got tested, and you knew you were more susceptible to this, and you have a family history of it, that you might want to avoid taking it to the extreme, not using plastic bottles or something? Would there be some steps that you might take to make sure that you minimized as much risk as possible for yourself?

DR. CHRISTMAN: I personally think that the access to genetic testing is a good thing. But as we were talking earlier, I think it needs to come with education. To make available a test that says you have this gene ABC for these variants is less useful than saying you have these gene variants and research shows that this will tend to cause these effects given certain behaviors. And that if you want to moderate these effects, then

you'll avoid plastic bottles or instead of eating tuna, you'll eat salmon, things that concentrate pollutants less up the food chain. One of the things that at least from my perspective we do differently in this country than in other countries is when there's a problem the first thing we do is look for a drug to fix the problem.

For instance if you travel in Europe you'll notice that's not the way people behave. If people are fat, they think, well, you need to eat better. It's a kind of a collective behavior that we have that we immediately look for a drug to fix whatever problem occurs, and that's certainly effective in some cases. But maybe our public health dollar would be better spent on education. Maybe that's where the most bang for the buck is.

Q: What about developing that evidence to build into the educational pace, so we – identifying the variant is fairly easy and we want to couple that with an educational program to go along with it that addresses, and so – blah blah blah blah – getting those sorts of studies that really identify what are the effective interventions. That's another – it seems to me that's another area where money could be potentially well spent on identifying and trying to elucidate what all of your options are, given whatever your variant is. I guess that was a question.

DR. CHRISTMAN: Well, I think with complex genetics you have to think in terms of statistics and big numbers, so for obesity, most people who are obese take that have that variant we discovered. And most people who have that variant aren't obese. Yet there's clearly a statistical association: it elevates your risk of becoming obese. So in that environment then I would argue that a test is relatively meaningless because you might be obese and have the protective gene, you might be skinny and have that gene and never be destined to get fat, because there are ten other genes that we don't know about that influence things as well.

It depends on what disease you're talking about. You can tell when somebody is obese, but you can't tell when someone might have a predisposition to an early stroke. So there I think the thinking is different. Modest risk may be worth paying attention to and being tested for. I am not saying that there's no role for genetic testing, but I think there's been a lot of hype about that and it's of limited value.

Q: Would you feel different, say, 10 years from now, when you know what all the genes are that would predispose someone to obesity and you could say, looking at all these genes, your risk of being obese is 27 percent higher than someone else?

DR. CHRISTMAN: Yes. I agree that if all that data is there then – and you had a more complete understanding, maybe it would make more sense. But it's still a complicated world because if you have a series of ten genes, then to study what a complete profile is for a given individual for those ten genes, you're talking about doing a study where 10 percent of the people have gene one, 10 percent have gene two, 10 percent of this 10 percent, 10 percent of that 10 percent also have gene three, and pretty

soon you can't do a study that big. I think that in principle if you had that information in hand, yes, but it's going to be a long time coming.

MS. SCOTT: There's a proposal to do a large study like that in the United States where hundreds of thousands of individuals are enrolled and they're studied for their genetic variance, and then in addition collect a lot of environmental information to try and tease apart what is the relative contribution of genes and environment in that.

The Genetics and Policy Center will be undertaking a public consultation project around that issue, and we will be going around to different locations around the United States to try to get an understanding about what people would be interested in participating or not in that kind of a project.

We have one more question.

Q: Khaled Bouri from the George Washington University School of Public Health. In the debate of obesity control here in the U.S., there are actually two main arguments. The first one is called responsibility of the person – it's a personal responsibility, and this argument is adopted by the food industry and junk food. And the other argument is held by the Public Health Agency, what argues that consumer is surrounded by a hostile environment – nutritional environment.

So in this new theory of genetic variation, do you have an idea how this argument could be used in either way to promote or to prevent legislation to control this kind of obesity?

DR. CHRISTMAN: I'm not entirely sure I understand the question. So could you – you were talking about the –

Q: Correct. That's – hence the argument that actually the person is responsible of his or her obesity because of their other genetic component or what they put in their mouth.

DR. CHRISTMAN: Well, again, it sounds like an equivocation, but the real answer is that there's some genetic determination and then some behavioral determination, too. Of course, if you eat fast food three times a day every day, you're going to gain weight, but the genetics provides this sort of set point high and low, and you're probably not going to leave that range for most of your life no matter how hard you try.

So clearly there's an influence of your behavior, and I think there are issues with the food industry. I've read the book by Morgan Spurlock, it's an interesting indictment of the food industry – of some of the practices to get people to super size. But I think the bottom line is just that there are genetics and environment that are contributing to this in roughly equal parts.

MS. SQUIRES: I can tell you that for example at the Washington Post we're moving to a health fund. That is, our major health fund and HMO are the two possibilities. When I first got to the Post, basically all medical insurance was covered completely by the Post. Now, and we're not atypical of most companies, but there's now this huge sharing.

Companies, if you look at Arkansas, Mike Huckabee who's been the governor down there, and had his own battle with weight and has lost more than 100 pounds and reversed his type 2 diabetes, he's now with the National Governors Association and he's really pushing how do we change the environment? So there's a combination of things, but I think the cost – the bottom line is what it's going to cost to treat people who have weight-related illnesses, and if you look at the World Health Organization's report that came out in March of 2003, weight-related illnesses are now overtaking infectious diseases as the leading cause – not just in the U.S., but worldwide – of morbidity and mortality.

Whether it ends up being genes or environment or personal responsibility, it's not going to matter, but we're going to have to get our arms around it, because we don't have the money to pay for all the illness that's going to go forward. And I suspect we'll find some kind of combination of things, like we always do. When you start to see what it costs GM to produce a car and how much of that car is related to health insurance, the balance is here. I mean, the tipping point of – former colleague, Malcolm Gladwell, wrote this book about tipping points, and I think we're experiencing one right now with the cost of obesity. So it's really not going to matter what the causes are, but we're going to have to find some solutions.

MS. SCOTT: And we should get out of those cars and walk anyway, right? Okay. Please join me in thanking our panelists for today. (Applause.) And I believe they will be staying around for a few minutes if you have some additional questions. Let me invite you to our Web site. We will be having additional GenePOPS series in the future, and we will be notifying you when that will occur. And the Web streaming for this one will be available on our Web site, I was told, in about four weeks. Thank you very much for attending.

(END)