**The Science Review - Risk & the Nature of Scientific Evidence: Climate, Crime, Addiction, Diet & Exercise**

With Tony Haymet, Amanda Pustilnik, George Koob, Ron Evans, & Beatrice Golomb

**ROGER BINGHAM**: Welcome to The Science Review. My guests today are, from this side, Tony Haymet, Director of Scripps Institution of Oceanography; Amanda Pustilnik, who conducts research and teaches in the area of law and neuroscience at Harvard Law School; and George Koob, who is Professor and Chair of the Committee on the Neurobiology of Addictive Disorders at The Scripps Research Institute. Ron Evans, who is a professor at the Salk Institute, which is where we are today, and an Investigator of the Howard Hughes Medical Institute; and Beatrice Golomb, who is a Professor of Medicine at UC San Diego, best known for her work on Gulf War Illness and her work on statins.

I was thinking today, looking at the fact that we're about a month away from the election, and the fact that the candidates had been pressed by an organization called the Science Debate 2008 to actually have a discussion about science and refused to do so, that one of the reasons that I heard was that they find science daunting. A no-win situation; that they get on a podium, in a situation where they're confronted with these difficult questions, and they just don't know the answers. They were in fact given 14 questions, which their advisors or they answered.

But these questions, it struck me, were all about specific issues that impact people's lives, not about science in general, but about science as a way of thinking, about science as a way of doing business. They were about things like the climate, the oceans, which is your business [speaking to Haymet]; things about violence in society, which you've written on, Amanda; addiction, George; diet, nutrition, metabolism, which is an area you work in [speaking to Evans]. Beatrice, you work on statins, which is another health-related issue, and also you work on conflict of interest issues in medicine.

So what I thought we could do was at least find an entrée into the larger topic by having each of you describe the latest state of play and the public's sense of reaction to the subject they're most interested in. So Tony, could we start with you, the oceans, the climate, even I suppose the price of gas.

**TONY HAYMET**: Well thank you Roger. I think both the candidates' websites are quite strong on the climate issue, and very different from the last eight years. So if we're looking for some good news, I think that's that. But it is true that the candidates have strenuously avoided having any kind of debate that would include climate change or any substantive exchange on energy policy. And so, you know, we've been reduced to "Drill baby, drill," which is, you know, not a great intellectual discussion. So I think there are some improvements in terms of written work, but no dialogue, no exchange, no back and forth about the issues that really confront us in the environment.

**BINGHAM**: Amanda, in your area?

**AMANDA PUSTILNIK**: My research focuses on criminal law and the uses of neuroscience in criminal law. And criminal law is a perennial favorite for politicians because it allows them to simultaneously say that they're very tough on crime, want to protect you and your family and your hometown, while remaining relatively vague on any specific proposals. Both of these candidates have had the opportunity to signal that they're tough on crime, although typically people who vote conservatively have more of a concern about declining social standards.

In fact, crime is not a very large problem for the American public, but unlike these scientific issues which are of much greater concern, crime can somehow seems to capture the imagination in a

way that scientific issues don't, and I wonder if that's because people have some kind of a basic sense of insecurity.

**BINGHAM**: But are we talking; the use of—one of the other panels that we've done, we were talking about the use of neuroscience also in this. So we'll come back to this in a second. But George, what's the story on addiction?

**GEORGE KOOB**: Addiction costs our society probably close to five- to six-billion dollars a year in medical costs and loss of productivity and so on, and that includes alcohol, tobacco, and illegal drugs, all together. And those costs are part of the problem witg the cost of healthcare that we have in general. So it's estimated that an enormous savings to the American society could be had by treating addiction; and that also includes a great number of drug addicts who are incarcerated and could be treated. So one of the emphases I think should be considered, by Washington, by politicians and by our society, is treating addiction. And we have—we're sitting on a mountain of wonderful science about the addiction and how the brain is involved in addiction and what goes wrong in the brain to cause addiction, and we know a lot about how we can treat it. And those things should be an emphasis of a new administration if they want to save money on healthcare costs, at a minimum, and if they want to save money on crime, as a secondary.

**BINGHAM**: Okay, well we'll all be talking to each other in a second. Ron, I mean you're in the news lately with a mouse story; just tell me the story quickly again.

**RONALD EVANS**: The story is basically that not enough people get exercise in this country. And we've been looking at the use of either genetic or pharmacologic tricks to enhance the ability of mice, in this case, to run farther and with more power. And what we described is two muscle-enhancing drugs that surprisingly give mice the ability to run long distances without exercising. And this kind of pharmacologic exercise is replacement of true exercise with a pill. While it sounds like it's kind of a trick, it actually does work, it works in a spectacular way, and then it holds the promise that this could be used for people who cannot exercise, or a large part of our society who gets insufficient exercise. So this would be a health-promoting drug that would have the potential to have a very widespread impact, both on people with problems, but also people who are actually healthy but could do better.

**BINGHAM**: So you haven't had lawsuits from 24 Hour Fitness and all the other places trying to…

**EVANS**: Well, we're not encouraging anyone to give up their gym subscription or to stop exercising. In fact, a lot of the people that have contacted me are either athletes or in good shape, but want an extra benefit from the time that they do put into exercise. It's actually difficult for most people to get anywhere near their recommended amount of exercise, which is 40 minutes minimum a day. And that's tough to book into most people's schedule. And so we have two drugs that work in different ways that tinker with the genetics of muscle cells that do some remarkable properties.

And the side benefit of that is that it improves metabolism, lowers blood sugar, lowers blood lipids, so it's a generally health-promoting type of pathway. I think there's a real future for this type of synthetic or pharmacologic exercise for people, in many different kinds of people that can't exercise effectively, or at all, or who have muscle problems that prevent exercise, and the larger society.

**BINGHAM**: So in terms of cholesterol, that takes us straight to Beatrice, because one of your studies is, in fact, on statins as cholesterol-lowering drugs. Drugs' predictive possibilities here, drugs' possibility of abuse, drugs'—

**BEATRICE GOLOMB**: [Interposing] Savings to U.S. healthcare dollars.

**BINGHAM**: --Savings to U.S. healthcare dollars; economy and drugs; conflict of interest in physicians prescribing, so.

**GOLOMB**: Well, healthcare costs have, as people know, been spiraling, and a substantial part of that increase in cost is with prescription drugs. And my concern is certainly, in the domain I look in, which includes statin drugs, which are the best-selling prescription drugs, and the top one of those is the best-selling prescription drug not only in the world but in history, actually are well over ten-billion dollars in the year, just for that one drug and drug class alone. And a substantial fraction of the people whom the current guidelines—written by people, most of whom have industry conflicts—a large fraction of the people whom the guidelines currently state should be treated, the evidence, even the evidence that's published does not suggest that benefits to the person exceed the risks. So that's one immediate place where, by implementing recommendations by non-conflicted sources, there would be potential to have quite significant healthcare savings.

And I would comment sort of more generally that there is a lag, or perhaps just a disconnect, between what evidence says and what recommendations say, and that is not all due to conflict of interest. And another domain is actually in the domain of diet. I viewed the recent recommendations for children regarding cholesterol in statin use, and among the recommendations were to implement low-fat diets. But we now actually have studies, "randomized control trials," which are considered the highest quality for drawing inferences, that actually show that lipid profiles, blood sugar, weight, inflammation markers—like the one that many people may have heard of, C-reactive protein—as well as a range of other of the indices that predict bad health outcomes, development of obesity, diabetes, et cetera, fare better with high-fat high-protein diets than they do with low-fat diets. So these recommendations have not caught up with the evidence.

**BINGHAM**: One of the underlying themes here is how do the people out there know how to interpret what they're getting. How do they know, when they're being bombarded with advertisements on the one hand and scientific studies on the other hand, where to go for advice and so on? So this is one of the things about science, isn't it, that people expect you to supply solutions, but at the same time they want a definitive solution, whereas science is in the business of doubt, it's in the doubt business. So it's very difficult to come up with definitive positions on anything.

So, climate for example; is there global warming, is there not global warming? Most of the scientific community, you would say there's an agreed consensus now that there is. In the country there isn't.

**HAYMET**: That's very true. And you can always find one scientist who's willing to say that, you know, HIV doesn't cause AIDS, or that, you know, CO2 doesn't cause the globe to warm. And with our current media profile, people like to have, cover both sides of the issue. They think it's an even-handed issue. So even if it's 99.9% to the other fraction, the press will portray it as a discussion, an open debate.

Of course, the other thing about science is we're always trying to move on to discover that last little bit. So even among the climate community, you know, people will try to assess, how much is the methane causing, how much is carbon soot causing global warming, you know. CO2 is 55% of the problem. That's a huge problem in itself, but you know, a lot of scientists have moved on to look for the other 45%.

So science and medicine have to describe how much, how to get this information out to the general public. It's not enough for us to comprehend. We have to simplify without misleading.

**KOOB**: Well one suggestion, Roger, that I think people could use, would be to go to the websites of the National Institutes of Health. I'm not even sure—I hate to sound elitist, but I'm not even sure that most Americans know that, A, there is a National Institutes of Health, B, that their tax dollars pay for the National Institutes of Health, and C, that each National Institutes of Health has its own website. So I can only speak for my Institutes that I work with, but if you go to the Alcohol Institute website, or the National Institute on Drug Abuse, or the National Institute on Mental Health you can find a wealth of information about all kinds of things—side effects of drugs, efficacy of drugs, or where to look for them, treatments for these conditions and so forth, and links to other societies that, presumably, like the National Alliance for Mentally Ill and so forth that would, you know, be helpful. So I think there are ways, as scientists, we can convey the fact that there are resources of information that are two or three clicks away on a computer for these issues. I'm assuming that climate change is covered by a number of resources that are available to the public.

**HAYMET**: Absolutely. National Academy sites and so on.

**BINGHAM**: Well, yeah, but which, but what about all the other blogs you go to that are completely, tell the opposite thing—

**HAYMET**: [Interposing] Well exactly, and it's the same thing, you have to know where to go for reliable information.

**PUSTILNIK**: I think this raises an issue that's been presented, expressly or implicitly, in many of the panels over the last few days, which is not just that there's a shortfall in public knowledge about specific scientific issues, but that rather there's a deficit in a demand for evidence-based information and general critical thinking skills, which is why it is so easy for people to get riled up on specific issues and not to understand what the legitimate position is. So whether it's the overemphasis and sensation mongering about crimes, through Nancy Grace-type shows—not to pick on one person, but that genre of television—or whether it's a lack of willingness to be able to distinguish between a Scripps or an NOAA versus a blog, it goes to a general sense of lack of critical thinking and lack of a demand for evidence, rather than just a specific lack of knowledge of scientific matter on the part of the American people.

**BINGHAM**: Lack of evidence?

**EVANS**: Yeah. I think, at least in my area, what I see is that people don't want to go for a lot of science. They like testimonials. When it comes to diets and weight and nutrition, people are very swayed by an advertisement or some type of show that says, I lost weight, or Oprah lost this. And they're ready to be convinced, because they want to be convinced by someone else. And there's so many diets and fad diets that are out there, and if there was a magic diet, as was claimed by every single diet that is advertised, and everyone is willing to sign up for these things—these books

sell millions of copies—we'd know about it. You wouldn't have the next new one coming up. But that isn't there.

And so I've touched on this inadvertently because of the kinds of programs that we've been developing that encourage muscle to burn more fat, that, as a result, the animals actually do lose weight. They eat the same amount but they lose weight. And so people who are overweight have been attracted; somehow they did get tuned into the science part, but not very deeply. They just say, "Where can I get the pill?" They'll trust you; "Don't give it to an animal, give it to me, I want it now."

And I've had a lot of people who are just willing to take something that's only been shown to work, now, in a mouse, and they are pleading for it. So there's not a lot of digging that I see that people want to do. A few people will do that, but most people want to believe in something and then will change their life around that kind of diet. And a lot of diets will work, in the short term. But most diets don't work in the long term, and that's the challenge with a real diet, getting it to work.

**GOLOMB**: I would observe that another factor is that I think the public feels, quite rightly, that they've repeatedly been bamboozled by scientific experts, in domains ranging from diet, where sort of ultra low-fat diets were the rage for a while; in the domain of drugs, where many people where advised by their physicians to take hormone replacement therapy with the promise that it would reduce rates of heart disease and dementia, where ultimately when the better quality studies were done, actually it was found to modestly but significantly increase the rates of both of those conditions.

And I have to say, in my examination of the literature, I'm not persuaded that many of the scientists and scientist physicians actually do as well as they need to do in their ability to evaluate evidence and inference. And for many of those examples, my opinion was that the evidence never supported the original recommendations to begin with. I certainly never advocated hormone replacement therapy because it was quite clear how a phenomenon called confounding could have produced the appearance of a connection between that drug and better outcomes, just because it's better educated wealthier people who go out and get medications, and we already know that they have much lower rates of heart disease and much lower rates of dementia. So unless you actually take comparable people that are on hormone replacement therapy and, say, placebo, in a randomized trial, where the groups are otherwise comparable, you can't actually draw inferences about whether the drugs will cause benefit or harm or either, just because there's an association with better outcomes.

So I actually feel, you know, as a member of the public, and even as a scientist, I no longer trust scientists in domains that I haven't examined myself, so I can't really fault the public for not trusting scientists.

**KOOB**: Beatrice, could you give us maybe an example where it has worked? In other words, where the inferences were correct. Is there a drug or treatment that has been effective, that would serve as a model for appropriate use in science?

**GOLOMB**: I think it often is the case that there are subgroups of the people for whom the drug has been recommended, and statins would represent one such example. Middle-aged men who have heart disease or are at particularly high risk, the evidence, at least from the kind of people who enroll in randomized trials, which may not actually be reflective of the general population,

but at least in those people the evidence is that actually, on average, the benefits exceed the risks. So it's not the case that there aren't success stories that emerge from science and from drug trials, but what is the case is that the representation of the evidence often departs somewhat from the reality of the evidence.

**KOOB**: So I have another question for you, and that is, do you think we should be advertising for drugs on television? In other words, should there be advertisements for medications for everything from mania to, you know, heart disease to Viagra. I mean, is this a viable way? I mean, I personally, watching through the years, have noticed that this overmarketing has led, in cases of my field—OxyContin was a good example, where overmarketing and mismarketing, in the sense that the claims that were made about that drug were incorrect—it had high abuse and was claimed not to have high abuse potential. I felt that a large motivation for that had to do with the marketing aspect, and I just wonder what you think of that aspect.

**GOLOMB**: Yeah, well actually I'm concerned that the information that's available, made both available to the public and also to physicians, is slanted. And there was an analysis published some years ago in the Annals of Internal Medicine in which experts reviewed a number of drug advertisements to physicians, and rated a large fraction of them as misrepresenting the risk-benefit balance, et cetera, and that other domains from which physicians get their information suggests that marketing in all of its forms may provide misrepresentation. I am not sure whether I would have an opinion in either direction about advertising to the public if I actually felt the information was portrayed in a fair and balanced fashion. But that isn't currently the case, and for that reason I would be opposed.

**BINGHAM**: See, there's a fundamental problem here, isn't it. If you're talking about, I mean, people assume that what happens in science is that you have a hypothesis; you test it; you get results; the results are refereed by appropriate people; if the referees pass the paper, the paper goes in the journals; it stays there until somebody refutes it, and that's what's "correct" in that field for that particular area, that claim, at that particular moment. But in some areas, like the ones we've just been talking about, or in climate change, as I said, the public does not seem to see a consensus; what they see is conflict within the expert communities that they expect are delivering to them a final answer.

**HAYMET**: Well, I mean I'd try to put it in a more positive way. Let me just first say that I think—

**BINGHAM**: Well I'm trying to put it in a, more like a, what I perceive as what's out there.

**HAYMET**: Well let me try this on you. I mean I think one of the problems we all have, in crime and addiction and climate change, is we want to invest money now to save money in the long run. And I think that's the real issue that we in the science community have with politics today. You know, the last great success was probably nuclear weapons, you know. The argument was, build these nuclear weapons and we'll prevent a nuclear war. Well so far we have prevented a nuclear war.

But as time has gone on these arguments, like the Stern report on climate change, had a big effect in many countries around the world, but the basic thesis was, it's more expensive to do nothing than to act, to cut our emissions in CO2. Certainly I think that's true; I think there's plenty of evidence to show that's true. I think my colleagues here are also arguing that in the areas of crime and addiction there are things we should invest in, in society; education, basically, other programs

that will save, you know, incarceration costs, healthcare costs later on. And we're unable to get the attention of government; we're unable to get the support of citizens.

Now to come back to your point about climate change; you know, I sort of take the long view. So 51 years ago, when Dave Keeling started measuring CO2, there were only a handful of people who thought that CO2 was a pollutant, that it was a problem. So rather than look at it as a failure, I think it's one of the great triumphs of science, the idea that human beings can change the whole planet. You look out at the vast ocean, it looks infinite, you know; it's been absorbing our sewage for all of mankind, and it's only the last 50 years, as we've gone from one billion people to three billion to 6.9 billion, heading towards nine billion, that we've learned that if there's enough of us then we can really change the planet. So I look at the last 50 years of climate change as a great success; we went from, you know, Roger Revelle and Dave Keeling and their wives thinking that this was a problem to, you know, basically 6.9 billion, minus a governor of Alaska or two who don't believe that it's an issue. I think that's a triumph of science communication. You now, and odorless colorless gas is going to fry the planet. That's an idea that, you know, took 50 years to take hold, but I regard it as a triumph.

You might argue that the failure has been, after some successes of IPCC and Kyoto, that the United States and the other large emitter, China, haven't agreed to a framework in which those emissions can be cut. And so yes, in the background of a big positive achievement for science, what to do about it and the policy framework for doing it is, so far, a failure. But I don't think it has to be like that; one could have great leadership from the president of China and the next president of the United States, and that could turn around in a hurry.

**BINGHAM**: Positives?

**GOLOMB**: No comment.

**BINGHAM**: You don't have any positives?

**GOLOMB**: Nothing to say right now.

**BINGHAM**: Okay. Ron, what about the notion of testimonials and so on, do you that's adequate for people to actually build an entire industry on?

**EVANS**: Well, the industry is driven commercially, I mean, it's strictly capitalistic. People want a simple cure; they want to be told what is good. And it's hard for the average person to know what's good, and it's hard to ask them to go to an NIH website and figure that out, because most people are not going to do that, realistically.

In fact, most people, as we know, don't listen to government statements that you should exercise more and eat less. I mean we've known that that's one way to reduce the inherent obesity that's in our society, which we pay a lot for in our healthcare dollar. But we know our society's about five billion pounds overweight, as Americans, and you just can't tell people, lose five billion pounds as a society. And so we're paying for that as our average, you know, adipose debt, our shared debt, in our healthcare budget. That is one of the biggest parts of our budget, and it's going to get worse because that problem is spreading to kids. And the earlier you enter into this type of metabolic disease, the more complicated the problems become as you approach adulthood and into adulthood or as you get older.

And so I don't think that testimonials are going to be the way to go. I do think that there is a real problem that we have, that is the way in which the government deals with food, the so-called "food pyramid". The way we disseminate information about what a portion is—because a portion size, which sets all the little amounts on packaging, how many calories are in a portion and what it's, is based on assuming that 2,000 calories a day is what an adult should be getting, and the adult male is basically what a portion size is set at. And that's not, it's not a real number; it's a negotiated number between physicians and the government. And to change it is such a huge financial cost to companies to wind back what a portion is. If you changed it by even 100 calories, they'd have to recalculate every packaging in the amount of pretzels they put in; they'd have to take one out. They're not going to, there's resistance to changing anything. And so we're in a society that what the norms are negotiated, what health is is negotiated, and I think it's very tough in our world, as we go along, where calories are cheap, to avoid the reality that we're in a society that is going to be chronically in poor health.

And that's one of areas that I'm concerned about, and why I think there actually is—it's sad to say, but I think we need some form of health-promoting drugs. That is, the FDA has no mechanism to develop a drug or to allow a drug to be developed that doesn't cure a disease. But there could be a whole class of drugs that could be health-promoting, that would actually help people before they're in disease and could give them a leg-up on many of these problems. And it's a whole area that's really neglected, but I would like to push the medical societies and the government to think more about health as opposed to just the disease side. You know, it's a big problem.

**GOLOMB**: I do have a positive that actually relates a little bit to what you said and shows that companies are capable of changing their serving size, and that is of course the trans fat legislation. In which, I'm actually very troubled by the fact that the food lobby was powerful enough to get permission to say zero grams trans fat if it's less than 0.5 grams per serving. But one positive consequence of that is that a lot of companies reduced the size of the serving in order to have a serving accommodate less than 0.5 grams trans fat, simply because they could say zero grams.

And speaking of positive changes, that is a positive change. Trans fats are oxidative stressors; they're pro-inflammatory; they block the body's production of the long-chain "omega-3" fatty acids that you've all heard about the health benefits of; they promote this insulin resistance metabolic syndrome phenomenon. And I saw—I must say it was a secondary report of, so I've not read the original study—but of a study in rats that claimed that if you calorie-deprived rats but gave them trans fats, they packed on weight, they packed on fat. So I do consider it a positive direction that there is more promotion toward lower trans fat foods. I do think it's dissembling to call .4999 grams per "serving", which you can identify or define as you like, as no trans fats, but I do think that's a positive development.

And I guess another positive development that I might comment on are Internet-based changes in medical publishing. And medical publishing has a history of having a pharmaceutical company influence, because many of the journals make their money from drug company advertising and also sales of reprints of industry-favorable articles to industry. But now with the expansion of more of these Internet-based journals, not all of which take advertising, and even things like Nature Precedings, that allows you to put out a work without peer review and at least allow it out there, there's at least opportunity for dissenting opinions to have air time they might not otherwise have had. And so I do think that's a positive development.

**BINGHAM**: George, you had a point?

**KOOB**: Well, I was just going to pat my field on the back for a positive development, which was tobacco. I mean, if you look back; since I've been a scientist, I can remember when scientists, when I was a graduate student, when you went into a colloquium everyone was smoking. And then I remember when they split the room in half so only one side was smoking and the other side was not smoking.

**GOLOMB**: So the smoking and the passive smoking I also remember.

**KOOB**: Yeah. And anyway, I could go on and on, but the fact of the matter is that in California there's no place to smoke anymore except in your own car, and these restrictions are slowly but surely spreading across the United States, spreading to Europe. Even the French now have restrictions about smoking in restaurants. I mean, I don't know whether you can imagine how cataclysmic that is in France, but it is quite cataclysmic.

**BINGHAM**: English pubs are no-smoking now as well.

**KOOB**: And I think this is all scientific-based, evidence-based information that ultimately filtered in. I'm not exactly sure how; I think there are lots of ways that this information eventually spread, but it clearly was strong evidence from issues such as flight attendants who were exposed, and moving from that direction, restaurants and passive exposure and all the data that was generated to stop, basically, an addiction in its tracks, more or less. And it's certainly, the increase has completely blunted in the United States; it's declining every year. And yes, people still smoke in other countries, and it's still rising in some countries, but I think that it will ultimately spread to other societies.

And at the same time, there have been fairly significant developments in the treatment of tobacco addiction that do aid people to stop smoking. And again, I don't want to sound pro-pharmaceutical industry, but Pfizer sales of varenicline, the new, it's a drug called Chantix, which is used for treating, helping people get off of nicotine, are estimated to be, I believe, 800 million dollars for the past year worldwide. And that is close to a blockbuster type drug for treatment of addiction. And that has two beneficial effects. One is, it shows that the drug can be used, possibly successfully, to help alleviate addiction, and it opens the door that if similar attempts were made for other drugs of abuse, like alcoholism and some of the other drug problems that plague us, that we could, again, have an opportunity for some beneficial effects to society and healthcare costs.

**PUSTILNIK**: Two areas where I look forward to science leading to benefits in the criminal law that aren't there yet, but that are on the horizon, arising out of neuroscience and medical research, are more rational approaches to questions of addiction, and also to questions of mental illness. Ron was talking before about the power of testimonials, and that goes to how people tend to be convinced more by the beliefs and experiences of others than by, often, hard evidence. And there are these cultural stories and myths about the mentally ill person or the drug addicted person as being bad people, weak people who just can't get it together and try hard enough. But I think there's the possibility to change social beliefs about what these diseases really are by promoting the science and showing the biological bases of them. And I think that'll have a strong positive impact on the culture, and then on the criminal law.

**BINGHAM**: So you're arguing, all of the argument you've all been making, in a sense, is that if I took another issue like, another source of confusion— is it dangerous if I stick a cell phone next to my head. Again, conflicts; new papers out; refutations; people say, oh sorry, they've got the stuff

wrong, I'm withdrawing that paper; so on and so forth. Your answer would be just, early days, don't have enough of a curve on this yet; we'll get there, we'll solve it.

**KOOB**: But don't go to bed at night holding your cell phone cradled on your ear.

**HAYMET**: Yeah. I think that's a part of, you know it's always been, well what do people say about the Romans believe in, or no, the Greeks believe in moderation, the Romans believe in moderation including moderation. You know, when I listen to people talk about diet and so on the message is, eat a little bit of everything, you know. If you hold a cell phone next to your ear for 24 hours a day, who knows, it might turn out to be not beneficial. So I think there's a kind of precautionary principle which we often appeal to in science and which we're having trouble establishing in the response to climate change.

In a way that we didn't have trouble with the ozone hole that, you know, let's face it, is another pretty good triumph of science and diplomacy. In the middle of the Cold War the Montreal Protocol was signed and then refined in subsequent meetings so that we actually stopped making CFCs. And the people that realized that that was a business opportunity to come up with replacement refrigerants, you know, it made money out of solving an inadvertent way of destroying the planet. You might argue the same is true with DDT. You know, the Rachel Carson *Silent Spring*; if we'd let DDT infiltrate much more of our food we may have faced a serious catastrophe.

So we've inadvertently, and you know, there's a common theme that comes up here—it's chemicals, it's things that we've invented to solve one problem turn out to create an even bigger problem. And we've managed to shy away from them several times in the last 50 years. So I think there's a resilience in our humanity that can, under pressure, deal with them. I think some of the issues we're dealing with now have to do with the political process. We used to be able to make the argument that we invest money here because it's going to save the planet, or help out children, or you know, lead to a more equitable living for the whole planet. I would say we've gone backwards in the last ten years; the idea of the precautionary principle and the idea of investing, basically, in education in order to save money in advance, we haven't been able to carry that case recently.

**BINGHAM**: Why is that?

**HAYMET**: I don't know. I think it—you know, I'm a guest in this wonderful country of yours. I see a difference between my homeland in Australia, where the big issue in the last election, a big issue, was one political party promised to sign Kyoto, the leader of the other political party said I will not sign Kyoto and didn't for 11 years. So, you know, that's a pretty intellectual argument to have an election on. I don't think, you know, what happened in this country, Clinton didn't even bring it to the Senate because he knew it would be 99:1. So I think you have to reflect country by country on how these things work out. Norway made a future fund of all of its revenues from its oil, you know, knowing well in advance that the oil was a finite resource, it would be gone. So instead of having a big party, like some other countries, they've invested it for all future generations.

So some societies are able to get their mind around investment for the future; other societies go back and forth. And I would say, I hope temporarily, the U.S. might be in a period where we haven't been able to carry the day. Maybe that's our fault for not being persuasive enough.

**PUSTILNIK**: Ah—sorry, go ahead Beatrice.

**GOLOMB**: I was going to comment on the issue, the precautionary principle. It's been my impression that there are a number of domains in which the U.S. does a less good job in that domain than perhaps Europe does. And I heard recently on a news show that in Germany the recommendation is for pregnant women and children under 16 not to use cell phones at all; whether or not they cause brain cancer, there are studies showing that they cause oxidative stress to muscle tissue, to brain tissue, and there are certainly reasons to be concerned that widespread use could be problematic. And in the chemical domain, my understanding is that, in the United States, it's sort of "innocent until proven guilty", whereas in Europe at least some safety tests are required before a new chemical can be introduced.

I was particularly struck by the disparity between Americans and at least some non-American opinions when I was in NIH review panel some years ago. The NIH wished to do a study in which they would test whether highly aggressive treatment in diabetics was better than current standard treatment, where highly aggressive treatment went for blood pressure treatment, blood sugar treatment, and also blood cholesterol treatment. And what struck me was that perhaps among 30 people around the room, there were three that considered it what's called a two-sided hypothesis, meaning that more aggressive treatment might be better, or it might be worse. And those three people were me, and the two people who were not from the U.S.—one from Sweden and one from Canada. And of the perhaps 40 proposals that came to the NIH, the tenor of the text in all but one of them seemed to be one-sided, that obviously more aggressive treatment would be better. And the one that was not from the U.S. was the one that treated it as a two-sided hypothesis; it came from Canada. So I was quite struck by what seemed to be a difference in attitude that does not necessarily come from the policy level down, but certainly is even at the scientist or physician scientist level, towards less of a precautionary principle in the U.S. than perhaps seems to be the case elsewhere.

**PUSTILNIK**: Roger, you were asking the question, if we're all making the point, that the reason certain advances don't come about is because we're conveying to the public that it's early days and that there's a lack of consensus. At least on the legal side, but I think in many of these other issues, that's not necessarily the problem. It's certainly been known for a long time that mental illnesses are medical conditions, and also that addiction causes discernable brain changes, and so it's not really that there's a lack of consensus about the state of medical knowledge, but that there's a disconnect between the way that state of knowledge then filters through to legal policies and social policies.

I can't really provide a comprehensive explanation for why we take such an expensive approach to the treatment of drug addiction and mental illness, not just in financial terms, but in terms of the human toll that it takes, but one suggestion that has been made is that it is easy to divide these kinds of issues along the line of a culture war and along the lines of the principle of individual responsibility. I mean, in theory everybody is in favor of a degree of individual responsibility, but it's become highly politicized and some people, if they're seriously medically ill, don't have the capacity to exercise "individual responsibility" over what is basically a physiological condition. So even where there is not a problem of us being cautious—saying, it's early days, we can't apply this yet, as I might in some of the neuroscience in the courtroom applications—the issues don't translate in a less biased way because they get caught up in the broader cultural narratives about whose values we want to believe in.

**KOOB**: On a positive side though, didn't health parities just pass the Senate?

**PUSTILNIK**: Yes. Fabulous. Pete Domenici's bill. After ten years of work, Pete Domenici, and also Senator Kennedy, managed to pass as part of the bailout package a mental healthcare parity bill that finally requires insurance companies that do provide coverage for mental health to provide coverage in equal rate for any physical illness. However, the bill does not require a policy to offer mental health coverage at all, but if it does offer it, it has to be at parity. That's a huge advance.

**KOOB**: So that actually is a little wedge in the door that may become a big wedge in the door, because that means that tobacco addiction can be treated equally, or depression.

**BINGHAM**: What's happening in addiction; what's up, what's down? Is alcohol use going up? Cigarette use is going down, you say; what's happening in other domains?

**KOOB**: Well it's pretty stable, as a matter of fact. I mean, tobacco use is going down, although it went up during the Camel ads for the young people, so there was a surge in use in high school students during that—what was his name, that camel?

**PUSTILNIK**: Joe Camel.

**KOOB**: Yes. The Joe Camel ads actually initiated a spike in tobacco use in young people, which I think is now resolving. There's been an increase in marijuana use with the decriminalization in California, because that has been interpreted as meaning that marijuana is safe. Alcoholism doesn't budge; it's pretty much stable across the board. And I believe methamphetamine use has spread into epidemic or endemic pockets throughout the United States, including the Midwest. It started in Hawaii, moved through California, and now has moved, I think, across the Mississippi. So there's still a major problem with stimulant abuse that doesn't go in big waves, but small pockets that seem to evolve and erupt in different areas. So that's pretty much, I think, what I know. I don't think there's been any decline in overall marijuana, alcohol, psychostimulant and opiate addiction in the last ten to 20 years.

**BINGHAM**: What do you do with the law then, with addiction? I mean, what would the consensus of scientists perhaps be, in terms of how do you deal with addiction? I mean, do you actually, is there any of them who would want to decriminalize drug use? Are there prisons just full of people who might be better off on some sort of rehabilitation program?

**KOOB**: I think, no, I think you heard a few talks at this meeting indicate that, I mean, treatment is the one word answer. Treatment of criminal populations, treatment of all people; have it available to anyone who needs it. And the important aspect that the public needs to understand, that treatment is not detoxification. That's another critical piece that has come out of the field in the last 20 years, and that's why treatment was dumped in the first place. You can't just put someone in a Betty Ford clinic, dry them out, and turn them loose back in their social milieu and expect that they're going to be cured. They're not cured. Treatment is like a mental illness treatment; it goes on for months and years. And so detoxification can be done in a few weeks, and you're off the drug—and of course it's a requirement, I mean you can't be cured of addiction if you don't detox. You can't be, you know, if you're still taking massive amounts of alcohol or cocaine every day, you're still an addict. But the fact is, when you're detoxed, that's not the cure; the cure is actual treatment. All kinds of steps have to be taken.

**BINGHAM**: As documented by this well-known science magazine, *People* magazine, which shows people going into rehab and two months later they're back on the cover again.

**KOOB**: Rehab and then rehab and then rehab and rehab. I think that's, you know, if the public hasn't figured that out. But I think the simple; again, I mean it's the issue of taking sound bites. If you just say, well that clearly shows that addiction treatment doesn't work—but that's not addiction treatment, it's addiction detoxification. A treatment is a much more complex issue that involves counseling, possibly pharmacotherapeutics to help bolster brain changes that have occurred as a result of the addiction, and so forth.

But I would say that where the public should be is with treatment; where science should be is a lot of other issues, but you know, we have plenty of basic research that needs to be translated. Another big bottleneck is that the basic research that we know about how the brain changes with addiction needs to be translated to ways of preventing, treating, and diagnosing addiction, and that's still a big challenge.

**BINGHAM**: I mean you're in the same business; you're also in the *People* magazine business, because there's people balloon-sized and they go off, and they've got this marvelous diet, and there they are skinny. And then there's the next cover of why they're too skinny, and then…

**EVANS**: That's right. And it's a little bit like what George was saying, is that obesity, there are many people who will go onto some type of diet, lose weight dramatically, and it's like detoxing, except food you have to eat. Drugs you don't have to have, but food you have to eat. But it gets tremendously abused, and in our society, whatever it is—the psychological pressures, the social pressures, the nature of the dietary changes and cultural changes—lead to a real challenge in losing weight and keeping it off. So it's a little bit like detoxing, but you're not really cured. You lose weight on a diet, but you really haven't gotten over the problem. And we know that 90-plus percent of people who lose weight, a year later, will at least be at the weight they started, typically even more, because of the rebound effect, takes you over what you used to be. And most people who go on a diet know they can lose weight; they also know that a year later, they're sad to find that they're back to where they were.

It is a challenge. About 2% or so of people are actually very successful at it and manage a long-term process, which usually involves a lifestyle change. And that's the hardest thing for people to impart upon themselves, is a true lifestyle change. That's a difficult thing to do, to really change any habits, because we're such habitual types of creatures. We get used to the foods we like, we associate them with some kind of pleasure or comfort, and it's hard to change that. It's hard to change a hamburger into a veggie burger. It just is the hardest thing in the world, and it doesn't happen very often.

**BINGHAM**: And you don't get a ticket for it.

**EVANS**: You don't get a ticket, and you have to eat. So food's required, so it's hard to legislate. And a McDonalds or Burger King, they can serve, you know, a double super cheeseburger with bacon that's 1200 calories for, you know, three and a half dollars, and it's a huge caloric hit, and everyone knows it's a good value to buy it. But it's the worse thing you could do with that three and a half dollars. But you can't legislate against someone making the next biggest burger. It's food, you know, and people love it. And it's very tough because we know, with tasters and tremendous sophistication, how to make foods that people can't resist. Doesn't mean that they're

healthy, but the smells and the texture and the sensations and the way they blend it, and we're kind of deceived all the time into making bad choices.

**KOOB**: And Roger, just, I want to add one thing to this, which is that dieting actually, it can promote binge eating. And my colleague Eric Zorrilla just did an experiment at Scripps where if he allows rats to binge on palatable food, in a diet-binge-diet-binge regime, they actually gain weight more than animals given the same amount of calories. So the way the body processes this, this feast-famine phenomenon—this binge, which happens also in alcoholism and other disorders—but the way the body, as Ron was saying, the way that the body processes these changes can lead to the pathology. And attribute to the pathology.

**EVANS**: That's right.

**GOLOMB**: And it's true both for too low of calorie diets and also too low of fat diets. Both promote this phenomenon of insulin resistance, which actually is associated with more weight gain, higher blood pressure, more waist circumference, worse blood sugar, et cetera. And it is unfortunate that some of the recommendations that we as a medical community have put out for some years, the ultra low-fat diets, may actually have contributed to the epidemic of obesity in our society.

**BINGHAM**: Amanda? Do you have any thoughts on this?

**PUSTILNIK**: I've never followed a low-fat diet because I never met the piece of butter or the brownie that I didn't like, that's my…

**EVANS**: That's true for most people, I have to say.

**BINGHAM**: So what was the response, I mean how much mail did you get from people saying, I want the pill, your pill?

**EVANS**: I got probably about five- or six-hundred emails on that. It was a gigantic—and I'm still getting emails, every single day I get emails on this.

**BINGHAM**: What's your cautionary disclaimer here?

**EVANS**: Well my cautionary disclaimer is that, while the drugs are actually in people, they haven't been developed for the purpose for which we describe, which is enhanced muscle performance and reduction of blood sugars and lipids. They're developed for other purposes, and so it's not ready yet for prime time. On the other hand, I think that this tells us that it's possible to develop a pill that would be equivalent to pharmacologic exercise. It may not reproduce everything that exercise does, and I would never recommend that anyone stop exercising; that's probably the healthiest thing that you can do. On the other hand, if you can't, then you can reproduce a fair amount of the benefits of exercise with a pill. I think that can be developed, and I think there's a lot of potential benefits that can be achieved if it's used in the right way.

**BINGHAM**: Okay. Beatrice, what's your take on—I mean you see patients as well,

**GOLOMB**: Right. Yeah, I give my patients, I never recommend—I never say, "lose weight," because, how? I mean that's a very easy thing to say. And I also never say, "restrict calories". I actually recommend insulin sensitivity-promoting diets—diets rich in fruits, vegetables, nuts, legumes; protein at every meal. And the reason for that is that when you have protein together

with your carbohydrates you release glucagon, and glucagon prevents the insulin that's released through the carbohydrates from leading the blood sugar to drop precipitously, which makes people hungrier and also promotes this insulin resistance phenomenon. And this may be part of why these high-protein diets, which are also high-fat diets, seem to protect against these phenomena.

And fat also blunts the rise in blood sugar that you get when you eat a carbohydrate. So ironically, if you eat your bread, you probably want to have butter with it. You probably do not actually want to be having nonfat milk, because then you're having the sugar, the lactose, without the blunting of the rise in blood sugar from the fat. If you have ice cream you may not actually want to be having nonfat ice cream, and having fat, again, blunts the rise in blood sugar, which blunts the rise in insulin, which blunts the drop in blood sugar, which blunts the development of this insulin resistance-promoting process.

And the studies that have actually shown heart health benefits to individuals with diet have not been low-fat, cholesterol-lowering diets. They have included, in the Lyon Heart study, a Mediterranean diet, which involved a lot of fruits, nuts, vegetables, legumes, et cetera—actually just the fish advice arm of something called the Diet and Reinfarction Trial, although that was before there was quite so much mercury in the oceans, so those findings might be a little bit different now. And then looking at—and both of those showed survival benefit, actually. One of those studies had a low-fat, cholesterol-lowering arm, which did nothing to help. And by the way, also had a high-fiber arm, which actually was associated with a trend toward worsening of mortality. And so people are confused by this, but the reason fiber looks good is because it's usually associated in a diet with things like fruits and vegetables, that actually contribute a lot of things that are helpful to the body.

So besides the Lyon Heart study with the Mediterranean diet and this fish-advice arm of the Diet and Reinfarction Trial, there are also studies like what's called the A to Z trial, that compared four different diets—an Atkins-style diet at one end, with the high-protein high-fat; an Ornish-style diet at the other end, with very low-fat; and then a couple of other diets, called LEARN diet and the Zone diet, sort of in the middle. And the one that fared the best on all parameters of real relevance at the end of that one year, including weight loss despite no fewer calories consumed and no more exercise performed, was the Atkins-style high-fat high-protein diet. Again, better markers of inflammation; a better lipid profile—what actually matters is the total of the HDL ratio, and triglycerides went way down and HDL went way up; LDL was a little bit worse, but the ratio was substantially better; waist circumference went down; weight went down; blood sugar, indexed by this long-term marker of blood sugar called hemoglobin A1c, went down. So sort of all of the markers that we care about that are linked to obesity, metabolic syndrome, et cetera, actually were favorably affected by a diet that is essentially the antithesis of what we had been recommending for many years.

**PUSTILNIK**: And I do have a slightly more serious comment than my love of butter. There is a way that this evidence that you're talking about relates to the regulatory framework and how we can use that to help change people's tastes. It's well known that we live in an environment of superabundance, with corporations that promote as much value per calorie, bang for your buck, as you can get. But the tastes that people have for the foods that they want to eat—and Ron and Beatrice would know more about this than me—are largely shaped by the foods that people have been exposed to.

And yet, in many low-income areas there is no access to fresh fruits and vegetables, because they have fast-food outlets in place of supermarkets. And two municipalities have been making real strides on this. Mayor Bloomberg in New York has authorized, I think, a thousand new licenses for fruit and veg carts to be placed on the street in low-income neighborhoods that lack supermarkets, so that people have not only the opportunity to eat actual fruits and vegetables, but to know what they are and to develop a taste for them. And in Cambridge, Massachusetts, where I live now, they've modified the food stamp program so that food stamps can be redeemable for fresh fruits and vegetables, not only at supermarkets but at farmers markets. And the food stamp program was, for a long time, subject to aspects of industry capture, so that very high-sugar low-nutrition foods were sometimes those for which people received the greatest food stamp allocations, which had all kinds of negative knock on health effects, as well as being taste-shaping for the kinds of foods people would then go out and seek. And so I think there are ways to use some clever limited amounts of regulation to move the needle towards more healthful foods.

**KOOB**: Bloomberg, by the way, had an op-ed in *Newsweek* about tobacco addiction, and a very strong one; I mean, I was very surprised. He was apparently, as mayor, was the one to push through the legislation in New York City for the restriction in smoking.

**PUSTILNIK**: Yeah.

**KOOB**: He's also seeking a third term.

**BINGHAM**: Well, all the talk of food makes me hungry, so I think this is perhaps a good time to go and get some food. Perhaps a stroll by the ocean, hoping it's not too polluted. I don't drink, but I'm sure George will have a glass of addictive stuff. And Beatrice can then count our calories and Ron can give us a pill to save us from having to exercise. It was a wonderful meeting; thank you for all being here, and that was The Science Review.