

## **Conversation between Holden Karnofsky (GiveWell), Cari Tuna (Good Ventures) and Peter Attia (Nutrition Science Institute) on July 31, 2012**

Note: this is not a verbatim transcript. It is a set of summary notes compiled by GiveWell in order to give an overview of the major points made in the conversation.

*Peter Attia:*

The Nutrition Science Initiative (NuSI) was founded by Gary Taubes and me. The organization is supported by the Laura and John Arnold Foundation (LJAF). Our organization exists to fund research on the most important questions pertaining to human health, beginning with “What regulates fat accumulation?” Our ultimate goal is to reduce the incidence of obesity and diabetes.

For 40-50 years, health organizations (e.g., American Heart Association, American Diabetic Association, American Medical Association, American Cancer Society, National Institutes of Health) have been recommending that people eat less and exercise more to avoid developing obesity and diabetes. These years have been accompanied by rising rates of obesity (2.5x) and diabetes (4.5x), suggesting that the recommendation is ineffective. The soundness of the recommendation has not been validated using the scientific method.

Typically, current funding for research on this subject is from organizations that seem to be looking to validate their beliefs rather than rigorously investigating what the facts are. There has been a great deal of bias toward confirming what people currently believe. NuSI is looking for donors who are not biased toward validating current beliefs. NuSI hypothesizes that if the best and brightest researchers in the field were freed of the typical funding mechanisms, they would be able to rigorously determine what regulates fat accumulation, and ultimately address this most important central question that seems to be completely vexing the current mainstream. Furthermore, this could be done for a fraction of the cost needed to develop a single FDA approved drug.

The current conventional wisdom is that the main factor driving fat accumulation is the number of calories eaten and burned. An alternative hypothesis is that *what* we eat drives the number of calories consumed and calories burned and therefore drives fat accumulation. This is a subtle distinction with profound implications. This had been conventional wisdom among obesity researchers and physicians until World War II.

NuSI reached out to about 15 nutrition and metabolic scientists who were doing rigorous experimental science in this area, convened a meeting at the NIH, and developed a road map to the first experiment that NuSI will fund. Prior to this meeting, John and Laura Arnold independently asked 25 scientists around the country to vet this plan and the scientists agreed with our approach, even if they did not agree with our hypothesis.

The first major study NuSI expects to fund will cost anywhere from \$12 to \$28 million.

NuSI is looking to build a broad coalition of donors, ranging from donors like LJAF and other who can make sizeable contributions, to those capable of giving less.

NuSI hopes to eventually spend approximately \$500 million on a five-year study of 100,000 people. (The usual cost for such a study would be \$2 billion but it can likely be reduced by a factor of four using technologies such as mobile phones for data gathering.) This study, like other major longitudinal studies, will evaluate the long-term safety and effectiveness of the macronutrient (e.g., diet) findings from the earlier and smaller studies.

*Holden Karnofsky:*

It seems to me as though the cost could be much more than for clinical trials of drugs on account of all of the potential dead ends and wrong turns. In the drug industry, many attempts don't show sufficient promise to make it to the clinical trial stage. For the drugs that do show enough promise, there's already a strong reason to expect them to work. Typically their potential efficacy has a biological basis and they've already been shown to work in animals. The idea that a few clinical trials and a large-scale study would be enough to learn about what causes obesity and diabetes assumes that the clinical trials would turn up something that works.

*Peter Attia:*

I have been fortunate to learn a bit about drug development from having worked at McKinsey & Company on these problems, and also from my fellowship in oncology, including my time at NIH. My intuition is that learning about how to reduce obesity and diabetes is easier than drug development.

Most drugs that show efficacy make it through FDA approval, but by stage of development, there is varying risk. I'll give you an example. About 60% of drugs make it from phase I to phase II (that is, they pass the "it won't harm people" test). About 50% of drugs make it from phase III to market (that is, they pass the "it works better than something else" test). Barely 30% of drugs make it from phase II to phase III - the stage where a drug's efficacy is tested, also referred to as the "proof of concept" phase. In other words, by far the riskiest stage of development for a drug is demonstrating it actually does what it's supposed to do.

Think about our problem. We already *know* that there's a way to reduce obesity and diabetes because 40 years ago people's rates of obesity and diabetes were much lower than they are now. The change must be due to environmental factors rather than solely genetic factors, because 40 years is not a long enough time for there to be genetic drift. I'm not saying genes don't play a role in obesity. They certainly do. But the population shift towards obesity and diabetes is not a genetic shift. So the right analogy is that we're already past the phase II of clinical testing, and into phase III. The success rates are very high when you've passed that test of "proof of concept."

*Holden Karnofsky:*

We don't know what the environmental factors are: they could be dietary factors, type of exercise, psychological factors or some combination of them. Even if we did know that it was because of dietary factors, we wouldn't know what those dietary factors are. I find it plausible that there's never been a large-scale study of the type that you're describing. But people experiment with many diets and it seems like there's been a lot of trial and error to find a diet that works for everyone. I believe that such a diet has not been found.

*Peter Attia:*

Certainly there could be many factors – likely linked – at play here. But never forget Occam's Razor: start with the most obvious cause first. What has changed most dramatically in the past 40 year? What we are told to eat, and as a result of that, the food “infrastructure” that now exists around us and creates a very different “default” eating pattern to the one that existed before.

Concerning the question of why so many people are still overweight if people have tried so many diets: you can never dismiss the issue of implementation. Even though we know what causes HIV transmission, in Botswana approximately 25% of people are HIV positive (versus less than 1% in the U.S.). The reasons for this are many, but two of the largest are as follows: 1) In Botswana the average person does not have the correct information about how the HIV virus is transmitted. 2) The infrastructure to prevent transmission is stacked against them, unlike in the U.S. where it is much easier (though still not “easy”) to take the necessary steps to protect yourself.

Just like in Botswana with HIV, we don't have the correct information about what *causes* obesity, or even the infrastructure to propagate correct information about what diet works if we had the right answers.

We need to get the information correct before we can work on implementation. NuSI will be focused on getting information correct. We want to figure out the fundamental laws of physiology that governs fat metabolism to get a better grounding for developing a set of dietary guidelines that work. There's also a substantial issue of communicating our results.

*Holden Karnofsky:*

I find it very believable that there's something wrong with conventional wisdom about diet, but I'm not aware of dietary recommendations are that well supported. So I see the endeavor of finding good dietary recommendations as exploratory and open ended, with no idea of how many dead ends there are going to be.

*Peter Attia:*

Fortunately, there aren't very many variables to study. We know that in 1960 people ate ratios of carbohydrates, protein and fat that didn't predispose them to the level of obesity

that we have today. The relevant quantity is likely the fat to carbohydrate to protein ratio in diet composition. Lots of studies show that protein shouldn't be reduced. So the first place to start is the fat to carbohydrate ratio in diet composition, and also the "quality" of the fat or carbohydrate consumed.

*Holden:*

My sense is that there are many variables: there are many kinds of food, many kinds of behaviors, many biological factors specific to individuals and many individual frames of mind. So it seems to me that the number of possible treatments is comparable to the number of possible chemical compounds. What evidence do we have that we're not just groping around in the dark, that there is a particular path that is particularly promising?

*Peter Attia:*

One of the things we did prior to our initial meeting with the large consortium of scientists was to do an exhaustive review of the literature. We looked at every single study done between 1940 and today, over 80 studies, that have attempted to ask this question directly or indirectly. This "prior art" as we call it, forms the basis of our starting point. I'll be happy to share this analysis with you, which also appears on our website.

*Holden Karnofsky:*

I have a smaller question: Why not start with animal studies?

*Peter Attia:*

Animals are too different from humans. For example, mice are herbivores and so have a different metabolic system from our own, especially when it comes to dealing with protein and fat intake. A lot of nutrition science and dogma is based on findings from studies with mice, which is obviously problematic. I like to use this silly example to make the point. If you did a study with 2 groups of mice, one put in room with cats, the other put a room with cat food, it's obvious which group will be "healthier." But just because the mice in the room with cats didn't survive, should we conclude that people should eat Kibbles & Bits and avoid cats at all costs?