

WHAT YOU NEED TO KNOW ABOUT CANCER AND METABOLIC CONTROL ANALYSIS

An Interview with Dr. Thomas N. Seyfried

by Robb Wolf

About three months ago I was surfing around on PubMed and found a few interesting papers on Intermittent Fasting (IF) and Caloric Restriction with Adequate Nutrition (CRAN) from researcher Dr. Thomas N. Seyfried Ph.D., Professor of Biology at Boston College. I sent an email to Dr. Seyfried asking some questions pertaining to IF and I received an amazing wealth of information in response. Dr. Seyfried's lab is conducting research in the areas of IF, CRAN, and ketogenic diets for the management of epilepsy, cancer, oxidative stress and neurode-

generative diseases. Everyone knows that I am a nerd Par Excellence, but you have to admit that is some super interesting material. Not only has Dr. Seyfried been kind enough to answer my pesky emails, but he has also agreed to an interview for the Performance Menu. We have an amazing amount to learn from this man and the work his lab is doing is some of the most interesting in all of biology. These folks are using Evolutionary Biology as a means of both investigation and interpretation. Kick-ass!

Dr Seyfried, Please tell our readers a little about yourself. How long have you been interested in Evolutionary Biology and your current areas of investigation? What drew you to these topics?

I have long been interested in evolutionary biology, but it has not always been obvious how evolution can provide answers to complex biological problems. We became more interested in evolutionary biology after observing how effective caloric restriction was in reducing epilepsy and in managing brain cancer in our mouse models.

One of the main tools of your research is Metabolic Control Analysis. Can you explain to our readers what this is and provide an example or two of some questions you are investigating with this technique?

Metabolic control analysis is an area of biochemistry and bioenergetics that attempts to define flux through pathways. For our research, these pathways involve glycolysis and respiration, the major energy generating systems of cells. Organisms have evolved to survive extreme changes in their environment according to the Ecological Instability theory of Rick Potts. The ability to survive under these extremes is encoded within the genome. Consequently, stressful environments can alter metabolic flux through pathways that facilitates survival. In the case of epilepsy, caloric restriction produces a new metabolic state that reduces brain excitation while enhancing inhibition. Epilepsy is thought to involve an imbalance of brain excitatory and inhibitory systems. CR

restores this balance following reductions in circulating glucose and elevations in circulating ketone bodies. In the case of brain tumors and most tumors for that matter, caloric restriction places tumor cells under considerable metabolic stress. Tumor cells are almost completely dependent on glucose for energy, due to defects in their mitochondria. Tumor cells cannot metabolize ketone bodies for energy. Normal cells, on the other hand, can metabolize either glucose or ketone bodies. The utilization of ketone bodies for energy is a conserved adaptation to spare protein during periods of caloric deprivation. All normal cells, with the exception of liver cells that use fatty acids, can metabolize ketone bodies for energy. Caloric restriction therefore kills glycolysis-dependent tumor cells while enhancing the health and vitality of normal cells through ketone body metabolism. Metabolic control analysis provides a framework for identifying the mechanisms by which CR manages these diseases.

One of your most striking papers is “Targeting energy metabolism in brain cancer: Review and hypothesis”. In this paper you describe a potential approach to the management of malignant brain tumors. Can you help our readers understand how a ketogenic diet, particularly in conjunction with caloric restriction, can play a powerful role in treating brain tumors? Do you see Intermittent Fasting as being a viable alternative to caloric restriction in this scenario? Should this protocol be effective against other non-brain cancers such as breast and prostate cancers?

Caloric restriction reduces glucose while elevating ketone bodies. The low carbohydrate, high fat ketogenic diet reduces glucose and elevates ketone bodies even more than that of calorically restricting a high carbohydrate diet. As mentioned above, tumor cells are unable to metabolize ketone bodies for energy when glucose is reduced. Thus, a restricted ketogenic diet is effective in reducing tumor growth. Intermittent fasting should also be an effective therapy for cancer as long as the fast can be maintained for at least four days. A 7-day to 10-day water only fast would be best. This would, however, require practice and considerable self-discipline. Several fasts over the course of a year may be necessary to eventually manage the tumors. This therapeutic strategy is presently under investigation in our mouse brain tumor models.

Dr. Seyfried, in one of our previous emails you expressed doubt that Intermittent Fasting can produce higher b-hydroxybutyrate and IGF-1 levels in humans than caloric restriction. The paper by Anson and Matson, “Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake,” seems to indicate otherwise. What do you think is happening in the case of IF in humans (let’s assume an alternate day fasting schedule)? Related to this, we have observed that an intermittent fasting schedule of simply compressing the eating window to say 6 hours has resulted in body fat loss, muscle gain and performance increase (absolute strength, strength endurance and aerobic endurance). We have conjectured that increased insulin sensitivity and possibly elevated IGF-1 levels may be at play here. Do these (admittedly non-controlled and subject to error) findings make any sense with what you know about IF?

It must be recognized that caloric restriction in mice is not the same as caloric restriction in humans. Basal metabolic rate is about seven-eight times greater in mice than in humans. A 24-hour fast in mice is comparable to a 6-7-day fast in humans. We recently published a paper showing that a 40 % CR in mice mimics a full therapeutic fast in humans. Thus, the health benefits attributed to CR in mice can be realized in humans who engage in water only therapeutic fasting for at least three to four days.

Our research in mice and that of other investigators shows that blood glucose levels influence IGF-1 levels, like that of insulin levels. When blood glucose levels fall as seen during caloric restriction, blood insulin and IGF-1 levels fall. Insulin sensitivity can be enhanced during CR since glucose levels are low. Glucose, insulin, and IGF-1 levels should be measured before and after intermittent fasting. Since these values may also differ widely among individuals, at least twenty individuals would be needed to get some meaningful data. There is

evidence from the past work of Benarr MacFadden that fasting for seven days significantly enhanced endurance and strength in athletes. No measurements of glucose, ketones, or IGF-1 were analyzed in these studies.

The “thrifty gene” hypothesis states that our ancestors experienced alternating periods of feast and famine and it was those who could store body fat the best, and who were “thrifty” with calories, who lived and ultimately passed on their propensity towards fat storage. This hypothesis has been largely embraced by those who have an inclination towards evolutionary biology. However, work by Loren Cordain and others has cast doubt upon this theory. Cordain has found that hunter gathers rarely experienced extended periods of famine but rather lived an active foraging lifestyle with a significant portion of each day spent in food procurement and thus a brief fast. Anthropological data indicates that modern HG’s and our ancestors actually lived at energy excess and this high energy flux appears to be highly correlated with both health and longevity. Given the insights of metabolic control theory, does it not make more sense that when considering many diseases of affluence, instead of a “thrifty gene” situation we are simply observing the results of a species moving ever further away from its normal genetic set point? Is it possible that we “need” periods of fasting and ketosis in order to express a normal healthy phenotype?

The thrifty gene is a complicated phenomenon and likely involves many genes, hormones, and metabolic pathways. It relates to the ability of organisms to become more energy efficient following periods of food deprivation. This can sometimes lead to increased weight gain following yo-yo dieting in some humans. We recently published that mice become more energy efficient following three weeks of caloric restriction (Mahoney et al., 2006, Lipids, Health, and Disease). The mice need fewer calories to maintain their body weight following CR. A similar situation in man could cause some people to gain weight following a fast or severe caloric restriction since body weight set points are more variable in humans than in mice.

It is not clear if early hominids lived at energy excess as some suggest. The work of Rick Potts would not support this claim. Humans, as have all species, evolved under extreme conditions of the environment. Moreover, this environment was largely deficient in high carbohydrate (caloric) foods in contrast to today’s environment. Most chronic diseases today are caused either directly or indirectly from the consumption of excess calories. There is no doubt that fasting and caloric restriction together with body movement (exercise) can retard the aging process and maintain health for longer periods.

Our readership tends to be interested in three inter-re-

lated concepts, namely performance, health and longevity. How might one incorporate IF into a scheme to optimize these concepts? Considering the potent protein sparing effects of fasting (if no overt insulin resistance exists) how long can one reasonably fast and not suffer significant muscle loss or hormonal derangement?

The maximum period of water only fasting differs widely among people and among the young, middle aged, and elderly. About 40 days is the maximum period of therapeutic fasting in normal sized young adults (about 160-175 lbs). The line is not always so clear between therapeutic fasting, which is healthy, and starvation which is pathological. This information comes from the studies of Drs. George Cahill and Oliver Owen, leading experts on starvation in man. Most people would need to train with shorter periods of food restriction prior to initiating a 40 day fast. Fat people (over 300 lbs) can fast for much longer periods (up to 12 months) than thin people according to Dr. Cahill. In general, water only fasting for 1-2 weeks would be healthy for most people who are in relatively good physical health.

I have put forward a plan that advocates IF as a way to elicit episodic, acute stress responses which appear to be highly beneficial to health. My hope has been that adequate feeding during ones “eat” phase should allow one to maintain androgen levels and thus performance while garnering the benefits of an acute stress response, improved insulin function etc. Does this seem a reasonable proposition?

Periodic stress responses are generally healthy for most normal people who are not on chronic drug medications. Fasting as an acute stress response can be very effective in managing various diseases as our research and that of other investigators shows. Fasting, however, may not be an option for people who are on performance enhancement drugs or drugs for certain illnesses. While therapeutic fasting is a more powerful health remedy for chronic diseases than drugs, fasting can alter drug metabolism and produce adverse side effects. Thus, fasting should not be combined with any kinds of drugs or medications.

Wrap Up

It appears that chronic disease such as cancer and some neuro-degenerative disorders may require lon-

ger therapeutic fasts than the simple alternate day fasts we have looked at. This makes sense in that reversing a full-blown disease state is much more involved than preventing the disease. That said it is unclear what contribution to health short alternate day or compressed feeding schedule fasts may offer. Can these shorter fasts and smart nutrition and lifestyle be preventative? This seems a reasonable assumption; however, it will be some time before we see a clinical trial/metabolic ward study looking at the following variables:

Intermittent fasting: Alternate day/limited daily feeding.

High fat paleo-type diet: Either Zone/Cyclic low carb

High intensity metabolic conditioning: Traditional 3-on-1off WOD/ME-Black Box

Imagine someone saying, “Show me a study that proves alternate day fasting on a cyclic low carb paleo diet with a 3-on-1-off training schedule is superior with regards to performance, health and longevity to a limited daily feeding, Zone diet with an ME-Black Box training schedule...” Just in that list of variables we can generate eight different experiments and that is only the start of our problems if we really want to tie this down. Science in the sense of running an experiment and getting a meaningful answer has some serious limitations when the question or the system being studied is highly complex. So are we without the ability to make informed decisions and use the technology at hand to our advantage? Absolutely not! For example we can draw a few conclusions from a recent study from Stanford University that showed one day of ad-libitum eating followed by a caloric restriction day (20-50% of ad-libitum) greatly improves insulin sensitivity and inflammatory markers. Our limited experience with IF (not controlled or scientific) has shown improved performance, body composition and sense of well-being. It would appear that any movement towards intermittent eating and punctuated periods of ketosis is highly beneficial with regards to performance, health and longevity.

Dr. Seyfried makes the point that mice placed on a high carb CRAN diet experience ketosis to a lesser degree than those fed a high fat diet. This suggests a smart therapeutic intervention could be a ketogenic diet followed by CRAN and/or IF. In fact the use of ketosis and CRAN is what Dr. Seyfried recommends in his paper on brain tumor treatment. Although largely speculative, I think it safe to assume that this integrated approach of smart nutrition, exercise and lifestyle represents a potent tool for optimized living.