Experience with Caloric Restriction Diet (1200- 1500 calories / day) Have an Impact on Patients with Widespread Cancer Disease (Bibliography attached)
George Yu 1/6/2014

There are extensive basic science and emerging primate and human research confirming the longevity effects of caloric restriction, CR. **What is less known is the attenuation effects of CR on cancer growth**. Basic science research shows that the severity of CR, caloric restriction (20 to 60% of normal calorie intake) is positively correlated with lesser cancer growth. However eradicating all cancer growth using CR is more difficult. The bibliography provided to will have comprehensive references.

CR can vary in animal research defined as limiting caloric intake to 20-50%, however for human compliance in **"real world scenarios"**; nutritional institutes such as the **CR society, Hippocrates Institute, Kushi Institute, Optimum Health Institute** generally use a total of 1200 to 1500 Calories consumed by members per day and are tolerable and acceptable as long as there is sufficient volume, fiber, flavor and nutritional density and ease of digestibility.

The first human study using CR was the **Biosphere 2** in 1989. Eight (8) humans 4 men and 4 women were confined in a self-contained sphere for 2 years and all their risk factors for modern diseases decreased - serum insulin, glucose, and blood pressures, weight etc. in all eight individuals.

There are institutions worldwide that practice CR with members eating a variety of foods from raw vegetable food, cooked vegetable-based foods with minimal animal protein (fish, eggs) and use simple and easily digestible foods with the aids of probiotics and digestive enzymes for efficient food breakdown and digestion. **All the practices have a common feature- the total calories consumed per day is around 1200 to 1500 calories.** These institutions have an average of 1000 new visitors yearly and the guests stay for 3-5 weeks to accustom themselves to the diet and learn food preparations. I have been privileged to perform audits on some of these organizations and have witnessed their practices and outcomes.

Dr. George Yu, M.D. – Personal Clinical Experience CR effect on Human Cancers Through the Hippocrates and Kushi Institutes and the Caloric Restriction Association

At George Washington University Medical Center and Anne Arundel Medical Center, I have been urological surgical oncologist and reconstructive surgeon for thirty five (35) years and worked as part of the team of medical oncologists, radiation oncologists in designing treatment plans for patients with advanced metastatic cancers. My area of interest has been on the biology of invasive bladder cancers and treatments including surgery, chemotherapy, radiation and CR.

A remarkable turn of events for me occurred in 1999 when I volunteered to act as an "auditor" for CAM (Complementary Alternative Medicine) for the "best case analysis"

program at National Institute of Health on nutritional interventions in terminal cancer patients with widespread disease. Specifically, working with the Kushi Institute using a "macrobiotic" diet (nutritional dense but caloric limited foods), I audited over 300 cases of people with a variety of primary cancers and usually with metastatic disease. Among cancers studied were people with pancreatic, melanoma, lung, lymphoma, breast cancers all with widespread metastasis who survived and some were cured using nutrition after conventional treatment failures. Dr. Larry Kushi, professor of Epidemiology formally at Columbia University and at present with the Kaiser Institute in California had initially reviewed these original cases as part of a study on nutrition and chronic disease.
The formal presentation was held on **February 25, 2002** at the NIH with fifteen (15) reviewers who all confirmed the positive results from diet alone and are documented in the archives of the National Institute of Health.

I continued to pursue further audits with institutions such as Hippocrates Institute in Florida. Their practice differed in their use of raw vegetable foods (no fruits, no sugar, and no diaries) with similar nutritionally dense but caloric restricted diets and found consistently similar results.

If I did not personally review these medical data charts, see the survivors and failures, consume their foods, I would never have believed or accepted that CR nutritional intervention could show such impressive effects on chronic cancerous diseases. People who practice CR are content and satisfied using low calorie diets as there is variety.

What is consistent after eating CR diet regimen for longer than 48 hours is that the hunger sensation diminishes markedly even for people who eat diets with calories up to 3000 per day normally.

Most researchers of Caloric Restriction do not believe that it is possible for humans to consume 1500 calories per day and feel satisfied because they have rarely experienced it themselves.

Around 2001, the publication by Stephen Spindler's research team at University of California Riverside showed that 70% of gene expression changed dramatically within 4 weeks of CR diets in animal studies suggesting that **STCR** Short Term Caloric Restriction replicated the effects of **LTCR** Long Term Caloric Restriction quickly. The implication is that human and animal genotype responded to external stimulus and adjusted rapidly by modulating gene expressions. This was a critical concept as long-term Cr has long- term adverse effects and as clinicians if we could "cycle on and off periods" of very strict CR and slight increase in the off periods the patient compliance is acceptable and realistic!

Cao, S. X., Dhahbi, J. M., Mote, P. L. & Spindler, S. R. Genomic profiling of short- and long-term caloric restriction effects in the liver of aging mice. (2001) Proc. Natl. Acad. Sci. U. S. A. 98, 10630-10635

What Did We Learn from monitoring CR cancer patients in 13 years

All groups practice a form of "Caloric Restriction" limiting total intake of 1200-1500 calories per day but the food was nutritionally dense and free from sugars, no fruits and diaries. The data from the administrators of these institutions and my own corroboration in these 13 years seem to show that approximately 1/3 of the cases go into complete remission but 2/3 improved both from objective studies (CAT scans + blood markers), physical examination and symptoms relief but later, developed a recurrence and die. At that point using CR diet will not stop progression of cancers.

The CAT scans uniformly showed shrinkage of tumors within 3-6 months while the "visceral defatting" all shrunk completely.

The patients lost 10% of their body weight

Blood sugars 80 to 90 mg/dl and ketones are present in their urine. Some patients examined have blood ketones up to 5 mmol.

Blood Insulin levels is between 5- 8 micro international units/ml

Hemoglobin A1C is 5 to 5.5%

The PET scans, using a glucose analogue 18F-flouro-2deoxyD glucose (FDG) showed improvement with less cancer uptakes after going on a Caloric Restricted diet.

Cancer recurrence will occur if they return to an unrestricted diet and will also regress if resuming a strict CR diet.

CR has negative effects such as bone and muscle loss and hormone dysregulations on long term use. We cycle CR as Short Term CR as noted above

I believe these cases all had one common feature: these aggressive solid tumor cancers depended on an inefficient metabolism, glycolysis and oxidative phosphorylation, and in layman's term limiting calories in their diet was a form of **"starvation"** of cancers. Low calorie and ketogenic diets disrupt cancer cell ATP energy production.

As James Watson, the Nobel Prize winner defining the structure of DNA emphasized in a lecture at Yale University in 2012- "Glycolysis is perhaps the Achilles Heel of Cancer Cells."

After observing and practicing CR in our oncological patients for over thirteen (13) years, I am convinced of the importance of Caloric Restriction and Caloric restricted with a Ketogenic component in retarding aggressive cancer growths. These findings are consistent with the concept that most cancers predominately have a defective metabolism with a predominance of cell glycolysis (Warburg Effect) and a Hexokinase 2 defect of the mitochondria as described by Pedersen and Ko. This may the reason why some of these CR diets had such a profound effect on their cancer growths. Yet only the minority has permanent results and the majority will respond but eventually fail but we do not know why certain individuals respond and others do not.

Ketogenic Diets with Caloric Restriction

The ketogenic diet (a high fat diet) yet low calories used to treat childhood epilepsy are well known to be effective and safe. This old regimen was further developed and

popularized at Johns Hopkins by John Freeman and associates. As simple CR diets (without the ketogenic part) often will show **"ketosis"** as a body adaptation to scares calories intake**,** the concept of using **ketones derived from oils** may also lead to a further insult to cancer cells but not to normal body tissue cell metabolism. In the nutritional and metabolic approach to cancer arrest, we can use the traditional CR diets as practiced by the above institutions but there should be allowances for a high fat ketogenic diet with caloric restriction as two arms of the nutritional approach to cancer eradication.

Research and Metabolic Strategy to Arrest Cancer Growth by Decreasing Supply of Glucose, Arresting Full ATP Energy Production, Mitochondrial Disruption, Electron Transfer Dysfunction of Mitochondria etc.

There is accumulated evidence from basic science research showing that most cancer cells use predominately **glycolysis (fermentation)** energy, but have a defective production of energy from the mitochondria or in other words "unable to utilize **oxidative phosphorylation** (Krebs Cycle) efficiently".

The basic science research has already been done by many researchers summarized in the recent publication 2012 by Thomas Seyfried **Cancer as a Metabolic Disease** confirming the "Warburg Effect" for most cancers. This is an excellent summary of all the research and experience worldwide and recommends all to read it.
PET scans using FDG **18F-flouro-2deoxyD glucose** uptake in cancer cells are an important diagnostic and prognostic tools and the basis of this study is the "glycolytic" nature of cancerous cells.

Most cancers will show glucose uptakes but interestingly, breast and prostate cancers are hormonally dependent but only breast cancers show early uptake whereas prostate cancers with a slow doubling time of 300 – 500 days do not show uptake till a later stage when the cancer becomes more progressive and aggressive.

There are many basic researchers and clinicians who are actively pursuing the metabolic approach to cancer disease. The goal is to destroy cancer cells while preserving normal cells.

The research done by Pamela Goodwin of University of Toronto leading a 3500 breast cancer patient study on the use of Metformin (diabetic medication to lower blood sugar and insulin) and its positive effect on patients with cancers suggests again a metabolic effect on cancers.

Clinicians such as neurosurgeon Joseph Maroon of University of Pittsburg has been focusing on eradicating brain tumor Glioblastoma and the use of caloric restricted ketogenic diet.

In the clinical nutritional field there are organizations such Ketogenic Therapies and the "Charlie Foundation" with Beth Aupec-Kania who used a similar ketogenic diet (treatment for childhood epilepsy) on cancer patients and have seen dramatic responses.

Thomas Seyfried of Boston College is a basic scientist who has been instrumental in pushing this concept for so long and wrote a comprehensive document, Cancer As A Metabolic Disease 2012.

Peter Pedersen of Johns Hopkins and Young Ko isolated a Hexokinase 2 in cancer cells and the use of a unique molecule 3BrPA, 3 Bromo Pyruvate, which blocks cancer ATP production while causing no harm to normal cells. Dr. Pedersen continued to champion research on cancer metabolism and was instrumental in the development of the clinical use of PET scans for cancer diagnostics.

Another basic scientist Dominic D'Agostino of University of South Florida has been working on animal models with ketogenic diets plus use of ketone esters.

My colleague Richard Veech of NIH and Karien Clarke of Cambridge University has developed liquid ketone esters.

Dr. Merrill Garnett (Garnett Mckeen laboratory) who tested 30,000 chemicals and found Palladium alpha Lipoic acid to disrupt cancer cell metabolism within the electron transfer system for energy generation in cancer cells while protecting normal cells.

Worldwide there are researchers such as Mark Coster's team of Griffith University in Australia who are selectively targeting cancers' mitochondria with an analogue of Vitamin E.

Chris Proud's team at University of Southampton, UK have isolated eFF2K which allows cancer cells to survive despite starvation- therefore blocking this molecule kills the cancer cells without harming normal cells.

There is a foundation especially created to fund research on this concept headed by Travis Christofferson called Single Cause Cure Foundation

All these dedicated workers are in one form of another approaching cancer from a metabolic model of cancer starvation and depriving cancer cells of "ATP energy production". I believe the "Tipping Point" (Malcolm Gladwell) is close at hand in a change in the paradigm from Somatic Mutation to a Metabolic theory of carcinomatosis.

Research work by Peter Pedersen at Johns Hopkins and Young Ko at University of Maryland, my close associates, show that it may be the cancers derive 60% of energy from glycolysis and up to 40% from an inefficient form of oxidative phosphorylation. In essence cancers may start as a metabolic disease but whether it is from a mitochondrial DNA mutation is unclear. Initiating from the defective metabolism in cancer cells, secondary DNA instability and mutations can take place. The elegant discussion by Drs. Pedersen and Ko below elaborates in detail the rationale of the "Warburg Theory" and their discovery of 3-bromo pyruvate, 3-BrPA. Pedersen and Ko describe 3-BrPA as a potent inhibitor of all ATP production from glycolysis and oxidative phosphorylation in cancerous cells.

Pressing Need to Use Caloric Restriction and Adjunctive Agents with Efficacy but Minimum Adverse Effects

Ongoing Clinical Studies

NIH ERGO NCT00575146 –Glioblastoma Feasibility – U. Hospital of Tuebingen , Germany -20 patients
NIH NCT00444054 – RECHARGE Trial o Metastatic Cancers
NIH NCT00932672 – Randomized study for Prostate Cancer using Atkins diet – Duke University
NIH NCT01092247 – Yet to Open Tel-Aviv Sourasky Medical Center Israel
NIH KETOPAN NCT01419483 – Phase 1 Ketogenic diet and Radiation for Pancreatic Cancer – U. of Iowa
NIH KETOLUNG NCT01419587 –Phase 1 Ketogenic diet for non-small cell lung cancer- U. of Iowa

As noted above, the majority or 2/3 of patients on Caloric Restriction will first respond and later progress, fail and finally die, therefore we need additional adjunctive treatments to improve their survival. How another version of Caloric Restricted Diet with a Ketotic component will fair is yet to be seen but promising as noted above in NIH supported trials.

The use of 3 Bromo Pyruvate, 2-Deoxyglucose, Dichloroacetate are among the few of the interesting molecules which may inhibit glycolysis and mitochondrial functions, which may be an important class of chemicals which may enhance the effects of CR caloric restriction as a more complete the metabolic approach to cancer eradication.