

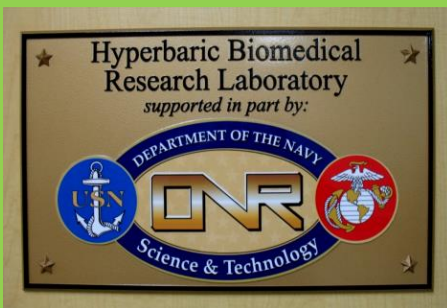
The Ketogenic Diet and HBOT for Cancer

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Hyperbaric Biomedical Research Lab

University of South Florida Morsani College of Medicine





Metabolic Therapy Research

- ✓ CNS Oxygen Toxicity (seizures)
- ✓ Neurological Disorders
- ✓ Metabolic Disorders
- ✓ Wound Healing
- ✓ Cancer



CNS Oxygen Toxicity

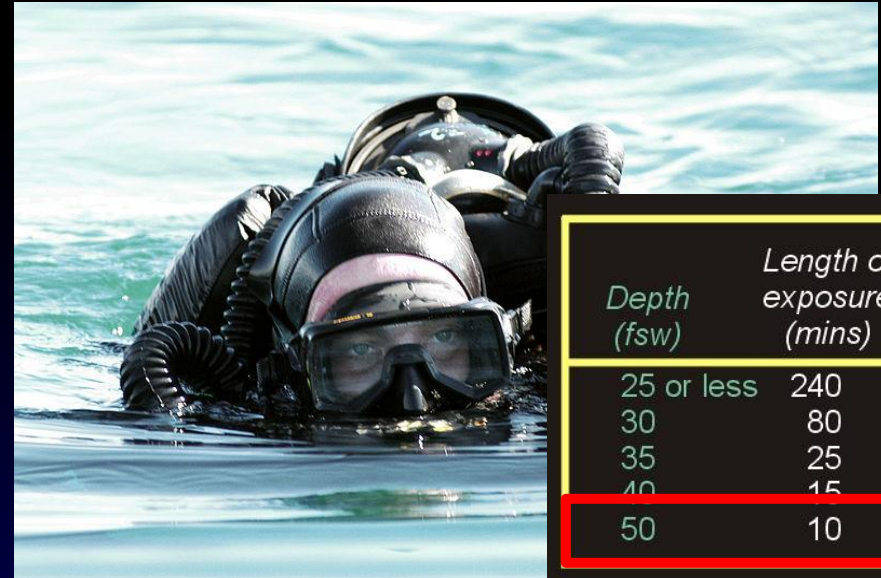


- **CNS-OT** results from breathing oxygen at >2.5 ATA O_2

Hyperbaric O_2 Therapy



Diving



- There is no way to prevent or predict CNS-OT
- What is the mechanism for CNS-OT?

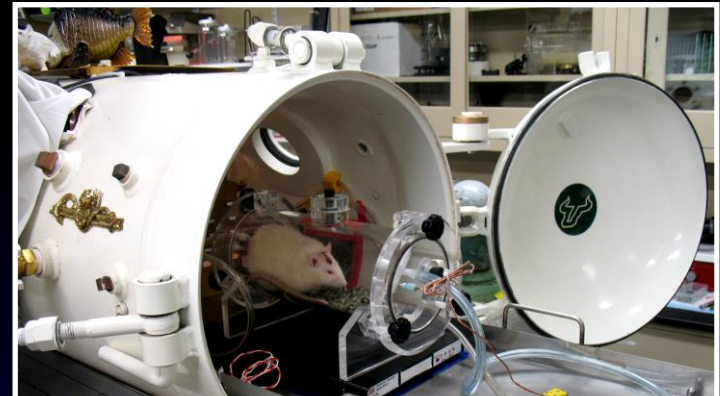
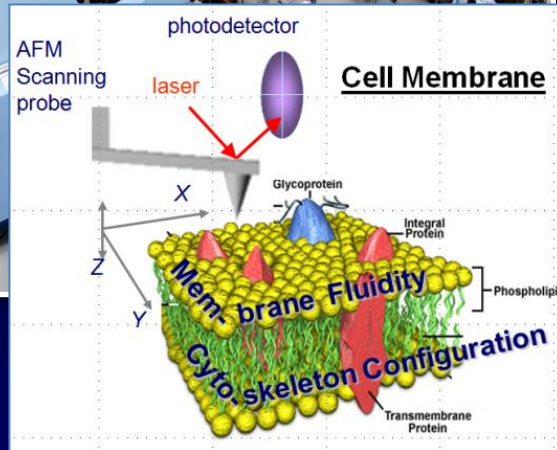
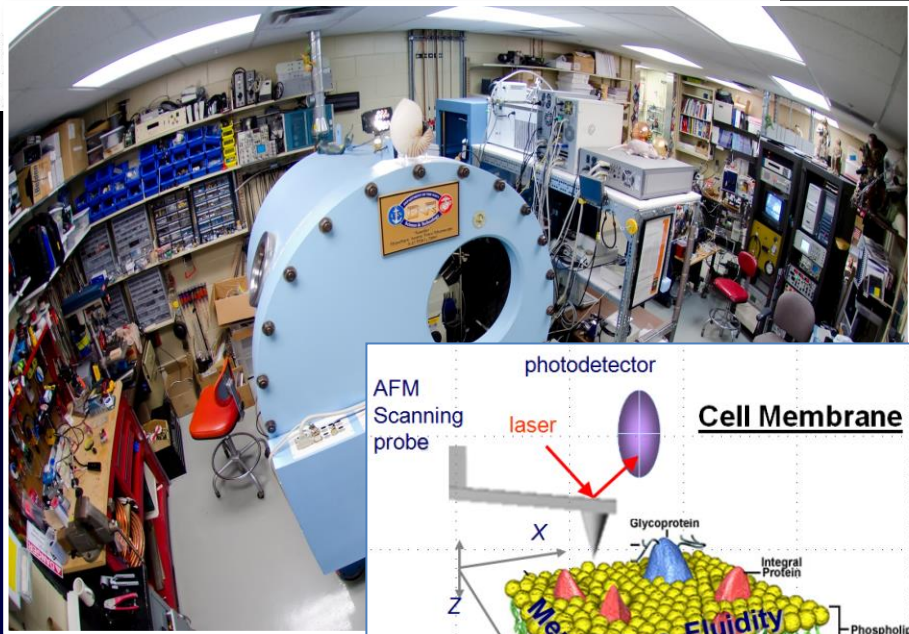


Methods to Study CNS-OT

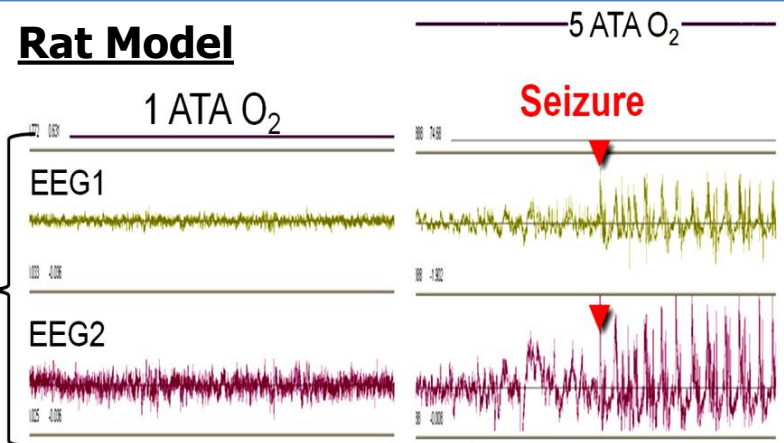
- ✓ Atomic Force Microscopy (AFM)
- ✓ Fluorescence Microscopy
- ✓ Laser Scanning Confocal Microscopy
- ✓ Electrophysiology
- ✓ Radio Telemetry (EEG)
- Adapted to hyperbaric chambers

Journal of
Microscopy
Journal of Microscopy, Vol. 246, Pt 2 2012, pp. 129–142
Received 30 July 2011; accepted 12 January 2012
doi: 10.1111/j.1365-2818.2011.03599.x

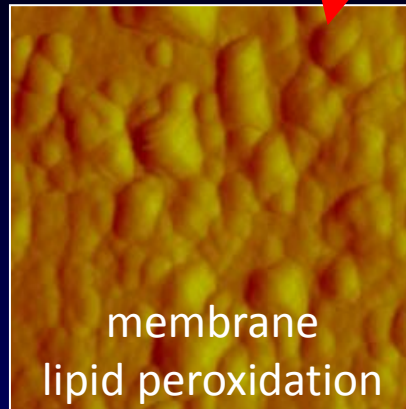
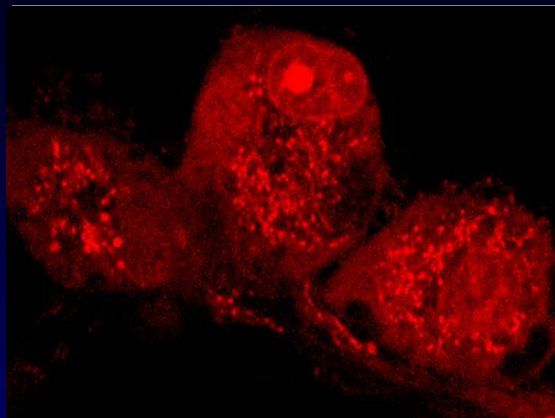
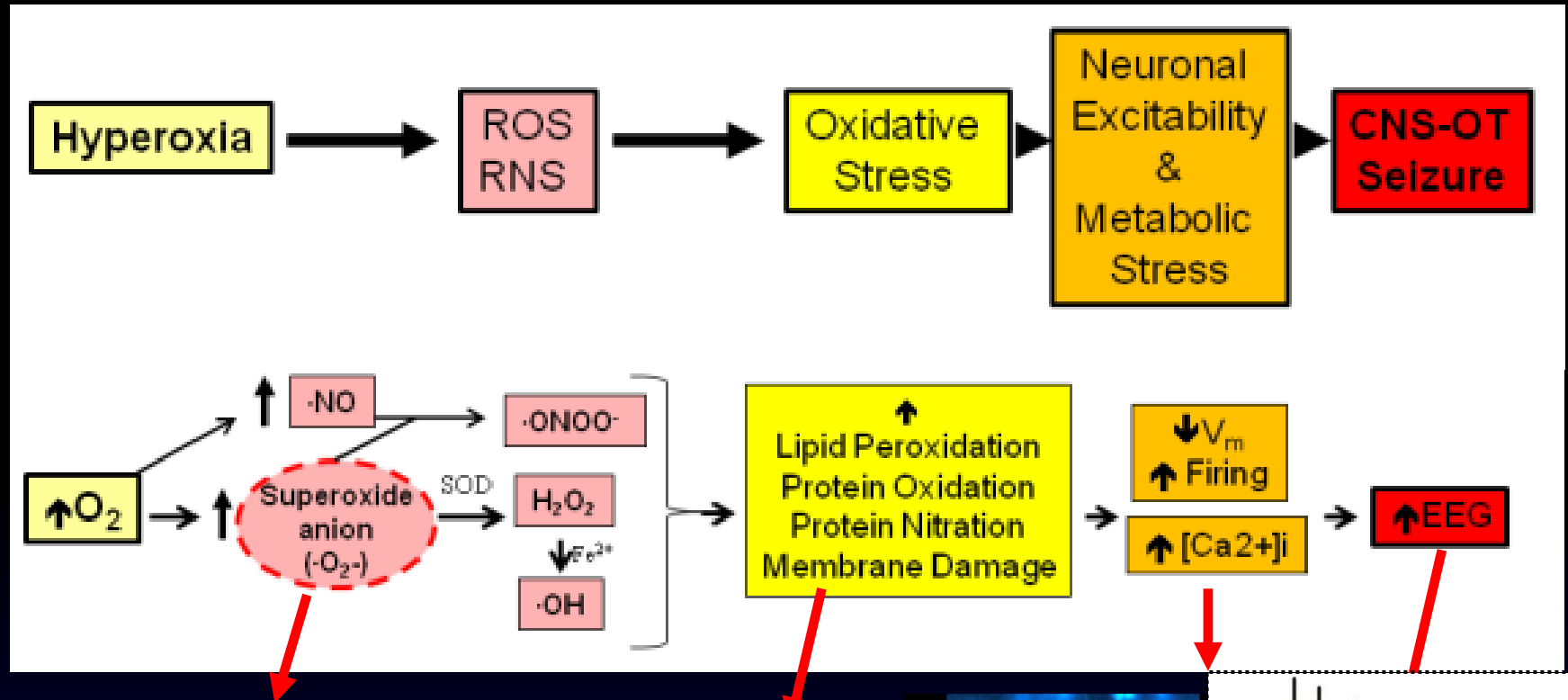
Development and testing of hyperbaric atomic force microscopy (AFM) and fluorescence microscopy for biological applications



Rat Model



Cellular Mechanism of CNS-OT



Strategies to prevent CNS O₂ toxicity

- ✓ Antioxidants
- ✓ Anti-Epileptic Drugs (AEDs)
- ✓ Preconditioning
- ✓ **Starvation** (>200% delay in latency to seizure)

Bitterman et al. . *Brain Res.* 761:146-50, 1997

Chavko et al. *Undersea Hyperb Med.* 26:99-103, 1999

How Does Starvation Change Brain Metabolism?

How Does Starvation Change Brain Metabolism?

FASTING AS EPILEPSY CURE.

Osteopaths Hear That 22 Days on Water Usually End Fits.

LOS ANGELES, July 5.—Epilepsy may be cured by fasting, Dr. Hugh Conklin told the twenty-sixth annual convention of the American Osteopathic Association, now in session here. Epilepsy, according to Dr. Conklin, is caused by the improper functioning of certain glands in the bowels. By fasting for twenty-two days, taking only water, a cure may be effected, he said.

"Many people," added Dr. Conklin, "fast thirty days and are never afflicted by fits again. The longest fast which any patient ever took under my direction lasted sixty days. Out of thirty-seven tests in which children were used as patients, only two still are affected by the disease. The children all were under the age of 11 years, but we effect cures in older patients in from 50 to 60 per cent. of the cases we undertake."

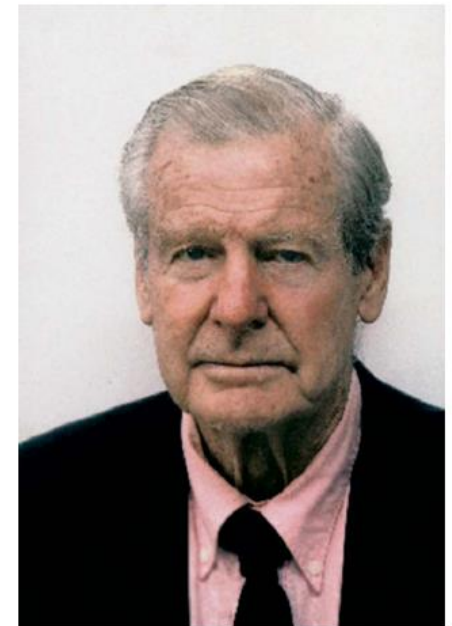
FUEL METABOLISM IN STARVATION

George F. Cahill, Jr.*

*Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115;
email: gcahill1@cheshire.net*

Key Words starvation, ketosis, β -h

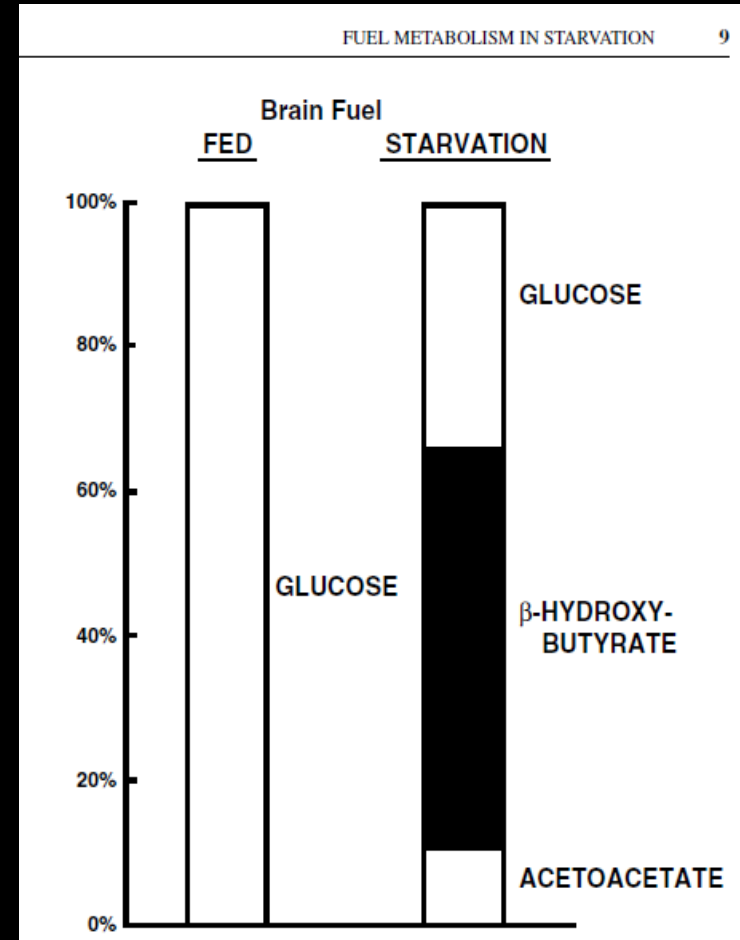
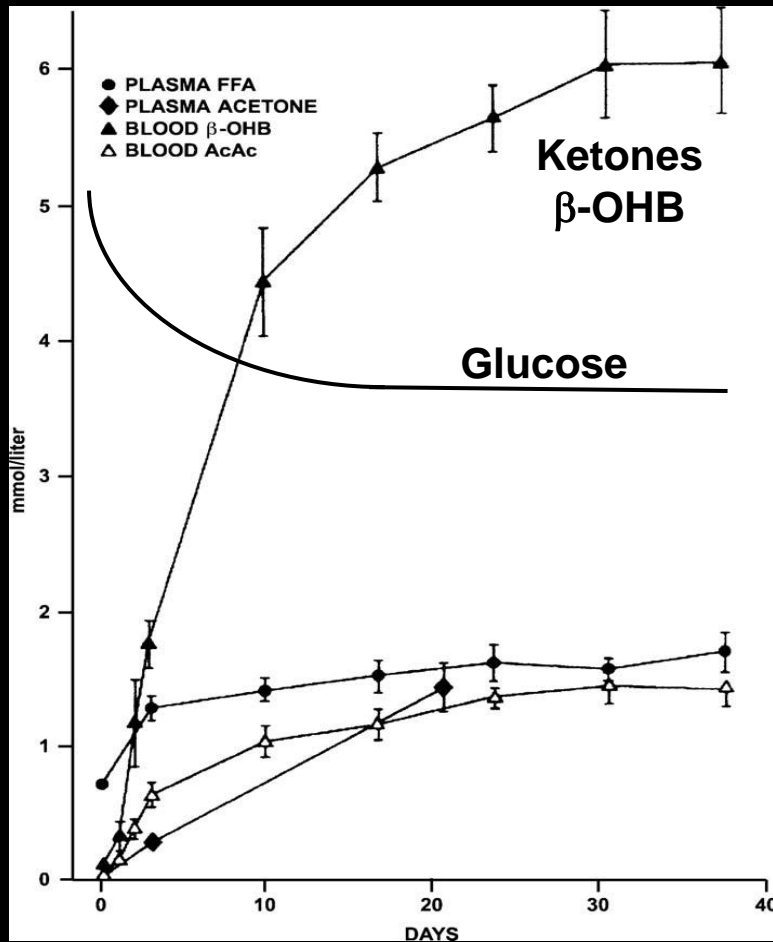
■ **Abstract** This article, which is a review of a life in academic medicine. It is a review of a life in academic and research medicine, from the beginning of human biology to college undergraduate (1953) treating a youngster in diabetes. The controls in human fuel metabolism known, insulin could not be measured which was difficult to measure, was the central role of insulin and the metabolic rate, and pyruvate, combined with insulin in a near-steady state, namely prolonged starvation. Due to its use by brain, D- β -hydroxybutyrate to survive prolonged starvation, but also a greater efficiency in providing cellular energy in the face of myocardial insufficiency, neonatal stress, fatigue.



George F. Cahill, Jr.

Annu. Rev. Nutr. 2006. 26:1-22
doi: 10.1146/annurev.nutr.26.061505.111258
Copyright © 2006 by Annual Reviews. All rights reserved.
First published online as a Review in Advance on May 9, 2006

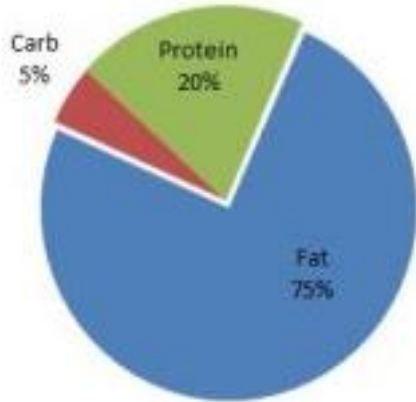
Ketone Bodies Fuel the Brain During Starvation



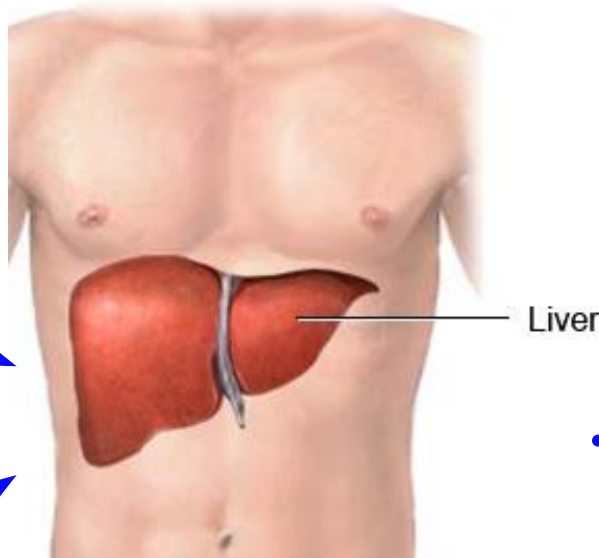
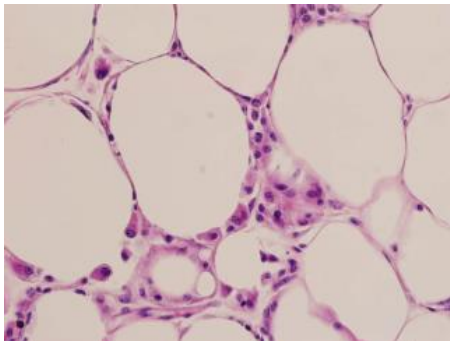
Modified Diagram from: Oliver E. Owen. "Ketone Bodies as a Fuel for the Brain during Starvation," *Biochemistry And Molecular Biology Education* Vol. 33, No. 4, 2005:246–251

Ketogenic Diet Mimics Fasting

Diet

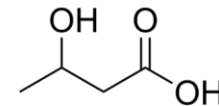
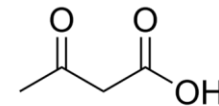
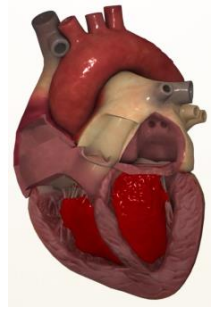
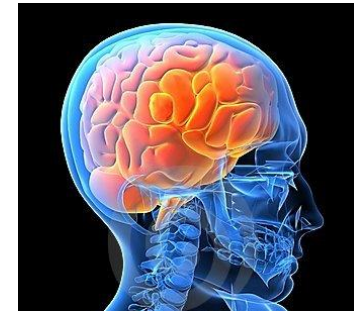


Body Fat

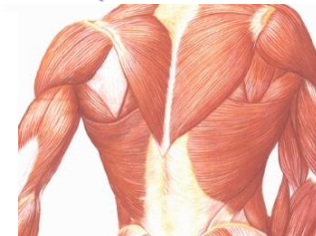


Glucose
Insulin

Difficult to sustain...



Ketones
(energy!)



Ketone Supplementation?

MCT oil



Ketone Salts
(KetoForce)



Naturally Derived

Ketone Esters

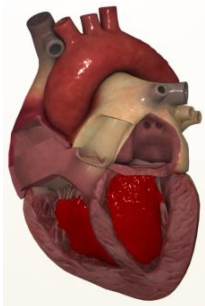
BHB



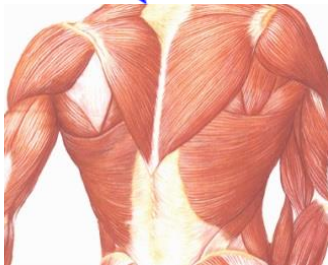
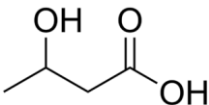
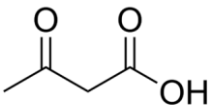
AcAc



Synthetic



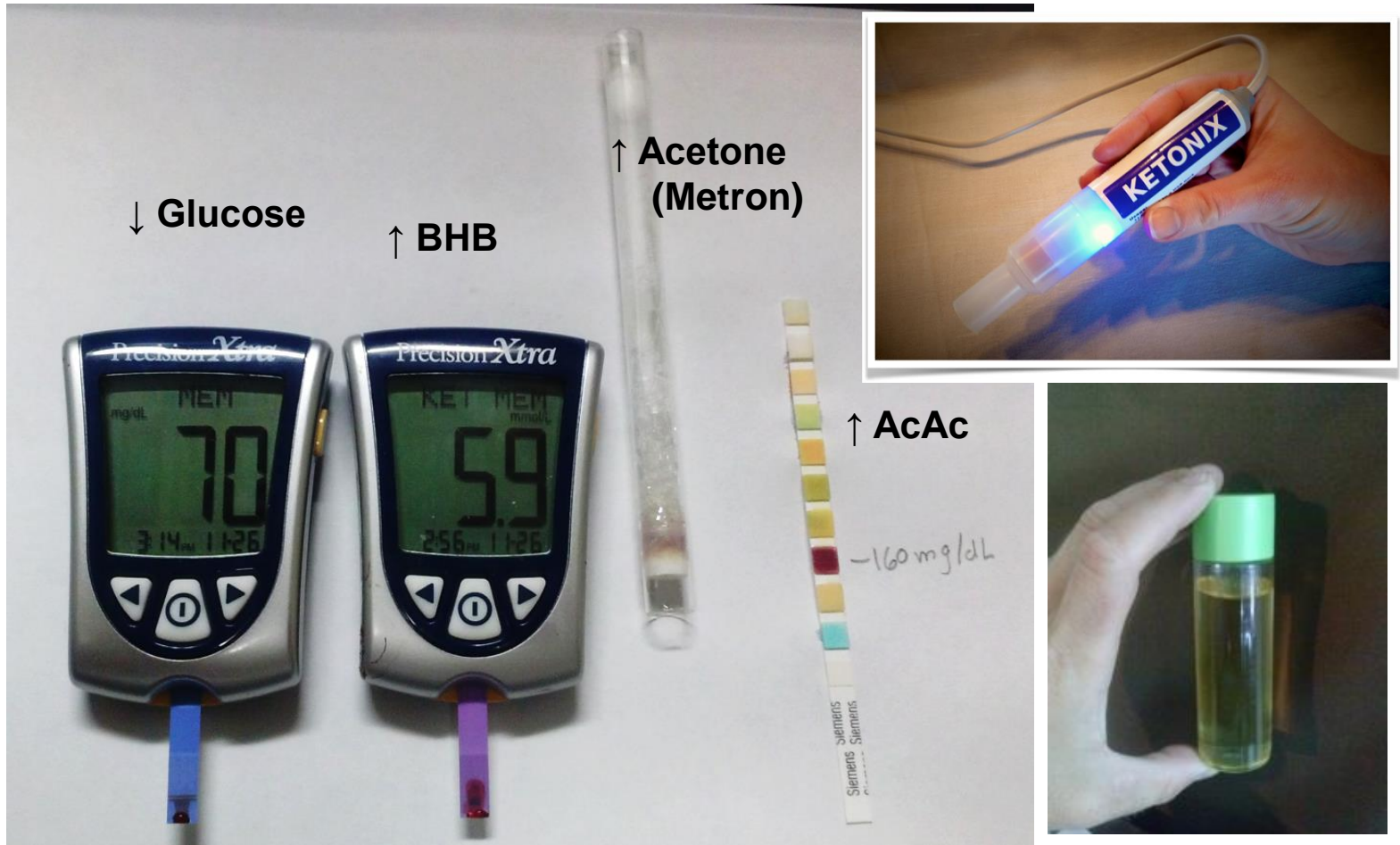
Ketones
(energy)



Ketone Supplementation (Single Dose)

Rapid Ketosis (15-30 minutes)

Sustained Ketosis (4-8 hrs)

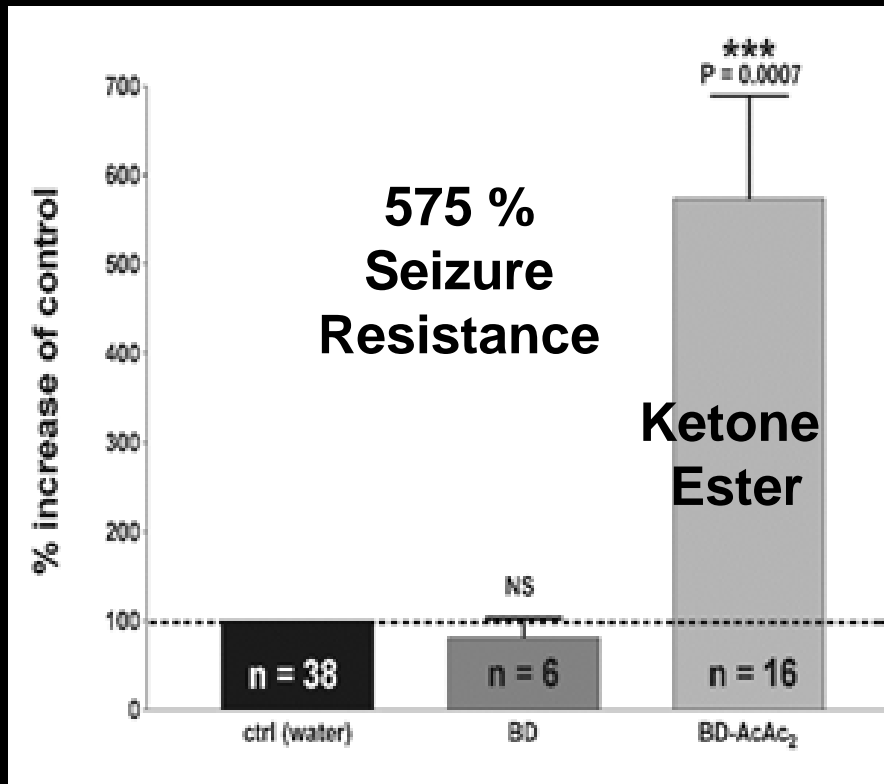


D'Agostino, D.P., et.al . *AJP Regulatory, Integrative and Comparative Physiology*, 2013 May 15;304(10):R829-36.

Kesi SL, et al. Methods of sustaining dietary ketosis in Sprague-Dawley rats. *FASEB Journal* (2014) vol. 28 no. 1 Supplement 643.5

Therapeutic ketosis with ketone ester delays central nervous system oxygen toxicity seizures in rats

Dominic P. D'Agostino,¹ Raffaele Pilla,¹ Heather E. Held,¹ Carol S. Landon,¹ Michelle Puchowicz,² Henri Brunengraber,² Csilla Ari,³ Patrick Arnold,⁴ and Jay B. Dean¹

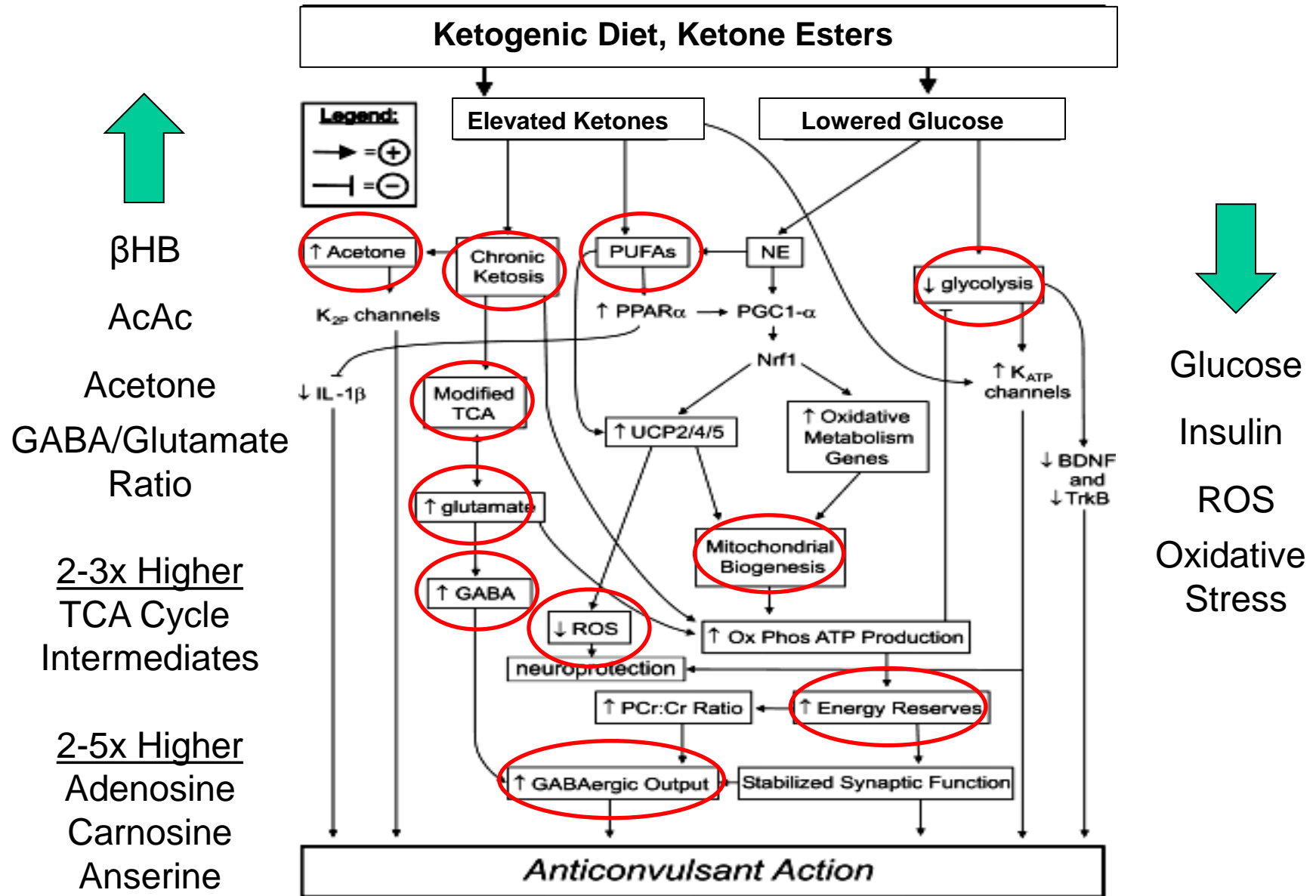


Ongoing testing in 4 seizure models

Special Ops Diving



↑ Physiological Resilience
Cognitive Performance
Physical Performance

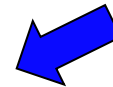
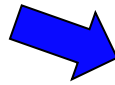


Adapted from: Kristopher Bough and Jong Rho. Anticonvulsant Mechanism of the Ketogenic Diet. *Epilepsia*, 48 (1): 43-58, 2007.

Metabolic Flexibility

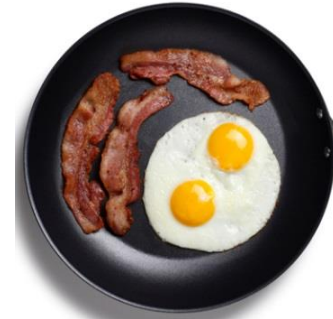
Glucose

**Normal Diet
(High Carb)**



Ketones

**Ketogenic Diet
(High Fat)**

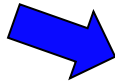


Healthy cells in the body can burn ketones for energy

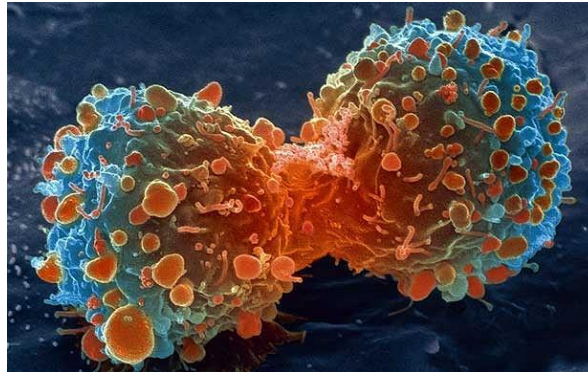
Cancer Lacks Metabolic Flexibility

Glucose

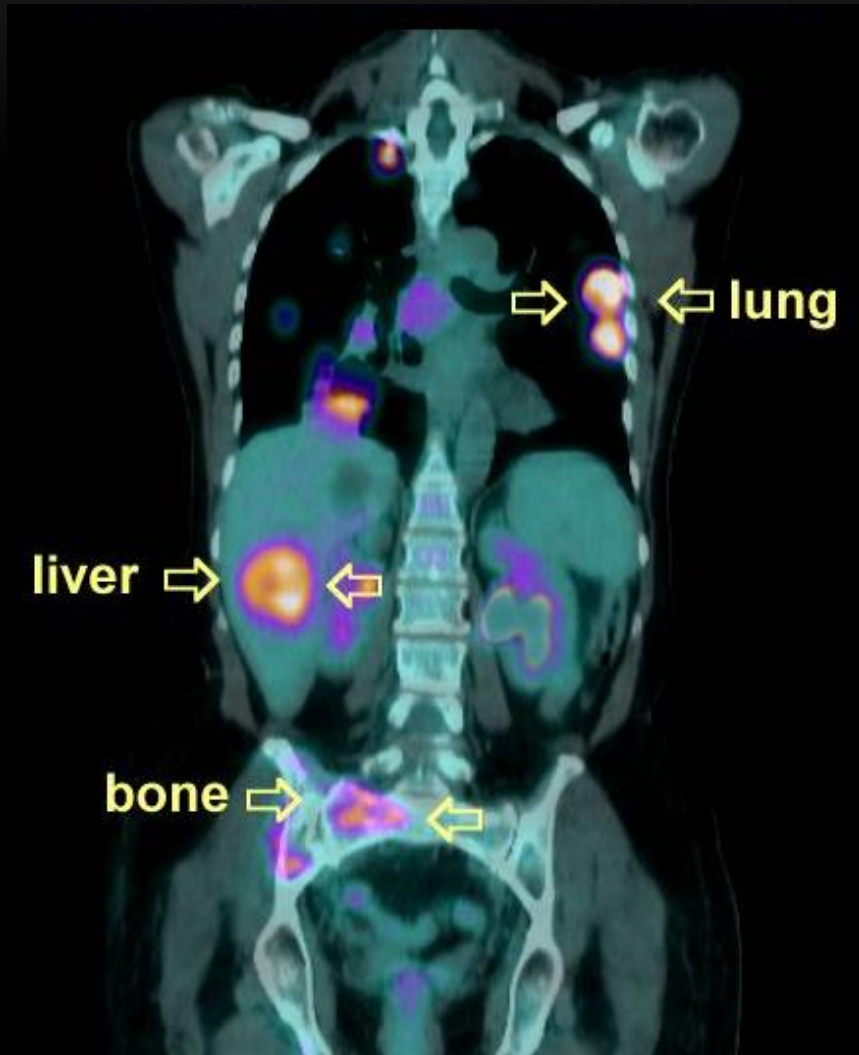
Normal Diet
(High Carb)



Cancer



FDG-PET Scan (metastatic cancer)

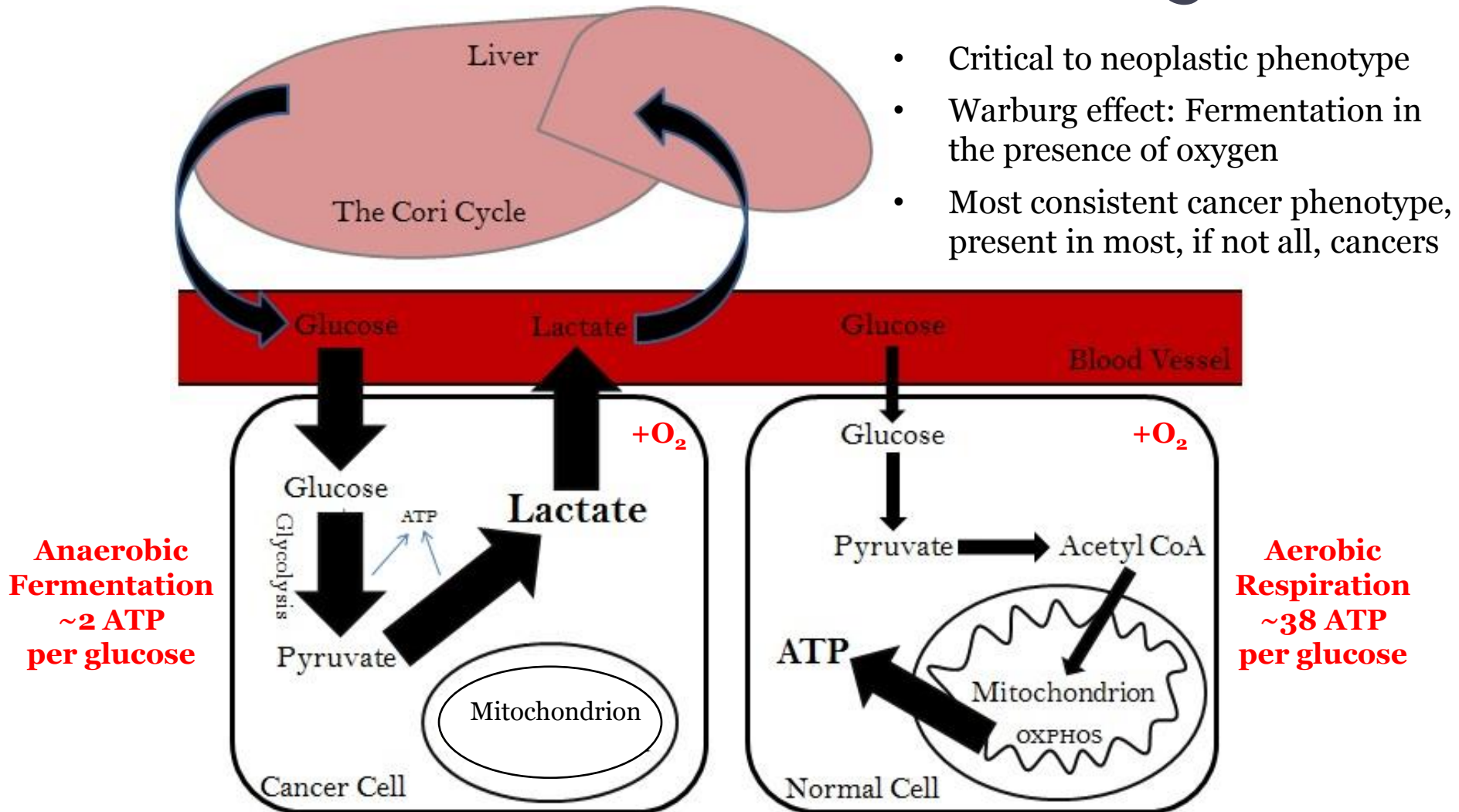


Otto H. Warburg
Nobel Prize (1931) Medicine



**First to Describe Cancer
as a Metabolic Disease**

Cancer Metabolism & The Warburg Effect



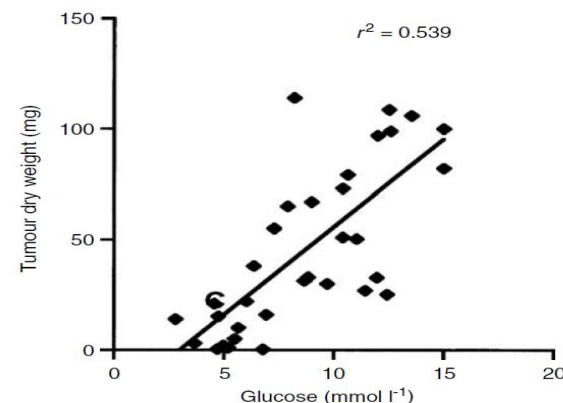
Elevated rates of glycolysis and fermentation, excessive lactate production

– up to 200 X rate of normal cells

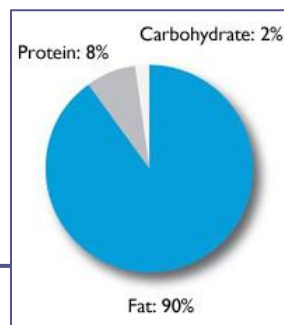


Cancers thrive on glucose but are vulnerable to energy stress

- High glycemic index diets increase risk of cancer
- Hyperglycemia = poor prognosis
- Blood glucose directly correlated to tumor growth
- Ketogenic diet: 4:1 fat : protein + carbohydrate
 - Induces ketosis
 - Anti-inflammatory
 - Suppresses insulin and IGF-1

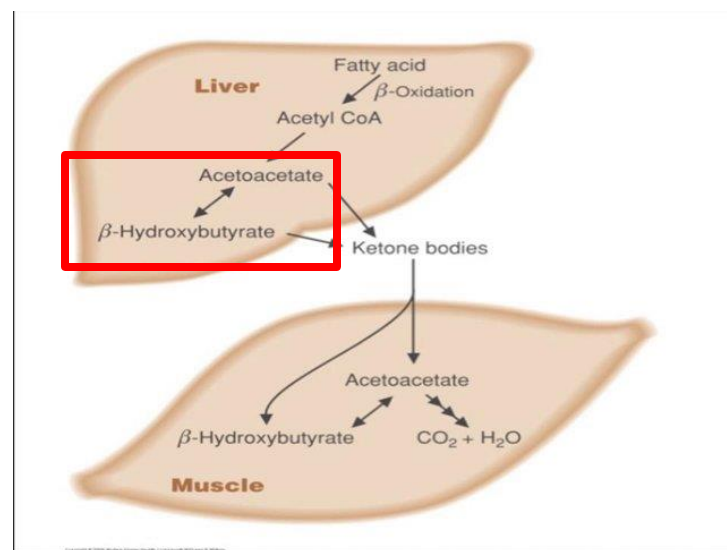


Seyfried et al. British Journal of Cancer (2003) 89, 1375 – 1382

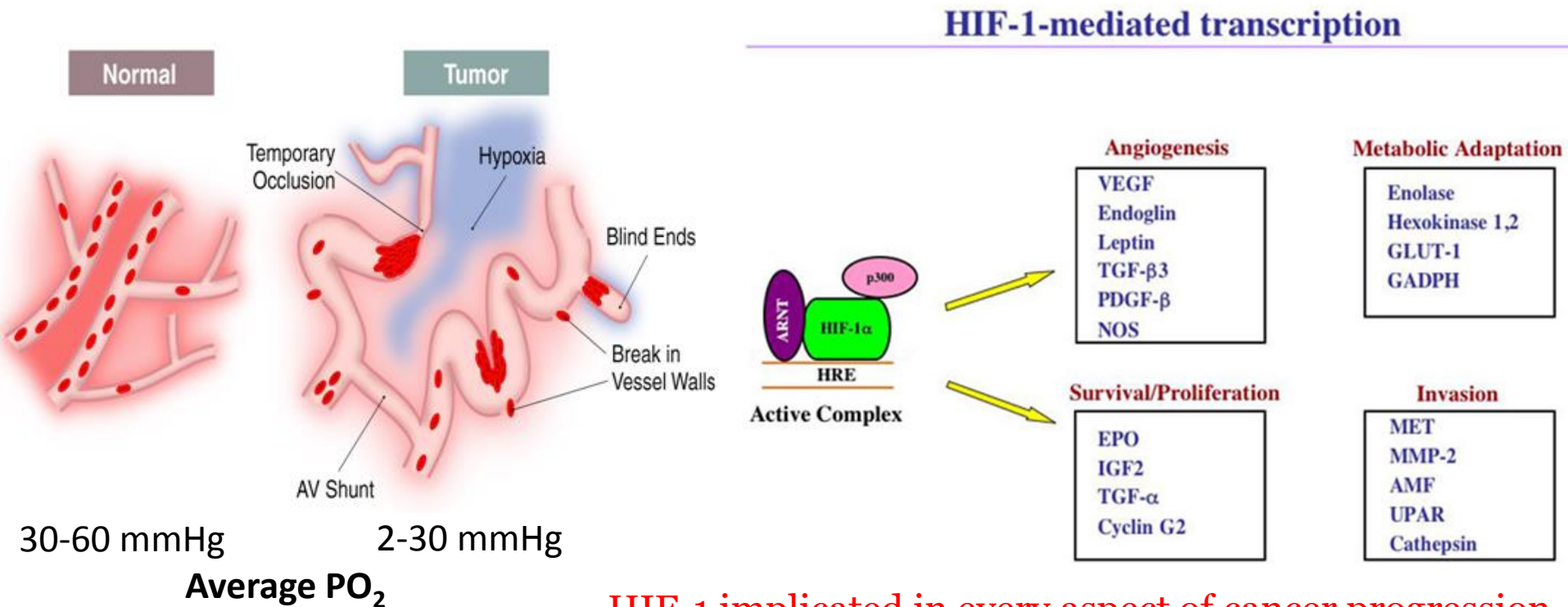


The American Journal of CLINICAL NUTRITION
 Glycemic index, glycemic load, and cancer risk: a meta-analysis

Gnagnarella, et al; 2008



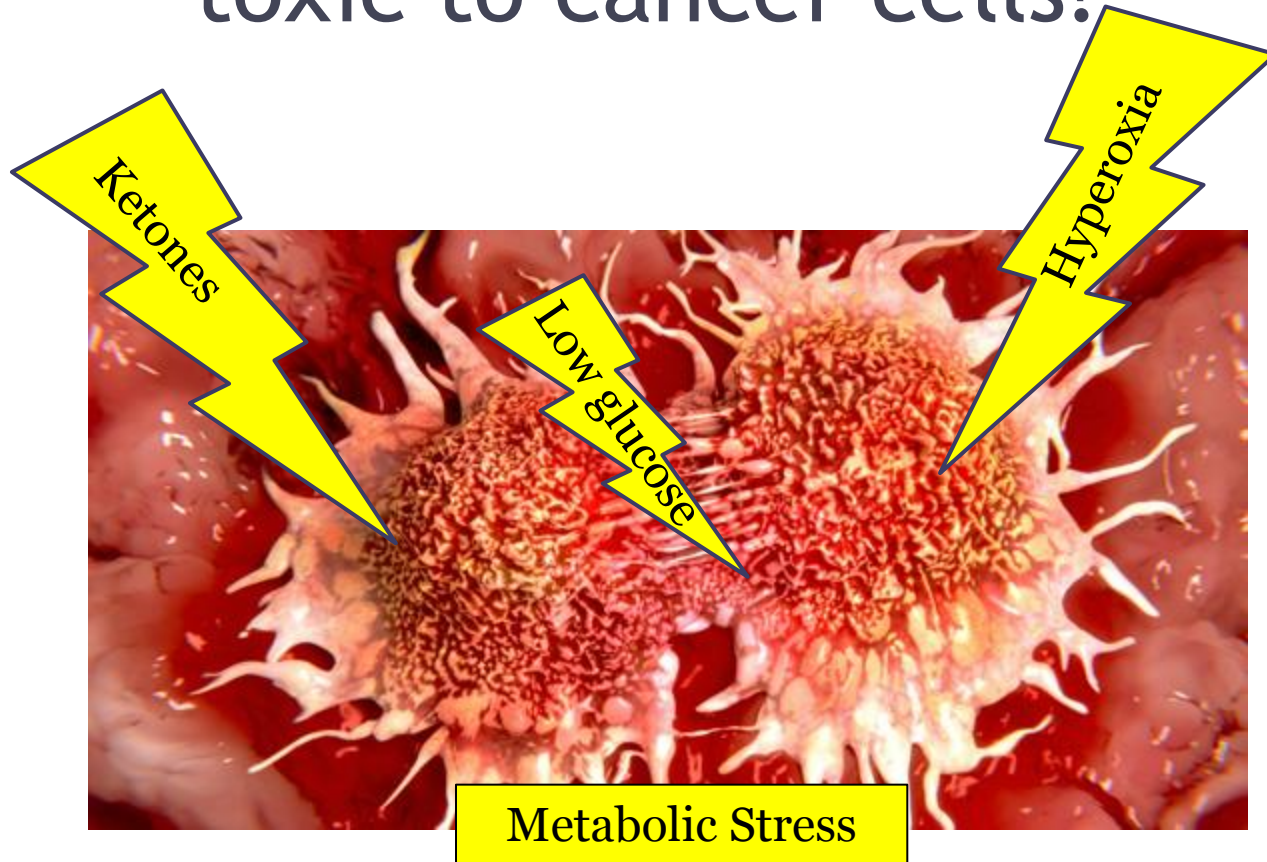
Tumor hypoxia promotes cancer progression and the Warburg Effect



HIF-1 implicated in every aspect of cancer progression

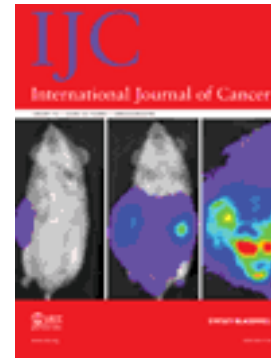
Confers chemo/radioresistance

Can we use ketosis and HBOT to create
a physiological environment that is
toxic to cancer cells?



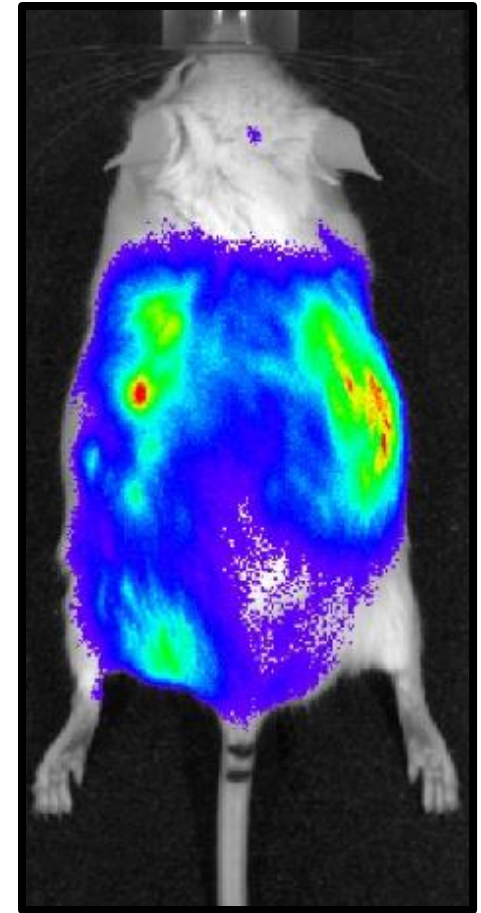
The VM-M3 Model of Metastatic Cancer

Developed by Dr. Thomas Seyfried, Boston College

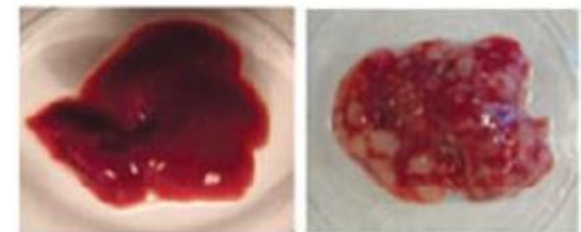


IJC, Volume 126

- Cells from spontaneous brain tumor
 - Natural tumorigenesis
- Syngeneic with VM/dK mice
 - Immunocompetent
- S.C. implantation → systemic metastasis
 - Shares many molecular and behavioral characteristics of human metastatic cancers
- Transduced with firefly luciferase gene
 - *In vivo* bioluminescence imaging



Liver Metastasis



Combining the Ketogenic Diet with Hyperbaric Oxygen

Methods: Treatment Groups

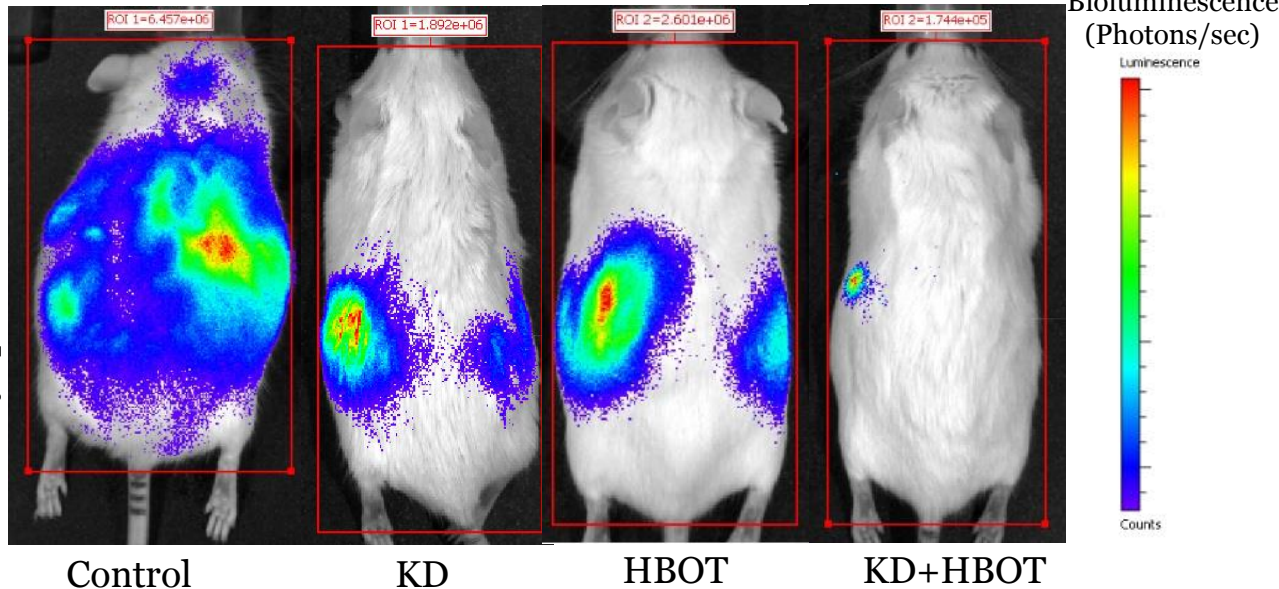
VM-M3 Survival Study:

- Control: Standard Diet *ad libitum*
- KD: Ketovolve *ad libitum*
- HBOT
 - Diet: SD *ad libitum*
 - HBOT: 2.5 ATA, 90 min, 3/week
- KD+HBOT:
 - Diet: Ketovolve *ad libitum*
 - HBOT: 2.5 ATA, 90 min, 3/week

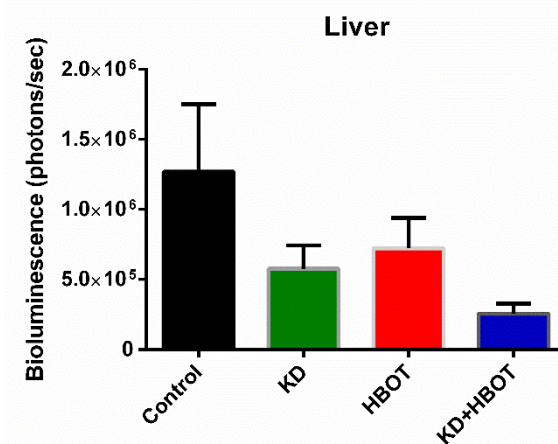
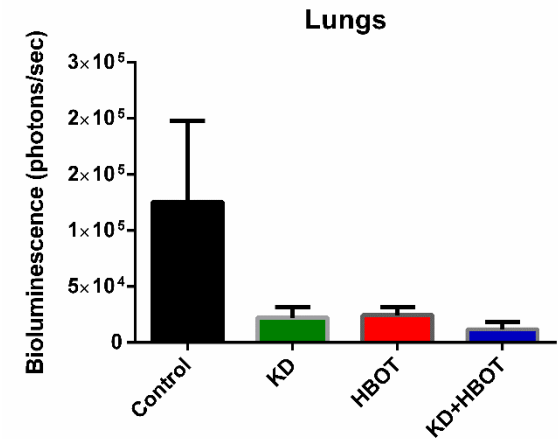
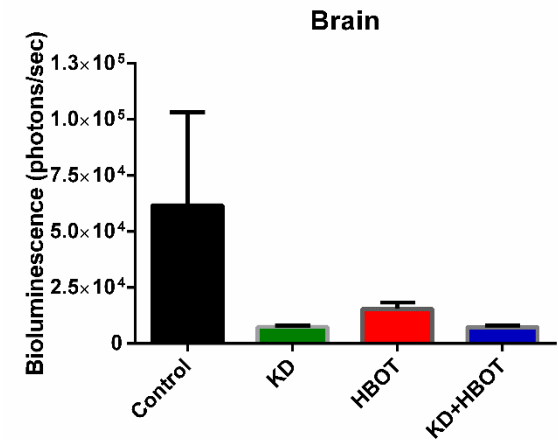
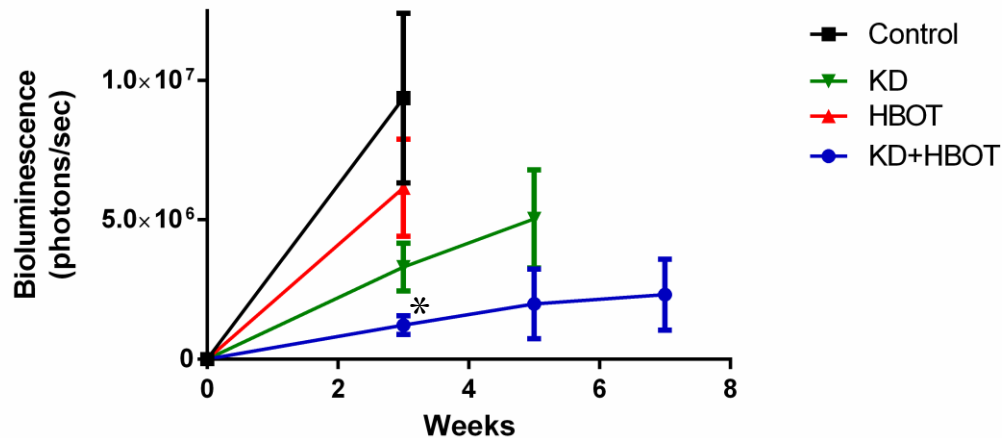


KD+HBOT inhibits tumor growth and metastatic spread

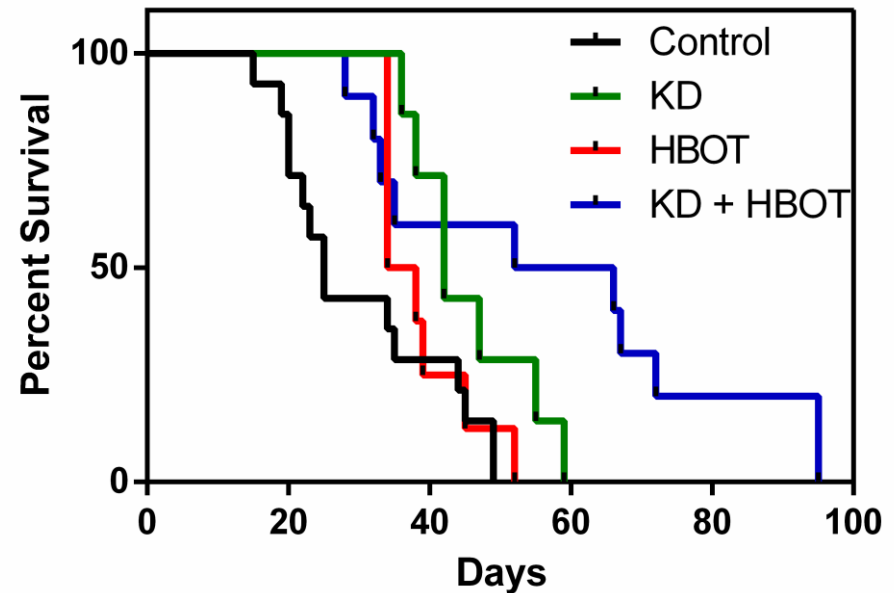
21 days post inoculation



Tumor Growth



KD+HBOT prolongs VM-M3 mouse survival



Treatment	Cohort Size (N)	Mean Survival Time (days)	Increase in Survival Time
Control (SD)	13	31.2	---
KD	8	48.9	56.7%*
HBOT	8	38.8	24.4% (NS)
KD+HBOT	11	55.5	77.9%***

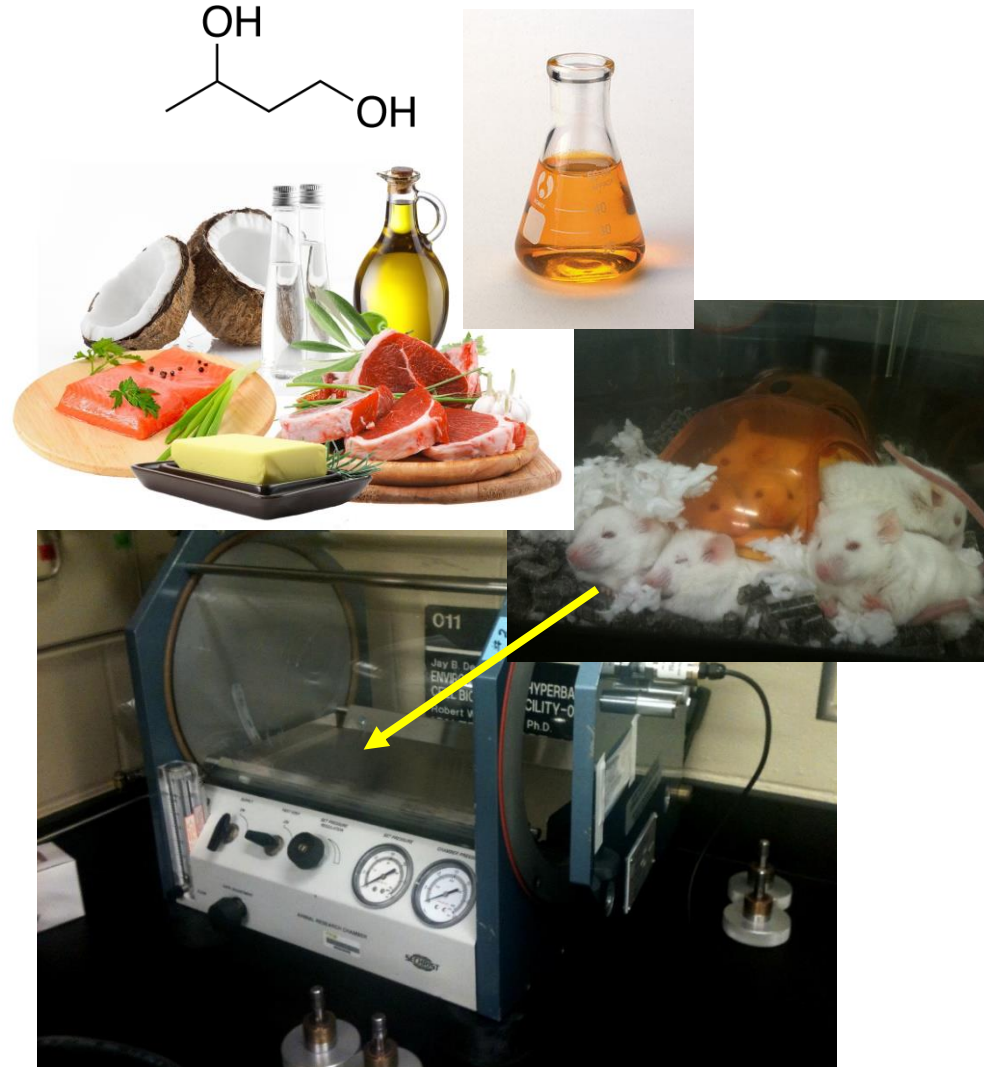
*p<0.05
***p<0.001

Combination Therapy: KD + Ketone Esters + HBOT

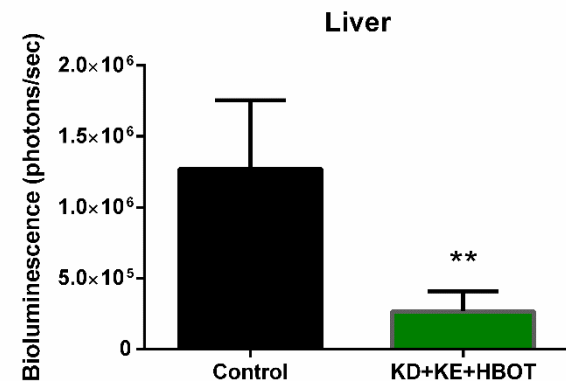
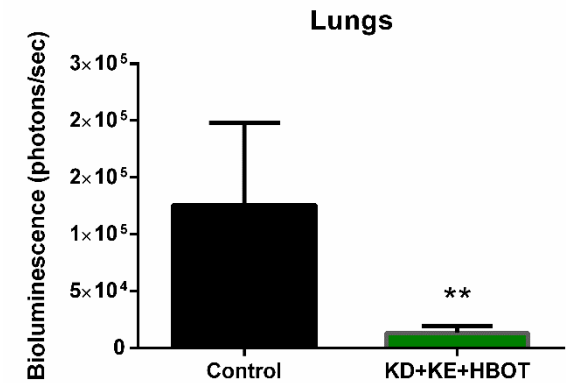
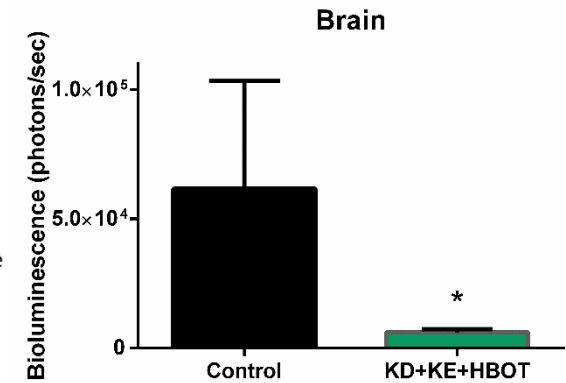
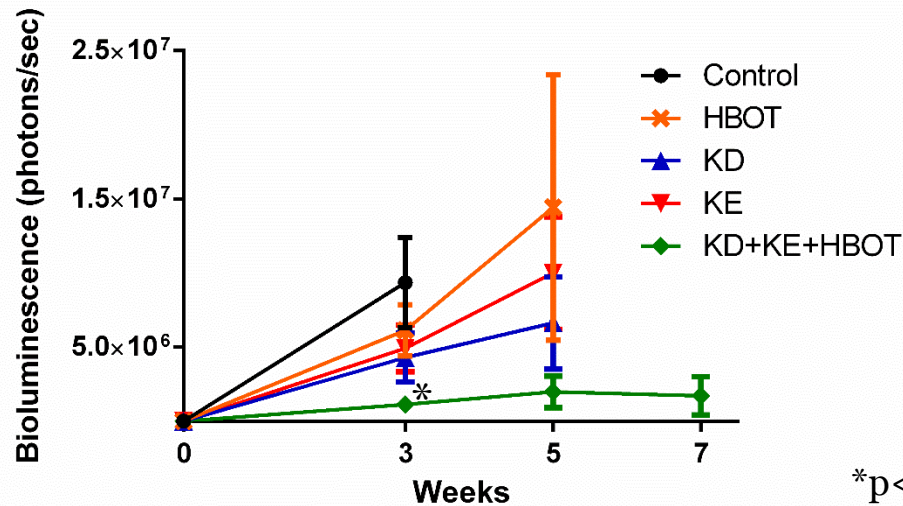
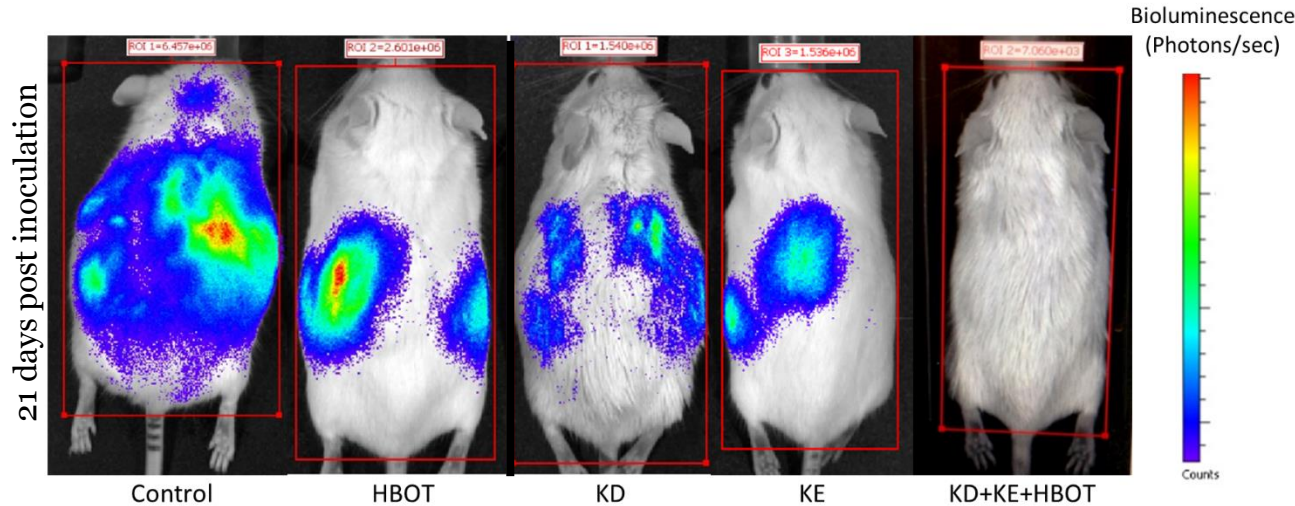
Multi-combination treatment to maximize therapeutic potential

Methods: Treatment

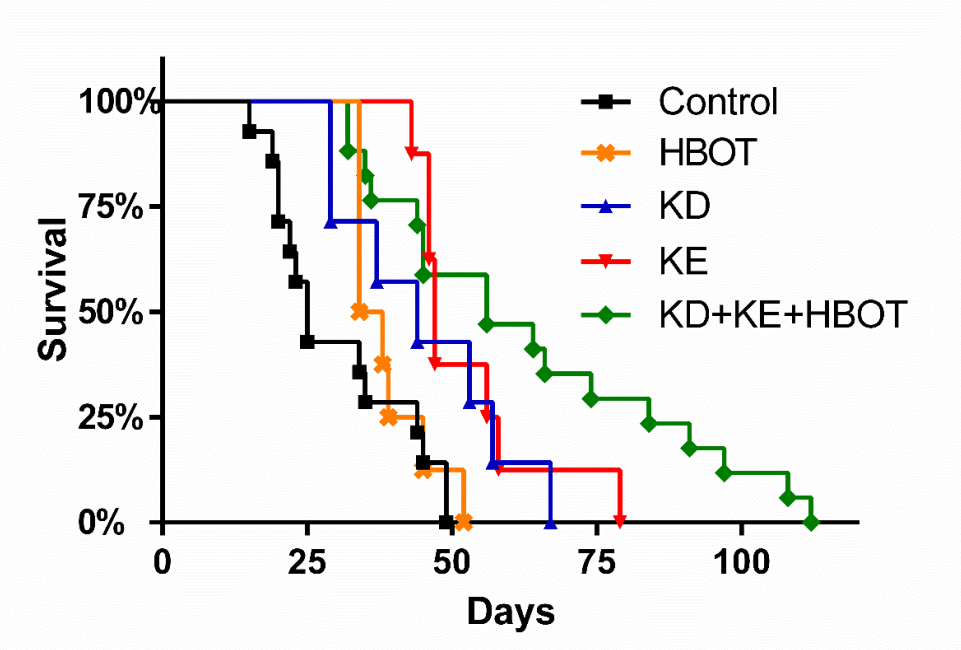
- Control: SD *ad libitum*
- KD+KE+HBOT:
 - Diet: KD-USF + 10% KE *ad libitum*
 - 1% saccharin
 - HBOT: 100% O₂, 2.5 ATA, 90 min, 3/wk



Combination therapy inhibits tumor growth and metastatic spread



Combination therapy doubles survival time in VM-M3 mice



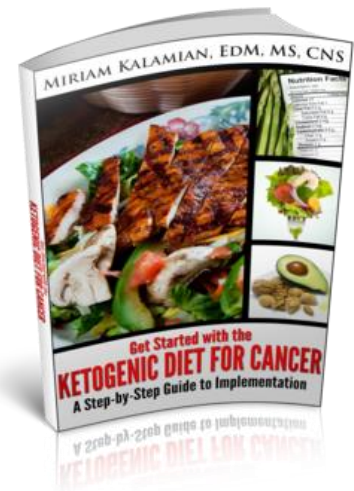
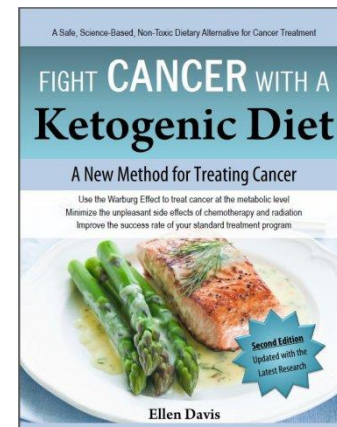
Treatment	Cohort Size (N)	Mean Survival (days)	Increase in Survival Time
Control	11	33.7	-----
HBOT	8	38.8	24.4%
KD	7	45.1	44.6%*
KE	8	52.8	69.2%***
KD+KE+HBOT	17	63.4	103.0%***

Practical Guidelines for Implementing Metabolic Therapy

- * Patients should be monitored by their own physician, while working closely with the Registered Dietitian

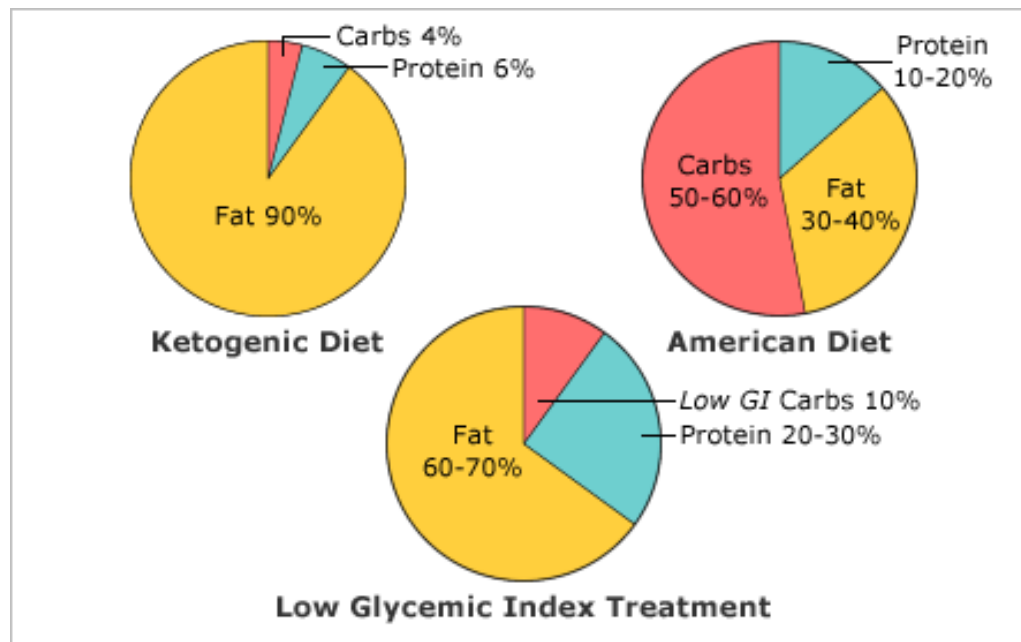


THE CHARLIE FOUNDATION
for Ketogenic Therapies



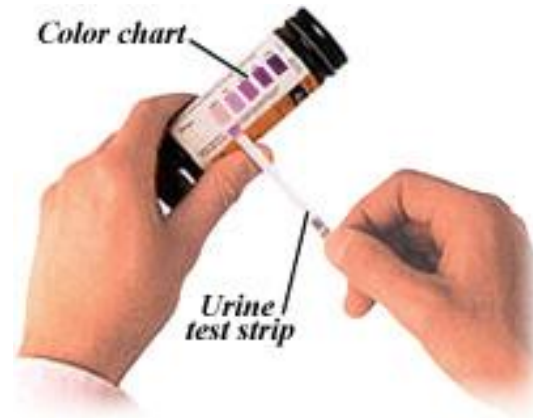
“Standard Diet” vs. “Ketogenic Diet”

- Ketogenic Diets differ from the Standard Diet in macronutrient distribution.
- Carbohydrate intake decreases to <10% of kcals.
- Ketogenic diet is NOT a HIGH PROTEIN diet



Monitoring Biomarkers

- Urine
- Blood
 - Finger stick
 - Precision Xtra®
 - Breath (Ketonix)



“Low Carb”



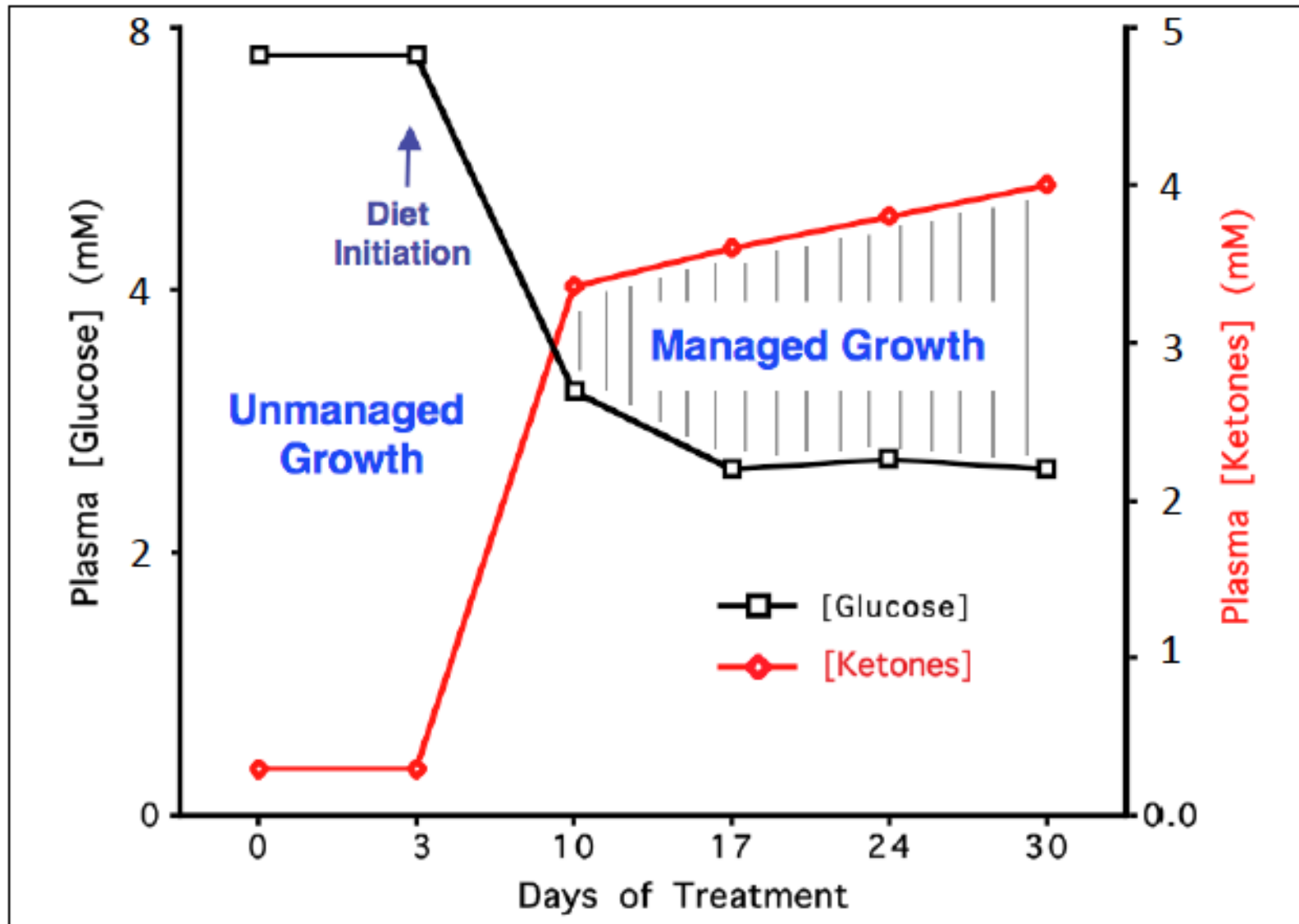
2:1 KD



4:1 KD



The Metabolic Zone



Challenges To Initiation

- Liver cancer and/or elevated liver enzymes
- Kidney stones and/or renal disease
- Pancreatitis
- Fat malabsorption issues
- Gallbladder obstruction or removal
- Medications
- Lack of support
- High cholesterol
- Food selection

Human Studies?

A Case Report Stage IV Glioblastoma

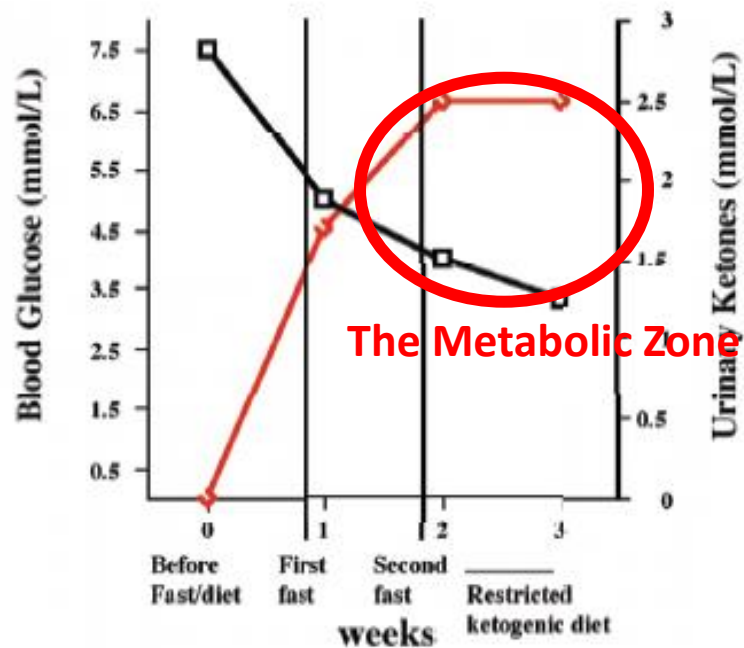


Figure 3 Levels of circulating glucose (black line) and urinary ketones (red line) in the patient during the period from January 8 to February 7, 2009. The values are within normal physiological ranges for people who maintain low calorie dieting [46].

Zuccoli G, et al.: Case Report. *Nutrition and Metabolism* (Lond). 2010 Apr 22;7:33.

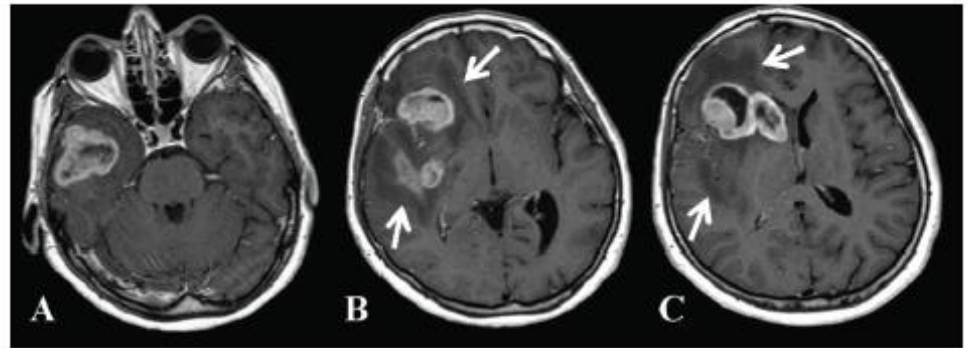


Figure 1 MRI contrast enhanced images of a large multi-centric mass involving the right hemisphere pole. (A) Temporal pole, (B) frontal operculum, insular lobe, posterior putamen, (C) frontal operculum, head of caudate nucleus. Note the presence of peripheral edema (arrows).

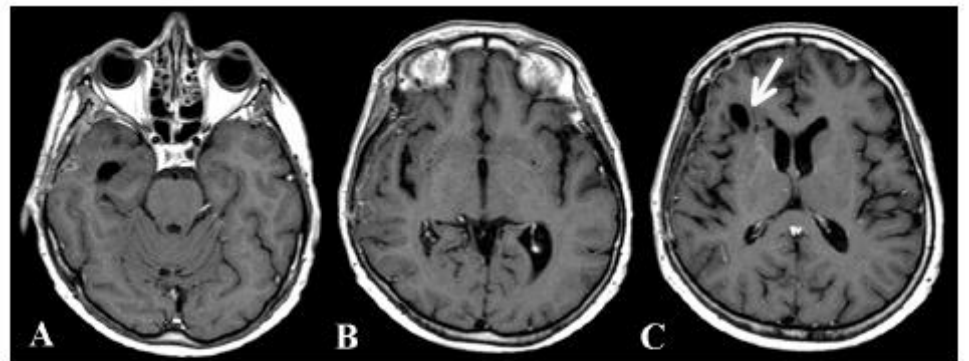


Figure 4 Brain MRI taken a few days after ending the standard radiotherapy plus concomitant temozolomide therapy together with KD-CR protocol. No clear evidence of tumor tissue or associated edema was seen. Arrow indicates porencephaly.

Clinical Trials

Schmidt et al. *Nutrition & Metabolism* 2011, 8:54
<http://www.nutritionandmetabolism.com/content/8/1/54>



RESEARCH

Open Access

Effects of a ketogenic diet on the quality of life in 16 patients with advanced cancer: A pilot trial

Melanie Schmidt, Nadja Pfetzer, Micheal Schwab, Ingrid Strauss and Ulrike Kämmerer*

Nutrition 28 (2012) 1028–1035



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Applied nutritional investigation

Targeting insulin inhibition as a metabolic therapy in advanced cancer: A pilot safety and feasibility dietary trial in 10 patients

There has been a surge in
New Clinical Trials

Rank	Status	Study
1	Recruiting	<u>Ketogenic Diet With Concurrent Chemoradiation for Pancreatic Cancer</u> Condition: Pancreatic Neoplasms Intervention: Dietary Supplement: Ketogenic diet
2	Recruiting	<u>Ketogenic Diet With Chemoradiation for Lung Cancer (KETOLUNG)</u> Condition: Carcinoma, Non-Small-Cell Lung Intervention: Dietary Supplement: Ketogenic diet
3	Unknown †	<u>The Effect of Ketogenic Diet on Malignant Tumors- Recurrence and Progress</u> Condition: Malignant Tumors Interventions: Other: Nutritional support with Standard diet; Other: Nutritional intervention with the Ketogenic diet
4	Recruiting	<u>Pilot Study of a Metabolic Nutritional Therapy for the Management of Primary Brain Tumors</u> Condition: Glioblastoma Intervention: Dietary Supplement: Energy restricted Ketogenic Diet (ERKD) (Metabolic Nutritional Therapy)
5	Recruiting	<u>Ketogenic Diet as Adjunctive Treatment in Refractory/End-stage Glioblastoma Multiforme: a Pilot Study</u> Condition: Glioblastoma Multiforme Intervention: Other: ketogenic diet
6	Recruiting	<u>Ketogenic Diet in Advanced Cancer</u> Condition: Cancer

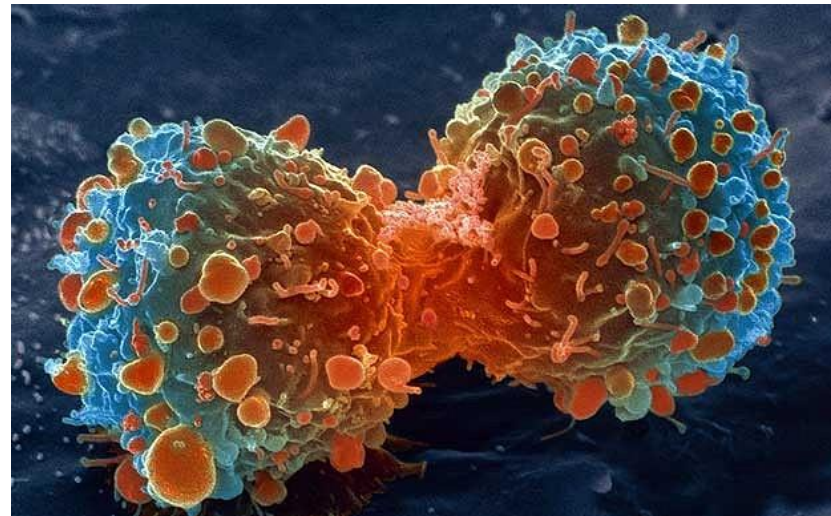
Implications for Cancer Therapy

- Non-toxic, cost-effective, readily implementable
- Possibly effective against aggressive, late-stage cancers
- Potential synergy with standard care
- Protection against toxic effects of standard care



Future Directions

- Determine most effective dosing protocol for KD, ketone supplements and HBOT
- Compare to “Standard American Diet”
- Evaluate therapies in other cancer models
- Investigate mechanism of action
- Combine with standard care and other metabolic therapies
- Clinical trials



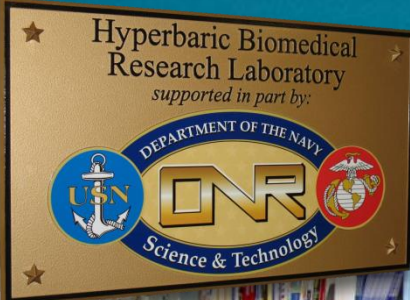
Questions and Topics of Discussion

- **All Cancers Responsive?**
- **Dose of HBOT?**
- **Low Carb vs Ketogenic?**
- **Integration with other Therapies?**

Resources

- www.ketogenic-diet-resource.com
- www.dietarytherapies.com
- <http://www.charliefoundation.org/>
- <http://www.rsg1foundation.com/>
- <http://www.nutritionchoices.ie/>
- www.ketonutrition.org

Questions ?



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Effect of High Pressure Oxygen

Healthy Cells

Cancer Cells

