Low Carb Breckenridge

Functional Medicine and Ketogenic Nutrition

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About Me

- Board certified in internal, integrative and obesity medicine
- Practice functional medicine at a private practice in Pasadena, CA.
- Member of the Institute of Functional Medicine.

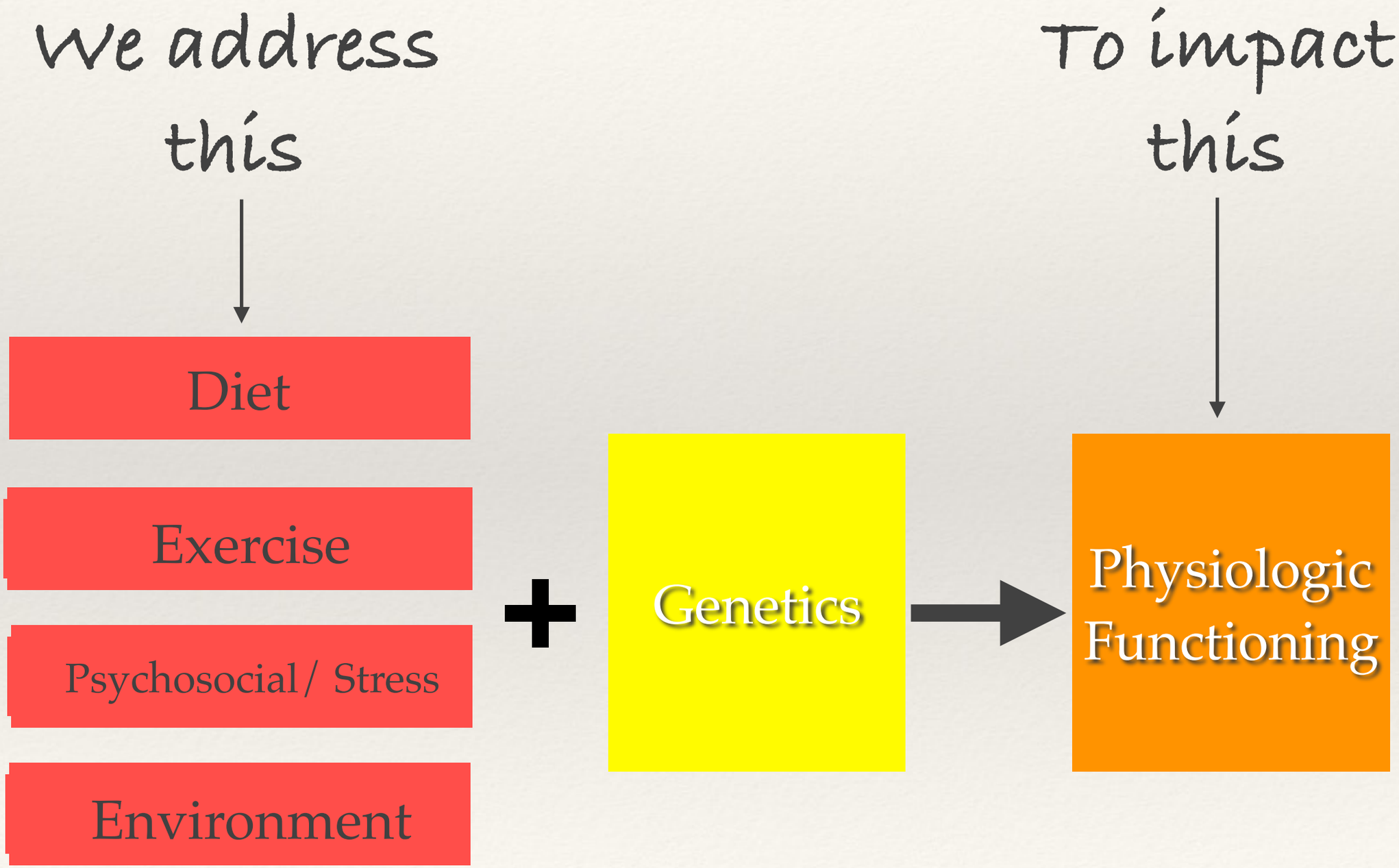
Objectives

- Explain what functional medicine is
- Why we need functional medicine
- Differentiate between functional and conventional medicine in the treatment of chronic disease
- Explain how and when ketogenic nutrition is successfully used in the functional medicine model

What is Functional Medicine?

- It is a systems based approach that focusses on reversing "the dysfunctions" that contributed to a disease state.
- The "dysfunctions" for each of us are the result of lifestyle, environment and genetic pre-disposition.

What is Functional Medicine?



What is Functional Medicine?

- Functional medicine is patient centered.
- Functional medicine is evidence based.
- Functional medicine looks for the root cause.
- Functional medicine is concerned with disease prevention.
- Functional medicine educates people.

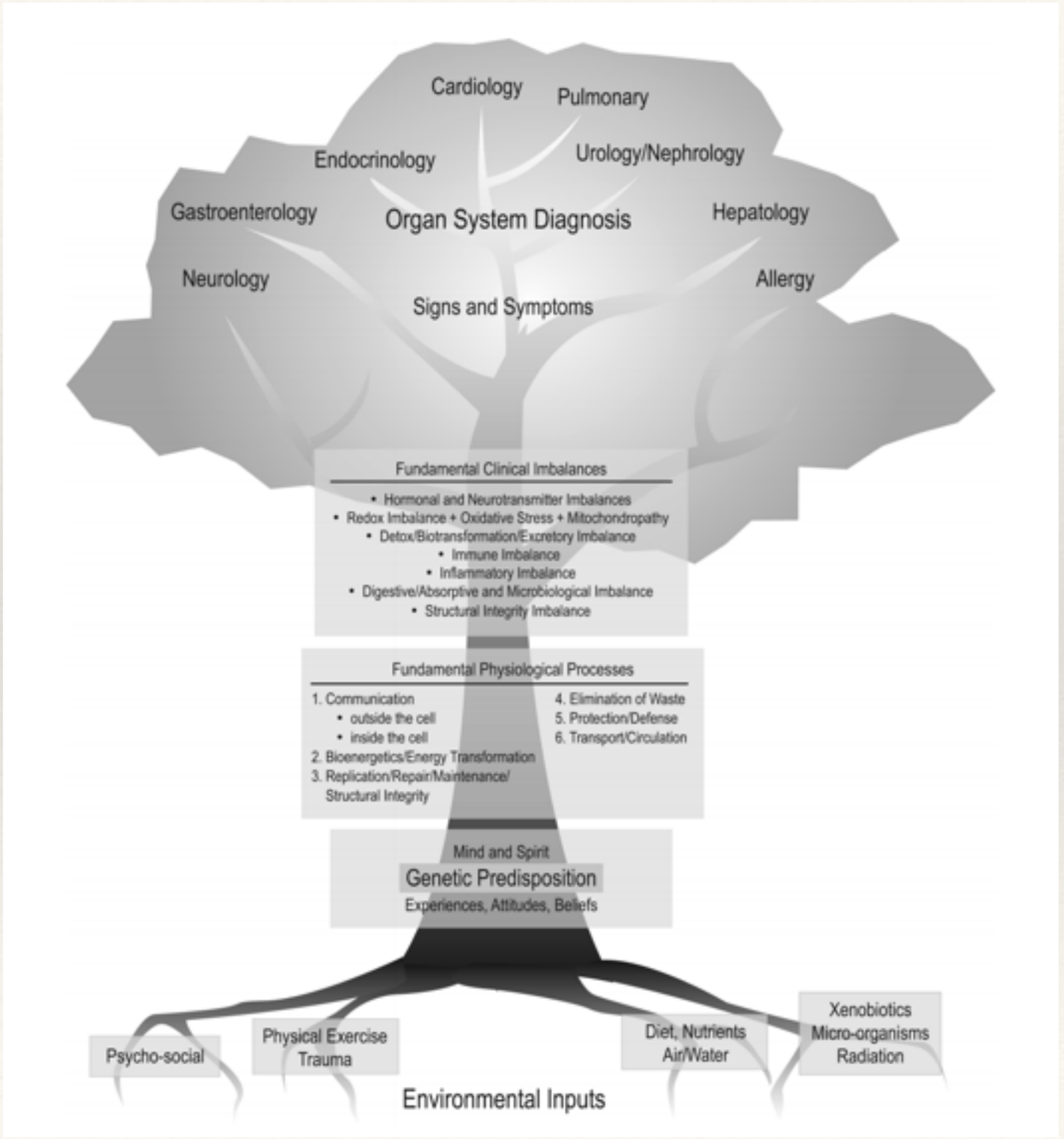
Functional Medicine is Balance

- Functional medicine is whole system balance
- With the goal of
  - 1. Understanding what causes imbalance.
  - 2. Removing what causes the imbalance.
  - 3. Providing what leads balance.

Functional Medicine is Balance

- The imbalances are examined by:
  - Communication (hormonal and neurotransmitter imbalance)
  - Energy (mitochondrial imbalances & ox/redox)
  - Biotransformation (detoxification imbalances)
  - Assimilation (digestive and absorptive imbalances)
  - Structural imbalances (sub-cellular membranes to musculoskeletal structure)
  - Defense and Repair (immune/inflammation)
  - Transport (cardiovascular and lymphatic)

What is Functional Medicine?



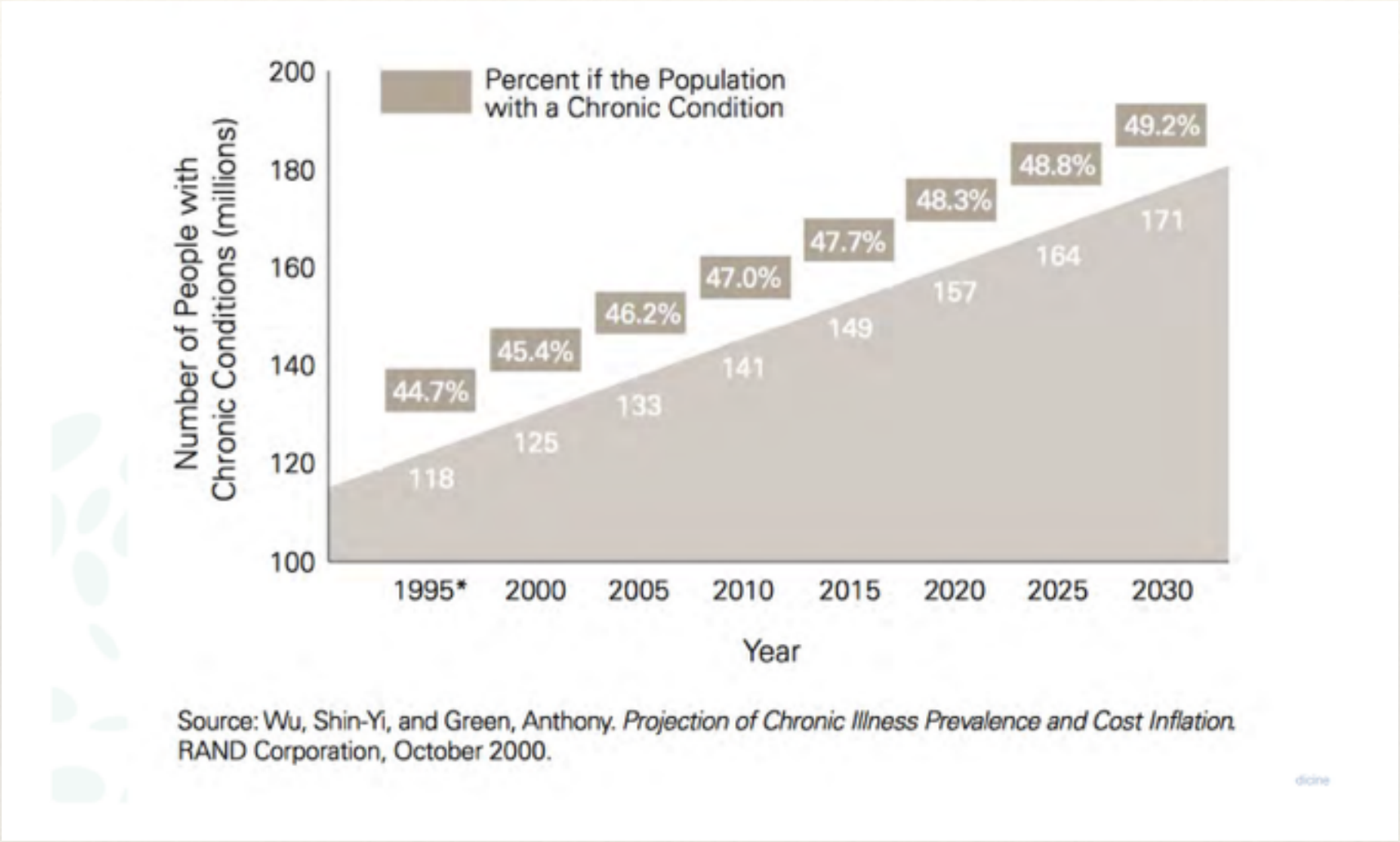
Why functional medicine

- Functional medicine is a dynamic approach to assess, prevent and treat complex **chronic** disease.
- 70-90% of US deaths are due to non-genetic modifiable disease.

- Functional medicine looks to treat these modifiable factors

Jones, D. 2010. Textbook of Functional Medicine.Gig Harbor, WA: Institute for Functional Medicine.

Why we need functional medicine

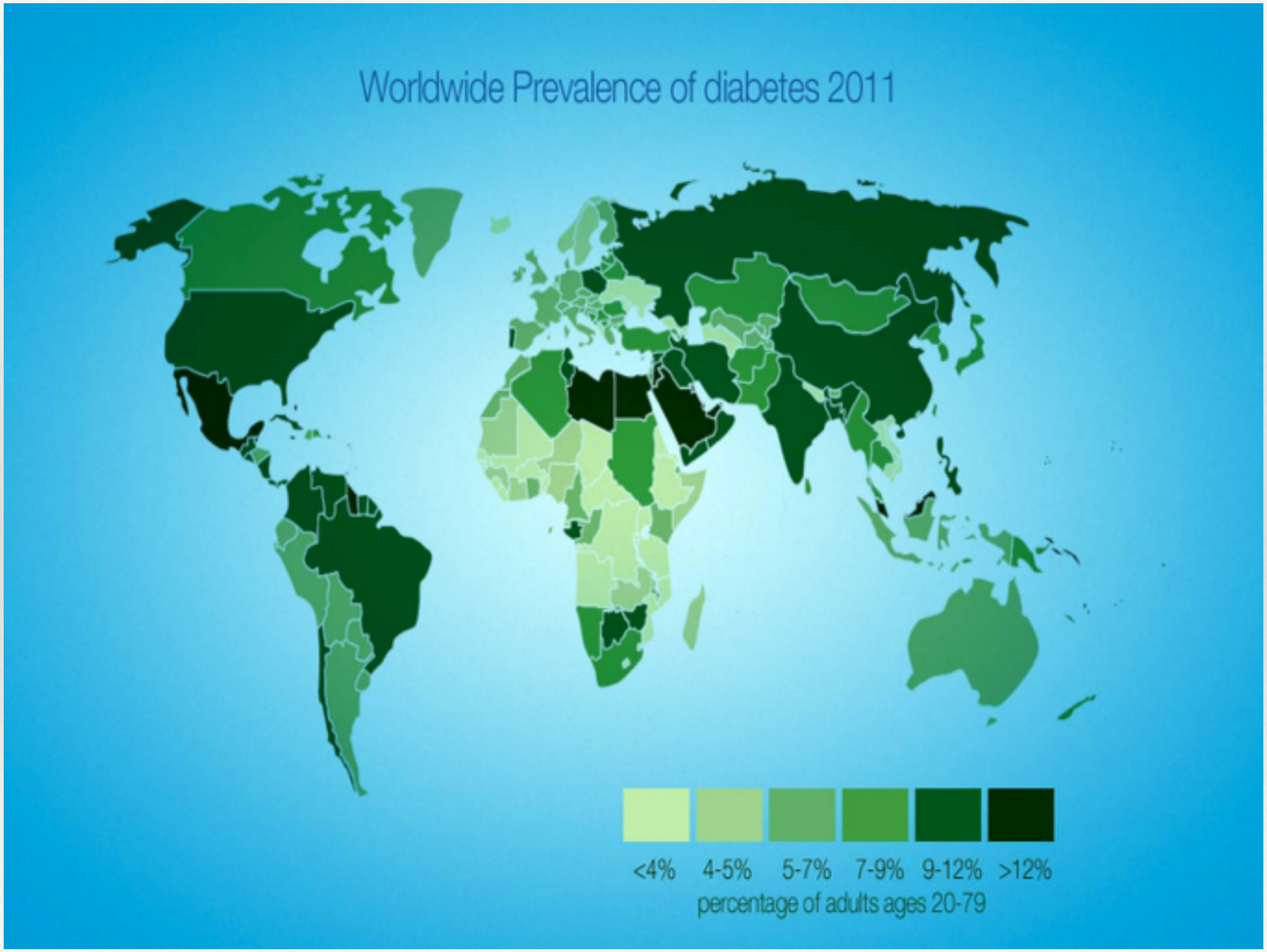


Source: Wu, Shin-Yi, and Green, Anthony. *Projection of Chronic Illness Prevalence and Cost Inflation.* RAND Corporation, October 2000.

- Research has shown that the current cost to our society for coronary artery disease, diabetes and obesity is a half trillion dollars.

Jones, D. 2010. Textbook of Functional Medicine.Gig Harbor, WA: Institute for Functional Medicine.

Why we need functional medicine



MAYO CLINIC

EDITORIAL

August 2013
Volume 88
Number 8

MAYO CLINIC
PROCEEDINGS

How Many Contemporary Medical Practices Are Worse Than Doing Nothing or Doing Less?

See also page 790

How many contemporary medical practices are not any better than or are worse than doing nothing or doing something else that is simpler or less expensive? This is an important question, given the negative repercussions for patients and the health care system of continuing to endorse futile, inefficient, expensive, or harmful interventions, tests, or management strategies. In this issue of *Mayo Clinic Proceedings*, Prasad et al[1] describe the frequency and spectrum of medical reversals determined from a review of all the articles published over a decade (2001-2010) in *New England Journal of Medicine* (*NEJM*). Their work extends a previous effort[2] that had focused on data from a single year and had suggested that almost half of the established medical practices that are tested are found to be no better than a less expensive, simpler, or easier therapy or approach. The results from the current larger sample of articles[1] are consistent with the earlier estimates: 27% of the original articles relevant to medical practices published in *NEJM* over this decade pertained to testing established practices. Among them, reversal and reaffirmation studies were approximately equally common (40.2% vs 38%). About two-thirds of the medical reversals were recommended on the basis of randomized trials. Even though no effort was made to evaluate systematically all evidence on the same topic (eg, meta-analyses including all studies published before and after the specific *NEJM* articles), the proportion of medical reversals seems alarmingly high. At a minimum, it poses major questions about the validity and clinical utility of a sizeable portion of everyday medical care.

Are these figures representative of the medical literature and evidence base at large? The sample assembled by Prasad et al is highly impressive, but it accounts for less than 1% of all randomized trials published in the same decade (an estimated >10,000 per year) and an even more infinitesimal portion of other types of study designs. If one could extrapolate from this sample by proportion, perhaps there have been several tens of thousands of medical reversal studies across all 23 million articles entered to date in PubMed. One has to be cautious with extrapolations, however. *New England Journal of Medicine* is clearly different from other journals in many ways besides having the highest impact factor among the list of 155 general and internal medicine journals.[3] It is widely read, and it has high visibility and impact both on the mass media and on medical practitioners. In this regard, the collection of 146 medical reversals reviewed by Prasad et al is a compendium of widely known, visible examples, and thus it can make excellent reading for medical practitioners and researchers, teachers, and trainees. At the same time, this characteristic is also a disadvantage: the articles published by *NEJM* are a highly selected sample, probably susceptible to publication and selective outcome reporting bias. There is substantial empirical evidence that the effect sizes of randomized trials published in *NEJM*, *Lancet*, or *JAMA* (the top 3 general and internal medicine journals in terms of impact factor[3]) are markedly inflated, in particular for small trials[4]; conversely, the effect sizes for large trials are similar to those seen in large trials on the same topic in other journals.[4] The interpretation of the results in *NEJM* is also likely to be more exaggerated compared with other journals because authors may feel pressured to claim that the results are impressive in order to get their work published in such a

creasingly focus on employee wellness, on one side, and disease management, on the other. Research funding increasingly sup-

tors, hospitals, and health systems will shift their activities from delivering health services within their walls toward a broader range

Center for Innovation; and the Wharton School, University of Pennsylvania — all in Philadelphia.

This article was published on August 29,

We must teach aspiring physicians about systems science…Medical school curricula should emphasize homeostasis and health, rather than only disease and diagnosis….Embedding prevention in the teaching, organization and practice of medicine can stem the unabated, economically unsustainable burden of disease.

N Engl J Med 2012;367:889-891

From Sick Care to Health Care — Reengineering Prevention into the U.S. System

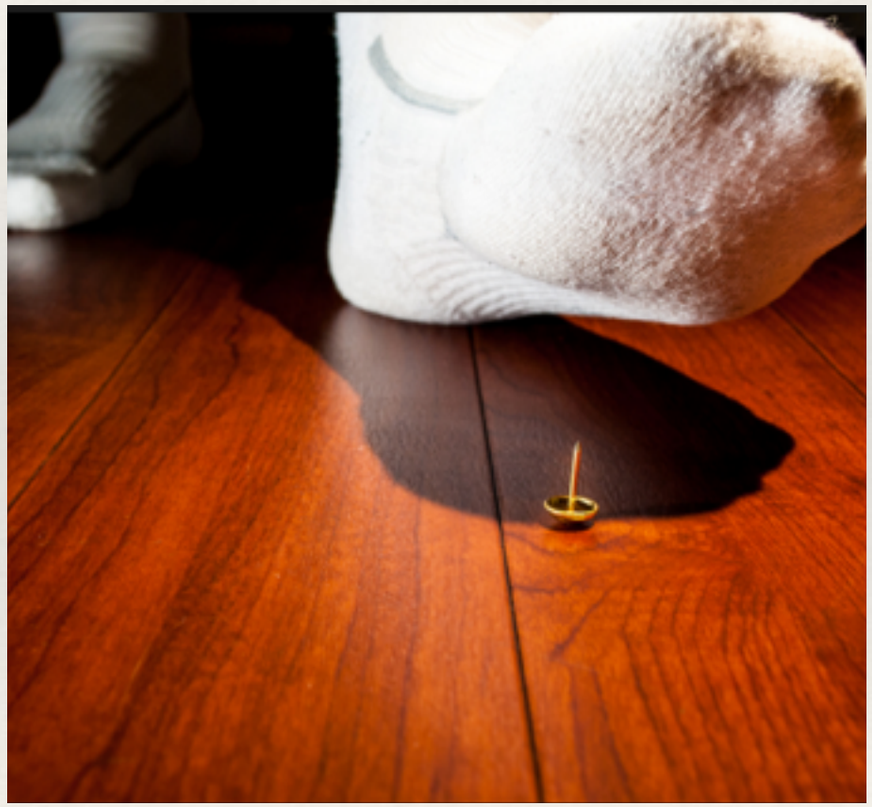
Farshad Fani Marvasti, M.D., M.P.H., and Randall S. Stafford, M.D., Ph.D.

Although the United States pays more for medical care than any other country, problems abound in our health care system. Unsustainable costs, poor outcomes, frequent medical errors, poor patient satisfaction, and worsening health disparities all point to a need for transformative change.[1] Simultaneously, we face widening epidemics of obesity and chronic disease. Cardiovascular disease, cancer, and diabetes now cause 70% of U.S. deaths and account for nearly 75% of health care expenditures.[2] Unfortunately, many modifiable risk factors for chronic diseases are not being addressed adequately. A prevention model, focused on forestalling the development of disease before symptoms or life-threatening events occur, is the best solution to the current crisis.

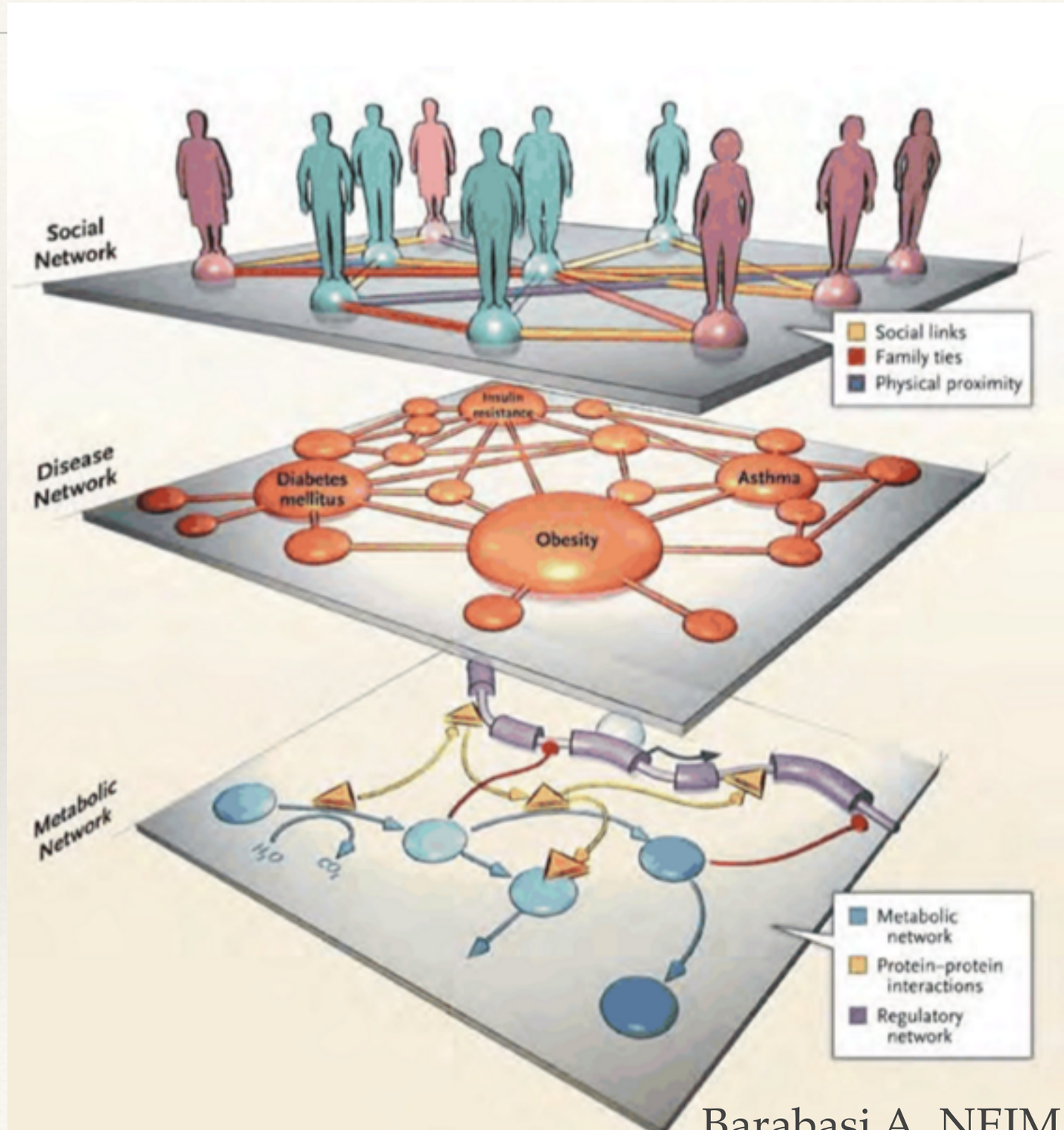
Disease prevention encompasses all efforts to anticipate the genesis of disease and forestall its progression to clinical manifestations. A focus on prevention does not imply that disease can be eliminated but instead embraces Fries's model of "morbid-

A Systems Based Approach

- We need a new way to research
- Sid Baker, MD - tack rules
  - 1. If standing on a tack, it takes a lot of aspirin to make it feel better.
  - 2. If standing on 2 tacks, taking one tack out does not make you 50% better.

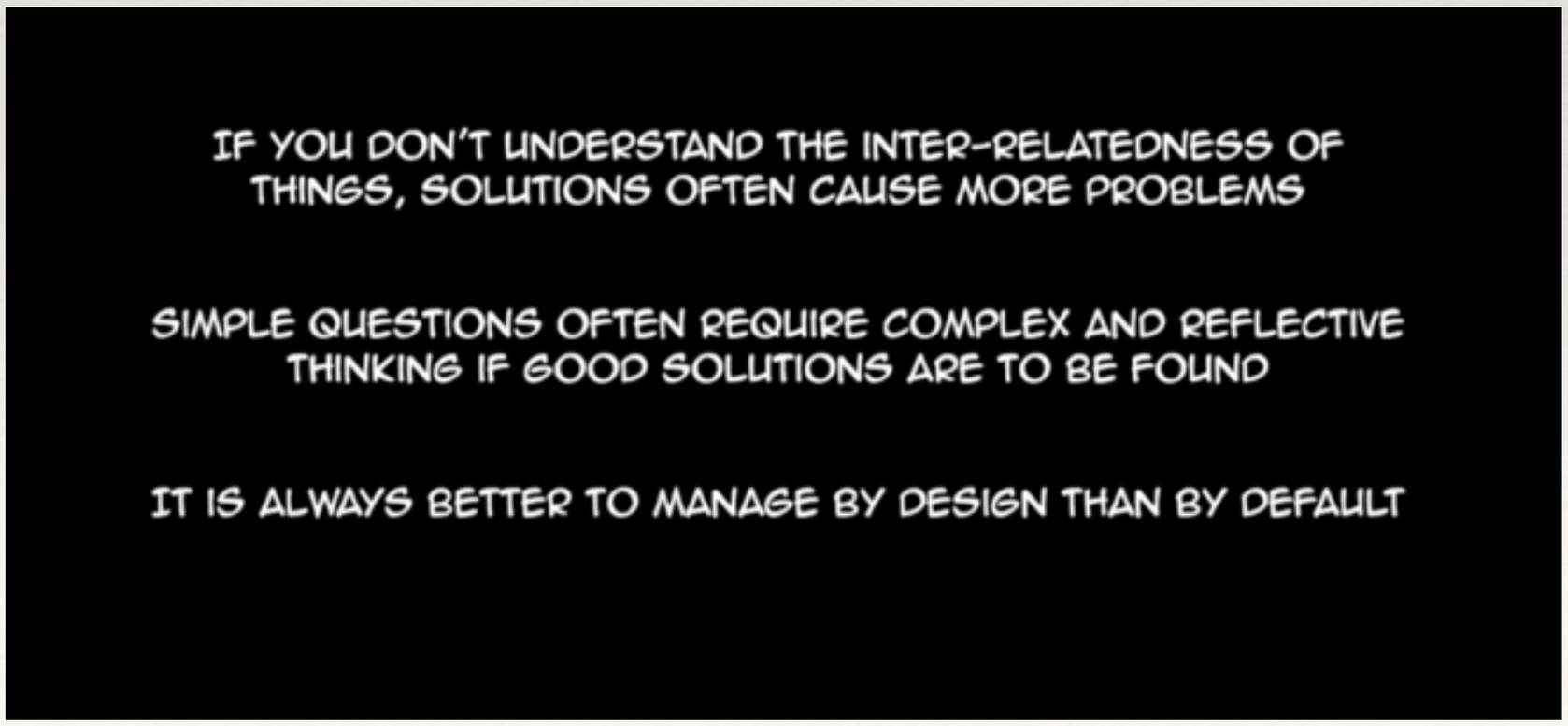


Functional Medicine Is a Systems Approach



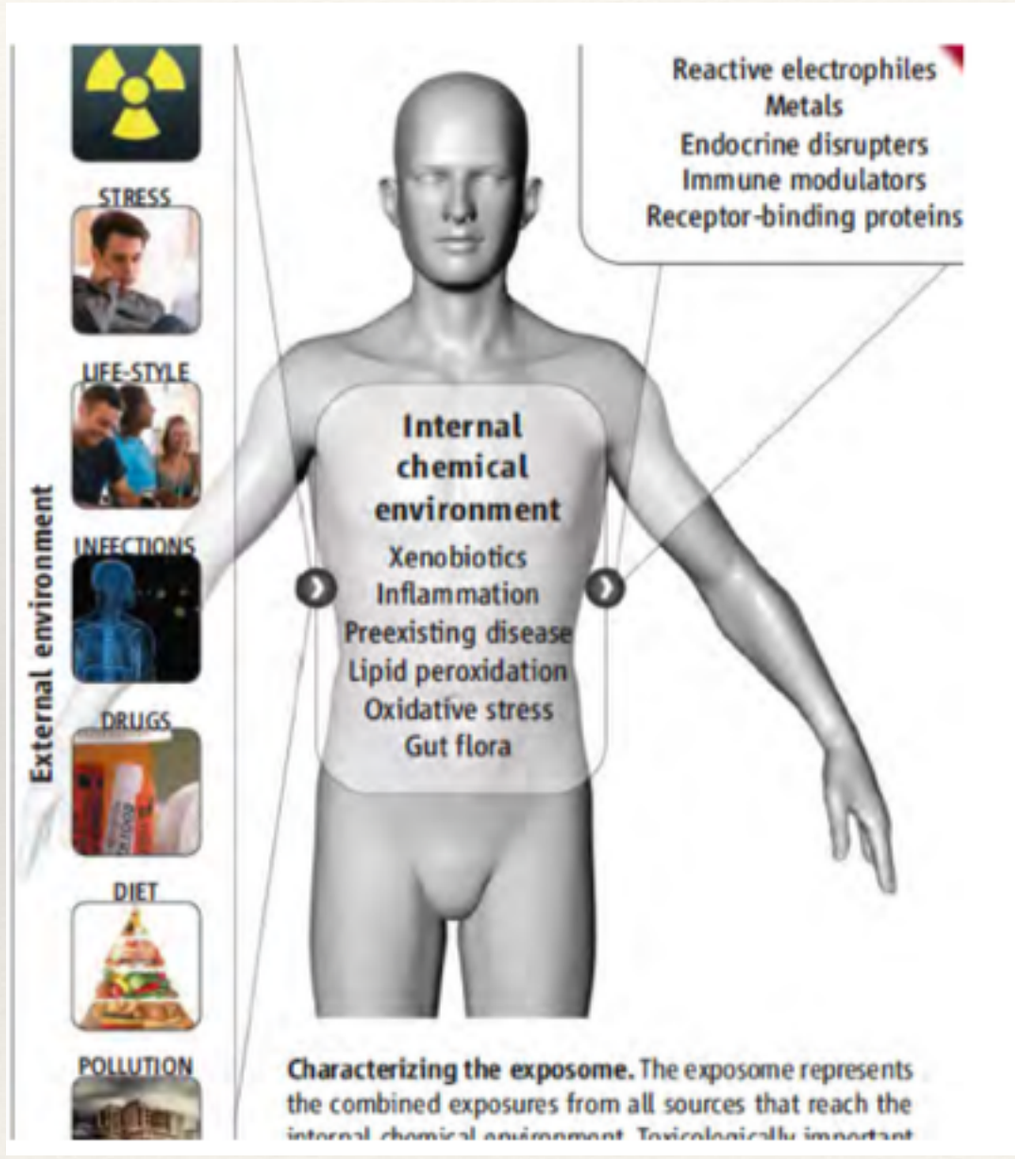
Barabasi A. NEJM 2007; 357:404-407.

Functional Medicine is a Systems Approach



Our Phenotype Is Modifiable

- Human genome has 20,000 genes -far fewer than we thought
- Our phenotypes is a function of genotype and environment
- 90% of chronic disease is driven by the environment- your "exposome"



Journal of Exposure Science and Environmental Epidemiology (2011) 21, 5–9

What is the best way to?

- Optimize 10,000s genes
- Improve protein net works
- Minimize inflammation
- Improve cell signal transduction factors
- Change expression of biology.

Food is Information

https://www.dietdoctor.com/low-carb#advice

Food is Information

- Food regulates all systems in the body
- Chronic disease is a food borne illness
- A calorie is not a calorie

Ketogenic Nutrition and Functional Medicine

- What type of nutrition can:
  - lower inflammation
    - improve metabolism
      - decrease seizures
        - decrease migraines
          - decrease pain perception
            - improve depression
              - lower the risk of heart disease?

Why Does Ketosis Work for Weight Loss?

- Direct appetite suppression from ketone bodies.
- Increases CCK production (helping you to feel satiated).
- Ketosis suppresses the increases of ghrelin (the hunger hormone) that occur with weight loss.
- Because it decreases insulin levels there is a reduction in lipogenesis and increased lipolysis.
- Increased metabolic cost of gluconeogenesis.

Sumithran P et al, Ketosis and appetite-mediating nutrients and hormones after weight loss. Eur J Clin Nutr. 2013 Jul; 67(7):759-64. doi: 10.1038/ejcn.2013.90. Epub 2013 May 1.
Paoli A et al. Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. Eur J Clin Nutr. 2013 Aug; 67(8): 789–796.
Dashti H et al. Long-term effects of a ketogenic diet in obese patients. Exp Clin Cardiol. 2004 Fall; 9(3): 200–205.

Why Does Ketosis Work in Metabolic Syndrome

- Many beneficial effects seen with ketogenic nutrition may be related to the decrease in circulating insulin

Hyperinsulinemia and Metabolic Syndrome

	Insulin's Mechanism			
High TG	Insulin stimulates de novo lipogensis specifically increasing Triglyceride Rich Lipoproteins (TRLs)- The liver packages TGs attempting to rid itself of excess TGs	+	Insulin prevents liver uptake of triglycerides (TGs)	→ **More TGs in circulation**
Low HDL	In high insulin states with many TRLs HDL will take up TGs	+	HDL loaded with TG will be rapidly hydrolyzed by hepatic lipase-	→ **Less circulating HDL**
Large Waist	Insulin prevents fat lipolysis (break-down)	+	Insulin promotes fat/ nutrient storage into adipose (fat) cells	→ **Increased adipose tissue**
HTN	Insulin causes increased cardiac output and vasoconstriction (sympathietic tone and vasoconstriction)	+	Insulin causes more salt and water to be retained	→ **Increased blood pressure (HTN)**
Insulin Resistance	By definition high levels of endogenous insulin - hyperinsulinemia	+	With standard amounts of glucose	→ **Insulin Resistance**

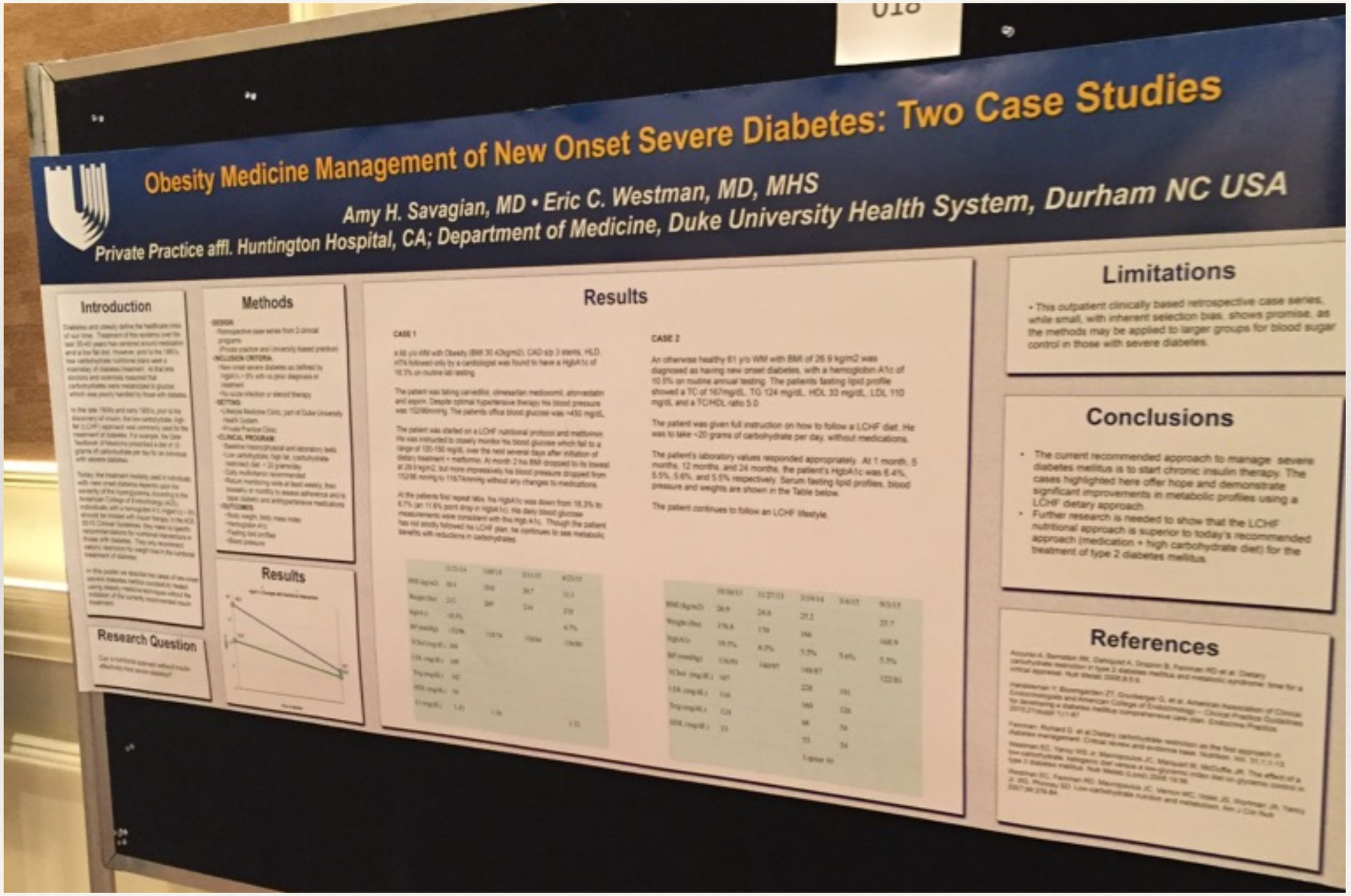
Gerber J, Cummins I, Savagian A, Challenging Traditional Cardiovascular Risk Factors, Ancestral Health Symposium, 2016

Why Does Ketosis Work for Diabetes

- Insulin resistance is the primary factor in T2DM.
- A person with insulin resistance will send a large part of dietary carbohydrate to the liver where it is converted to fat.
- When dietary carbohydrate is restricted below the level where it turns to fat- the signs and symptoms of insulin resistance improves.
- Some studies have shown improvements in metabolic profile positively correlated with ketone levels.

Jornayvaz FR et al. The role of muscle insulin resistance in the pathogenesis of atherogenic dyslipidemia and nonalcoholic fatty liver disease associated with the metabolic syndrome. Annu Rev Nutr. 2010;30:273–290.
Gumbiner B et al Effects of diet composition and ketosis on glycemia during very-low-energy-diet therapy in obese patients with non-insulin-dependent diabetes mellitus. Am J Clin Nutr. 1996;63:110–115.

Ketogenic Nutrition and Diabetes

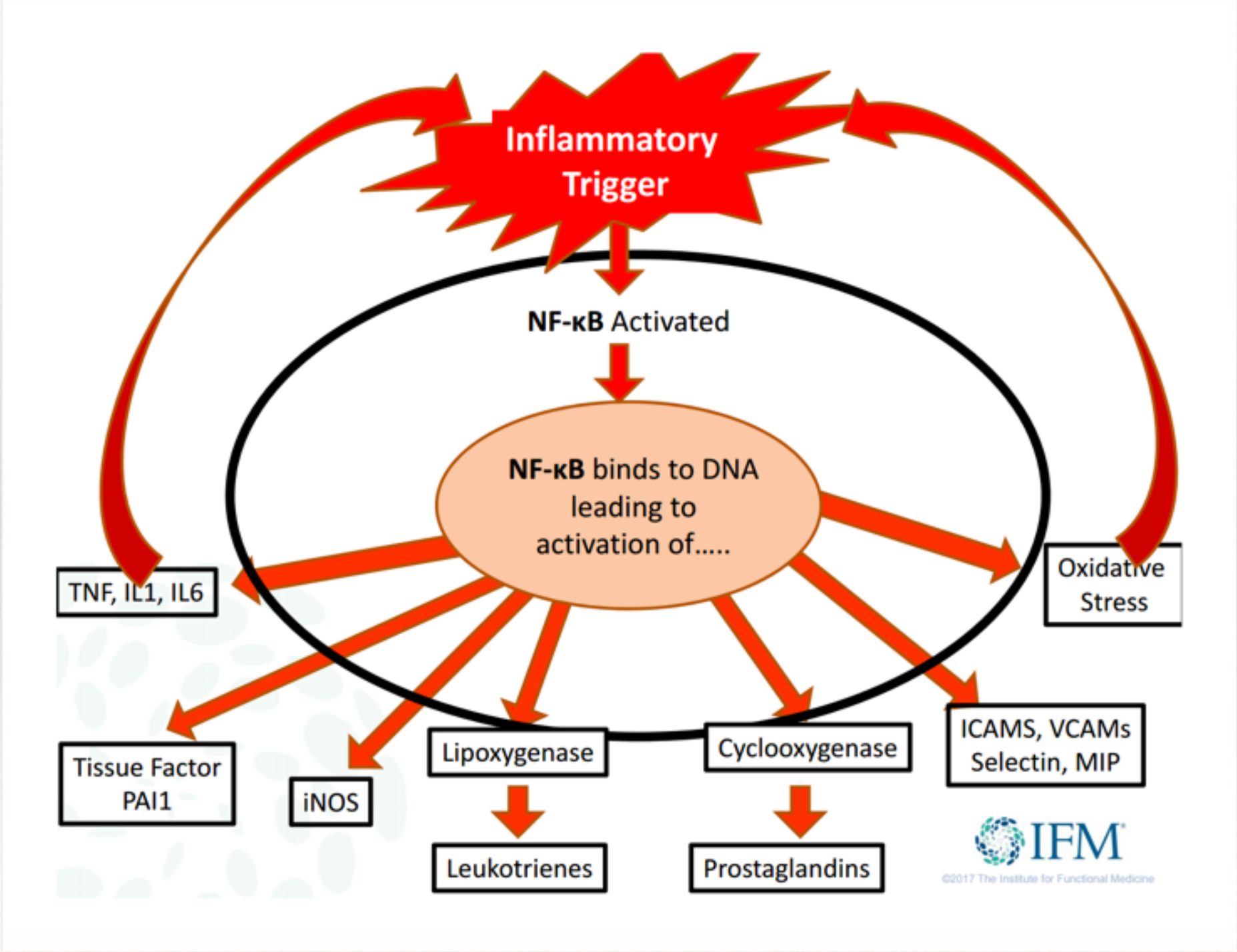


Why Does Ketosis Work for Inflammation

- Ketosis minimizes insulin release and insulin release causes inflammation.
- Inflammation-> **free radical production**.
- Free radicals attack convenient targets- often the cell membrane polyunsaturated fats.
- Membrane PUFAs are important determinants of cell function- eg insulin sensitivity.
- In studies of low fat (with higher insulin levels) vs low carb (with lower insulin levels)- markers of inflammation fall in those on the low carbohydrate diet.

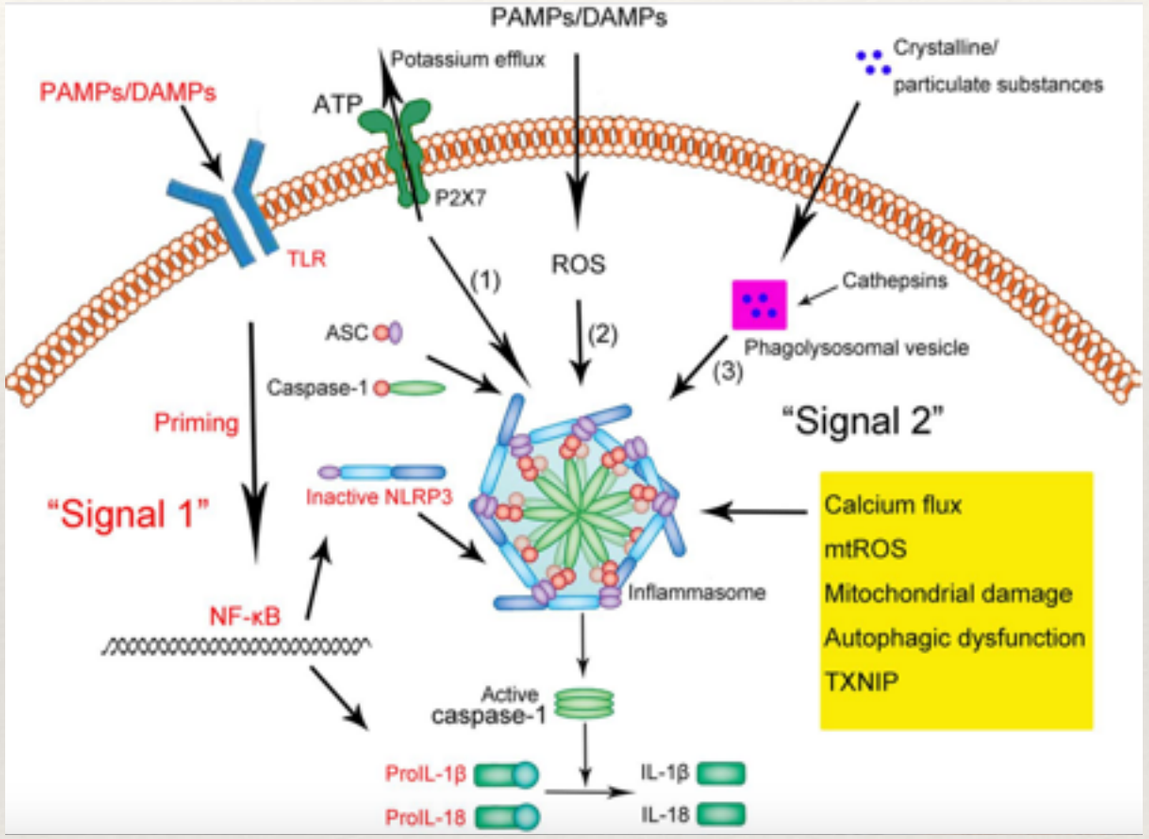
Phinney S, Volek J. 2011. The Art and Science of Low Carbohydrate Living. Beyond Obesity

Why Does Ketosis Work for Inflammation



Why Does Ketosis Work for Inflammation

- The NLRP3 inflammasome is part of our innate immune system and depends on pattern recognition.
- The NLRP3 inflammasome is responsible for the production of inflammatory cytokines il-1 and il-18.
- Drives inflammation in many chronic diseases.
- Beta hydoxybutyrate blocks the activation of the NLRP3 inflammasome.



Shao BZ et al. NLRP3 inflammasome and its inhibitors: a review. Front. Pharmacol., 05 November 2015

Youm YH, Nguyen KY, Grant RW, et al. The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. Nat Med. 2015.
Vandanmagsar B, Youm YH, Ravussin A, et al. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med. 2011;17(2):179-88.

Why Does Ketosis Work for Seizures?

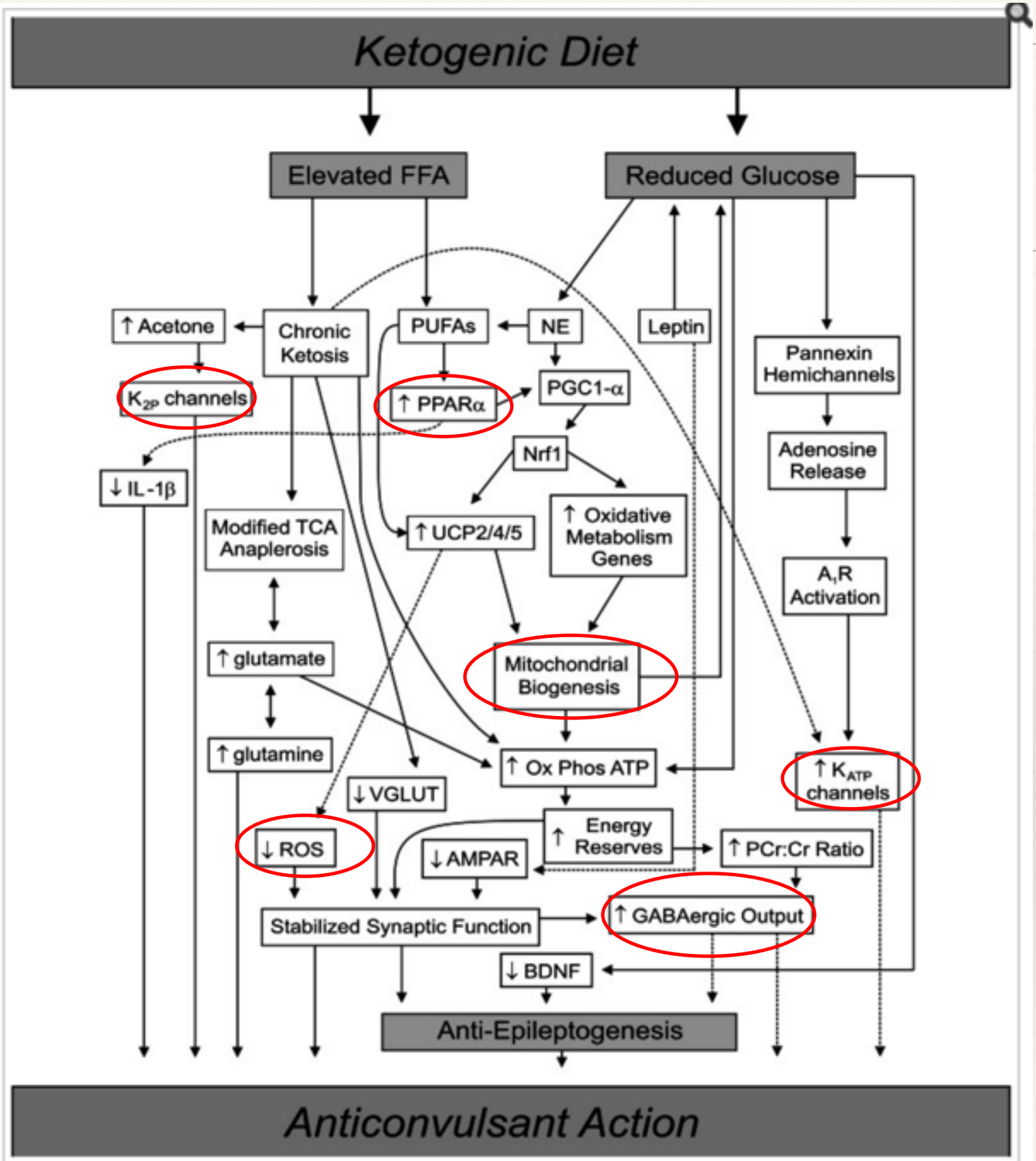


Figure 4 Hypothetical pathways leading to the anticonvulsant effects of the ketogenic diet (KD)

Masino s et al, Mechanisms of Ketogenic Diet Action, Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th edition.

Why Does Ketosis Work for Seizures

- Improved energy availability:
  - Increased beta-hydroxybutyrate
  - Increased number of mitochondria.
- Suppression of the mTOR.
- Decreases excitability of neurons through potassium channels and increased GABAergic output.
- Decreased oxidative damage.

Janigro D, Blood-brain barrier, ion homeostatis and epilepsy: possible implications towards the understanding of ketogenic diet mechanisms. Epilepsy Res. 1999 Dec;37(3):223-32.
Cullingford TE et al, The ketogenic diet upregulates expression of the gene encoding the key ketogenic enzyme mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase in rat brain. Epilepsy Res. 2002 Apr;49(2):99-107.

Why Ketosis in Depression?

- Global cerebral hypometabolism is a characteristic of the brains of depressed or manic individuals.
- Ketosis results in beneficial changes in brain-energy profile.
- Ketosis causes a decrease in intracellular sodium concentrations, which a common property of all effective mood stabilizers.

El-Mallakh RS. The ketogenic diet may have mood-stabilizing properties.Med Hypotheses. 2001 Dec;57(6):724-6.

Why Ketosis May Work in Alzhiemers

- Decades of high sugar nutrition can cause brain cells to become insulin/IGF-1 resistant. These cells can't utilize glucose well so they have a lack of fuel or cellular energy failure.
- Chronic insulin resistance /IGF resistance increases oxidative stress by increasing ROS.
- Over time the lack of fuel and the oxidative damage results in cell dysfunction and cell death.

Bredesen D, Reversal of cognitive decline: A novel therapeutic program, Aging. 2014 Sep; 6(9): 707–717.
de la Monte SM et al, Brain metabolic dysfunction at the core of Alzheimer's disease, Biochem Pharmacol. 2014 Apr 15; 88(4): 54

Why Ketosis May Work in Alzhiemer's

- Ketosis has also been shown to reduce oxidative damage through denovo glutathione biosynthesis in the mitochondria.
- Ketone bodies may be an effective energy alternative for these cells.
- Preliminary studies have shown memory improvement in patients through preposed mechanisms of reduced inflammation and enhanced energy metabolism.

Seneff S, et al, Nutrition and Alzheimer's disease: The detrimental role of a high carbohydrate diet, Eur J Intern Med (2011)
Jarrett, SG et al. The ketogenic diet increases mitochondrial glutathione levels. J. Neurochem. (2008) 106, 1044–1051.
Krikorian R, et al. Dietary Ketosis enhances memory in mild cognitive impairment. Neurobiol Aging. 2012 Feb;33(2):425.e19-27
Henderson S et al, Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial, Nutr Metab (Lond). 2009; 6: 31.

Why Ketosis May Help in Cancer

- Normal cells metabolize ketone bodies for energy, and when they use ketone bodies as energy source they produce less ROS- so there is less oxidative damage.
- Many cancer cells have deranged metabolism and can not use ketone bodies for energy. The ketone bodies actually lead to an increase in ROS in the cancer cells.
- Diets that can decrease glucose availability while elevating circulating ketone bodies may be a non-toxic therapeutic strategy for managing those tumor cells that express the Warburg effect.

Seyfried T et al, Cancer as a metabolic disease: implications for novel therapeutics, Carcinogenesis. (2014) 35 (3): 515-527.
Tan-Shalaby J et al, Modified Atkins diet in advanced malignancies - final results of a safety and feasibility trial within the Veterans Affairs Pittsburgh Healthcare System. Nutr Metab (Lond). 2016; 13: 52.

Why Ketosis May Work in Migraines

- Thought to be related to neuronal energy deficits and sterile inflammation.
- blood glucose spikes are a known trigger and those suffering from migraines often have dysfunctional glucose responses.
- Ketone bodies provide more energy than glucose with less oxidative damage.
- Ketone bodies also block the neural inflammation.
- Ketogenic nutrition improved glucose response and preventing blood glucose spikes.

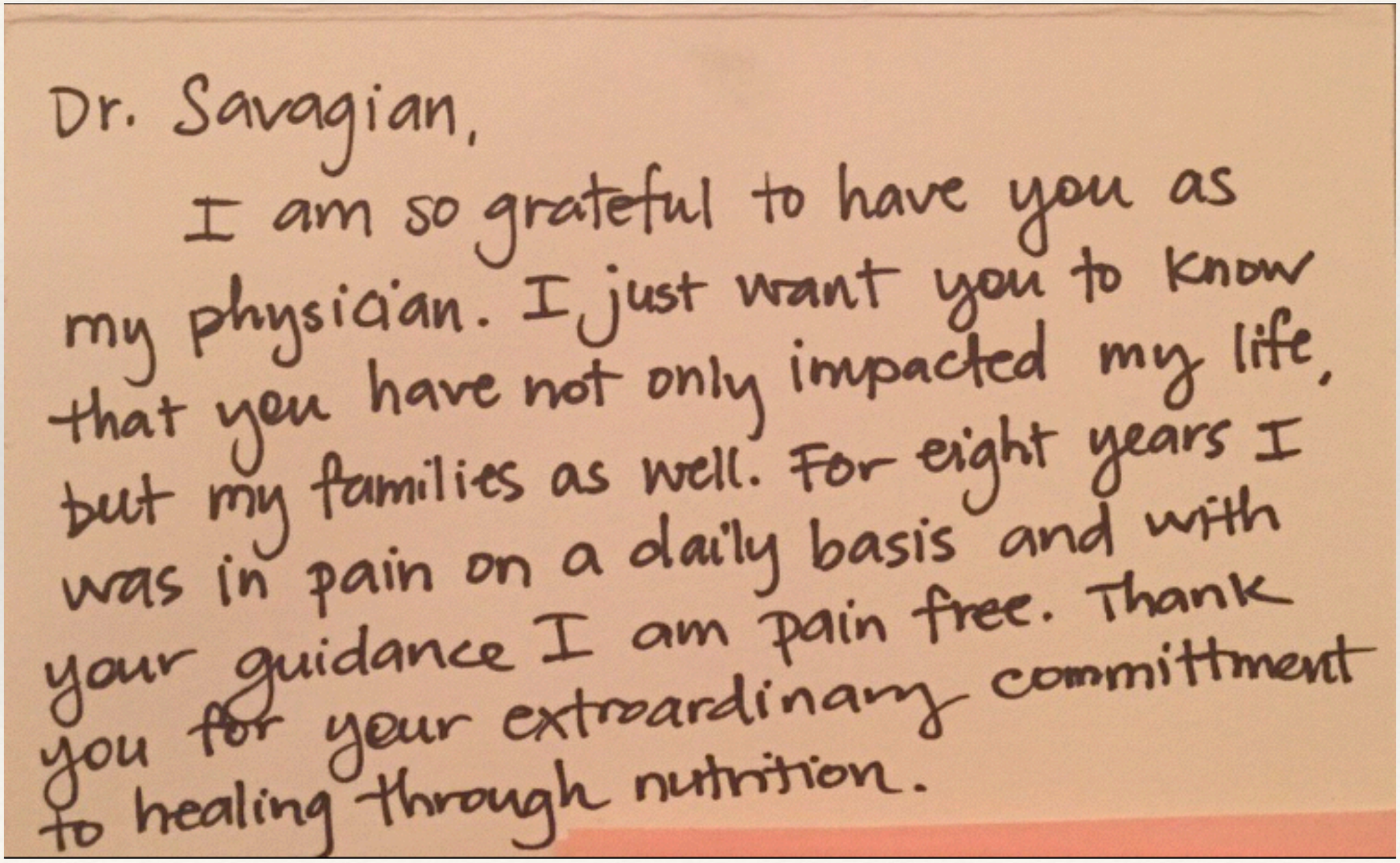
Di Lorenzo C et al, Cortical functional correlates of responsiveness to short-lasting preventive intervention with ketogenic diet in migraine: a multimodal evoked potentials study. The Journal of Headache and Pain (2016) 17:58.

Why Ketosis for Pain and Inflammation

- Thought to involve hyper excitable neurons- similar to what is seen in epilepsy.
- Also, reducing glucose appears to lower inflammation as does ketogenic nutrition itself..
- Reduction of chronic pain appears to involve inhibition of pro-inflammatory pathways involving **Nuclear Factor κB**, Signal Transduction And Transcription-1, and Nuclear Factor of Activated T-cells.

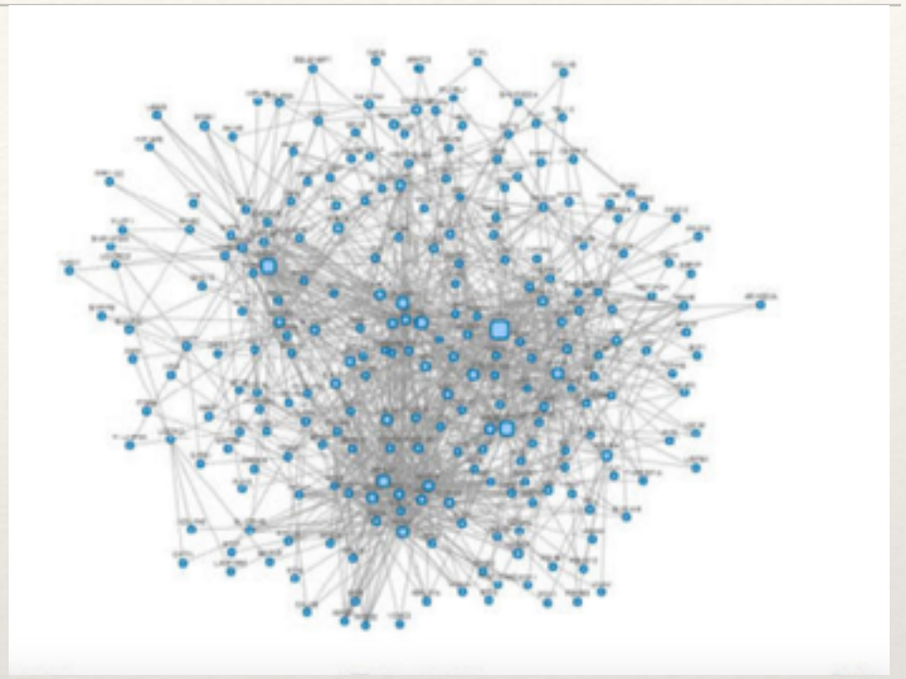
Masino S, Ruskin D. Ketogenic Diets and Pain. J Child Neurol. 2013 Aug; 28(8): 993–1001.

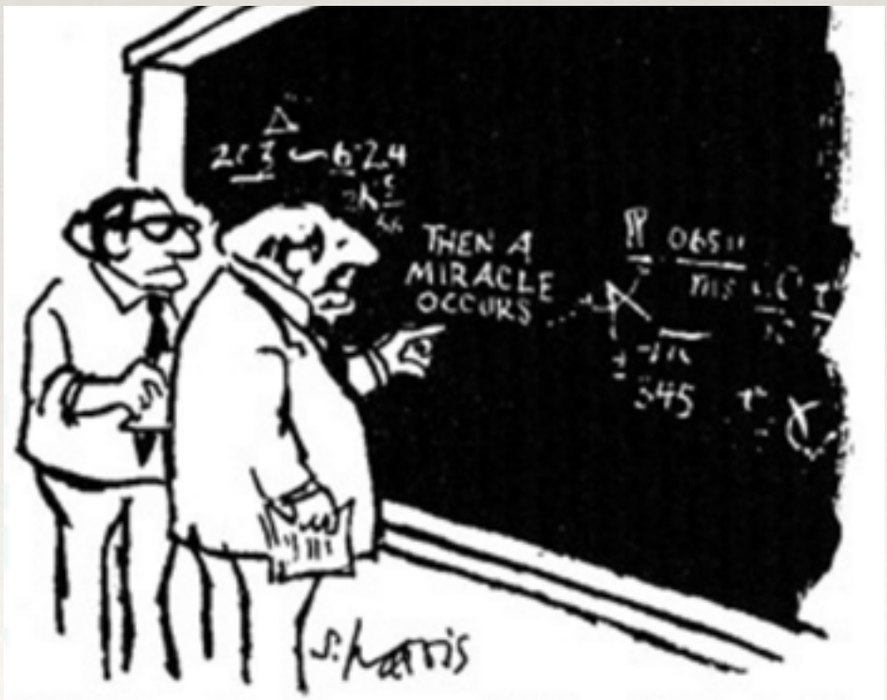
Ketosis for Pain, Inflammation & Autoimmune



Functional Medicine & Ketosis

- Illness is not random. Result of complex interactions of genes and environment.
- Complex conditions deserve thoughtful solutions.
- Ketogenic nutrition may be a beneficial component in these solutions.





"I think you should be more explicit here in step two."

Thank you!