Men's Sexual Health

Dr. N.D. Victor Carsrud
MD, MBBS, DC, MS², DABCI, DCBCN

Who is this guy?

Dr. N.D. Victor Carsrud

MD, PhD, MBBS, DC, MS², DABCI, DCBCN

- Integrative Medical practitioner
  - *Lakeline Wellness Center, Austin, Texas*
    - (512) 337-3625
    - lakelinewellnesscenter@gmail.com
    - www.LakelineWellness.com

- Board Member – ACA-CDID College of Pharmacology and Toxicology
- Independent Medical Researcher and Author
- Opinion Leader – NuMedica, Inc.
- Functional Medicine consultant

Sex is the culminant expression of vitality - the status of health necessary to attract a mate, procreate and (hopefully) bring offspring to further your lineage.

It is the culmination of cardiovascular, metabolic, endocrine, and neurologic balances needed to bring about a competitive state of reproduction.

"The 3 H's: Happy, Healthy, Horny."

Outline

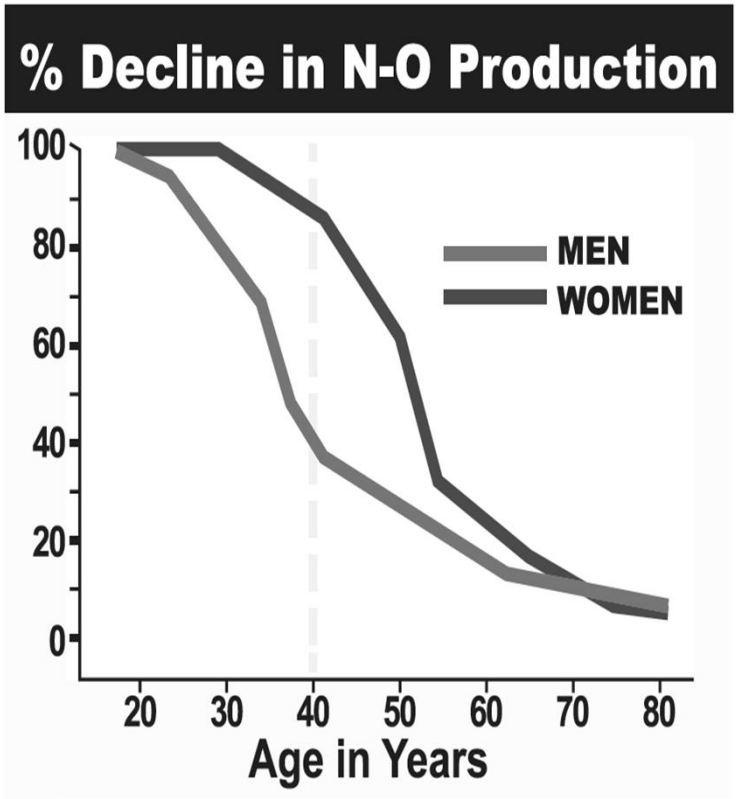
- Cardiovascular and Nitric Oxide
- Cellular health and Stem Cells
- Hormones: You've lost that lovin' feeling.
- Endocrine disruptors and Detox
- Neurotransmitter balance
- Metabolism and Chronoethnobiology
- Sociologic manifestations

Your baseline 3 supports to show improvements in basic symptoms.

1. Herbal blend to induce endogenous steroidogenesis (bid)
2. Increase nitric oxide (qd to bid)
3. Glandular based adrenal support (bid)

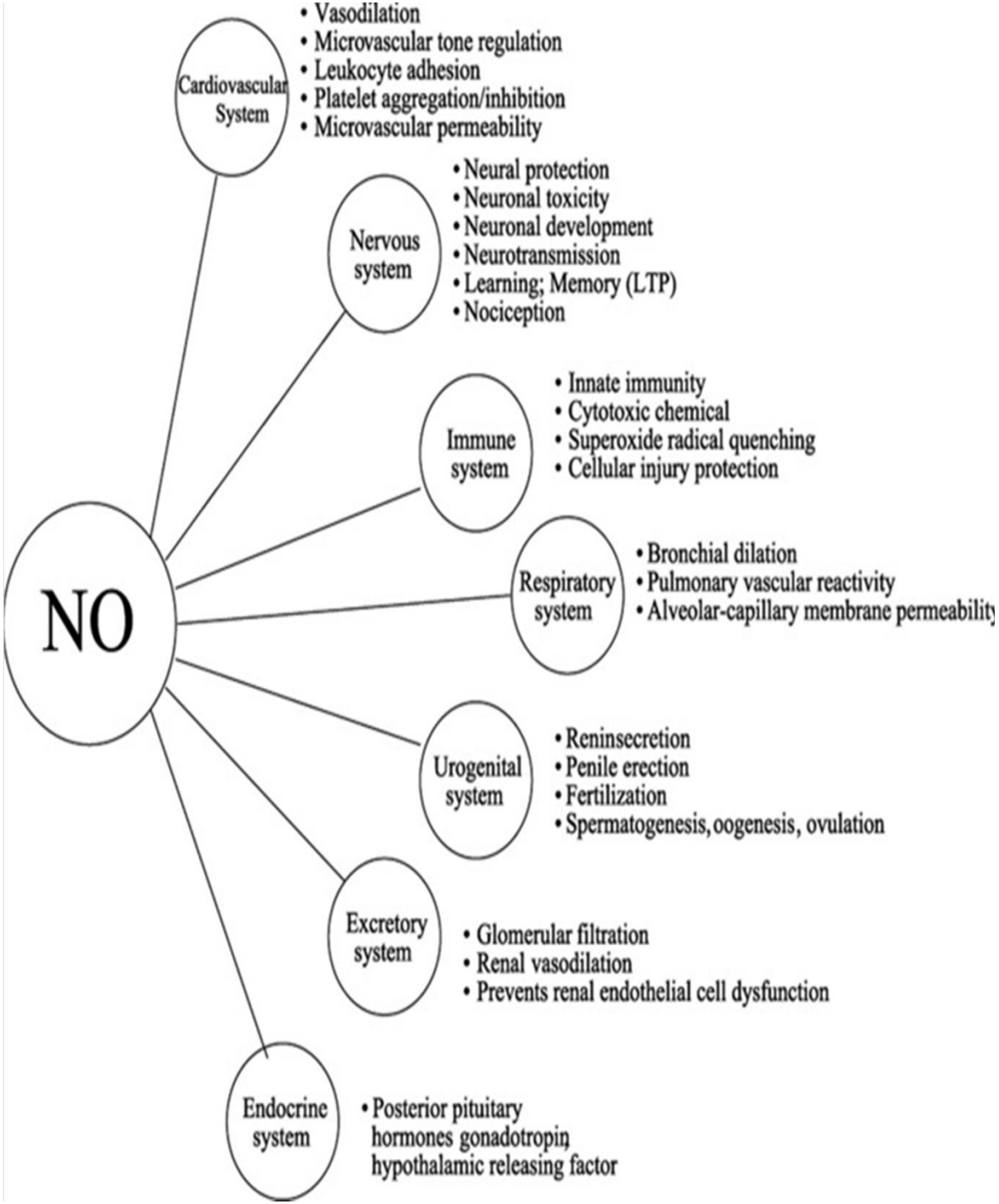
Reduced Nitric Oxide Production

- The nation's aging population is growing rapidly. By 2030, the number of adults age 65 and older will nearly double to 70 million.
- Twenty percent of the Medicare population has at least five chronic conditions i.e., hypertension, diabetes, arthritis, etc. Studies in experimental models and even humans reveal that constitutive production of nitric oxide (NO) is reduced with aging and this circumstance may be relevant to a number of diseases that plague the aging population.

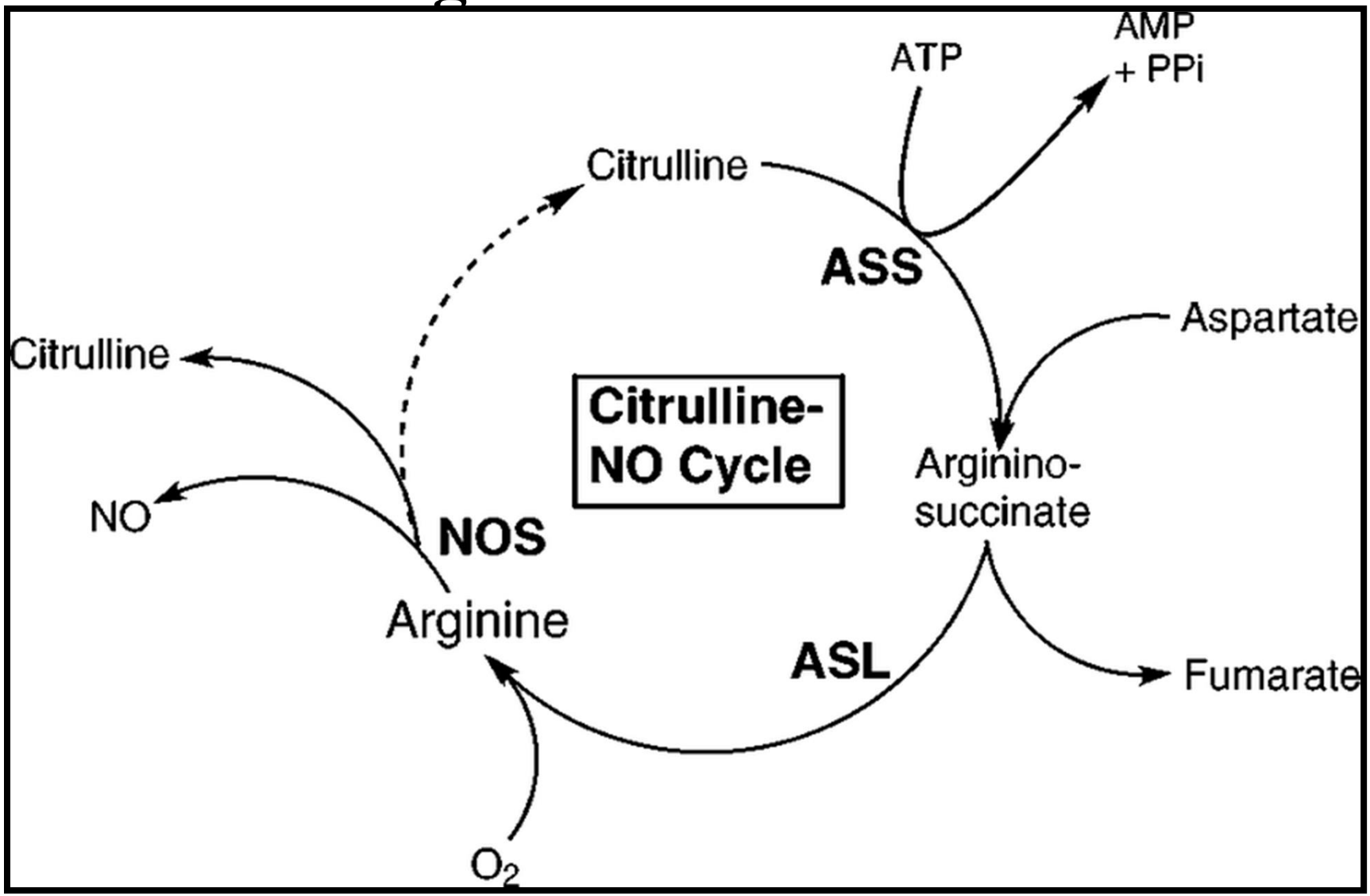


- J Geriatr Cardiol. 2011 Dec; 8(4): 230–242.doi: 10.3724/SP.J.1263.2011.00230 PMCID: PMC3390088 PMID: 22783310

- Implications of disturbed NO production in diseases are various and depend on whether lack or excess of NO production occurs. Dietary factors potentially can modulate NO production.
- Substrate bioavailability is crucial, but citrulline supplementation may be a good alternative as arginine precursor.
- Curr Opin Clin Nutr Metab Care. 2010 Jan; 13(1): 97–104.



Nitric Oxide synthesis
l-Arginine vs l-Citrulline



Induction of Nitric Oxide: Citrulline instead of L- Arginine

- **Citrulline: Better than Arginine**
- **Arginine is a direct producer of NO, while citrulline acts in a rescue fashion**

- L-citrulline serves as an L-arginine precursor, but the body is constantly converting the two amino acids back and forth.
  - *There is a limit to how much arginine can circulate in the liver, but there's no such limit for citrulline.*

- This may be why animal studies indicate that *supplementing with citrulline is a more efficient way to keep stores of arginine and nitric oxide at optimal levels.*[*,]

- Because arginine breaks down quickly, citrulline provides a more long-lasting effect, especially for men over 40. *

- Supplemental citrulline has proven effective at raising levels of nitric oxide synthase — a group of enzymes that catalyze the production of nitric oxide — and keeping blood pressure within normal limits in a placebo-controlled human trial.* In another study, participants who drank watermelon juice, which is rich in citrulline, were also better able to maintain blood pressure within healthy limits.*

- Agarwal, 2017.
- Wijnands, 2012.
- Jingbo Q, et al. Poster session 2: Blood Pressure Management. *J Hypertens*. 2012 Sep;e150.
- Ali I, Abdallah A. Poster session 14. PS 14-56: Effect of watermelon juice consumption on brachial blood pressure and global arginine availability among Sudanese hypertensive patients. *J Hypertens*. 2016 Sep;34:e449. https://journals.lww.com/jhypertension/Abstract/2012/09001/509_L_CITRULLINE_SUPPLEMENTATION_REDUCED.482.aspx

Direct detrimental effects of L-arginine upon ischemia--reperfusion injury to myocardium

K Takeuchi [1], F X McGowan, H C Danh, P Glynn, E Simplaceanu, P J del Nido PMID: 7473786 DOI: 10.1006/jmcc.1995.0133

Abstract

The effects of L-arginine on recovery of myocardial contractile function and oxidative metabolism were investigated in a model of reversible global normothermic, ischemic injury using an isolated, buffer-perfused rabbit heart preparation. One mM L-arginine was infused into hearts for 2 min at the onset (group 1) of a 35 min period of ischemia or at the onset of reperfusion (group 2).

In non-ischemic hearts, L-arginine caused a slight increase in developed pressure but had no effects on diastolic pressure, oxygen consumption (MVO2), coronary flow, or lactate production. When administered either before or after ischemia-reperfusion. L-arginine caused a significant increase in the diastolic pressure-volume relationship (PVR) and decline in systolic function when compared to untreated control hearts receiving the same ischemic injury. Recovery of MVO2 and high energy phosphates (phosphocreatine and ATP), measured by 31P-NMR spectroscopy, were significantly impaired in L-arginine-treated hearts compared to reperfused control hearts. Lactate release on reperfusion was also higher in both arginine-treated groups. Nitric oxide release into the coronary circulation (measured in separate experiments by the conversion of [15N]L-arginine to [15N]nitrate/nitrite using gas chromatography/mass spectroscopy) was not increased by L-arginine administration.

Thus, we conclude that L-arginine acts synergistically with ischemia reperfusion to augment myocardial injury, which includes inhibition of oxidative metabolism and mitochondrial function.

Citrulline Supplementation Improves Organ Perfusion and Arginine Availability under Conditions with Enhanced Arginase Activity

Karolina A P Wijnands [1], Dennis M Meesters [2], Kevin W Y van Barneveld [3], Ruben G J Visschers [4], Jacob J Briedé [5], Benjamin Vandendriessche [6 7], Hans M H van Eijk [8], Babs A F M Bessems [9], Nadine van den Hoven [10], Christian J H von Wintersdorff [11], Peter Brouckaert [12 13], Nicole D Bouvy [14], Wouter H Lamers [15], Anje Cauwels [16 17], Martijn Poeze [18]
Affiliations
•PMID: 26132994 PMCID: PMC4516994 DOI: 10.3390/nu7075217

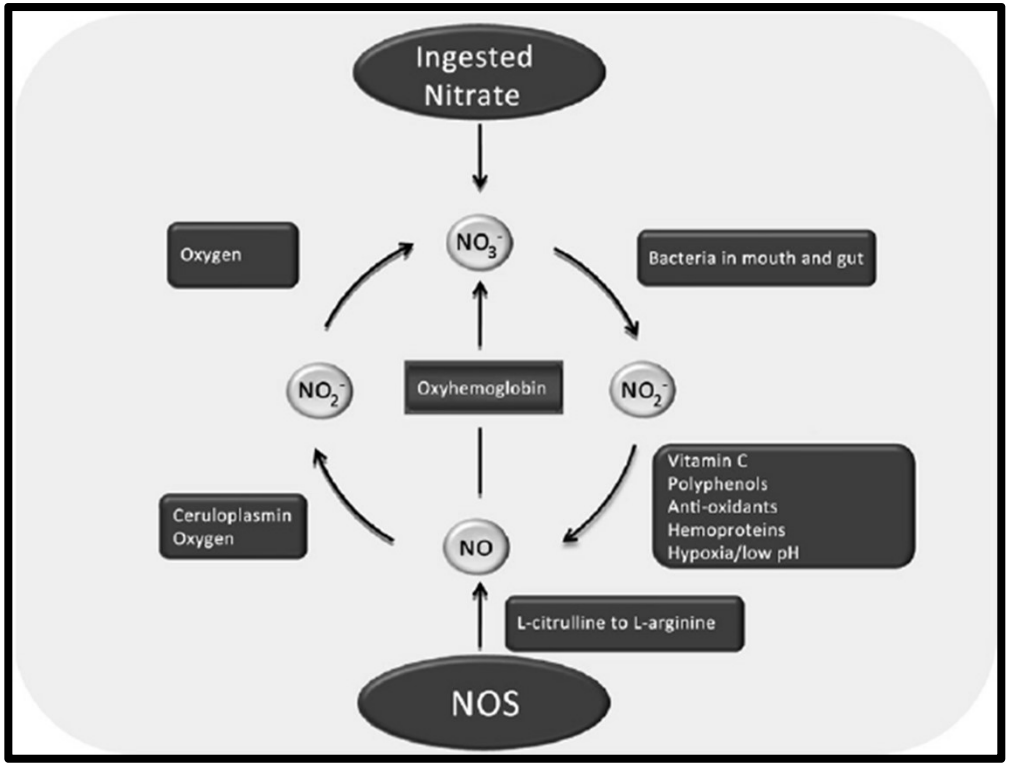
Enhanced arginase-induced arginine consumption is believed to play a key role in the pathogenesis of sickle cell disease-induced end organ failure. Enhancement of arginine availability with L-arginine supplementation exhibited less consistent results; however, L-citrulline, the precursor of L-arginine, may be a promising alternative. In this study, we determined the effects of L-citrulline compared to L-arginine supplementation on arginine-nitric oxide (NO) metabolism, arginine availability and microcirculation in a murine model with acutely-enhanced arginase activity. The effects were measured in six groups of mice (n = 8 each) injected intraperitoneally with sterile saline or arginase (1000 IE/mouse) with or without being separately injected with L-citrulline or L-arginine 1 h prior to assessment of the microcirculation with side stream dark-field (SDF)-imaging or in vivo NO-production with electron spin resonance (ESR) spectroscopy. Arginase injection caused a decrease in plasma and tissue arginine concentrations. L-arginine and L-citrulline supplementation both enhanced plasma and tissue arginine concentrations in arginase-injected mice. However, only the citrulline supplementation increased NO production and improved microcirculatory flow in arginase-injected mice. In conclusion, the present study provides for the first time in vivo experimental evidence that L-citrulline, and not L-arginine supplementation, improves the end organ microcirculation during conditions with acute arginase-induced arginine deficiency by increasing the NO concentration in tissues.

Citrulline a more suitable substrate than arginine to restore NO production and the microcirculation during endotoxemia

- PMID: 22666356 PMCID: PMC3362574 DOI: 10.1371/journal.pone.0037439

- Conclusion/significance: L-Citrulline supplementation during endotoxemia positively influenced the intestinal microvascular perfusion compared to L-Arginine-supplemented and control endotoxemic mice. L-Citrulline supplementation increased plasma and tissue concentrations of arginine and citrulline, and restored intracellular NO production in the intestine. L-Arginine supplementation did not increase the intracellular arginine availability.
- Jejunal tissues in the L-Citrulline-supplemented group showed, compared to the endotoxemic and L-Arginine-supplemented endotoxemic group, an increase in degree of phosphorylation of eNOS (Ser 1177) and a decrease in iNOS protein level. In conclusion, L-Citrulline supplementation during endotoxemia and not L-Arginine reduced intestinal microcirculatory dysfunction and increased intracellular NO production, likely via increased intracellular citrulline and arginine availability.

Nitric Oxide and Human Nitrogen cycle

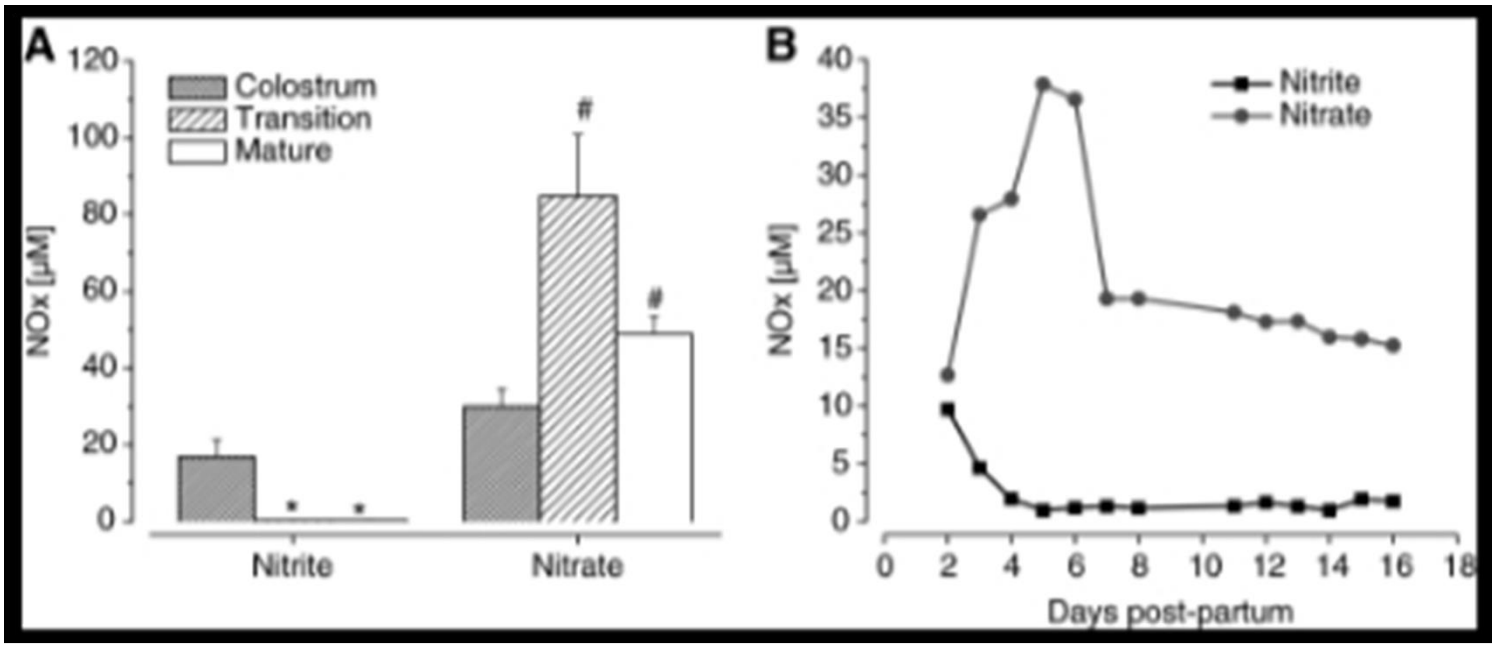


- Nitrites also boosted by colostrum, and later breast milk.
- Oral microflora reduce 20% of nitrate to nitrite
  - Nitrates turned to nitrites by endogenous mouth flora (see Dr. Bryan's work), in both vegetable based and meat based diets (amino groups).
    - High Carbohydrate and processed diets glycate the necessary enzyme for this process.
  - Stay AWAY from mouth washes and fluoride based toothpastes, consider regular rebalancing of oral probiotic loads.
- Low gastric pH reduces nitrite to NO
  - Avoid antacids

Mouth Wash: The Taste that Kills

Multiple studies show induced hypertension with mouthwash and reduction to normotensive status with it's removal due to nitric oxide inhibition.

- Joshipura K, Muñoz-Torres F, Fernández-Santiago J, Patel RP, Lopez-Candales A. Over-the-counter mouthwash use, nitric oxide and hypertension risk. Blood Press. 2020 Apr;29(2):103-112. doi: 10.1080/08037051.2019.1680270. Epub 2019 Nov 11. PMID: 31709856; PMCID: PMC7125030.
- Pignatelli P, Fabietti G, Ricci A, Piattelli A, Curia MC. How Periodontal Disease and Presence of Nitric Oxide Reducing Oral Bacteria Can Affect Blood Pressure. Int J Mol Sci. 2020 Oct 13;21(20):7538. doi: 10.3390/ijms21207538. PMID: 33066082; PMCID: PMC7589924.
- Batista RIM, Nogueira RC, Ferreira GC, Oliveira-Paula GH, Damacena-Angelis C, Pinheiro LC, Tanus-Santos JE. Antiseptic mouthwash inhibits antihypertensive and vascular protective effects of L-arginine. Eur J Pharmacol. 2021 Sep 15;907:174314. doi: 10.1016/j.ejphar.2021.174314. Epub 2021 Jul 8. PMID: 34245745.
- Bondonno CP, Liu AH, Croft KD, Considine MJ, Puddey IB, Woodman RJ, Hodgson JM. Antibacterial mouthwash blunts oral nitrate reduction and increases blood pressure in treated hypertensive men and women. Am J Hypertens. 2015 May;28(5):572-5. doi: 10.1093/ajh/hpu192. Epub 2014 Oct 30. PMID: 25359409.



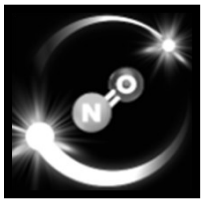
A) Dietary colostrum and breast milk have high levels of endogenous nitrates for early NO production

B) Nitrate is enriched in colostrum and declines as gut bacteria colonize

Hord NG, Ghannam JS, Garg HK, Berens PD, Bryan NS. Nitrate and nitrite content of human, formula, bovine, and soy milks: implications for dietary nitrite and nitrate recommendations. Breastfeed Med. 2011 Dec;6(6):393-9. doi: 10.1089/bfm.2010.0070. Epub 2010 Oct 19. PMID: 20958096; PMCID: PMC3228598.

Nitric Oxide

- Detection
  - NO test strips – *a parlor trick*
  - *Best indicators are serum nitrates and Uric acid (<5)*
    - *See Dr. Perlmutter's book, "Dropping Acid"*
- "Nitric Oxide Formula"
  - L-Citruline (Arginine Free)
  - Grapeseed Extract
  - Hawthorn
  - Green coffee bean
  - Beet Root powder
  - Vitamin C
  - Magnesium
  - Zinc



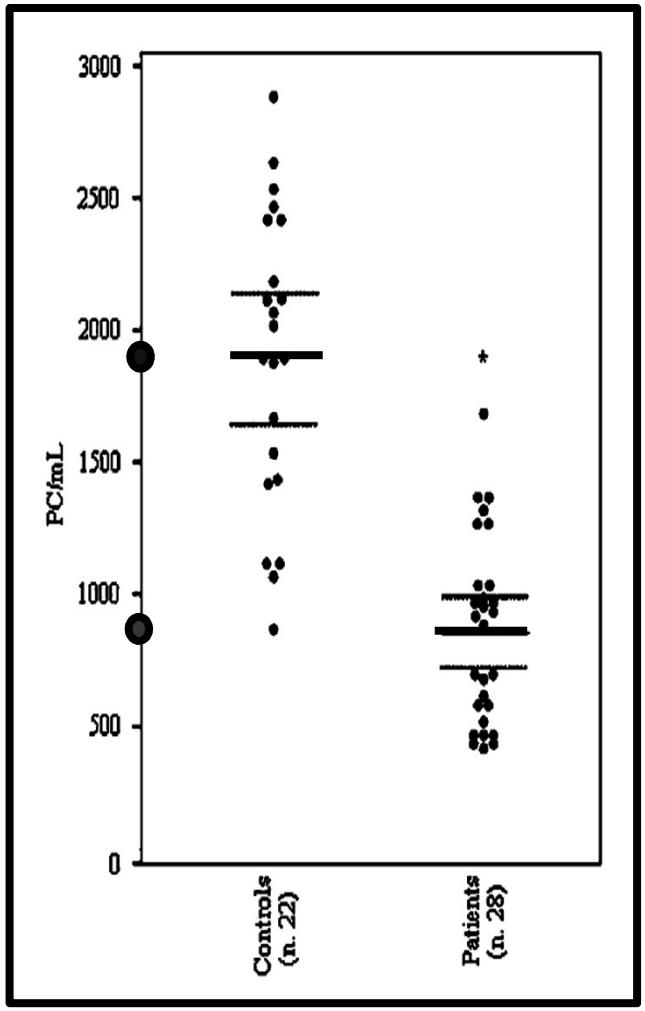
Stem Cells for vascular/sexual health

How long does it take to get from 6:30 to 10 to 7?

It's a lot faster when you're young, or at least your cells are.

Strongly suggest looking up the work of Dr. Christian Drapeau

Stem Cells and Erectile Dysfunction



International Journal of Impotence Research (2005), 1–3

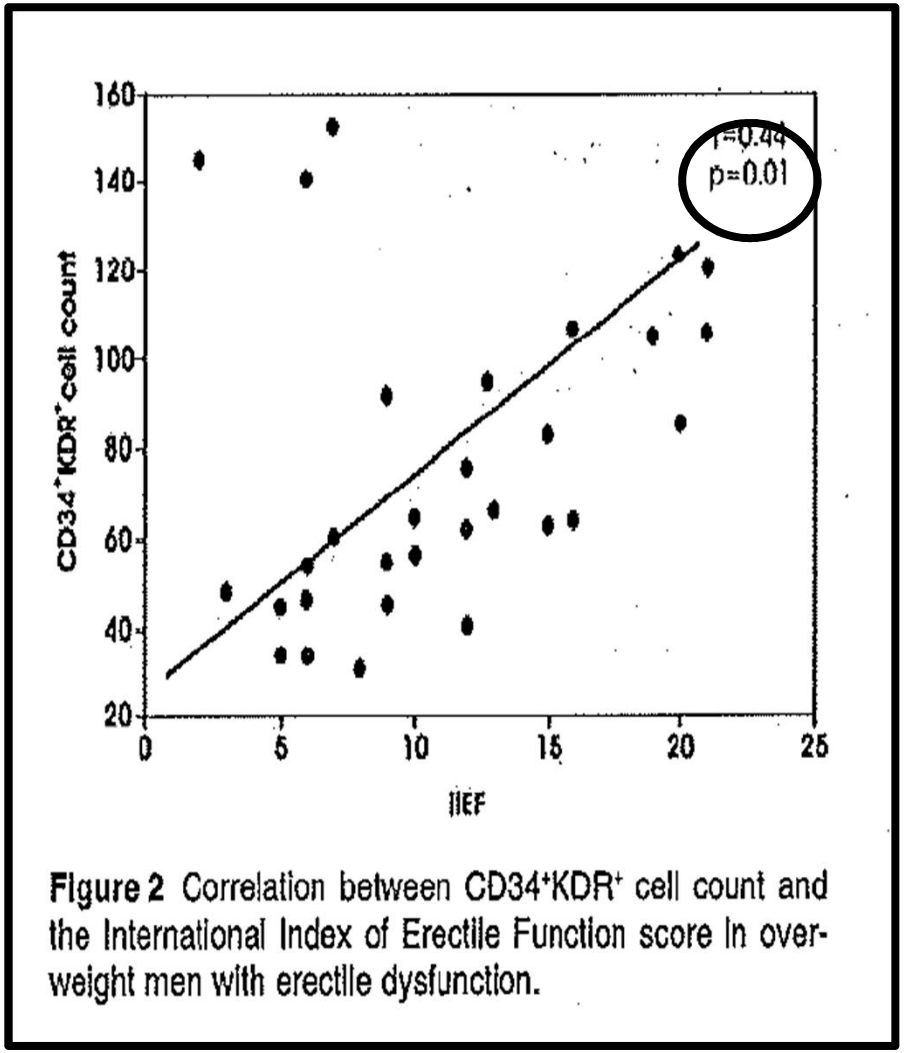
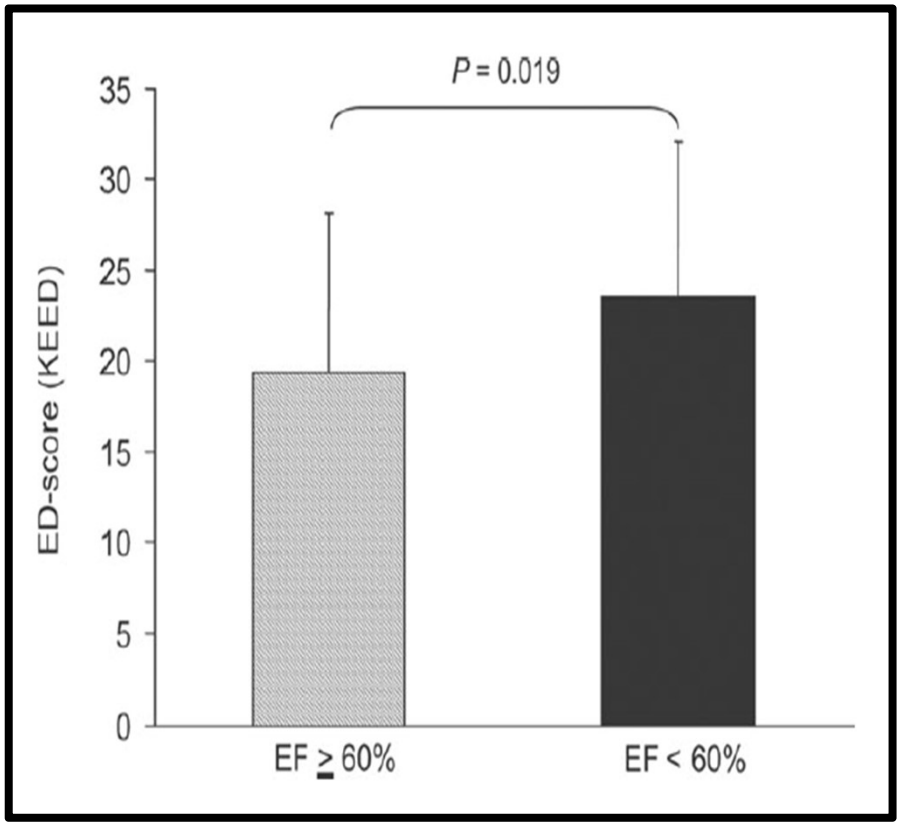


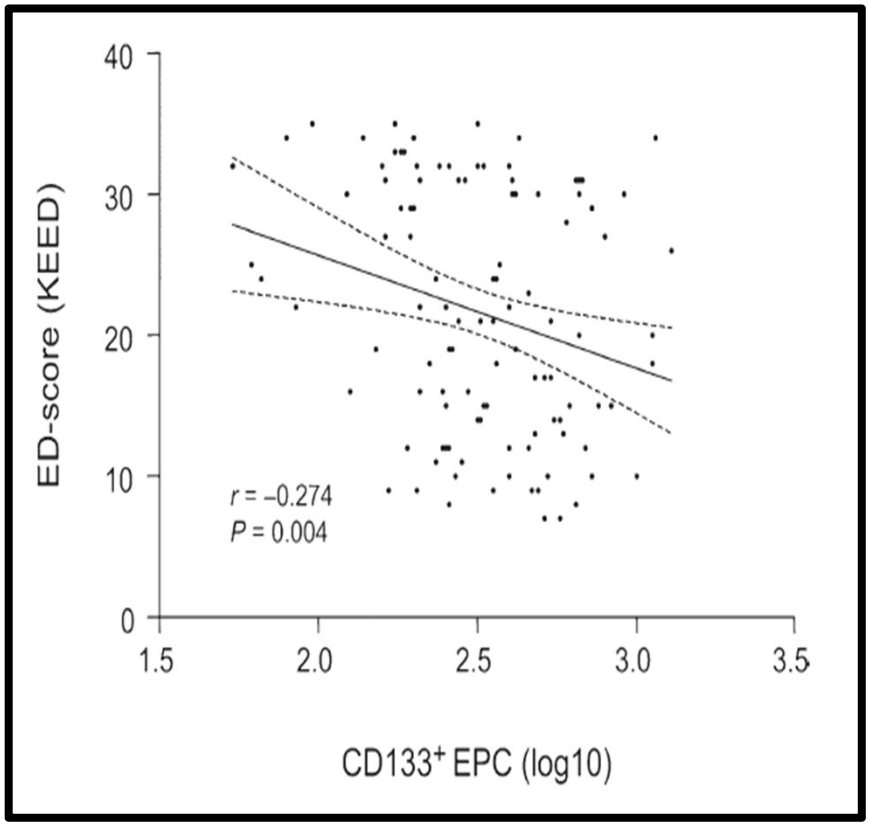
Figure 2 Correlation between $CD34^+KDR^+$ cell count and the International Index of Erectile Function score in overweight men with erectile dysfunction.

J Sex Med 2009, 6:107-114

International Journal of Impotence Research (2005), 1–3

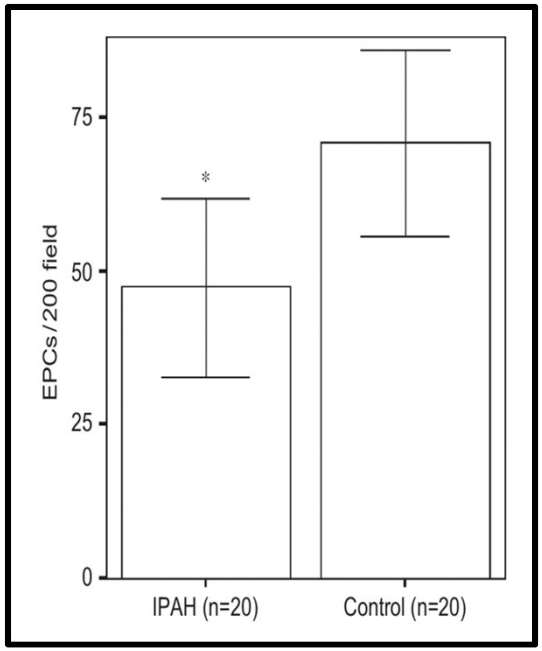
Stem Cells and Erectile dysfunction

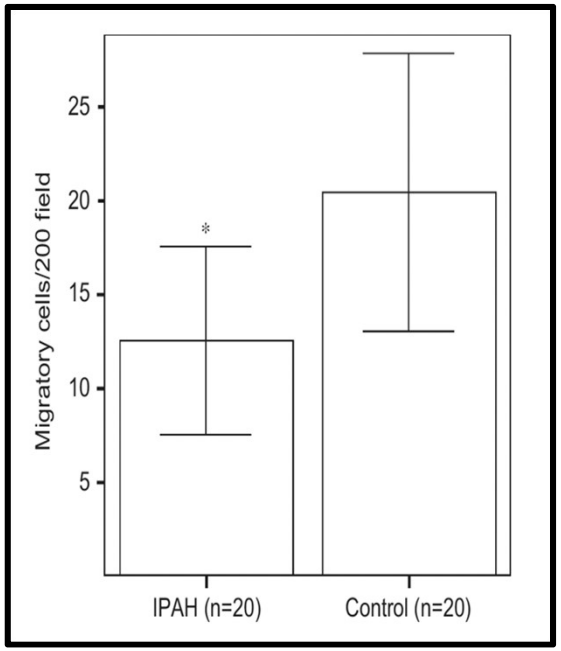


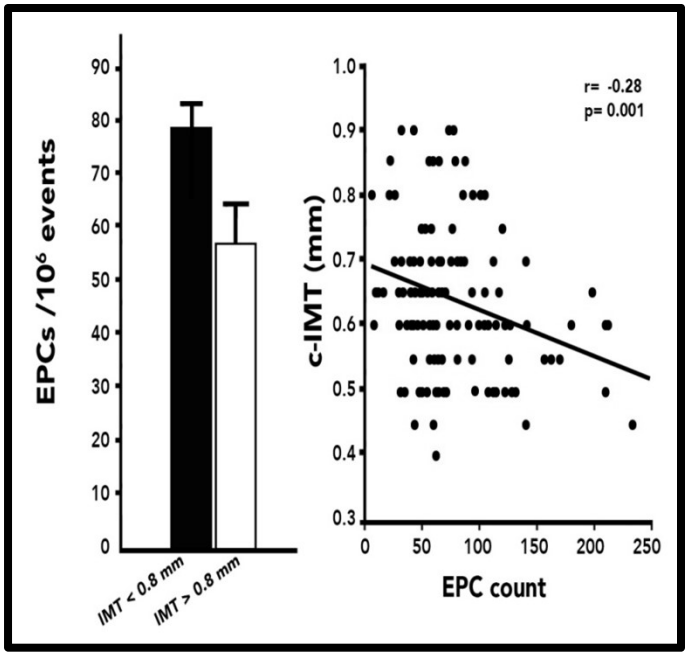


European Heart Journal (2006) 27, 2184–2188

Stem Cells and Vascular Diseases

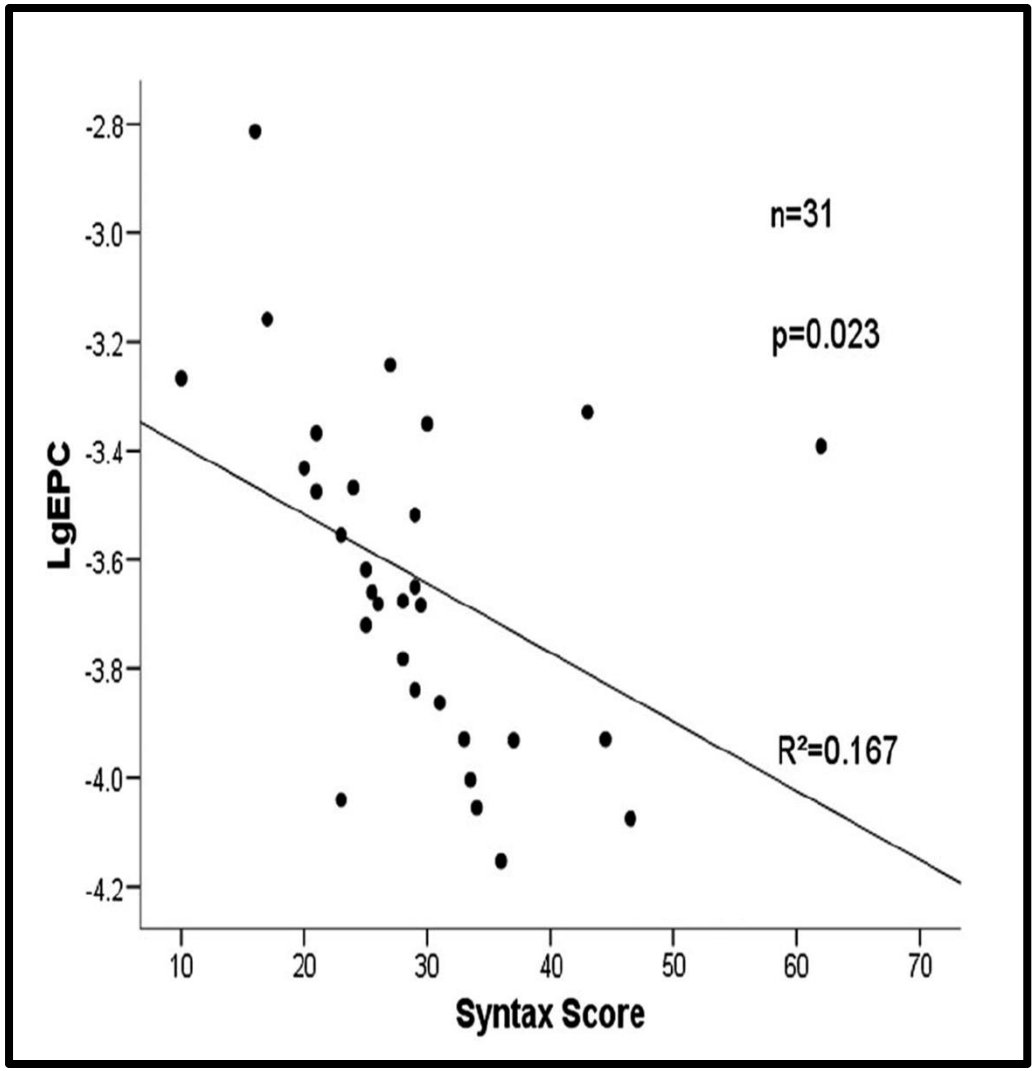






Respiratory Medicine (2008) 102, 1073–1079

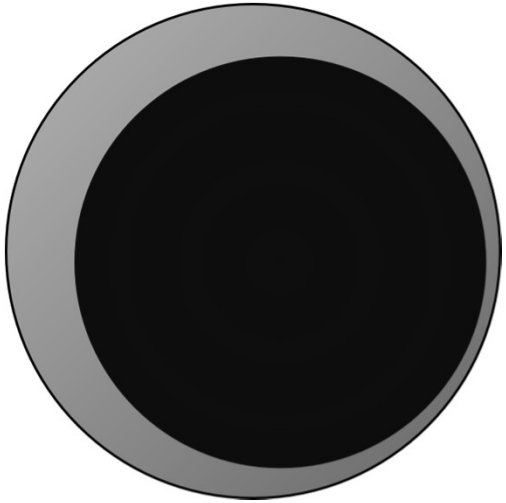
Stem Cells and Atherosclerosis



The American Journal of the Medical Sciences Volume 347, Number 6, June 2014

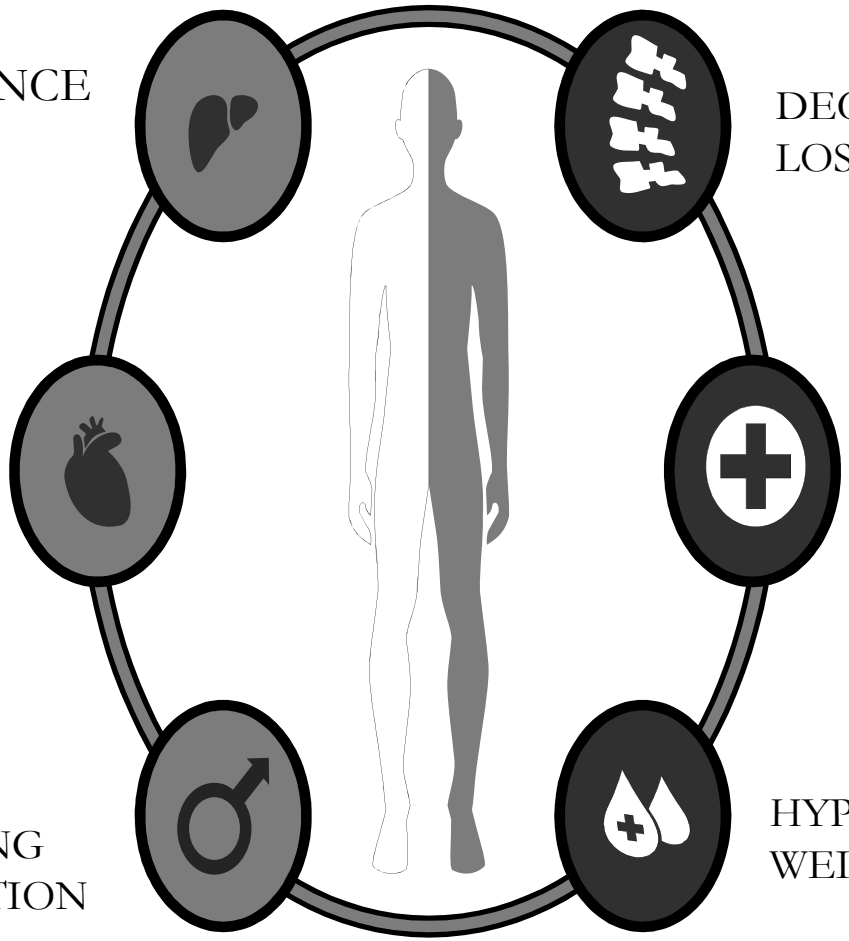
Stem Cell support protocols

- CoQ10 w PQQ
- D-ribose
- NAD/nicotinamide riboside
- L-orthinine, acetyl-l-carnitine, methionine
- ALA
- TMG
- Malic Acid
- Magnesium threonate
- Botanical blends
  - H. rhamnoides, Aphanizomenon flos-aquae, noto-ginseng, Aloe Vera, and beta-glucans
- Fasting
- Red light therapy
- Ketones/Ketogenic Diet



Andropause

Roughly defined as Low testosterone =250 ngm/dl or less



INSULIN RESISTANCE
DIABETES

DECREASED FLEXIBILITY
LOSS OF MUSCLE MASS

HYPERTENSION
CARDIOVASCULAR
DISEASE

NIGHT SWEATS
HOT FLASHES

REDUCED LIBIDO
BURNED OUT FEELING
ERECTILE DYSFUNCTION

HYPERCHOLESTEROLEMIA
WEIGHT GAIN-WAIST

The United States is currently undergoing a endocrinologic crisis

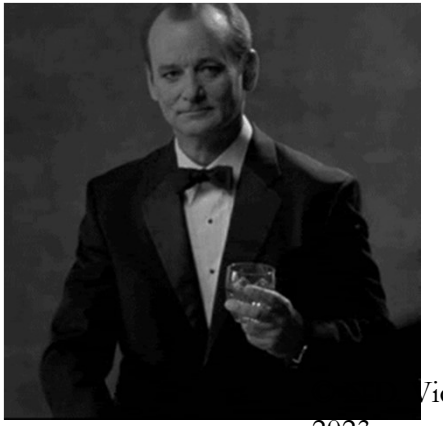
There is drastic reduction in testosterone values across virtually all cohorts of the American male population.

- 2007- Average of 501 ng/dL of testosterone in Massachusetts men aged 45-71 in 1987-1989.
  - By 2002-2005 the average testosterone in men aged 57-80 had fallen to 391 ng/dL.
    - J Clin Endocrinol Metab. 2007; 92: 196-202

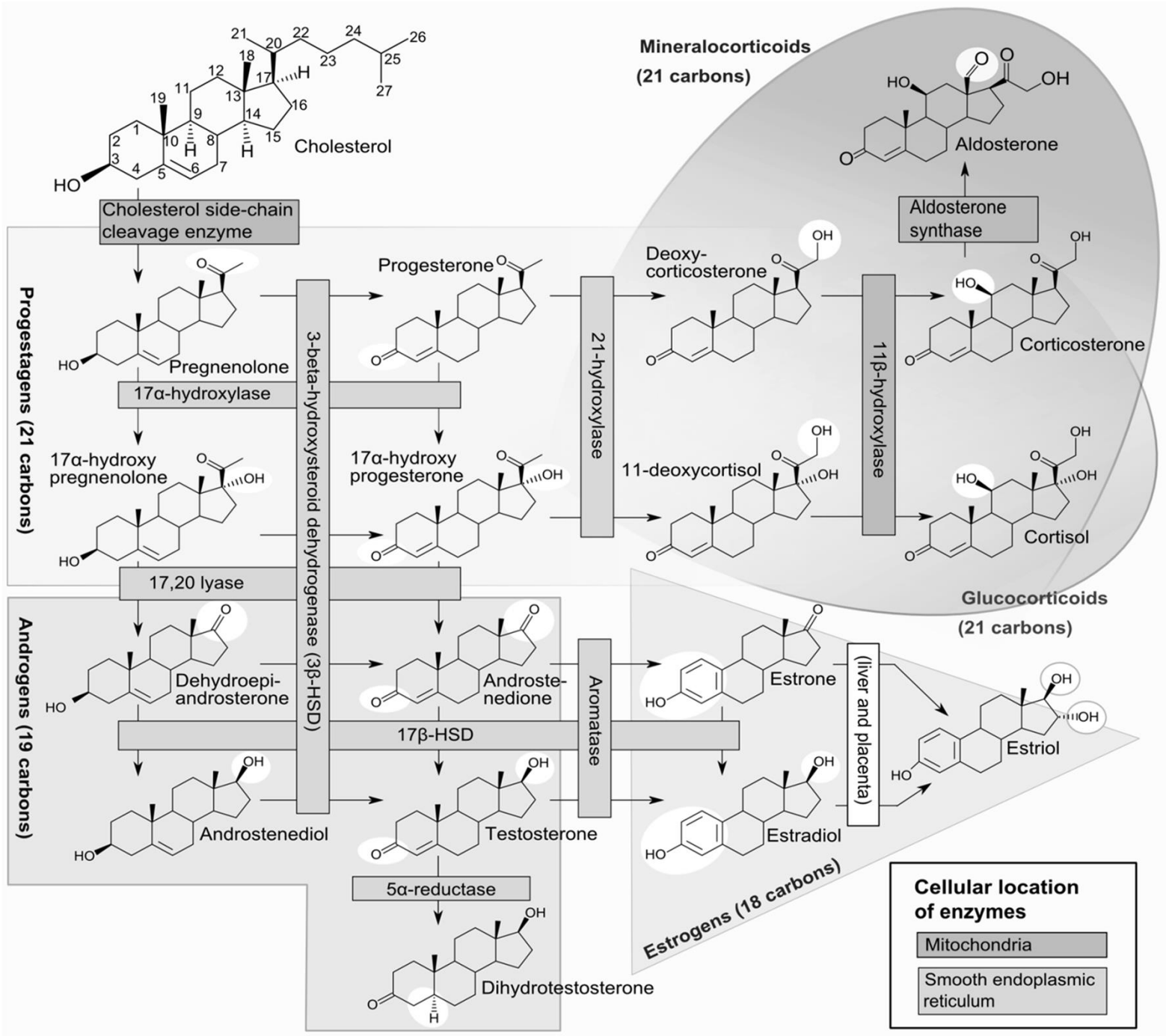
- When observed over time, the average total testosterone value in American males has decreased dramatically since the mid-1900's, a trend that bears **suspicious correlation** with the increasing levels of diabetes mellitus and metabolic syndrome over the same time frame.
  - This decreasing level of testosterone appears in all age cohorts in the population, suggesting this is not just a consequence of aging, but of environmental factors predisposing a global reduction in testosterone values in men and women.
    - Exp Gerontol. 2004 Jul;39(7):975-84. The health of normally aging men: The Massachusetts Male Aging Study (1987-2004). O'Donnell AB1, Araujo AB, McKinlay JB.
    - A Population-Level Decline in Serum Testosterone Levels in American Men
      Thomas G. Travison Andre B. Araujo Amy B. O'Donnell Varant Kupelian John B. McKinlay, The Journal of Clinical Endocrinology & Metabolism, Volume 92, Issue 1, 1 January 2007, Pages 196–202, https://doi.org/10.1210/jc.2006-1375

- Potential contribution of low testosterone values to the increasing rates of metabolic syndrome and diabetes have been noted across the literature.
  - Testosterone deficiency induced by progressive stages of diabetes mellitus impairs glucose metabolism and favors glycogenesis in mature rat Sertoli cells. Rato L1, Alves MG1, Duarte AI2, Santos MS3, Moreira PI4, Cavaco JE1, Oliveira PF5. Int J Biochem Cell Biol. 2015 Sep;66:1-10. doi: 10.1016/j.biocel.2015.07.001. Epub 2015 Jul 3.
  - Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Muraleedharan V1, Marsh H, Kapoor D, Channer KS, Jones TH. Eur J Endocrinol. 2013 Oct 21;169(6):725-33. doi: 10.1530/EJE-13-0321. Print 2013 Dec.
  - Is a Previously or Currently Reduced Testosterone Level in Male Patients with Type 2 Diabetes Mellitus a Risk Factor for the Development of Coronary Artery Disease? A Systematic Review and Meta-analysis. Huang F, Diabetes Ther. 2018 Apr 4. doi: 10.1007/s13300-018-0415-3. [Epub ahead of print]
  - Testosterone and All-Cause Mortality in Older Men: The Role of Metabolic Syndrome.
    Laouali N1, Brailly-Tabard S2,3,4, Helmer C5,6, Ancelin ML7, Tzourio C5,6, Singh-Manoux A1, Dugravot A1, Elbaz A1, Guiochon-Mantel A2,3,4, Canonico M1., J Endocr Soc. 2018 Feb 26;2(4):322-335. doi: 10.1210/js.2018-00005. eCollection 2018 Apr 1.

- In men, multiple studies have supported increasing relatively circulating levels of testosterone to around the 500 ng/dl level to reduce both Diabetes Mellitus and Metabolic syndrome.
  - Tibblin G. Diabetes 1996;45(11):1605-9
  - Kapoor D et al. Euro J Endocrin 2006;154:899-906
  - Brikeland KI. J CEM 1993;76(2):275-8
  - Chang, Gerontology 1994;40(5):260-7
  - Haffner S., Metabol 1994;43(5):599-3



Victor Carsrud, 2023


Cholesterol
Cholesterol side-chain cleavage enzyme
Progestagens (21 carbons)
Pregnenolone
17α-hydroxylase
17α-hydroxy pregnenolone
17,20 lyase
Dehydroepi-androsterone
Androstenediol
3-beta-hydroxysteroid dehydrogenase (3β-HSD)
Progesterone
17α-hydroxy progesterone
Androste-nedione
17β-HSD
Testosterone
5α-reductase
Dihydrotestosterone
Androgens (19 carbons)
21-hydroxylase
Deoxy-corticosterone
11-deoxycortisol
11β-hydroxylase
Corticosterone
Cortisol
Mineralocorticoids
(21 carbons)
Aldosterone synthase
Aldosterone
Glucocorticoids
(21 carbons)
Aromatase
Estrone
Estradiol
(liver and placenta)
Estriol
Estrogens (18 carbons)
Cellular location of enzymes
Mitochondria
Smooth endoplasmic reticulum

Novel mixture for induction of steroidogenesis

Zinc (as zinc bisglycinate chelate)- 10 mg
To increase Zinc-finger domain activity in testosterone metabolism

Longjack (Eurycoma longifolia; Tongkat Ali) (root) -300 mg
To enhance endogenous production of testosterone

Ashwagandha (Withania somnifera)(root) (4.5% withanolides) - 250 mg
An adrenal adaptogen to reduce conversion of testosterone to cortisol

Tribulus terrestris (fruit) extract (60% saponins) - 200 mg
To enhance endogenous production of testosterone.

Ginseng (Panax) (rhizome) extract (4% ginsenosides) - 200 mg
An adrenal adaptogen to reduce conversion of testosterone to cortisol

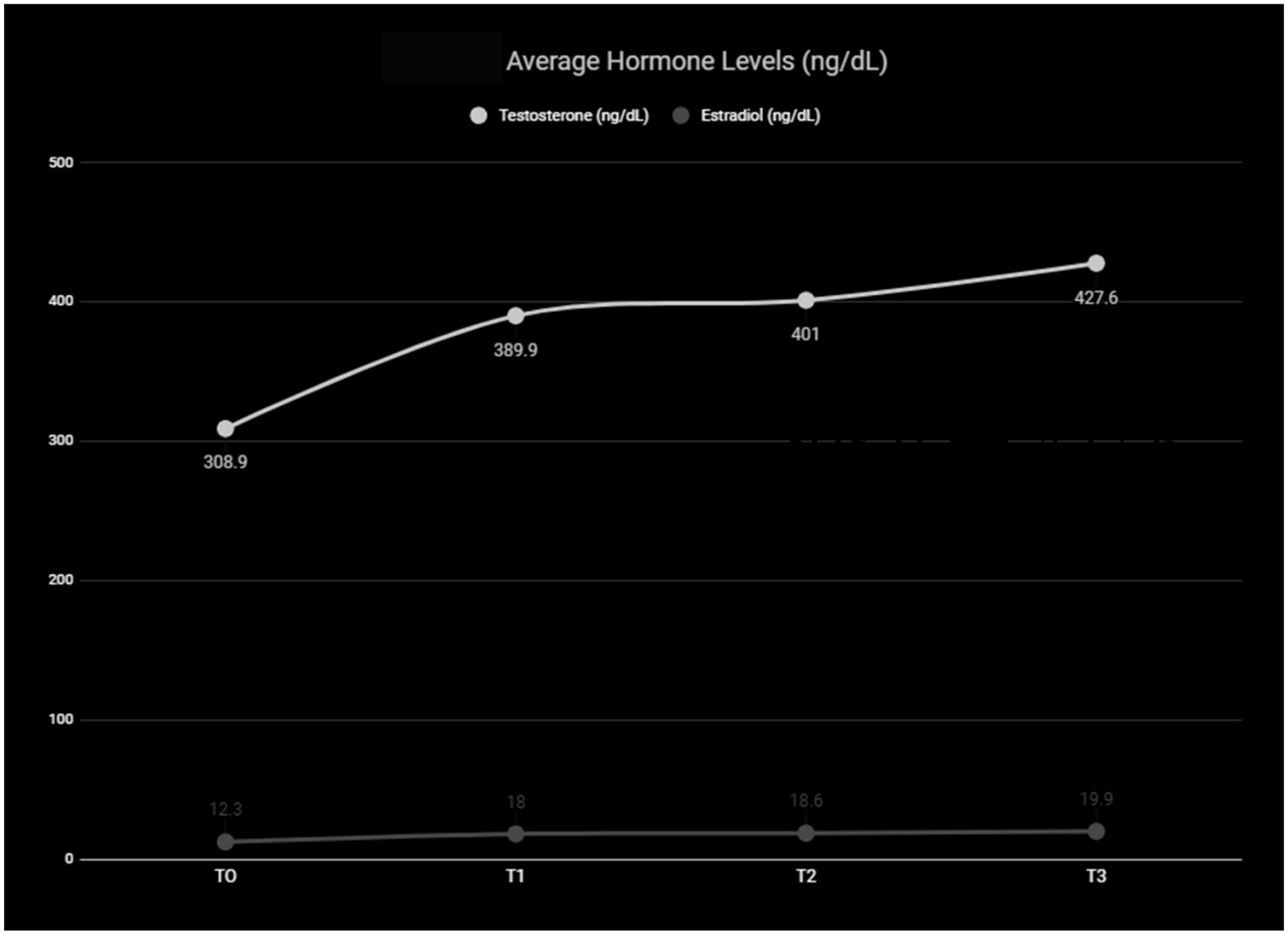
Nettle (Urtica dioica) (root) extract (4:1) - 100 mg
To reduce the binding strength and efficacy of SHBG

Velvet bean (Mucuna pruriens) (seed) extract (99% L-Dopa) - 100 mg
To increase dopamine concentration and by association, testosterone.

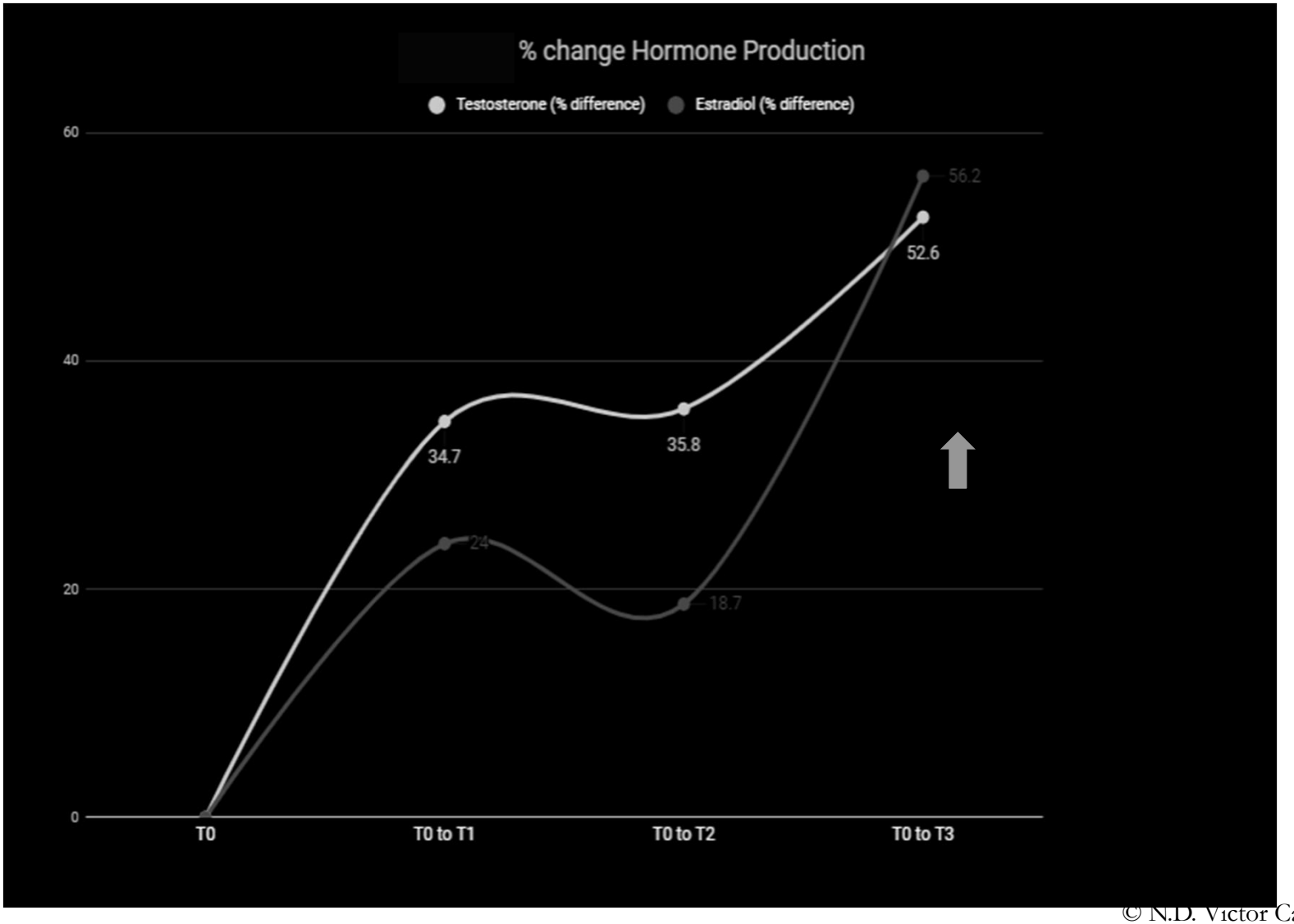
Grape seed extract (Vitis vinifera)(95% proanthocyanidins) - 10 mg
A preservative.

Dosage: 2 capsules , 2x/day

Nutribotanical induction of endogenous steroidogenesis



Hormone % change

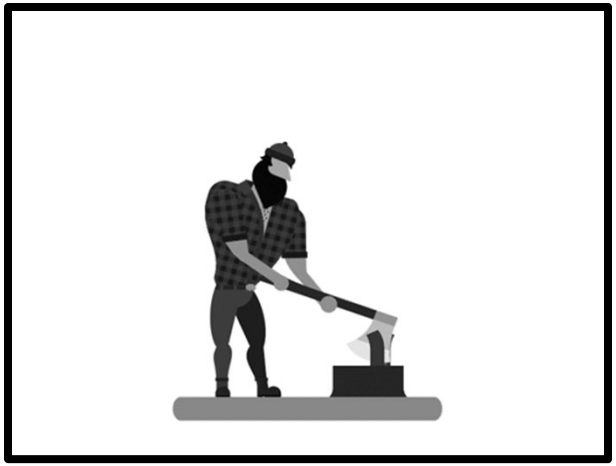


You can't get out of this with just pills
Epigenetic considerations

- Need for diet and exercise as part of testosterone generation
- Lower carb, higher protein/fat diets are essential for testosterone generation.
  - Whittaker J, Harris M. Low-carbohydrate diets and men's cortisol and testosterone: Systematic review and meta-analysis. Nutr Health. 2022 Dec;28(4):543-554. doi: 10.1177/02601060221083079. Epub 2022 Mar 7. Erratum in: Nutr Health. 2022 Dec;28(4):783. PMID: 35254136; PMCID: PMC9716400.
  - Paoli A, Cenci L, Pompei P, Sahin N, Bianco A, Neri M, Caprio M, Moro T. Effects of Two Months of Very Low Carbohydrate Ketogenic Diet on Body Composition, Muscle Strength, Muscle Area, and Blood Parameters in Competitive Natural Body Builders. Nutrients. 2021 Jan 26;13(2):374. doi: 10.3390/nu13020374. PMID: 33530512; PMCID: PMC7911670.
  - Vidić V, Ilić V, Toskić L, Janković N, Ugarković D. Effects of calorie restricted low carbohydrate high fat ketogenic vs. non-ketogenic diet on strength, body-composition, hormonal and lipid profile in trained middle-aged men. Clin Nutr. 2021 Apr;40(4):1495-1502. doi: 10.1016/j.clnu.2021.02.028. Epub 2021 Feb 26. PMID: 33743284.
- Exercise, particularly resistance exercise is essential for the positive feedback loop for testosterone steroidogenesis.
  - Hooper DR, Kraemer WJ, Focht BC, Volek JS, DuPont WH, Caldwell LK, Maresh CM. Endocrinological Roles for Testosterone in Resistance Exercise Responses and Adaptations. Sports Med. 2017 Sep;47(9):1709-1720. doi: 10.1007/s40279-017-0698-y. PMID: 28224307.
  - Gharahdaghi N, Phillips BE, Szewczyk NJ, Smith K, Wilkinson DJ, Atherton PJ. Links Between Testosterone, Oestrogen, and the Growth Hormone/Insulin-Like Growth Factor Axis and Resistance Exercise Muscle Adaptations. Front Physiol. 2021 Jan 15;11:621226. doi: 10.3389/fphys.2020.621226. PMID: 33519525; PMCID: PMC7844366.
  - Kraemer WJ, Ratamess NA, Nindl BC. Recovery responses of testosterone, growth hormone, and IGF-1 after resistance exercise. J Appl Physiol (1985). 2017 Mar 1;122(3):549-558. doi: 10.1152/japplphysiol.00599.2016. Epub 2016 Nov 17. PMID: 27856715.

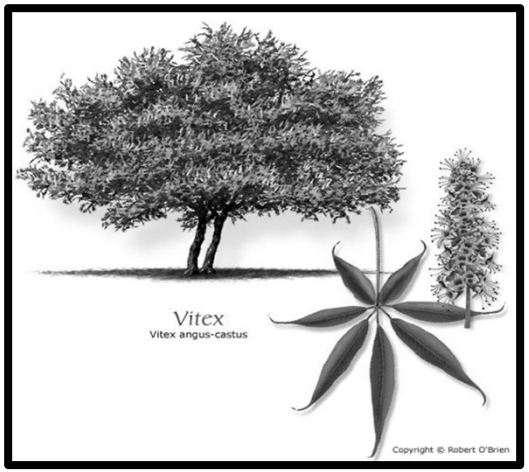
Endocrine/Hormone Support protocols

- Tribulus/Tongkat based herbal mixture – 2 bid
  - for steroidogenesis
- Adrenal glandular/adaptogenic herbal mixture - 2 bid
  - to avoid cortisol steal.
- Pregnenolone (if needed) – 20-30 mg
  - for additional protection from cortisol steal
- Niacin – 1-1.5 grams
  - if tolerated for additional vasodilation
- IC3, DIM, calcium d-glucarate
  - If needed for estrogenic detoxification
- RESISTANCE exercise
- Ketogenic/Paleo (no crappy food)



Detoxing Estrogen dominance in women is comparatively easy

- Calcium d-glucarate (1000 mg)
- Di-indolmethane (DIM) (200 mg)
- Indole-3-Carbinol (I3C) (150 mg)
- Chasteberry (vitex agnus-castus) (225mg)
  - *But Chasteberry has unfortunate effects on men*
  - *So no, with the exception of BPH patients.*



-The treatment of premenstrual syndrome with preparations of Vitex agnus castus: a systematic review and meta-analysis -Epub 2017 Feb 22 - Am J Obstet Gynecol
- Use of Vitex agnus-castus in migrainous women with premenstrual syndrome: an open-label clinical observation Epub 2013 Mar– Acta Neurol Belg.. 2003 May;10(4):348-57.
- Chaste tree (Vitex agnus-castus)--pharmacology and clinical indicationsW Wuttke 1, H Jarry, V Christoffel, B Spengler, D Seidlová-Wuttke
-In Vivo. 2010 Jul-Aug;24(4):387-91. Diindolylmethane (DIM) spontaneously forms from indole-3-carbinol (I3C) during cell culture experimentsH L Bradlow 1, M A Zeligs
-Mol Med Rep. 2013 Feb;7(2):384-8. doi: 10.3892/mmr.2012.1198. Epub 2012 Nov 23. I3C and ICZ inhibit migration by suppressing the EMT process and FAK expression in breast cancer cells
Jin-Nyoung Ho 1, Woojin Jun, Ryowon Choue, Jeongmin Lee

Poisoning the Well
Environmental Toxins

Environmental Estrogens/Xenoestrogens

Estrogen-mimickers are found in everything from plastics to cosmetics containing parabens and phthalates, pesticides, dry cleaning chemicals, dairy products and more.

Xenoestrogens

- Juvenile male fish develop female organs.
  - Adult male fish show 50% decline in fertility when given a low concentration, short term exposure to synthetic estrogens
  - Example: Triclosan (antimicrobial)
    - *Env Tox and Chem 6/04*

- Pesticides and hypothyroidism also drive 16-alpha hydroxyesterone (16E1), the more carcinogenic form of E1 breakdown (measure 2:16 ratio) than 2-hydroxyestrone (2E1)
  - 2E1 promoted by I3C, exercise, lignans, EPA, and flaxseed.

Endocrine disruptors

- Other disruptors include:
  - Alkylphenols
  - Bisphenol A (BPA)
  - DDT
  - Polychlorinated biphenyls
  - Phthalates
  - Polybrominated diphenyl esters
- Lower dosages far worse sometimes than elevated dosages. (*LD 50 not as important*).

- BPA present in most recycled paper, flyers, magazines, bus and train tickets, envelopes, newspapers, food wrappers and cartons, airplane boarding passes, printing paper, business cards, napkins, paper towels, and toilet paper(!?). Also lines food cans and functions as epoxy resin in everything from medical equipment to receipt paper
- In nearly 5000 adult Americans, greater urinary BPA levels associated with a much higher body fat percentage and greater risk of obesity
- Study points to lowering BPA exposure as primary treatment for obesity in the U.S.
- BPA increases body fat because it alters insulin sensitivity, slows metabolism, causes inflammation, and decreases levels of hormone adiponectin that regulates fat burning
- In addition, BPA mimics estrogen in the body, contributing to fat gain as well as <u>altered behavior and cognitive function</u>

- Trasande, L., Association between Urinary BisphenolA Concentration and Obesity Prevalence in Children and Adolescents. Journal of the American Medical Association. 2012. 308(11), p.1113-20
- Shankar, A., TeppalaS., et al. Urinary BPA Levels and Measures of Obesity: Results from the NHANES 2003-2008. International Scholarly Research Network-Endocrinology2012. Article ID 965243

Environmental Endocrine Disruptors

- Toxins blocking LH and stimulation of testosterone receptors - endocrine receptors
- Atrazine (chlorinated herbicide) and glyphosate (herbicide) are among the most potent and well documented of endocrine disruptors for testosterone functionality.

- Abarikwu SO, Costa GMJ, de Lima E Martins Lara N, Lacerda SMSN, de França LR. Atrazine impairs testicular function in BalB/c mice by affecting Leydig cells. Toxicology. 2021 May 15;455:152761. doi: 10.1016/j.tox.2021.152761. Epub 2021 Mar 22. PMID: 33766575.
- Abarikwu SO, Akiri OF, Durojaiye MA, Adenike A. Combined effects of repeated administration of Bretmont Wipeout (glyphosate) and Ultrazin (atrazine) on testosterone, oxidative stress and sperm quality of Wistar rats. Toxicol Mech Methods. 2015 Jan;25(1):70-80. doi: 10.3109/15376516.2014.989349. PMID: 25403740.
- Rimayi C, Odusanya D, Weiss JM, de Boer J, Chimuka L, Mbajiorgu F. Effects of environmentally relevant sub-chronic atrazine concentrations on African clawed frog (Xenopus laevis) survival, growth and male gonad development. Aquat Toxicol. 2018 Jun;199:1-11. doi: 10.1016/j.aquatox.2018.03.028. Epub 2018 Mar 23. PMID: 29602044.
- Zhu S, Zhang T, Wang Y, Zhou X, Wang S, Wang Z. Meta-analysis and experimental validation identified atrazine as a toxicant in the male reproductive system. Environ Sci Pollut Res Int. 2021 Jul;28(28):37482-37497. doi: 10.1007/s11356-021-13396-6. Epub 2021 Mar 13. PMID: 33715114.
- Zhao L, Zhang J, Yang L, Zhang H, Zhang Y, Gao D, Jiang H, Li Y, Dong H, Ma T, Wang X, Wu M, Wang A, Jin Y, Yuan Y, Chen H. Glyphosate exposure attenuates testosterone synthesis via NR1D1 inhibition of StAR expression in mouse Leydig cells. Sci Total Environ. 2021 Sep 1;785:147323. doi: 10.1016/j.scitotenv.2021.147323. Epub 2021 Apr 25. PMID: 33957581.
- Pham TH, Derian L, Kervarrec C, Kernanec PY, Jégou B, Smagulova F, Gely-Pernot A. Perinatal Exposure to Glyphosate and a Glyphosate-Based Herbicide Affect Spermatogenesis in Mice. Toxicol Sci. 2019 May 1;169(1):260-271. doi: 10.1093/toxsci/kfz039. PMID: 30785197.
- Ferramosca A, Lorenzetti S, Di Giacomo M, Murrieri F, Coppola L, Zara V. Herbicides glyphosate and glufosinate ammonium negatively affect human sperm mitochondria respiration efficiency. Reprod Toxicol. 2021 Jan;99:48-55. doi: 10.1016/j.reprotox.2020.11.011. Epub 2020 Nov 26. PMID: 33249231.

Case Study: "Toxic Masculinity"

- 46 yo Caucasian male
- Brain fog, rage issues, weight fluctuations, fatigue, intractable myalgias, ADD
- Former military, highly athletic, current contractor
- Identified and controlled food allergies – gluten sensitive.
- History of wild fluctuations in neurochemistry
  - Indolamines and catecholamines fluctuate with normal range glutamate.
- Testosterone continues to fall.

What to do?

- PCP has put him on Clomid
- Rebound in testosterone, but patient became highly agitated and aggressive.
- Is this a signaling issue?
  - Endocrine disruptor

Heavy Metals (Creatinine)

Test name	In Control	High Risk	In Control Range	High Risk Range	Previous ()
Urine Creatinine (mg/ml)	1.10		0.25–2.16	≤0.24 ≥2.17	
Aluminum (ug/g)		85.12	≤54.00	≥54.01	
Antimony (ug/g)	0.05		≤0.78	≥0.79	
Arsenic (ug/g)	7.69		≤116.00	≥116.01	
Barium (ug/g)	<1.00		≤6.90	≥6.91	
Beryllium (ug/g)	<0.10		≤0.90	≥0.91	
Bismuth (ug/g)	<0.10		≤14.90	≥14.91	
Cadmium (ug/g)	<0.10		≤1.50	≥1.51	
Cesium (ug/g)	3.12		≤9.90	≥9.91	
Gadolinium (ug/g)	<0.05		≤0.39	≥0.40	
Lead (ug/g)	0.50		≤4.40	≥4.41	
Mercury (ug/g)	0.12		≤3.90	≥3.91	
Nickel (ug/g)	2.04		≤11.90	≥11.91	
Palladium (ug/g)	<0.10		≤0.20	≥0.21	
Platinum (ug/g)	<0.05		≤0.99	≥1.00	
Tellurium (ug/g)	0.17		≤0.79	≥0.80	
Thallium (ug/g)	0.20		≤0.80	≥0.81	
Thorium (ug/g)	<0.01		≤0.50	≥0.51	
Tin (ug/g)	<0.20		≤9.90	≥9.91	
Tungsten (ug/g)	<0.04		≤0.99	≥1.00	
Uranium (ug/g)	<0.01		≤0.13	≥0.14	

Environmental Toxins - High

Test Name	In Control	Moderate	High	Current Level	Previous Level
Diethyldithiophosphate (DEDTP) (mcg/g)	≤0.20	0.21~0.48	≥0.49	0.89	
Monoethyl Phthalate (MEP) (mcg/g)	≤5.90	5.91~678.89	≥678.90	1889.64	
mono-2-ethylhexyl phthalate (MEHP) (mcg/g)	≤5.00	5.01~23.89	≥23.90	26.11	
mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) (mcg/g)	≤42.00	42.01~168.99	≥169.00	413.85	
Tiglylglycine (TG) (mcg/g)	≤0.10	0.11~11.29	≥11.30	36.11	

Environmental Toxins - Moderate

Test Name	In Control	Moderate	High	Current Level	Previous Level
Diethylthiophosphate (DETP) (mcg/g)	≤0.70	0.71~2.76	≥2.77	0.82	
Glyphosate (mcg/g)	≤0.75	0.76~2.29	≥2.30	0.99	
Triclosan (mcg/g)	≤45.00	45.01~417.98	≥417.99	177.29	

Mycotoxins - High

Test Name	Species Name	In Control	Moderate	High	Current Level	Previous Level
Roridin E (ng/g)	Fusarium, Myrothecium, Stachybotrys	≤1.00	1.01–2.00	≥2.01	3.19	

Mycotoxins - Moderate

Test Name	Species Name	In Control	Moderate	High	Current Level	Previous Level
Aflatoxin B1 (ng/g)	Aspergillus	≤5.20	5.21–10.40	≥10.41	6.81	
Citrinin (ng/g)	Penicillium	≤9.40	9.41–18.80	≥18.81	12.13	
Isosatratoxin F (ng/g)	Stachybotrys chartarum	≤0.10	0.11–0.30	≥0.31	0.22	

Toxins Summary

		Current	Previous Result
Environmental Toxins	Organochlorine pesticides		
	Organophosphate pesticides	Diethyldithiophosphate (DEDTP) ●, Diethylthiophosphate (DETP) ○	
	Other pesticides/herbcides	Glyphosate ○	
	Phthalate Metabolites	Monoethyl Phthalate (MEP) ●, mono-2-ethylhexyl phthalate (MEHP) ●, mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) ●	
	Parabens		
	Acrylic Metabolites		
	Other Metabolites	Tiglylglycine (TG) ●	
	Alkylphenol	Triclosan ○	
	Volatile Organic Compounds (VOCs)		
	Urine Creatinine		
Mycotoxins V2	Aflatoxin	Aflatoxin B1 ○	
	Other	Citrinin ○	
	Trichothecenes	Roridin E ●, Isosatratoxin F ○	
	Urinary Creatinine		
Heavy Metals	Heavy Metals (Creatinine)	Aluminum ●	

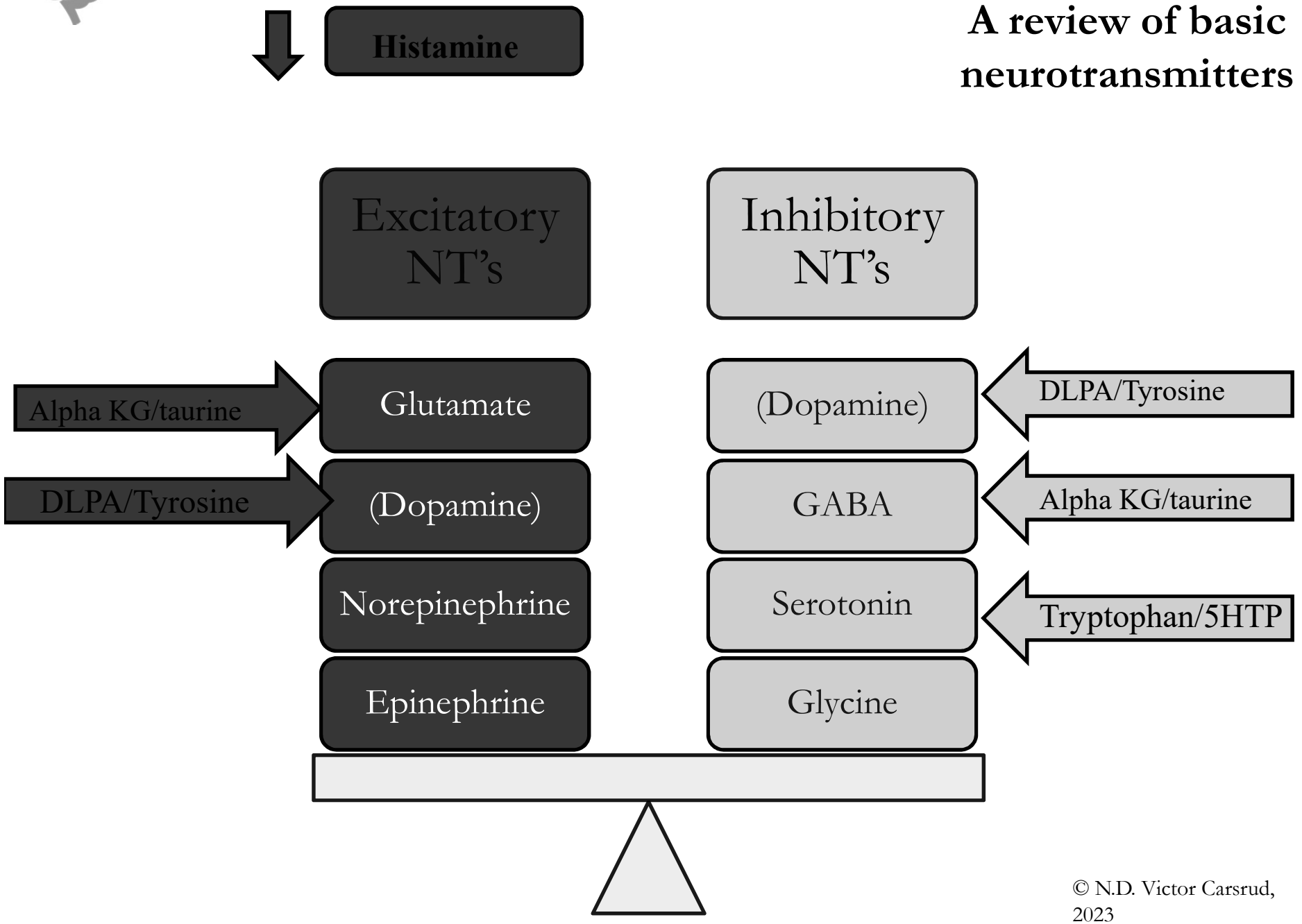
DETOX!

- Sunlight
- Exercise
- Milk Thistle combination
  - Methyl folate, artichoke, ALA, NAC, green tea, calcium d-glucarate, MSM, pomegrante
- NAC
- Liposomal Glutathione
- Probiotics – 50 bil cfu/day or more
- Binder: Charcoal, zeolite, or humic/fulvic acid

- Improvement in neurologic and MSK symptoms after initial healing crisis.
- Testosterone levels gradually improving

And now a gratuitous picture of a large sexual organ

A review of basic neurotransmitters

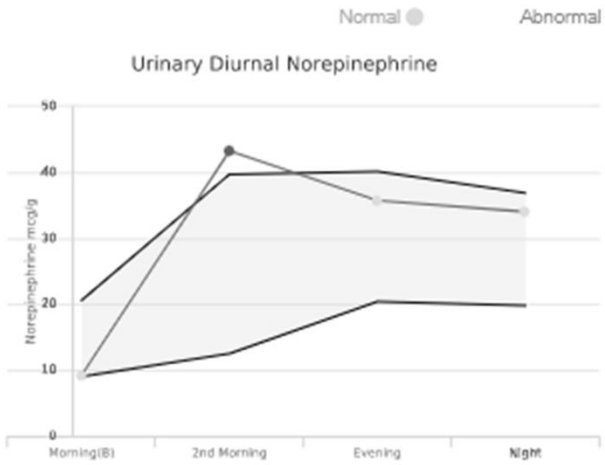


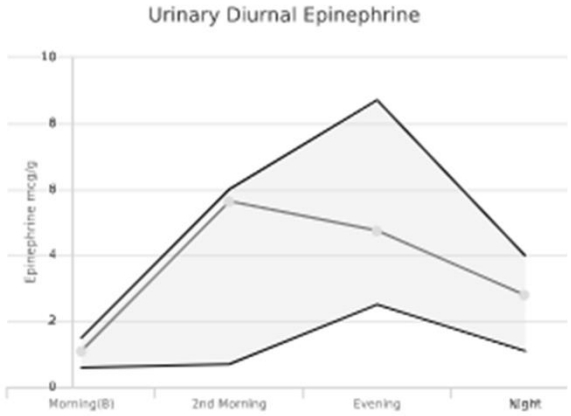
Neurotransmitters need to be examined comprehensively.

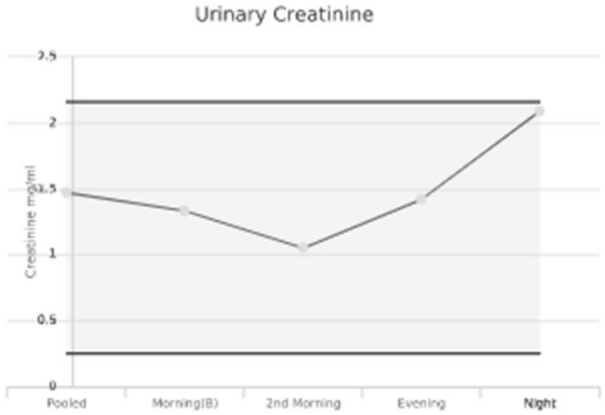
URINARY EXCITATORY NEUROTRANSMITTERS			
Test name	**Current Result**	**Previous**	**Reference Range**
Dopamine	168.98		125.20~254.70 mcg/g
Norepinephrine (pooled)	30.57		15.40~34.30 mcg/g
Epinephrine (pooled)	3.57		1.20~5.10 mcg/g
Histamine	17.94		4.80~21.70 mcg/g
Glutamate	1506.79		1479.80~3566.90 mcg/g
Aspartate	2718.00		900.50~3178.70 mcg/g
Tryptophan	10.30		4.15~15.90 mg/g
Acetylcholine	4.32		1.70~5.90 mcg/g
PEA	14.50		4.10~22.40 mcg/g
DOPAC	1536.32		577.30~1655.50 mcg/g
HVA	5039.53		3535.00~8455.00 mcg/g
Normetanephrine	19.66		15.00~36.70 mcg/g
VMA	3819.27		2411.20~5047.80 mcg/g
Oxytocin	255.07		250.10~705.00 mcg/g

OTHER NEUROTRANSMITTERS			
Test name	**Current Result**	**Previous**	**Reference Range**
Metanephrine	108.79		40.60~127.80 mcg/g
Tryptamine	59.70		15.80~115.70 mcg/g
Tyrosine	10255.80		5011.00~12668.00 mcg/g
Tyramine	291.54		200.10~457.20 mcg/g
Serine	23.49		13.70~40.90 mg/g
5-HTP	48.35		11.40~185.60 mcg/g
L-DOPA	520.03		0.10~855.80 mcg/g
3-Methoxytyramine (3-MT)	33.03		13.60~35.20 mcg/g
Xanthurenic acid	0.10		0.10~1.60 mg/g
Quinolinic acid	1161.96		610.30~2432.90 mcg/g
Kynurenic acid	457.10		125.60~991.30 mcg/g

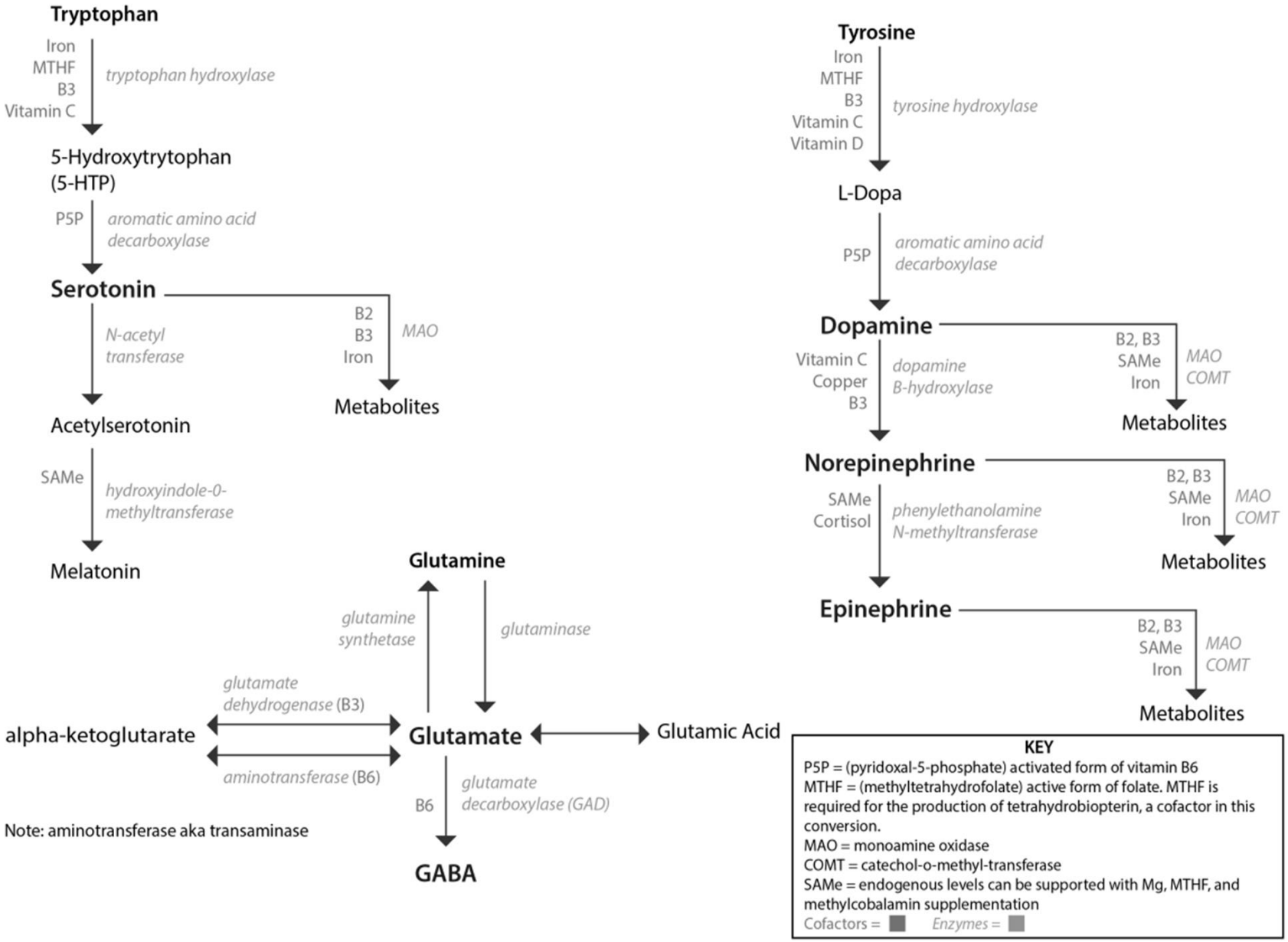
And in context of daily cycle







Nutritional components of NT generation



Nutraceutical Modulation of Serotonin

- 5-HTP: 50–100 mg tid with meals
  - Increases serotonin
  - Reduce dosage to 100 mg qd 1 hr before bed if taken with St. John's wort
  - Should be taken with pyridoxal 5-phospate (P5P)
- St. John's wort: 300 mg tid (0.3% hypericin content)
  - Works synergistically with 5-HTP
- SAM (S-adenosyl-methionine): 1,600 mg qd
  - Possibly raises dopamine levels
- Melatonin: 2–20 mg qd one hour before bed
- *Try slowly with individual patients, monitor response, and alter dosage accordingly.*
- *Use carefully with SSRIs/SNRIs or MAOIs!*
  - *Caruso I, et al. J Int Med Res. 1990;18:201-209. Puttini, PS, Caruso I. J Int Med Res. 1992;20:182-189*

Additional support for Serotonin

- Also consider Phosphatidylserine
  - Adaptogenic Effects for Adrenals and methylation cascades
- Avoid licorice, rhodiola, and ginseng, as they can be stimulants.
  - American ginseng is ok, german cammomile
- Promote proper sleep, circadian rhythm, and stress management.
- Additional papers
  - Schneider M, Brady DM. Fibromyalgia Syndrome: A New Paradigm for Differential Diagnosis and Treatment JMPT, Vol. 24, No. 8, Oct. 2001
  - CMAJ, Sept 17, 2013, 185 (13)

Additional Inhibitory NT support

- Vitamin B6
- Folate (5-MTHF)
- Vitamin B12
  - Methylcobalamin
  - Hydroxycobalamin
- Magnesium glycinate
- Zinc
- Selenium
- Taurine
- L-theanine
- GABA
  - Liposomal preferred
- Tyrosine
- DL Phenylalanine
  - PEA
- N-acetyltyrosine
- Mucuna cochinchinensis
- Mucuna pruriens (velvet bean)

Dopamine, Epinepherine, and NorEpinepherine

- **Low dopamine**
  - N-acetyl l-tyrosine
    - 50-1500 mg
  - Macuna Pruriens
    - 200-400 mg
  - L-theanine
    - 100-400 mg bid
  - Vitamin D
    - 1,000-10,000 IU
  - Cofactors
    - Vitamin C - 4-6 gm
    - Iron - 25-50 mg
    - Vitamin B3 - 50 mg
    - P5P - 50-200 mg
    - MTHF – 1-3 mg/day or more

- **High dopamine**
  - L-theanine
    - 100-400 mg bid
  - Co-factors
    - *(to support MAO/COMT)*
    - Vitamin B2: 50 mg
    - Vitamin B3: 50 mg
    - Iron: 25-50 mg
    - SAMe: 250-500 mg
  - Co-factors
    - *(if NorEpi low or low range)*
    - Vitamin C
      - 4,000-6,000 mg
    - Copper: 0.5-1 mg
    - Vitamin B3: 50 mg

The Culture of Stimulation

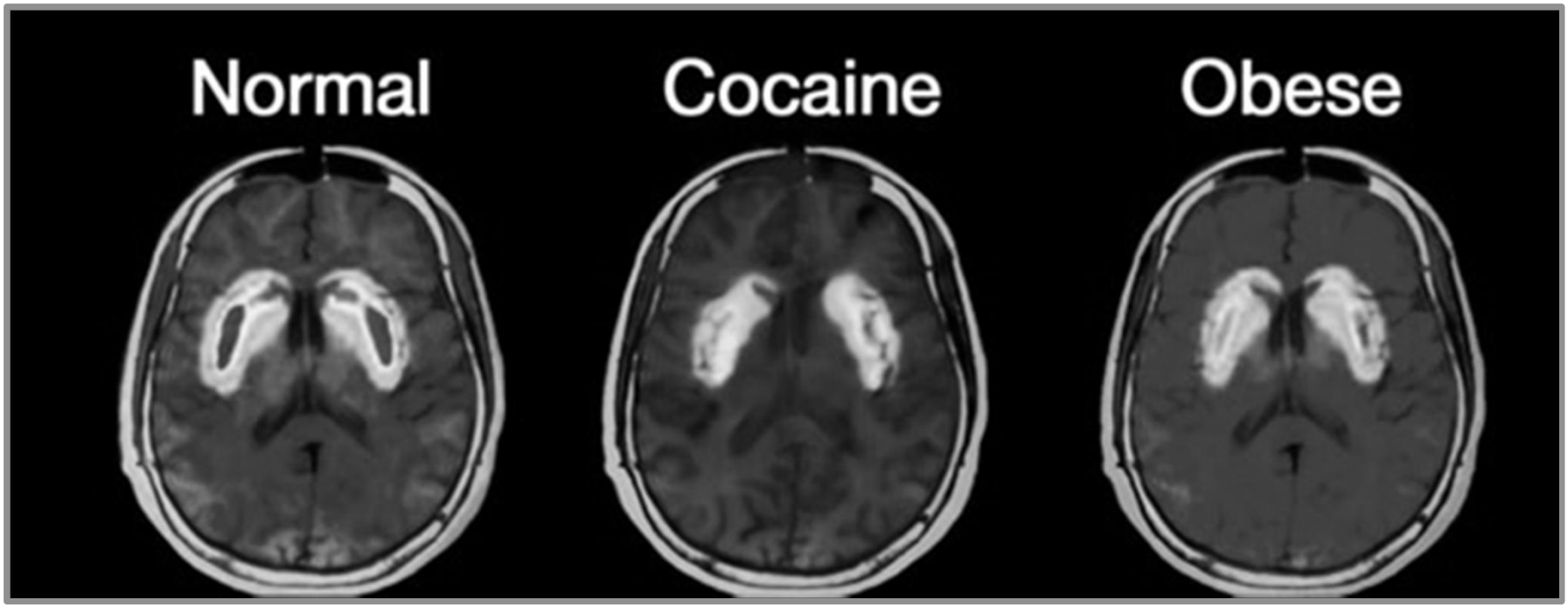
- All dopamine stimulation contributes
  - Phones, Social media, etc.
- Pornography - dopamine hit, increasing stimulation with higher and higher threshold
- Porn gives escalating dopamine hit with no oxytocin/vasopressin balance for pair bonding and nesting instincts.
  - Mooney SJ, Douglas NR, Holmes MM. Peripheral administration of oxytocin increases social affiliation in the naked mole-rat (Heterocephalus glaber). Horm Behav. 2014 Apr;65(4):380-5. doi: 10.1016/j.yhbeh.2014.02.003. Epub 2014 Feb 13. PMID: 24530845.
  - Hathaway GA, Faykoo-Martinez M, Peragine DE, Mooney SJ, Holmes MM. Subcaste differences in neural activation suggest a prosocial role for oxytocin in eusocial naked mole-rats. Horm Behav. 2016 Mar;79:1-7. doi: 10.1016/j.yhbeh.2015.12.001. Epub 2015 Dec 21. PMID: 26718226.
  - Chappell AR, Freeman SM, Lin YK, LaPrairie JL, Inoue K, Young LJ, Hayes LD. Distributions of oxytocin and vasopressin 1a receptors in the Taiwan vole and their role in social monogamy. J Zool (1987). 2016 Jun;299(2):106-115. doi: 10.1111/jzo.12332. Epub 2016 Mar 1. PMID: 27453637; PMCID: PMC4956092.
- More separation between sex and love - increasing risky behavior with higher dopamine threshholds, since the gratification signals are not enforced by subsequent oxytocin release.
- The earlier in life this occurs, the more permanent the damage, as we as a society are seeing from the hypersexualization of media exposed to our children and subsequent dopamine threshold desensitization.
  - Kühn S, Gallinat J. Brain structure and functional connectivity associated with pornography consumption: the brain on porn. JAMA Psychiatry. 2014 Jul 1;71(7):827-34. doi: 10.1001/jamapsychiatry.2014.93. PMID: 24871202.
  - Karila L, Wéry A, Weinstein A, Cottencin O, Petit A, Reynaud M, Billieux J. Sexual addiction or hypersexual disorder: different terms for the same problem? A review of the literature. Curr Pharm Des. 2014;20(25):4012-20. doi: 10.2174/13816128113199990619. PMID: 24001295.
  - Love T, Laier C, Brand M, Hatch L, Hajela R. Neuroscience of Internet Pornography Addiction: A Review and Update. Behav Sci (Basel). 2015 Sep 18;5(3):388-433. doi: 10.3390/bs5030388. PMID: 26393658; PMCID: PMC4600144.

Metabolism

The Sad Reality of our American Diet

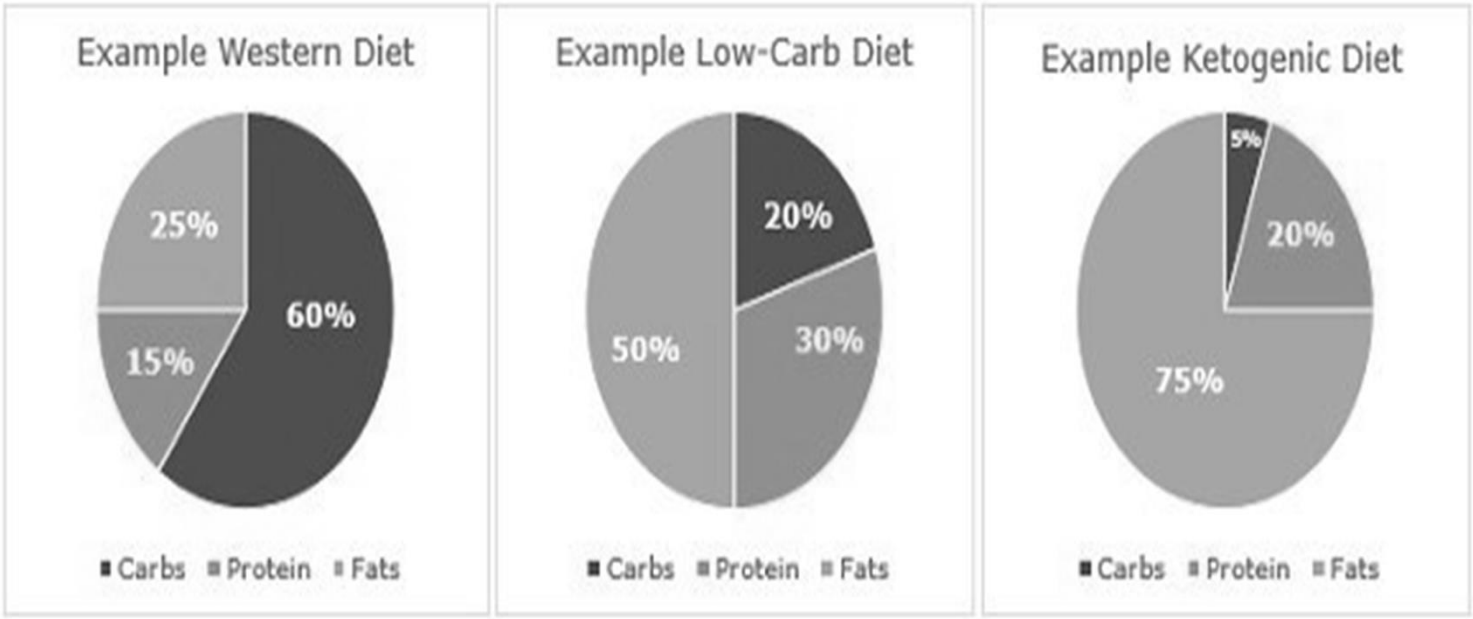
You eat fats and proteins for nutrition.

You eat carbohydrates for emotional reasons


Normal
Cocaine
Obese

Effects of a Ketogenic Diet

- Reduces NFKB activity/inflammation
- Enhances mitochondrial numbers
- Enhances ATP production and cellular energy
- Reduces Reactive Oxidative Stress
- Reduces programmed cell death (apoptosis)

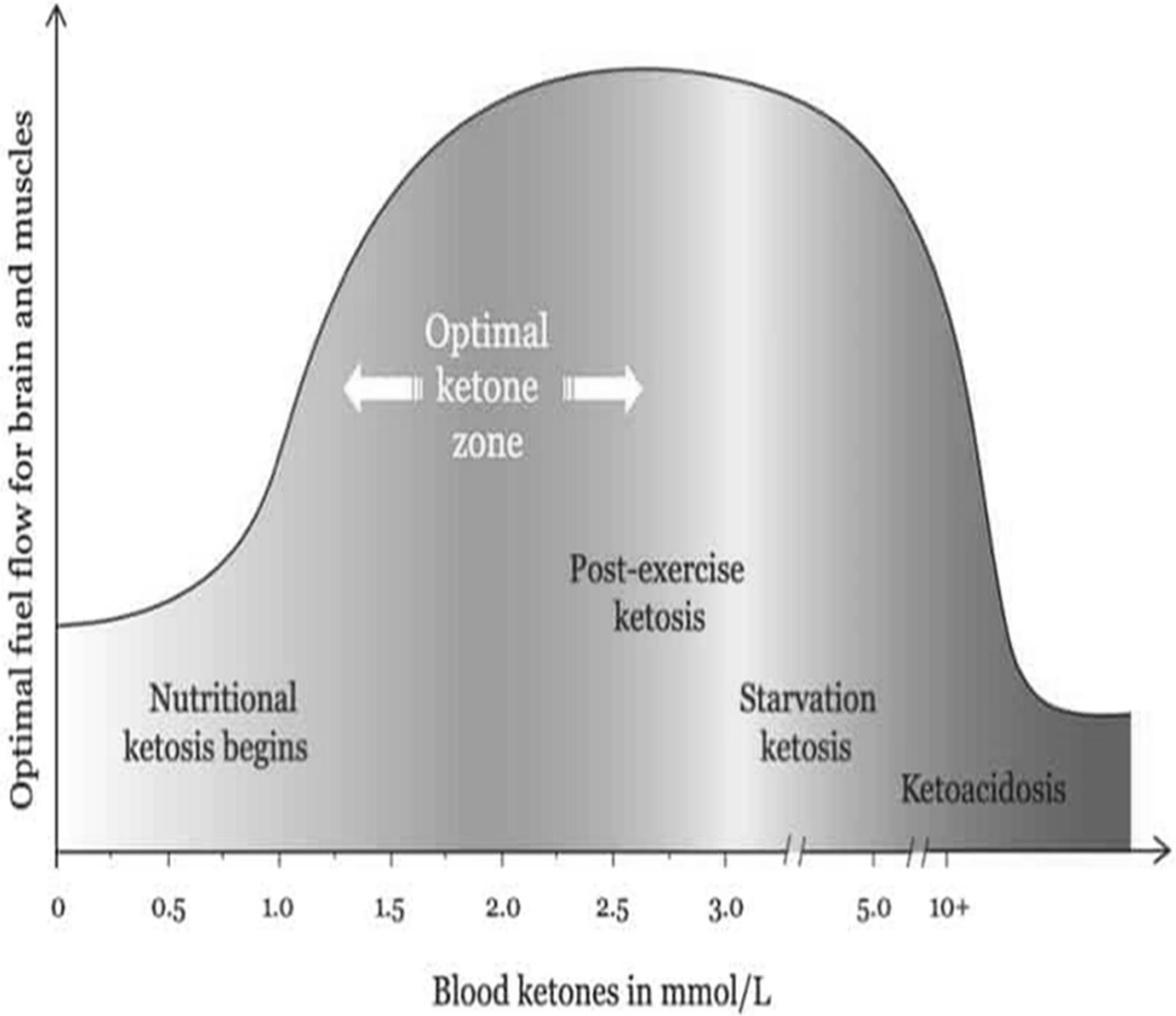


Strict keto: 20-30 g net carbs – the hard line

70% fat, 25% protein, 5% carb

Modified keto: 40-50% fat, 30% protein, 20-30% carb,

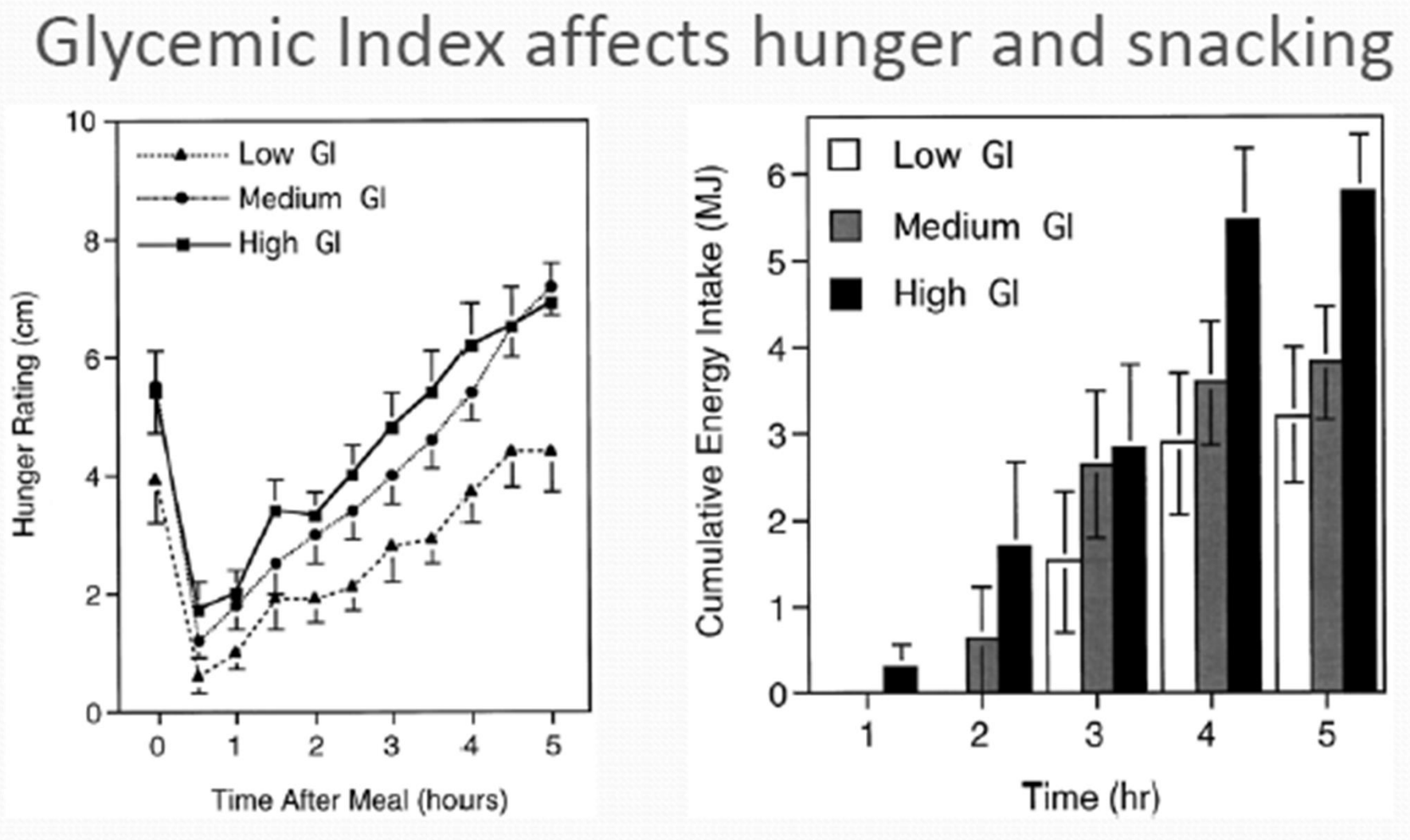
(Increase net carbs on exercise 3 days per week)



Spritzler, F. RD, CDE & Scher, B., MD. (2020 March 23). *The Complete Guide to Ketosis.* Diet Doctor.

Not as hungry on Low GI diets than High GI diets

Pediatrics 1999, 103(3)



Ketogenic diet enhanced with:

- Coconut oil/MCT oil
- Restricted carbohydrates
- Increased dietary fat
- Exercise
- Good salt
- Intermittent fasting
- Regular exercise
- Lower stress
- Good sleep

Problems with Keto

- It's complicated
- It requires math – a LOT of math.
  - Which makes me stressed.
  - Which makes me want to eat.
- We did not evolve in the middle of an avocado plantation.

"Will I be doing this forever?"

ChronoEthnoBiology

Lessons from our tribal ancestors.

Keto part of year, carbs toward winter for fats, antioxidants in spring.

We are designed to be carnivores

- Teeth designed closer to an obligate carnivore than an herbivore.
- Pancreatic insulin output matches proteins and fats, but consistently overshoots carbohydrates.
- Steroscopic, forward facing eyes.
- Stomach pH more acidic, similar to a lion's rather than the more alkaline pH of an herbivore.
- A brain that operates more efficiently on ketone bodies than on blood glucose.

Humans Are Meant To Eat Meat

@ancestralhealthguy

Stomach Acid PH:



1.5 2.5 5.5 Neutral

0 1 2 3 4 5 6 7

Acidic

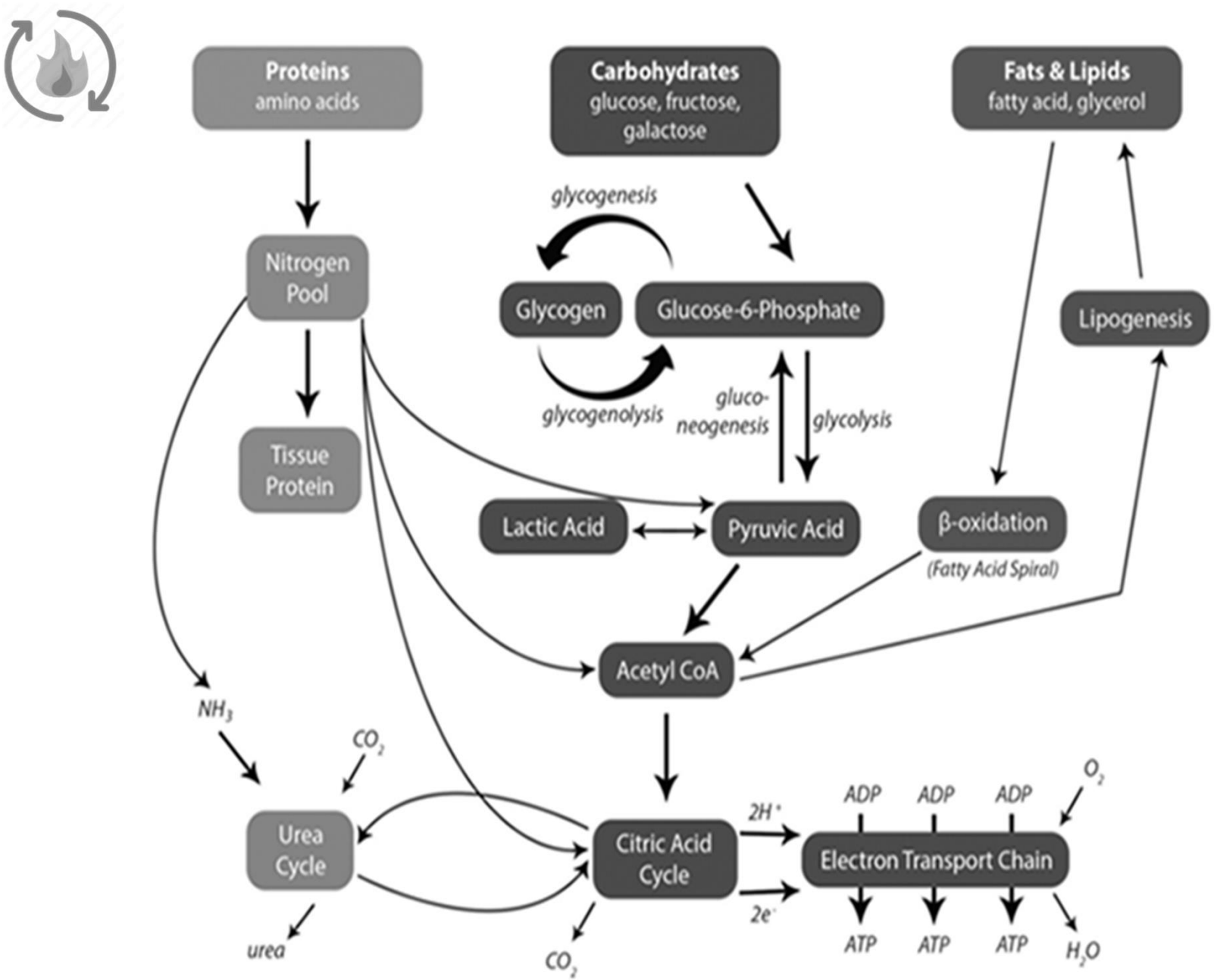
2

4.7

6.5

CARNIVORE

- A ketogenic, carnivorous diet is what allows lengthy, natural fasting and naturally stimulates an intermittent fasting habit with good functioning and little to no hunger.
- Micronutrients in prized meats by Indians and Lions
  - "What do they go for first?"
- Importance of organ meats periodically for micronutrients.
- Exercise - at end of fasting period



Everything they taught you about normal cellular metabolism is a lie.

Carnivore

ORIGINAL RESEARCH

Nutritional Requirements and Status

CURRENT DEVELOPMENTS IN NUTRITION

Behavioral Characteristics and Self-Reported Health Status among 2029 Adults Consuming a "Carnivore Diet"

Belinda S Lennerz,[1,2,3] Jacob T Mey,[4] Owen H Henn,[1,2] and David S Ludwig[1,2,3]

[1]New Balance Foundation Obesity Prevention Center, Boston Children's Hospital, Boston, MA, USA; [2]Division of Endocrinology, Boston Children's Hospital, Boston, MA, USA; [3]Department of Pediatrics, Harvard Medical School, Boston, MA, USA; and [4]Integrated Physiology and Molecular Medicine, Pennington Biomedical Research Center, Baton Rouge, LA, USA

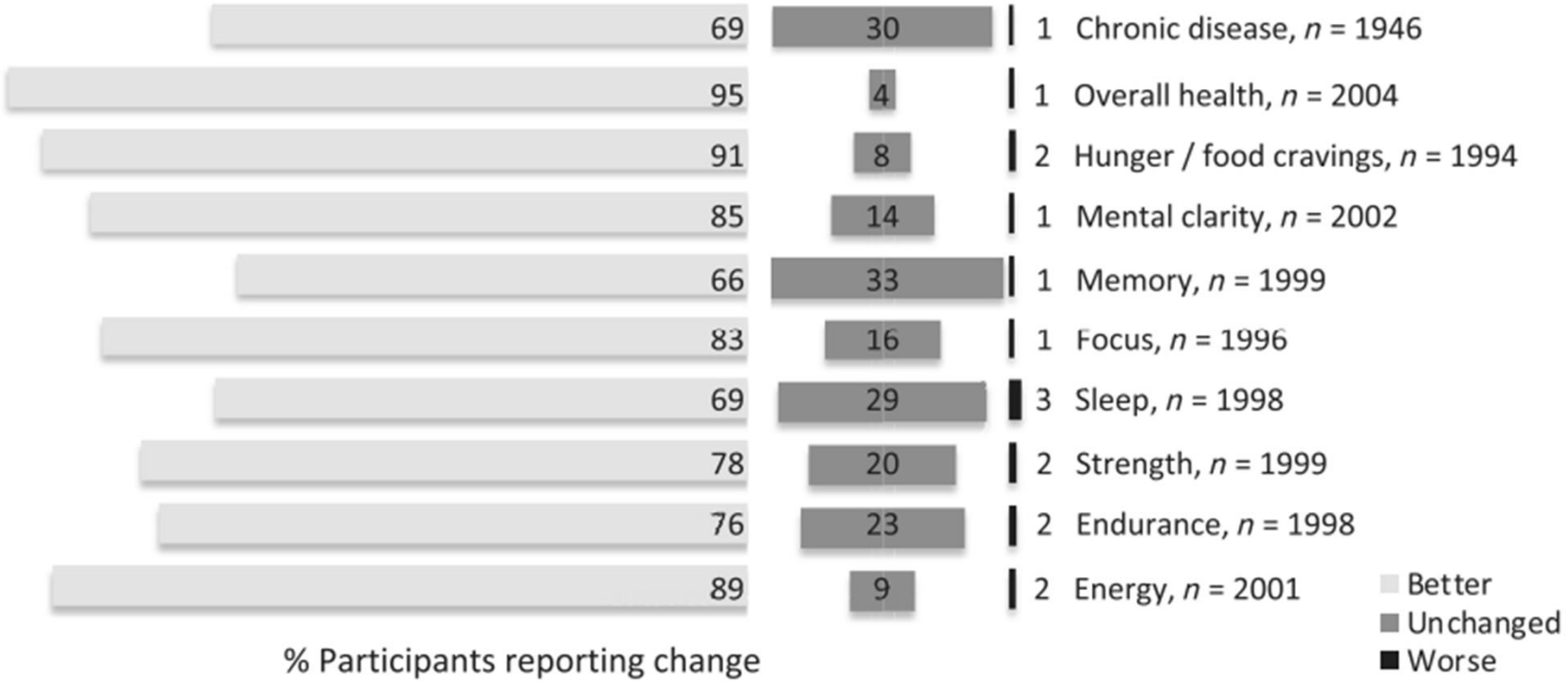
ABSTRACT

Background: The "carnivore diet," based on animal foods and excluding most or all plant foods, has attracted recent popular attention. However, little is known about the health effects and tolerability of this diet, and concerns for nutrient deficiencies and cardiovascular disease risk have been raised.

Objectives: We obtained descriptive data on the nutritional practices and health status of a large group of carnivore diet consumers.

Methods: A social media survey was conducted 30 March–24 June, 2020 among adults self-identifying as consuming a carnivore diet for ≥6 mo. Survey questions interrogated motivation, dietary intake patterns, symptoms suggestive of nutritional deficiencies or other adverse effects, satisfaction, prior and current health conditions, anthropometrics, and laboratory data.

Results: A total of 2029 respondents (median age: 44 y, 67% male) reported consuming a carnivore diet for 14 mo (IQR: 9–20 mo), motivated primarily by health reasons (93%). Red meat consumption was reported as daily or more often by 85%. Under 10% reported consuming vegetables, fruits, or grains more often than monthly, and 37% denied vitamin supplement use. Prevalence of adverse symptoms was low (<1% to 5.5%). Symptoms included gastrointestinal (3.1%–5.5%), muscular (0.3%–4.0%), and dermatologic (0.1%–1.9%). Participants reported high levels of



Chronic condition	Prevalence, *n* (%)	Changes when following diet, %				
		Resolved	Improved	Unchanged	Worsened	New
Obesity/overweight	928 (46)	52	41	5	1	0.2
Underweight	100 (5)	52	28	14	5	1
Lipid abnormalities	429 (21)	27	29	18	19	8
Hypertension	374 (18)	61	32	7	0.3	0.0
Cardiovascular	126 (6)	41	43	15	0.8	0.8
Diabetes/insulin resistance	402 (20)	74	24	1	0.0	0.0
Gastrointestinal	531 (26)	59	38	1	1	0.2
Endocrinologic	191 (9)	40	48	12	0.5	0.0
Autoimmune	369 (18)	36	53	11	0.0	0.0
Musculoskeletal	502 (25)	42	54	4	0.0	0.2
Neurological	89 (4)	42	42	16	1	0.0
Cognitive	100 (5)	42	54	4	0.0	0.0
Psychiatric	479 (24)	48	48	4	0.0	0.0
Respiratory	354 (17)	51	34	14	0.0	0.0
Urologic	181 (9)	76	16	8	0.0	0.6
Dermatologic	690 (34)	44	48	7	0.6	0.1
Ophthalmologic	327 (16)	12	36	51	0.6	0.6
Hematologic	127 (6)	66	18	14	0.0	2
Oncologic	75 (4)	41	12	47	0.0	0.0
Other	208 (10)	42	45	13	0.0	1
Diabetes medications		**Discontinued**	**Decreased**	**Unchanged**	**Increased**	**New**
Insulin	29 (1)	52[2]	38	3	0.0	7
Insulin (T2DM only)	13 (0.6)	92	0.0	0.0	0.0	8
Diabetes injectables, other	16 (0.8)	100	0.0	0.0	0.0	0.0
Oral diabetes medications	82 (4)	84	14	2	0.0	0.0

[1]Participants were asked if they had ever suffered from or taken any of the listed conditions or medications. *n* (%) of positive responses is given in the first column (prevalence) and is the denominator for percentages in the subsequent columns. Positive respondents were then asked to rate the severity of each condition relative to the time before starting the carnivore diet on a 5-point scale. For visualization, response frequencies are color-coded dark gray if ≥70%, and in increasing brightness if 40%–69%, 20%–39%, 10%–19%, 5%–9%, 1%–4%, and <1%. T2DM, type 2 diabetes mellitus.

[2]Includes people with type 1 diabetes mellitus and T2DM.

- *The power of social media to spread unconventional approaches.*
- 72 yo male, Keto for 6 years.
- Regression of plaque from 99% to 37% stenosis in 1 year on Carnivore.

Fasting and Carnivore Overcoming plateaus

- Add fasting starting month 2
- Exercise even through fasting - looking to maximize HGH and stem cells on day 3
- At least one 3 day fast per month for this effect
- Resistance exercise mostly to maximize HGH increase muscle increase testosterone feedback
  - The best exercise: 'Pick up heavy things and put them back down again."

Fasting

Day 1: Drop in blood sugar and insulin, continues throughout

Day 2: Weight loss begins as body passes into ketosis

Day 3: Peak in Autophagy and induced HGH levels

Day 4: Plateau of Intestinal, musculoskeletal, and Immune stem cells

- Fasting is easier when already in a ketogenic state.
- Milder effects can be seen with intermittent fasting.
- Similar effects can be had with a **guided Fasting Mimicking Diet** for 3-5 days once a month.

- Wilhelmi de Toledo F, Grundler F, Bergouignan A, Drinda S, Michalsen A. Safety, health improvement and well-being during a 4 to 21-day fasting period in an observational study including 1422 subjects. PLoS One. 2019 Jan 2;14(1):e0209353. doi: 10.1371/journal.pone.0209353. PMID: 30601864; PMCID: PMC6314618. https://pubmed.ncbi.nlm.nih.gov/30601864/
- Antunes F, Erustes AG, Costa AJ, Nascimento AC, Bincoletto C, Ureshino RP, Pereira GJS, Smaili SS. Autophagy and intermittent fasting: the connection for cancer therapy? Clinics (Sao Paulo). 2018 Dec 10;73(suppl 1):e814s. doi: 10.6061/clinics/2018/e814s. PMID: 30540126; PMCID: PMC6257056. https://pubmed.ncbi.nlm.nih.gov/30540126/

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CLINICAL AND TRANSLATIONAL REPORT

A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan

Sebastian Brandhorst[15], In Young Choi[15], Min Wei, Chia Wei Cheng, Sargis Sedrakyan, Gerardo Navarrete, Louis Dubeau, Li Peng Yap, Ryan Park, Manlio Vinciguerra, Stefano Di Biase, Hamed Mirzaei, Mario G. Mirisola, Patra Childress, Lingyun Ji, Susan Groshen, Fabio Penna, Patrizio Odetti, Laura Perin, Peter S. Conti, Yuji Ikeno, Brian K. Kennedy, Pinchas Cohen, Todd E. Morgan, Tanya B. Dorff, Valter D. Longo

[15] Co-first author

Published Online: June 18, 2015

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DOI: https://doi.org/10.1016/j.cmet.2015.05.012 | CrossMark

Article Info

▾Highlights

- FMD rejuvenates the immune system and reduces cancer incidence in C57BL/6 mice
- FMD promotes hippocampal neurogenesis and improves cognitive performance in mice
- FMD causes beneficial changes in risk factors of age-related diseases in humans

▾Summary

Prolonged fasting (PF) promotes stress resistance, but its effects on longevity are poorly understood. We show that alternating PF and nutrient-rich medium extended yeast lifespan independently of established pro-longevity genes. In mice, 4 days of a diet that mimics fasting (FMD), developed to minimize the burden of PF, decreased the size of multiple organs/systems, an effect followed upon re-feeding by an elevated number of progenitor and stem cells and regeneration. Bi-monthly FMD cycles started at middle age extended longevity, lowered visceral fat, reduced cancer incidence and skin lesions, rejuvenated the immune system, and retarded bone mineral density loss. In old mice, FMD cycles promoted hippocampal neurogenesis, lowered IGF-1 levels and PKA activity, elevated NeuroD1, and improved cognitive performance. In a pilot clinical trial, three FMD cycles decreased risk factors/biomarkers for aging, diabetes, cardiovascular disease, and cancer without major adverse effects, providing support for the use of FMDs to promote healthspan.

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Images/Data

Figure 1 ▼ View all Images/Data

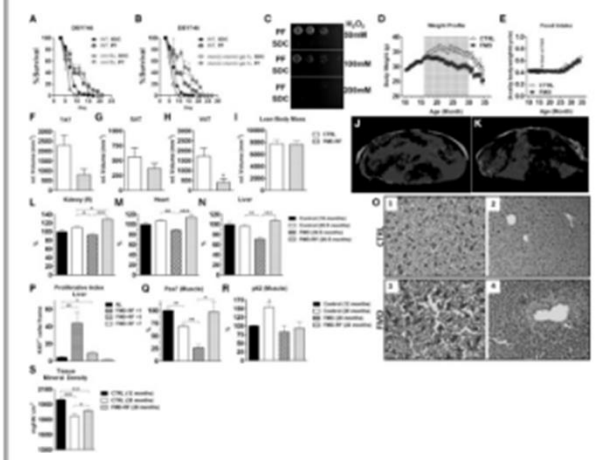
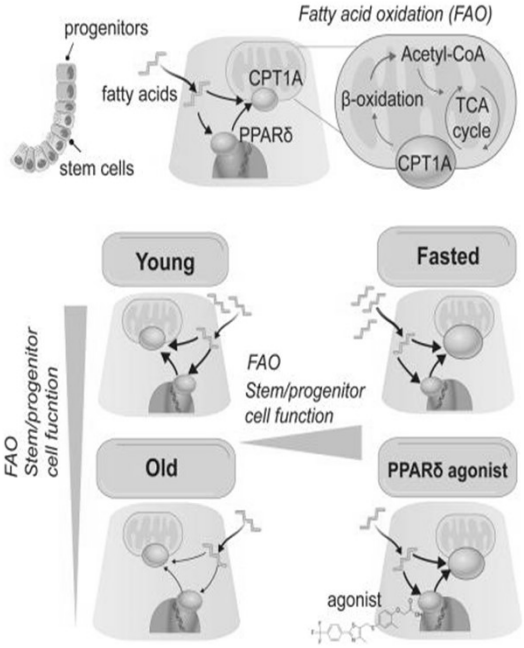


Figure 1

Periodic FMD Promotes a Lean Bodyweight, Improves Healthspan, and Promotes Tissue Regeneration

Fasting boosts stem cells' regenerative capacity

"This study provided evidence that fasting induces a metabolic switch in the intestinal stem cells, from utilizing carbohydrates to burning fat," Sabatini says. "Interestingly, switching these cells to fatty acid oxidation enhanced their function significantly. Pharmacological targeting of this pathway may provide a therapeutic opportunity to improve tissue homeostasis in age-associated pathologies."



Further studies, including sequencing the messenger RNA of stem cells from the mice that fasted, revealed that fasting induces cells to switch from their usual metabolism, which burns carbohydrates such as sugars, to metabolizing fatty acids. This switch occurs through the activation of transcription factors called PPARs, which turn on many genes that are involved in metabolizing fatty acids.

In fasting mice, cells begin breaking down fatty acids instead of glucose, a change that stimulates the stem cells to become more regenerative. The researchers found that they could also boost regeneration with a molecule that activates the same metabolic switch. Such an intervention could potentially help older people recovering from GI infections or cancer patients undergoing chemotherapy, the researchers say.

MIT Biology, May 1, 2018 - Mihaylova MM, Cheng CW, Cao AQ, Tripathi S, Mana MD, Bauer-Rowe KE, Abu-Remaileh M, Clavain L, Erdemir A, Lewis CA, Freinkman E, Dickey AS, La Spada AR, Huang Y, Bell GW, Deshpande V, Carmeliet P, Katajisto P, Sabatini DM, Yilmaz ÖH. Fasting Activates Fatty Acid Oxidation to Enhance Intestinal Stem Cell Function during Homeostasis and Aging. Cell Stem Cell. 2018 May 3;22(5):769-778.e4. doi: 10.1016/j.stem.2018.04.001. PMID: 29727683; PMCID: PMC5940005.
https://biology.mit.edu/fasting-boosts-stem-cells-regenerative-capacity/

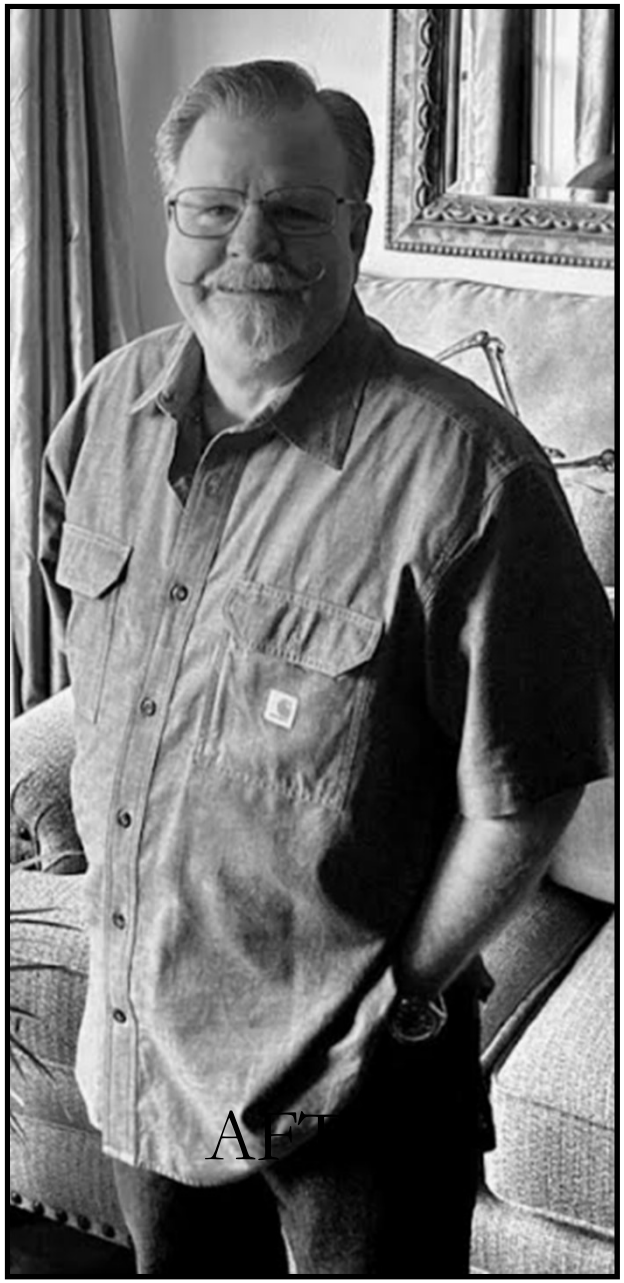
Case Study

- 55 yo Caucasian male – 300+ lbs
  - Spinal Stenosis
  - Andropause
  - Diabetic II
  - Adrenal Exhaustion
  - Sub clinical hypothyroid
  - High Trig
  - Low Vit D
  - High hsCRP
  - Elevated PSA
  - Elevated uric acid
  - Arthritis
  - Obstructive Sleep Apnea

Tx

- Carnivore diet
  - No dairy, no eggs (tested allergy)
- Nitric Oxide support
- Adrenal support w/ glandular
- Curcumin based anti-inflammatory
- B6/folate/B12 combination
- Herbal steroidogenic support for testosterone

- 55 lb weight loss
- Spinal Stenosis – symptoms: Mild improvement.
- Calprotectin - 13 mcg/g (was 133.5) (inflam)
- hsCRP 8.0 H (was 10.8) (<3)
- HCy - 7.6 (was 16)
- Fast Gluc 119 (was 126)
- Ki better
- HbA1c - 5.1 (was 7.7)
- Uric Acid - 7.6 (was 7.8) ** (NO need)
- FT3 - 3.2 (was 2.8)
- Sed Rate 11 (was 28 H)
- Lp(a) 251 nmol/L H (<75) (was 278.5 nmol/L)
- AM Cortisol 19.5 (was 8.1)
- PSA 7.54 (was 3.94) **
- (likely steroidogeneis or estrogenic detox)
- Insulin - 21.4 H (was 33.3)
- Testosterone - 237 L (was 79.5)
- Vit D - 36 (was 19.9)
- Tot Chol - 159 (was 196)
- HDL 36 (was 34) Trig 148 (was 240)
- LDL - 98 (was 114)
- Chol/HDL - 4.4 (was 5.8)



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Of Mice and Men: Societal factors

Calhoun's Mice

Reproductive measures and environment

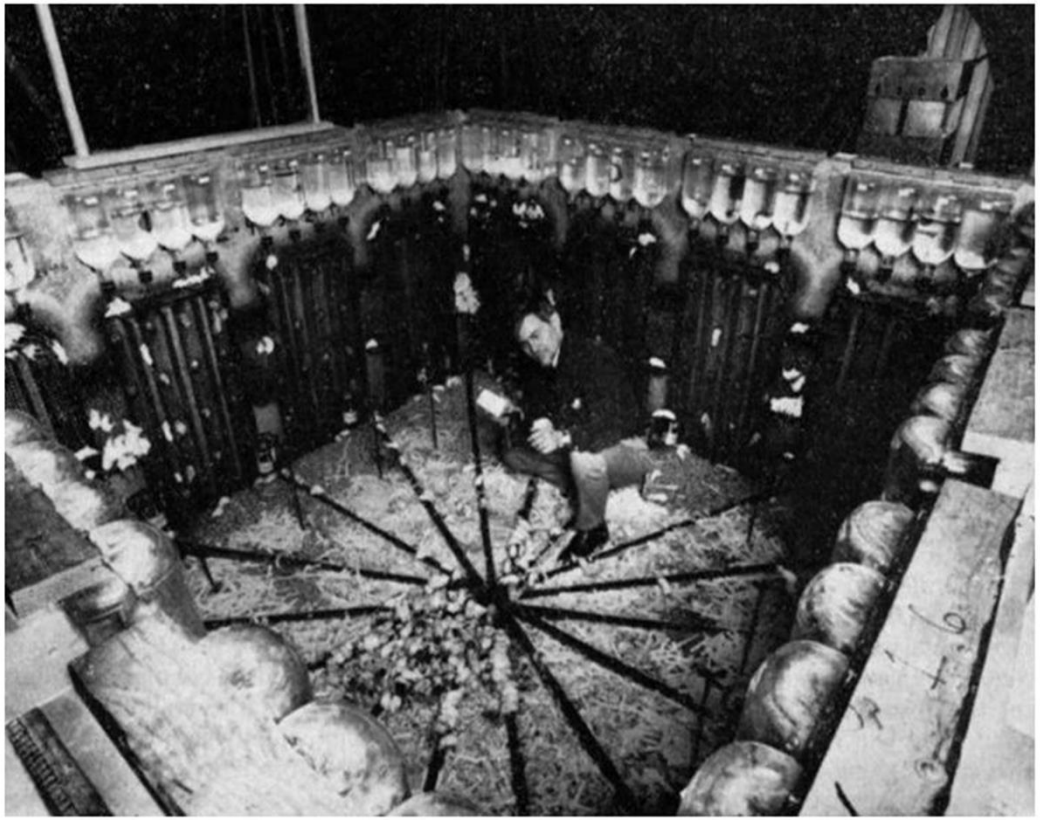


Image Credit: Public Domain (via Smithsonian Magazine)

Calhoun enclosed four pairs of mice in a 9 x 4.5-foot metal pen complete with water dispensers, tunnels, food bins and nesting boxes. He provided all the food and water they needed and ensured that no predator could gain access. It was a mouse utopia.

Calhoun, John B. (1973). "Death Squared: The Explosive Growth and Demise of a Mouse Population". Proc. R. Soc. Med. 66 (1 Pt 2): 80–88. PMC 1644264. PMID 4734760.

At first, the mice did well. Their numbers doubled every 55 days. But after 600 days, with enough space to accommodate as many as another 1,600 rodents, the population peaked at 2,200 and began to decline precipitously —straight down to the extinction of the entire colony—in spite of their material needs being met with no effort required on the part of any mouse.

The turning point in this mouse utopia, Calhoun observed, occurred on Day 315 when the first signs appeared of a breakdown in social norms and structure. Aberrations included the following: females abandoning their young; males no longer defending their territory; and both sexes becoming more violent and aggressive. Deviant behavior, sexual and social, mounted with each passing day. The last thousand mice to be born tended to avoid stressful activity and focused their attention increasingly on themselves.

Other young mice growing into adulthood exhibited an even different type of behavior. Dr. Calhoun called these individuals "the beautiful ones." Their time was devoted solely to grooming, eating and sleeping. They never involved themselves with others, engaged in sex, nor would they fight. All appeared [outwardly] as a beautiful exhibit of the species with keen, alert eyes and a healthy, well-kept body. These mice, however, could not cope with unusual stimuli. Though they looked inquisitive, they were in fact, very stupid.

Is this why birth rates are plummeting?

Is this why testosterone levels are decreasing?

Are we becoming Calhoun's mice?

Are we becoming the “Beautiful Ones”?

Lessons from Calhoun's Mice

- Calhoun's model used space restriction to put social pressures on mouse society
- This can be physical limitations, or in a more applicable sense, limitations placed on roles and purpose due to a lack of pressure or adversity which define an individual's sense of purpose, impart drive, and engage competitive behaviors and biology to maximize reproductive potential.

While Sex is about Vitality.

Vitality is only strengthened through Adversity:

Biologically, Psychologically, and Culturally.

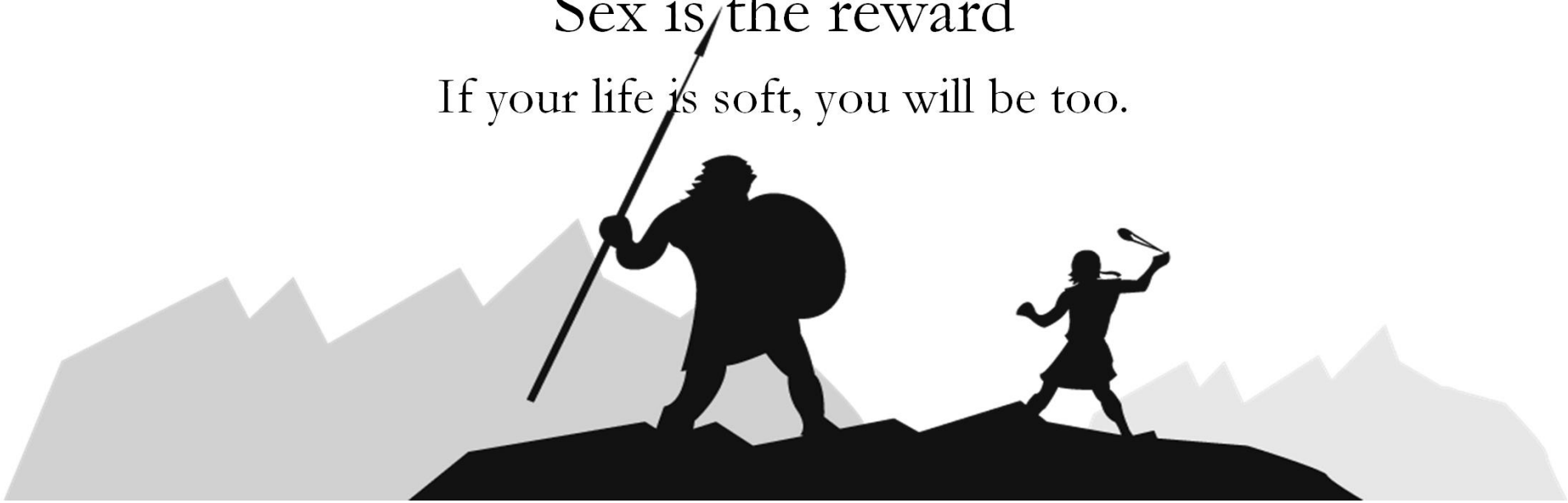
Purpose driven life with adversity

Seek separation from a society that biochemically, behaviorally and sociologically drives a reduced reproductive status and reduced vitality.

Life is hard.

Sex is the reward

If your life is soft, you will be too.



Let me leave you with this

Case #3

The Rut of Hopelessness

Thank you for your time and attention