Using Ozone To Stimulate Oxygen Utilization "It's all about NAD"

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Outline

1. Aging and the diseases of aging are caused primarily by decreased oxygen utilization.
2. This decrease leads to the excessive free radical production that results in degenerative disease.
3. Decreased ozygen utilization is caused by both pre-mitochondrial and mitochondrial factors.
4. Decreased oxygen utilization exerts its effects by causeing a decrease in the NAD/NADH ratio.
5. Ozone therapy is effective for so many diseases including the infirmaties of aging because it normalizes this ratio.

Aging and the diseases of aging are caused primarily by decreased oxygen utilization

It Works – But How?

- Coronary artery and cardiovascular disease.
- Claudication.
- Gangrene.
- Pain
- Macular degeneration.
- Aging.
- Oncology.
- Chronic viral infection.

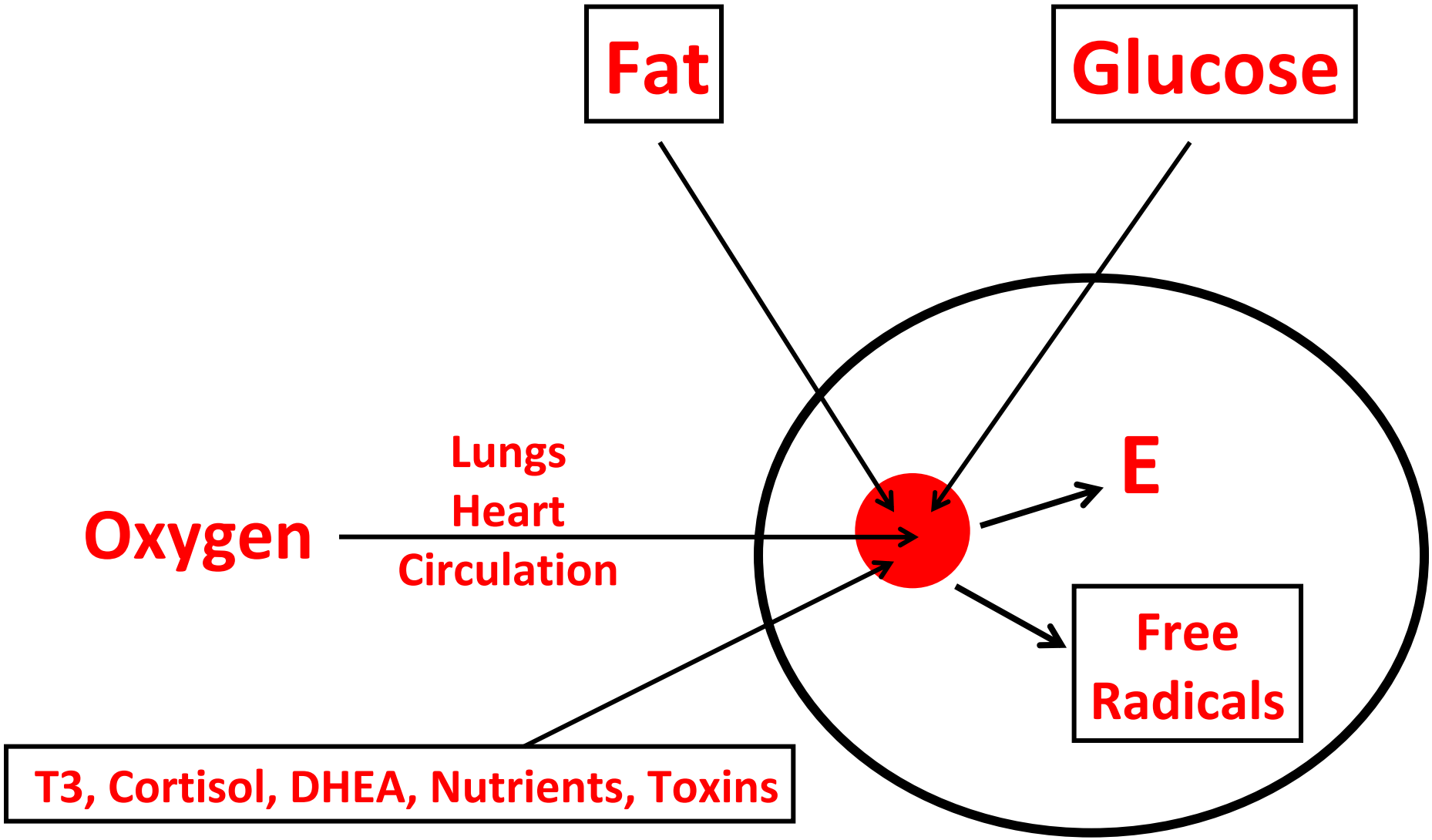
Oxygen – The Forgotten Nutrient

- The most critical nutrient.
- It's not what you take in, it's what you utilize.
- The difference between you at 20 and you at 70.
- The key to the treatment and prevention of disease is optimum oxygen utilization.
- Local and systemic oxygen utilization.
- The good news – oxygen utilization can be measured and improved.

Oxygen Utilization (Aerobic Capacity)

- The process whereby oxygen metabolizes either fat or glucose into water, heat, NAD (nicotinamide adenine dinucleotide), and ATP.
- Oxygen works through NAD and ATP (and to a lesser degree NADP and FAD). These “oxygen intermediates” are the bottom line for all cellular function.

Oxygen Utilization



Aging and Oxygen Utilization

Nothing is as consistent and as predictable as the gradual, linear decline in oxygen utilization seen in all aging populations.

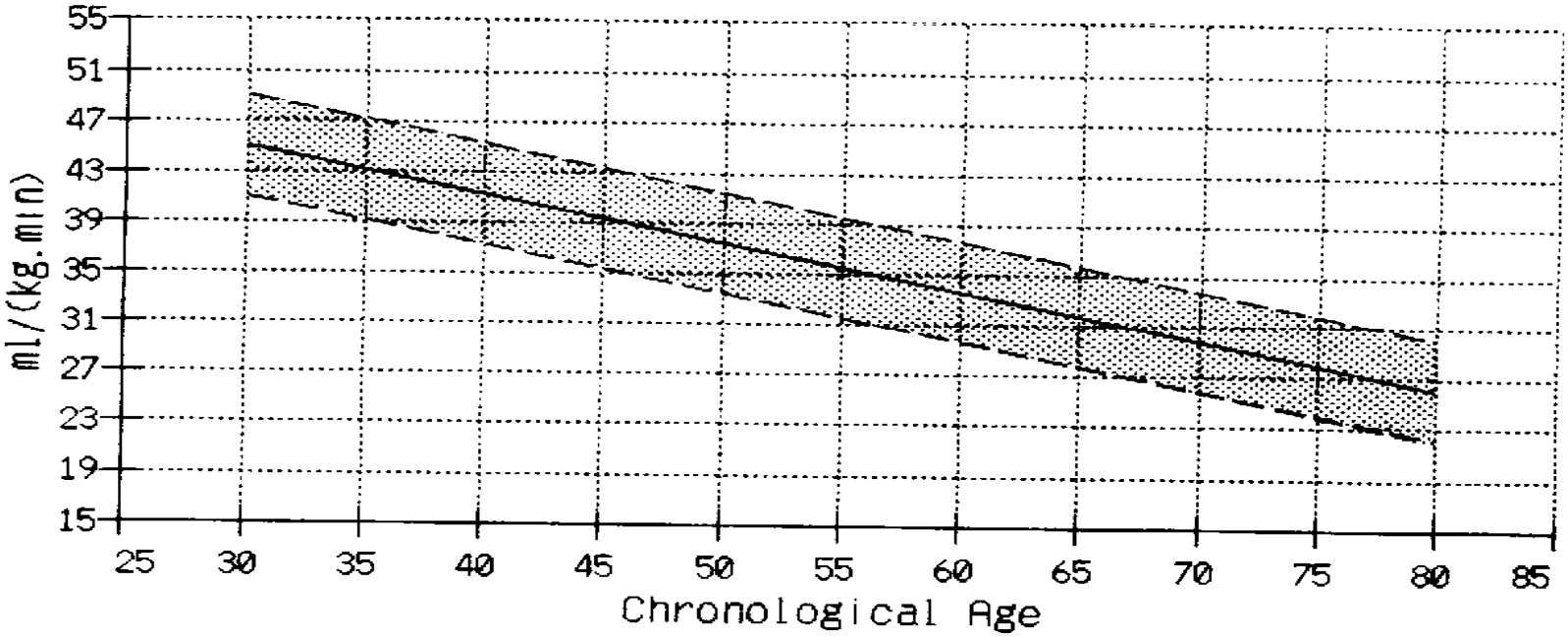


Fig. B. 1-8. **Maximal oxygen uptake—men, in ml/kg min** (Dehn and Bruce).

“Meta-analysis of the age associated decline in maximal aerobic capacity in men: relation to training status.”

Wilson & Tanaka, Am. J. Physiol. Heart Circ. Physiol. Vol. 278: 829-834, 2000

- Maximal aerobic capacity means maximal oxygen utilization.
- “Maximal aerobic capacity [not VO2max] is an independent risk factor for cardiovascular disease, cognitive dysfunction, and all cause mortality.”
- Even highly trained marathon runners showed a decrease in oxygen utilization. This means that oxygen utilization is the determining factor in aging not VO2max
- VO2 max is neither global nor sensitive enough.

Premature ageing in mice expressing defective mitochondrial DNA polymerase.

Trifunovic A, Wredenberg A, et al.
***Nature.* 2004 May 27;429(6990):417-23.**

- Mice are genetically manipulated to develop mtDNA mutations at a rapid rate. This results in an accelerated reduction in oxygen utilization over their lifespan.
- Significantly reduced lifespan.
- Premature onset of age-related phenotypes such as lean body mass loss, alopecia, kyphosis, anemia, osteoporosis, reduced fertility, and cardiomegaly.
- These results provide a causative link between decreased oxygen utilization and aging.

Uncoupled and surviving: individual mice with high metabolism have greater mitochondrial uncoupling and live longer.

Speakman JR, Talbot DA, et al.
***Aging Cell*. 2004 Jun;3(3):87-95.**

- Examined associations between longevity and individual variations in resting oxygen utilization in a cohort of mice.
- A positive association between oxygen utilization and lifespan was noted.
- Mice in the upper quartile of oxygen utilization lived **36% longer** than mice in the lowest quartile.

Oxygen Utilization and Disease

- Varanasi SS, Francis RM, et al. Mitochondrial DNA deletion associated oxidative stress and severe male **osteoporosis**. Osteoporos Int. 1999;10(2):143-9.
- Liang FQ, Godley BF. Oxidative stress-induced mitochondrial DNA damage in human retinal pigment epithelial cells: a possible mechanism for RPE aging and **age-related macular degeneration**. Exp Eye Res. 2003 Apr;76(4):397-403.

Oxygen Utilization and Disease

- Patwari P, Lee RT. Thioredoxins, mitochondria, and **hypertension**. Am J Pathol. 2007 Mar;170(3):805-8.
- Eerola E, Pulkki K, et al. Abnormal mitochondria in cultured synovial fibroblasts in **rheumatoid and reactive arthritis**? Br J Rheumatol. 1988;27 Suppl 2:128-31.

Oxygen Utilization and Disease

- Modica-Napolitano JS, Kulawiec M, et al. Mitochondria and **human cancer**. Curr Mol Med. 2007 Feb;7(1):121-31.
- Gerbitz KD, Gempel K, Brdiczka D. Mitochondria and **diabetes**. Genetic, biochemical, and clinical implications of the cellular energy circuit. Diabetes. 1996 Feb;45(2):113-26.

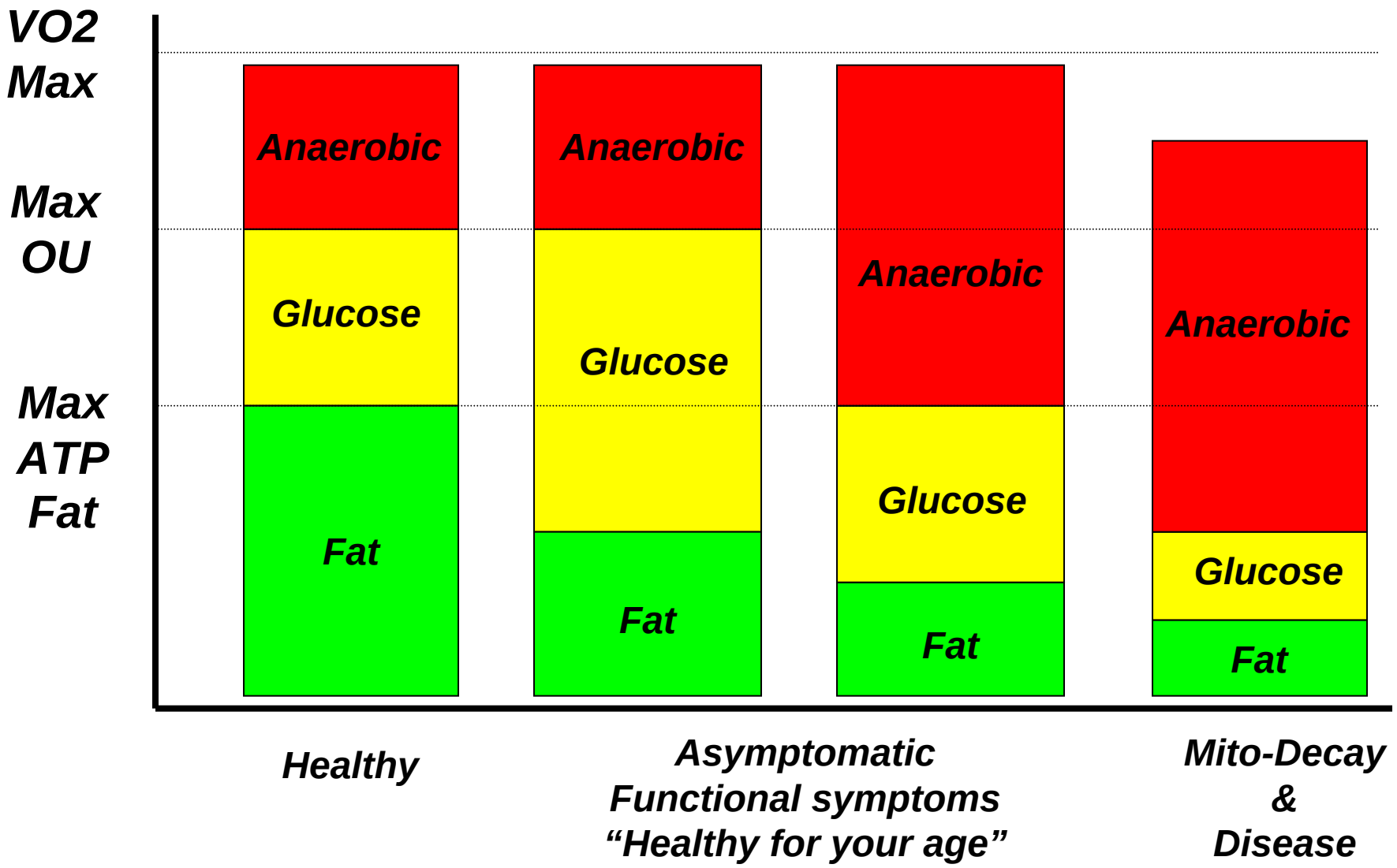
Oxygen Utilization and Disease

- Biskup S, Moore DJ. Detrimental deletions: mitochondria, aging and **Parkinson's** disease.Bioessays. 2006 Oct;28(10):963-7.
- Moreira PI, Cardoso SM, et al. The key role of mitochondria in **Alzheimer's** disease. J Alzheimers Dis. 2006 Jul;9(2):101-10.

Oxygen Utilization and Disease

- Tsutsui H. Oxidative stress in **heart failure**: the role of mitochondria.
  Intern Med. 2001 Dec;40(12):1177-82.
- Marin-Garcia J, Goldenthal MJ. **Heart mitochondria** signaling pathways: appraisal of an emerging field. J Mol Med. 2004 Sep;82(9):565-78

The Stages Of The Aging Process



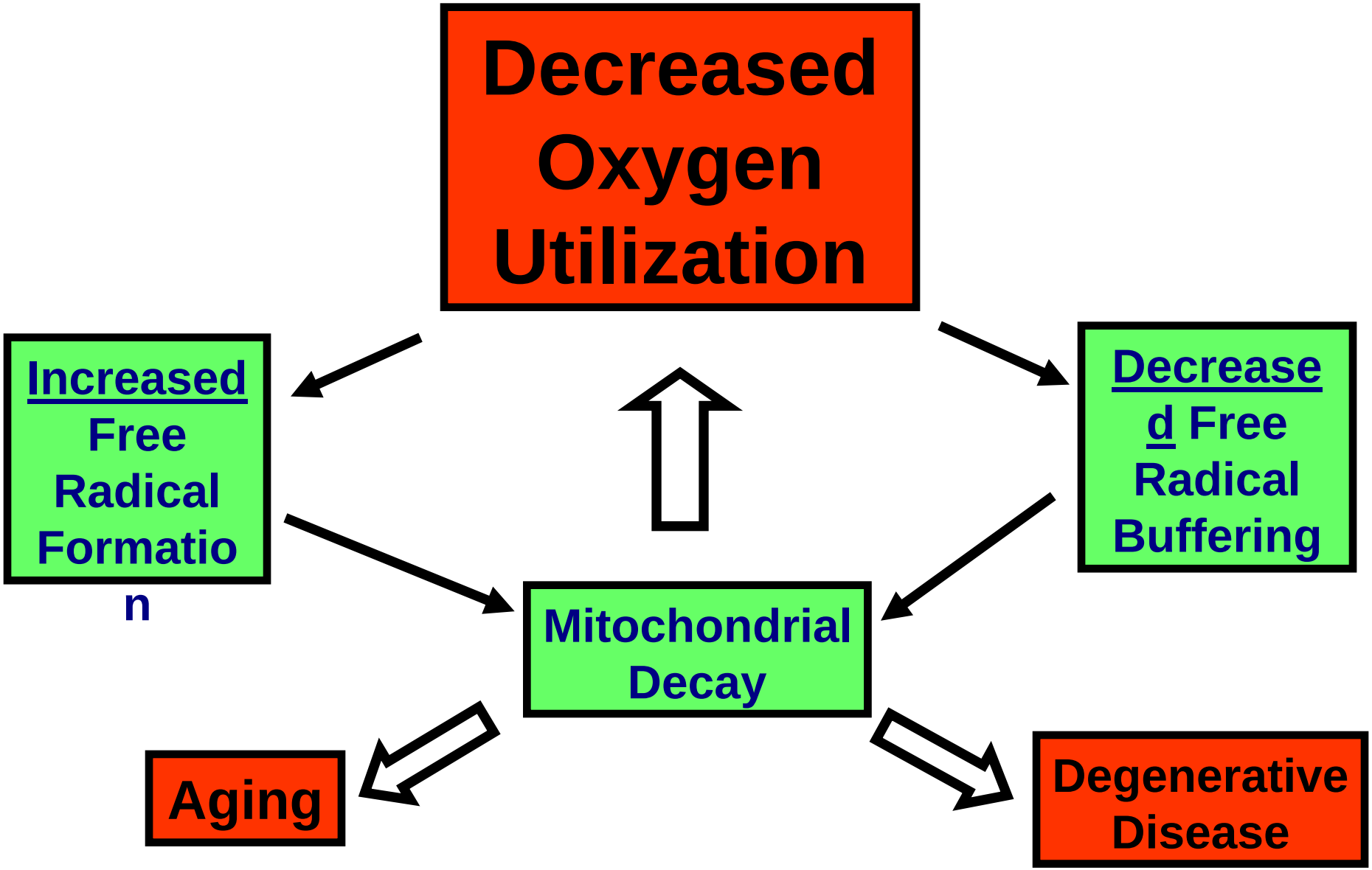
Decreased oxygen utilization causes degeneration changes secondary to excessive free radical activity.

Free Radical Damage is Caused By Decreased Oxygen Utilization

"Decreased oxygen utilization is toxic to the cell by exacerbating free radical generation in membranes housing electron transfer assemblies."

Antioxidant Adaptation
Levine & Kidd

- Decreased oxygen utilization creates a "functional hypoxia" which 1) accelerates free radical formation, and 2) exhausts anti-oxidant buffering capacity.


Decreased Oxygen Utilization
Increased Free Radical Formation
Decreased Free Radical Buffering
Mitochondrial Decay
Aging
Degenerative Disease

Decreased oxygen utilization is caused by both pre-mitochondrial and mitochondrial factors.

What Causes Decreased Oxygen Utilization?

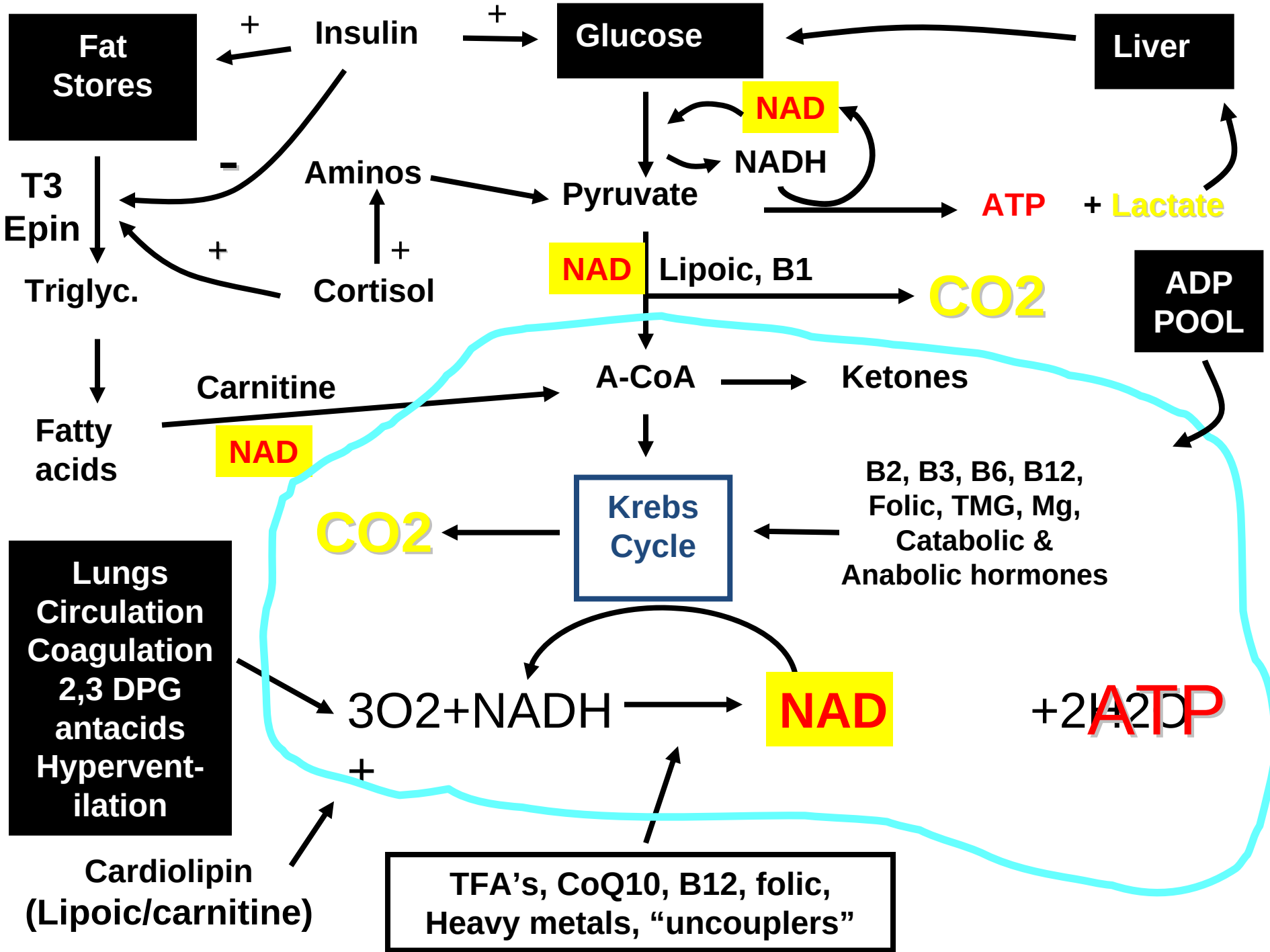
<u>Pre-Mitochondrial</u>

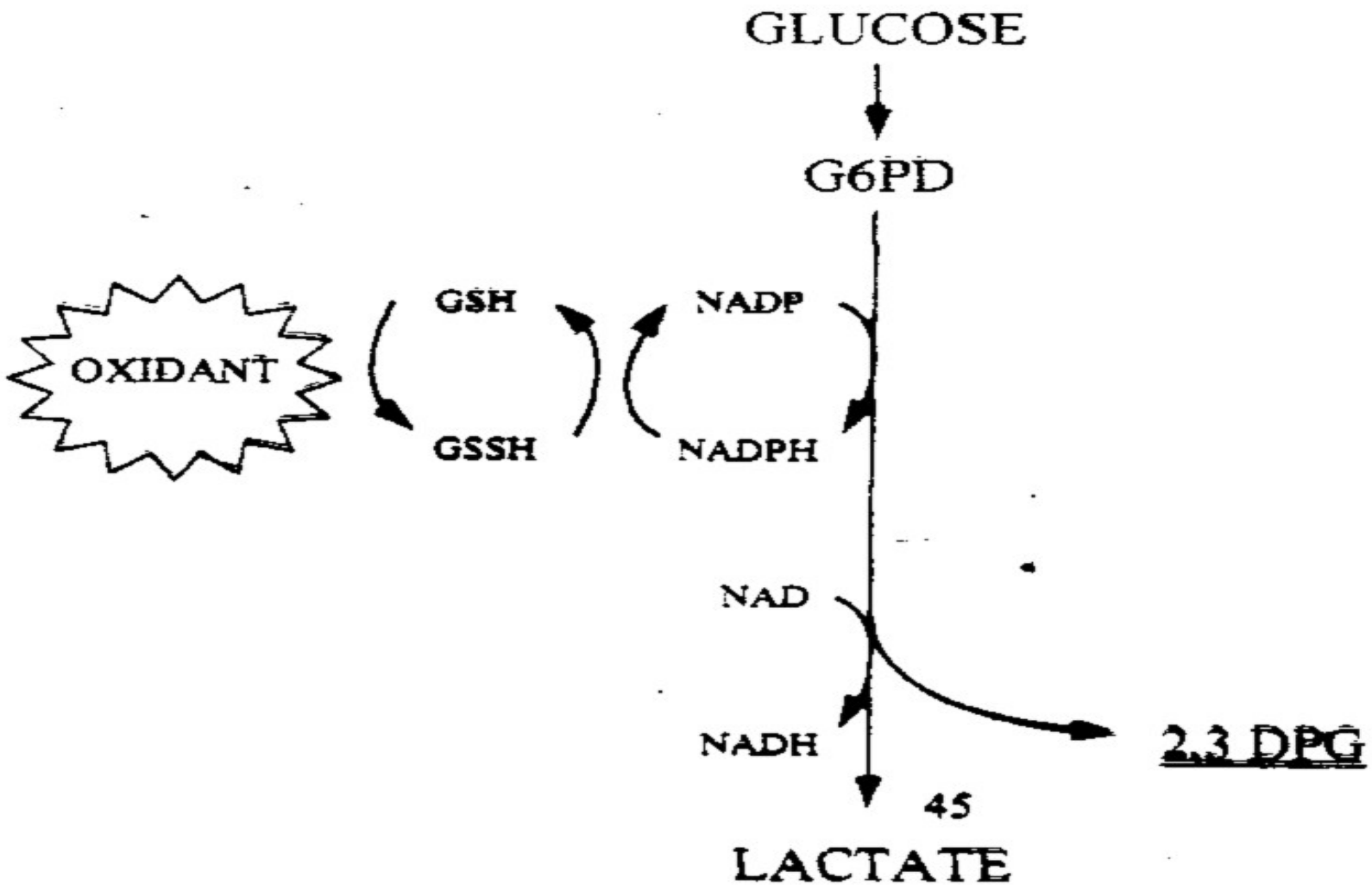
1. Decreased lypolysis.
2. Hypoglycemia
3. Ischemia.
3. Hypoxia.
4. Decreased methylation.
5. Inflammation

<u>Mitochondrial</u>

1. Toxicity and infections.
2. Stress.
3. Nutritional deficiencies.
4. Hormonal deficiencies.
5. Decreased fitness.

Decreased oxygen utilization exerts its negative effects by causing a decrease in the NAD/NADH ratio.


Fat Stores
Insulin
Glucose
Liver
NAD
NADH
T3
Epin
Aminos
Pyruvate
ATP
+ Lactate
Triglyc.
Cortisol
NAD
Lipoic, B1
CO2
ADP POOL
Carnitine
A-CoA
Ketones
Fatty acids
NAD
Krebs Cycle
CO2
B2, B3, B6, B12, Folic, TMG, Mg, Catabolic & Anabolic hormones
Lungs
Circulation
Coagulation
2,3 DPG
antacids
Hypervent-ilation
3O2+NADH
NAD
+2ATP
Cardiolipin
(Lipoic/carnitine)
TFA's, CoQ10, B12, folic,
Heavy metals, "uncouplers"



Pentose Phosphate Pathway

Nicotinamide adenine dinucleotide, a metabolic regulator of transcription, longevity and disease

Lin SJ, Guarente L. Current Opinion in Cell Biology 2003, 15:241–246

- “NAD has emerged as a putative metabolic regulator of transcription, longevity and several age-associated diseases, including diabetes, cancer and neurodegenerative diseases.”
- “Calorie restriction (CR) has been shown to decrease the incidence or delay the onset of some of these diseases.”
- “Studies in yeast suggest that CR functions by increasing the NAD level and/or the NAD/NADH ratio.”

NAD and Cell Signaling

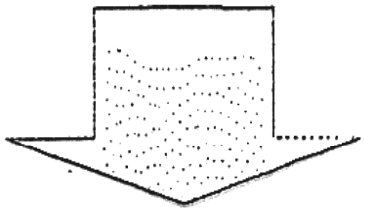
- NAD is rate limiting for ADP-ribosylation. ADP-ribosylation reactions are involved in cell signaling and the control of many cell processes in the cell nucleus, including DNA repair, apoptosis, and telomere maintenance.
- Another function of NAD in cell signaling is as a precursor of cyclic ADP-ribose, which regulates intracellular calcium channels.

NAD and Sirtuins

- Sir stands for Silent Information Regulator genes. Sir2 is short for Silent mating type Information Regulatior-2. So sirtuins are Sir2-homologs. Sirtuins act by removing acetyl groups from proteins in the presence of NAD.
- Sirtuins are hypothesized to play a key role in an organism's response to stresses (such as heat or starvation) and to be responsible for the lifespan-extending effects of calorie restriction.
- The sirtuins regulate nuclear transcription through deacetylating histones and altering nucleosome structure. These activities of sirtuins are particularly interesting because of their importance in the regulation of aging.
- Sirtuins are NAD-dependent, and are thus classified as "NAD - dependent deacetylases.

Ozone therapy is effective for so many diseases including the infirmaties of aging because it normalizes the NAD/NADH ratio.

ENERGY



O_2 ⇒ Generator ⇒ $O_2 + O_3$

Ozone Forms Peroxides

- Free radicals only in a pH greater than 8.
- Reacts ionically with double bonds to produce peroxides called ozonides.
- Most ozonides are formed from the short chained lipids in cell membranes.
- Ozonides are stable for days to weeks, easily penetrate cell membranes, and are selectively reactive.
- Once in the cells, these ozonides oxidize NADH to NAD.

It's All About The NAD/NADH Ratio

- Oxygen does not directly catalyze cellular reactions. It indirectly catalyzes them with NAD.
- The normal cytosol ratio of NAD/NADH is 700, guaranteeing an emphasis on oxidation.
- When NAD catalyzes a reaction, it is converted to NADH.
- The problem with decreased oxygen utilization is that is results in decreased levels of NAD.
- As the NAD/NADH ratio decreases, all cellular activity slows down.
- NADH is removed in order to achieve a healthy NAD/NADH ratio.
- The decrease in NADH further decreases oxygen utilization.
- Ozone therapy, by oxidizing NADH to NAD corrects the ratio and thus improves oxygen utilization by stimulating increasing levels of NADH.
- Oxidation therapies are enhanced with the addition of oral NADH.

Pharmacological Stimulation of NADH Oxidation Ameliorates Obesity and Related Phenotypes in Mice.

Hwang JH, Kim DK, Jo EJ, et al. Diabetes Apr;58(4):965-74. Epub 2009 Jan 9

- The NAD/NADH ratio “plays a crucial role in cellular energy metabolism, and dysregulated NAD/NADH ratio is implicated in metabolic syndrome.”
- Used beta-lapachone to oxidize NADH in diet-induced obesity mice.
- NADH oxidation “strongly provoked mitochondrial fatty acid oxidation in vitro and in vivo, and dramatically ameliorated their key symptoms such as increased adiposity, glucose intolerance, dyslipidemia, and fatty liver.”
- “The treated mice also showed higher expressions of the genes related to mitochondrial energy metabolism (PGC-1alpha, NRF-1) and caloric restriction (Sirt1), consistent with the increased mitochondrial biogenesis and energy expenditure.”
- “Conclusions: Pharmacological activation of NADH oxidation by NQO1 resolves obesity and related phenotypes in mice, opening the possibility that it may provide the basis for a new therapy for the treatment of metabolic syndrome.”

It Happens Locally

- Chronic localized pain is caused by localized areas of chronically decreased oxygen utilization.
- Vicious cycle starts with trauma or infection.
- Edema, inflammation, hyper-coagulation, and endothelial damage lead to localized decreased oxygen utilization.
- Decreased oxygen utilization disables the healing mechanisms, and condition becomes chronic resulting in permanent edema, inflammation, hyper-coagulation, endothelial damage, and pain.

Take Home Message

The most effective way to maximize the effects of ozone therapy is to combine it with other therapies aimed at eliminating the causes of decreased oxygen utilization