The Causes of Cancer

~30% Smoking
~35% Unbalanced Diets
  Too Many Calories: Obesity
  Too Little Fiber & Micronutrients
~20% Chronic Infections
  Mostly in Poor Countries
~20% Hormones
  Breast, Endometrial, Etc.
~2% Occupation
<1% Pollution
  Mostly Heavy Air Pollution

Total = 107% because of multiple causes

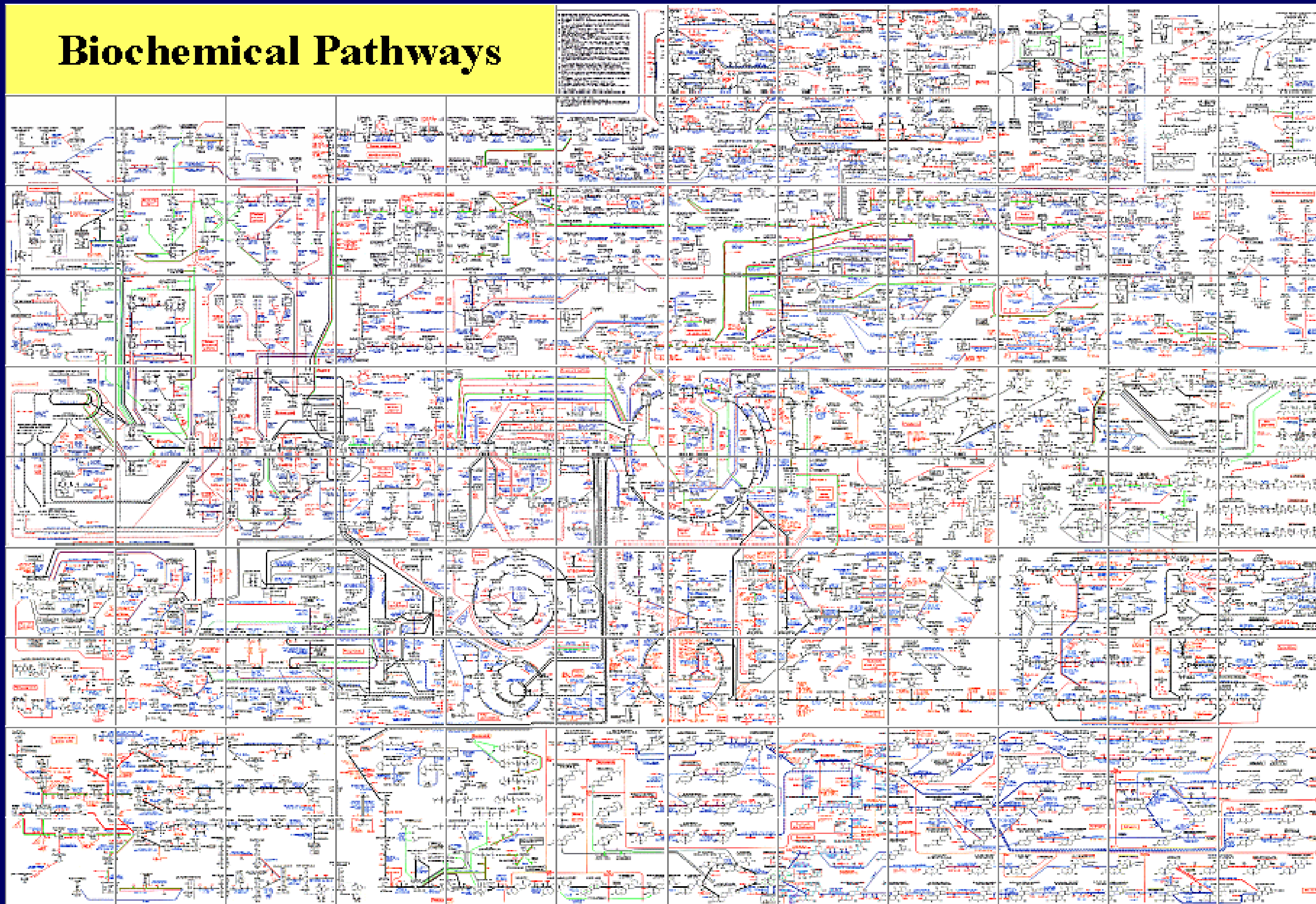
Micronutrient Undernutrition in Americans

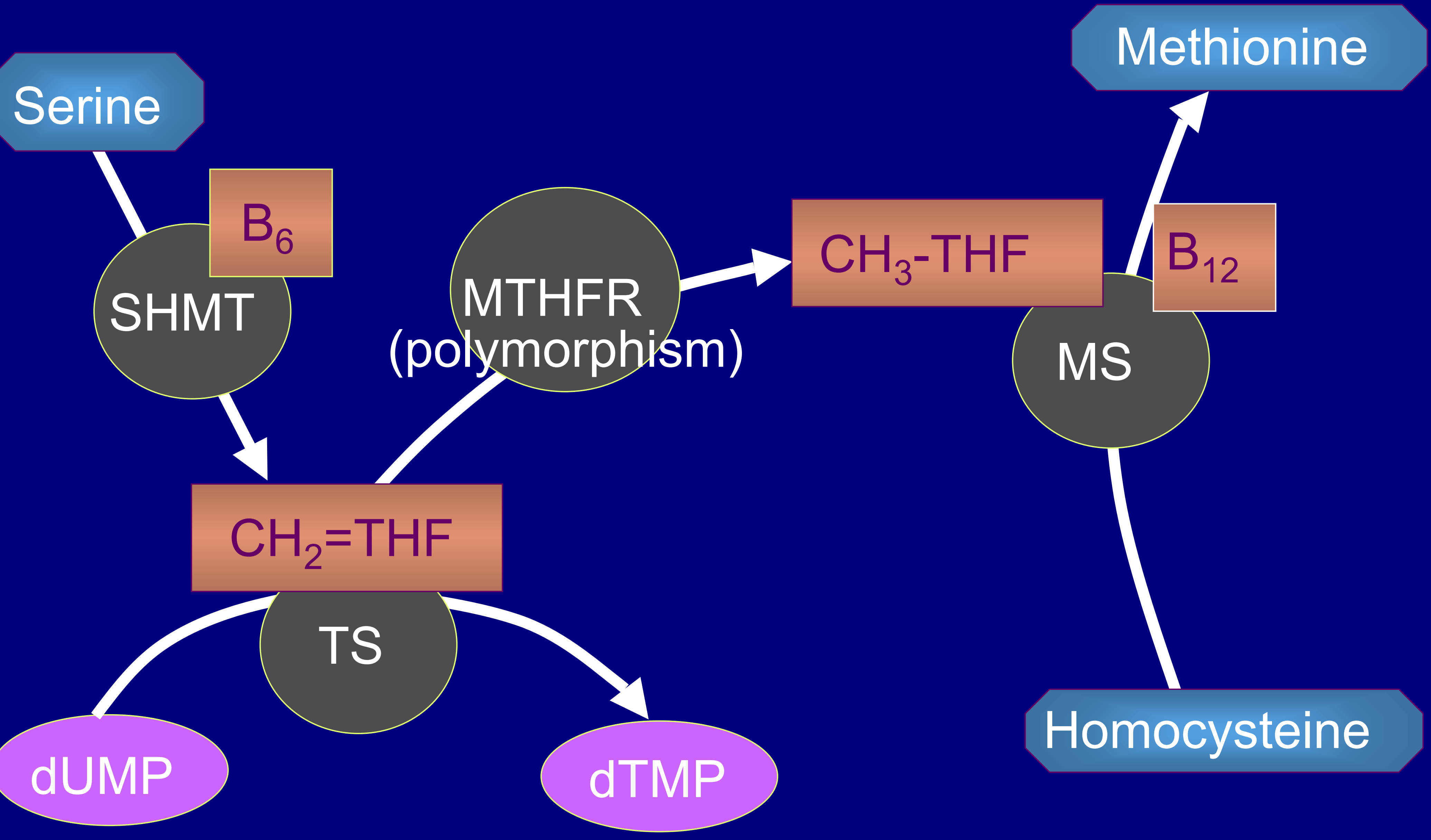
Nutrient	Population Group	RDA	% ingesting < RDA	% ingesting <50% RDA
Minerals				
Iron	Women 20-30 years	18 mg	75%	25%
	Women 50+ years	8 mg	25%	5-10%
Zinc	Men; Women 50+ years	11; 8 mg	50%	10%
Vitamins				
B6	Men; Women	1.7; 1.5 mg	50%	10%
Folate**	Men; Women	400 mcg	75%	25%; 50%
B12	Men; Women	2.4 mcg	10-20; 25-50 %	5; ~10-25%
C	Men; Women	90; 75 mg	50%	25%

•Wakimoto and Block (*2001*) *J Gerontol A Biol Sci Med Sci.* Oct; 56 Spec No 2(2):65-80.

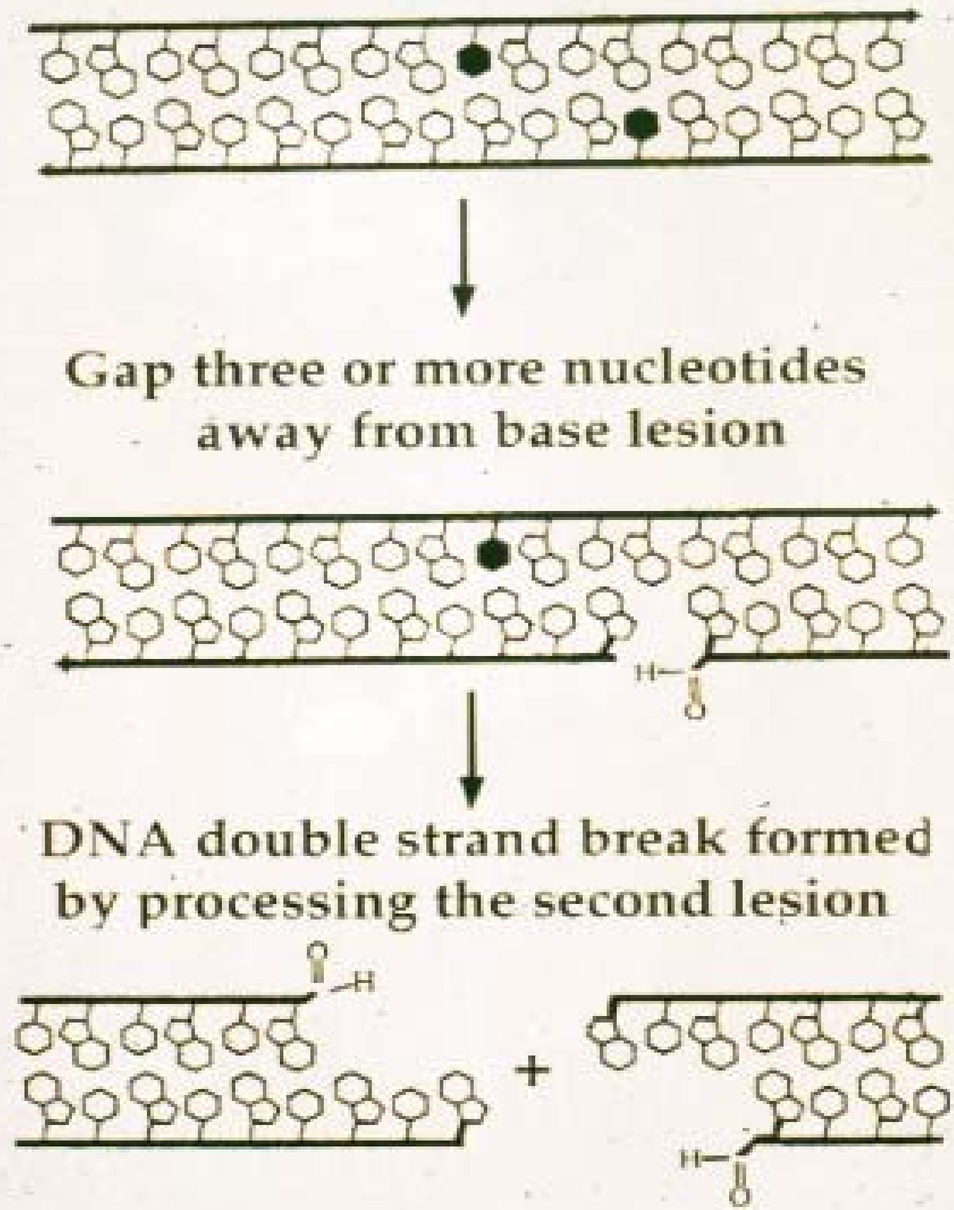
** Before U.S. Food Fortification

Biochemical Pathways

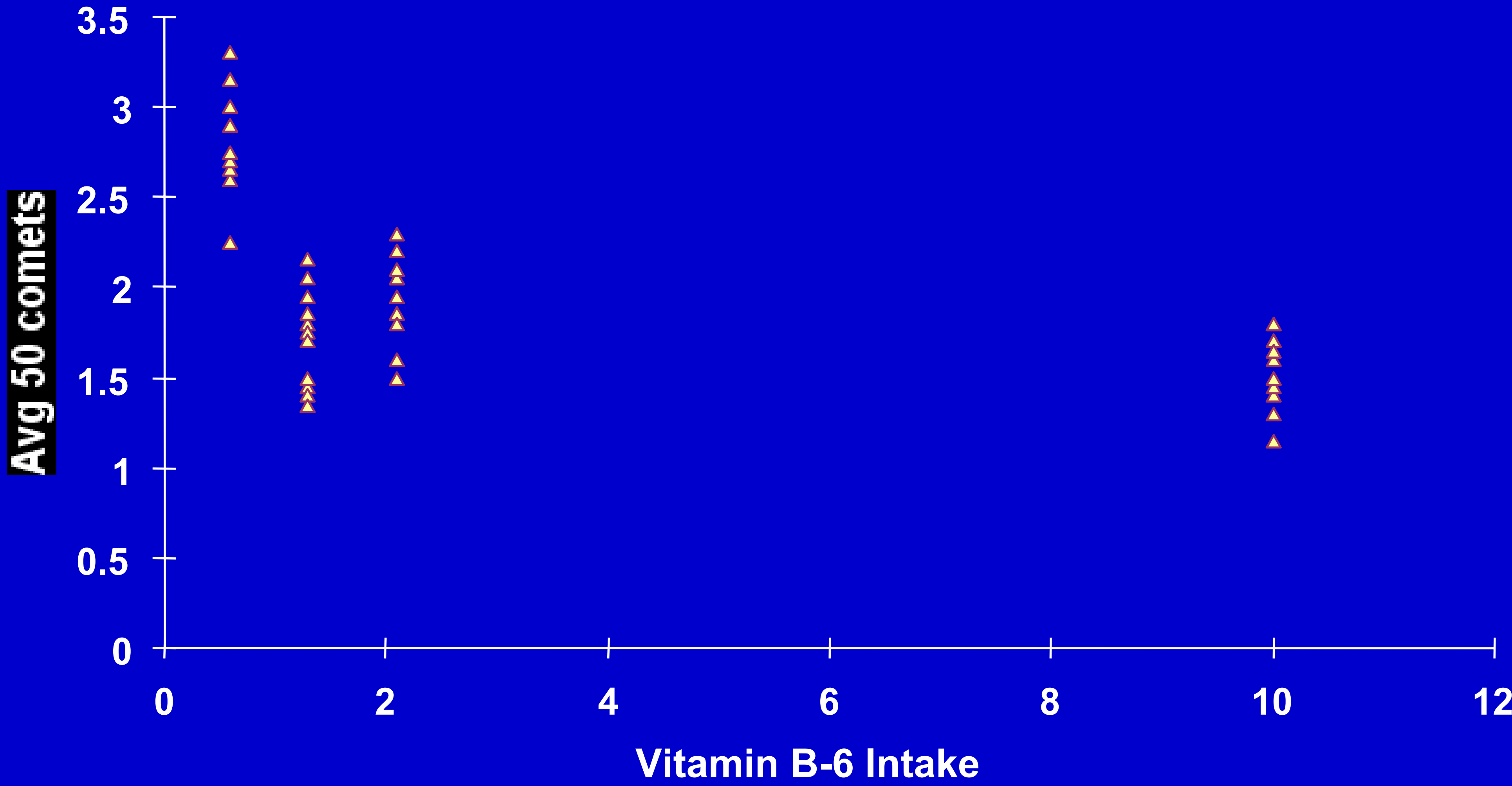



Serine
B6
SHMT
MTHFR
(polymorphism)
CH3-THF
B12
Methionine
MS
CH2=THF
TS
dUMP
dTMP
Homocysteine

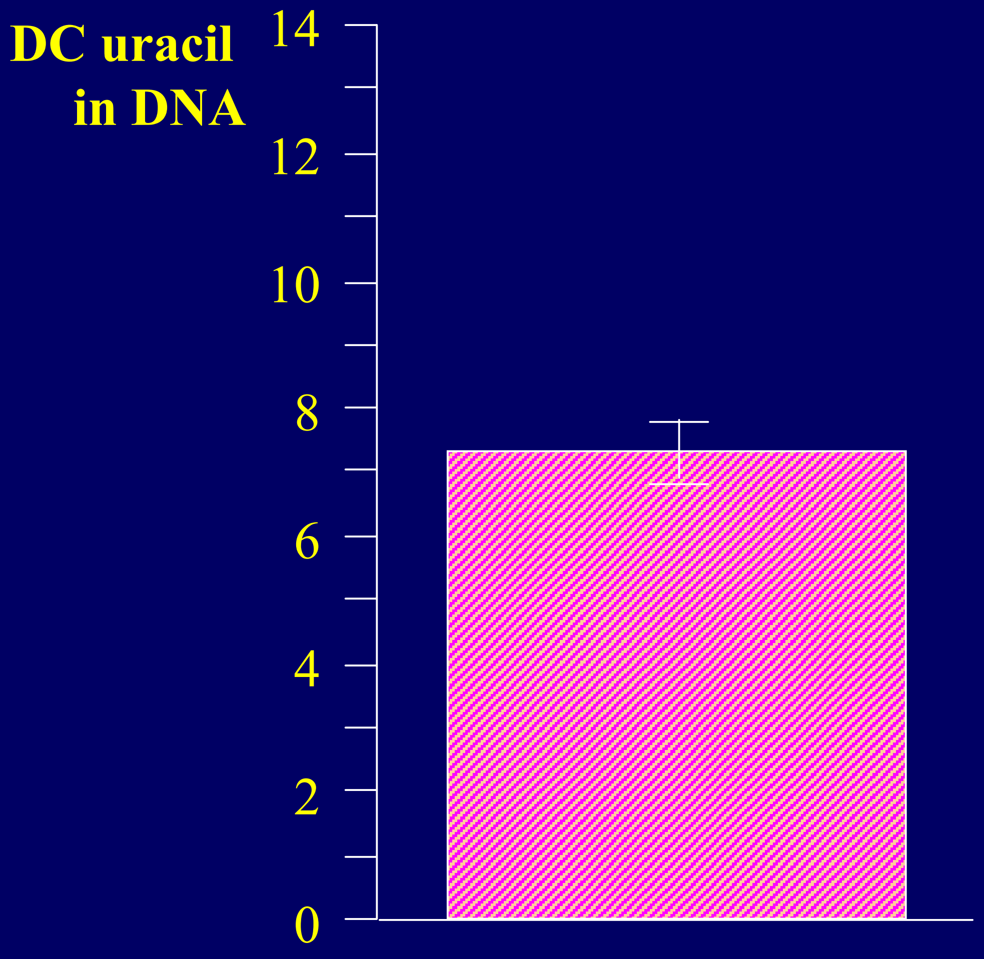
Base excision repair processing of opposed lesions



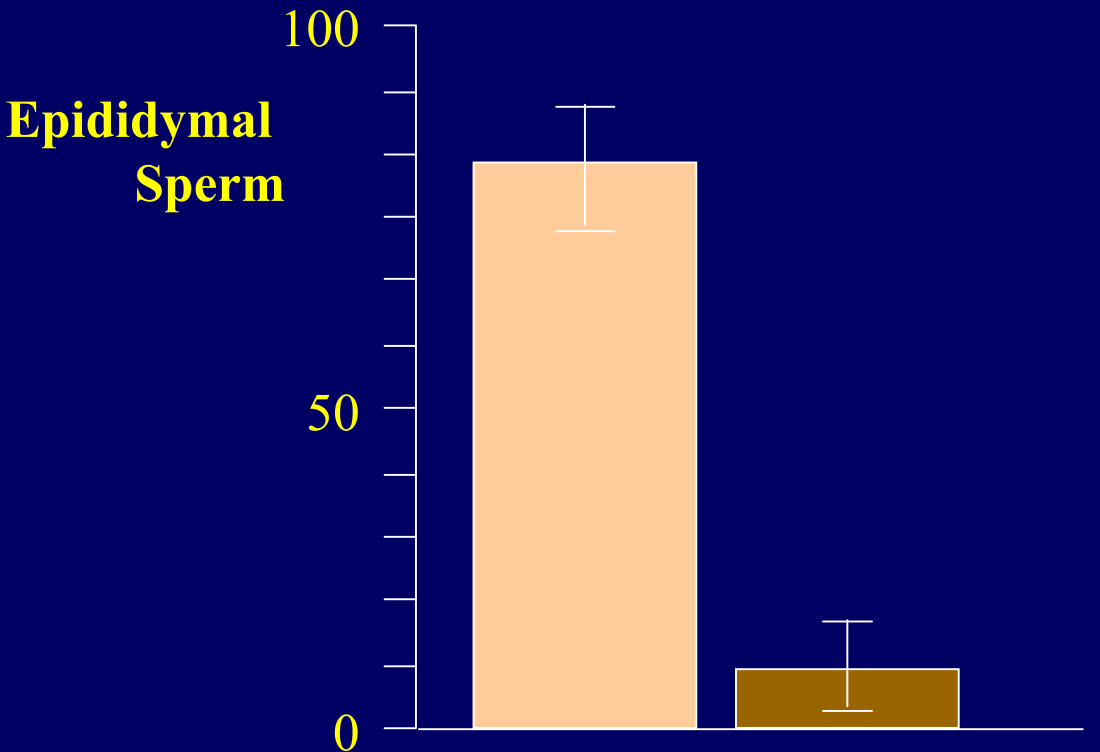
Human Lymphocyte DNA Strand Breaks (Comet Assay) vs. B-6 Intake



Mean uracil content in sperm DNA from 23 men on diets low in fruits and vegetables



Folate Deficiency Study epididymal Sperm Count



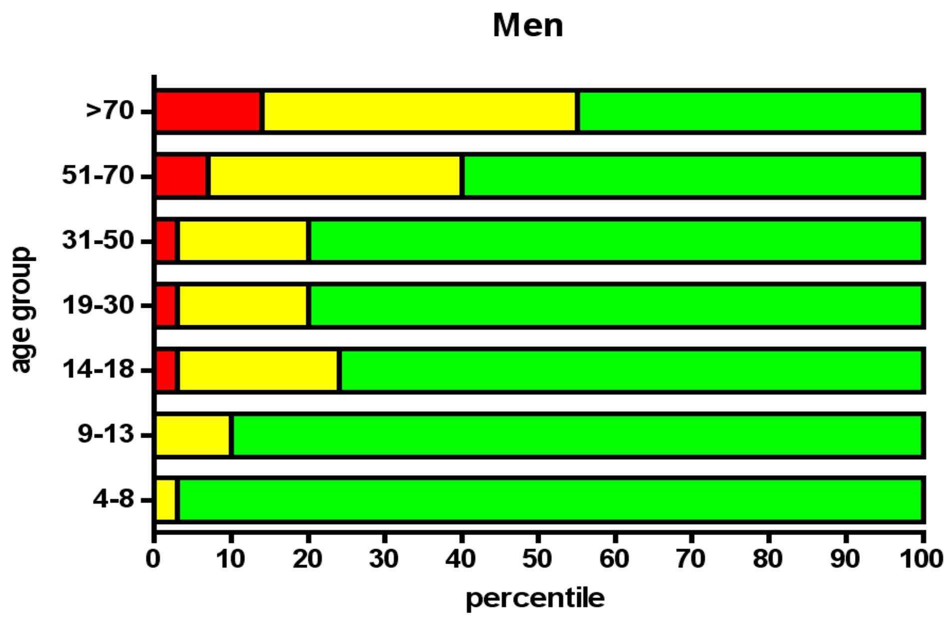
Seminal plasma folates vs. semen quality

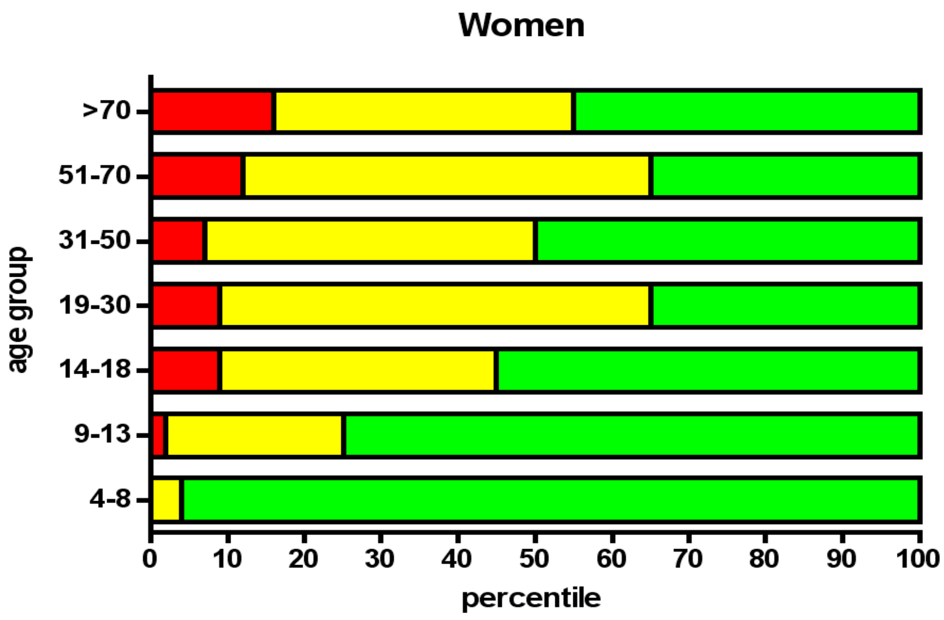
Correlation coefficient (r); n=48

Seminal Plasma	*Sperm Density (10^6/mL)*	*Total Sperm Count (10^5)*
Non-methyl THF (methylene-THF, etc.)	* 0.37	* 0.31
5-Methyl THF	0.08	0.07

$^*p<0.05$

Vitamin B6 Deficiency

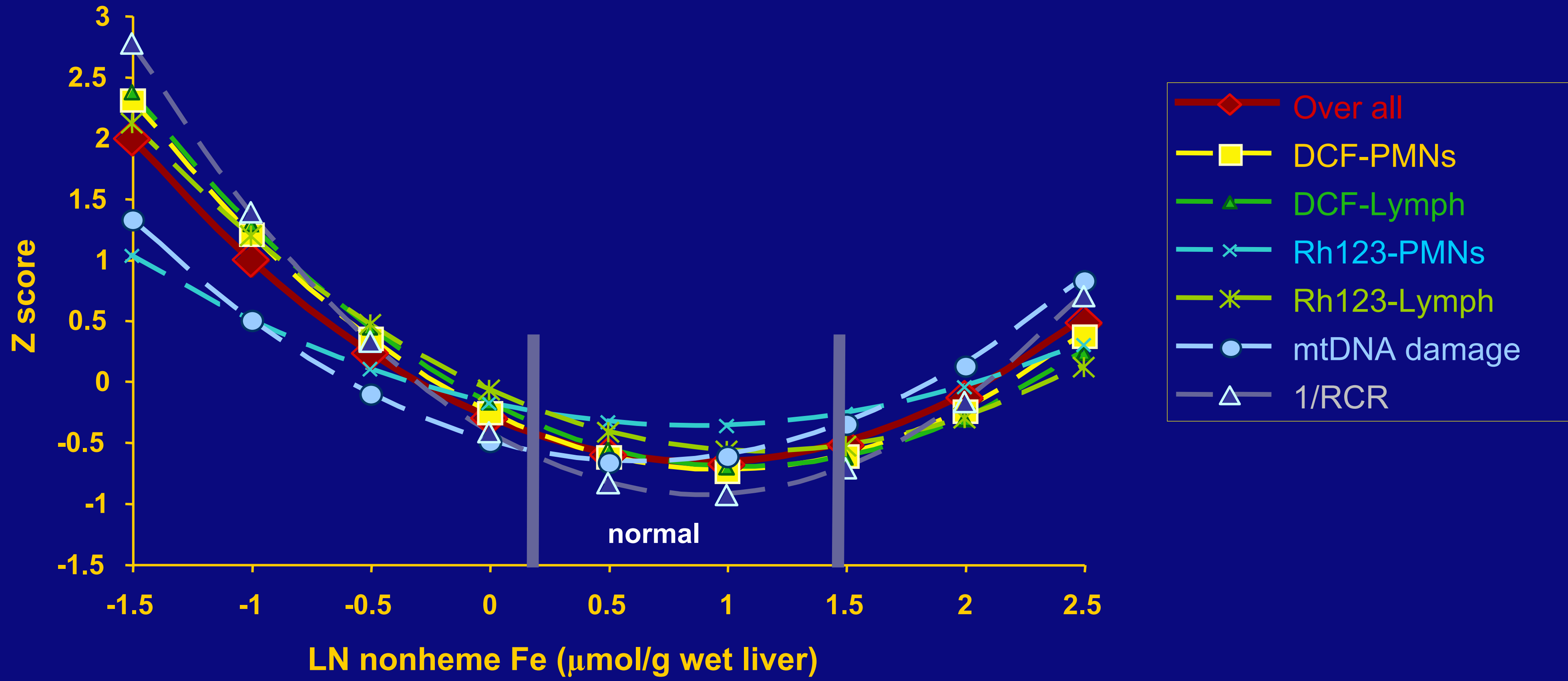




Mean intake by ethnic group (mg)			
	20 yrs	40 yrs	60 yrs
RDA	1.3	1.3	1.7
White	2.3	2.2	2.1
Black	2.4	1.9	1.5
Hispanic	2.3	2.1	1.7

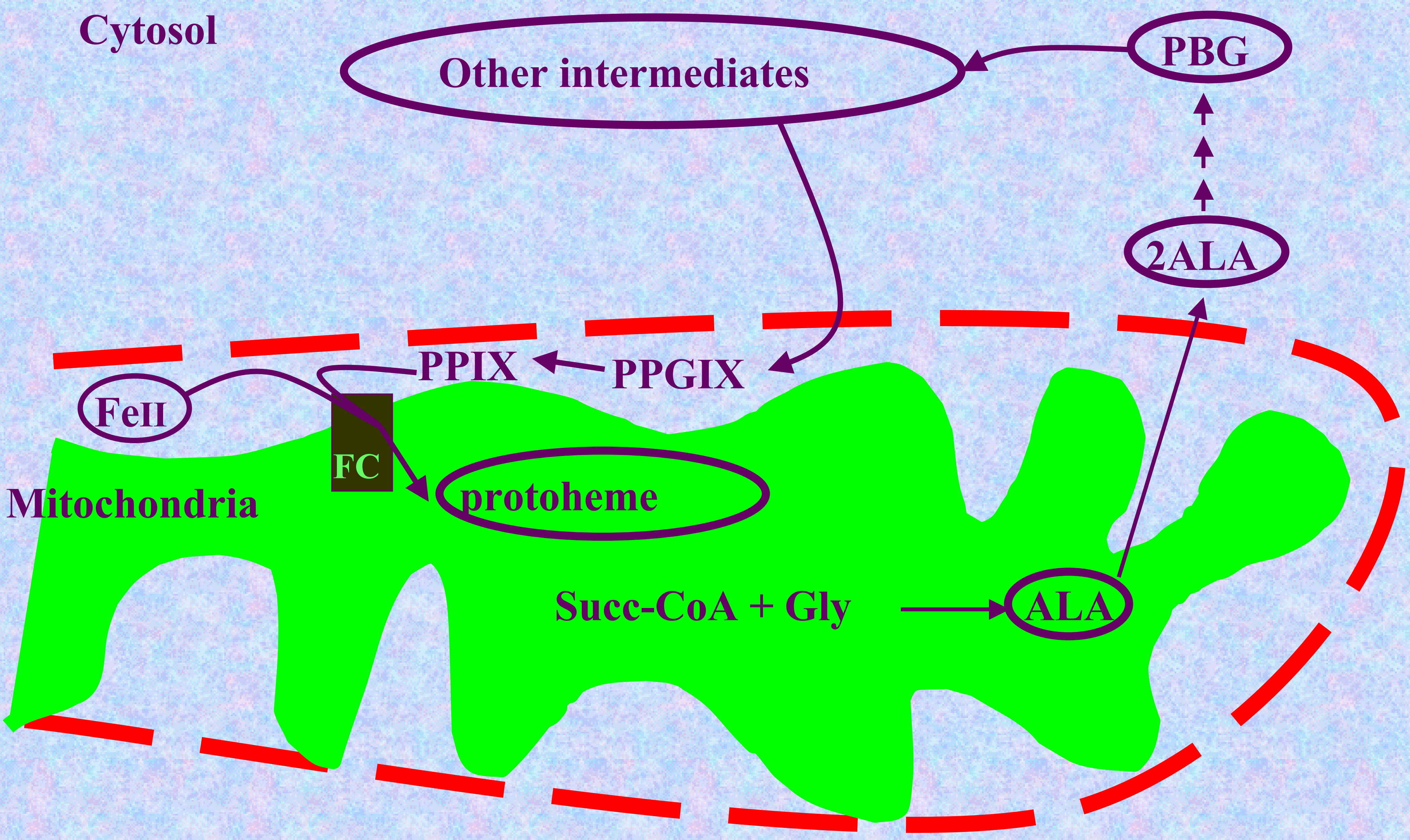
Mean intake by ethnic group (mg)			
	20 yrs	40 yrs	60 yrs
RDA	1.3	1.3	1.5
White	1.5	1.4	1.7
Black	1.5	1.2	1.3
Hispanic	1.6	1.4	1.3

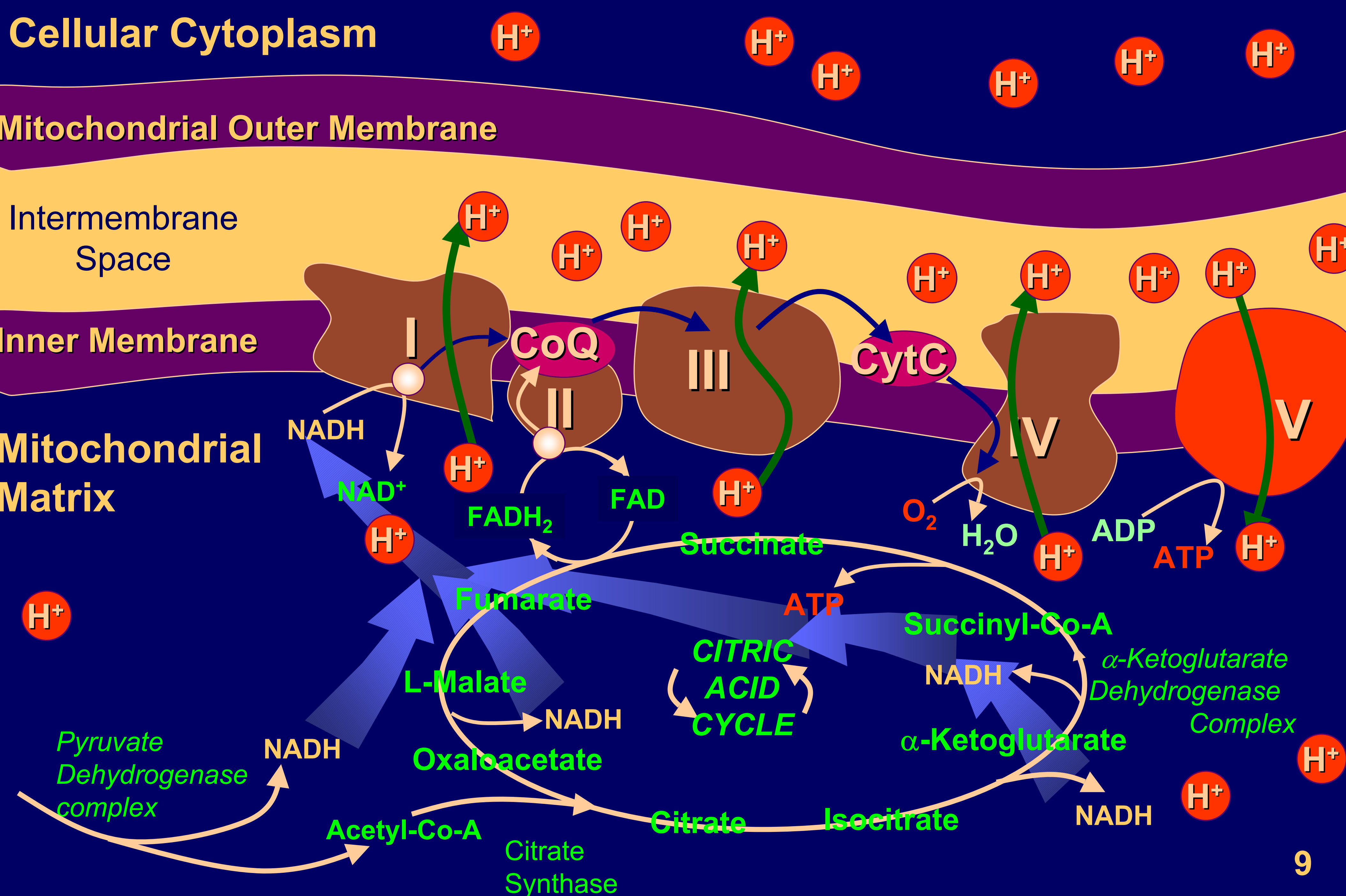
Analysis of nonlinear regression models: comparison of an overall model and individual models of Z-transformed values vs. ln- nonheme liver iron



. Each of the six dependent variables (that were analyzed by nonlinear regression in former figures) were transformed to Z scores and modeled as a quadratic function of the ln-liver nonheme iron as the independent variable. The equation for the RCR ratio's Z score was obtained from inverted RCR values (1/RCR) so that normal rats had the lower instead of the higher values. For presentation purposes each model line was obtained from 9 values of liver iron. All statistics were performed as in materials and methods.

Synthesis of Heme





Cellular Cytoplasm
Mitochondrial Outer Membrane
Intermembrane Space
Inner Membrane
Mitochondrial Matrix
H^+
I
CoQ
II
III
CytC
IV
V
NADH
NAD^+
$FADH_2$
FAD
O_2
H_2O
ADP
ATP
Succinate
Fumarate
ATP
Succinyl-Co-A
CITRIC ACID CYCLE
NADH
α-Ketoglutarate Dehydrogenase Complex
L-Malate
NADH
α-Ketoglutarate
Pyruvate Dehydrogenase complex
NADH
Oxaloacetate
Acetyl-Co-A
Citrate Synthase
Citrate
Isocitrate
NADH

Similarity Between the Consequences of Heme Deficiency and Normal Aging/neurodegeneration

Factor in Study	Heme Deficiency	Aging/Neurodegeneration
Complex IV	Loss of complex IV **9**	Loss of complex IV
Iron	Accumulation **11**	Accumulation
Oxidative Stress	Increased **9**	Increased
APP	Decreased and aggregate appear **11**	dimmer or aggregate
NOS	Increased **11**	Increased
Cell-cycle and differentiation	Disabled differentiation or proliferation **11**	Loss of Axons; neuronal death
Metabolism	Mitochondrial decline **9,10**	Hypometabolism
Calcium	Corrupted **9**	Corrupted
Ferrochelatase	Increased **9**	Increased in senescent cells **9***
Heme synthesis	Decreased **10**	Decreased with age**

***Not Determined in vivo. **Not determined in the aging brain**

9) Atamna et al (2001) JBC. **10) Atamna et al (2002) ABB.**
11) Atamna et al (2002) PNAS.