Is Less More?

Optimizing Lifespan and Healthspan Through Dietary Restriction

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More from less?

More of what?

- Lifespan
- Healthspan

Less of what?

- Food
- Drink

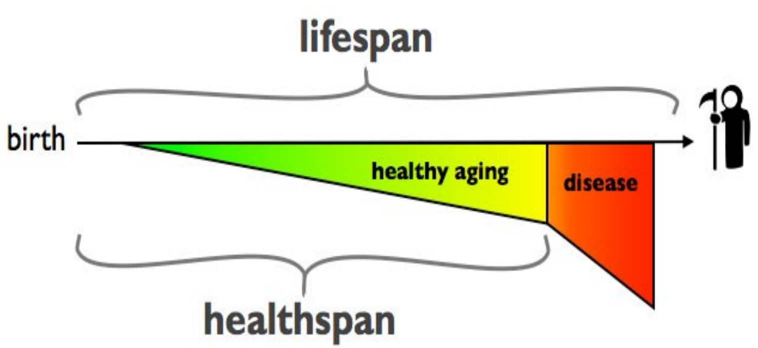
Lifespan and healthspan

Lifespan

- The length of time one is alive, from birth to death

Healthspan

- Relatively new concept
- "The length of time in one's life where one is in optimal health"
- Remains free of debilitating diseases and conditions

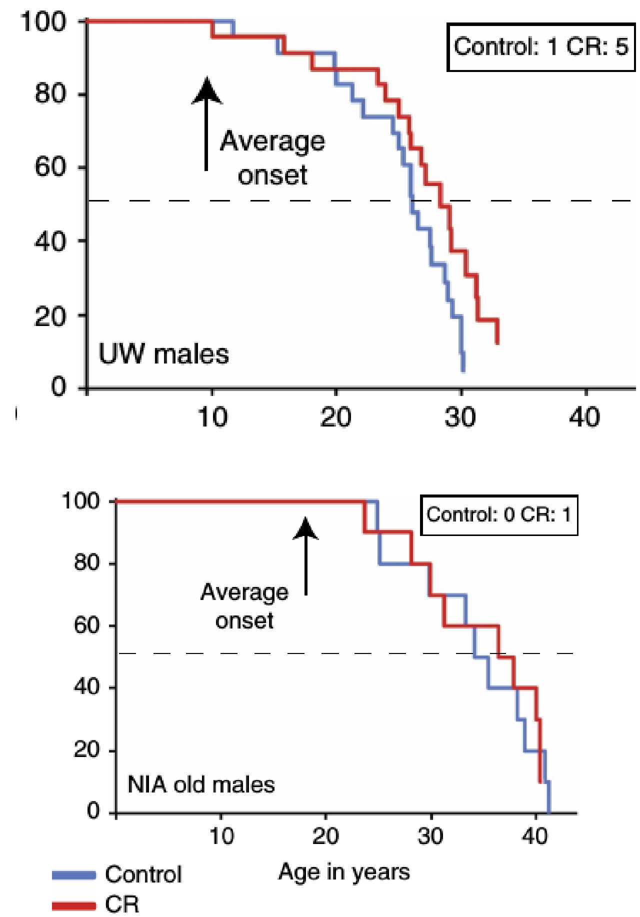


Lifespan

Every species has a well-defined maximum potential lifespan

But is it possible to push the envelope – extend the maximum?

- Male rhesus monkeys at the National Institute of Aging lived nearly 10 years longer than expected from peers elsewhere



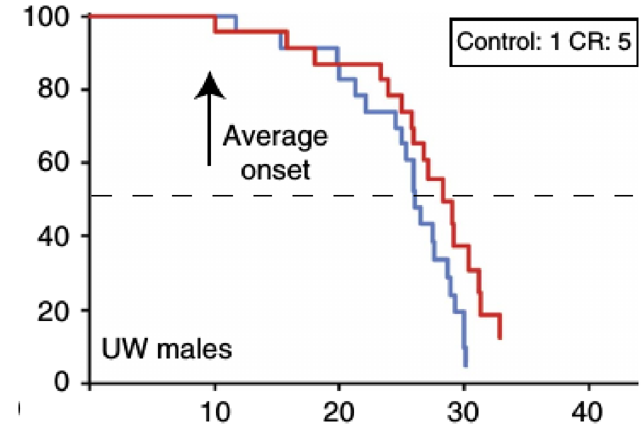
Healthspan

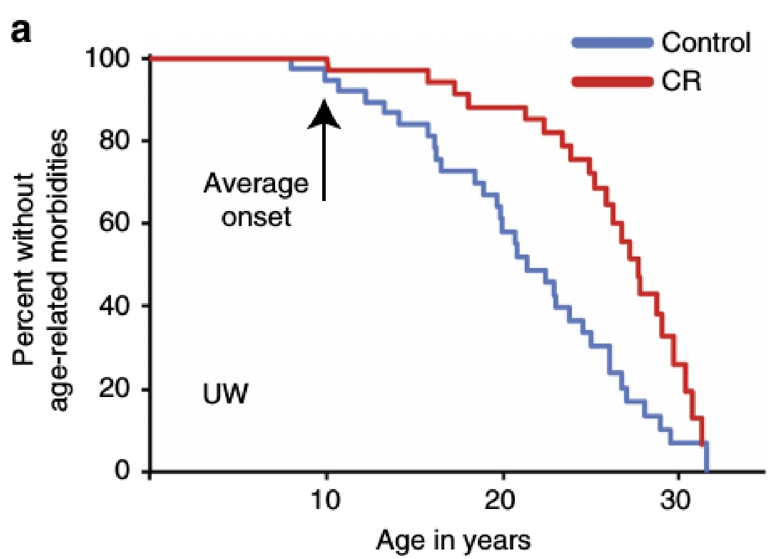
Setting aside extending the maximum lifespan, can we have a longer period of healthspan within the available lifespan?

Lifespan and healthspan in rhesus monkeys on calorie-restricted diet vs. *ad libitum* diet

Lifespan (upper) was slightly longer for calorie-restricted monkeys

Healthspan was substantially longer for calorie-restricted monkeys

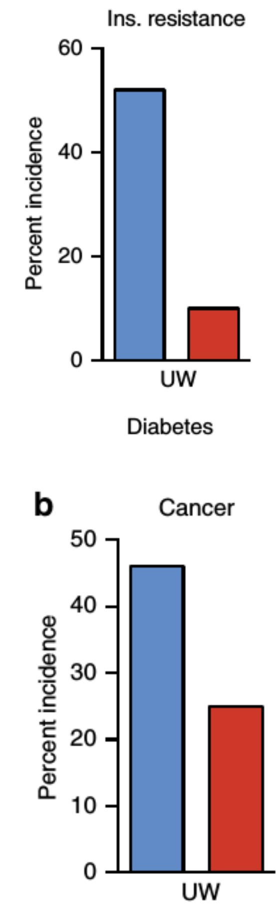




Healthspan

How was health of the calorie-restricted monkeys better?

- Half the incidence of cancer
- Only 20% the incidence of insulin resistance (diabetes)



What are practical goals?

Lifespan

- Immortality still beyond our reach; all organisms eventually perish
- Modest extension of lifespan seems achievable, based on animal models

Healthspan

- Compressing morbidity (disease, disability) into a smaller fraction of available lifespan also seems achievable
- Lengthening healthspan should also reduce costs of caring for the aging portion of the population

Today's takeaways

Much evidence suggests that lifespan, and especially healthspan, can be substantially modified by lifestyle changes, especially diet

The main effective modifiers are restriction of calories and restriction of dietary protein

The modifications must be applied in the appropriate stages of life to be safe and most effective

- The adult stage is ideal
- Growing developing individuals need more nutrient inputs and elderly may need more protein

Some modifications are easier than others

- Restricting protein is easier than restricting calories

Much has been learned about the underlying physiology and biochemistry

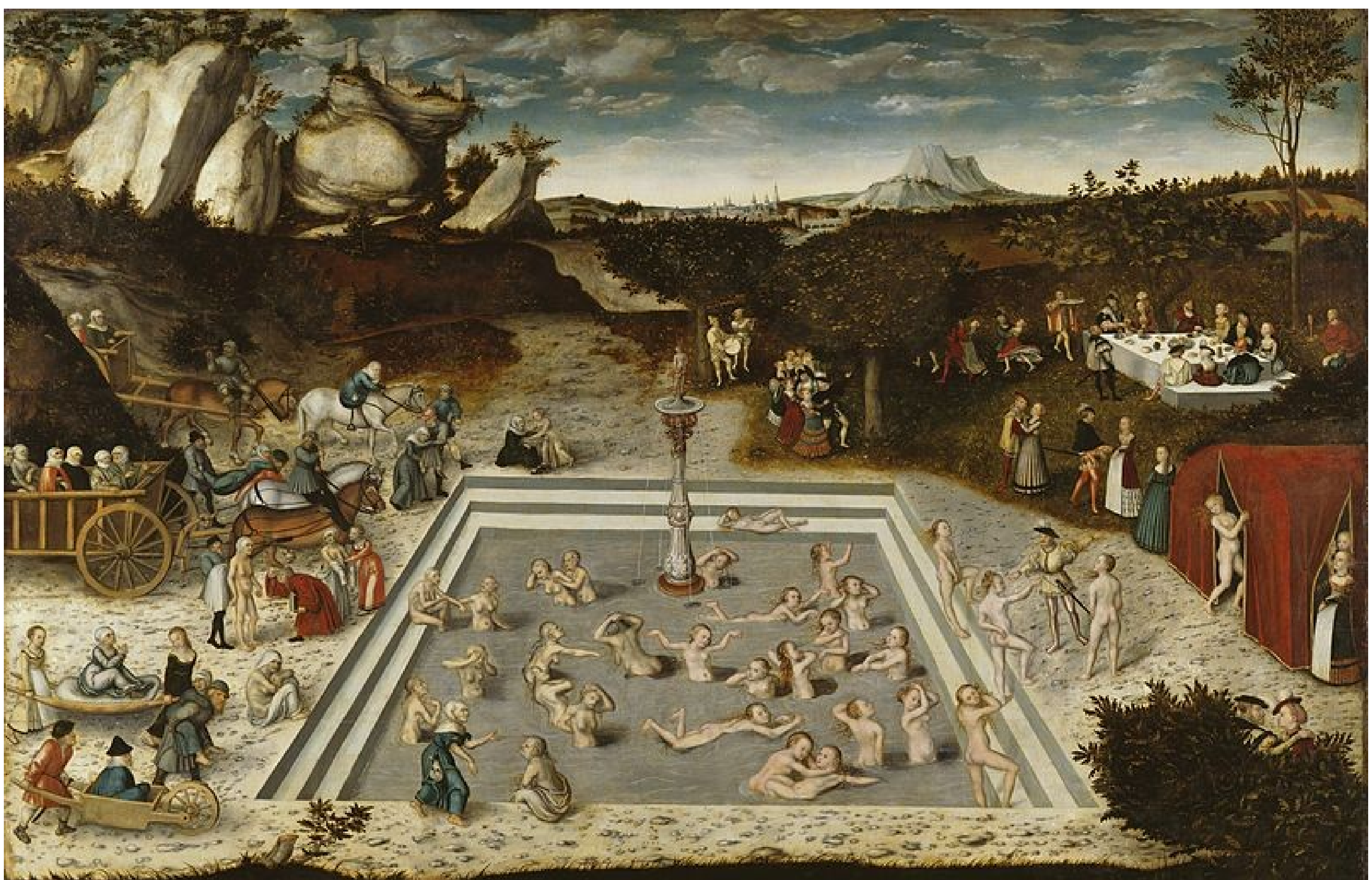
Expect pharmaceutical solutions to be offered in the future that simulate dietary restriction

The Fountain of Youth

For time immemorial, people have sought longer life, eternal youth

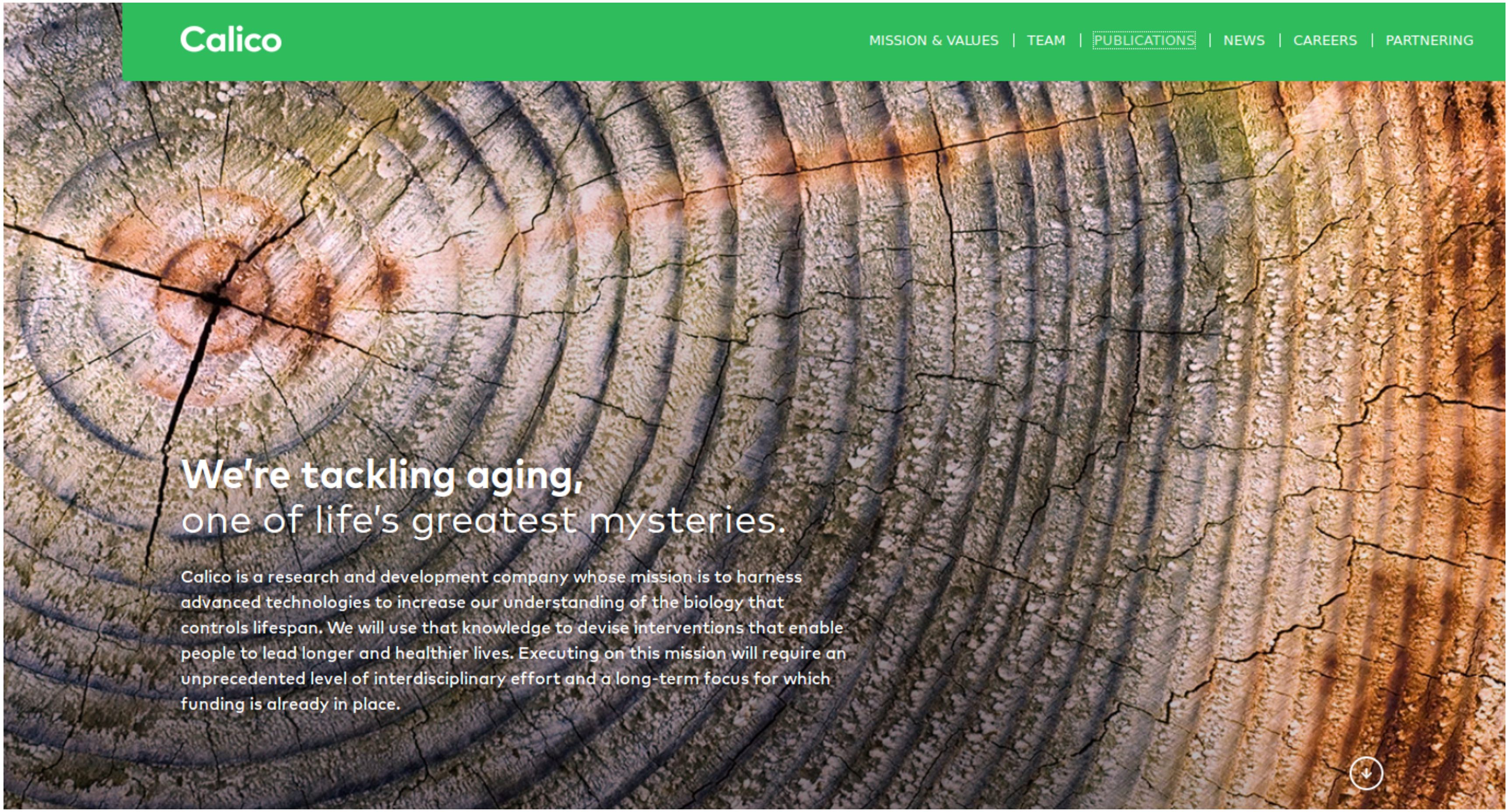
Ancients sought baths and elixirs that would extend life or make them immortal

Ponce de Leon was reportedly seeking waters that would restore youth



Anti-aging industry

Companies have been started to identify the mechanisms behind aging and develop ways to inhibit



Starvation: Humanity's major dietary challenge

Malnutrition is single gravest threat to human health world-wide

- 842 million people are undernourished (1 in 8)
- Obesity affects 1 in 8, with poor food quality in impoverished areas contributing

Largest contributor to child mortality

- 3.1 million children under 5 die annually with severe malnutrition as underlying factor

Overfeeding: Humanity's other nutritional challenge

2.16 billion adults are overweight or obese

- 170 million children in addition

Adiposity is linked to avoidable diseases

- Type 2 diabetes mellitus
- Hypertension
- Coronary heart disease
- Stroke
- Cancer
- Non-alcoholic liver disease
- Neurodegenerative disease
- Accelerated aging

Nutrient requirements

Energy

- Fuel to run the body's engine
- Generally referred to as *calories*
- Can be supplied by carbohydrates, fats and proteins (macronutrients)

Building blocks

- Feedstock for making proteins, membranes, other large molecules
- Amino acids (proteins), essential fatty acids

Vitamins, minerals and other essential material in small amounts

- Micronutrients

Microbiome food

- Fiber

How much food energy do we need?

Direct observation

- Observe a subject who is healthy, and record what they eat
- Determine calorie content of food eaten

Calorimetry

- Measure rate of oxygen consumption and compute from that
- Doubled labeled water

When done carefully, these agree

Human energy requirement

Basal metabolic rate (BMR)

- 10*Wt + 6.25*Ht – 5*Age + S
- Wt in kg, Ht in cm, Age in years
- S is 5 for male, -161 for female
- Mifflin modification of Harris-Benedict equation
- Amount of energy required to meet body's needs at absolute rest without weight gain or loss

Total energy expenditure (TEE)

- Includes digestion, activity
- TEE = BMR * PAL
- PAL is Physical Activity Level
- PAL ranges from 1.4 in sedentary state to 1.75 in moderate activity to 2.0 and up in vigorous activity

Example

- Male, age 73, wt 180 lbs, ht 69 in → BMR 1554
- TEE: sedentary 2175, moderately active 2719, vigorously active 3107

Two ways of determining dietary energy restriction

Observe subject's habitual intake in the steady-state on an *ad libitum* diet

- Make a percentage reduction relative to that

Calculate subjects requirements from a standard formula (e.g., Harris-Benedict)

- Make a percentage reduction relative to that

Restriction of other nutrients

Determine minimum daily requirement from nutritional research

Apply restriction relative to that

Protein, for example

- Numerous studies indicate 0.7-0.8 g per kg body wt per day as MDR
- Nutritionists often recommend 1.0-1.2 g/kg "for good measure", assuming more protein can only be better
- Many people get as much as 1.6 g/kg
- A "protein-restricted" diet, then, might be at the MDR

Dietary restriction vs. calorie restriction

Calorie restriction

- A reduction in total calories below amount predicted to maintain stable weight from Harris-Benedict-Mifflin equation
- Usually implies “normal” balance among macronutrients (fats, proteins, carbohydrates)
- Can involve restriction of micronutrients (vitamins and minerals) or quality (refined grains vs. whole grains, amount of fresh fruits and vegetables, protein source) to address specific research questions
- Ambiguous without exact specification of diet quality and severity

Dietary restriction

- Chronic and coordinated reduced intake of all dietary constituents except vitamins and minerals
- May involve imbalance in macronutrients, for example, disproportionate reduction in protein

Lifespan and healthspan impacts of calories and specific nutrients

Studies in model organisms reveal dramatic lifespan extensions and disease reduction

- Caloric restriction
- Nutrient restriction (proteins, specific amino acids)

Studies in humans reveal health differences correlating with lifestyle modification

- Population studies with unintentional calorie restriction
- Randomized controlled trials of calorie restriction
- Observational studies correlating diet histories with outcomes (diagnosis of disease, mortality)

Seminal research in dietary retardation of aging

PROLONGING THE LIFE SPAN

By Dr. C. M. McCAY and MARY F. CROWELL

ANIMAL NUTRITION LABORATORY, CORNELL UNIVERSITY

THESE TYPICAL RATS ARE BOTH 900 DAYS OLD

THE ONE ON THE LEFT GREW RAPIDLY AND "NORMALLY" TO MATURITY WHILE THE PHYSIOLOGICALLY YOUNG ANIMAL ON THE RIGHT WAS RETARDED IN GROWTH AND FORCED TO MATURE SLOWLY.

The Scientific Monthly, 1934

Calorie restricted mice mature more slowly

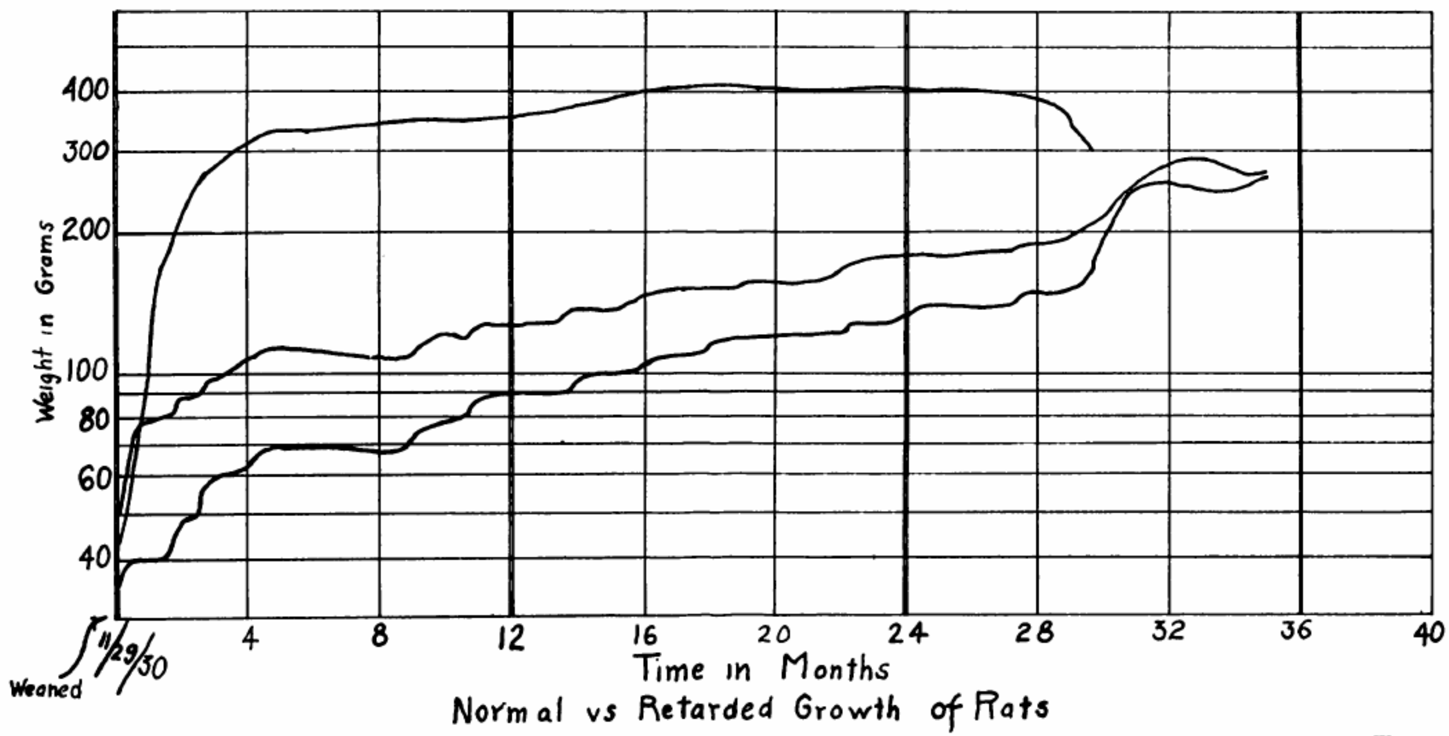


CHART. THE TOP CURVE SHOWS THE GROWTH OF A "NORMAL" ANIMAL FROM GROUP 1. THE TWO LOWER CURVES ARE TYPICAL FOR ANIMALS RETARDED IN GROWTH.

Calorie restricted mice grow more slowly - and survive longer

TABLE I

LIFE SPANS OF RATS THAT MATURE SLOWLY COMPARED WITH THOSE MATURING RAPIDLY

Diet	Mean Life Span (Days) ♂	Mean Life Span (Days) ♀	Median Life Span (Days) ♂	Median Life Span (Days) ♀
I—Adequate calories (rapid growth)	509	801	522	820
II—Deficient calories (slow growth)*	(792)	(755)	797	904
III—Deficient calories (slow growth)*	(883)	(824)	919	894
Stock Diet (75) (rapid growth)†	503 ± 12		*Note:* Campbell discards early deaths while our data include them.	
Campbell‡ (A) (rapid growth)	576 ± 10	604		
Campbell‡ (B) (rapid growth)	635 ± 12.9	664		

* Values in parenthesis are still increasing, since the animals are alive.

† From unpublished data obtained from our rat colony five years ago.

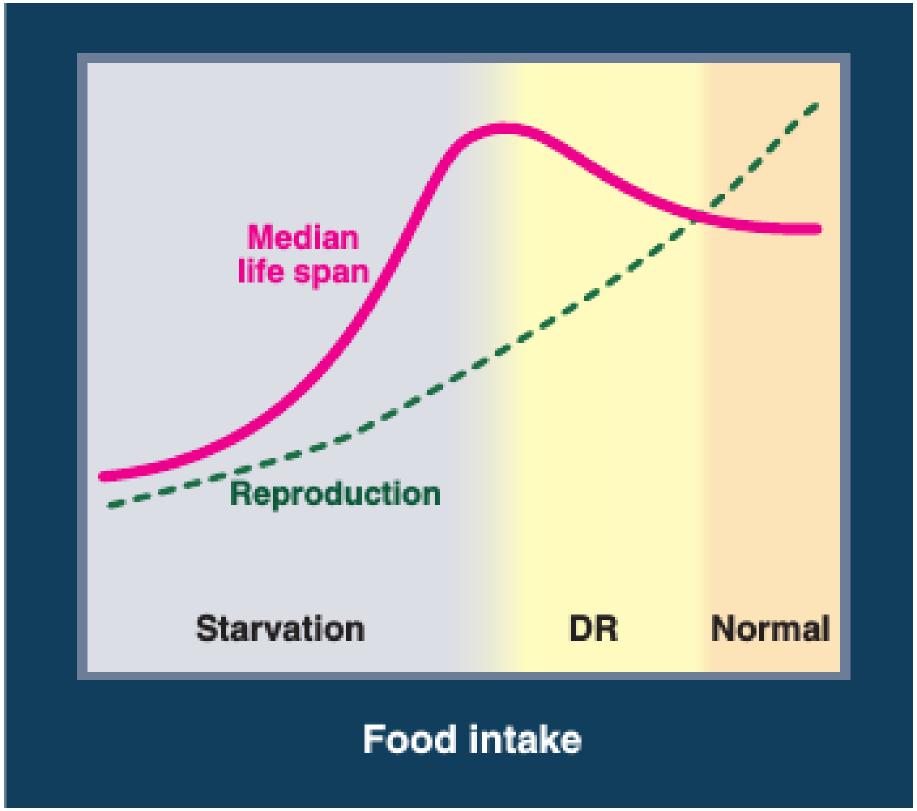
‡ H. Louise Campbell, Thesis, Columbia University (1929).

Dietary restriction: a tightrope

If restriction of food includes insufficient nutrients, organisms may die early or have severe retardation

Calorie restriction with adequate nutrients otherwise has a relatively narrow window of success

- Too severe calorie restriction results in death, inability to reproduce or failure to thrive



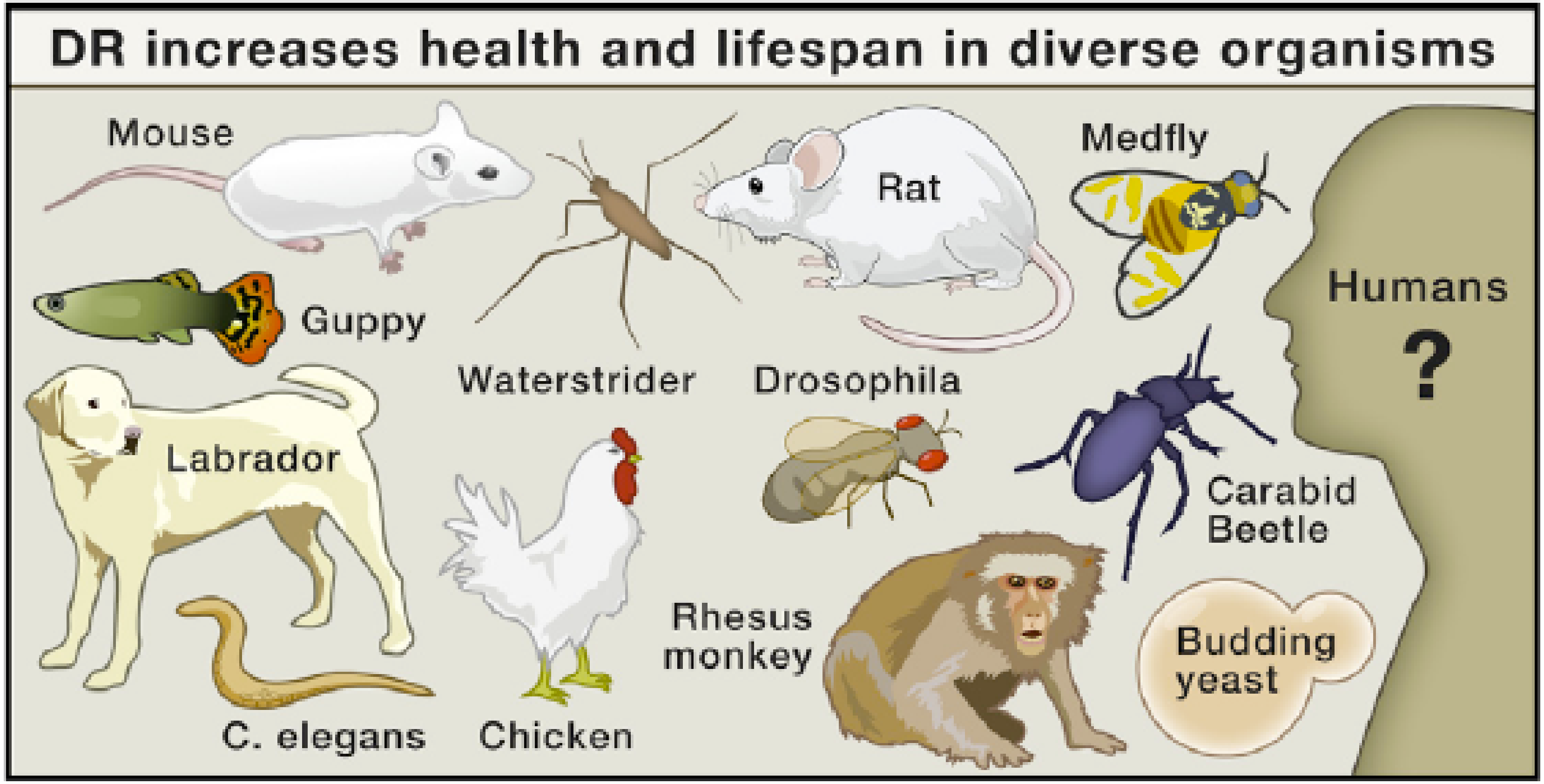


Figure 1. Dietary Restriction Increases Healthy Lifespan in Diverse Single-Celled, Invertebrate, and Vertebrate Animals

Exceptionally long-lived animals: naked mole rat

Native to West Africa

Burrows underground

Naked mole rat has longest life span of rodents

- Can exceed 30 years!

Mortality rate does not increase with age

Exceptional resistance to developing cancer

Has remarkably slow metabolism

Under intense study to discover mechanisms of aging

Mutations that affect aging

Ames dwarf mouse

- Spontaneous mutation described 1961
- Absent growth hormone, thyroid stimulating hormone, prolactin secretion
- 45-70% increase in lifespan
- Reduced IGF-1
- Reduced glucose and insulin
- Reduced reactive oxidative species

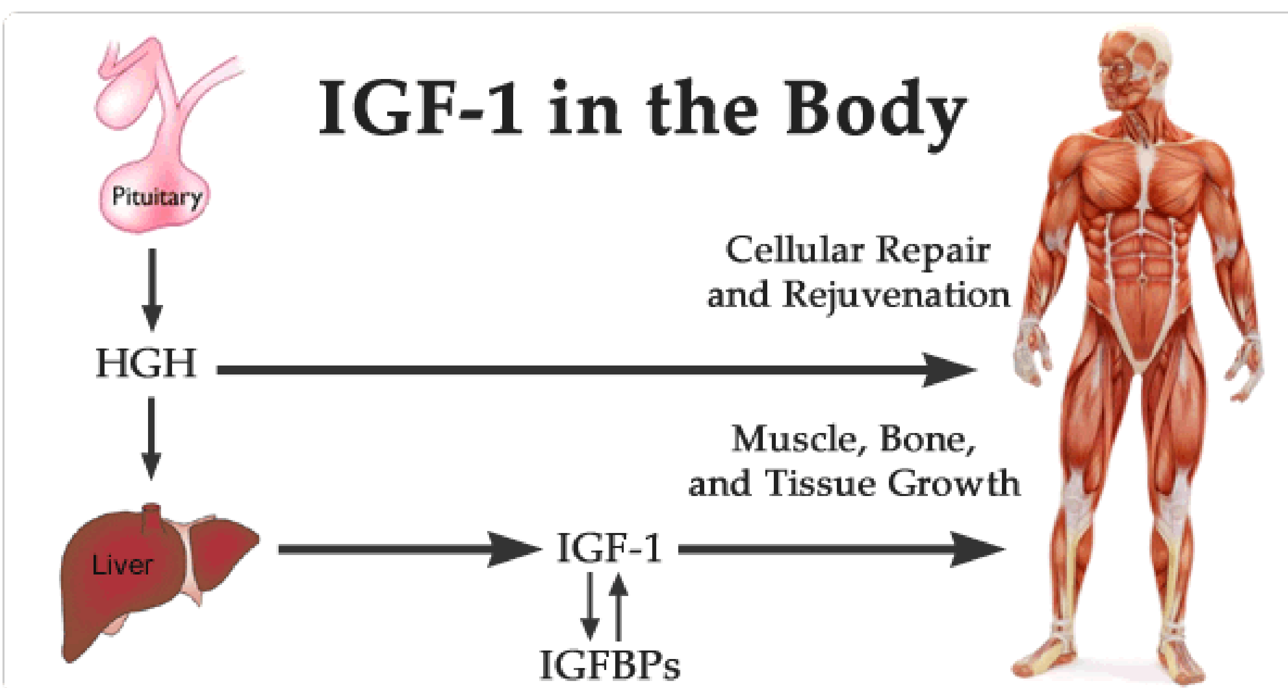
GH and IGF-1

Growth hormone (GH) is released by the pituitary and stimulates IGF-1 (insulin-like growth factor) production in the liver

IGF-1 stimulates proliferation of bones, muscles and other organs and tissues

Failure in GH and/or IGF-1 lead to short stature / dwarfism

Mutations in mice affecting GH (deficiency) and IGF-1 signaling are associated with longer life and striking reduction in cancer



Pathways to delayed aging

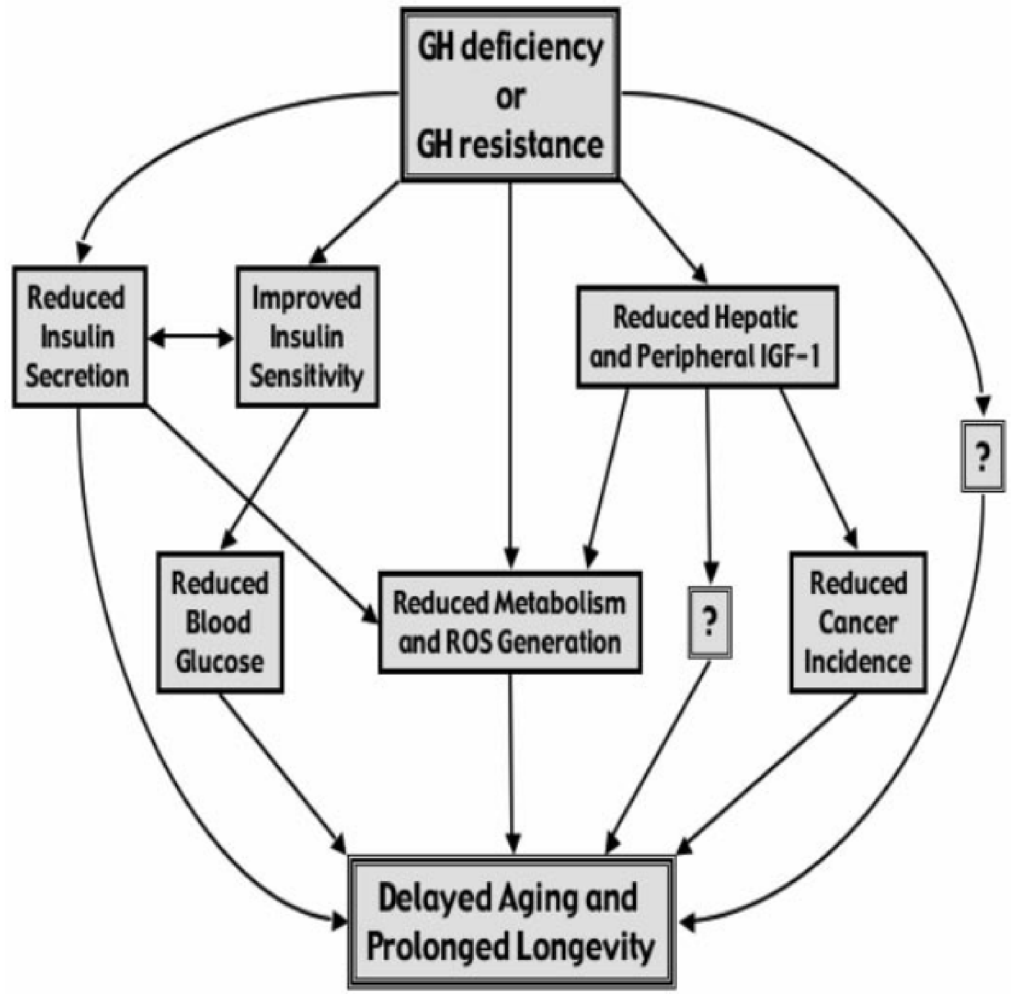
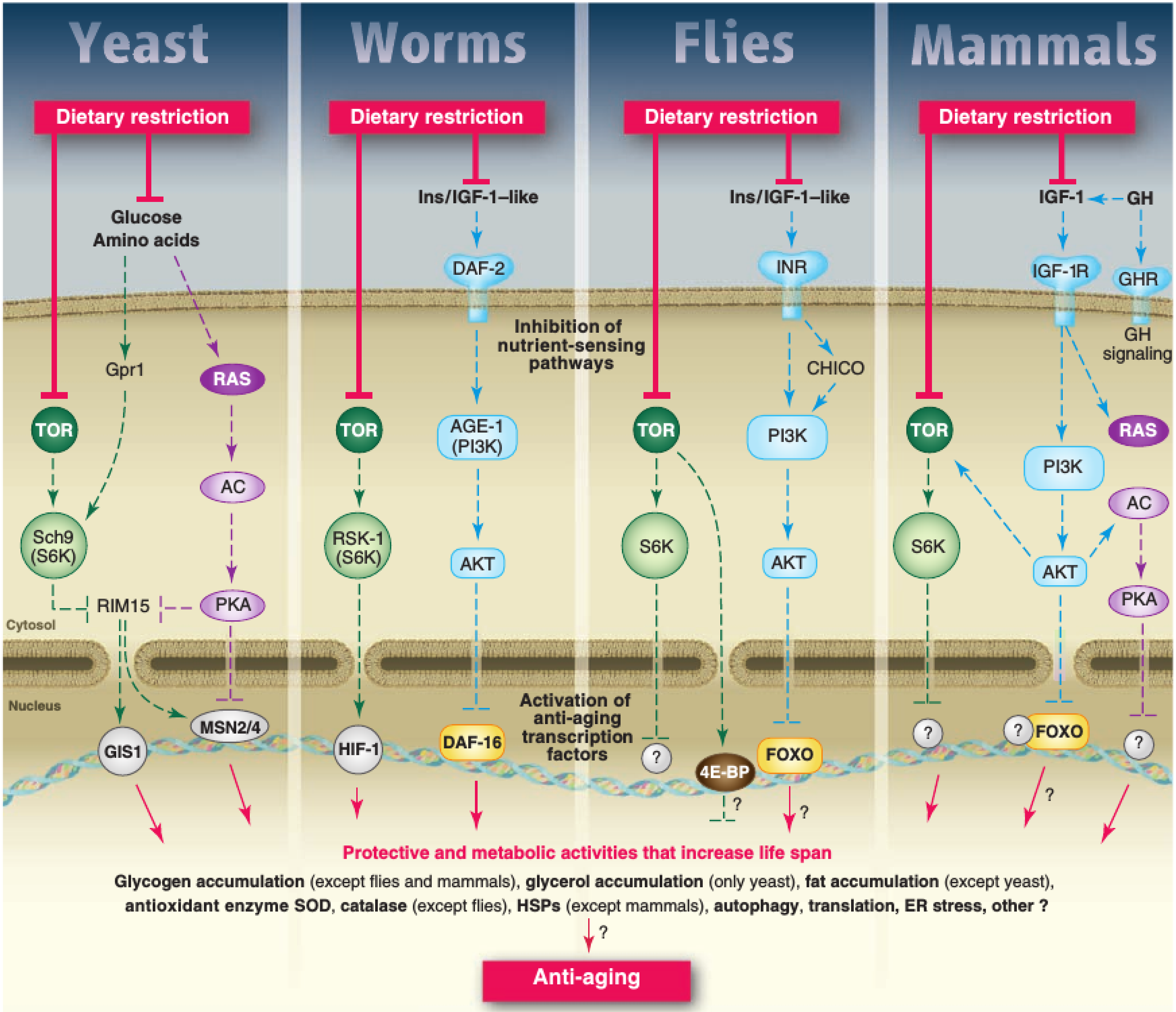


FIG. 1. Proposed mechanisms of prolonged longevity of hypopituitary, GH-deficient, and GH-resistant mice.



Yeast
Worms
Flies
Mammals
Dietary restriction
Dietary restriction
Dietary restriction
Dietary restriction
Glucose
Amino acids
Gpr1
RAS
TOR
AC
Sch9 (S6K)
RIM15
PKA
Cytosol
Nucleus
GIS1
MSN2/4
Ins/IGF-1–like
DAF-2
TOR
AGE-1 (PI3K)
RSK-1 (S6K)
AKT
HIF-1
DAF-16
Inhibition of nutrient-sensing pathways
Activation of anti-aging transcription factors
Ins/IGF-1–like
INR
CHICO
TOR
PI3K
S6K
AKT
4E-BP
FOXO
IGF-1
GH
IGF-1R
GHR
GH signaling
RAS
TOR
PI3K
AC
S6K
AKT
PKA
FOXO
Protective and metabolic activities that increase life span
Glycogen accumulation (except flies and mammals), glycerol accumulation (only yeast), fat accumulation (except yeast), antioxidant enzyme SOD, catalase (except flies), HSPs (except mammals), autophagy, translation, ER stress, other ?
Anti-aging

Rapamycin

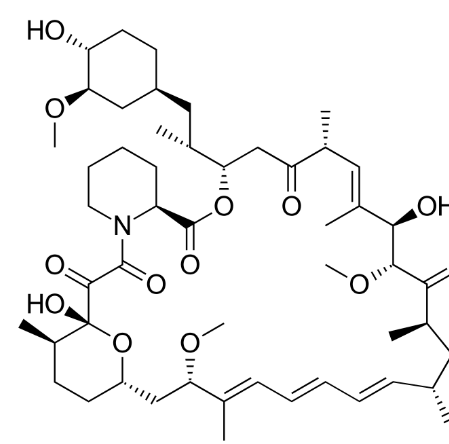
Macrolide antibiotic produced by bacteria found on Easter Island (Rapa Nui) in 1970s

Side effect – immunosuppression – led to its abandonment as an anti-fungal agent

Re-discovered for use to prevent transplant rejection (known as sirolimus)

Found in 2000s to increase lifespan in yeast, flies, worm and – finally - mice

Anti-aging effects are due to inhibition of TOR activation



TOR

TOR = "Target of rapamycin"

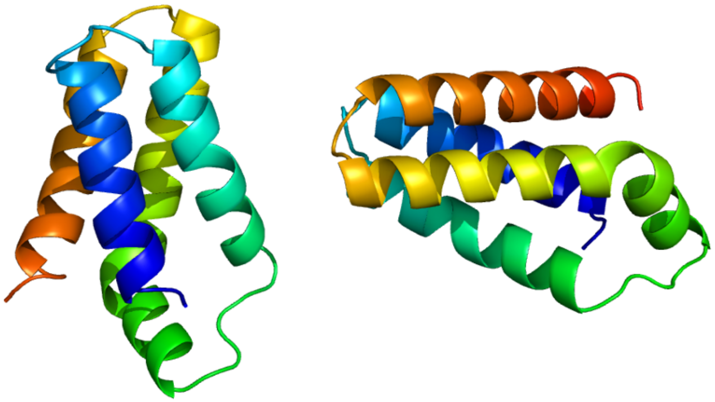
Protein widely present throughout the spectrum of living organisms – yeast to humans

Involved in many different metabolic processes and pathways

- Nutrient sensing: amino acids activate TOR
- Regulation of cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy, and transcription
- Insulin and insulin-like growth factor receptor (IGF-1) activate TOR

Inhibition and reduction of TOR activation are associated with increased life span

- Inhibition by rapamycin
- Reduction of activation by dietary restriction



Next best thing to humans – rhesus monkeys

Monkeys share 93% of the genome with humans

They share numerous aspects of anatomy, physiology, behavior, nervous system, hormonal, and immune system function

Development, maturation, and aging show similar features

Diseases and their manifestations are similar (cancer, diabetes, cognitive decline)

Lifetime is short enough to follow entire lifespan in a single "experiment"

Adaptable to captivity, where they can be studied in detail

Rhesus monkey (Macaca mulatta)

Native to India and China

Lifespan in captivity averages 26 years (median) with 10% alive at 35 yr and none beyond 40, according to a registry

Univ. of Wisconsin project

- Initiated in 1989
- 76 rhesus monkeys – 46 male, 30 female
- All reared at Wisconsin National Primate Center
- All of Indian origin
- Caloric restriction begun after full maturity reached (8+ yrs)
- Controls fed amount determined by baseline consumption *ad libitum* immediately prior to on-study
- Calorie-restricted monkeys fed at 30% reduction
- All females bore young, up to a maximum of three

National Institute of Aging (NIA) project

Initiated 1987

121 rhesus monkeys – 62 males, 59 females

Obtained from a variety of sources

Mixture of Indian and Chinese origin

Controls fed according to age and weight, with care to prevent overfeeding

Calorie restriction begun as juveniles, adolescents, adult or old ages

Calorie-restricted monkeys fed at 30% reduction

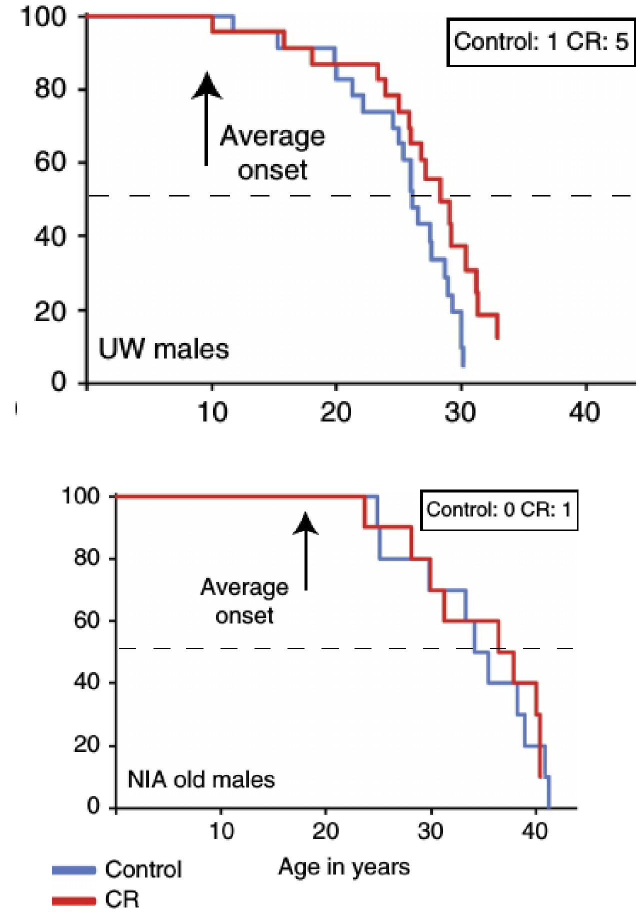
No females were bred

Rhesus monkeys and caloric restriction

UW males showed a small but statistically significant increase in lifespan with CR

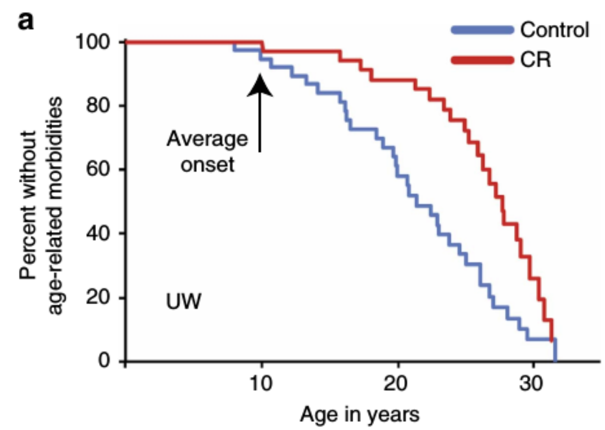
NIA males showed no increased lifespan with CR vs control, but their lifespan was substantially *greater* than UW and standard rhesus monkey experience

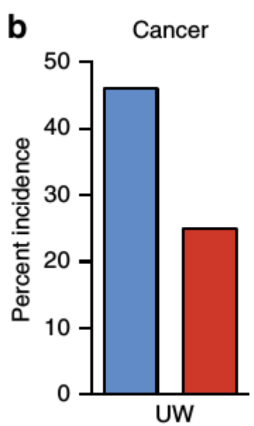
NIA controls were likely CR by comparison to *ad libitum*, so may have been optimally restricted

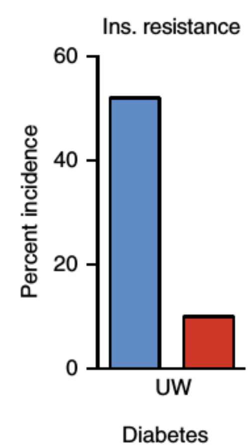


CR and healthspan

Calorie restricted rhesus monkeys had a substantial reduction in chronic diseases in aging







Natural experiments in human calorie reduction: Wartime

Denmark

- During WW I, residents forced to reduce caloric intake for 2 years
- Nutrition quality maintained by careful planning – whole grains, vegetables, milk
- Death rates fell 34% in this interval

Norway

- During WW II, 20% calorie restriction in Oslo for 4 years
- Nutrition quality maintained – fresh vegetables, potatoes, fish, whole cereals
- Death rates fell 30% compared to pre-war

Okinawa: A natural experiment in calorie reduction

Okinawa

- Island south of Japan
- Population 1.3 million
- Approximately 70 miles by 7 miles

Characteristic diet

- Lower in calories
- Lower in protein (9%)
- Rich in fresh vegetables, fruits, sweet potatoes, soy and fish

Okinawa: longevity vs. calories

Okinawans typically consumed fewer calories than average Japanese (-17%) and US (-40%)

This deficit was absolute

- Okinawans had 10-15% lower energy intake than predicted from energy requirements of BMR equation
- Therefore, not just a relative decrease due to overeating of Japanese and Americans

Yet Okinawans have longer lifespans (83.8 yr) than Japanese (82.3) or Americans (78.9)

- Exceptional number of people living age 100+

The CALERIE trials

Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy

Controlled trials ranging from 6-24 months

Supported by National Institute of Aging

Observing multiple biological markers as proxies for aging and chronic disease

Analysis on-going

Concerns regarding bone health

Less of what? Calories or specific nutrients?

Earlier studies focused on calorie restriction as a factor in human aging

- This focus was based on flawed interpretation of a famous study in the 1980s

More recently (since 2010), the spotlight is on protein restriction as the effective intervention

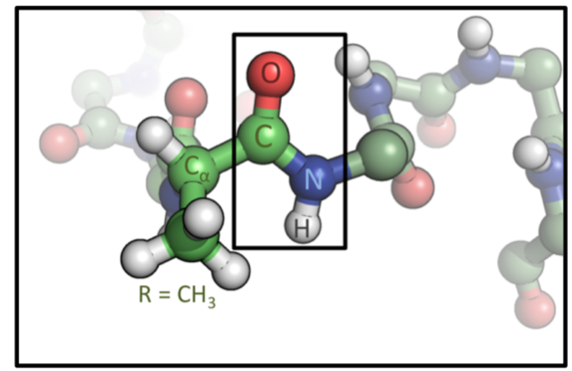
- Restriction of calories was found not to be effective in extending lifespan unless protein was restricted
- A systematic study in mice pinpointed protein restriction as the effective measure in life extension; more about this in the next slide
- Restriction of specific amino acids has now been shown to be responsible for prolonged survival in a variety of models from yeast to flies and rodents
- Effects of protein and amino acid restriction in reducing activation of the mTOR and IGF-1 networks are indications those pathways are involved

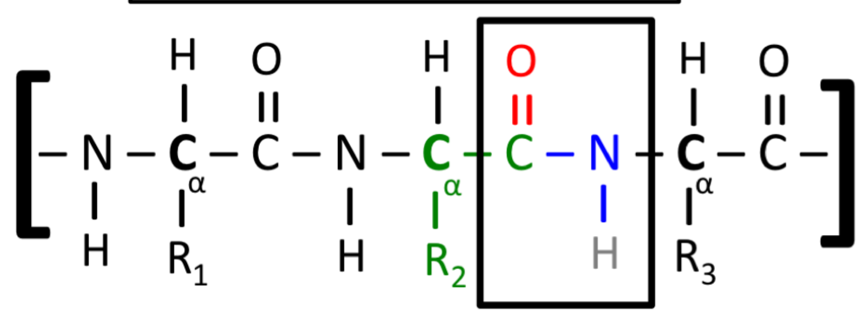
Proteins and amino acids

Proteins are chains of amino acids

Amino acids are organic compounds consisting of a carboxyl (-COOH), amine ($-NH_2$), and side chain (R)

Amino acids link to one another in peptide bonds (-CONH-) to form polypeptides and proteins





Amino acids (AA)

20 standard amino acids are found in proteins

- 2 non-standard AA (not encoded in DNA)

9 are *essential* AA

- Cannot be synthesized in humans from other substrates
- Must be obtained from the diet

6 conditionally essential AA

- May be required from diet during stress, development, repair, etc.

Essential	Conditionally essential[3][4]	Non-essential
Histidine (H)	Arginine (R)	Alanine (A)
Isoleucine (I)	Cysteine (C)	Aspartic acid (D)
Leucine (L)	Glutamine (Q)	Asparagine (N)
Lysine (K)	Glycine (G)	Glutamic acid (E)
Methionine (M)	Proline (P)	Serine (S)
Phenylalanine (F)	Tyrosine (Y)	Selenocysteine (U)
Threonine (T)		Pyrrolysine* (O)
Tryptophan (W)		
Valine (V)		

Branched-chain amino acids (BCAA)

Leucine, isoleucine, and valine

All have branched aliphatic side chains

All are essential AA

Collectively make up 40% of preformed AA required by mammals

Calories vs. nutrients re: aging

The Ratio of Macronutrients, Not Caloric Intake, Dictates Cardiometabolic Health, Aging, and Longevity in Ad Libitum-Fed Mice

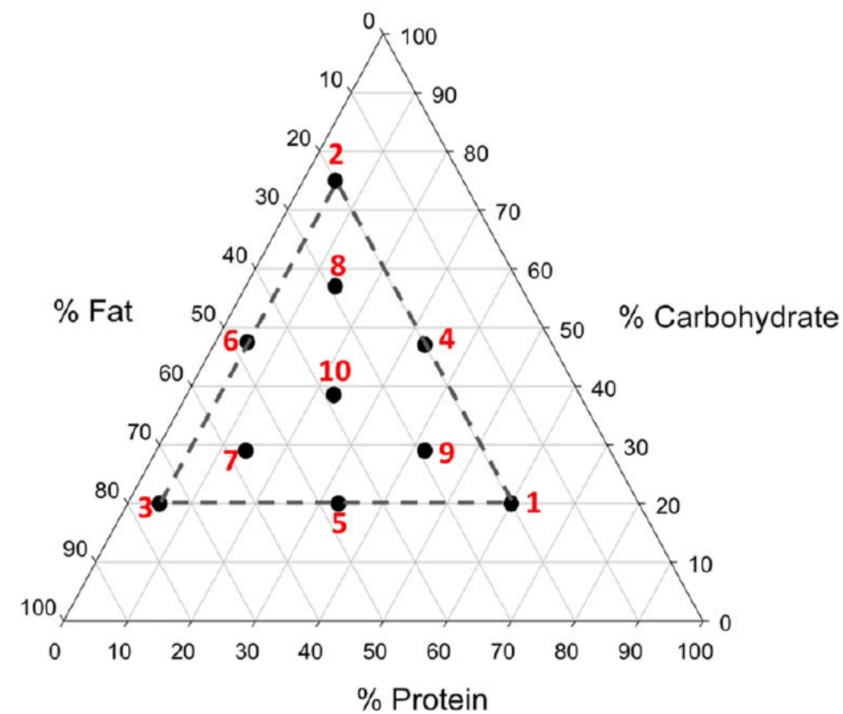
Samantha M. Solon-Biet,[1,2,3,4,13] Aisling C. McMahon,[1,2,3,13] J. William O. Ballard,[5] Kari Ruohonen,[6] Lindsay E. Wu,[7] Victoria C. Cogger,[1,2,3] Alessandra Warren,[1,2,3] Xin Huang,[1,2,3] Nicolas Pichaud,[5] Richard G. Melvin,[8] Rahul Gokarn,[2,3] Mamdouh Khalil,[3] Nigel Turner,[9] Gregory J. Cooney,[9] David A. Sinclair,[7,10] David Raubenheimer,[1,4,11,12] David G. Le Couteur,[1,2,3,*] and Stephen J. Simpson[1,4,*]

858 mice were fed one of 25 diets system-atically differing in protein, fat, carbohydrate and energy density, exploring a 3D nutrient space ("Geometric Framework") *Cell Metabolism*, 2014

Geographic framework (GF) for nutrition

A state-space modeling approach to explore how an animal responds to varying nutrient environments

Capable of reconciling diverse and conflicting conclusions from unsystematic studies



GF nutrient matrix for mice

Diet		1	2[a]	3[b]	4	5	6[a]	7	8	9	10
%P		60	5	5	33	33	5	14	14	42	23
%C		20	75	20	47	20	48	29	57	29	38
%F		20	20	75	20	47	48	57	29	29	38
Low 8 kJ g^{-1}	P	5.03	0.42	0.42	2.77	2.77	0.42	1.17	1.17	3.52	1.93
	C	1.67	6.28	1.67	4.02	1.67	4.02	2.43	4.77	2.43	3.18
	F	1.67	1.67	6.28	1.67	4.02	4.02	4.77	2.43	2.43	3.18
Medium 13 kJ g^{-1}	P	7.54	0.63	0.63	4.15	4.15	0.63	1.76	1.76	5.28	2.89
	C	2.51	9.41	2.51	6.02	2.51	6.02	3.64	7.15	3.64	4.77
	F	2.51	2.51	9.41	2.51	6.02	6.02	7.15	3.64	3.64	4.77
High 17 kJ g^{-1}	P	10.06	0.84	0.84	5.53	5.53	0.84	2.35	2.35	7.04	3.86
	C	3.35	12.55	3.35	8.03	3.35	8.03	4.85	9.54	4.85	6.36
	F	3.35	3.35	12.55	3.35	8.03	8.03	9.54	4.85	4.85	6.36

Energy density varied by adding indigestible cellulose to dilute energy content

Mice were allowed to eat *ad libitum, i.e.*, as much as they wanted

Of 30 combinations, 5 lowest protein and energy excluded because of early failure to thrive

Results of GF trials

At lowest carbohydrate density, mice consumed more food, resulting in higher relative amounts of dietary protein

At lowest protein density, mice consumed more food, resulting in higher relative amounts of dietary carbohydrate

At lowest fat density, mice did not consume more food, so total energy intake was less

Carbohydrate and protein seeking drove appetite more than fat seeking

Allowed exploring the third dimension of total energy as an aging factor

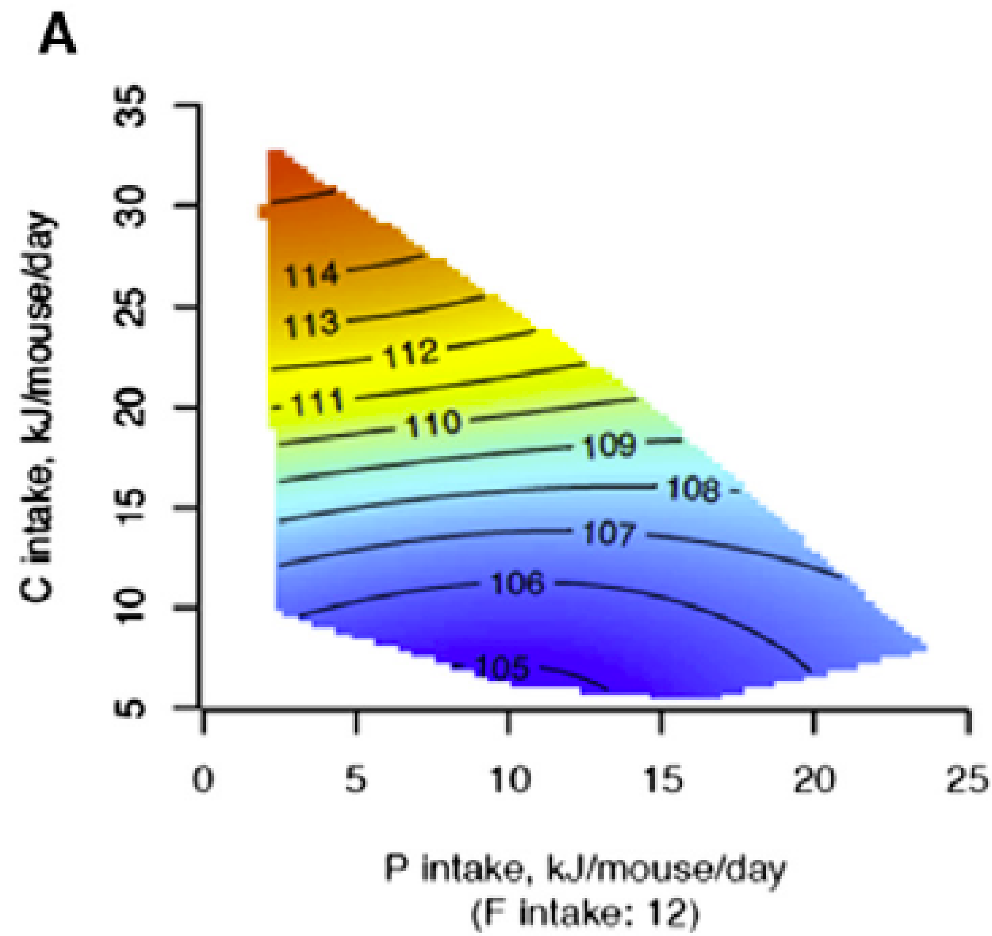
Lifespan (weeks) vs protein, carbs and total energy

Fat intake fixed

As protein intake went from high to low (and carb went from low to high), lifespan increased from 105 to 115 days

Lifespan was most related to protein:carbohydrate ratio

Lifespan was not related to total calories consumed



Biochemical effects of dietary protein in mice by GF

Increasing protein intake was accompanied by increased levels of blood branched chain amino acids (BCAA)

Activation of liver mTOR was strongly influenced by combination of blood BCAA and glucose levels

Given the evidence in other settings that activation of mTOR promotes aging, these results support the conclusion that the mTOR pathway is where low protein intake extends lifespan by keeping activation low

Mice on low protein, high carbohydrate diets had lower blood pressure, higher HDL, lower LDL, and lower triglycerides, markers associated in humans with lower cardiovascular risk

Conclusions of mouse GF study

"Our results show that healthy aging is not achieved in mice fed high-protein diets and/or diluted diets to reduce calorie intake, but rather by low-protein diets (especially, we might predict, those low in BCAAs), where additional energy requirements are met by dietary carbohydrates rather than fats. A priority is to establish whether the same applies for humans, especially considering that high-protein diets are widely promoted for weight loss and health."

Swedish Women's study

Swedish Women's Lifestyle and Health Cohort (Uppsala)

Objective: Association of cardiovascular disease with dietary protein and carbohydrate

43,396 women age 30-49 at entry

Intake: 1991-92   Followup: 15.7 yrs

Endpoint: Diagnosis of cardiovascular disease

Events: Total cardiovascular disease 1270, ischemic heart disease 703, ischemic stroke 294, hemorrhagic stroke 70, subarachnoid hemorrhage 121, peripheral artery disease 82

Swedish Women's study

Food frequency questionnaire

Foods transformed to scores for daily average total protein and carbohydrate amounts

Protein score: 1 (lowest) – 10 (highest)

Carbohydrate score: 1 (highest) - 10 (lowest)

Combined protein and carbohydrate score: Protein score+carbohydrate score, ranging 2-20

Multiple regression analysis

- Adjustment for age, body mass index, smoking, education, hypertension, energy intake, saturated and unsaturated fat, alcohol, physical activity

Swedish women's study

Relative Risk of Overall Cardiovascular Disease					
P+C Score	6 or less	7-9	10-12	13-15	16 or more
Relative Risk	1.0 (ref)	1.13	1.23	1.54	1.60

An increasing proportion of protein in the diet, especially when coupled with decreasing carbohydrate, was associated with a striking increase in cardiovascular diseases

Swedish women's study

"[Our results] draw attention to the potential for considerable adverse effects on cardiovascular health of [low carbohydrate – high protein] diets when they are used on a *regular* basis"

Regular refers to the long-term habitual diet

Did not exclude the possibility of beneficial effects of short-term use of such diets

NHANES III study

Low Protein Intake is Associated with a Major Reduction in IGF-1, Cancer, and Overall Mortality in the 65 and Younger but Not Older Population

Morgan E. Levine[a,1], **Jorge A. Suarez**[a,b,1], **Sebastian Brandhorst**[a,b], **Priya Balasubramanian**[a,b], **Chia-Wei Cheng**[a,b], **Federica Madia**[a,h], **Luigi Fontana**[c,d,e], **Mario G. Mirisola**[a,b,i], **Jaime Guevara-Aguirre**[j], **Junxiang Wan**[a,b], **Giuseppe Passarino**[f], **Brian K. Kennedy**[g], **Pinchas Cohen**[a,b], **Eileen M. Crimmins**[a], and **Valter D. Longo**[a,b,2]

National Health and Nutrition Examination Study

Cell Metabolism 2014

NHANES III study

6,381 subjects aged 50+ U.S. citizens, representative sample

- 3,039 age 50-65
- 3,342 age 66+
- 55% female

Followup: 18 years (intake 1988-94)

Outcomes: Mortality – all-cause (40%), cardiovascular (19%), cancer (10%), diabetes (1%)

Protein consumption: Low (<10% of calories) – 437, medium (10-19%) - 4,798, high (20%+) - 1,146

NHANES: Mortality vs protein

Relative Risk of All-Cause Mortality vs. Dietary Protein as Percent of Calories			
Age Protein →	Low (<10%)	Medium (10-19%)	High (20%+)
50-65 yrs	1.0 (ref)	1.34*	1.74
65+ yrs	1.0 (ref)	0.79	0.72

All-cause mortality increased with increasing dietary protein in middle age but decreased in older subjects as protein intake increased

Statistical significance: All $p<0.05$ except * (not significant)

NHANES: Mortality vs protein

Relative Risk of **Cancer** Mortality vs. Dietary Protein as Percent of Calories			
Age Protein →	Low (<10%)	Medium (10-19%)	High (20%+)
50-65 yrs	1.0 (ref)	3.06	4.33
65+ yrs	1.0 (ref)	0.67*	0.40

Cancer mortality increased with increasing dietary protein in middle age but decreased in older subjects as protein intake increased

Statistical significance: All p<0.05 except * (not significant)

NHANES: Mortality vs protein

Relative Risk of **Cardiovascular** Mortality vs. Dietary Protein as Percent of Calories			
Age Protein →	Low (<10%)	Medium (10-19%)	High (20%+)
50-65 yrs	1.0 (ref)	0.79*	1.03*
65+ yrs	1.0 (ref)	0.80*	0.78*

Cardiovascular mortality did not vary with amount of dietary protein for either middle aged adults or older adults

Statistical significance: All * (not significant)

NHANES III study: Conclusion 1

"We propose that up to age 65 and possibly 75, depending on health status, 0.7 to 0.8 grams of proteins/kg of body weight/day ... should be recommended instead of the 1–1.3 g grams of proteins/kg of body weight/day consumed by adults ages 19–70"

NHANES III study: Conclusion 2

"We also propose that at older ages, it may be important to **avoid** low protein intake and gradually adopt a moderate to high protein possibly mostly plant based consumption to allow the maintenance of a healthy weight and protection from frailty"

Conclusions

Adequate nutrition is certainly essential to a healthy life, but accumulating evidence suggests that we could be healthier if we consumed less than we do *ad libitum*

Restricting calories is difficult

- It's hard to imagine it will become widespread without a massive cultural shift
- Advertising and industrial pressures work against

Restricting protein intake is more feasible

- Is the evidence sufficient to embrace it?

Age and optimum diet

Developing individuals (infants, children, adolescents) need sufficient energy, adequate protein and micronutrients

Mature individuals appear to benefit from relatively low protein intake (10% of calories) as the primary diet intervention to slow aging and cardiometabolic disease

Advanced age individuals may benefit from increasing to higher protein percentage to prevent sarcopenia and osteopenia

Thank you!

Edwin Cox, M.D.

OLLI Course: What to Eat – and Why!

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Observational studies

Obtain a large sample of individuals with some well defined common attributes (nationality, occupation, age, etc)

Record age, weight, height, blood pressure, educational level, exercise level, blood tests

Obtain dietary history by food frequency questionnaire (FFQ), food diary, or 24 hr recall

Follow up to determine end points: death, cause of death, and/or onset of specific diseases

Food frequency questionnaire

BREADS (include use as toast and sandwiches)	Never or rarely	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day	Standard Serving Size	Standard	1/2 or less	1 1/2 or more
White bread, rolls, buns, or French bread	○	○	○	○	○	○	○	○	○	2 slices or 1 bun/roll	○	○	○
Whole grain bread, rolls, buns, or oatmeal bread	○	○	○	○	○	○	○	○	○	2 slices or 1 bun/roll	○	○	○
Corn bread, Johnnycake	○	○	○	○	○	○	○	○	○	2 slices or pieces	○	○	○
Other breads, bagels, biscuits you eat? (*please write them in - use* CAPITAL *letters*):													
1. ______	○	○	○	○	○	○	○	○	○	2 slices or pieces	○	○	○

Major observational studies

Nurses Health Study (NHS) 100K 30yrs

Health Professional Followup Study (HPFS) 50K 25yrs

Physicians' Health Study (PHS) 50K 25yrs

NIH-AARP Diet and Health Study (AARP) 500K 10yrs

European Prospective Investigation into Cancer and Nutrition (EPIC) 500K 18yrs

Adventist Health Study (AHS)

Health Survey for England (HSE)

Is Longevity a Matter of Choice?

Ten Years of Life

Is It a Matter of Choice? FREE

Gary E. Fraser, MB, ChB, PhD; David J. Shavlik, MSPH

Dr. Fraser is professor of medicine and public health at Loma Linda U. in California, where he directs the famous Adventist Health Study focusing on vegetarian eating patterns

Article is from Archives of Internal Medicine, 2001

Seventh-day Adventists

Protestant Christian denomination

Adventists emphasize diet and healthy habits

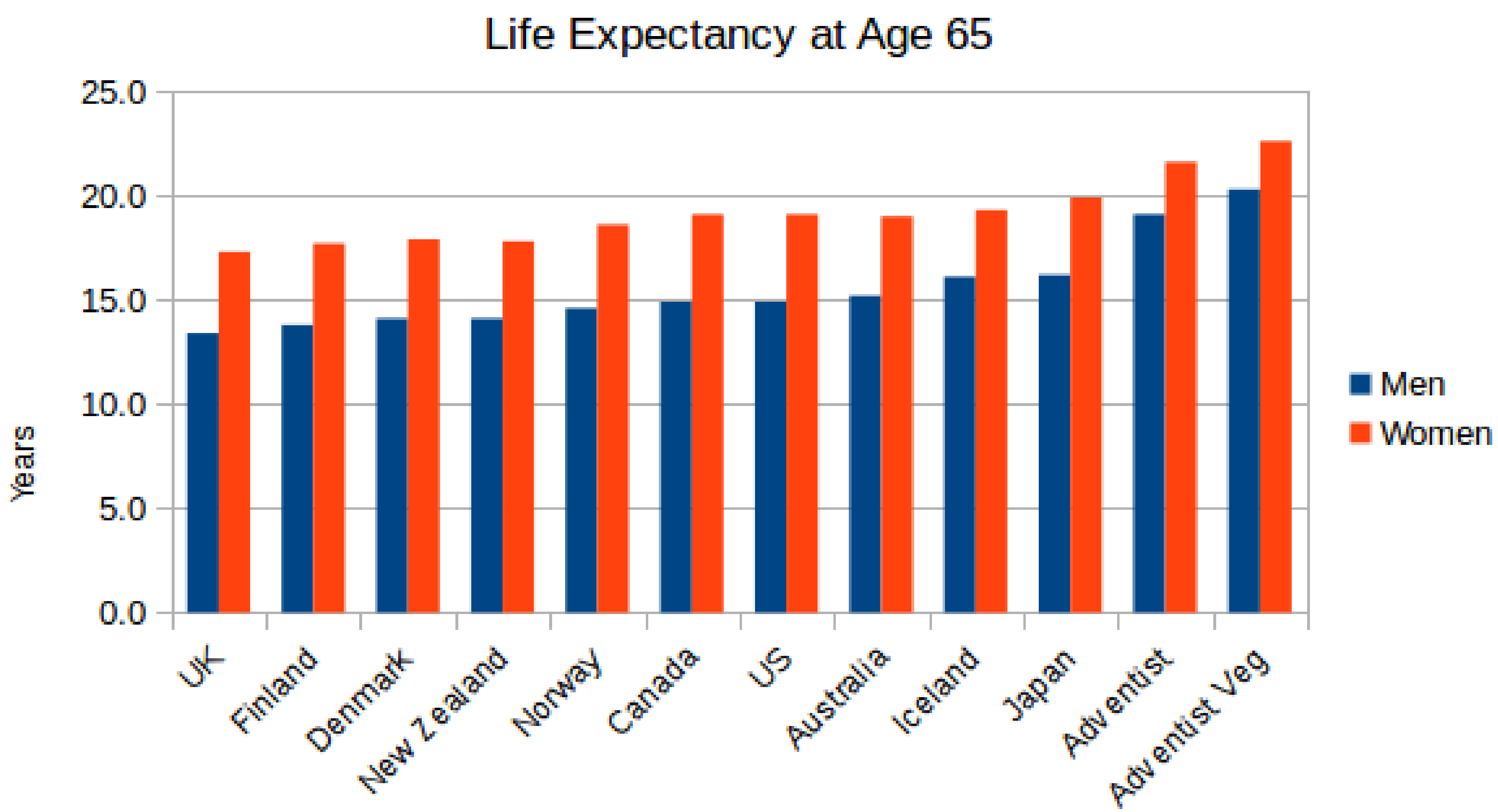
- Avoidance of meat
- Vegetarian diet common
- Abstinence from alcohol and tobacco

Notable members included John Harvey Kellogg

- Development of breakfast cereals as a health food
- Brother William founded Kellogg's

Enclave of Adventists in California (Loma Linda)

Adventists live longer!



Additional Life Expectancy (Adventist Men)

Higher nut consumption +2.7 yrs

Higher physical activity +2.7 yrs

Vegetarian +1.5 yrs

Lower body mass index +1.4 yrs

Never smoker +1.3 yrs

All factors favorable +9.7 yrs

Lifespan impact of specific foods in observational studies