Why do we age ?

周成功
長庚大學生命科學系教授
3月9日

Reading assignment: 啟動長壽基因

David A. Sinclair and Lenny Guarente

科學人2006/04

生、老、病、死：人生的必經之路！

每個人都會因為年紀增長，
伴隨而來各種病痛。

“老”是一種病嗎？

- 整體生理功能逐漸減退，伴隨而來生殖能力的喪失與死亡率的增加。
- 但它不是病，因為它沒有特定致病的原因！

每個人老了之後，身体都會經歷相似的各種變化。

身體中有一個 “遺傳程式” 在指揮老化的進展嗎？

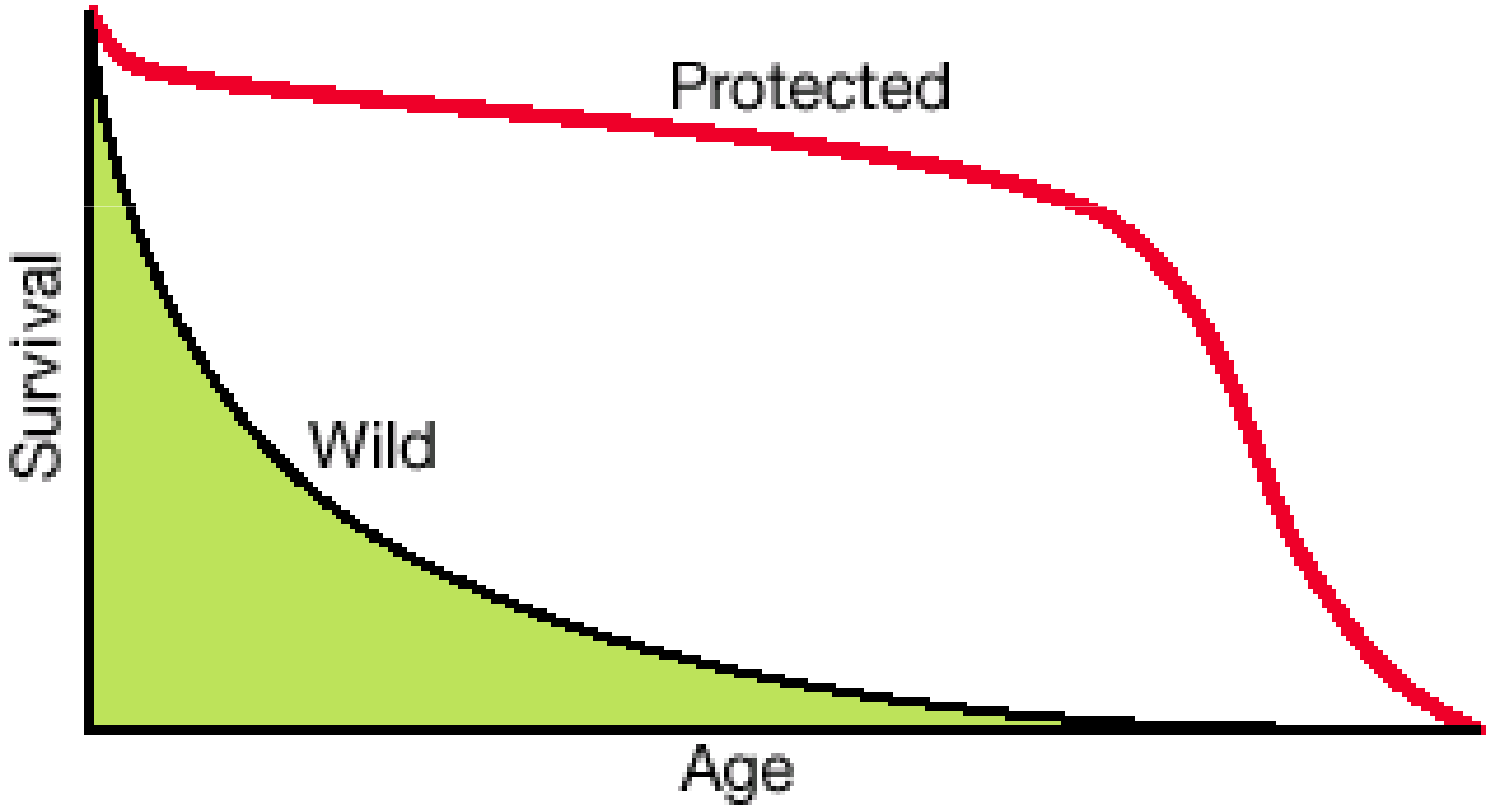
- ***Yes！***
  - 鮭魚產卵後即*老死*！
  - 限制族群的人口，保留有限的資源給年青的後代、、、、
- ***But***、、、

在非洲野外能不能找到
很老的斑馬？

要到那裡才看的到老的班馬？

動物園！

在動物園裡才能看到老的斑馬：
老化是文明的產物！



人為什麼會老？

今天我要從兩個完全不同的角度，
來和大家一起探索這個吸引人的問題！

生物為什麼會演化出產生老化現象的機制？
(Why we age?)

老化是由那些機制的運作而顯現？
(How we age?)

生物為什麼會*演化*出產生老化的機制？
Why we age?

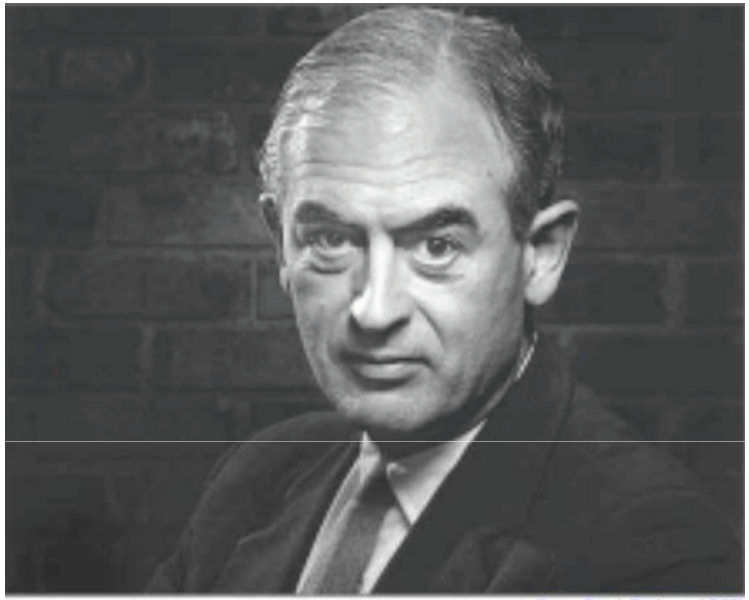
為什麼小鼠的壽命年限只有2-3年，
而人可以超過一百歲？

如何從演化的觀點來瞭解「老化」？

Accumulation of germ-line mutations with late-acting deleterious effects

在平均年齡30歲的族群中累積了許多60歲才會發作的基因突變

…the forces of natural selection *weakens* with increasing age …. If a genetical disaster… happens late enough in individual life, its consequences may be completely unimportant. Even in such a crude and unqualified form, this dispensation may have a real bearing on the origin of innate deterioration with increasing age.

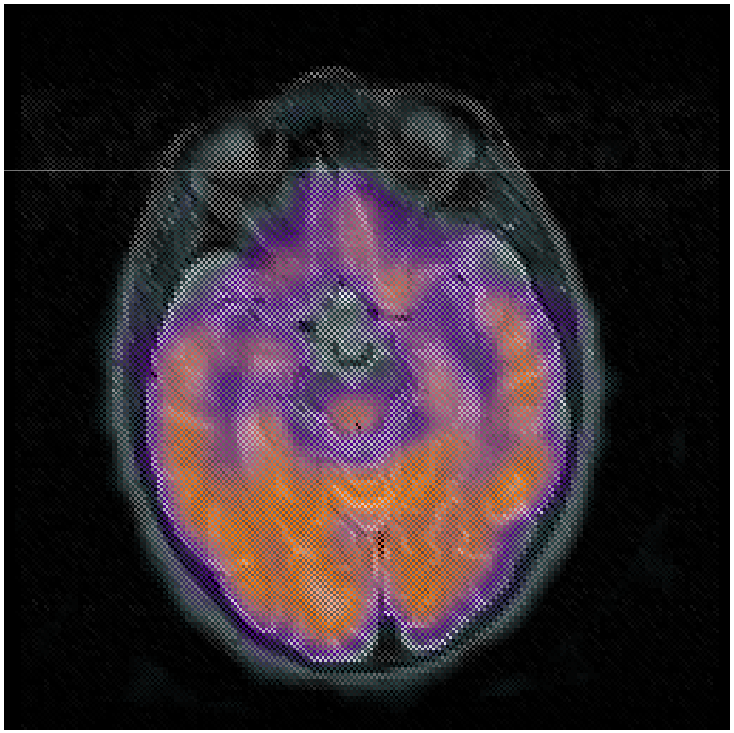


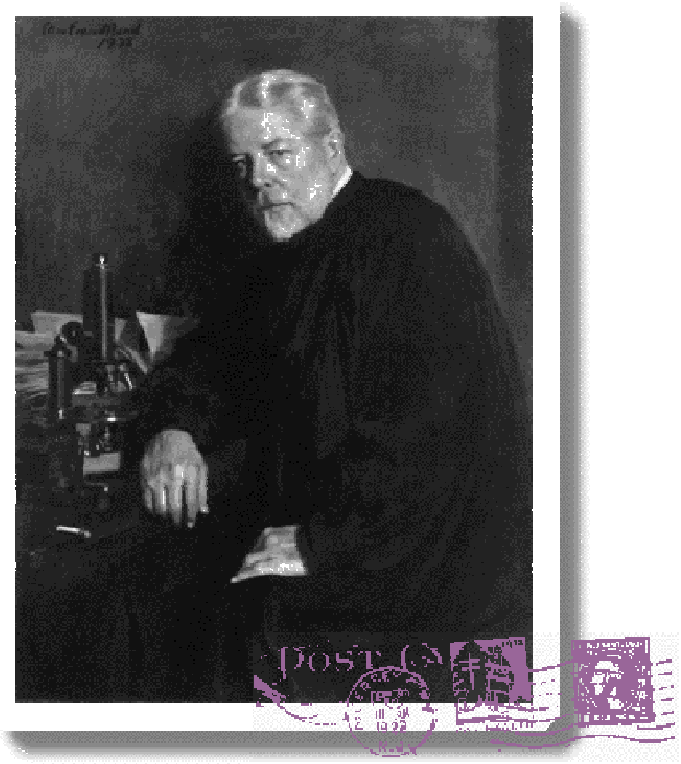
Medawar, 1952

杭丁頓舞蹈症:遺傳到突變的基因所產生神經的病變。

４０歲以後才會發病、死亡！

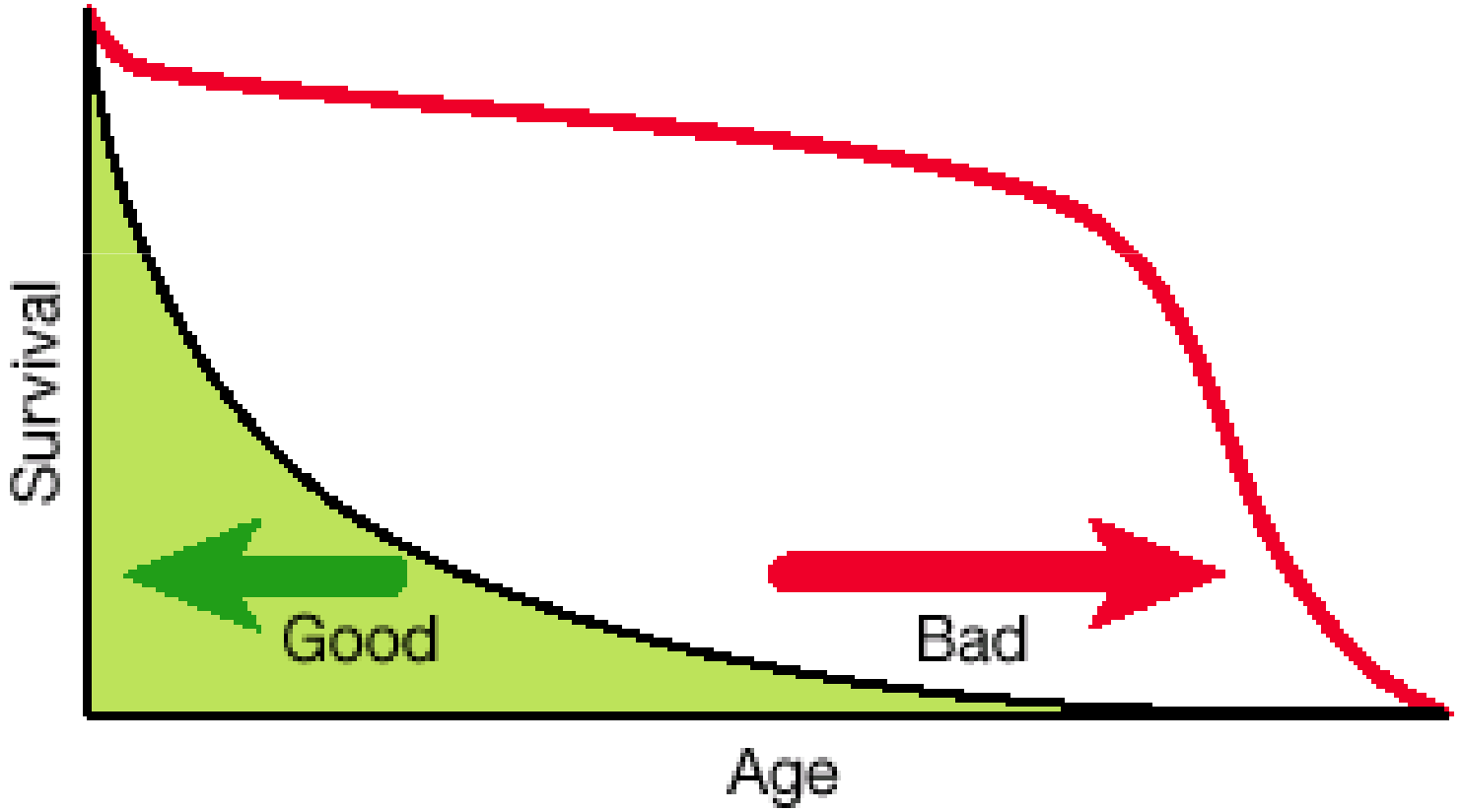
如果１０歲就發病、死亡，情況會如何？

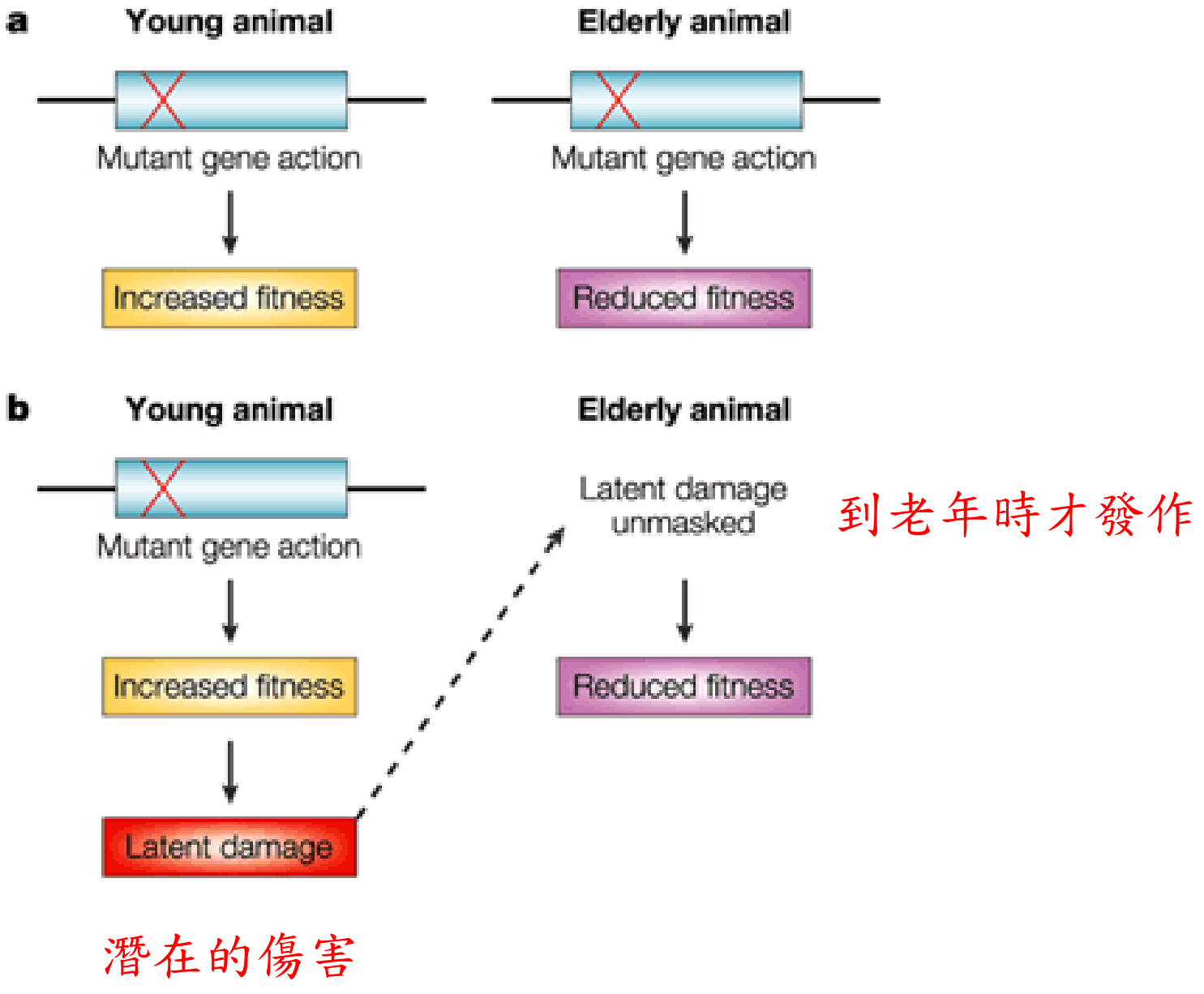




George Sumner Huntington

維持年青活力必須付出的代價：一個基因，在年青身體上的作用和在老年身體上恰恰相反！

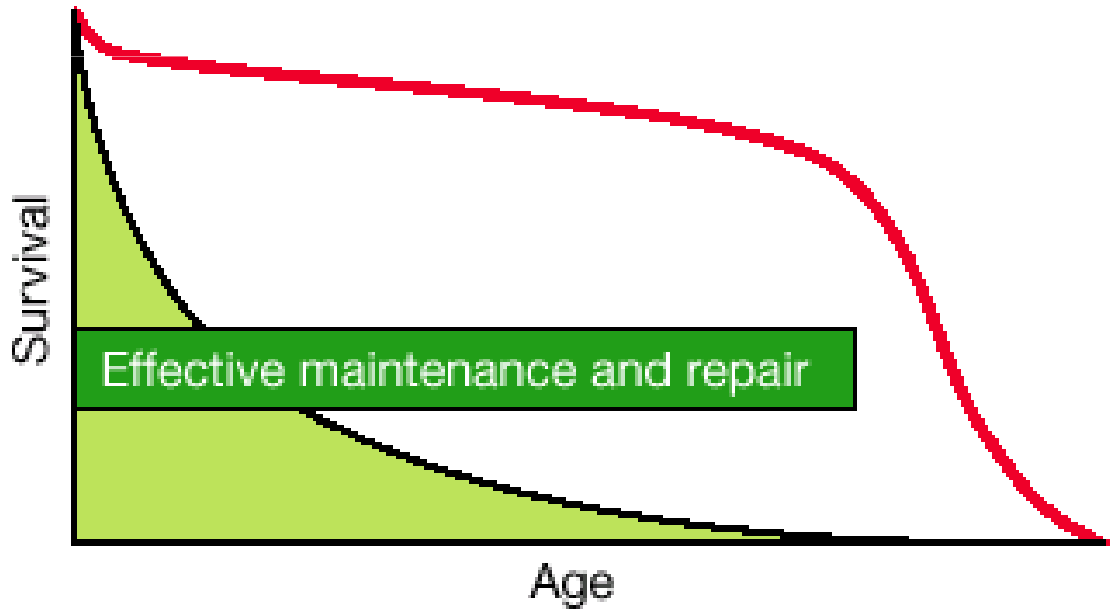




到老年時才發作

潛在的傷害

資源是是有限的時候，
物種在演化過程中，它投資的抉擇是什麼？
修補保養 or 及早生育？



如果你是小鼠，你的投資抉擇是什麼？

如果老化的投資抉擇理論是對的，那麼我們可以在實驗室裡作些什麼樣的預測？

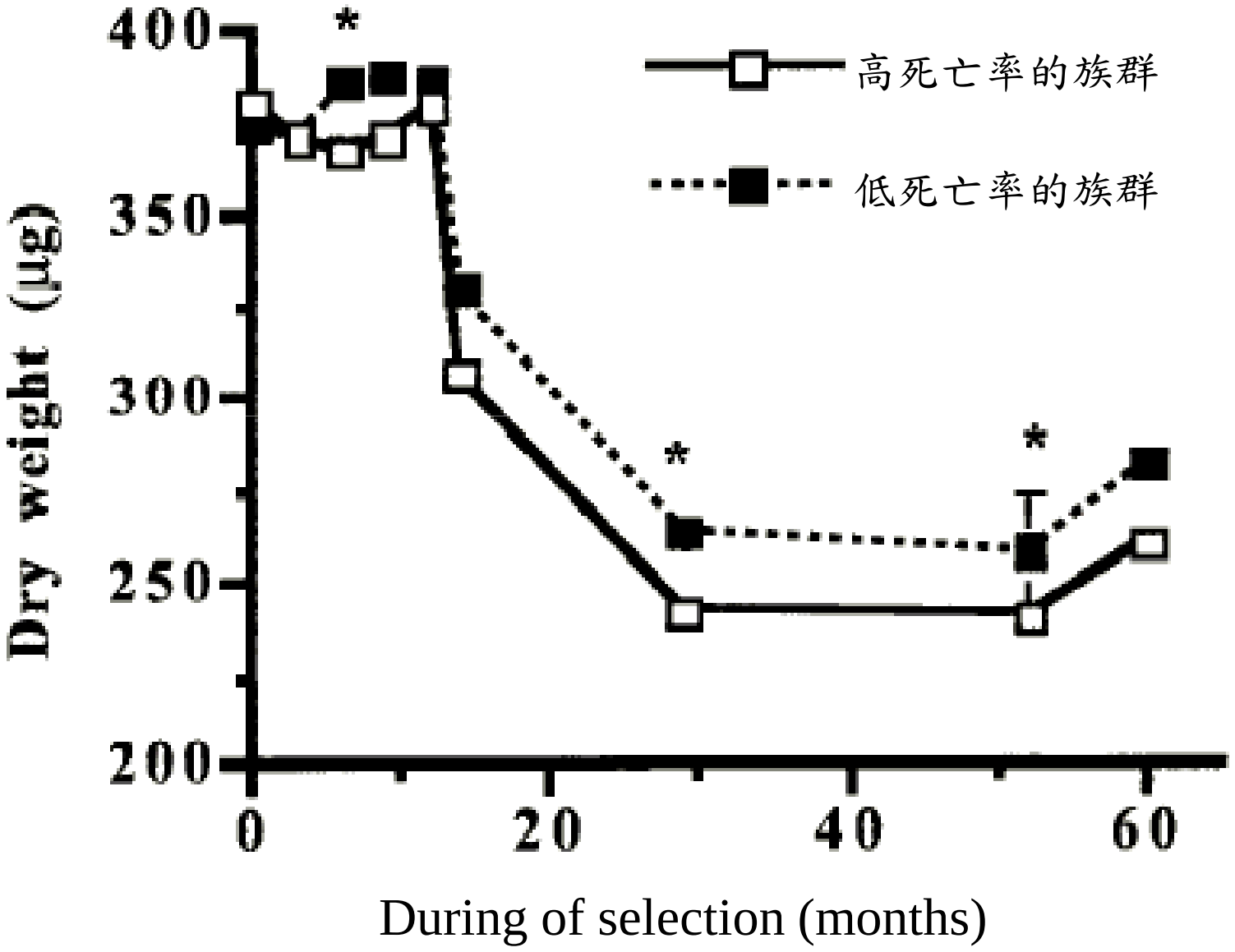
老化的模式動物

長期在死亡率高或低的環境中繁殖，會演化出什麼樣的族群？

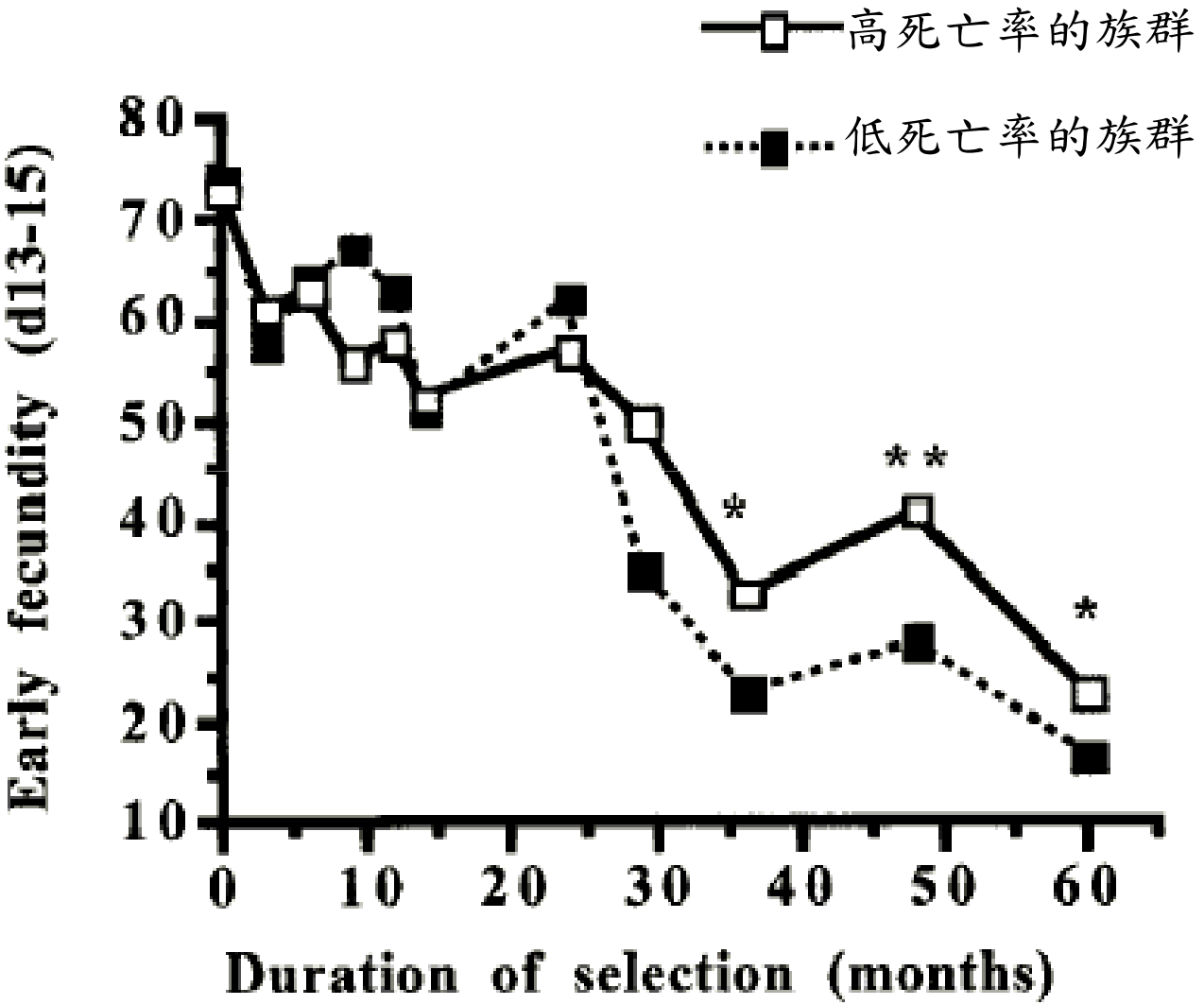
投資在修補保養：體型較大

投資在及早生育：生殖成熟較早

高死亡率的族群演化出較小體型的後代



高死亡率的族群演化出較早開始生殖的後代



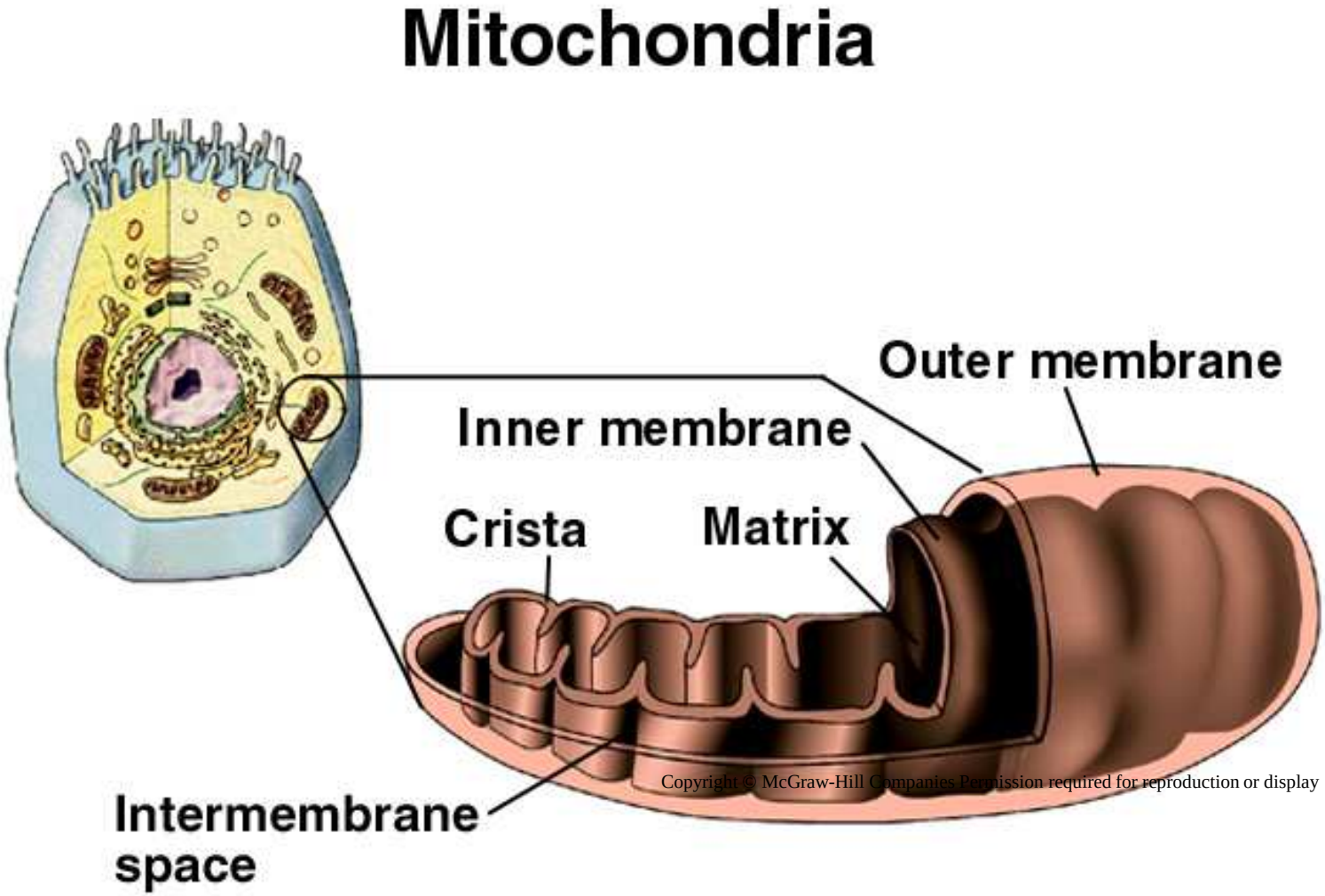
老化現象產生的分子機制是什麼?
How we age?

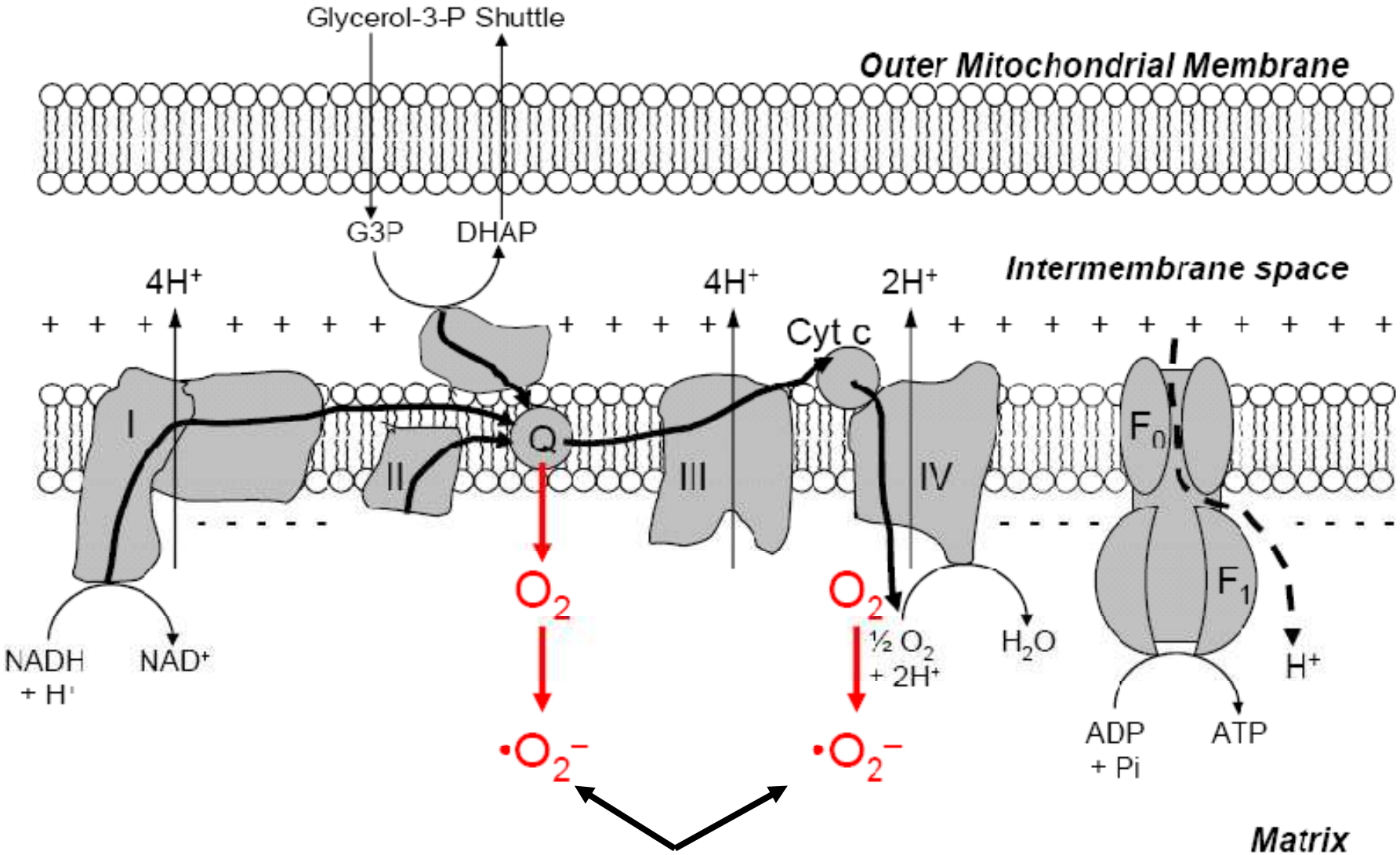
都是氧化壓力惹的禍？

氧化壓力是什麼？

食物燃燒產生的副產品！

粒腺體：細胞內的火力發電廠！




Glycerol-3-P Shuttle
Outer Mitochondrial Membrane
G3P
DHAP
4H+
4H+
2H+
Intermembrane space
Cyt c
I
II
Q
III
IV
F0
F1
NADH
+ H+
NAD+
O2
O2
½ O2
+ 2H+
H2O
•O2−
•O2−
ADP
+ Pi
ATP
H+
Matrix

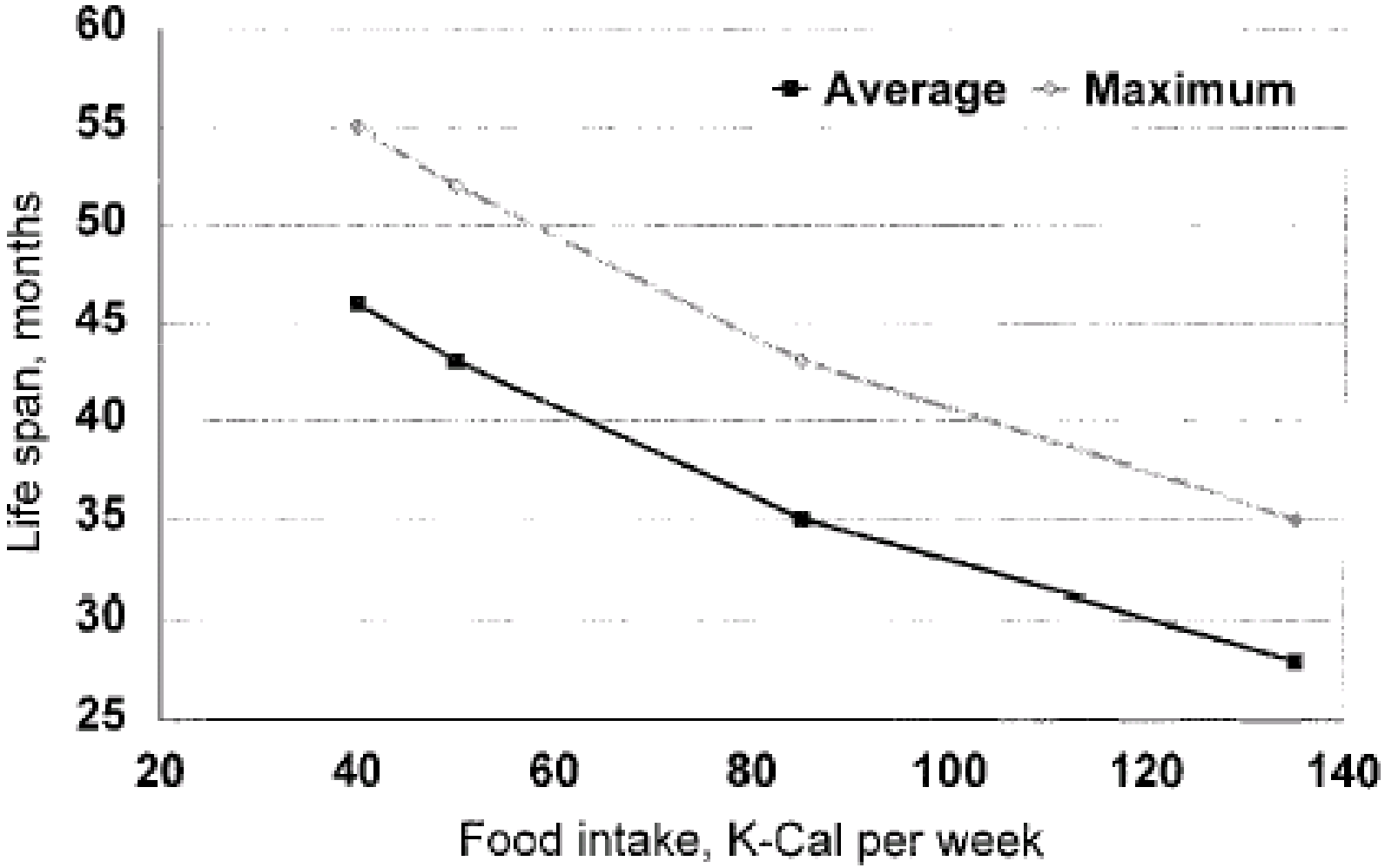
氧的自由基

氧的自由基會攻擊細胞內的各種結構，
包括**DNA**和細胞膜造成損傷！

如果老化都是氧化壓力惹的禍

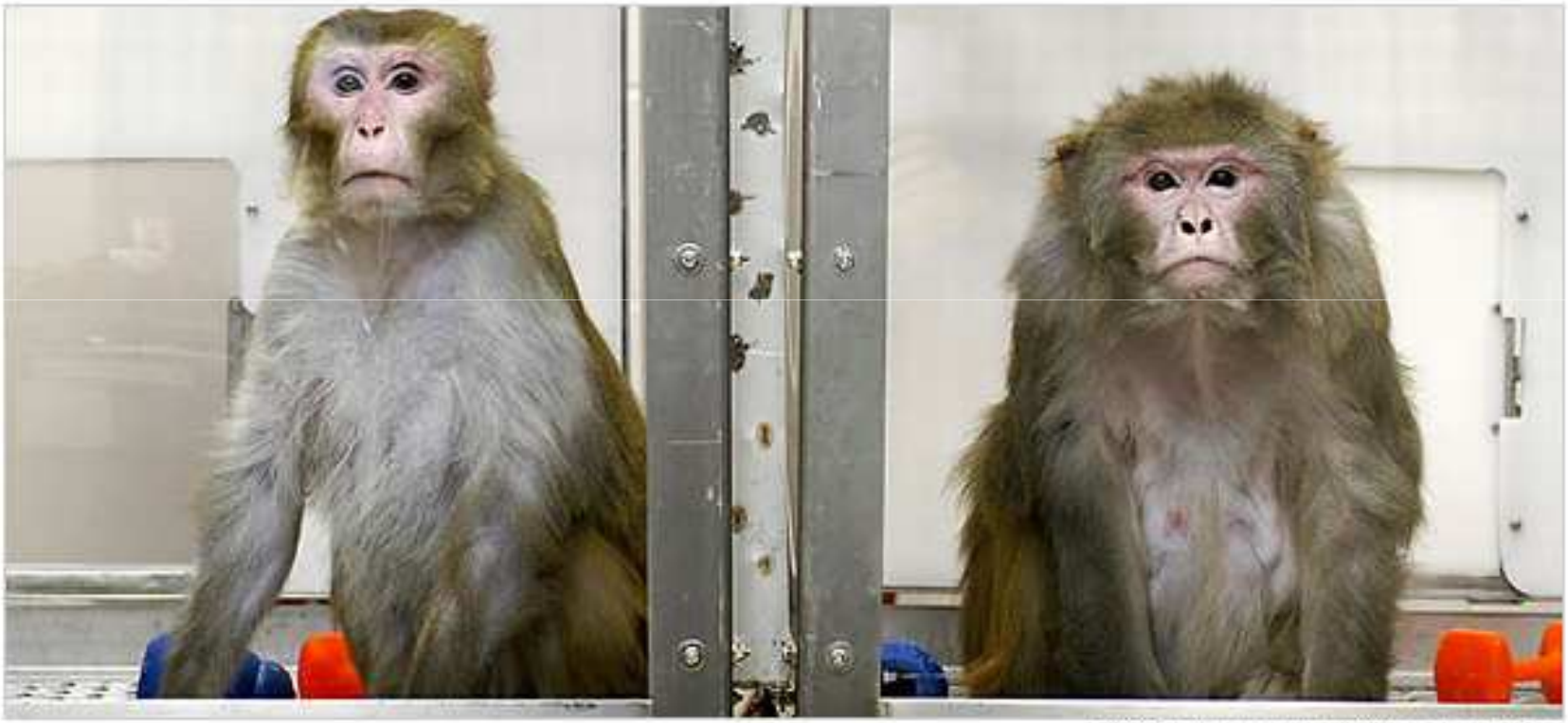
少吃一點會如何？

減低每天熱量的攝取，的確能延長老鼠的壽命！



誰看起來比較老？

One for the Ages: A Prescription That May Extend Life



Jeff Miller/University of Wisconsin-Madison

答案揭曉：年紀相同！

CALORIE RESTRICTION DIET

Canto, 25

Although a senior citizen — the average rhesus monkey lifespan in captivity is 27 — Canto, above, is aging fairly well. Outwardly, he has a nice coat, elastic skin, a smooth gait, upright posture and an energetic demeanor. His bloodwork shows he is as healthy as he looks.

Human equivalent Meals prepared by Mike Linksvayer, 36

Breakfast fermented soybeans and garlic

Lunch tofu, konyakku and carrots

Dinner vegan sausage, kale, tomato sauce and salad

MONKEY MENU

Daily calories

445 **885**

Monkeys also receive an apple each day.

HUMAN MENU

Daily calories

2,000 **3,000**

Beverages, snacks and desserts not shown. Diet varies according to body type, sex and activity level.

NORMAL DIET

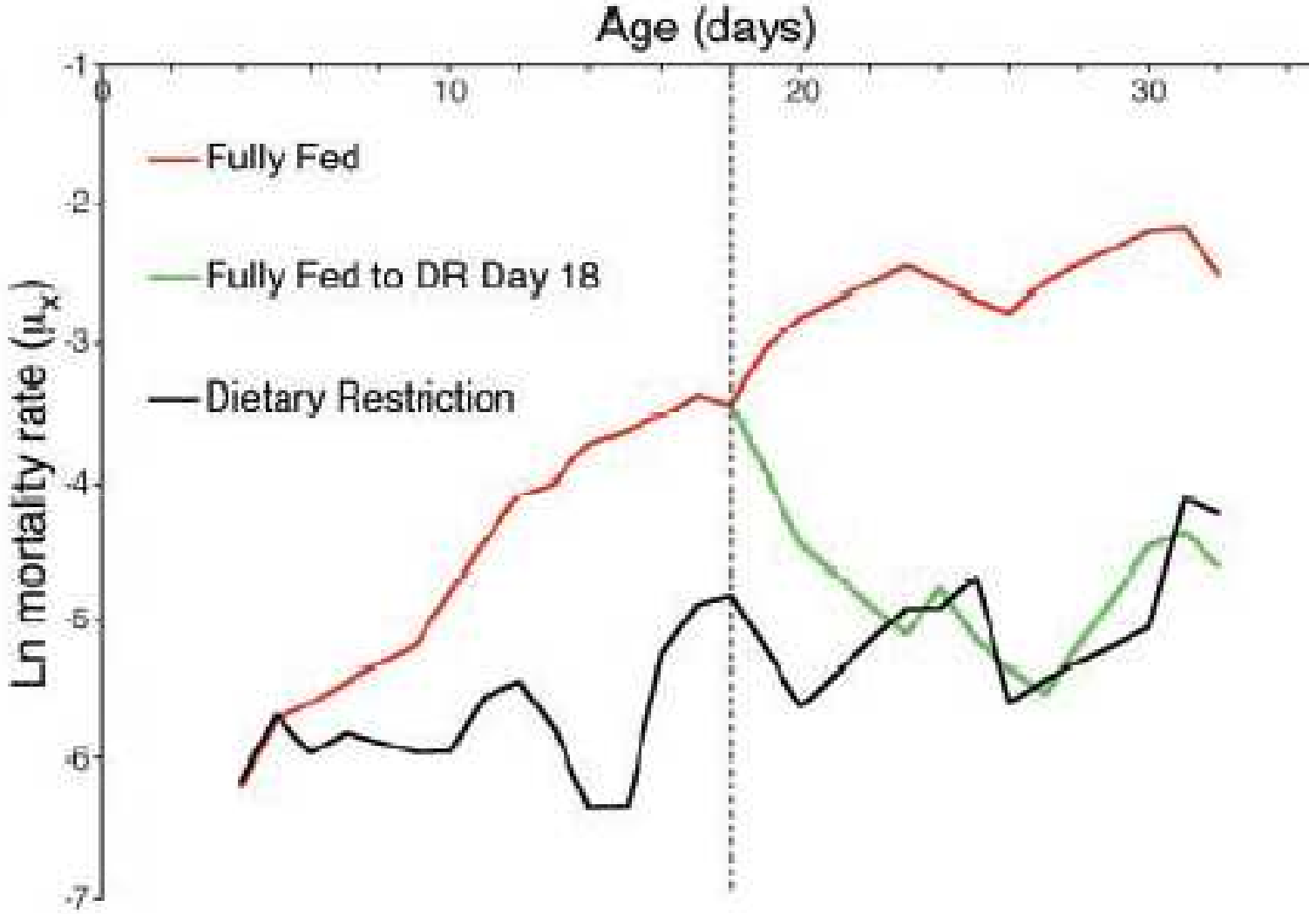
Owen, 26

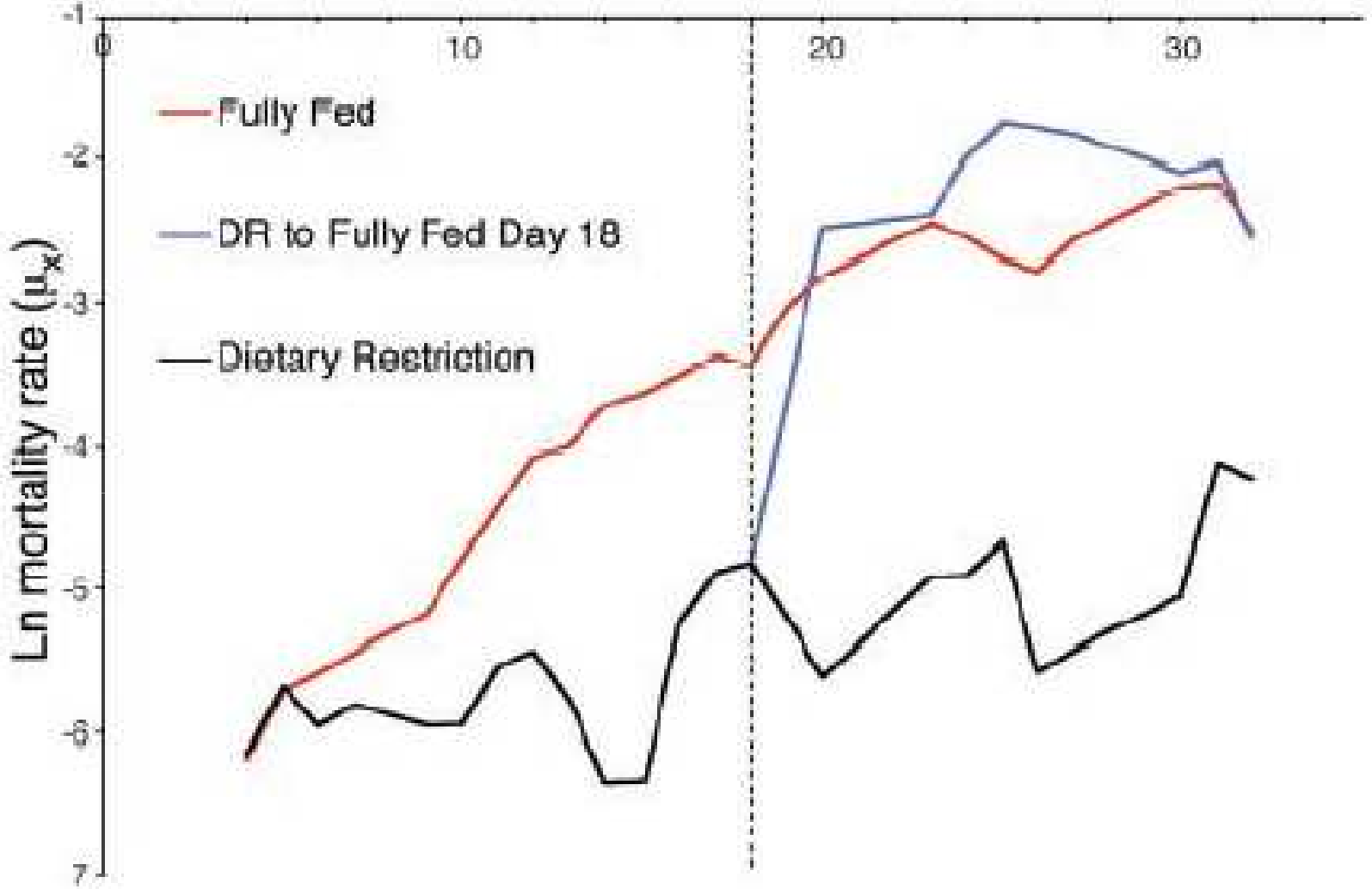
He gets more food, but Owen, above, isn't aging as well. His posture has been affected by arthritis. His skin is wrinkled and his hair is falling out. Owen is frail and moves slowly. His bloodwork shows unhealthy levels of glucose and triglycerides.

Diet of an average, active human male of 36

Photos by Jim Wilson and Tony Cenicola/The New York Times and Lars Klove for The New York Times

Is it too late?


Age (days)
0
10
20
30
-1
-2
-3
-4
-5
-6
-7
Ln mortality rate (μ_x)
Fully Fed
Fully Fed to DR Day 18
Dietary Restriction


Fully Fed
DR to Fully Fed Day 18
Dietary Restriction
Ln mortality rate (μ_x)
-1
-2
-3
-4
-5
-6
-7
0
10
20
30

For fly, it’s never too late！

(但是必須持之有恒，才不會功虧一簣)

Science 301: 1731 (2003)

壽命長短的遺傳基礎

如何找尋会影响壽命長短的基因？

秀麗線蟲

成蟲全身959個細胞；

身長約0.5-1mm。

以吞食洋菜膠上的細菌為生。

在攝氏20度下可正常存活約20天。

在攝氏35度下可存活約

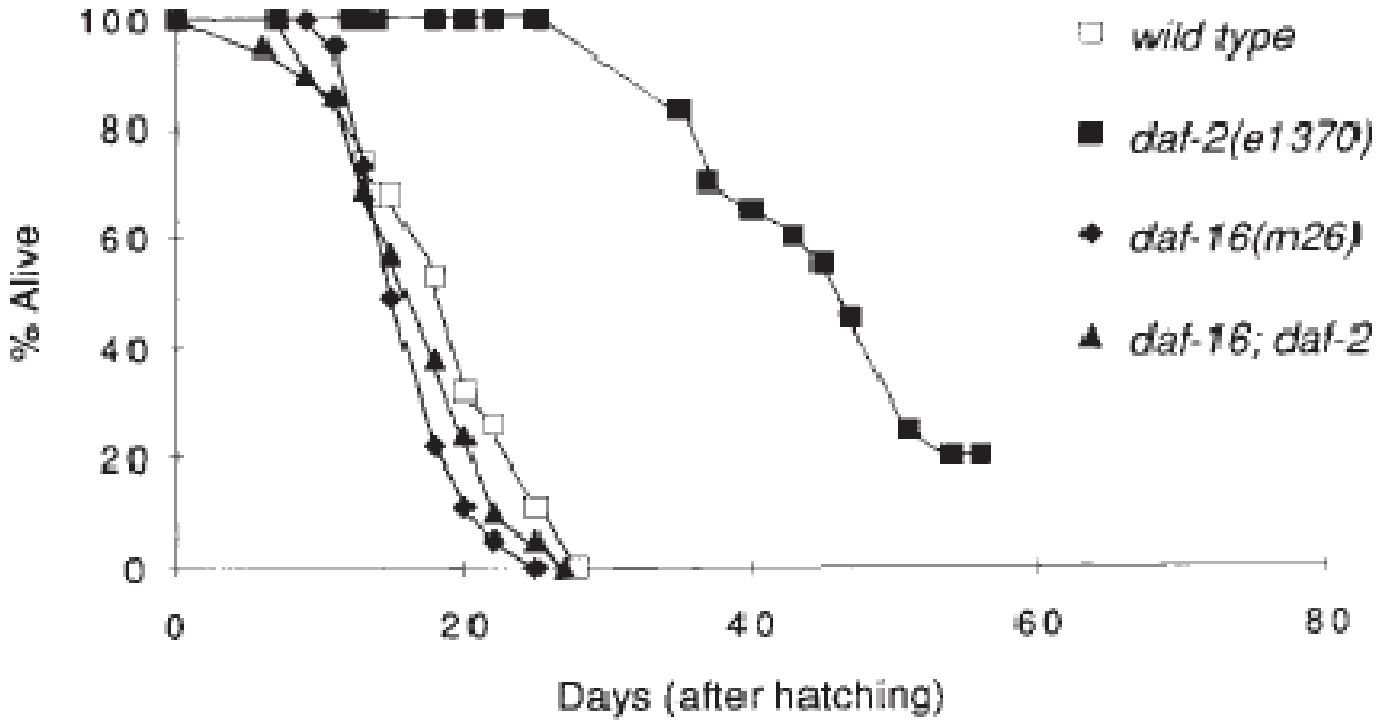
10-14小時。

照片由長庚大學生命科學系羅時成教授提供！

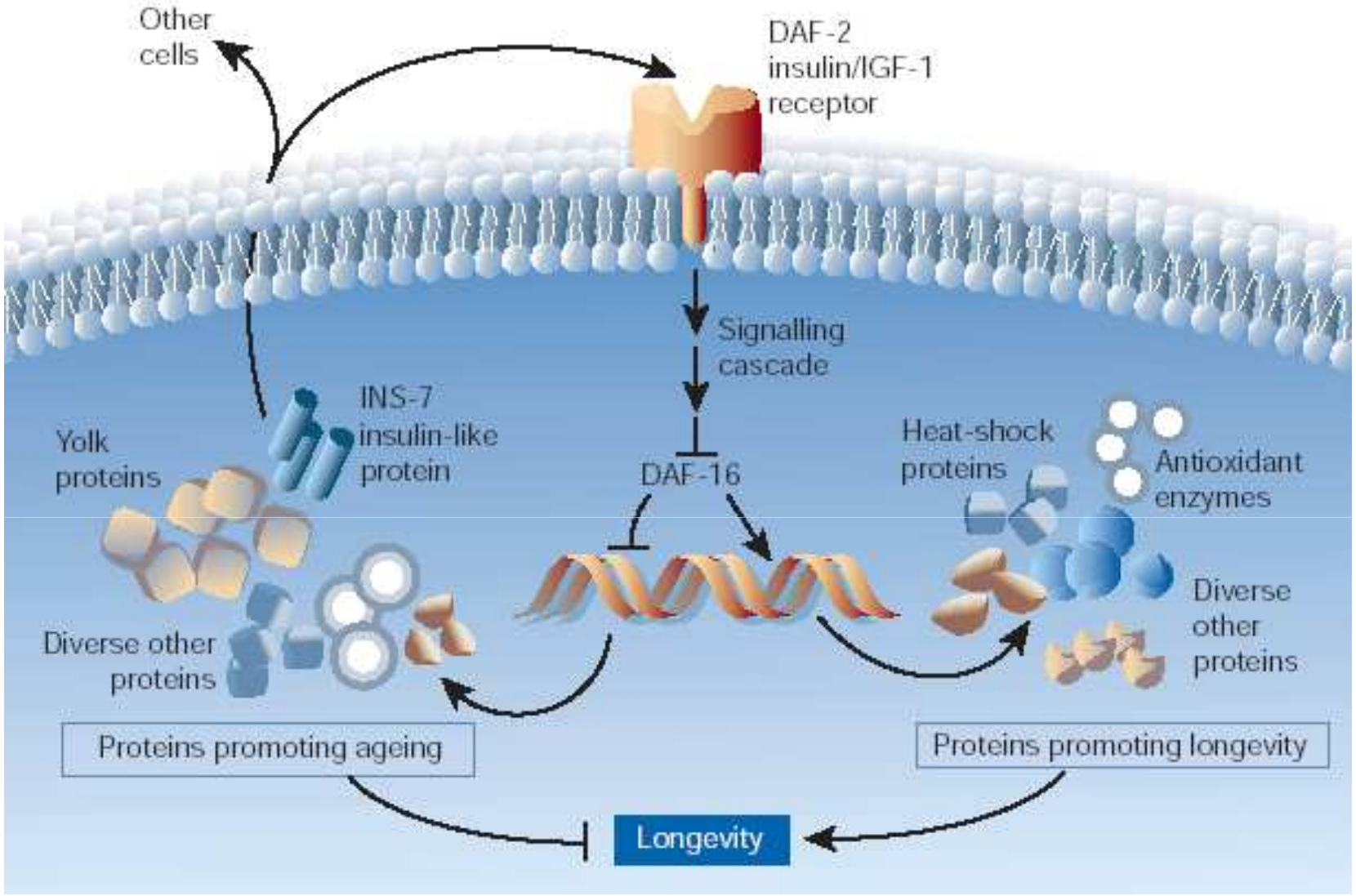
A *C. elegans* mutant that lives twice as long as wild type

Cynthia Kenyon, Jean Chang, Erin Gensch, Adam Rudner & Ramon Tabtiang

Nature 366: 461-64; 1993



daf-2 和 daf-16這二個基因在線虫身上是作什麼用的?



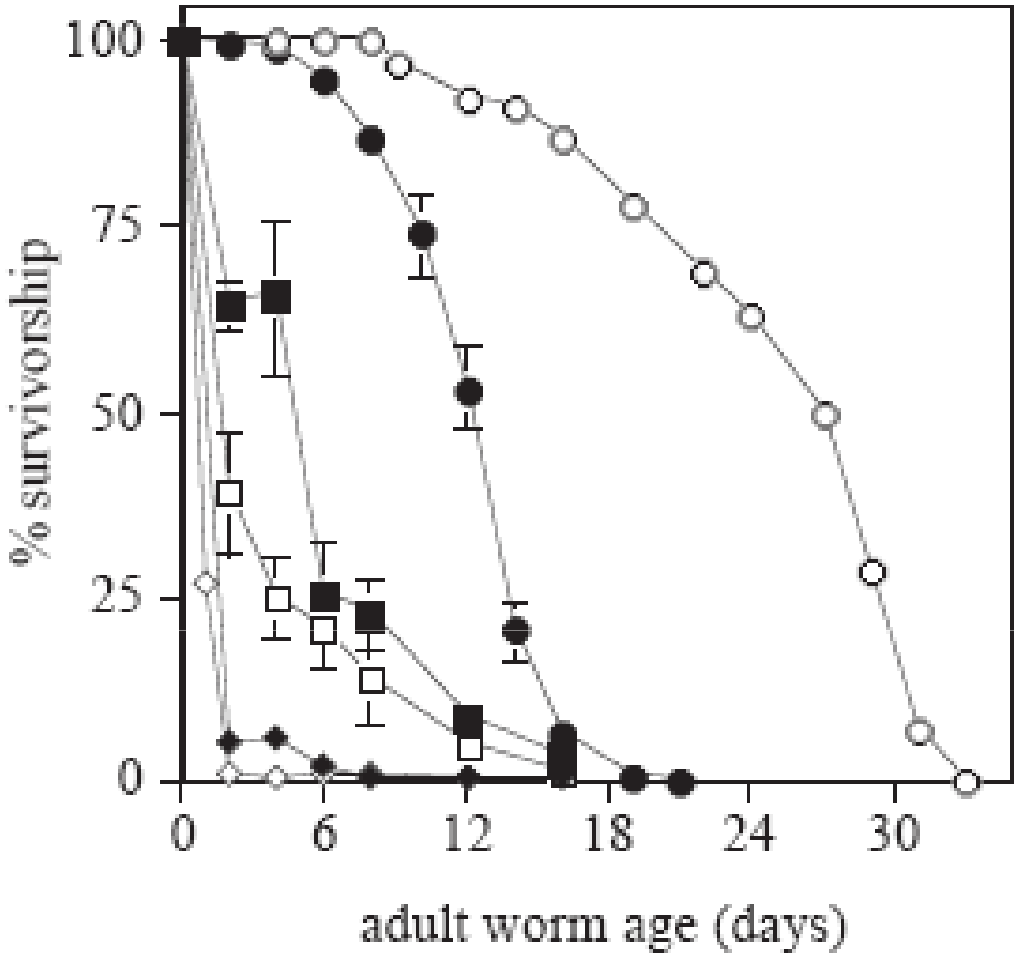
Nature 424: 620 (2003)

Reduction of daf-2 activity extends lifespan of C. elegans

Is daf-2 a "bad guy" to the worm?

The longevity of *Caenorhabditis elegans* in soil

Biol. Lett. 2005 **1**, 247-249.

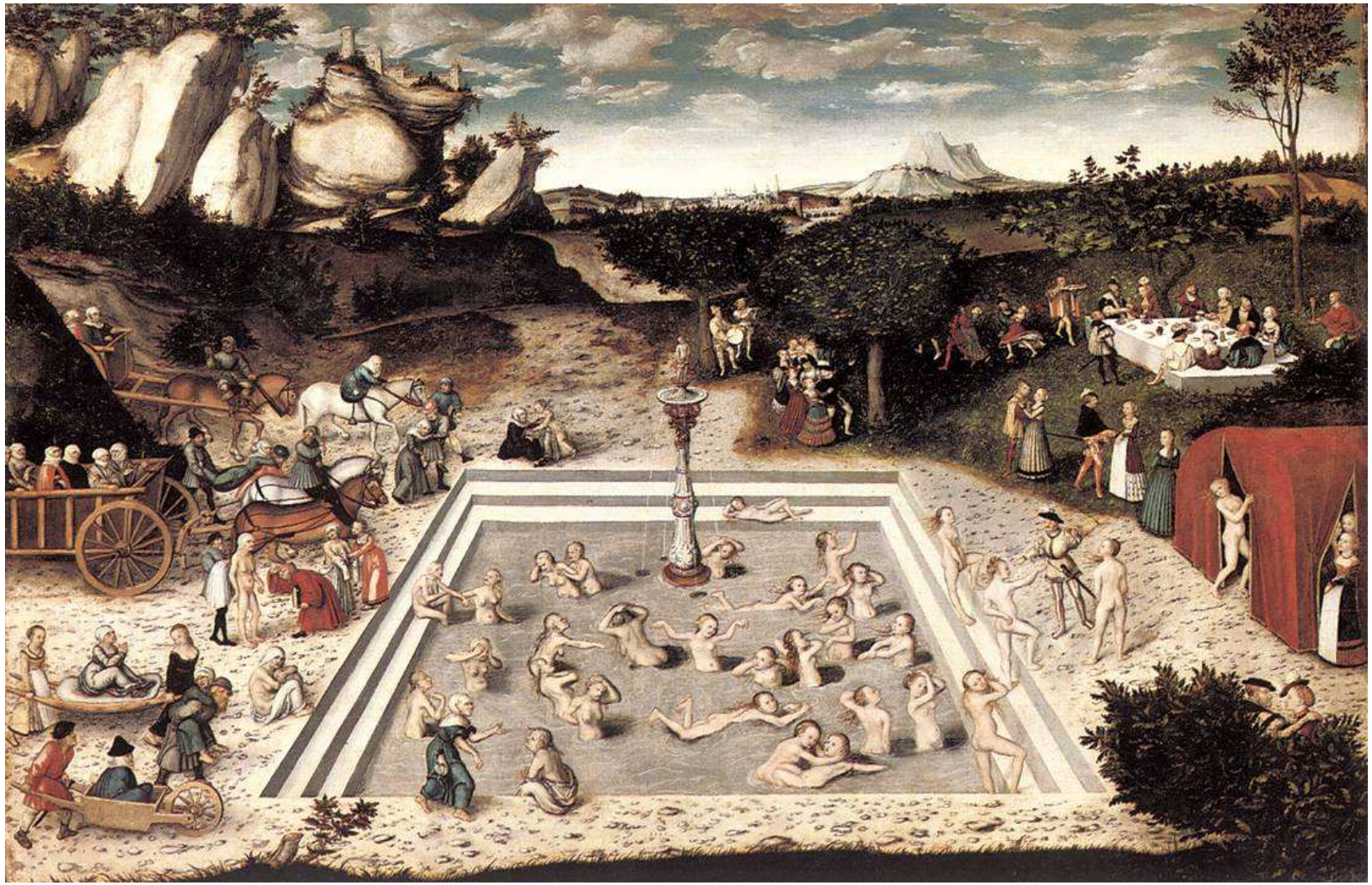


The median adult survivorship of daf-2 worms was 0.8 days in heat-treated soil (open diamond), 1.8 days in sand (open square) and 27 days on agar (open circle).The median adult survivorship of wild-type was 1.0 days in heat-treated soil (filled diamond), 4.5 days in sand (filled square) and 12 days on agar (filled-circle).

C. elegans mutants
that live twice as long as wild-type worms in laboratory conditions typically die sooner than wild-type worms in a natural soil.

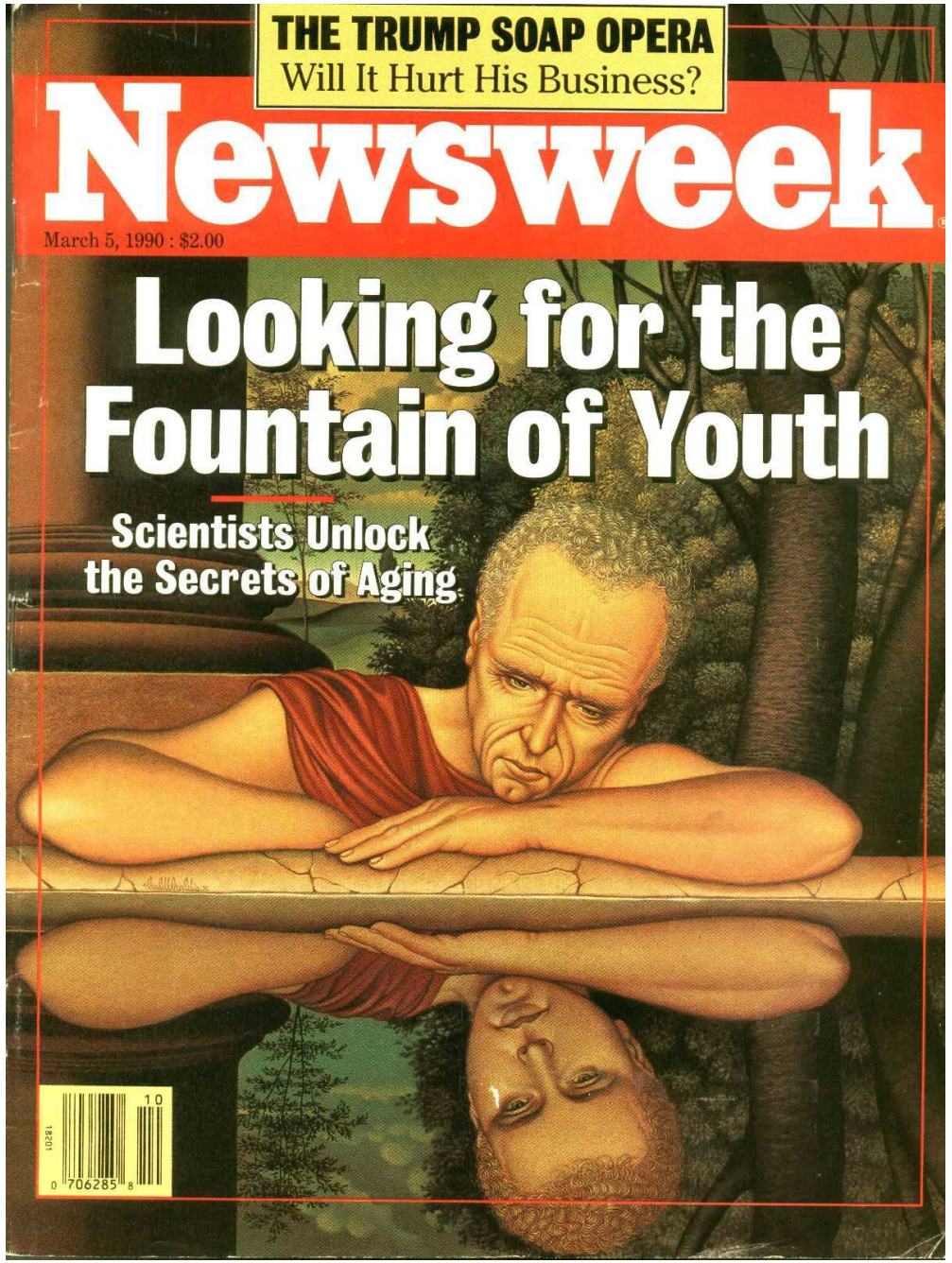
尋找青春之泉！

The Fountain of Youth



Lucas CRANACH (1546)

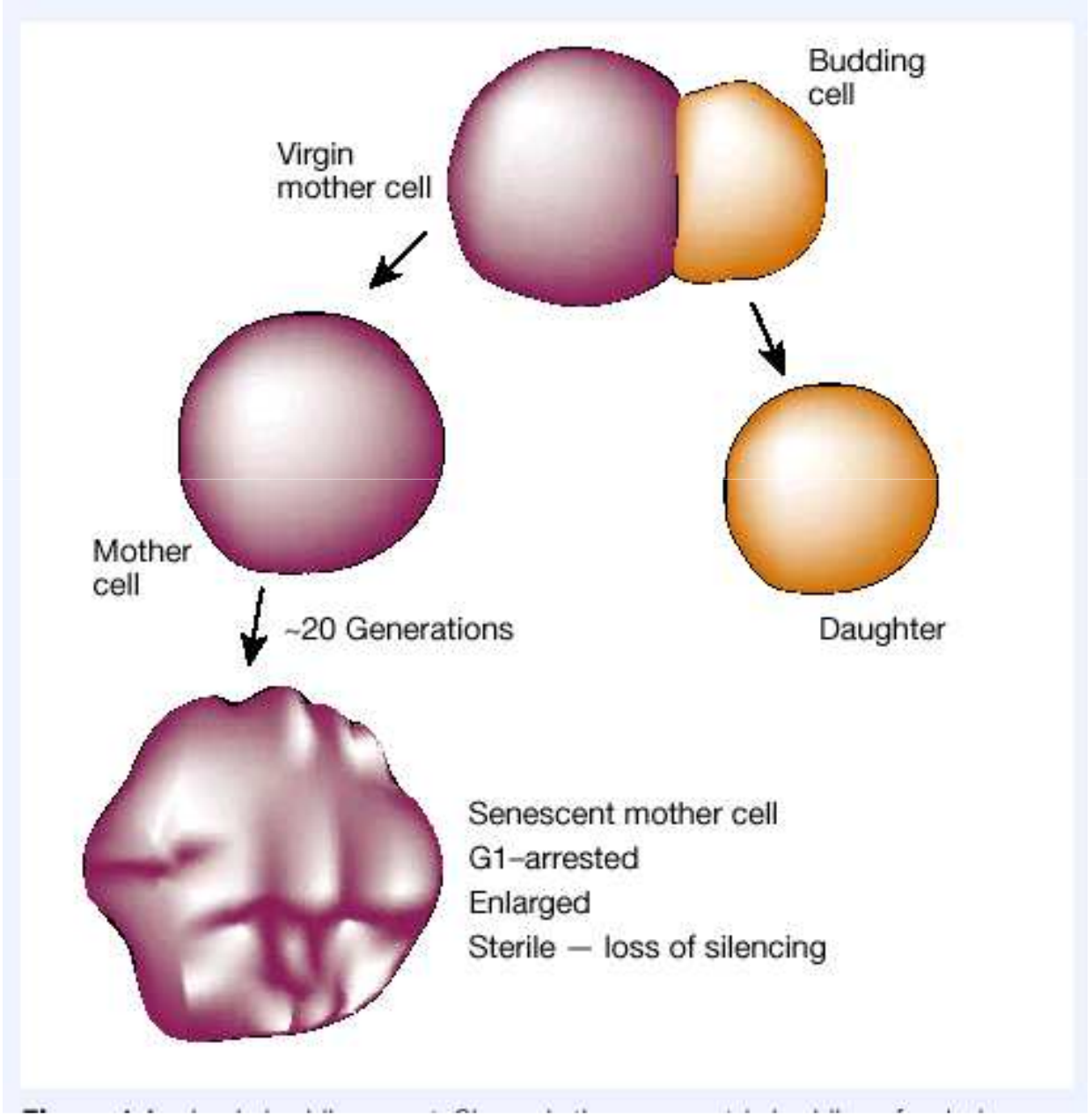
In the spring of 1512, the Spanish explorer Ponce de León left Puerto Rico in search of the fountain of youth.


THE TRUMP SOAP OPERA
Will It Hurt His Business?
Newsweek
March 5, 1990 : $2.00
Looking for the Fountain of Youth
Scientists Unlock the Secrets of Aging
10
19201
0 706285 8

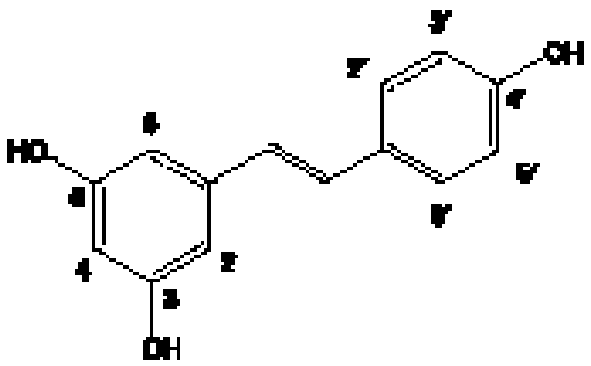
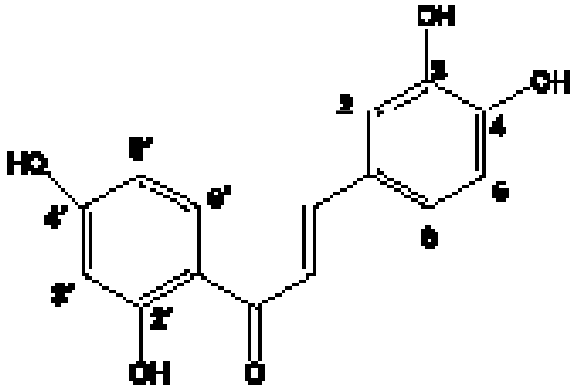
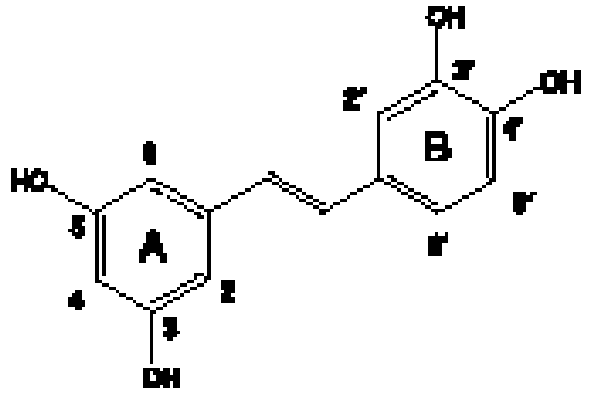
能否去尋找可以使酵母菌長壽的藥物？

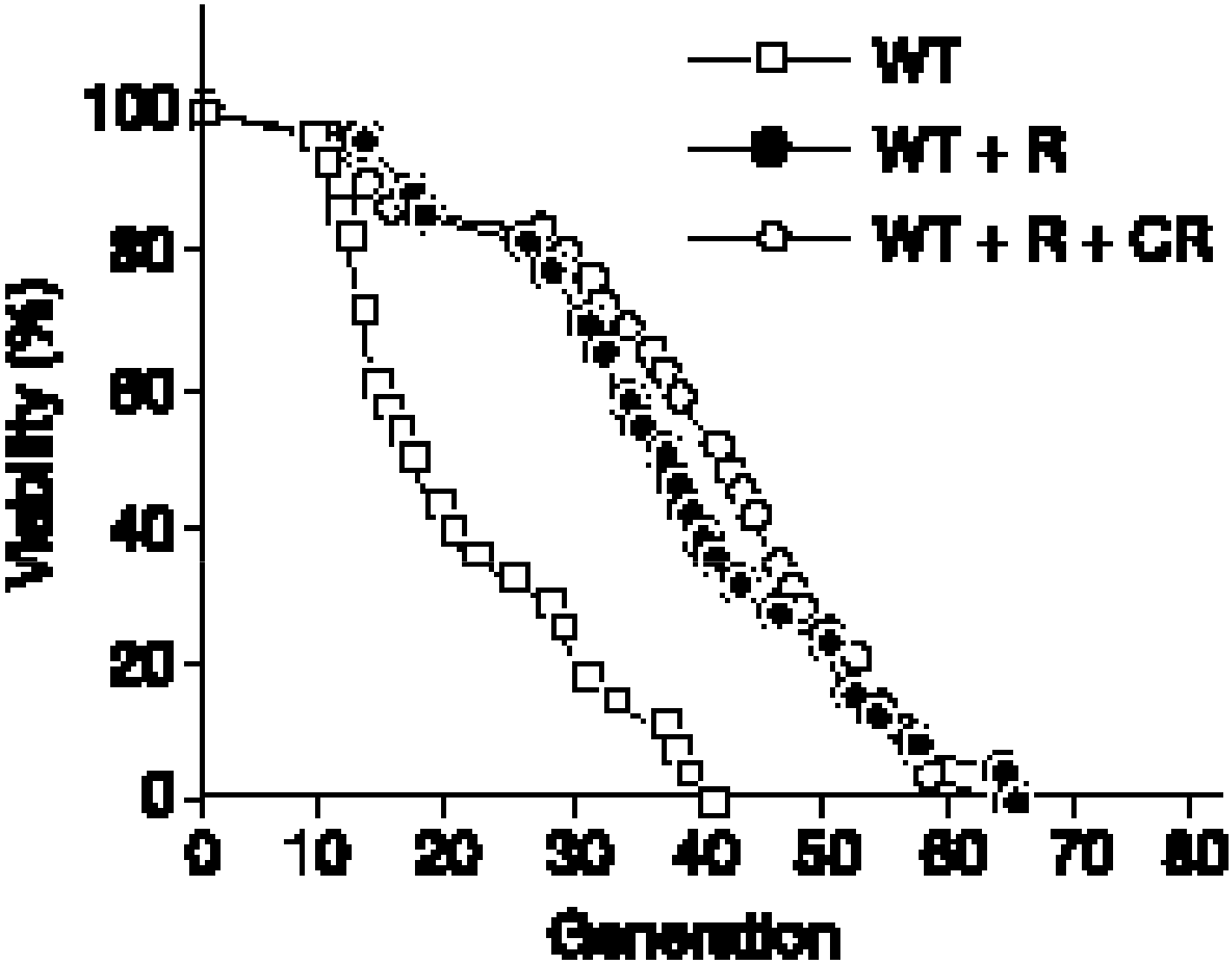
Nature Sept. 11, 2003. Page 191

出芽酵母菌的老化現象

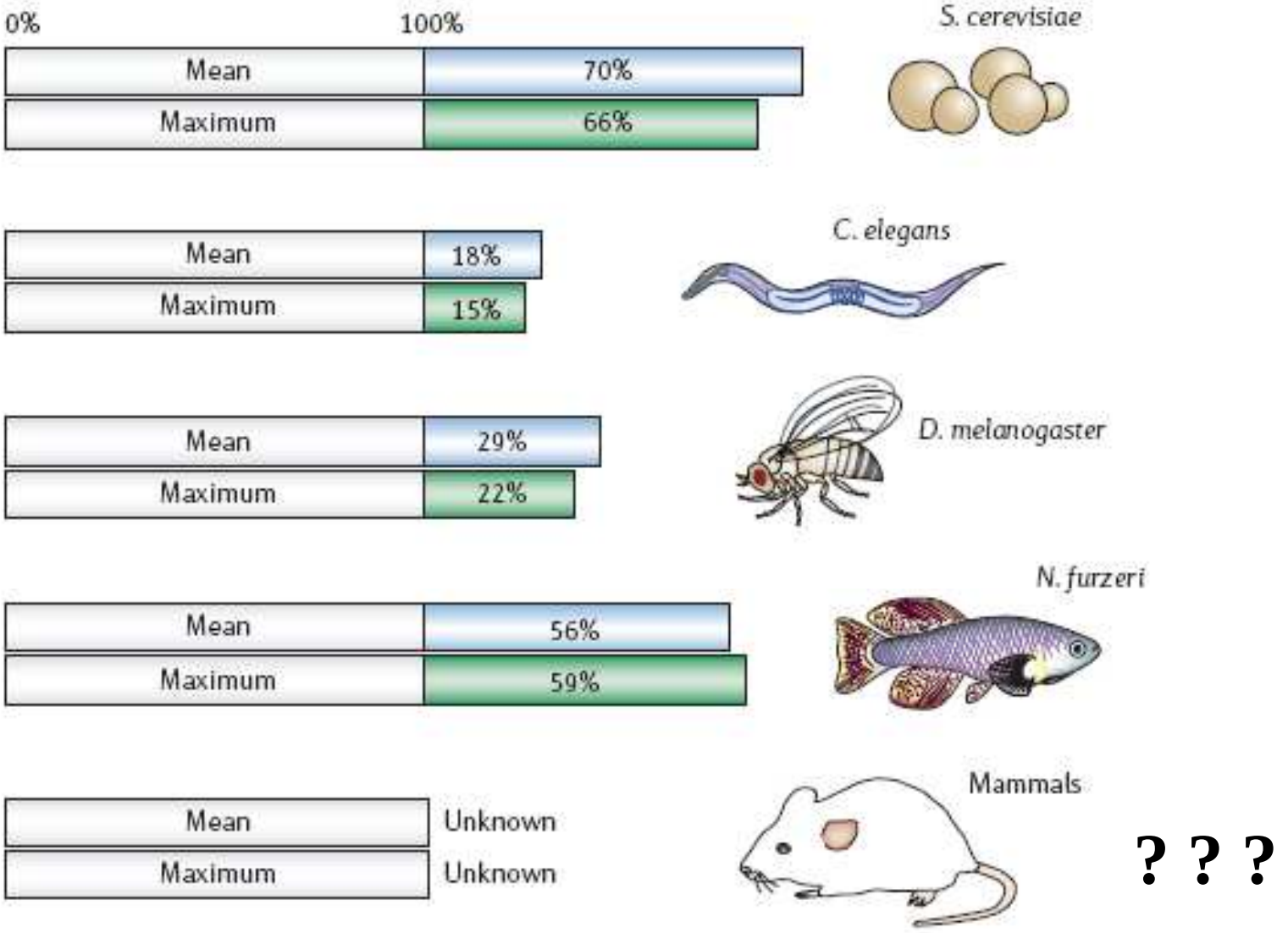

Budding
cell
Virgin
mother cell
Mother
cell
~20 Generations
Daughter
Senescent mother cell
G1–arrested
Enlarged
Sterile — loss of silencing

Stimulation of SIRTI catalytic rate by plant polyphenols

Compound (100 μM)	Ratio to control (mean ± s.e.)	Structure
Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene)	13.4 ± 1.0	
Butein (3,4,2′,4′-tetrahydroxychalcone)	8.53 ± 0.89	
Piceatannol (3,5,3′,4′-tetrahdroxy-*trans*-stilbene)	7.90 ± 0.50	



Average lifespan for wild type (WT) untreated, 19.0 generations;wild type plus resveratrol (WT+R), 37.8; glucose (calorie)-restricted plus resveratrol (WT+CR+R), 39.9.



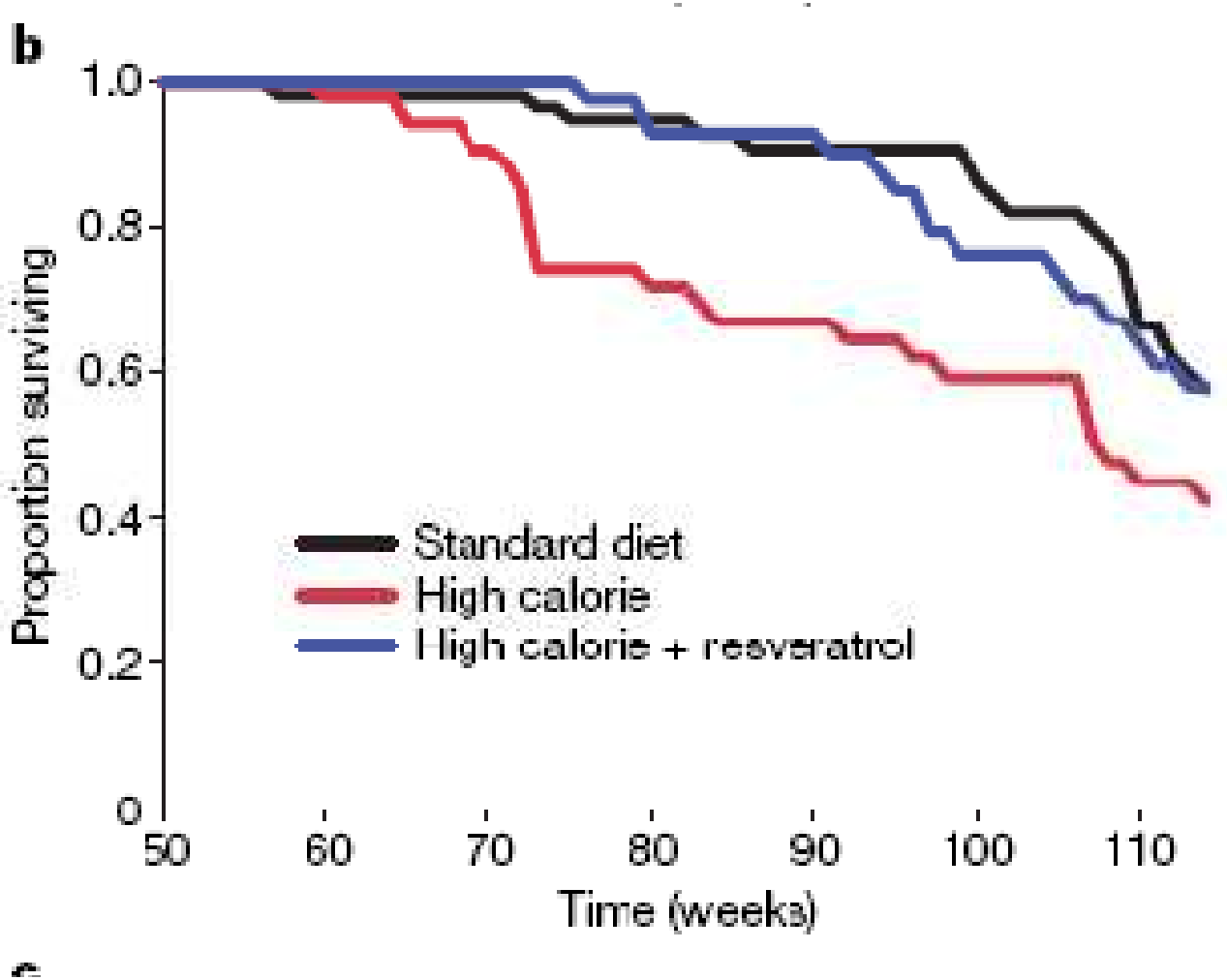
The increases in lifespan for various species treated with resveratrol
Nature Review of Drug Discovery June 2006

Grape expectations: *The Triumph of Bacchus*, painted by Cornelis de Vos (1584–1651).

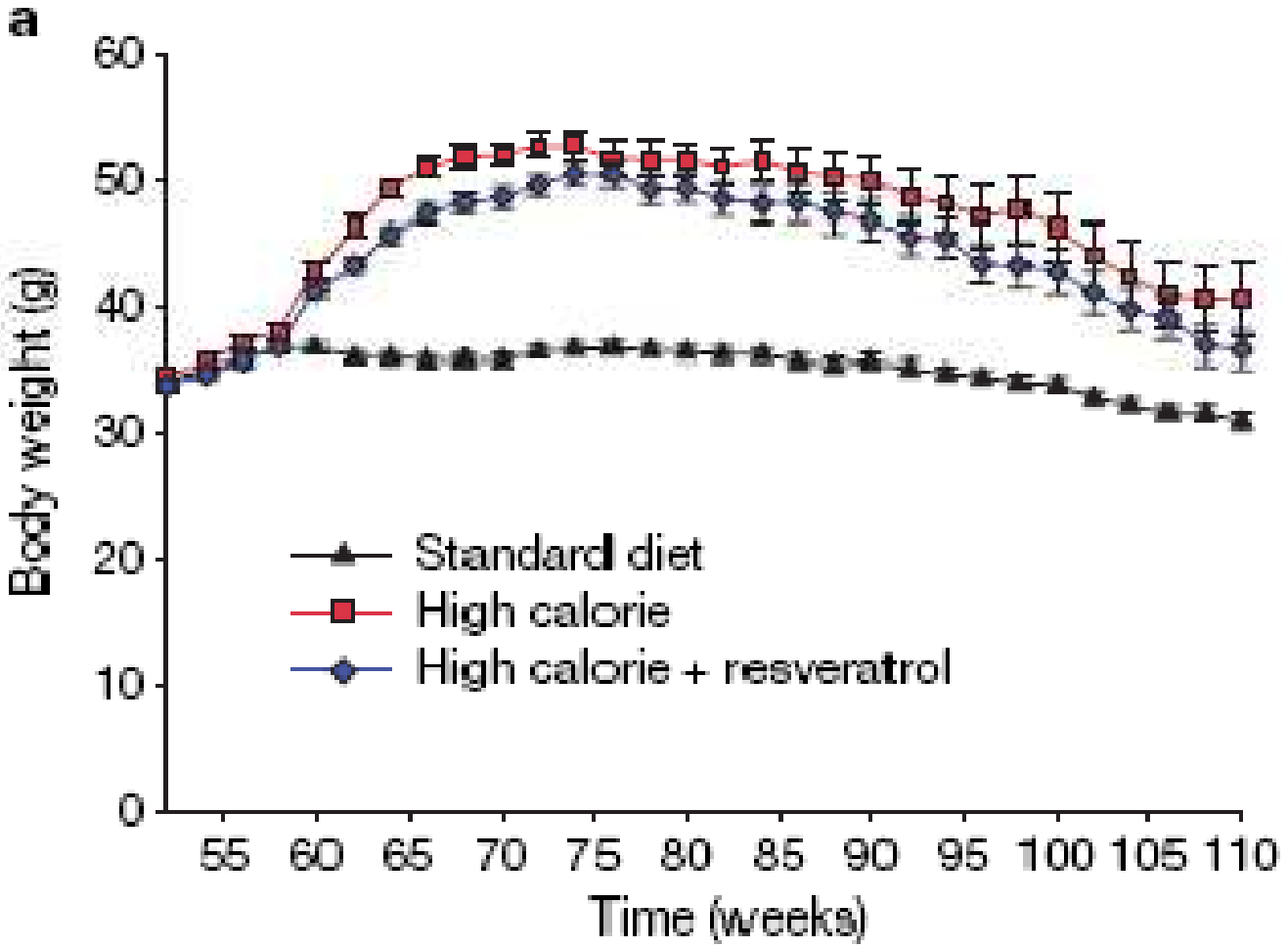
Baur, J. A. *et al.* Nature 444: 337 – 342, 2006

Resveratrol可以保護高熱量飲食引起的早衰死亡!

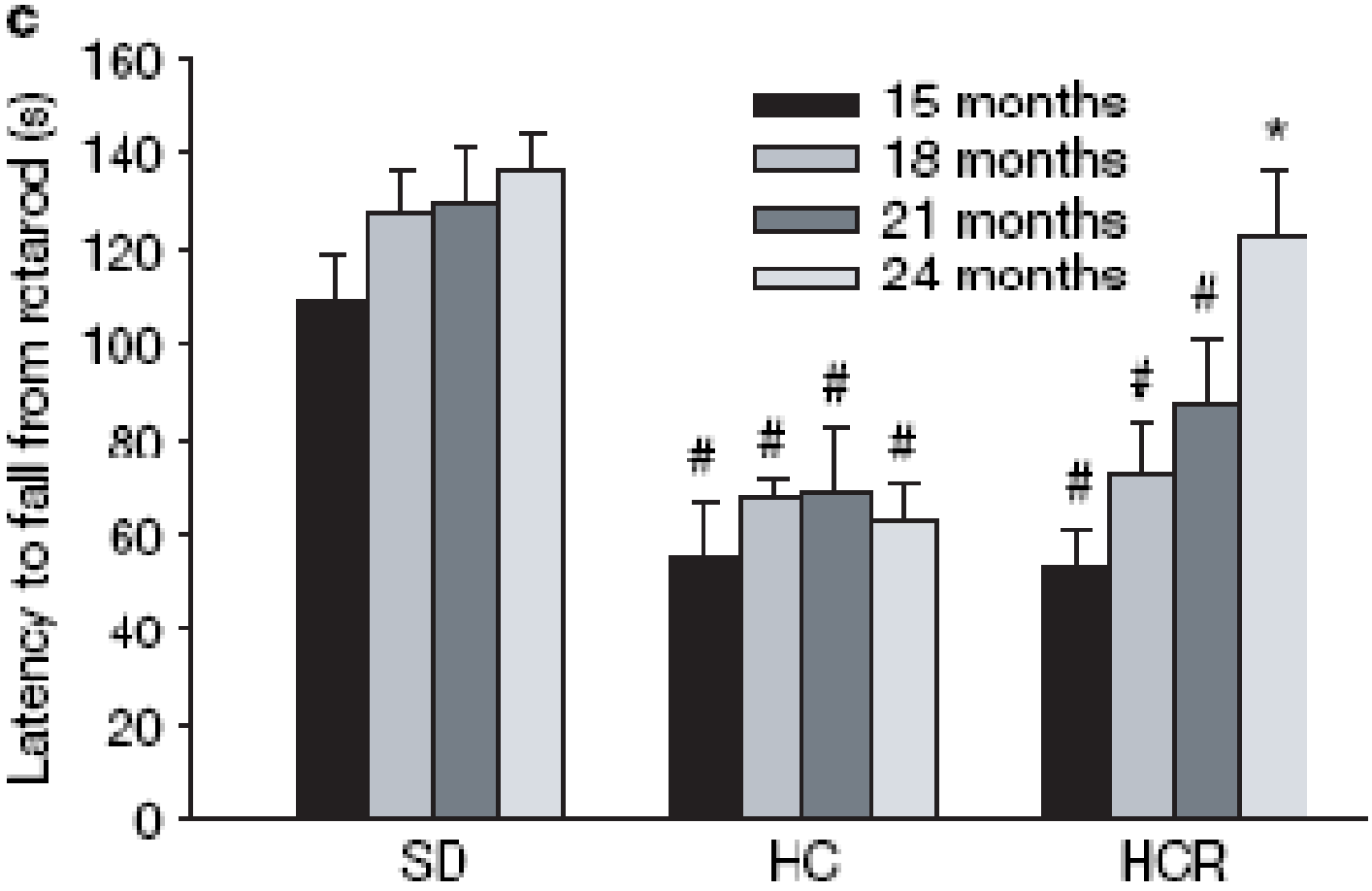
(New York Times Nov.7, 2006)



Resveratrol 不會讓胖子變瘦



Resveratrol 能讓胖子精力充沛



What is resveratrol?

- 1963年從中國草藥 *Polygonum cuspidatum* (*虎杖;紅川七;木川七*)中分離出的一個化合物.
- 具有一些抗氧化的能力
- 也可以活化一些細胞內酵素的活性

Fountain of youth juice.

法國人的祕密

除了吃同樣多高脂肪食物，法國人比
美國人得心臟病的機會少了40%！

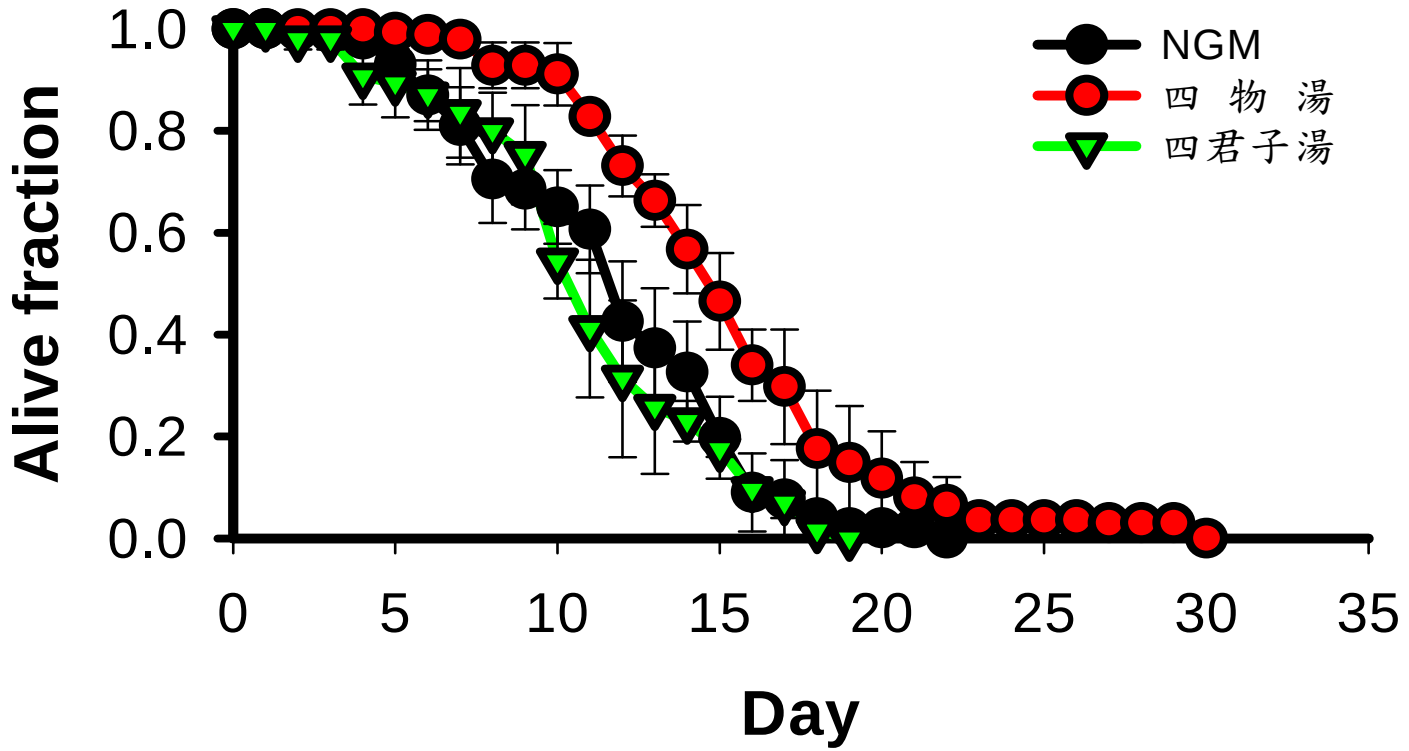
適度飲用紅葡萄酒？！

Source	*trans*-Resveratrol concentration
Dietary	
Red wines	0.1–14.3 mg l^{-1}
White wines	<0.1–2.1 mg l^{-1}
Ports and sherries	Generally <0.1 mg l^{-1}
Grapes*	0.16–3.54 µg g^{-1}
Dry grape skins	24.06 µg g^{-1} (average)
Red grape juices	0.50 mg l^{-1} (average)
White grape juices	0.05 mg l^{-1} (average)
Cranberry raw juice	~0.2 mg l^{-1}
Blueberries	Up to ~37 ng g^{-1}
Bilberries	Up to ~16 ng g^{-1}
Other *Vaccinium* berries	7–5,900 ng g^{-1} (dry sample)
Peanuts	0.02–1.92 µg g^{-1}
Roasted peanuts	0.055 µg g^{-1}
Boiled peanuts	5.1 µg g^{-1}
Peanut butters	0.3–0.4 µg g^{-1} (average)
100% Natural peanut butters	0.65 µg g^{-1} (average)
Pistachios	0.09–1.67 µg g^{-1}
Groundnuts (*Arachis hypogaea*)	ND
Rhubarb	ND
Hops	0.5–1 µg g^{-1}
Itadori (*Polygonum cuspidatum*) tea	0.68 mg l^{-1}
Herbal	
Veratrum (Lily)	ND
Cassia quinquangulata	ND
Gnetum klossii	ND
Polygonum cuspidatum	0.524 mg g^{-1}
Rhubarb (*Rheum rhaponticum*) dry root	3.9 mg g^{-1}

" Rhubard ": 大黃 or 香港稱為芋莢

我們能找出中國人祕密嗎？

四物湯(而非四君子湯)能使線蟲在高溫(25℃)下的壽命延長



老化研究真正的挑戰

- 老鼠或線蟲都不等於人；
- 人類老化伴隨而來最主要的問題是心臟和大腦，而非身體其他器官；
- Aging death is a stochastic nature

The stochastic (random) nature of ageing….

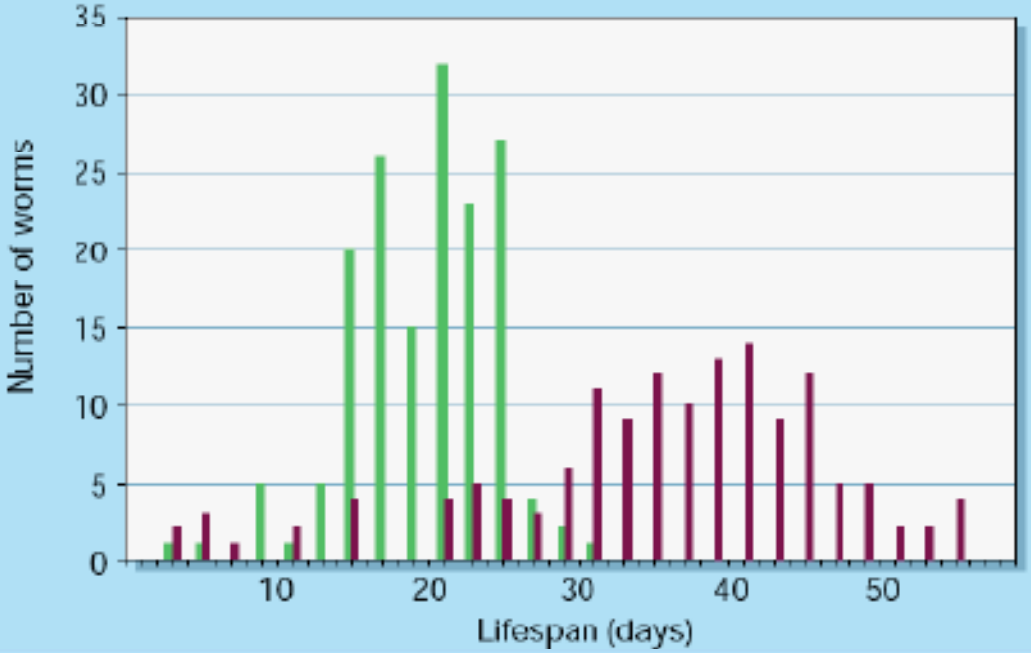


Figure 1 Lifespan distributions for individual *Caenorhabditis elegans* nematodes in isogenic populations of wild-type (green) and long-lived *age-1* (purple) strains. Although the distributions have different mean values, the spread of both (compared to the mean value) is similarly broad. The range of lifespans in nematodes is indicative of the randomness of the ageing process, which Herndon *et al.*[4] have now investigated at the cellular level (data provided by T. E. Johnson[1]).

想青春永駐？

有好的基因加上少一點壓力！

（心靈與氧化）

在這個基因的時代中，我們該如何面對老化社會的挑戰?

了解與智慧

謝謝大家!