The Biology of Age-Related Disease: Interaction of Aging, Infections & Chronic Inflammatory States

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Who Wants to Live Forever?

- "Old Age may have wisdom, but it will always envy youth for its potential." *Gretchen Vogel, Science v286, 2238,'99*

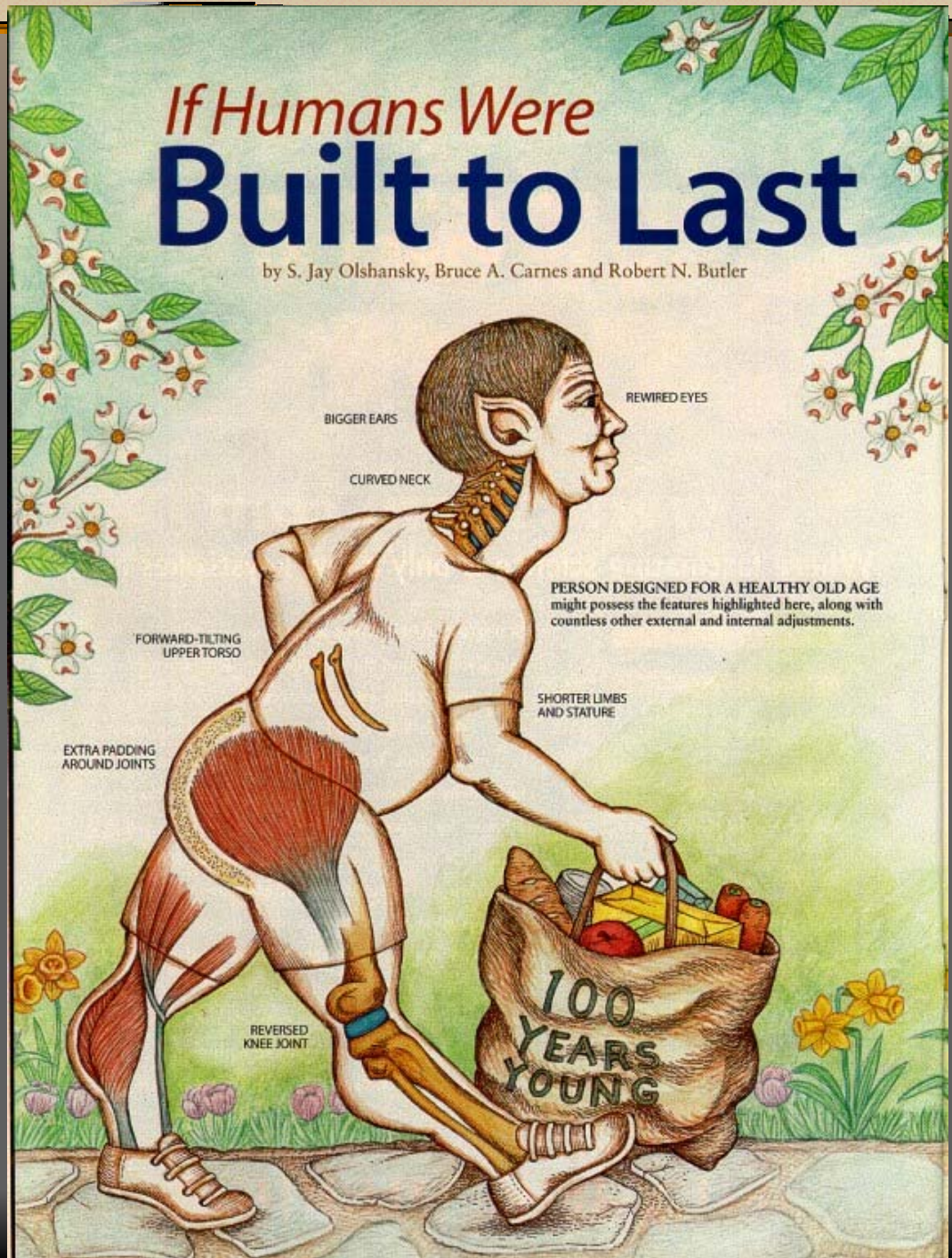
- "New research gives a glimpse into a world in which aging-and even death-may no longer be inevitable." *John Harris, Science v288, 59,'00*

Theories of Aging

- Programmed Theories v. Accumulation of Errors
  - Interaction of genetic make-up and exposure to elements that result in gene expression/activation
  - Average Life Expectancy/ “Successful Aging”- 70% explained by environmental exposure vs. 30% genetic make up (Mac Arthur Studies)
  - Centenarian Studies- Genetic influence markedly more important in survival to extreme old age (New Eng C.S.)
- Antagonistic Pleiotropy-What shaped Genetic Map?
  - Genetic package evolved to deal with stress *and when*
  - Evolutionary pressure: reproduction linked to senescence
  - Don’t fool with mother nature…
    - Steroid/Hormone Replacement, regulation of immunity
    - Downstream consequences

Theories of Aging

- Programmed (Genetic) Theories- replicating tissue
  - Progressive loss of integrity/reserve capacity- 'homeostenosis', results in an impaired stress response
    - Autoimmune- chronic inflammation
    - Neuroendocrine- loss of response, late expression of death hormone
  - Evidence for Genetic theory: Werner's syndrome (progeria)- mutation of helicase- impaired gene activation to stress
  - DNA microarray- 1% of genes incr, 1% decr expression
- Accumulation of Errors- **brain and muscle**
  - Cross-linking- stiffness of tissue, DNA
  - Wear and Tear- infections, stress
  - Rate of living- limited supply of energy (genetic+ environment)- damage to mitochondria
  - Oxidative stress- most 'Marketed' theory



Olshansky SJ
Scient Am
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Sardina's Mysterious Male Methuselahs
R Koenig
Science 291, 01 2075-6

Interaction of Genes & Exposure
Yin & Yang

- Tissue response to injury/stimulation/stress-developmental change vs. pathology
- Cellular proliferation v. apoptosis v. necrosis/inflam or repair capacity in non-replicative tissue
  - Alteration in transcription factors- oxidative stress
- Development of Disease-response to stress
  - Aging-dependent disease- accumulate as we age
    - Cell Accumulation- CV disease, cancer (some)
    - Cell loss- Alzheimer's, Parkinson, stroke, diabetes, osteoporosis
    - Delay in progression is key
  - Age-dependent- occur at a proscribed age
    - Werner's, MS, ALS, cancer (many)
    - Delay of onset is crucial

Response of a cell to stimulation- Genes + environment

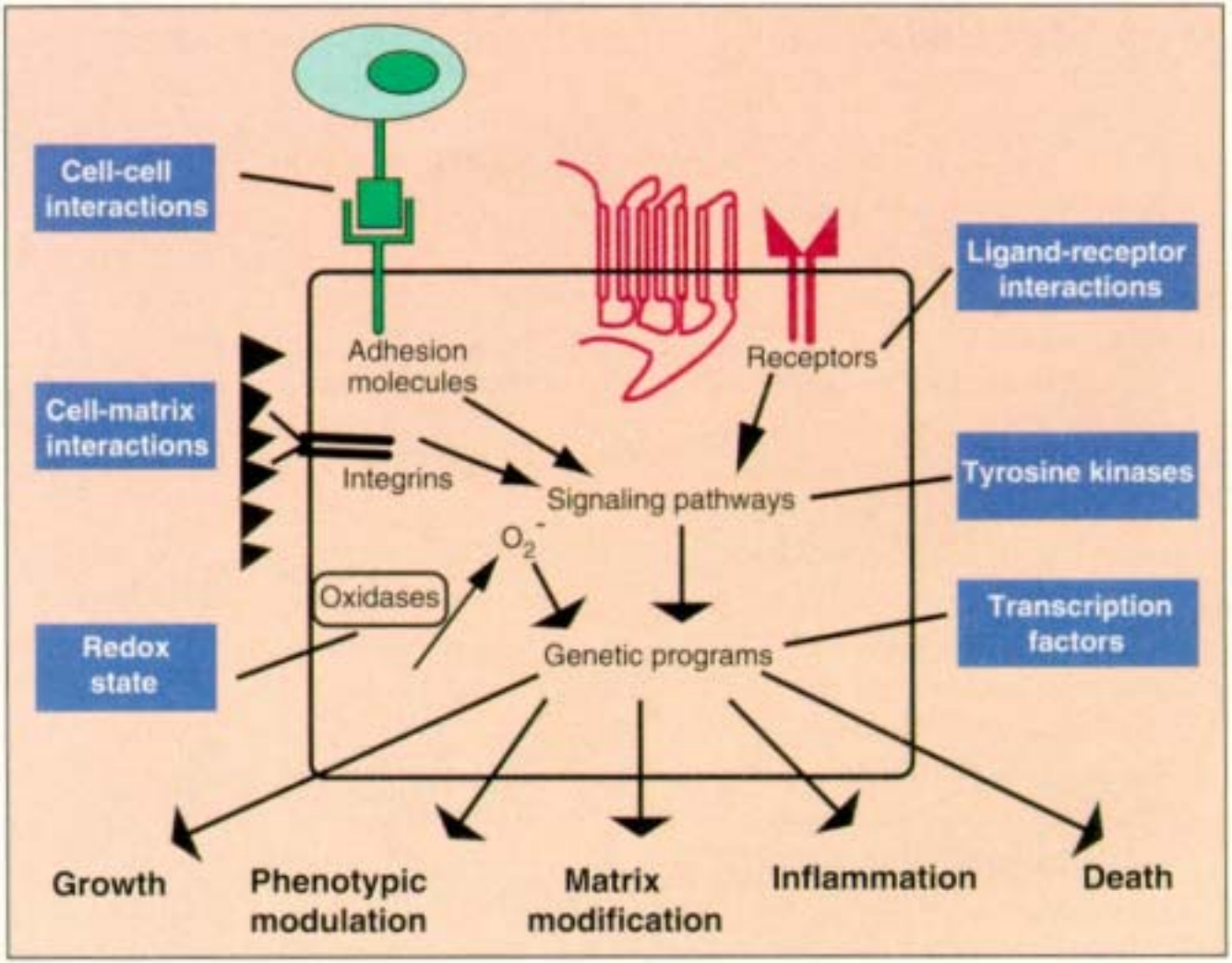
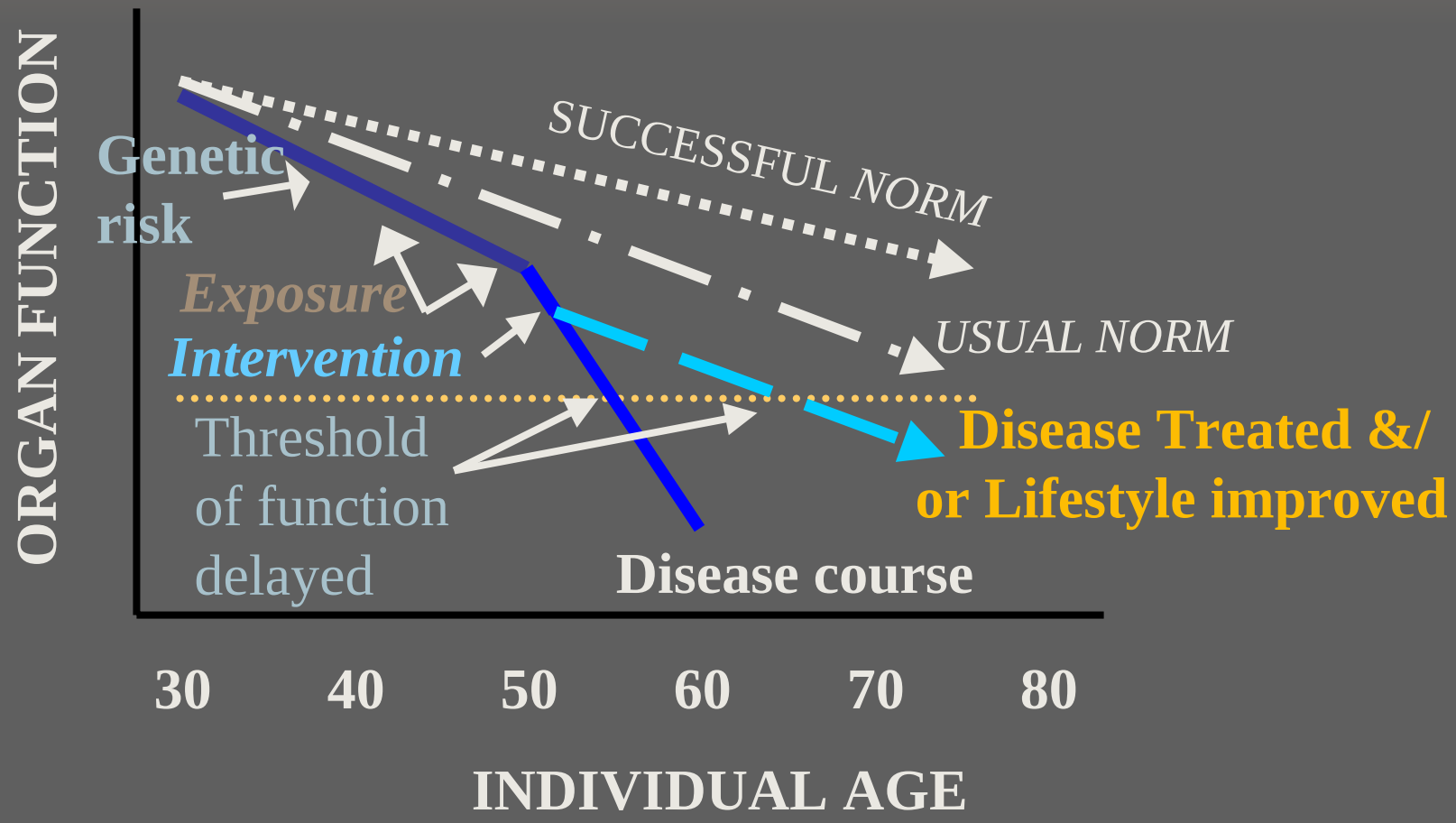


Fig. 1. Schematic model of a "generic" vascular cell, showing the potential targets for molecular therapeutics in vascular disease.

SUCCESSFUL AGING

CHANGING THE "GLIDEPATH" OF A DISEASED ORGAN



Castle interpretation of Rowe, Kane

LONGEVITY UPDATE

Anti-Aging Breakthroughs!

Jetsetters, Celebrities Taking Anti-Aging Formula

Life Expectancy Upped 30% With Special Supplements

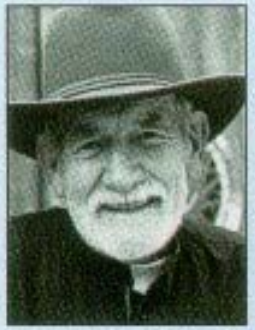
Depression, Sexual Problems Linked To Nutrient Defiency

Age Spots First Sign Of Senility

Scientists Pinpoint How To Spot Them

9 Nutrients For Super Brain Uncovered

Changing His Name To GH3



"I'm thinking of changing my middle name to 'Gero Vita' because GH3 has made a new man of me. I'm 81 and have a tremendous zest for life. I can accomplish so much now. Everyone is very fortunate that you've made GH3 available."
—Mr. C. Molle, California.

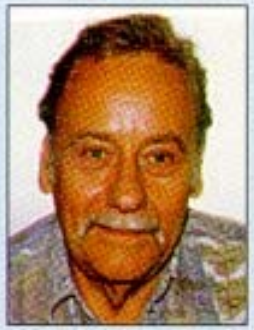
Could Hardly Walk Before

"I was so crippled with arthritis I could hardly walk or get out of a chair. After taking GH3 only two weeks, I felt 100% better. Now, I can do my housework, drive a car again and even climb stairs. I'm 86. Thanks for a wonderful product."
—Mrs. A. Jansai, Utah.

No Illness Since GH3

"I'm 81. I've been taking GH3 for years and haven't had any health problems since I was introduced to it. At my age, that is quite amazing, but, of course, I try to live healthily, too. Thank you for such a great medicine."
—Mr. A. Proffitt, North Carolina.

Exploding With Energy



"GH3 is absolutely phenomenal! I take three tablets in the morning on an empty stomach, and my energy just explodes. I feel great and really healthy. There is no question in my mind that this is the best anti-aging remedy ever created."
—Mr. R. Bellas, Florida.

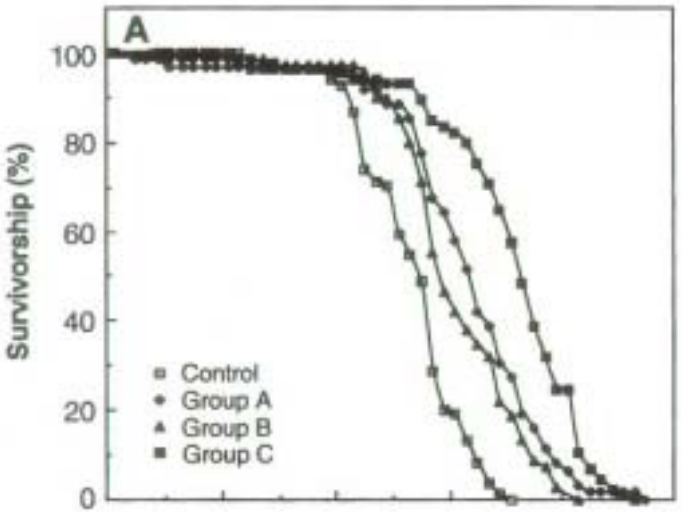
Was 88, Now 68

"I'm 88, and I have been taking GH3 for three years. I want everyone to know about this product because it has done so much for me. People say I've really changed and look 20 years younger. I would not be without it."
—Ms. R. Schwartz, Michigan.

Loaded With Stamina

"GH3 has given me a lot of energy and stamina. I've been able to increase the amount of exercise I do, and I don't tire very easily. At night, I sleep much better. It has helped me in many ways—a valuable product." —Mr. J. S. Camar, New York.

Overexpression of SOD & Catalase in *Drosophila*



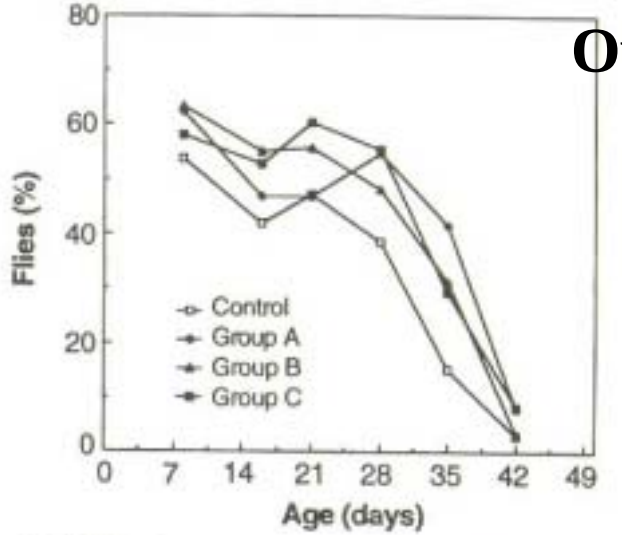


Fig. 3. Walking movement of flies at different ages. Negative geotaxis is a behavioral characteristic of flies to walk against gravity. Groups

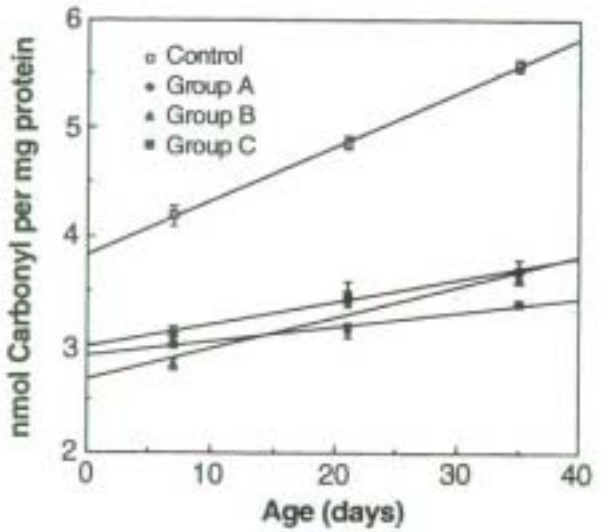


Fig. 2. Protein carbonyl content of flies at different ages. Protein carbonyls were measured

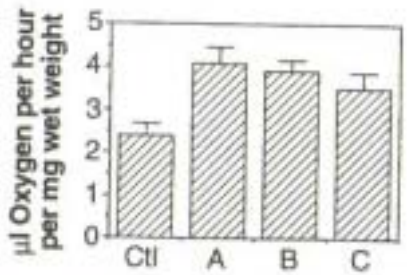


Fig. 4. Rate of oxygen consumption of flies at 40 days of age. Oxygen consumption was

WC Orr
Science
‘94:263;
1128-30

Worm Genes Imply a Master Clock

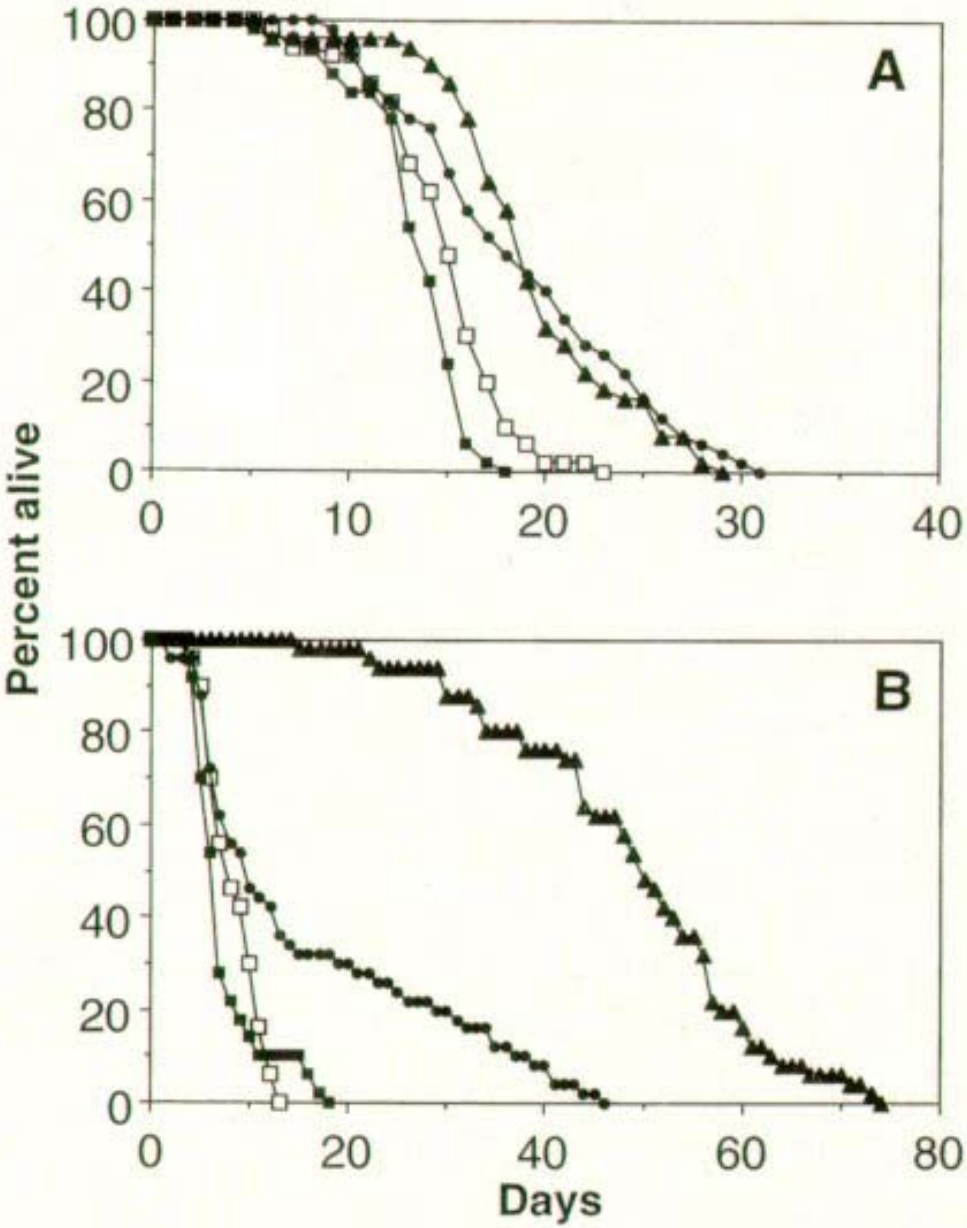
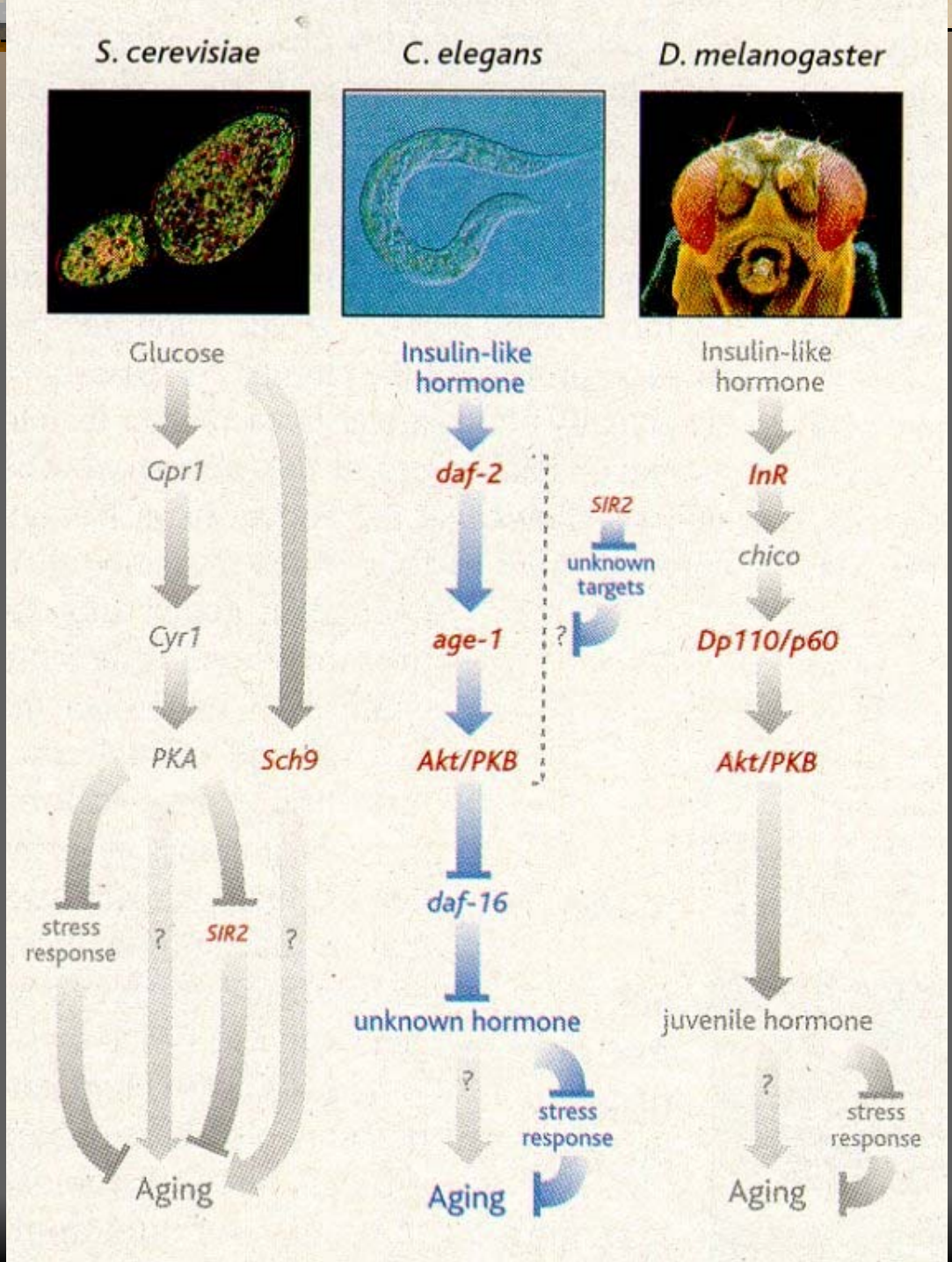


Fig. 2. Interaction of *clk-1* with *daf-2* and *daf-16*.

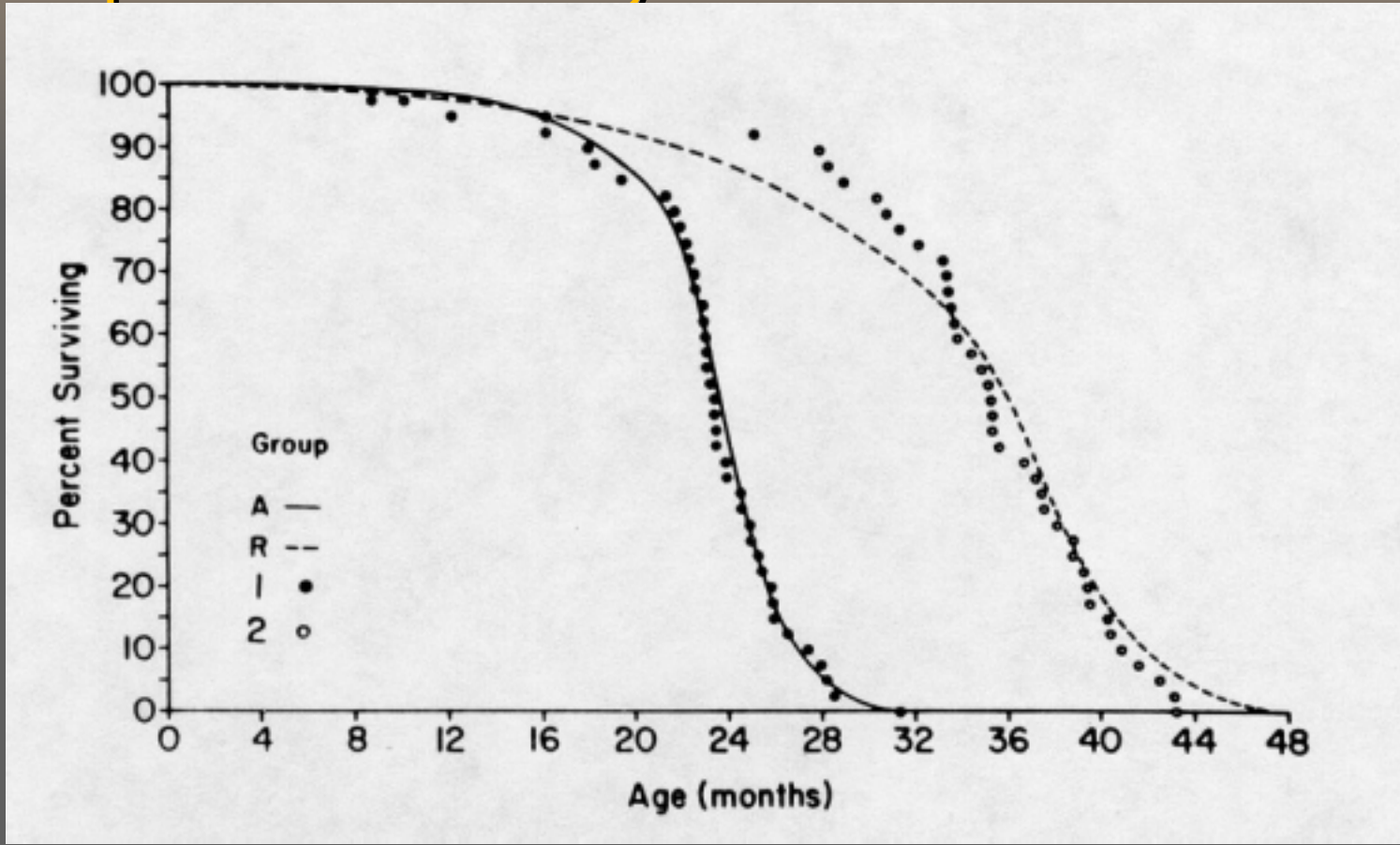
B Lakowski Science ‘96:272; 1010-3; comment p949-50



Similar Control of Aging across species

E. Straus
Science ‘01:292;42-3

Life span extension by Caloric Restriction



CK Lee, Science v285,1390;'99- Microarray

Improved biosynthesis, more efficient metab

Less macromolecule damage, less stress response

Replicative capacity of cells

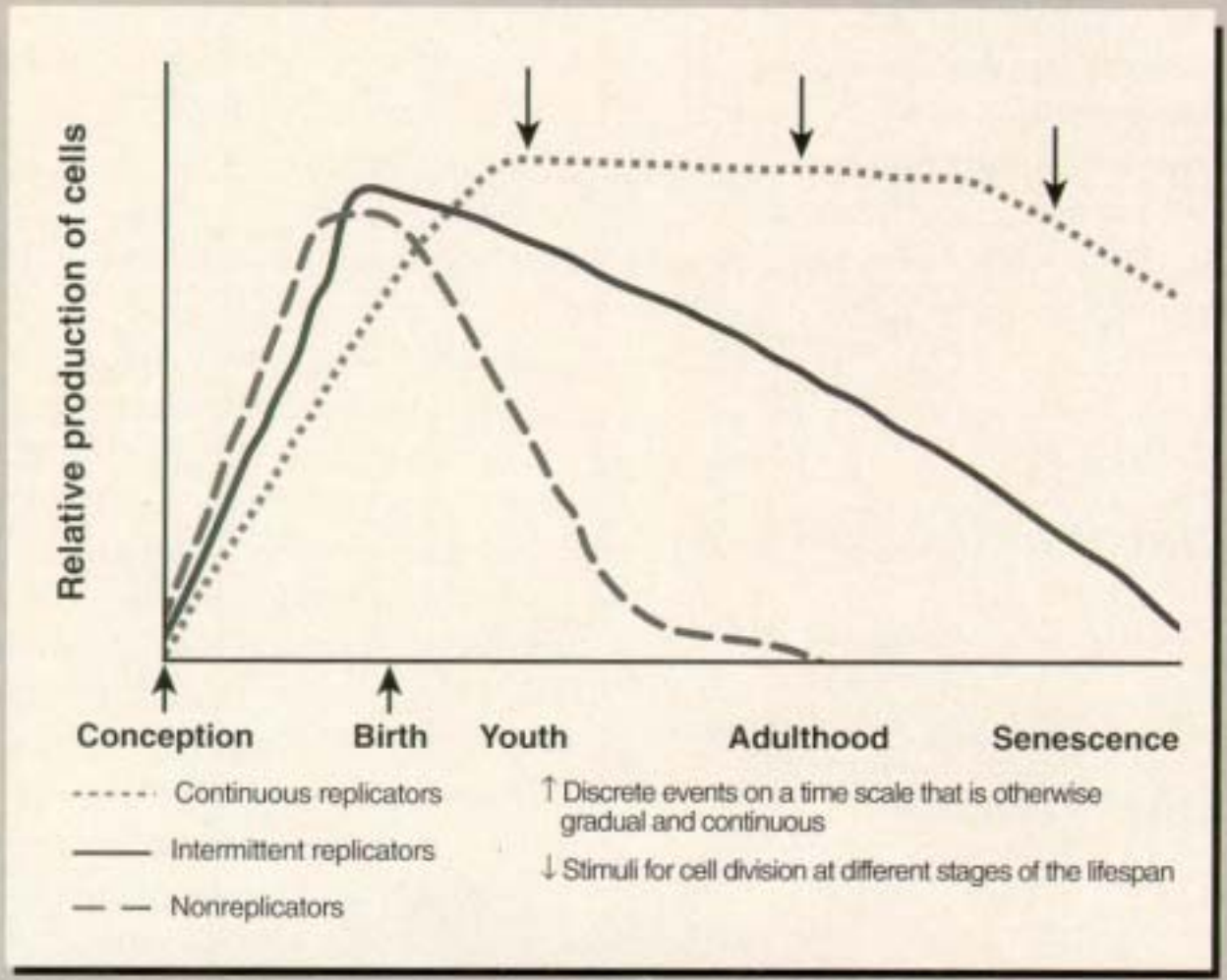


Figure 1. Replicative capacity of cells during various stages of the lifespan. Cells are classified according to their replicative ability during adulthood.

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S Goldstein
Geriatrics
‘93:48;76-82

Correlation of age and replicative lifespan of fibroblasts

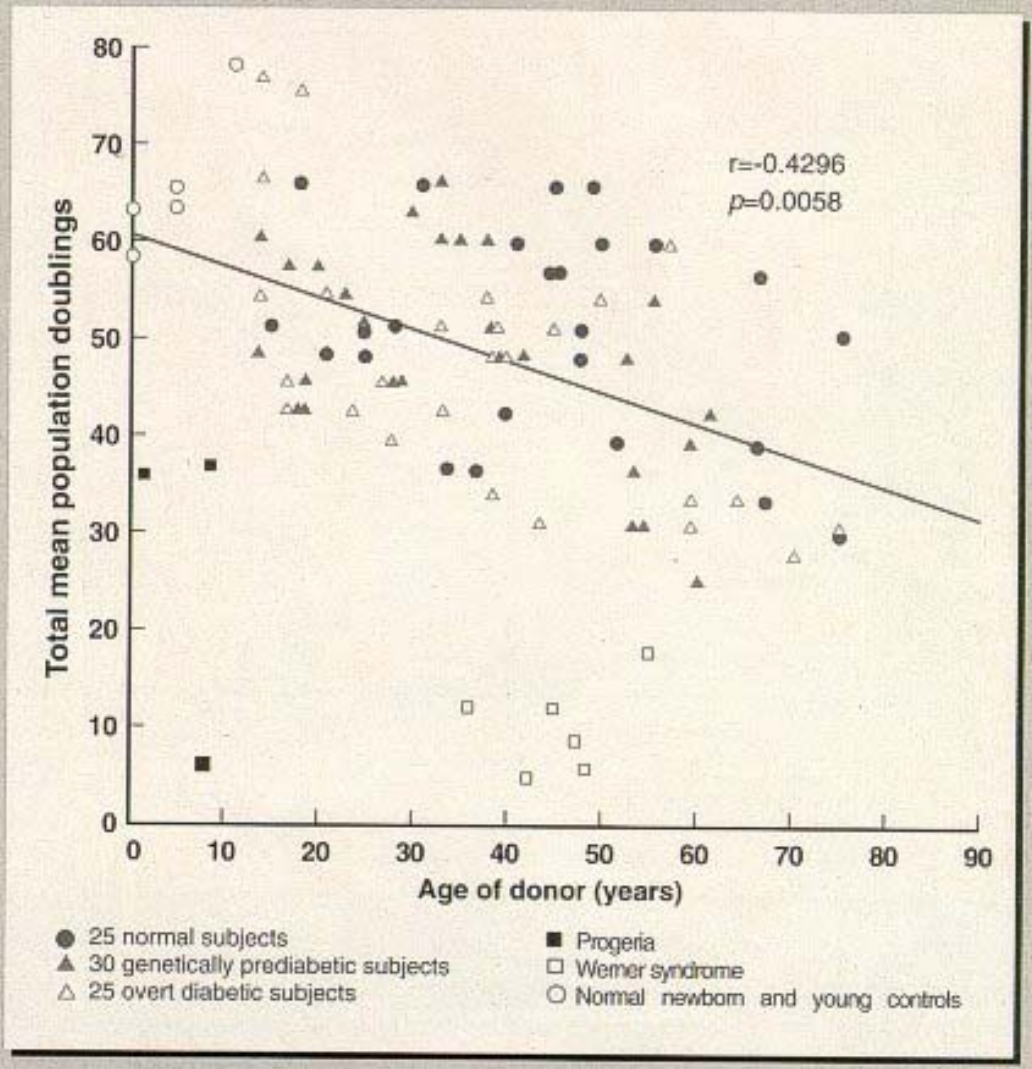

Figure 2. The total number of mean population doublings—the average number of times a fibroblast population can divide—is negatively related to the chronological age of the tissue donor. (Note that first three symbols in key represent a comparative study involving three groups of subjects.)

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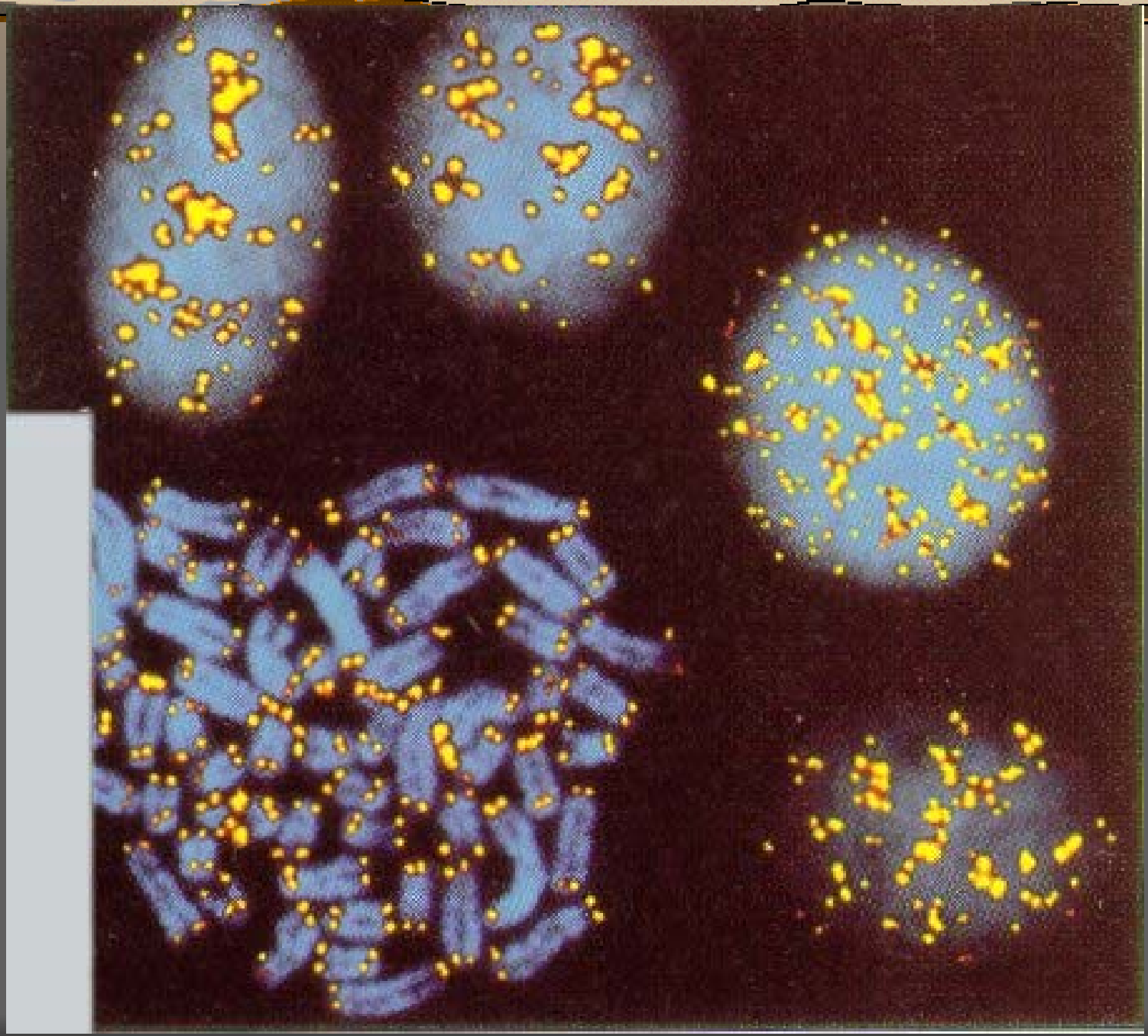
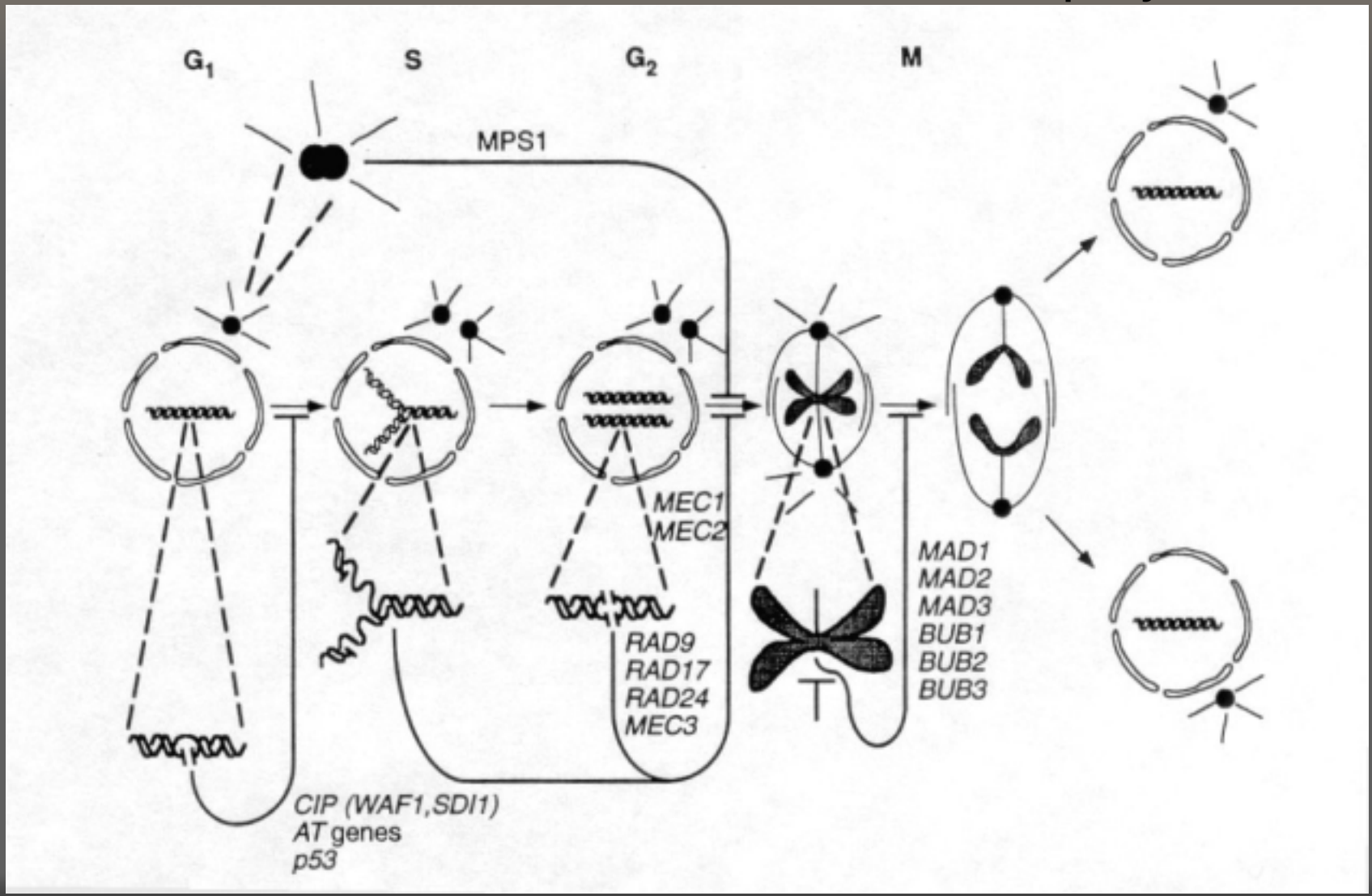
The Hayflick Phenomenon

S Goldstein Geriatrics '93:48;76-82



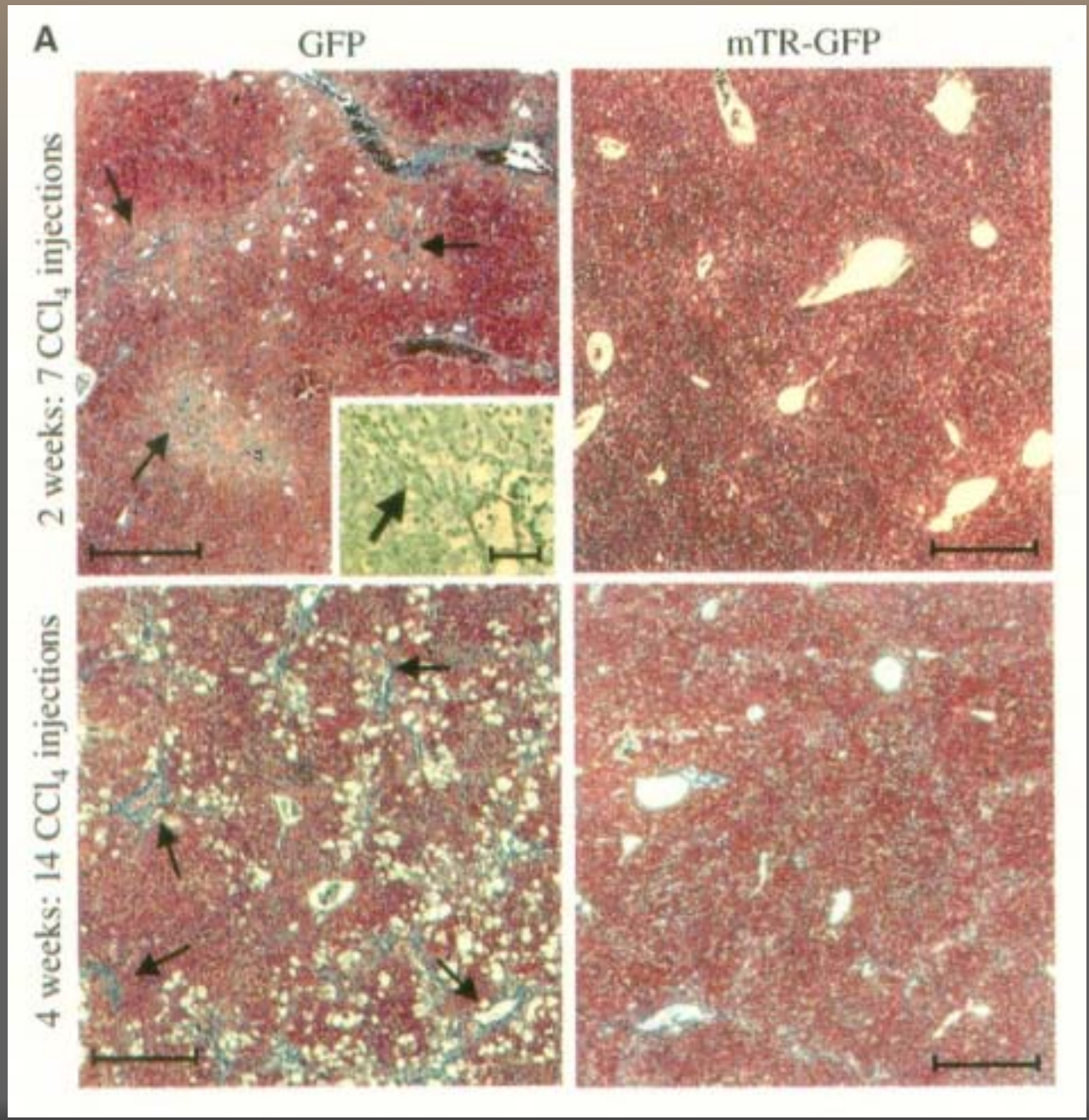
Telomere:
end of chromosome- attachment of DNA polymerase



Inhibition of Cirrhosis in Mice via Telomerase Gene Delivery

KL Rudolph, Science v287,1253;'00

- Accelerated telomere loss may contribute to chronic disease
- Hepatocyte proliferative arrest found in Cirrhosis, related to telomere attrition?
- Telomerase-deficient mice (mTR-/-)
  - early cirrhosis in response to injury
- Adenovirus delivery of Telomerase mRNA in to mTR-/- (short telomeres)
  - alleviated cirrhotic pathology & improved liver function

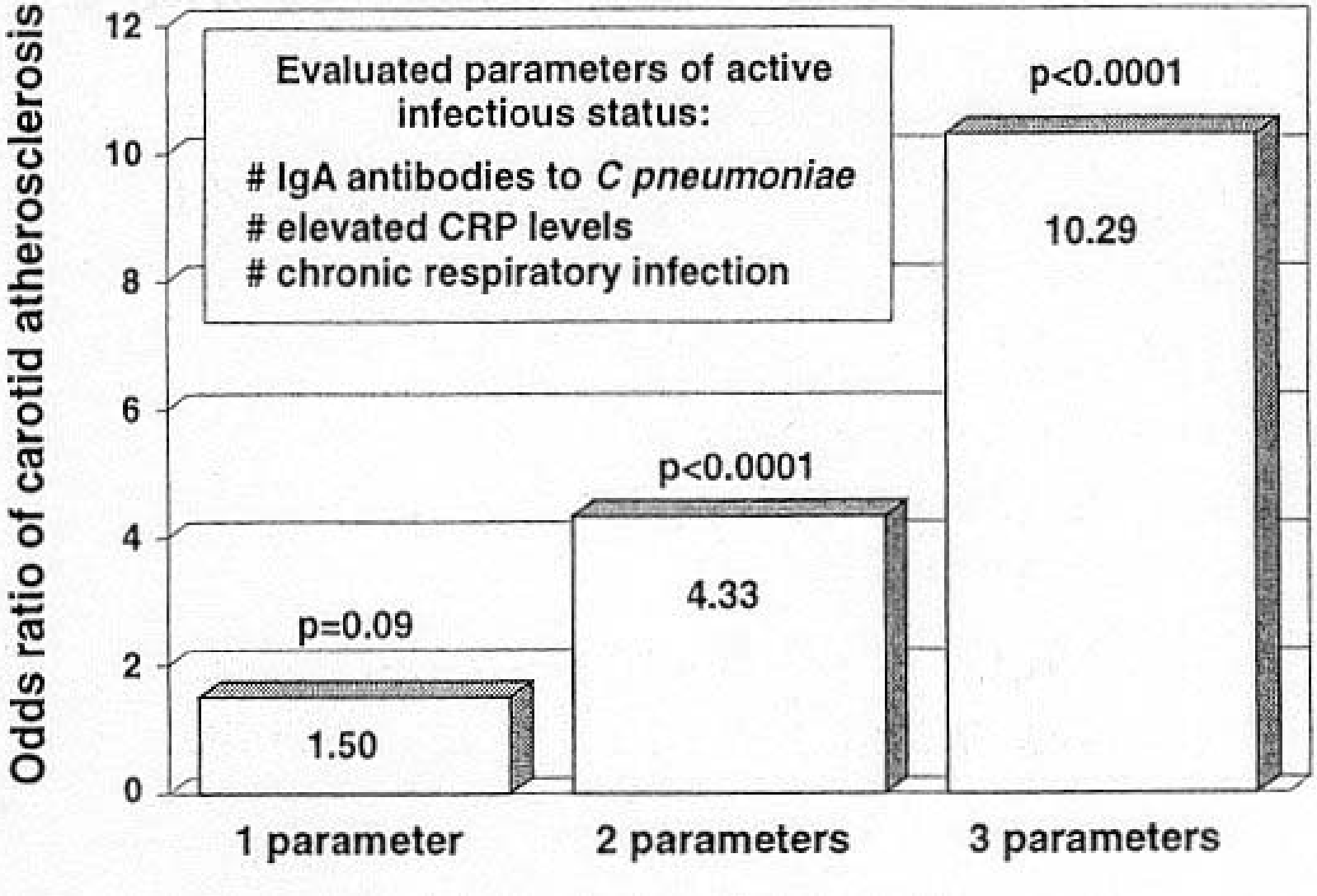


Inhibition of Cirrhosis in mice by telomerase gene delivery

KL Rudolph. Science ‘00:287;1253-8

Role of Chronic Inflammation in Age-Related Disease

- Atheroslerosis- *Chlamydia, CMV, H. pylori*
  - Disease occurs in individuals with no risk factors
  - Only 50% of disease prevented when risk factors treated
  - Markers of immune activation predict disease
- Alzheimer's Disease
  - Inflammatory proteins assoc with plaques/local glial cells
  - Polymorphisms of acute-phase proteins & cytokines incr risk or predispose to earlier onset of AD
  - Epidemiological studies of NSAID use- slow disease
- Timing of immunomodulation is KEY-
  - prevention v. treatment



M Mayr, Circulation 102 833-9, '00

TABLE 4. Association of Seropositivity to *C pneumoniae*, *H pylori*, and CMV With Immune Reactions to mHSP65

	Mean Anti-mHSP65 Antibody Titer±SEM	*P*
IgA to *C pneumoniae*		
<16 (n=245)	240±13	...
≥16 (n=581)	294±12	0.003
IgG to *H pylori*		
Negative (n=118)	213±21	...
≥8 U/mL (n=708)	289±10	0.002
IgG to CMV		
Negative (n=226)	269±15	...
≥5 U/mL (n=600)	281±12	0.533

P values were derived from a paired Student's *t* test.

M Mayr, Circulation 102 833-9, '00

Interaction of Chronic Disease/Infection & Host Defense/Progression of Disease

- Chronic infections may contribute to chronic diseases- promote autoimmunity
- Chronic diseases increase susceptibility to acute infections, & impair eradication of chronic infections
- Infections may result in progression of disease, or accelerate decline in reserve capacity associated with aging.

Prevention of Disease, Maintenance of Healthy Aging

- Downregulation of unregulated/ inappropriate inflammation in disease states
- Boosting of immunity against pathogens/ cancer
- Early detection/intervention of dysregulation
  - Exercise and Diet
  - Disease management
  - Targeted interventions- population/timing, local/systemic
    - Cytokine balance- type 1 vs. type 2
    - Vitamin E
    - Cox 2 inhibitors