Bedside-to-Bench Conference
September 9-11, 2009
"Inflammation and Nutrient Metabolism"

Cardiovascular Markers and HIV

"Yep, son, we have met the enemy and he is us!"
Pogo to Porky (as written by Walt Kelly), 1971

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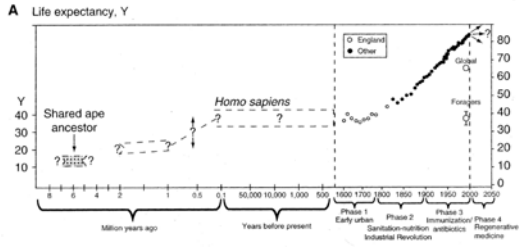
CVD, Inflammation, and Aging

General issues concerning age-related decline in function

How long should we live?
Forces that have shaped our genetic architecture



Finch C. *The Biology of Human Longevity*. Academic Press. 2007

Atherosclerosis as a Model for Age-Related Functional Decline: Key aspects

Lipid Translocation to media — Driven at least in part by Mass Action; mechanism(s) uncertain

↓

Lipid retention — Driven at least in part by GAGs;

↓

Lipid modification — Driven at least in part by oxidative stress;

↓

Activation of innate immunity — Macs, CRP, etc

↓

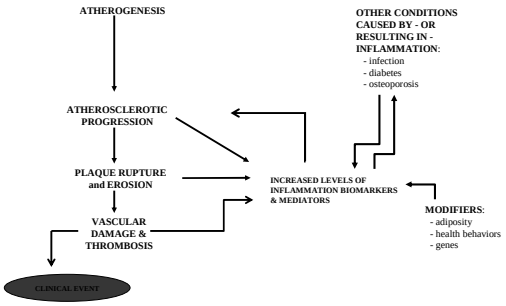
System in balance?

Yes: no atherosclerosis
No: progression to activation of adaptive immunity and atherosclerosis

→ Very rapid: explosive development of atheroma → vulnerable plaque & MI

→ More slowly: chronic development of "sclerosis" → heart failure

The interplay of atherothrombosis and plasma risk markers



Modified from: Tracy R. *Thrombos. Haemostas.* 1999;82:826-831

Association of Markers of Inflammation With Chronic Disease

The "Inflammation Hypothesis" of Chronic Disease and Aging

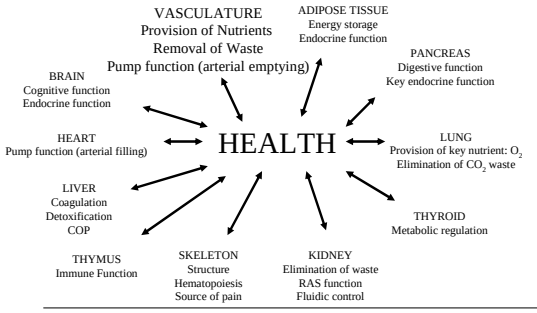
1. In providing a necessary "interface" to the environment, "inflammation" can result in damage.

2. The better our responses and/or the more environmental stress to which we respond, the more damage we do.

3. We trade short-term benefit for long-term damage; a good trade from an evolutionary standpoint

Humans as integrated organisms: a decline in one system affects all
Is vascular decline of particular importance?

"Longevity is a vascular question, which has been well expressed in the axiom 'a man is as old as his arteries.' To a majority of men, death comes primarily or secondarily through this portal." William Osler, 1892.

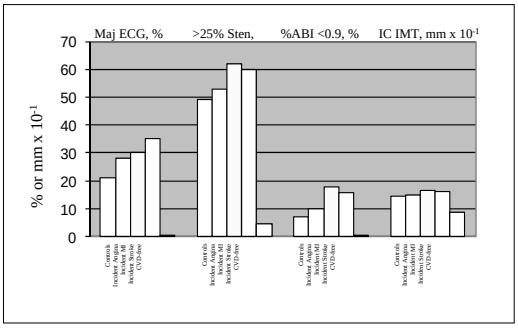


Increased Inflammation in the Elderly:

Are Diseases of Older Age the Cause?

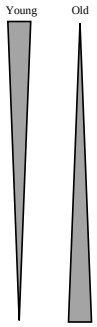
Is Vascular Disease Particularly Important?

There's a lot of vascular disease in the elderly

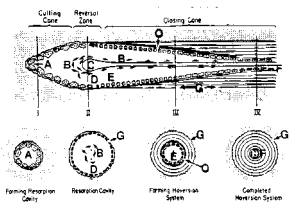


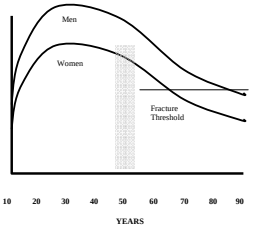
Four Levels of "Inflammation" Affecting Circulating Biomarkers and Mediators

1. Remodeling Associated With Growth / Aging: Initially improved organ function, but in older age decreased organ function; cause?
2. Physiology-Enabled: adiposity, insulin resistance
3. Wound Repair: decreased organ function (e.g., scar tissue)
4. Response to Chronic Pathogenic Stimulation:
   - viral infections, e.g., HIV-based lymphatic fibrosis
   - lipid infiltration, e.g., atherosclerosis
   - toxin exposure, e.g., alcoholic cirrhosis, cigarette smoke
5. Response to the Presence of Disease:
   - Atherosclerotically damaged blood vessels → inc coagulation



Bone Remodeling: a Model for a Lifetime of Change?





- In bone remodeling, we resorb and replace ~10% of our skeleton/year;
- Other tissues are slower (brain) or faster (intestinal epithelium);
- Overall rates in all tissues: ??
- This is inflammation too…..

The origins of age-related proinflammatory state

Luigi Ferrucci, Annamaria Corsi, Fulvio Lauretani, Stefania Bandinelli, Benedetta Bartali, Dennis D. Taub, Jack M. Guralnik, and Dan L. Longo

We hypothesized that the rising levels of inflammatory markers with aging is explained by cardiovascular risk factors and morbidity becoming progressively more prevalent in older persons. Information on inflammatory markers, cardiovascular risk factors, and diseases was collected in 595 men and 748 women sampled from the general population (age, 20-102 years). In both men and women, older age was associated with higher levels of interleukin-6 (IL-6), IL-1 receptor antagonist (IL-1ra), IL-18, C-reactive protein (CRP), and fibrinogen, while soluble IL-6 receptor (sIL-6r) increased significantly with age only in men. Adjusting for cardiovascular risk factors and morbidity, the age regression coefficients became substantially smaller in models predicting IL-6, IL-1ra, IL-18, and fibrinogen and larger in the model predicting sIL6r. Adjustment for cardiovascular morbidity substantially reduced the effect of age on CRP in men but not in women. Findings were confirmed in a subgroup of 51 men and 45 women with low risk profile and no cardiovascular morbidity. Part of the "proinflammatory state" in older persons is related to the high prevalence of cardiovascular risk factor and morbidity. (Blood. 2005;105: 2294-2299)

Inflammatory Cytokines Go Up with Age

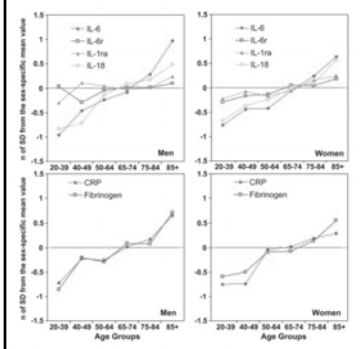
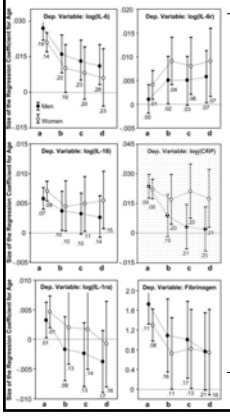


Figure 1. Mean values of inflammatory markers according to sex and age group expressed as number of standard deviations from the population mean to make them independent of different units of measure. (Top row) ♦ indicates IL-6; □, IL-6r; ▲, IL-1ra; and ○, IL-18. (Bottom row) ◆ indicates CRP; □, fibrinogen.

InChianti: Information on inflammatory markers, cardiovascular risk factors, and diseases was collected in 595 men and 748 women sampled from the general population (age, 20-102 years)

Ferrucci et al., Blood. 2005;105: 2294-2299

Little/No Increase with Age After Adjusting for CVD



Age regression coefficients and their 95% CIs estimated from linear models predicting level of inflammatory markers:

- "a" estimates the crude affect of age;
- "b" is adjusted for cardiovascular risk factors;
- "c" is also adjusted for subclinical cardiovascular diseases;
- "d" is adjusted for CHD, CHF, stroke, PAD, COPD, diabetes, hypertension, osteoporosis, CFR, cancer, dementia, and depression.

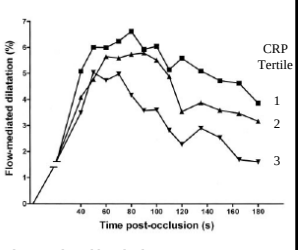
R^2 values reported below the confidence interval are for the model used to estimate the age regression coefficients.

Ferrucci et al., Blood. 2005;105: 2294-2299

Adiposity-related proinflammatory changes in the young start at an early age

	BOYS		GIRLS	
	n	r	n	r
Age	1479	0.13†	1367	0.11†
BMI percentile	1470	0.39†	1358	0.41†
Systolic blood pressure*	1093	0.20†	1062*	0.20†
Diastolic blood pressure*	1093	0.09‡	1062*	0.07
Total cholesterol	1455	−0.01	1349	0.02
Triglycerides	…		…	
Glucose	…		…	
HbA1c	…		…	
Homocysteine	1478	0.04	1367	0.10†

Correlation Coefficients Between LnCRP and CVD Risk Factors
Boys & Girls 3 to 17 Years of Age in NHANES 1999 to 2000

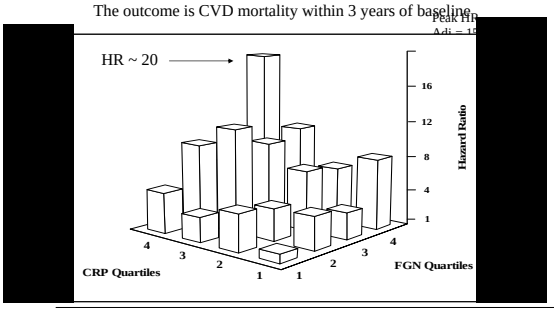


Flow-mediated brachial artery responsivity in 79 healthy boys and girls, mean age = 10.5 years

Ford ES. *Circulation*. 2003;108:1053-1058
Jarvisalo et al., *ATVB* 22:1323, 2002

Fibrinogen and CRP are independent biomarkers of early mortality in elderly men

Cardiovascular Health Study: N ~2500 men >65 years at baseline
The outcome is CVD mortality within 3 years of baseline



Jenny N, et al., *Am J Epidemiol*, 2007

Association of Markers of Inflammation With CVD Risk:

So, given these various activities, could these markers of inflammation be specific for cardiovascular disease ?

No

Association of Markers of Inflammation With CVD Risk

Other outcomes associated with higher inflammation markers:

Type 2 diabetes
Congestive Heart Failure
Some cancers (short "lead times")
Cognitive decline
Frailty
All-cause and CVD Death

All chronic diseases of old age ?

SMART Case – Control Study

Sampling Point	Biomarker	Deaths, Median (25th, 75th %ile)	Controls, Median (25th, 75th %ile)	Difference after Log_{10}	p-Value[a]
Study entry[b]	hsCRP (μg/ml)	4.26 (2.12, 7.49)	2.14 (0.84, 5.68)	0.21 (0.07)	0.005
	Amyloid A (mg/l)	4.75 (2.80, 9.06)	3.65 (1.90, 8.08)	0.10 (0.06)	0.11
	Amyloid P (μg/ml)	58.8 (43.1, 82.3)	67.8 (48.8, 94.1)	−0.08 (0.03)	0.009
	IL-6 (pg/ml)	3.80 (2.72, 7.20)	2.31 (1.51, 3.33)	0.29 (0.04)	<0.0001
	D-dimer (μg/ml)	0.49 (0.27, 1.16)	0.26 (0.17, 0.45)	0.35 (0.06)	<0.0001
	F1.2 (pmol/l)	344.0 (245.8, 565.8)	351.4 (255.5, 533.4)	0.01 (0.04)	0.81
Latest level[c]	hsCRP (μg/ml)	5.26 (2.19, 19.3)	2.00 (0.78, 4.80)	0.47 (0.09)	<0.0001
	Amyloid A (mg/l)	6.88 (2.40, 16.7)	3.35 (2.00, 6.75)	0.28 (0.08)	0.002
	Amyloid P (μg/ml)	57.7 (34.9, 78.5)	67.3 (49.6, 88.1)	−0.09 (0.03)	0.009
	IL-6 (pg/ml)	7.84 (3.08, 15.5)	2.72 (1.60, 4.39)	0.45 (0.06)	<0.0001
	D-dimer (μg/ml)	0.70 (0.34, 1.64)	0.34 (0.22, 0.63)	0.39 (0.07)	<0.0001
	F1.2 (pmol/l)	339.5 (260.6, 463.7)	321.1 (218.8, 507.4)	−0.01 (0.04)	0.93

- Cases generally higher than Controls;
- Levels increased in Cases but not in Controls;
- Compared to healthy reference groups, the baseline values tended to be high, especially in Cases, but not extraordinarily so. For example:
  - CRP tertile cut points are 1 ug/ml and 3 ug/ml
  - D-dimer values are generally $\leq$ 0.4 ug/ml

Kuller LH, Tracy R, Neaton JD, et al. *PLoS Med*. 2008;5:e203

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SMART: Risk of death associated with biomarker at study entrance

Biomarker	Type of Analysis	<25th Percentile (Reference)	25th–49th Percentile OR (95% CI)	25th–49th Percentile p-Value	50th–74th Percentile OR (95% CI)	50th–74th Percentile p-Value	≥75th Percentile OR (95% CI)	≥75th Percentile p-Value	OR associated with One IQR Higher Biomarker Level after Log_{10} Transformation OR (95% CI)	OR associated with One IQR Higher Biomarker Level after Log_{10} Transformation p-Value
hsCRP (μg/ml)	No.*	16/45	9/42		20/28		40/55			
	Univariate	1.0 (ref.)	0.6 (0.2–1.5)	0.29	2.0 (0.9–4.6)	0.09	2.0 (1.0–4.1)	0.05	1.7 (1.2–2.4)	0.005
	Adjusted	1.0 (ref.)	0.7 (0.2–2.1)	0.50	2.5 (0.9–7.2)	0.08	3.1 (1.2–8.0)	0.02	2.3 (1.4–3.7)	0.001
Amyloid A (mg/l)	No.	11/46	17/35		28/33		29/56			
	Univariate	1.0 (ref.)	2.0 (0.8–5.2)	0.13	3.4 (1.5–7.7)	0.005	3.2 (0.9–5.2)	0.07	1.3 (0.9–1.7)	0.11
	Adjusted	1.0 (ref.)	3.4 (1.0–11.1)	0.04	3.5 (1.2–10.2)	0.02	3.1 (1.0–9.5)	0.05	1.3 (0.9–1.9)	0.12
Amyloid P (μg/ml)	No.	25/44	20/25		16/43		24/56			
	Univariate	1.0 (ref.)	1.5 (0.7–3.1)	0.32	0.7 (0.3–1.4)	0.32	0.7 (0.4–1.5)	0.39	0.7 (0.6–0.9)	0.009
	Adjusted	1.0 (ref.)	1.5 (0.6–4.0)	0.42	0.8 (0.3–2.0)	0.65	1.1 (0.4–3.0)	0.78	0.7 (0.5–1.0)	0.06
IL-6 (pg/ml)	No.	8/48	10/41		26/48		40/29			
	Univariate	1.0 (ref.)	1.3 (0.5–3.6)	0.62	3.2 (1.3–7.9)	0.01	8.3 (3.3–20.8)	<0.0001	3.4 (2.2–5.4)	<0.0001
	Adjusted	1.0 (ref.)	1.0 (0.3–3.6)	0.98	4.5 (1.4–14.2)	0.01	12.4 (3.6–42.6)	<0.0001	4.1 (2.3–7.3)	<0.0001
D-dimer (μg/ml)	No.	8/51	22/54		18/40		37/25			
	Univariate	1.0 (ref.)	3.2 (1.1–9.0)	0.03	4.0 (1.3–12.3)	0.02	12.4 (4.2–37.0)	<0.0001	3.9 (2.3–6.6)	<0.0001
	Adjusted	1.0 (ref.)	8.3 (1.9–36.8)	0.005	12.6 (2.4–65.1)	0.003	41.2 (7.5–225.6)	<0.0001	5.3 (2.6–10.9)	<0.0001
F1.2 (pmol/l)	No.	17/29	21/43		15/43		31/53			
	Univariate	1.0 (ref.)	0.8 (0.4–1.9)	0.64	0.6 (0.3–1.5)	0.28	1.0 (0.5–2.1)	0.92	1.0 (0.8–1.4)	0.81
	Adjusted	1.0 (ref.)	1.0 (0.4–2.9)	0.94	0.9 (0.3–2.6)	0.82	1.3 (0.5–3.4)	0.64	1.1 (0.7–1.6)	0.71

Adj: age, race, use of ART and HIV-RNA level, CD4+cell count, smoking status, BMI, prior CVD, diabetes, use of BP medication, use of lipid-lowering medication, total/HDL cholesterol, co-infection with hepatitis B or C, and treatment group.
No significant interactions based on treatment

Kuller LH, Tracy R, Neaton JD, et al. *PLoS Med*. 2008;5:e203

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Issues to Consider in Viral Infection

- General features of viral infection
  - Tissue damage → activation of innate immunity
- Specific features of the infection; e.g., in HIV:
  - Loss of T helper function → opportunistic infections & loss of surveillance
  - Loss of lymph node function → general loss of adaptive immunity
  - Loss of GALT function → activation of coagulation
- Common co-infections; e.g., for HIV this might be HCV:
  - HCV → decreased liver function → "aging"
  - → altered biomarker profile
- Therapy; again in HIV:
  - ART → decreased inflammation due to control of viral load
  - → possible proinflammatory effects (? Mechanism)

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