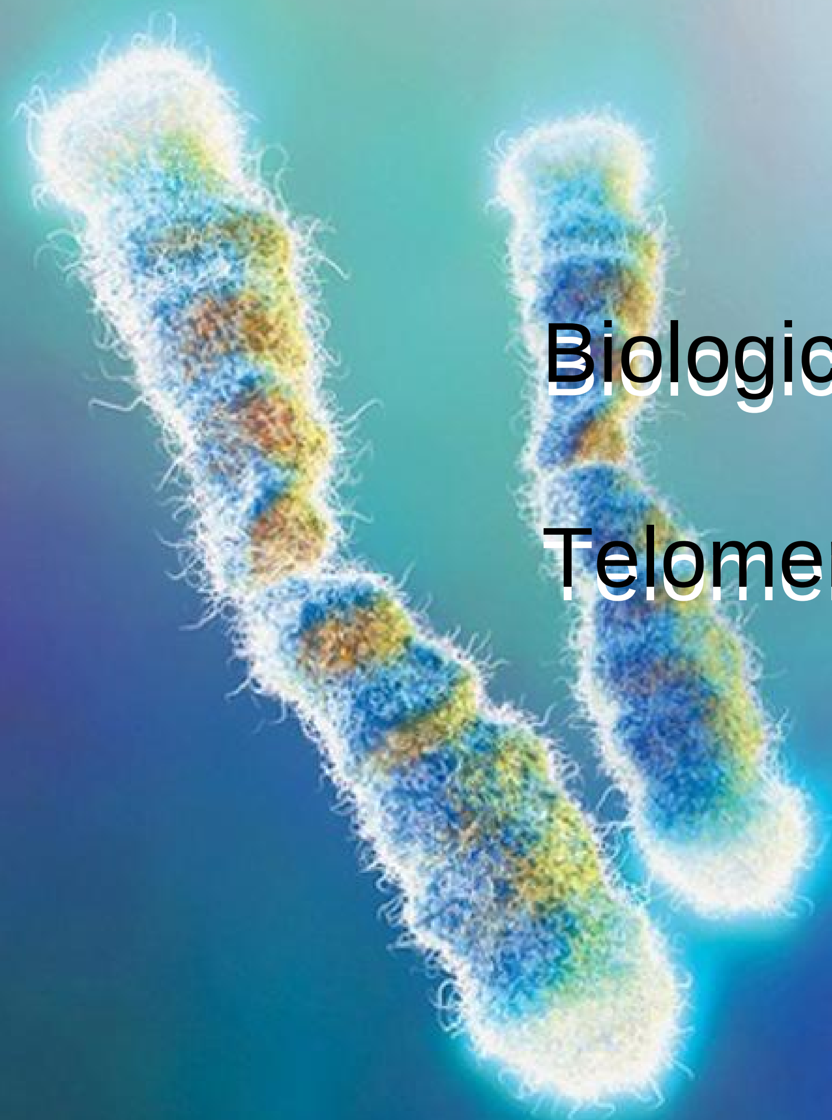
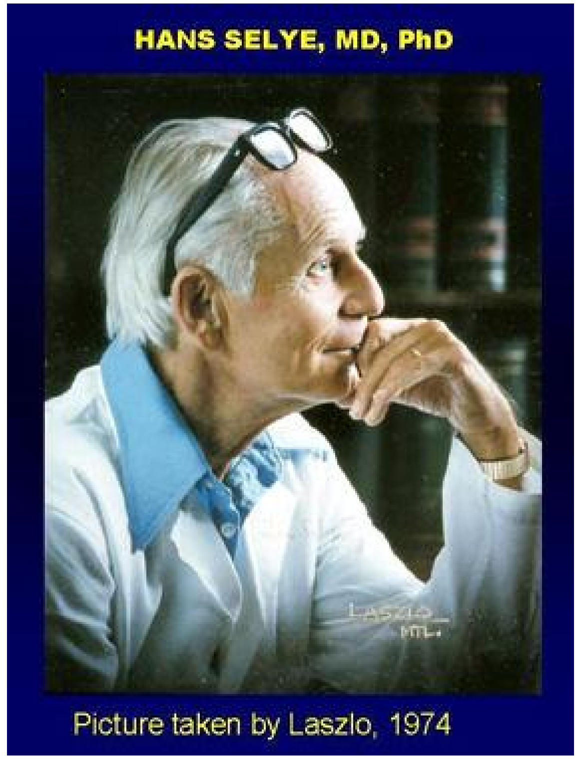


Biological embedding of life stress?

Telomeres and Telomerase

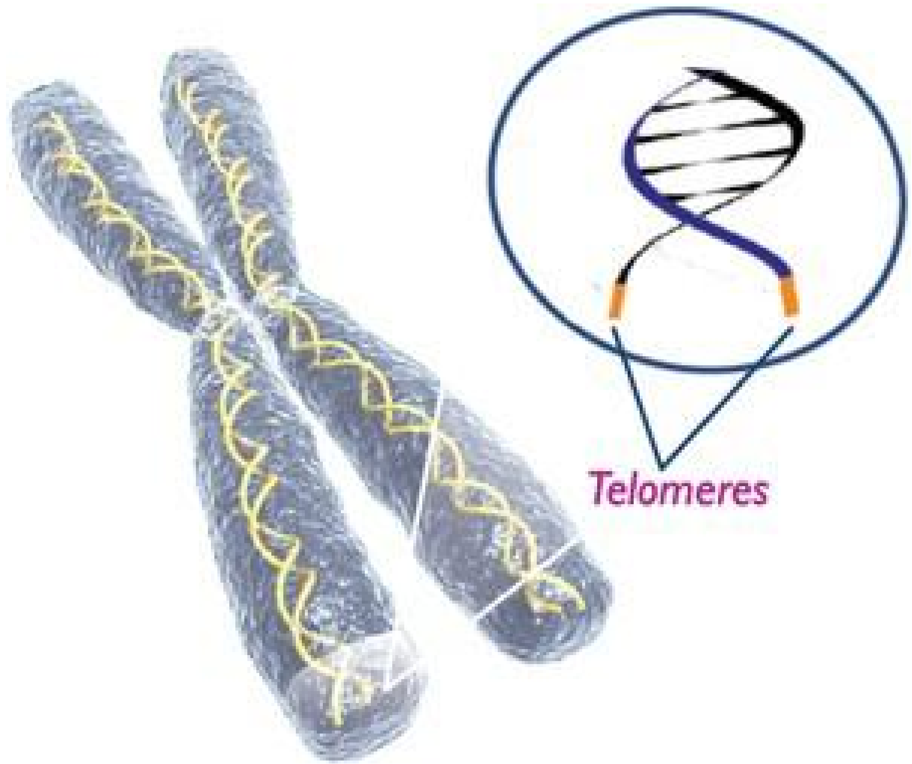
Elissa Epel, UCSF



"Every stress leaves an indelible scar, and the organism pays for its survival after a stressful situation by becoming a little older."

-Hans Selye

Cell Aging: Telomere Length



Telomeres

non-coding sequences capping ends

A “senescence clock” (Blackburn, 1978)

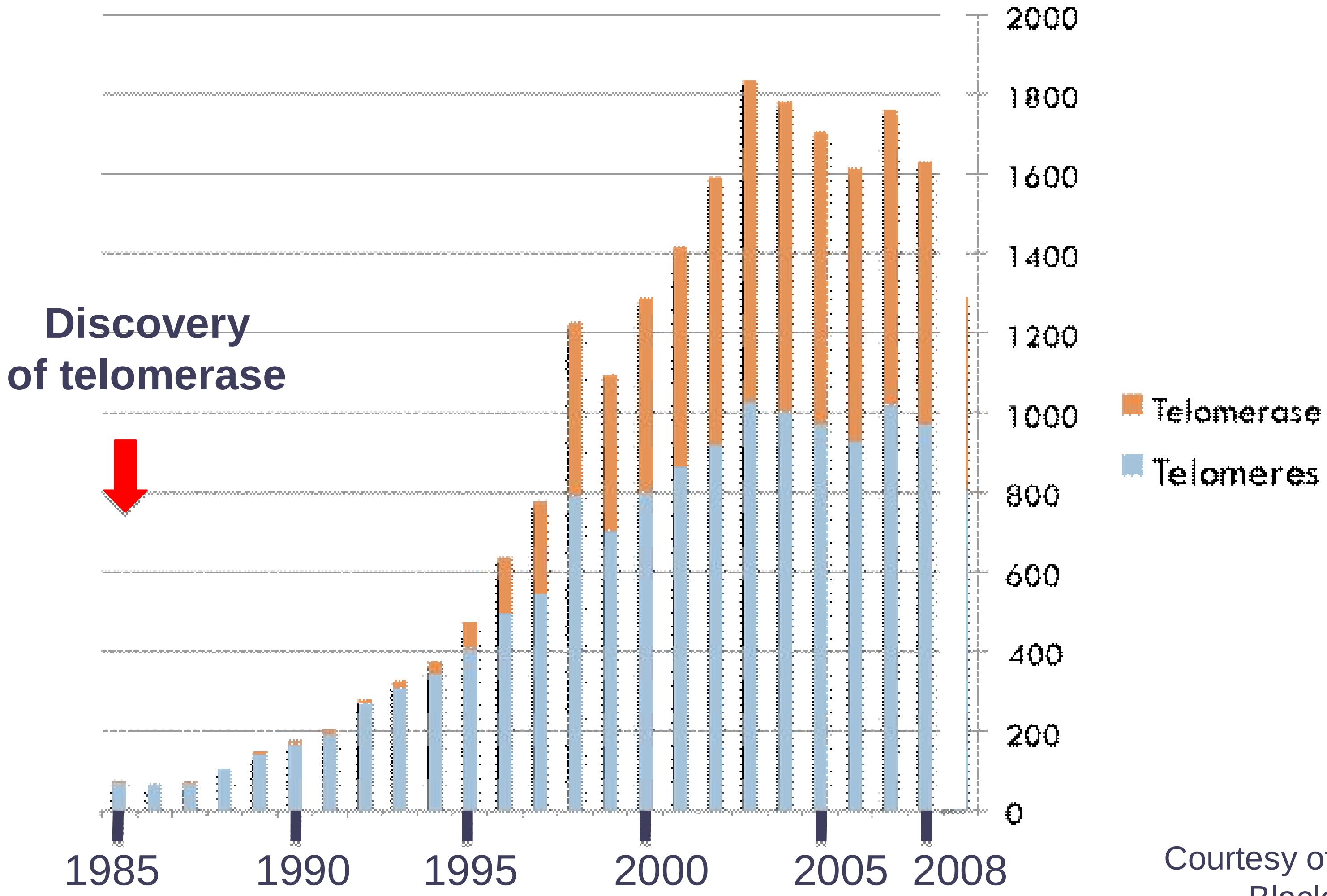
Stops proliferation

Telomerase:

enzyme that prevents telomere shortening

Promotes cell resilience.

Publications on telomeres and telomerase



Courtesy of Elizabeth Blackburn

Telomere Length predicts healthspan and mortality (8 studies)

Longer telomeres:

increased years of healthy life (Njajou, 2009)

Shorter telomeres:

- Lower 17-year survival from aggregate of all causes (infectious, CVD) (Cawthon, 2003)
- Lower 10 year survival (Erlenbach, 2009)
- Lower 12 year survival in women (Epel, 2009)
- CAD patients (4.4 years) (Farzaneh-Far, 2008)
- Alzheimers patients (Honig, 2006)
- Twin studies (Baykasa, 2007; Kimura, 2008)

WHR still leads to shortening

Table 3. Independent predictors of leukocyte telomere shortening as a dichotomous variable (multivariable logistic regression with backward selection of candidates in table 1 retained at $p<0.1$).

Variable	Odds Ratio for Telomere Shortening	95% CI	P value
Baseline T/S (per SD)	7.6	5.5, 10.6	<0.001
Age (per 10 yrs)	1.6	1.3, 2.1	<0.001
Male	2.4	1.3, 4.7	0.007
Waist-to-hip ratio (per 0.1 increase)	1.4	1.0, 2.0	0.04

Farzaneh-far, Lin, et al, 2010, PLoS One

Low Telomerase is associated with major risk factors for CVD

In the largest epidemiological study of risk factors for cardiovascular disease, the top six prominent factors were shown to be:

smoking	---------------	• smoking
poor lipid profile	---------	• cholesterol/blood lipids
high blood pressure	---------	• resting cardiovascular activity
diabetes	---------	• Fasting glucose
abdominal obesity	---------	• adiposity
psychological stress	---------	• psychological stress

(Yusef et al, Lancet 2004:304)

↕

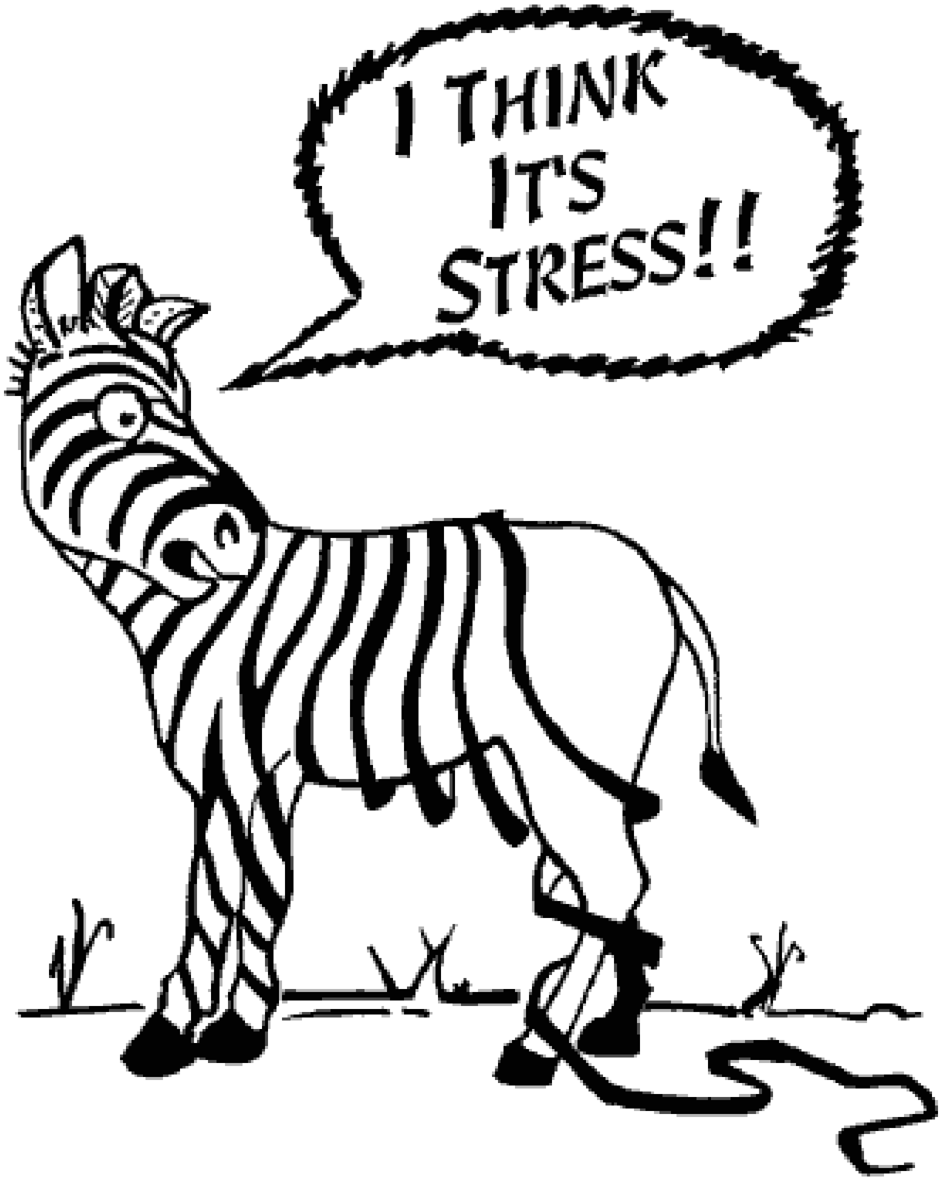
Lower telomerase activity

(Epel et al, 2006, Psychoneuroendocrinology)

Biological embedding??

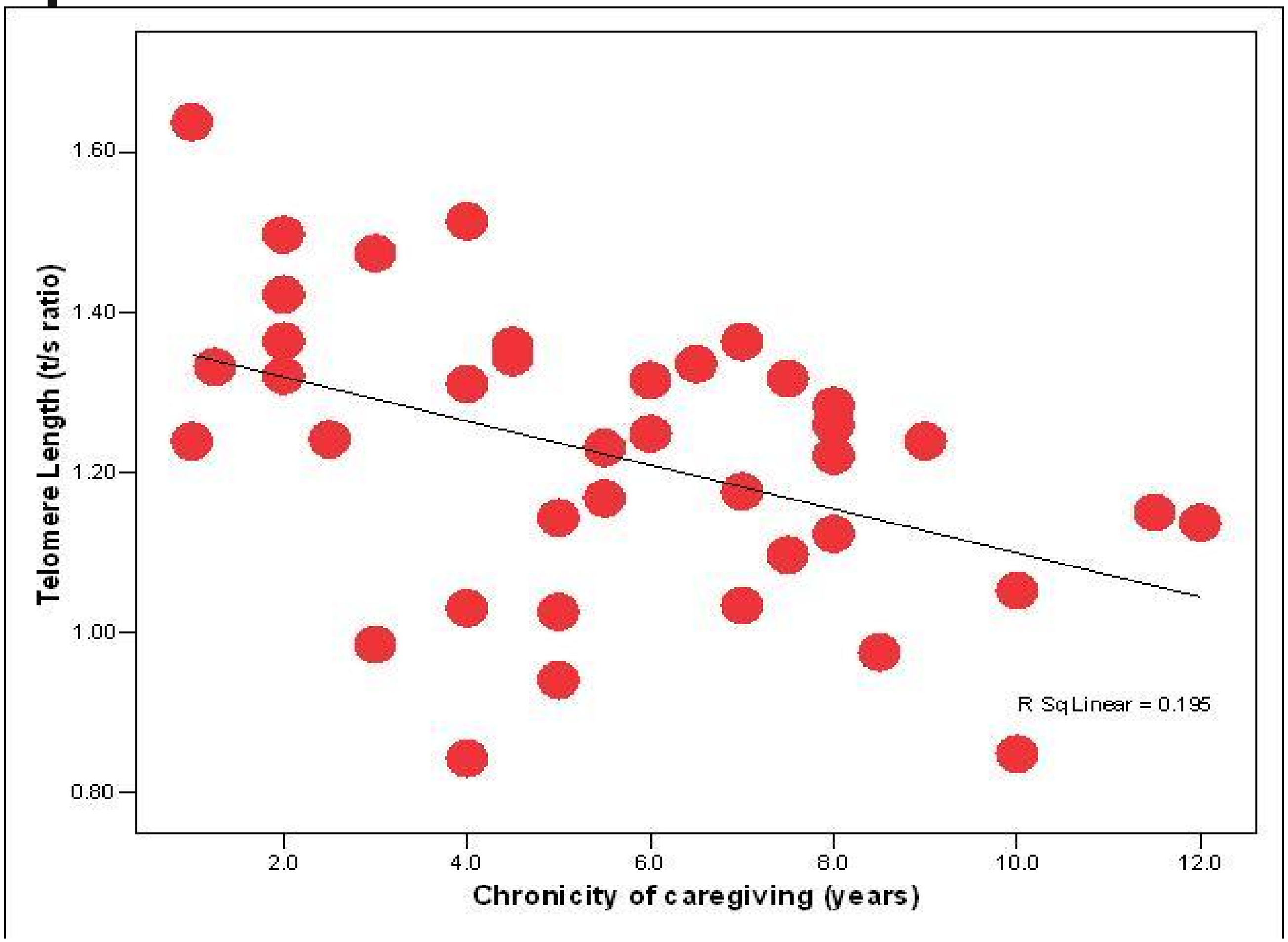
1) Relations with stress, early life stress
2) What makes cell aging unique?
3) Developmental course: Little Data!
4) Future directions

Telomeres: A new psychobiomarker? (Epel, 2009)


I THINK
IT'S
STRESS!!


1

Telomere Length covaries with exposure to a chronic stressor



Epel, Blackburn et al, 2004, PNAS

Indices of 'stress' and Telomere Length

Low SES (Cherkas et al, 2006)

Psychological Stress (Epel et al, 2004; Damjanovic et al, 2006; Parks et al, 2009)

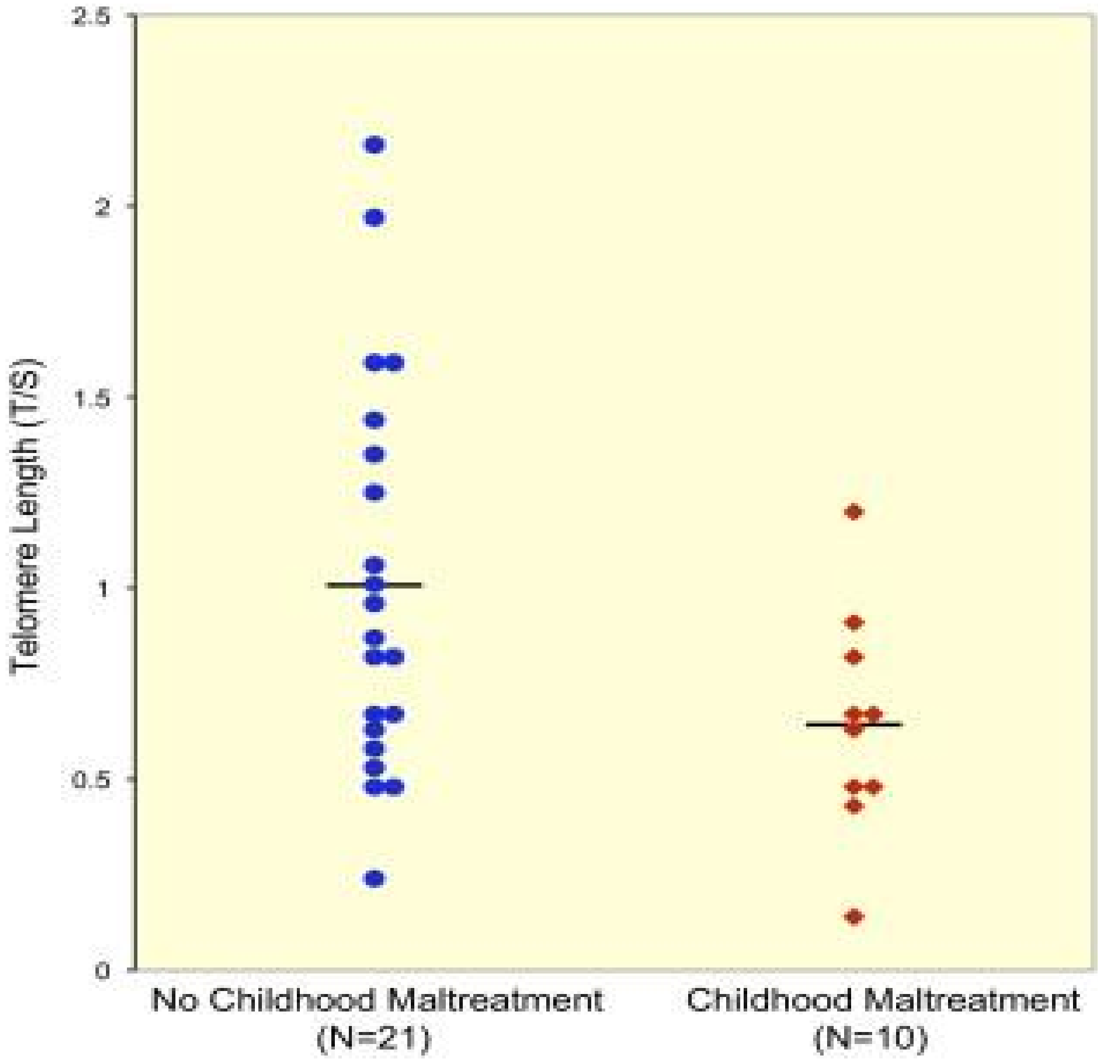
Stressed female mice (Kortschral, 2006

Depression (Simon et al, 2006; Lung et al 2007)

Mental Health (SF-36) (Huzen et al, 2010)

Early Trauma (Tyrkas et al, 2010)

Telomeres are shorter in those with childhood maltreatment



Tyrka et al, 2010

Unique biomarker?

Telomere maintenance: a master integrator?

Infectious exposures

Nutrition **Mental states** **Exercise**

Biochemical Stressors

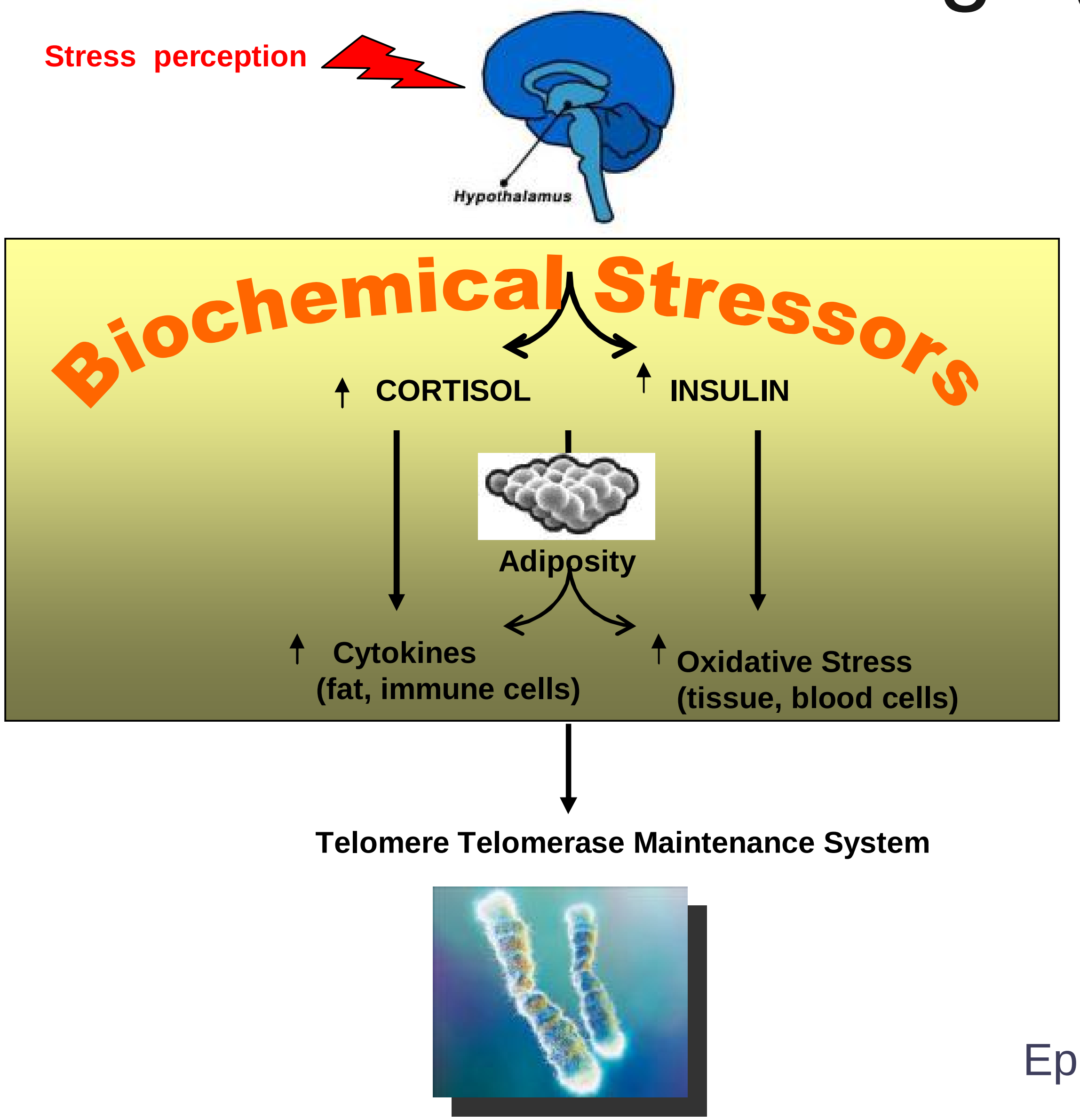
Genes

Risks for aging-related diseases/Poor immune function

Psychiatric disorders **Cardiovascular disease** **Cancer**

Metabolic disease **Fibrosis**

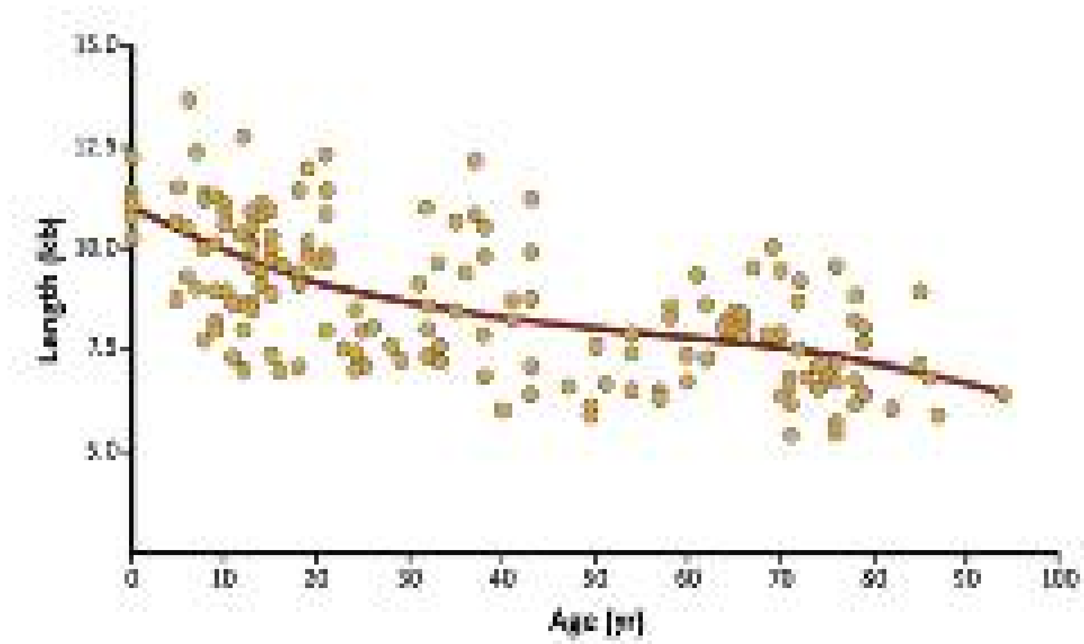
Pathways to cell aging



Epel, Hormones, 2009

DEVELOPMENTAL FRAMEWORK: CRITICAL PERIODS VS. LIFECOURSE LOAD?

Telomere length: Large variance across the lifespan



Average human leukocyte telomere length is 11kb at birth, and drops to 6 kb at age 90. (Yamaguchi, NEJM, 2005)

Telomere Attrition by Age

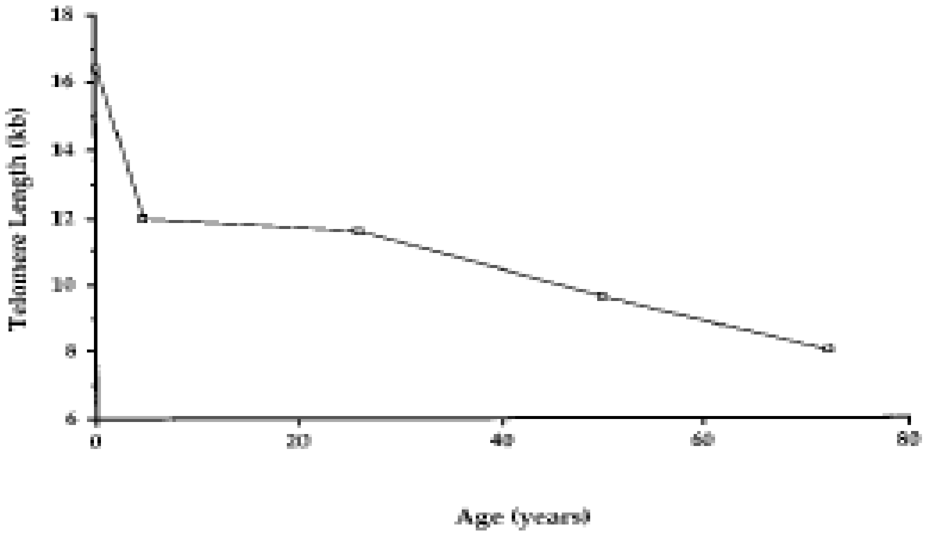


FIG. 3. Phases of telomere shortening in normal PBLs. The point shown for age 5 is taken from the oldest child shown in Fig. 2. The initial phase is characterized by rapid loss of telomeric repeats. An apparent stabilization then occurs between age 5 and young adulthood. Telomere loss resumes at a slower rate later as adults grow older. See text for further discussion.

Frenck et al., 1998; PNAS

Development of immune system

“Pruning” in early years

Dramatic decrease in telomere length

Unknown mechanisms

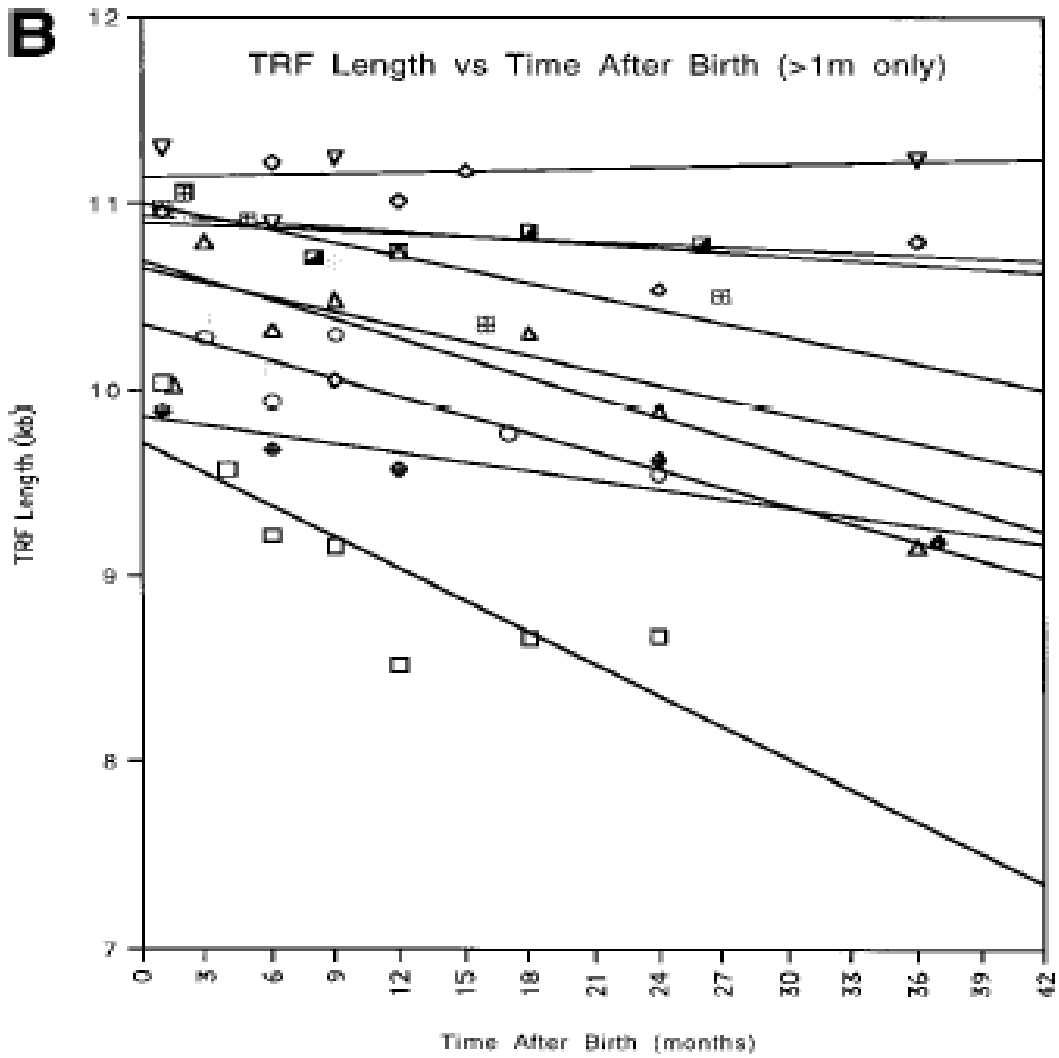
Fetal environment

Stem cell status

No longitudinal studies from early life to adult!

Telomere Attrition in Infants

ZEICHNER ET AL



270 bp/year,

4x higher than adults

Telomeres and Infant Growth

Jennings, 1999

- Rat pups studied with protein restriction prenatally or postnatally, vs. controls
  - Telomere attrition mirrored growth (shortened most during early growth, and then at end of life)
  - Postnatal growth restriction **à** longer TL, longevity
- Prenatal growth restriction **à** shorter TL, earlier mortality (due to catch up growth?)

Implications?

Prenatal development and Infancy appear to be critical periods for telomere attrition

Set up for life long (but malleable) “trajectory” for disease?

CHALLENGES

Challenges

Make few assumptions

-Dogma is vast, data is scarce

Whole blood vs. specific cell types

-Need mechanistic studies

Cross sectional vs. longitudinal

Telomerase is reactive! (Epel et al, 2010, BBI)

(need resting baselines)

Some next steps

Methodological:

TL in other cells / assay types / effects on behavior (Puterman, Lin, Blackburn, Schamarek)

Clinical studies

Trajectories & functional significance of immune senescence in caregivers & controls

Interventions (Hecht, Kemeny, Moran, Daubenmier, Blackburn, Lin)

Telomeres in caloric restriction (Tomiyama)

Populations

TL: SES/ethnicity, predicting mortality in NHANES

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