

Janice Kiecolt-Glaser, PhD

Chronic Stress: Implications for Immune and Endocrine Function



Wexner
Medical
Center

Institute for Behavioral Medicine Research



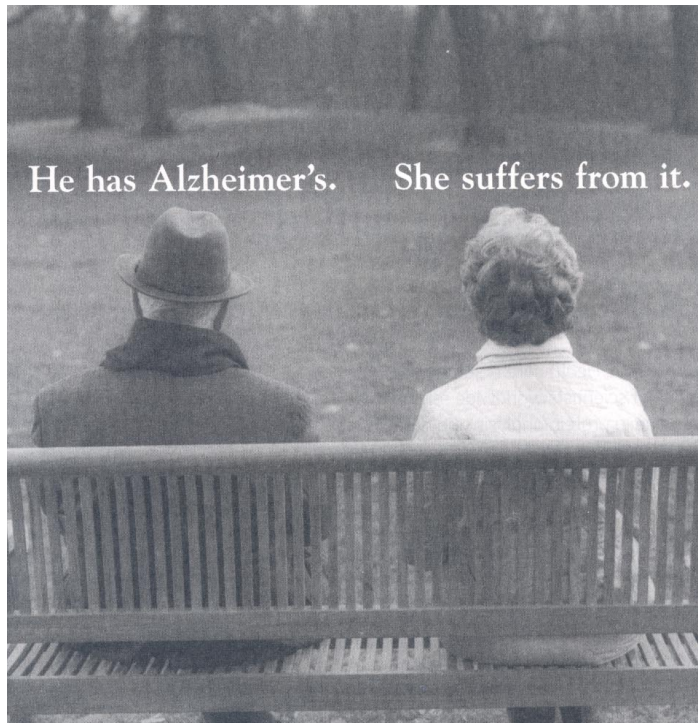
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MIND • BODY • HEALTH



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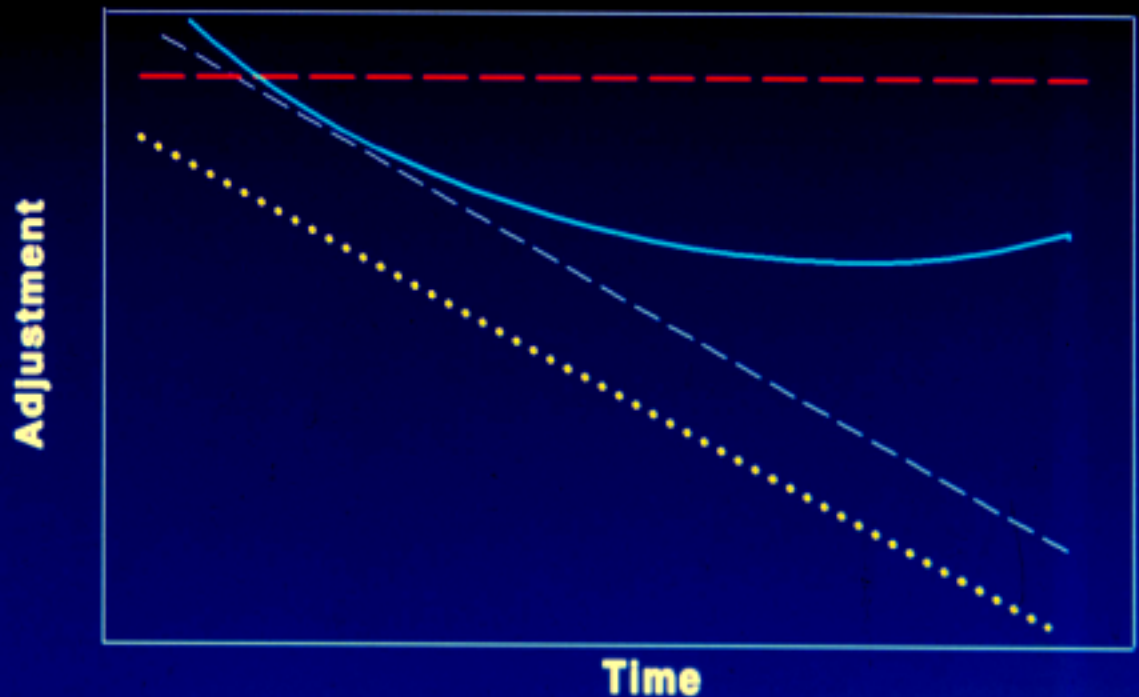
Dementia family caregiving as a chronic stressor



“The 88-year old former airline pilot had been ill for five years, during which time his cognitive abilities had steadily deteriorated. At times he did not recognize his wife and accused her of being a stranger. He could only follow the most simple of commands. His moods were extremely labile, with frequent crying spells and occasional outbursts of anger. He often followed his wife around the house, interrupting her activity with questions and demands. Urinary incontinence and night time agitation were bothersome problems. He often paced at night, occasionally leaving the house and becoming lost... His wife of forty years now devoted her time to looking after her husband. She rarely left home except to do necessary shopping or bill paying, and rarely invited neighbors or friends to her home because of embarrassment about her husband’s behavior.”

Barnes et al., *Journal of the American Geriatrics Society*, 1981





..... Patient Decline

--- Wear and Tear Model

--- Trait Model

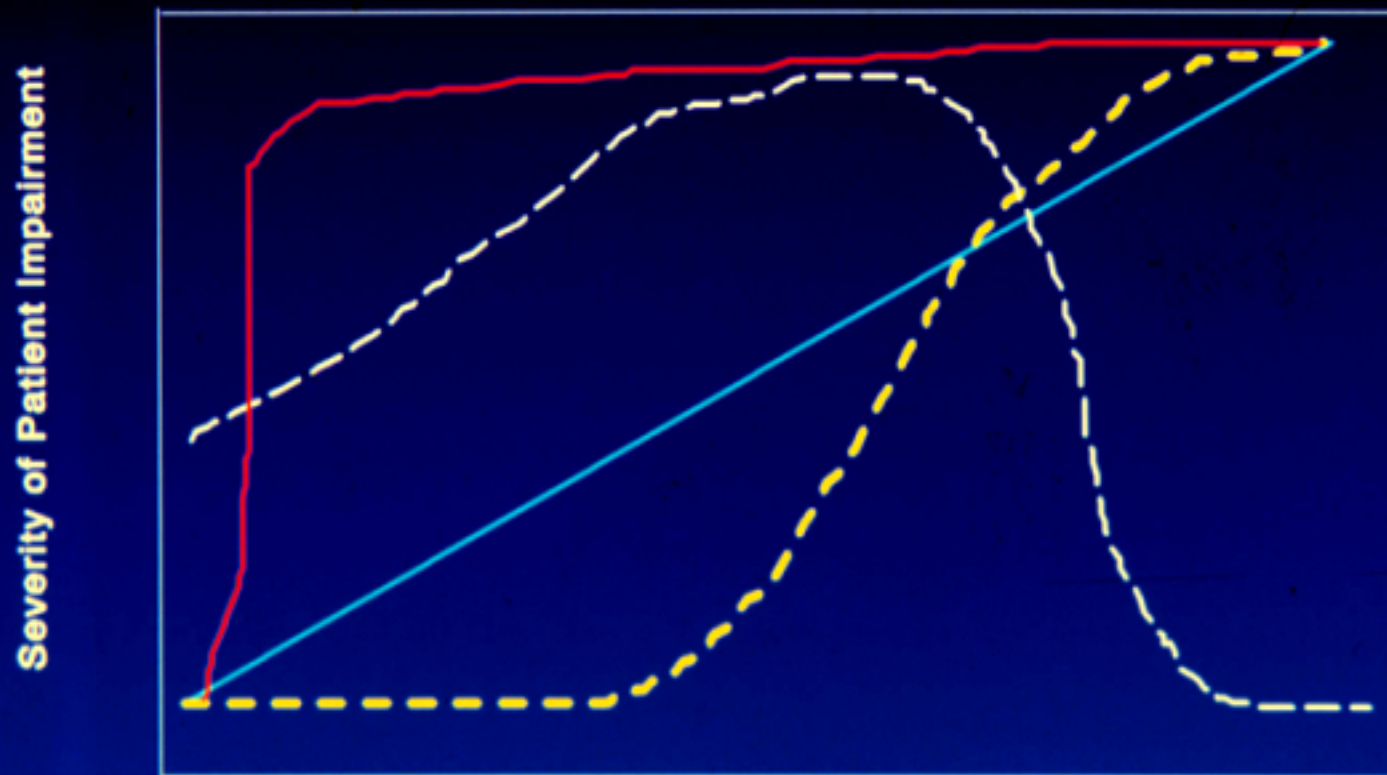
— Adaption Model

Models of caregiver adjustment to patient decline.

Haley & Pardo (1989).

Psychology and Aging





Time

**Disruptive Personality
and Behavioral Problems**

Basic Level Self-Care (ADL) Impairment

Higher Level Self-Care (IADL) Impairment

Intellectual Impairment

Severity of dementia and type of patient impairment.

Haley & Pardo (1989).

Psychology and Aging

Caregivers' Mental Health

- Stress: Lack of predictability and controllability
- Heightened levels of depressive and anxiety symptoms
- Heightened risk of clinical depression and anxiety
 - 30% of caregivers, 1% of controls



THE BACK PAGE BY WILLIAM STEIG

THE VIRUS THAT'S GOING AROUND



CAREGIVERS, COMPARED TO CONTROLS:

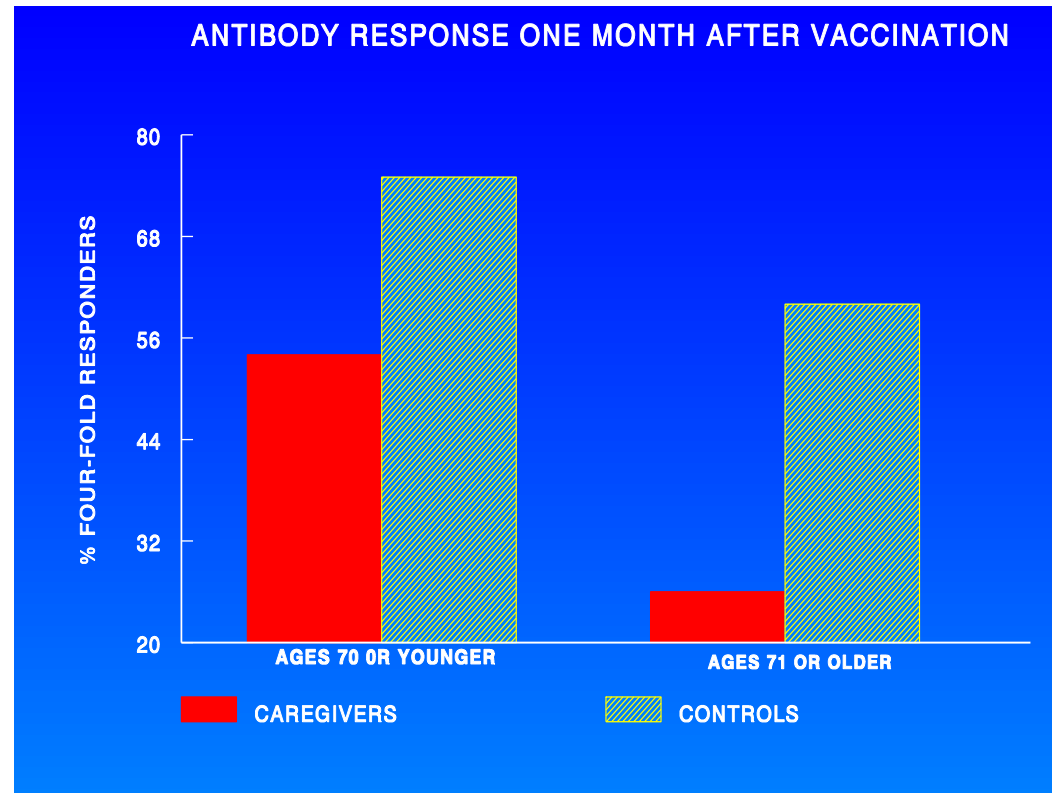
- Poorer blastogenic response to mitogens (PHA, Con A)
- Poorer blastogenic response to HSV-1
- Poorer T-cell receptor-induced blastogenesis using a monoclonal antibody to the T-cell receptor
- Lower percentages of IL-2 receptor positive PBLs after mitogen stimulation
- Enhancement of natural killer cell lysis by cytokines:
(No difference in NK lysis without cytokines)
Poorer response with gamma interferon
Poorer response with IL-2
- Higher antibody titers to Epstein-Barr virus (EBV) and HSV-1, i.e., poorer control of latent herpesviruses
- Lower IL-1b
- Higher plasma ACTH
- Lower growth hormone mRNA
- Elevated circulating nerve growth factor (NGF)
- Shifts in Th1/Th2 cytokine responses
- More respiratory infections, more days ill



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STRESS ALTERS VACCINE RESPONSES

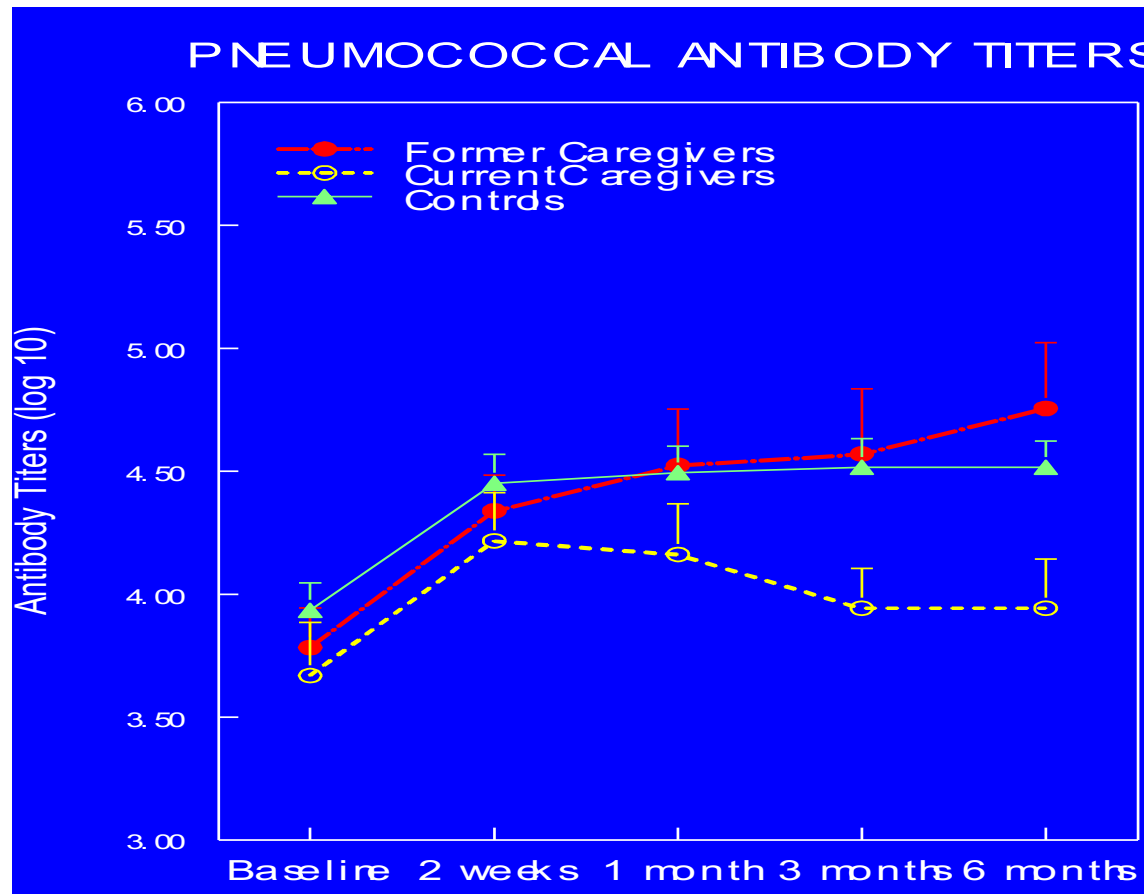
Caregivers' antibody responses to influenza vaccine were substantially poorer than well-matched non-caregivers



Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, Sheridan:
Proceedings of the National Academy of Sciences, USA, 1996



STRESS ALTERS VACCINE RESPONSES



Glaser, Sheridan, Malarkey, MacCallum, & Kiecolt-Glaser: Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. *Psychosomatic Medicine*, 2000



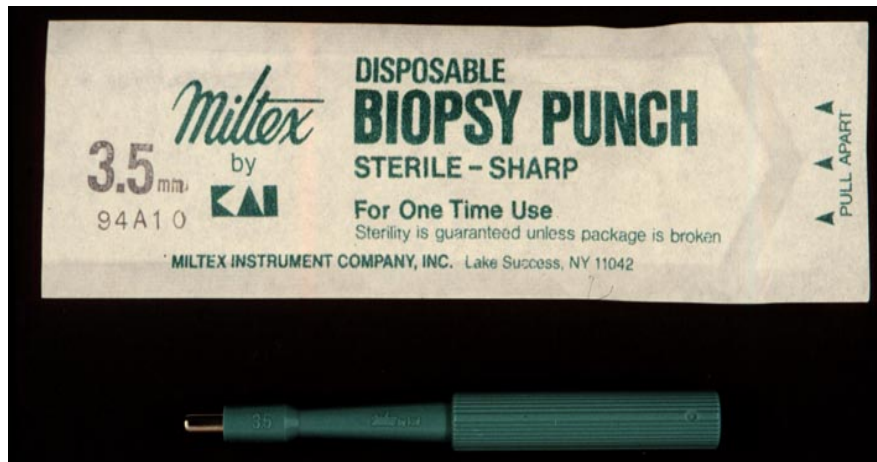
Vaccine responses provide a proxy for responses to infectious disease

- Multiple labs have shown stress-related alterations in both antibody and T-cell responses to viral and bacterial vaccines including
 - Hepatitis B
 - Influenza virus
 - Pneumococcal pneumonia
 - Rubella
 - Meningitis C conjugate
 - Tetanus

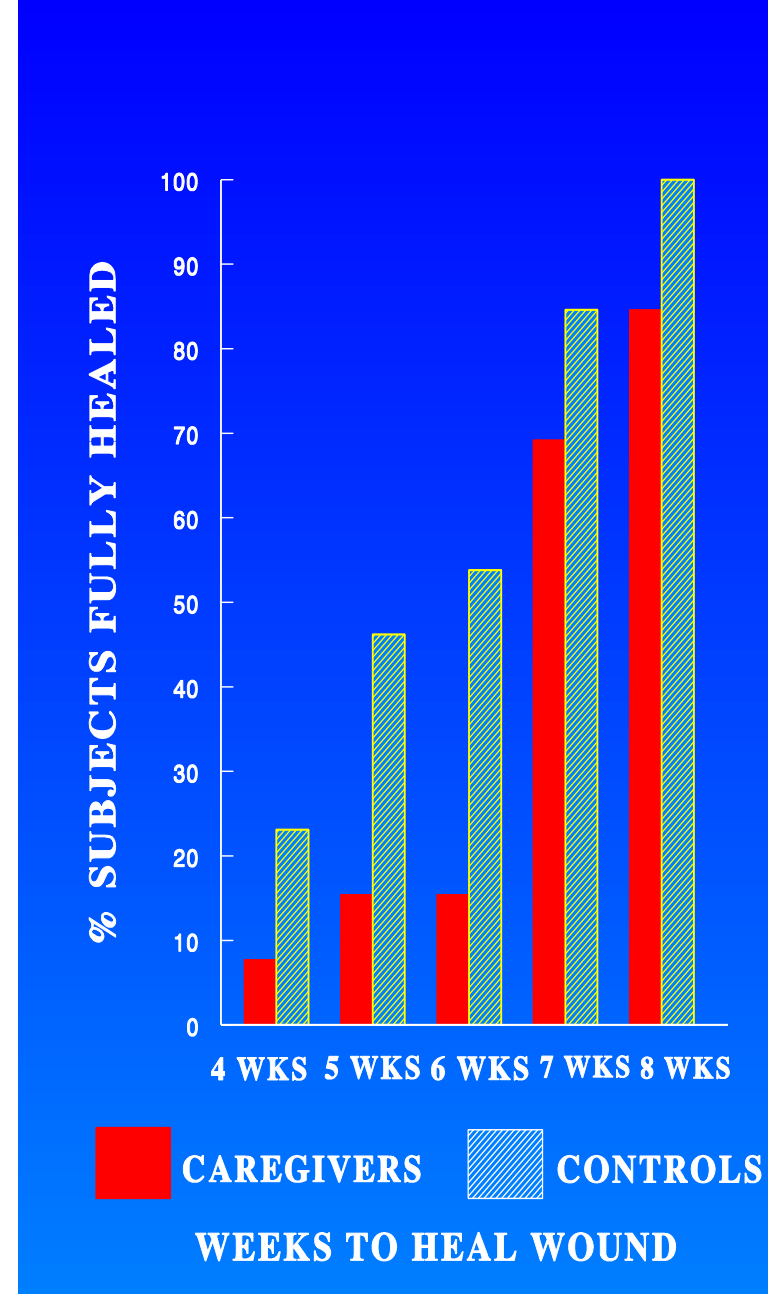


STRESS SLOWS WOUND HEALING

Caregivers took an average of 24% longer than well-matched controls to heal the same small, standardized wound.



Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser: ***Lancet***, 1995



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“...Healing is a living process, greatly under the influence of mental conditions. It has often been found that the same wound received in battle will do well in the soldiers that have beaten, that would prove fatal in those that have just been defeated.”

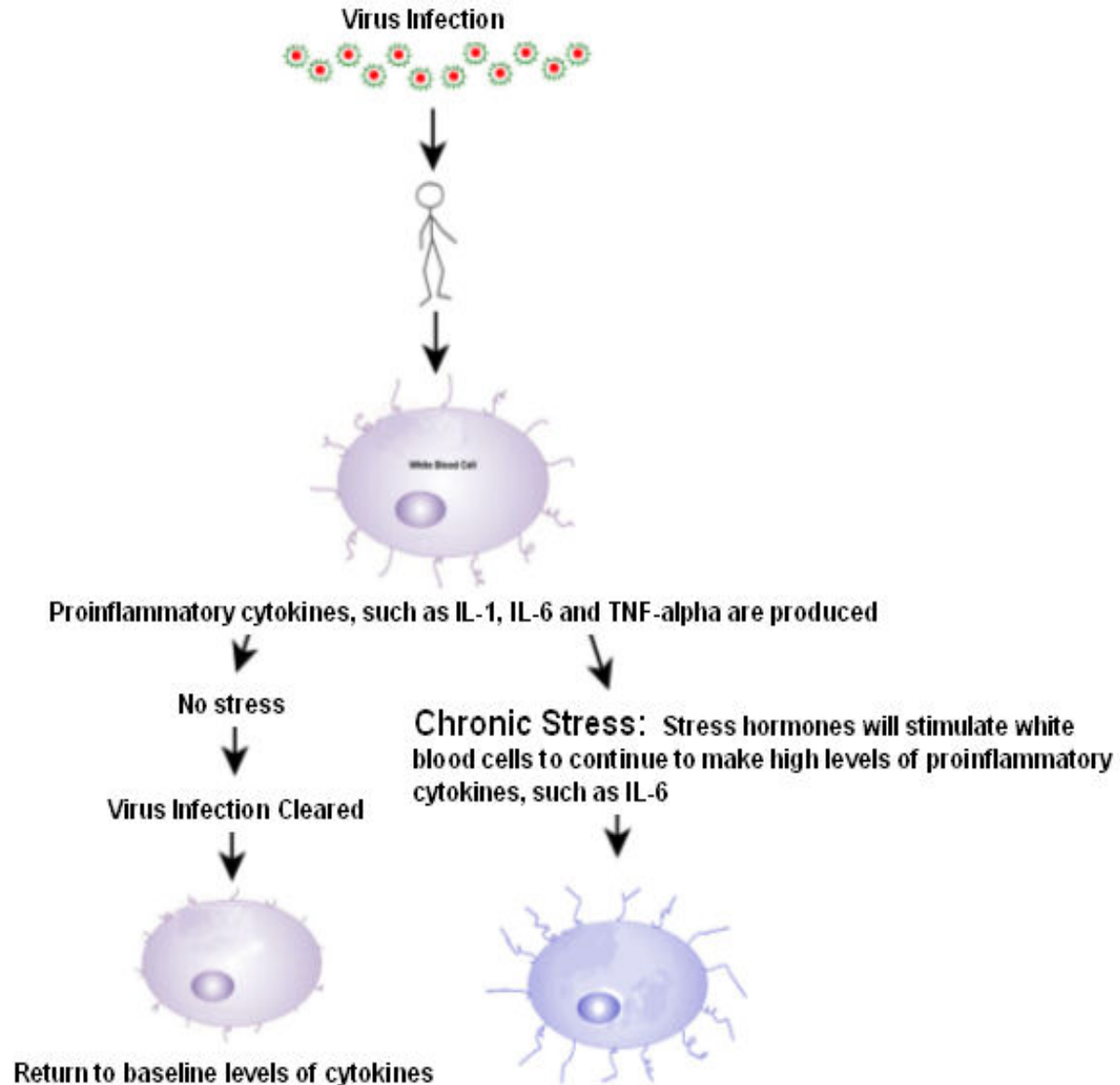
--Oliver Wendell Holmes, 1854



Infection and Trauma Trigger the Inflammatory Response

- Inflammatory mechanisms are critical to resolving infections and repairing tissue damage
- Proinflammatory cytokines attract immune cells to sites of infection or injury, and activate the cells to respond to the insult





FEBRUARY 23, 2004

BUSH'S
MILITARY RECORDS
IS DISNEY MOUSETRAPPED?

TIME

THE SECRET KILLER

- The surprising link between **INFLAMMATION** and **HEART ATTACKS, CANCER, ALZHEIMER'S** and other diseases
- What you can do to fight it

www.time.com AOL Keyword: TIME

AGE-ASSOCIATED DISEASES LINKED TO INFLAMMATION

Cardiovascular disease

Type 2 diabetes

Cancer

Osteoporosis

Arthritis

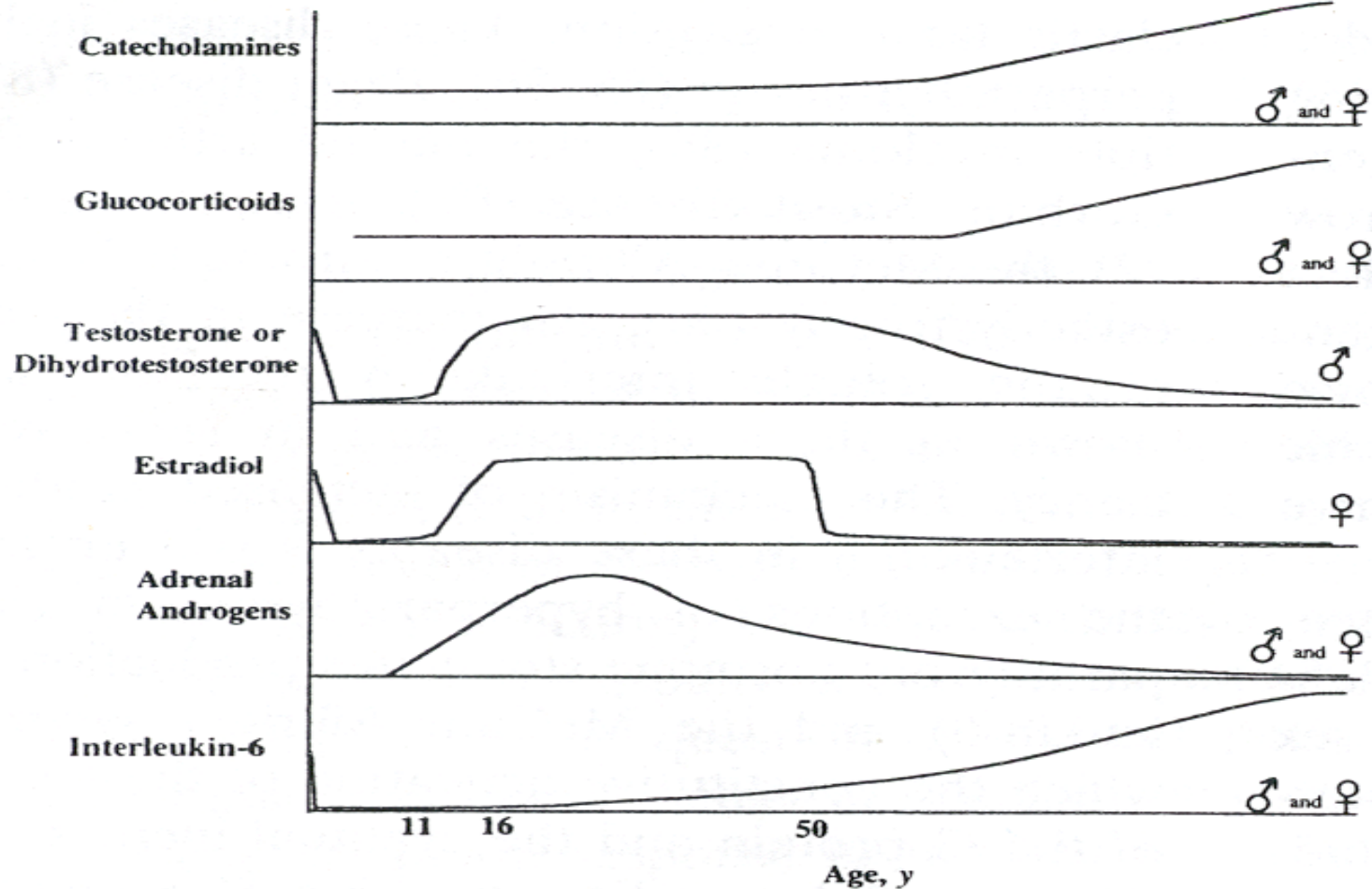
Periodontal disease

Frailty & functional decline



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Changes in circulating hormones and IL-6 with aging



Papanicolaou et al. Annals of Internal Medicine 1998



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CRITICAL PERIODS: MAXIMAL HEALTH IMPACT FROM STRESSORS

- ➡ Infants and children: immature immune and endocrine responses
- ➡ Older adults: normal age-related immune senescence, which increases risk



“Nothing to worry about, it’s all part of the aging process.”

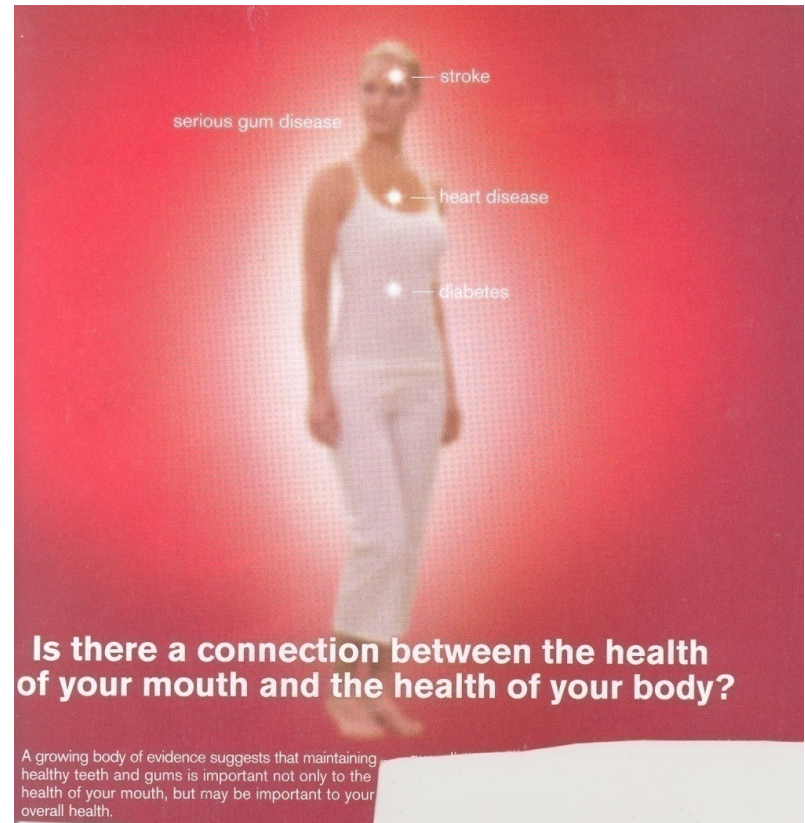


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Chronic or Recurring Infections Can Provoke Pathological Changes

Low levels of persistent inflammation may be provoked by chronic infectious processes, e.g.,

- + periodontal disease
- + urinary tract infections
- + *Helicobacter pylori*
- + chronic pulmonary disease
- + *Chlamydia pneumoniae*



- Stress/depression



- Immune dysregulation



- Enhanced risk of infection/prolonged infections/delayed wound healing



- Increased inflammation



STRESS AND DEPRESSION BOOST INFLAMMATION

- Major depression increases production of proinflammatory cytokines
- Depressive symptoms and depressive mood matter—with dose-response relationships in large community and clinical samples
- Chronic stressors like caregiving have been associated with heightened IL-6 compared to noncaregivers
- Acute stressors promote production of proinflammatory cytokines





- Stress/depression



- Immune dysregulation



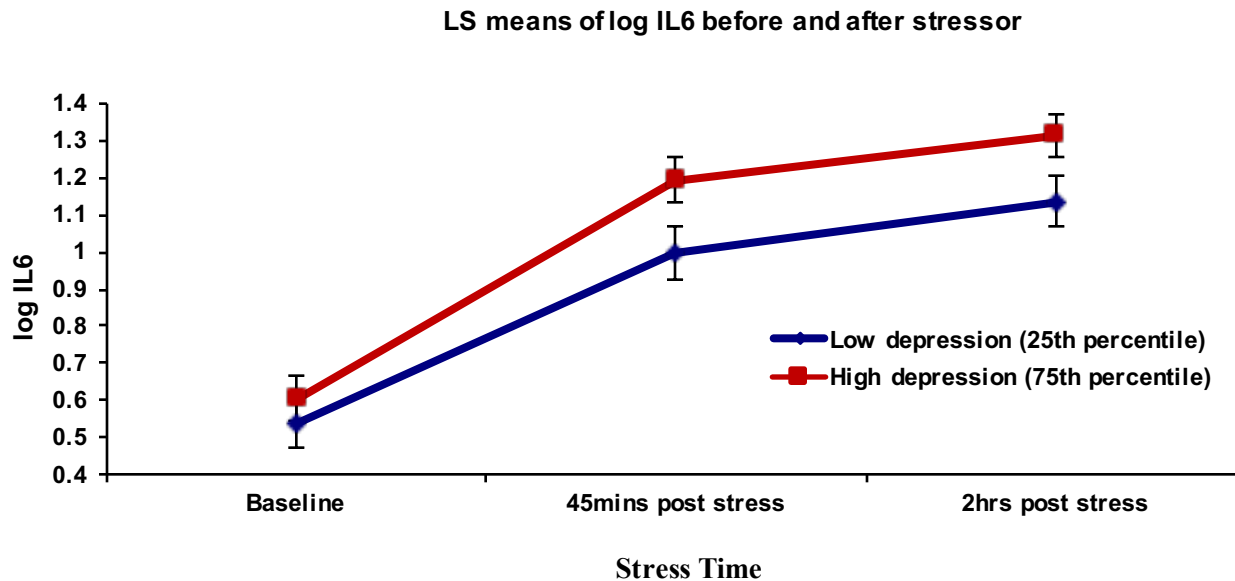
- Enhanced risk of infection/prolonged infections/delayed wound healing



- Increased inflammation



DEPRESSIVE SYMPTOMS ENHANCE STRESS-INDUCED INFLAMMATORY RESPONSES

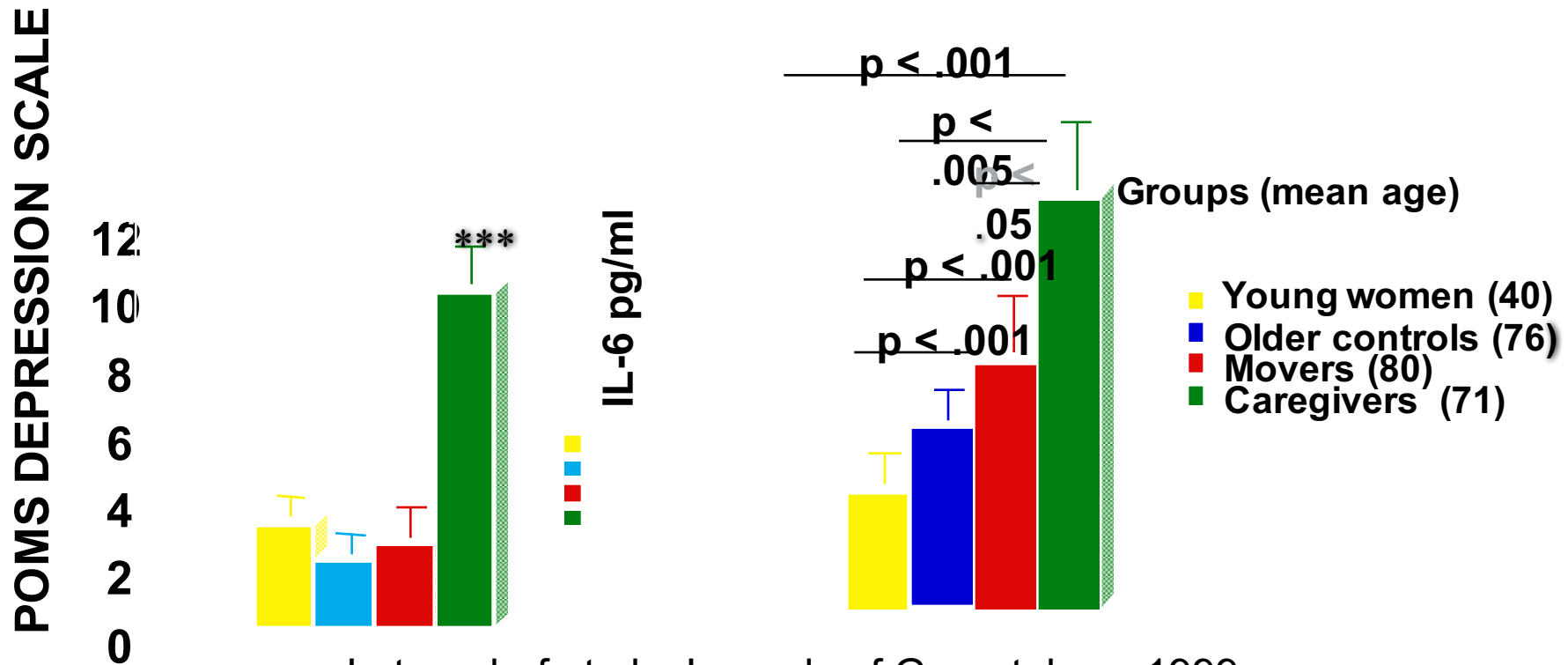


138 healthy adults: those with more depressive symptoms produced more IL-6 in response to the stressor

Fagundes, Glaser, Hwang, Malarkey, Kiecolt-Glaser *Brain, Behavior, and Immunity*, 2013.



Interleukin-6 in 4 Groups of Community Women



Lutgendorf et al., Journals of Gerontology, 1999



What happens with chronic stress?

Longitudinal community study spanning 6 years:

119 caregivers

106 noncaregivers

(mean age at study entry, 71)

Key Measures:

IL-6 in frozen plasma samples, 2x/year

Health behaviors associated with IL-6

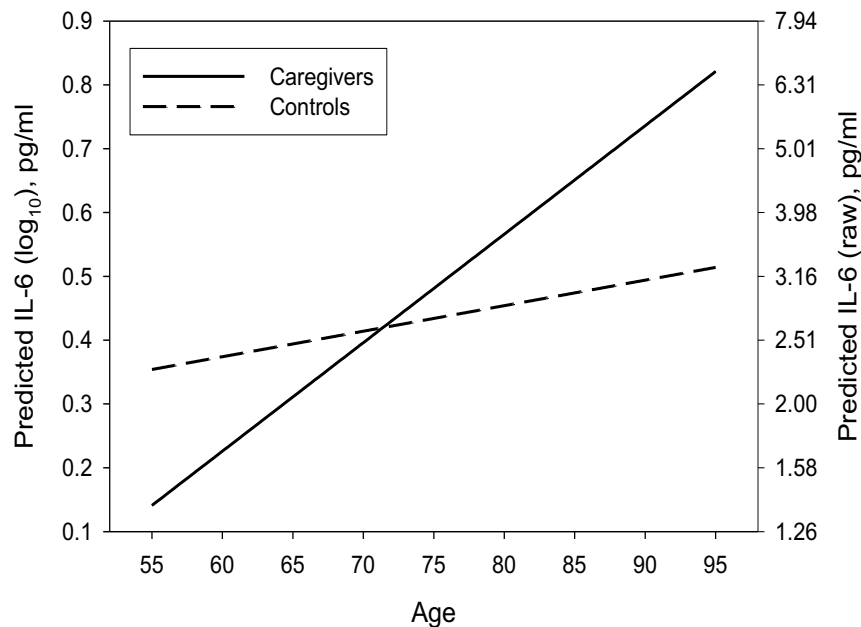
Depressive symptoms

Kiecolt-Glaser, Preacher, MacCallum, Atkinson, Malarkey, & Glaser (2003).
Proceedings of the National Academy of Sciences, USA



MODELED CHANGE IN IL-6 IN CAREGIVERS VS. NONCAREGIVERS

IL-6 is represented as a linear function of age; each individual's pattern of change is represented by a straight line defined by an intercept (predicted level of IL-6 at age 55) and slope (predicted change in IL-6 per year).



➤ **3.19 = upper quartile, epidemiologic studies**

Caregivers' average rate of increase in IL-6 was about **four times as large** as that of noncaregivers, and the two slopes were significantly different from one another, $p = .01$.

Kiecolt-Glaser, Preacher, MacCallum, Atkinson, Malarkey,
& Glaser: *PNAS*, 2003



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WHAT HAPPENS WHEN CAREGIVING ENDS?

Normal bereavement: higher incidence of depression and anxiety in widows and widowers within the first several months after the spouse's death compared to nonbereaved controls.

These group differences are typically not significant in follow-up data collected one to two years later (Harlow et al., 1991; Lund et al., 1989; Thompson et al., 1991).

Thus—caregivers should look no different than noncaregivers ~2 years after the spouse's death



“I COULDN’T BEGIN TO TELL YOU HOW MUCH I MISS HIM – I LOVED TAKING CARE OF HIM, AND WHEN YOU TALK ABOUT STRESS, I KNOW IT NOW.”

MRS. S., WRITING ABOUT HER FEELINGS FOLLOWING HER HUSBAND’S DEATH FROM ALZHEIMER’S DISEASE A MONTH AND A HALF EARLIER.

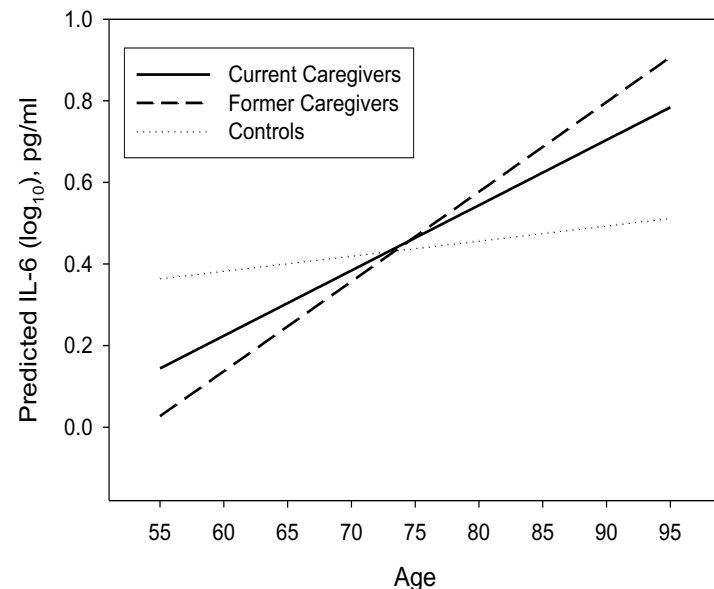


On entry into this portion of the longitudinal study, 28 of the caregivers' spouses had already died; an additional 50 of the 119 spouses died during the 6 years of this study.

Selected for this analysis: continuous caregivers vs. those bereaved 3 or more years

Former caregivers' average rate of annual change in IL-6 did not differ from that of current caregivers, even several years after the death of the impaired spouse

Kiecolt-Glaser, Preacher,
MacCallum, Atkinson, Malarkey, &
Glaser (2003). *Proceedings of the
National Academy of Sciences, USA*





Social Support

Social Support--Roles x Contacts



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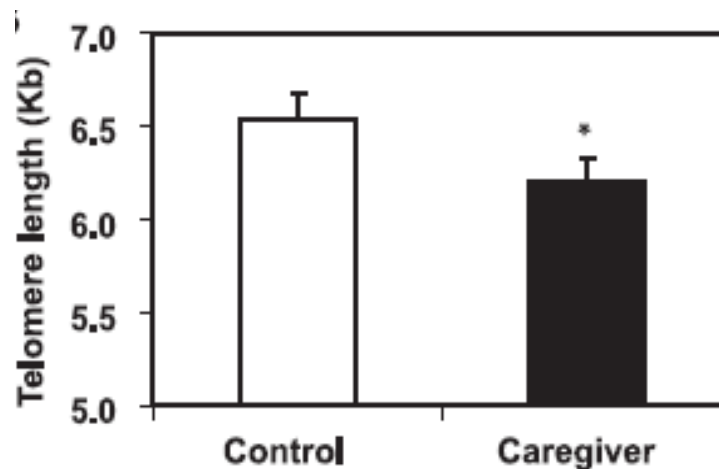
TELOMERES

- ➡ Inflammation triggers T-cell proliferation and enhances the leukocyte turnover rate, resulting in telomere shortening.
- ➡ Telomeres--bits of DNA on the ends of chromosomes that promote chromosomal stability and regulate cells' lifespan. Each time a cell divides, it loses a little of its DNA at the ends. The more often that cells divide, the more DNA is lost—resulting eventually in cell senescence.
- ➡ Shortened telomeres have been linked to health behaviors like obesity and smoking, as well as aging, age-related diseases, and mortality.



CAREGIVERS HAVE SHORTER TELOMERES THAN CONTROLS

First Report: Epel, Blackburn et al. *Proc Natl Acad Sci* 2004



Damjanovic, Yang, Glaser, Kiecolt-Glaser, Nguyen, Laskowski, Zou, Beversdorf, Weng, *Journal of Immunology*, 2007

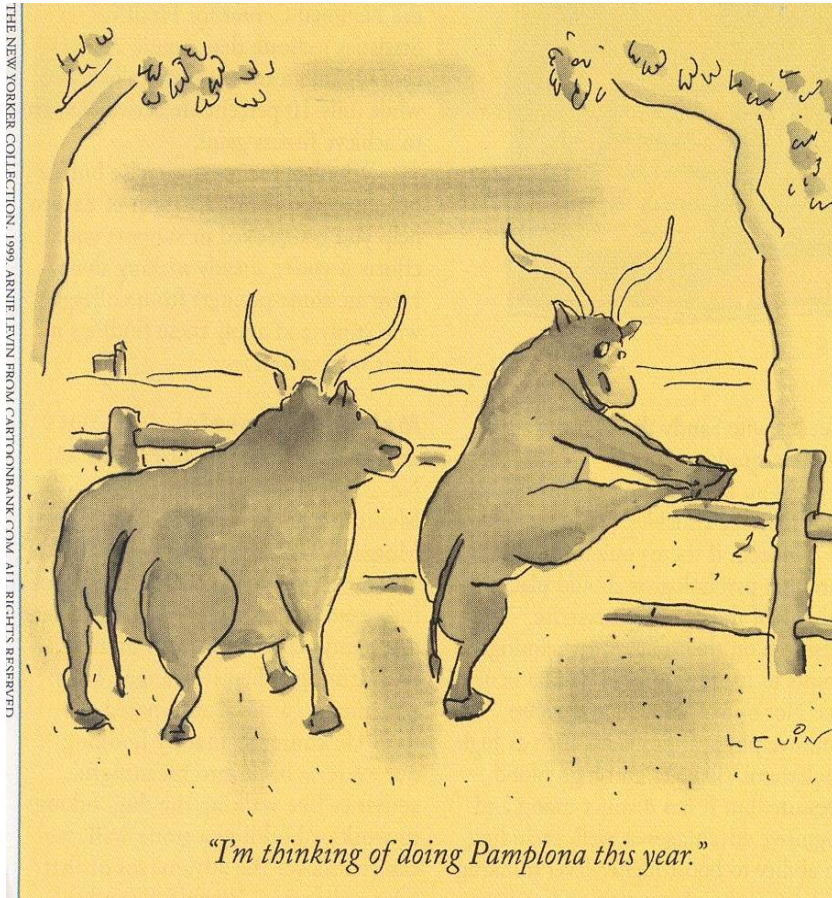


STRESS PROMOTES POOR HEALTH BEHAVIORS THAT BOOST INFLAMMATION

- Comfort food--high saturated fat, calorically dense
- Less exercise
- Poorer sleep
- Smoking
- Alcohol abuse



Physical Activity is Inversely Associated with Inflammation (and it lowers depressive symptoms)

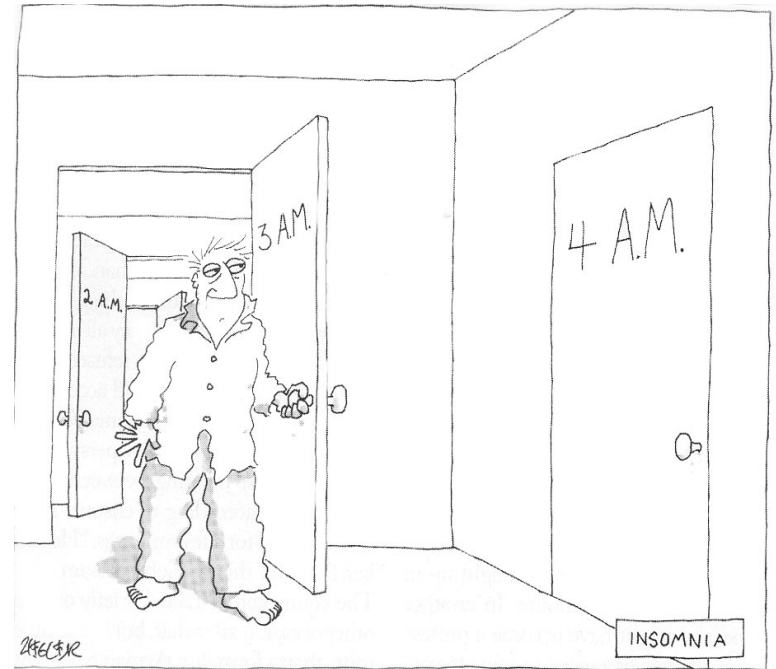


- When assessed rigorously and objectively by maximal exercise testing, fitness is inversely associated with inflammation (Kasapis, *J Am Coll Cardiol* 2005)
- Large population-based cohort studies consistently show an inverse association between markers of systemic inflammation and physical activity or fitness status (Beavers et al., *Clin Chim Acta* 2010)

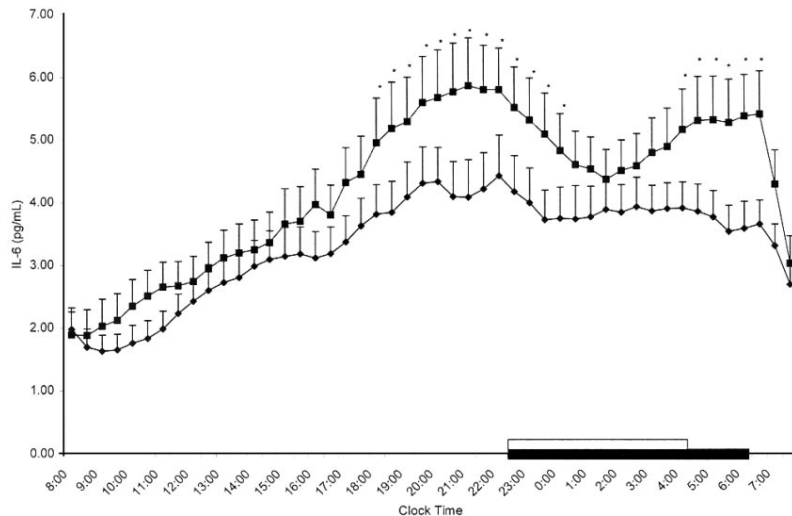


Stress, anxiety, and depression interfere with sleep:

- Trouble falling asleep
- Awakening during the night and finding it difficult to get back to sleep
- Sleeping fitfully with shallow sleep and frequent awakenings
- Early morning awakening
- Aging compounds the problems—medications, chronic health conditions, less restful sleep
- Poor sleep in the Alzheimer family member means poorer sleep for the caregiver

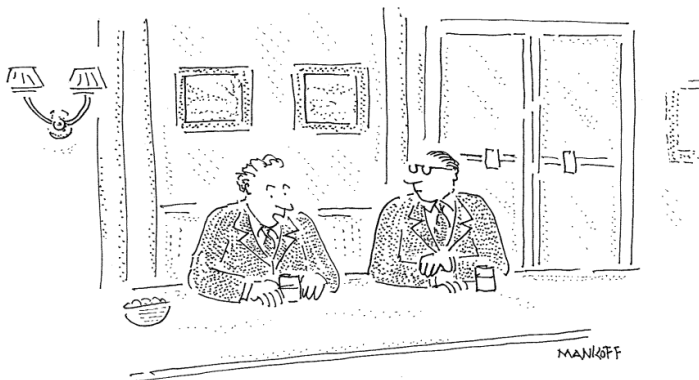


Modest sleep deprivation enhances IL-6 production



24-hour IL-6 circadian secretory pattern before (bottom) and after (top) sleep restriction (2 hours/night for 1 week) in 25 healthy men and women, ages 19-34.

The thick black bar on the abscissa represents the sleep recording period during baseline. The open bar on the abscissa represents the sleep recording period during partial sleep restriction. Vgontzas et al., 2004, *J Clin Endo Metab*



"No, I don't need an alarm clock—anxiety is my alarm clock."



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STRESS AND DEPRESSION PROMOTE UNHEALTHY DIETS



"What do you eat for anxiety?"



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“Western” vs. Mediterranean Diet

- Western diet: high in red and processed meats, sweets, desserts, fried food, and refined grains (Nurses' Health Study)
- Mediterranean Diet: high in cereals, vegetables, fruits and nuts, legumes, fish, a high dietary ratio of monounsaturated to saturated fatty acids (as reflected by high olive oil consumption), and moderate alcohol consumption
- Dai, J., et al. (2008). "Adherence to the Mediterranean diet is inversely associated with circulating interleukin-6 among middle-aged men: a twin study." Circulation



Depression and Stress Promote Obesity

- Depressed people have a 58% increased risk of becoming obese Luppino et al., *Arch Gen Psychiatry*, 2010
- Large prospective study: older depressed adults gained visceral fat over five years, while non-depressed adults lost visceral fat Vogelzangs et al., *Arch Gen Psychiatry*, 2008
- Stressful events are associated with weight gain and adiposity Block et al., *Am J Epidemiol*, 2009; Sinha & Jastreboff, *Biol Psychiatry*, 2013
- Chronic stress and stressful life events enhance the development of the metabolic syndrome, which has central obesity as its cornerstone Troxel et al. *Arch Intern Med*, 2005; Chandola et al. *Br Med J*, 2006

BACK TO INFLAMMATION: WEIGHTY MATTERS



Electron microscopic features of adipose tissue (Matsuzawa, 2005)

➡ Individuals with a higher body mass index have higher levels of inflammation: IL-6, TNF- α and CRP

➡ Up to 30% of IL-6 may be produced by adipose tissue

Mohamed-Ali 1997, *J Clin Endo Metab*



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- Stress/depression



- Immune dysregulation



- Enhanced risk of infection/prolonged infections/delayed wound healing



- Increased inflammation: **Depressive symptoms, fatigue, pain, cognitive problems**



Compared to noncaregivers, men and women who provide care to a spouse with a stroke or a dementia are at greater risk for

- developing diabetes
- becoming hypertensive
- coronary heart disease (CHD)
- risk for metabolic syndrome

Lee et al., 2003; Shaw et al., 1999; Vitaliano et al., 1996, 2002



CAREGIVER MORTALITY

- After adjusting for sociodemographic variables and baseline health status, spousal caregivers who experienced strain had 63% higher mortality than noncaregiving controls over the subsequent four years.
- The data represent a “best case” scenario, with caregiving defined very broadly.

Schulz & Beach, JAMA, 1999



Funding: NCI, NIA, NIMH, NIDCR, NCCAM

Chief collaborators:

Ronald Glaser, Ph.D

Martha Belury, PhD

William Malarkey, MD



"WE COLLABORATE. I'M AN EXPERT, BUT NOT AN AUTHORITY, AND DR. GELBIS IS AN AUTHORITY, BUT NOT AN EXPERT."



Papers from our lab:
<http://pni.osumc.edu/>



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