The Science of Stress and Stress Reduction

Ana Maria Lopez, MD, MPH, MACP
Professor and Vice Chair, Medical Oncology
Chief of Cancer Services, Jefferson Health New Jersey, SKCC, NCI Designated
Thomas Jefferson University

Stress by any other name....

smithsonianmag.com; apa.org

Stress symptoms

- Feeling overwhelmed
- Feeling out of control
- Difficulty relaxing
- Can’t quiet mind, can’t focus
- Worrying, forgetful, disorganized
- Pessimism, low self-esteem, lonely, worthless, depressed
- Fatigue, headaches, TMJ, GI sx, poor sleep, frequent colds, anhedonia

May be in response to an actual event or an anticipated event

Common

- In US, 25% reported high stress
- 50% report a major stressful event in the prior year
- Nearly half report more stress than last year

Blendon, R., Steel Fisher, G., Weldon, K., Benson, J., Brule, M., Mann, F., & Kramer, A. (2014). The burden of stress in America. *NPR/Robert Wood Johnson Foundation Harvard School of Public Health*, 1-12.

Objectives

- Improve our understanding of the physiology of stress
- Outline evidence-based interventions
    - What can we do?
    - What can our patients do?

Science of stress

- What is stress?

Stress is not

- Only about how you feel

- It is not strictly psychological
- It has real impact and physical health

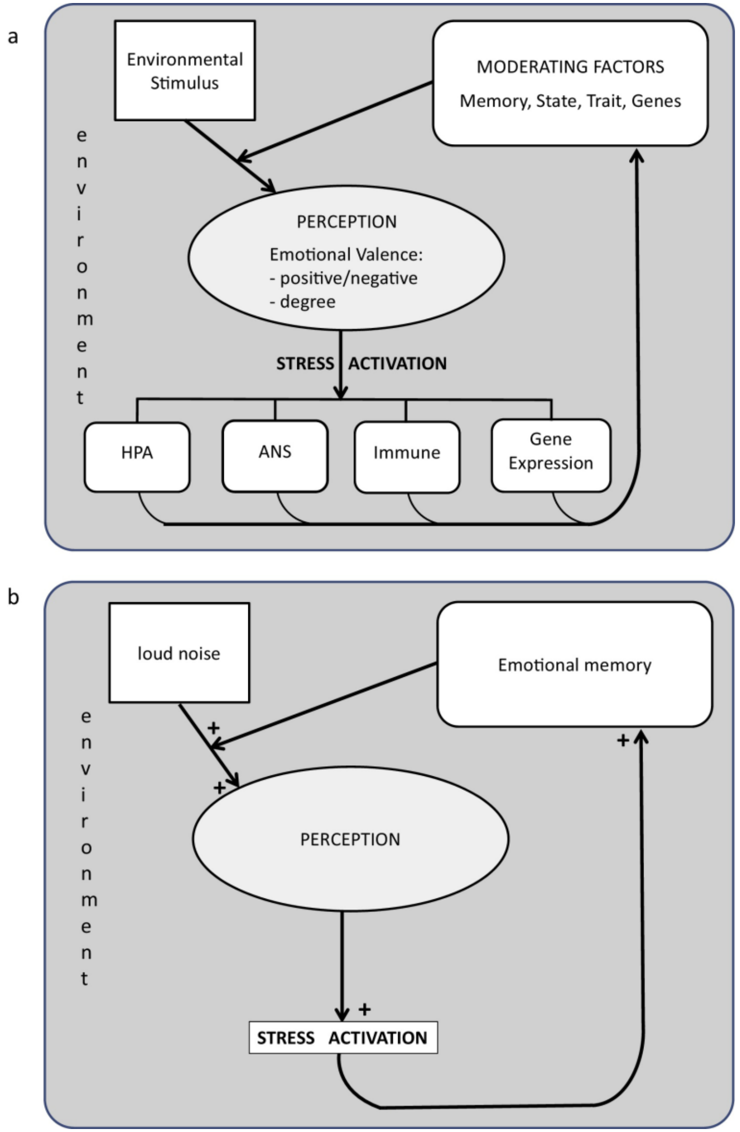
Stress

- Source can vary: environment, physical, emotional, psychological
- Release of stress hormones: adrenaline, noradrenaline, cortisol-– ”fight or flight” response
- Can be positive for that moment: help us focus, motivated, alert
- Adverse outcomes with sustained exposure
  - Sustained stress response: wear and tear on body, mind, and spirit

Mind *and* Body

- Interconnection between psychological stress (feelings) and physical health
    - Impact of brain-body pathways

Gianaros, P. J., & Wager, T. D. (2015). Brain-body pathways linking psychological stress and physical health. *Current Directions in Psychological Science*, *24*(4), 313-321.



Oken, B. S., Chamine, I., & Wakeland, W. (2015). A systems approach to stress, stressors and resilience in humans. *Behavioural brain research*, *282*, 144-154.

So stress has metrics!

- The brain/the self interprets what is stressful
  - Self-rated scales

So stress has biological metrics!

- Stress can be identified through physiological changes: biomarkers
  - Hypothalamic-Pituitary-Adrenal axis: free cortisol, ACTH
  - Activation of the locus coeruleus–norepinephrine–sympathetic nervous system pathway: blood pressure, skin temp, RR, HR, HRV
  - Immune system: cytokines
  - Genes: epigenetic changes, telomere shortening
  - Metabolic activity fluctuations
  - Muscle activity: muscle activity contraction

Kiecolt-Glaser, J. K., McGuire, L., Robles, T. F., & Glaser, R. (2002). Psychoneuroimmunology and psychosomatic medicine: back to the future. *Psychosomatic medicine*, *64*(1), 15-28.

Epel, E. S., Blackburn, E. H., Lin, J., Dhabhar, F. S., Adler, N. E., Morrow, J. D., & Cawthon, R. M. (2004). Accelerated telomere shortening in response to life stress. *Proceedings of the National Academy of Sciences*, *101*(49), 17312-17315.

Example: what does stress look like?

- Begins above your shoulders
- Amygdala: processes environmental data and communicates with hypothalamus to turn on the sympathetic system:
  - Increases heart rate
  - Constricts some blood vessels and dilates others
  - Slows intestines and inhibits digestive secretions
  - Cortisol is released
    - Disturbed circadian rhythms
    - Sleep-wake cycle is disturbed
    - Memory disruption
    - Brain fog

Stress physiology

Cardiac:

- Increased epinephrine and norepinephrine: heart rate, vasoconstriction, electrodermal activity, catecholamine release, and blood pressure.
- Increased cortisol and thyroxine: exacerbates inflammation and arterial plaque
    - If persist: damage blood vessels and arteries.
- Increased risk for HTN, MI, CVA.

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature reviews neuroscience*, *10*(6), 434.Merz, C. N. B., Dwyer, J., Nordstrom, C. K., Walton, K. G., Salerno, J. W., & Schneider, R. H. (2002). Psychosocial stress and cardiovascular disease: pathophysiological links. *Behavioral Medicine*, *27*(4), 141-147.

Stress physiology

Respiratory:

- Increase respiratory rate (get more O_2 to tissues)
- May result in quick, shallow breathing
- Hyperventilation
  - patients with asthma, anxiety, panic attacks may feel the stress more

Stress physiology

Musculoskeletal system:

- Muscles tense up to protect self from injury and pain
- Repeated muscle tension:
  - aches and pains
  - e.g. tense shoulders/neck
    - tension headaches and migraines

Stress physiology

Gastrointestinal system:

- Hypothalamus stimulates adrenals to release epinephrine and norepinephrine: impacts digestive process
  - Reflux
  - Stomach ache
  - Bloating, nausea, diarrhea, constipation
  - Change in ability to absorb nutrients

  - “stress eating”: eat more, eat less, eat differently-more sugar, more fat

Stress physiology

Endocrine:

- Metabolic changes.
- Release of stress hormones triggers the liver to produce more glucose-energy to deal with stress.
  - If stress response persists, metabolic disruption.

Stress physiology

Reproductive system:

- Decrease hormonal production-
  - Women
    - Impact fertility: impacts implantation
    - Impact menstrual cycle
  - Men
    - decrease sperm production

Stress Physiology

- Neurological:
  - Epilepsy
  - Parkinson’s disease
  - Multiple sclerosis

Novakova, B., Harris, P. R., Ponnusamy, A., & Reuber, M. (2013). The role of stress as a trigger for epileptic seizures: a narrative review of evidence from human and animal studies. *Epilepsia*, *54*(11), 1866-1876.
Hemmerle, A. M., Herman, J. P., & Seroogy, K. B. (2012). Stress, depression and Parkinson's disease. *Experimental neurology*, *233*(1), 79-86.
Burns, M. N., Nawacki, E., Kwasny, M. J., Pelletier, D., & Mohr, D. C. (2014). Do positive or negative stressful events predict the development of new brain lesions in people with multiple sclerosis?. *Psychological medicine*, *44*(2), 349-359.

Stress and the immune system

- Cortisol release
  - Immunosuppression
  - Increased inflammatory pathways
  - Increased infections
  - Increased chronic inflammatory conditions

Stress and emotional well-being

- Stress hormones contribute to hyperarousal
  - Poor sleep
    - Chronic health problems, obesity
  - Poor concentration, attention
  - Adversely impacts memory, learning

Furukawa, S., Fujita, T., Shimabukuro, M., Iwaki, M., Yamada, Y., Nakajima, Y., ... & Shimomura, I. (2017). Increased oxidative stress in obesity and its impact on metabolic syndrome. *The Journal of clinical investigation*, *114*(12), 1752-1761.

Stress and emotional well-being

- Fatigue, mood swings, irritability, easily frustrated
- Catastrophizing: constantly thinking negative thoughts
- Addiction/self medication: substance disorder, eating disorder
- PTSD

Cleck, J. N., & Blendy, J. A. (2008). Making a bad thing worse: adverse effects of stress on drug addiction. *The Journal of clinical investigation*, *118*(2), 454-461.

Impact of stress on the brain

- Post-traumatic stress and fear conditioning: impact mediated by cortisol
    - Decline in prefrontal cortex
    - Increased size of portions of the amygdala
    - Hippocampal atrophy
        - Damages cognitive function
        - Interferes in the process of creating memories
        - Impacts:
            - Behavior
            - Ability to form a stable, realistic, and cohesive sense of self

Sapolsky, R. M. (2001). Atrophy of the hippocampus in posttraumatic stress disorder: how and when?. *Hippocampus*, *11*(2), 90-91.

Stress Physiology

Stress and the brain

- Stress particularly impacts prefrontal cortex
- Cognitive function: memory altered by stress
- May affect speed, attention, and executive function
- May become more evident when compounded by age
  - Highly stressed elders: caregivers of patient with dementia

McEwen, B. S., & Sapolsky, R. M. (1995). Stress and cognitive function. *Current opinion in neurobiology*, *5*(2), 205-216
Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature reviews neuroscience*, *10*(6), 434.
Arnsten, A. F. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*, *10*(6), 410.
Stawski, R. S., Sliwinski, M. J., & Smyth, J. M. (2006). Stress-related cognitive interference predicts cognitive function in old age. *Psychology and Aging*, *21*(3), 535.

Job stress

- High demand
- Small sphere of control: low decision-making power
- Increase risk for cardiovascular disease
    - Type “D” personalities: chronic distress

Karasek, R. A., Russell, R. S., & Theorell, T. (1982). Physiology of stress and regeneration in job related cardiovascular illness. *Journal of Human Stress*, *8*(1), 29-42.

ELSEVIER

The Journal of Urology

Volume 174, Issue 3, September 2005, Pages 1065–1070

Adult Urology: Outcomes/Epidemiology/Socioeconomics

INTENSIVE LIFESTYLE CHANGES MAY AFFECT THE PROGRESSION OF PROSTATE CANCER

DEAN ORNISH[†], GERDI WEIDNER, WILLIAM R. FAIR, RUTH MARLIN, ELAINE B. PETTENGILL, CAREN J. RAISIN, STACEY DUNN-EMKE, LILA CRUTCHFIELD, F. NICHOLAS JACOBS, R. JAMES BARNARD, WILLIAM J. ARONSON, PATRICIA McCORMAC, DAMIEN J. McKNIGHT, JORDAN D. FEIN, ANN M. DNISTRIAN, JEANMAIRE WEINSTEIN, TUNG H. NGO, NANCY R. MENDELL, PETER R. CARROLL[‡]

Show more

Prostate Cancer

- Impact of lifestyle changes on early prostate cancer (UCSF)
- Who: men with early prostate cancer who chose observation, Gleason <7, PSA 4-10 ng/ml randomized to control or lifestyle intervention group

Assessment: Biological Endpoints

- PSA: baseline and at 1y (MSKCC)
- Testosterone
- Clinically relevant tissue culture: LNCaP cells
  - androgen sensitive prostate cancer cells from a human metastatic PC lesion
  - change in LNCaP cell growth is a standard test used for evaluating the effects of conventional treatments on prostate cancer in the laboratory
    - Expose LNCaP cells to patient serum exposed to therapeutic intervention/control to assess response

Study Population

- 181 eligible
- 73 declined: not willing to be randomized and either follow or not follow lifestyle changes or declined periodic testing
- 15 actually had Gleason scores $\geq$7ng/ml
- 93 enrolled:
  - 44 intervention, 3 withdrew—too difficult to follow
  - 49 control

Participant demographic and baseline characteristics

	Intervention	Control	p Value
No. subjects	44	49	
Mean age ± SD	65 ± 7	67 ± 8	0.25
% Married/cohabitating	66	76	0.31
% Employment:			0.64
Full/part time	54	49	
Retired	46	51	
Mean PSA ± SD (ng/ml)	6.32 ± 1.72	6.28 ± 1.66	0.92
Mean cholesterol ± SD (mg/dl)	204 ± 42	203 ± 39	0.90
Mean low density protein ± SD (mg/dl)	129 ± 36	127 ± 33	0.75
Mean high density protein ± SD (mg/dl)	48 ± 11	50 ± 13	0.57
Mean triglycerides ± SD (mg/dl)	133 ± 77	135 ± 88	0.94
Mean Ln-CRP ± SD	−0.0310 ± 1.1	0.2767 ± 0.8	0.16
Mean wt ± SD (kg)	80 ± 13.6	80 ± 11.3	0.75
Mean LNCaP apoptosis ± SD (% FBS)	48.16 ± 22.1	44.33 ± 33.0	0.55
Mean testosterone ± SD (ng/dl)	414 ± 860	387 ± 100	0.20
Mean Gleason ± SD (Sum)	5.7 ± 0.5	5.7 ± 0.7	0.80

To convert cholesterol, LDL and HDL to mmol multiply by 0.0259, to convert triglycerides to mmol multiply by 0.0113 and to convert testosterone to nmol multiply by 0.0347.

Study Intervention

- A nurse case manager contacted patients by telephone once weekly for the first 3 months and once monthly thereafter.
- A registered dietitian was available for nutrition education and counseling.
- All therapeutic decisions, including whether to undergo conventional treatment during the study course, were deferred to the personal physician of each patient.
- Control group patients were asked to follow the advice of their physicians regarding lifestyle changes.

Lifestyle Intervention

- Vegan diet: 1 daily serving of tofu, fortified soy protein powdered beverage, predominantly fruits, vegetables, whole grains (complex carbohydrates), legumes and soy products, low in simple carbohydrates and with approximately 10% of calories from fat.
  - In earlier studies most patients were able to adhere to this diet for at least 5 years
- Supplements: fish oil (3 gm daily), vitamin E (400 IU daily), selenium (200 mcg daily) and vitamin C (2 gm daily)
- Physical activity: moderate aerobic exercise (walking 30 minutes 6 days weekly)
- Stress management techniques (gentle yoga based stretching, breathing, meditation, imagery and progressive relaxation for a total of 60 minutes daily)
- 1-hour support group once weekly to enhance adherence to the intervention

Lifestyle Changes

Differences in lifestyle change scores between groups ($p < 0.001$)

Group	Mean Baseline ± SE	Mean 12 Mos ± SE	Mean Baseline-12-Mo Change ± SE	F (df)
Dietary fat (% calories from fat):				
Experimental	28.9 ± 1.8	11.2 ± 0.4	−17.7 ± 1.4	130.7 (1.81)
Control	26.2 ± 1.2	25.3 ± 8.8	−0.9 ± 1.1	
Dietary cholesterol (mg/day):				
Experimental	230.4 ± 21.6	7.5 ± 1.9	−222.9 ± 21.8	98.3 (1.81)
Control	218.0 ± 19.2	182.1 ± 19.3	−35.9 ± 16.0	
Exercise (days/wk):				
Experimental	3.1 ± 0.4	4.8 ± 0.3	1.7 ± 0.4	14.7 (1.80)
Control	3.3 ± 0.4	3.3 ± 0.4	0.0 ± 0.4	
Exercise (mins/wk):				
Experimental	120.8 ± 18.8	262.9 ± 38.8	142.1 ± 32.7	11.4 (1.80)
Control	186.1 ± 27.6	160.6 ± 21.3	−25.5 ± 26.8	
Stress management (days/wk):				
Experimental	2.1 ± 0.4	5.7 ± 0.3	3.6 ± 0.4	46.2 (1.80)
Control	2.0 ± 0.4	2.3 ± 0.5	0.3 ± 0.4	
Stress management (mins/wk):				
Experimental	39.6 ± 11.0	315.7 ± 20.9	276.0 ± 20.9	102.5 (1.80)
Control	71.3 ± 22.1	75.7 ± 19.1	4.4 ± 18.0	
% Overall lifestyle index:				
Experimental	41.4 ± 3.8	94.8 ± 3.8	53.4 ± 4.2	115.2 (1.80)
Control	45.4 ± 2.9	45.1 ± 3.5	−0.3 ± 3.0	

Results

Group	Mean Baseline ± SD	Mean 12 Mos ± SD	Mean Baseline-12-Mo Change ± SD	p Value
PSA (ng/ml):				
Experimental	6.23 ± 1.7	5.98 ± 1.7	−0.25 ± 1.2	0.016
Control	6.36 ± 1.7	6.74 ± 2.1	0.38 ± 1.3	
Total cholesterol (mg/dl):				
Experimental	205.0 ± 42	172.6 ± 34	−32 ± 39.4	<0.001
Control	200.6 ± 39	202.8 ± 37	2 ± 25.7	
Low density protein (mg/dl):				
Experimental	130.9 ± 35	101.2 ± 25	−30 ± 31.3	<0.001
Control	125.2 ± 33	124.1 ± 30	−1 ± 25.2	
High density protein (mg/dl):				
Experimental	47.3 ± 10	41.9 ± 12	−5 ± 8.3	<0.001
Control	48.3 ± 12	49.3 ± 12	1 ± 6.8	
Triglycerides (mg/dl):				
Experimental	133.0 ± 78	138.0 ± 96	5 ± 65.4	0.52
Control	137.1 ± 91	150.9 ± 93	14 ± 77.5	
LNCaP growth (% FBS):				
Experimental	105.50 ± 19.0	35.56 ± 9.2	−69.94 ± 19.5	<0.001
Control	91.40 ± 19.2	82.34 ± 36.8	−9.06 ± 42.8	
LNCaP apoptosis (% FBS):				
Experimental	48.16 ± 22.1	125.38 ± 127.0	77.23 ± 120.6	0.27
Control	45.16 ± 33.7	90.18 ± 128.0	45.02 ± 112.7	
Ln-CRP (mg/l):				
Experimental	−0.0310 ± 1.1	−0.2782 ± 1.0	−0.2472 ± 0.8	0.07
Control	0.2767 ± 0.8	0.2121 ± 0.9	−0.0646 ± 0.9	
Testosterone (ng/dl):				
Experimental	414.2 ± 86	443.3 ± 117	29 ± 96	0.53
Control	387.0 ± 100	435.0 ± 155	48.0 ± 123	
Wt (kg):				
Experimental	80 ± 13.8	76 ± 10.0	−4.5 ± 6.2	<0.001
Control	80 ± 11.4	80 ± 11.4	0 ± 3.9	

Results

- Lifestyle intervention:
  - No evidence of progressive disease or PSA increase
  - PSA decreased 4%
  - Growth of LNCaP prostate cancer cells (American Type Culture Collection, Manassas, Virginia)
    - Inhibited almost 8 times more by serum from the experimental than from the control group (70% vs 9%, $p < 0.001$).
    - Changes in serum PSA and also in LNCaP cell growth were significantly associated with the degree of change in diet and lifestyle.
- Control:
  - PSA increased 6%, $p = 0.016$
  - 4 experienced increase in PSA, 2 disease progression: entered standard therapy

Conclusion

- Intensive lifestyle changes may affect the progression of early, low grade prostate cancer in men. Further studies and longer term follow-up are warranted.

Question

- *Experimental serum seemed to contain something that differentially inhibited cell line growth but so what. Just because these serums were different does not mean that they were good. They might have also killed normal cells.*
- Although it is true that chemotherapy and radiation may kill normal as well cancerous cells, we are not aware of any evidence that fruits vegetables, whole grains, legumes and soy products kill normal cells. Indeed, (this) evidence suggests that substances present in these foods, such as lycopene, flavonoids, sulphoraphanes, omega-3 fatty acids, isoflavones, polyphenols, lignans and other substances, are protective of normal cells.
  - The significant correlation between degree of changes in diet and lifestyle and degree of change in PSA and LNCaP cell growth adds to the strength of evidence.

Follow-up

THE LANCET Oncology

Volume 14, No. 11, p1112–1120, October 2013

Articles

Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study

Prof Dean Ornish, MD, Jue Lin, PhD, Prof June M Chan, PhD, Elissa Epel, PhD, Colleen Kemp, RN, Prof Gerdi Weidner, PhD, Ruth Marlin, MD, Steven J Frenda, MA, Mark Jesus M Magbanua, PhD, Jennifer Daubenmier, PhD, Ivette Estay, PhD, Nancy K Hills, PhD, Nita Chainani-Wu, DMD, Prof Peter R Carroll, MD, Prof Elizabeth H Blackburn, PhD

Published Online: 17 September 2013

Summary: Background

- Telomere shortness in human beings is a prognostic marker of aging, disease, and premature morbidity.

Methods

- Follow-up study in men with biopsy-proven low-risk prostate cancer and had chosen to undergo active surveillance.
- Eligible participants were enrolled from previous studies.
  - Intervention: comprehensive lifestyle changes--diet, activity, stress management, and social support
  - Control: active surveillance.
- Biological correlates: blood samples at 5 years and compared relative telomere length and telomerase enzymatic activity per viable cell with those at baseline, and assessed their relation to the degree of lifestyle changes.

Results

- Relative telomere length increased from baseline in the lifestyle intervention group, but decreased in the control group (p=0·03).
- Adherence to lifestyle changes was significantly associated with relative telomere length after adjustment for age and the length of follow-up (p=0·005).
- At 5 years, telomerase activity had decreased from baseline by 0·25 (–2·25 to 2·23) units in the lifestyle intervention group, and by 1·08 (–3·25 to 1·86) units in the control group (p=0·64), and was not associated with adherence to lifestyle changes (relative risk 0·93, 95% CI 0·72–1·20, p=0·57).

Conclusion

- Comprehensive lifestyle intervention was associated with increases in relative telomere length after 5 years of follow-up compared with controls

Commentary

- This report undoubtedly will excite the aficionados and devotees of lifestyle changes for cancer but it should also give pause to the skeptics.
- For those of us taking care of patients with prostate cancer it will reinforce the use of lifestyle changes in management.
- For those of us living life, it will enhance interest in lifestyle medicine
  - Increase in data re: the impact of nutrition, physical activity, and stress reduction on favorable health outcomes

Question

- Even if scientific evidence is still meager, complementary medicine approaches have strong appeal in practicing the medical art since they *give the patient an active role in his care and promote an attitude of optimism and hope.*

Where to start?

- Identify your pressure points

Teach happiness

- What activities boost positive affect
  - Seek them
  - Practice them
  - Enjoy them
- Reducing your stress levels can not only make you feel better right now, but may also protect your health long-term.

Five Take Aways

- Identify what's causing stress
- Support and build strong relationships
- Step away from anger
- Rest
- Seek others

Thank you!

anamaria.lopez@Jefferson.edu