STRESS

HarborHolistic
COUNSELING

Stress

- Definition and types of stress
- Causes of stress
- Effects of stress
- Basic stress medical terminology
- Stress and your health: What the research says
- How to manage stress

Definition & Types of Stress

Harbor Holistic
COUNSELING

What is Stress?

- Stress (an experience):
  - The body's response to physical, mental, or emotional pressure.
- Distress (a feeling):
  - Emotional, social, spiritual, or physical pain or suffering that may cause a person to feel sad, afraid, depressed, anxious, or lonely, and feel unable to cope.
    - Cancer patients, for example, may feel distressed over their diagnosis, physical symptoms, and/or treatment.

Bench C, et al. Changes in regional cerebral blood flow on recovery from depression. *Psychol Med* 1995 Mar 25(2):247-261

Three Types of Stress

- According to the American Psychological Association, there are 3 types of stress:
  - Acute Stress
  - Episodic Acute Stress
  - Chronic Stress

American Psychological Association. https://www.apa.org/helpcenter/stress-kinds.aspx

Acute Stress

- Most common form of stress
- Comes from demands and pressures of the recent past and anticipated demands and pressures of the near future.
- Often normal: Like the stress associated with giving a presentation to a large group.

- Excess short-term stress can lead to:
  - Psychological/emotional distress
  - Muscular problems like tension headaches, back pain, jaw pain, etc.
  - Stomach, gut and bowel problems, like heartburn, diarrhea, constipation and IBS.
  - Transient symptoms like high blood pressure, rapid heart beat, chest pain, dizziness, etc.

American Psychological Association. https://www.apa.org/helpcenter/stress-kinds.aspx

Episodic Acute Stress

- Frequent acute stress – often related to personality.
- “Type A” personalities – competitive, aggressive, impatient, hurried
- “Worry warts” – always see disasters, foreboding calamities, etc

- Symptoms: Persistent tension headaches, migraines, hypertension, chest pain and heart disease.

American Psychological Association. https://www.apa.org/helpcenter/stress-kinds.aspx

Chronic Stress

- Long-term stress, often associated with life situations such as living in poverty, an abusive/unhappy marriage, a war-torn country or working in despised work conditions.
- Can also develop during childhood trauma that persists into adulthood.

- Has serious health effects.
- Can lead to:
  - Bad habits to cope (like smoking, drugs, alcohol, overeating)
  - Suicide
  - Violence
  - Heart attack
  - Stroke
  - Cancer Growth[2]

[1] American Psychological Association. https://www.apa.org/helpcenter/stress-kinds.aspx

[2] McDonald PG, Antoni MH, Lutgendorf SK, et al. A biobehavioral perspective of tumor biology. *Discovery Medicine* 2005;5(30):520-526.

Causes of Stress

Causes of Stress

- There is no one thing that causes stress. Everyone reacts differently to situations.
  - Think of the mother who happily and easily manages 4 children, versus the mother who is overwhelmed and stressed out with 1 child.
- Common Causes of Stress
  - Relationship Issues (especially divorce, living with abuse and/or drugs & alcohol)
  - Financial Issues
  - Work Issues
  - Health Issues (especially a potentially fatal diagnosis and chronic pain)
  - Parenting Issues (especially being a single parent)
  - Death (especially losing a family member)

Effects of Stress

HarborHolistic
COUNSELING

Effects of Stress

- Abnormal levels of stress can cause or contribute to[1]:
  - Anxiety disorders
  - Depression
  - Substance abuse
  - Skin rashes or hives
  - High blood pressure
  - Cardiovascular Disease
  - Certain GI diseases
  - Cancer
  - Headaches
  - Asthma
  - Fluctuations of blood sugar in people with diabetes.
- There also is scientific evidence showing that people experiencing psychological stress are more prone to developing colds and other infections.

[1] https://www.medicinenet.com/stress/article.htm#conclusions_about_the_effects_of_stress

Effects of Stress

- Memory can be affected
  - When stress occurs, the limbic system of the brain is affected, which impacts memory.
    - This is likely one reason why mothers often say they can't remember a thing!
- Pregnant mothers' stress levels affect their babies[1]
  - Stress hormones like cortisol pass through the blood to the fetus
  - Drugs, alcohol, nicotine and other chemicals from substances used to control the stress are also passed along to the fetus.

[1] Kolassa, Iris - Tatjana (2016). "Biological memory of childhood maltreatment – current knowledge and recommendations for future research" (PDF). *Ulmer Volltextserver - Institutional Repository der Universität Ulm*. doi:10.18725/OPARU-2420. Retrieved 30 March2014.

Basic Stress Medical Terminology

Harbor Holistic
COUNSELING

Stress Hormones

- Cortisol, epinephrine (also called adrenaline) and norepinephrine are released in your body under stressful conditions.
- Stress hormones can [1]:
  - Increase blood pressure
  - Increase blood sugar
  - Aid in the metabolism of fat, carbohydrates and protein
  - Decrease bone formation
  - *Suppress the immune system*

[1] Hoehn K, Marieb EN (2010). Human *Anatomy & Physiology*. San Francisco: Benjamin Cummings. ISBN 978-0-321-60261-9.

Stress Hormones

- Because stress hormones suppress the immune system, it makes people more prone to fall ill to infections (like flu), and have sleep problems, headaches, depression and anxiety.

Harbor Holistic COUNSELING

Dopamine

- Dopamine is a neurotransmitter. It works in various areas of your body (including in your blood vessels, kidneys and pancreas) but is most well known for the effects on your brain. It is associated with increased feelings of happiness and pleasure.
- In blood vessels, dopamine inhibits norepinephrine release.

Epigenetics

- Epigenetics is the study of why genes express
  - Epigenetics studies what factors (like stress, smoking, diet, etc) turn your genes "on" and "off".
- If you have a "bad" gene, like a mutation in a BRCA gene, it does not mean that you will get breast cancer – it means your risk is higher.
  - By age 70, ~50% of women with the BrCA gene will not have breast cancer[1], and by age 80, ~30% will not have breast cancer![2]
- However, if the BrCA gene is *expressed* (turned "on") then you will likely get breast cancer.
- Glucocorticoids (mainly cortisol), which are increased under stress, have been found to alter gene expression in the brain[5].

[1] Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers. *JAMA.* 2017;317(23):2402–2416. doi:10.1001/jama.2017.7112

2 National Cancer Institute. Genetics of breast and gynecologic cancers (PDQ®) - health professional version. https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq#link/_113_toc, 2018.

3 Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 25(11):1329-33, 2007.

4 Antoniou AC, Cunningham AP, Peto J, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer. 98(8):1457-66, 2008.

[5] Lee RS, Tamashiro KL, Yang X, et al. Chronic corticosterone exposure increases expression and decreases deoxyribonucleic acid methylation of Fkbp5 in mice. *Endocrinology*. 2010;151(9):4332-43.

Angiogenesis and VEGF

- Angiogenesis
  - Angio = vessels and Genesis = new, so angiogenesis means the creation of new blood vessels.
- VEGF (Vascular Endothelial Growth Factor) is like a signal that the body gives out to start producing new blood vessels under certain conditions.
  - Ex: When a blood vessel is blocked to the heart, the heart sends out a signal that it needs more oxygen, VEGF is increased, and new blood vessels – called collateral vessels – are formed around the blockage, allowing blood to get to the heart.
    - But VEGF can grow vessels that are harmful, such as blood vessels that feed tumors
  - For a tumor to grow >1mm, it requires angiogenesis.[1]

[1] Folkman J. Toward an understanding of angiogenesis: search and discovery. Perspect. Biol. Med. 1985;29(1):10–36.

Stress & Your Health

What the Medical Research Has to Say …

Harbor Holistic
COUNSELING

Stress and Cancer

- There is no strong evidence that stress directly affects cancer initiation. In other words, we don't have any proof that stress *causes* cancer.
- However, there is ample evidence that once cancer has been initiated, stress can cause it to progress and metastasize.[1]

[1] Moreno-Smith M, Lutgendorf SK, Sood AK. Impact of stress on cancer metastasis. *Future Oncol*. 2010;6(12):1863-81.

Stress Hormones and Cancer

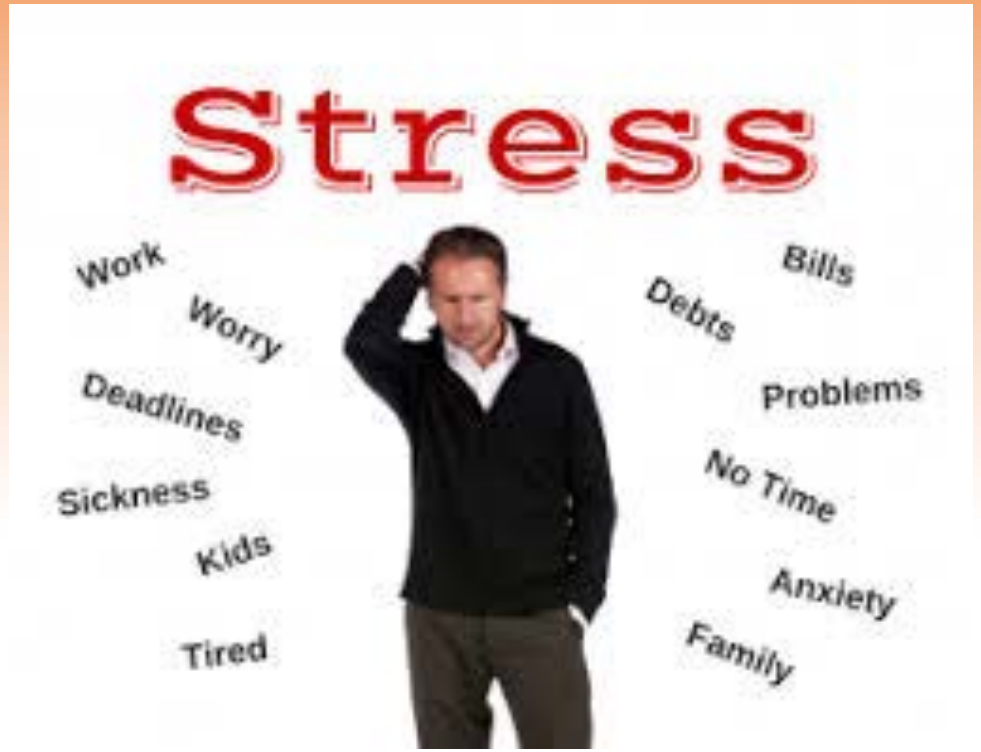
- Stress levels of norepinephrine increased the *in vitro* invasiveness of ovarian cancer cells by 89–198%.[1]

[1] Sood AK, Bhatty R, Kamat AA, et al. Stress hormone-mediated invasion of ovarian cancer cells. Clin. Cancer Res. 2006;12(2):369–375.

Harbor Holistic COUNSELING

Stress Hormones and Cancer

- Patients with cancer recurrence showed higher cortisol levels.[1]



[1]Thornton LM, Andersen BL, Carson WE., 3rd Immune, endocrine, and behavioral precursors to breast cancer recurrence: a case–control analysis. Cancer Immunol. Immunother. 2008;57(10):1471–1481.

Harbor Holistic COUNSELING

Stress Hormones and Cancer

- *During chronic stress situations, elevated levels of glucocorticoids (like cortisol) have been shown to be immunosuppressive.* Breast cancer patients with higher mean diurnal cortisol concentrations also showed suppressed immunity against commonly encountered antigens, suggesting blunting of the cellular immune response.[1,2]

[1]Vedhara K, Cox NK, Wilcock GK, et al. Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. Lancet. 1999;353(9153):627–631.
[2] Kiecolt-Glaser JK, Ricker D, George J, et al. Urinary cortisol levels, cellular immunocompetency, and loneliness in psychiatric inpatients. Psychosom. Med. 1984;46(1):15–23.

Stress Hormones and Cancer

- Epinephrine and norepinephrine bind to adrenergic receptors which has been linked to accelerated tumor growth in breast cancer.[1,2,3]

[1] Badino GR, Novelli A, Girardi C, et al. Evidence for functional β-adrenoceptor subtypes in CG-5 breast cancer cell. Pharmacol. Res. 1996;33(4–5):255–260.
[2] Vandewalle B, Revillion F, Lefebvre J. Functional β-adrenergic receptors in breast cancer cells. J. Cancer Res. Clin. Oncol. 1990;116(3):303–306.
[3] Marchetti B, Spinola PG, Pelletier G, et al. A potential role for catecholamines in the development and progression of carcinogen- induced mammary tumors: hormonal control of β-adrenergic receptors and correlation with tumor growth. J. Steroid Biochem. Mol. Biol. 1991;38(3):307–320.

Stress and Hormones and Cancer

- Catecholamine (stress hormone) levels in the ovaries are known to be increased in response to stress.[1-5]

[1] Lara HE, Porcile A, Espinoza J, et al. Release of norepinephrine from human ovary: coupling to steroidogenic response. Endocrine. 2001;15(2):187–192.
[2] Greenwald G, Roy S. Follicular development and its control. In: Knobil E, Neill J, editors. The Physiology of Reproduction. Raven Press; NY, USA: 1994. pp. 629–724.
[3] Nankova B, Kvetnansky R, Hiremagalur B, et al. Immobilization stress elevates gene expression for catecholamine biosynthetic enzymes and some neuropeptides in rat sympathetic ganglia: effects of adrenocorticotropin and glucocorticoids. Endocrinology. 1996;137(12):5597–5604.
[4] Paredes A, Galvez A, Leyton V, et al. Stress promotes development of ovarian cysts in rats: the possible role of sympathetic nerve activation. Endocrine. 1998;8(3):309–315.
[5] Lara HE, Dorfman M, Venegas M, et al. Changes in sympathetic nerve activity of the mammalian ovary during a normal estrous cycle and in polycystic ovary syndrome: studies on norepinephrine release. Microsc. Res. Tech. 2002;59(6):495–502.

Stress Hormones and Angiogenesis

- Both norepinephrine and epinephrine are elevated in ovarian and other peritoneal tissues in preclinical models of chronic stress. These hormonal increases were related to greater tumor burden, which was mediated by increased angiogenesis.[1]

[1] Thaker PH, Han LY, Kamat AA, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nat. Med. 2006;12(8):939–944. ■■ First study to demonstrate the impact of stress hormones on cancer angiogenesis.

Stress Hormones and Angiogenesis

- Studies have found that the stress hormone norepinephrine may promote angiogenesis and metastasis.[1]

[1] McDonald PG, Antoni MH, Lutgendorf SK, et al. A biobehavioral perspective of tumor biology. *Discovery Medicine* 2005;5(30):520-526.\

Stress Hormones and Angiogenesis

- Norepinephrine and epinephrine have been implicated in increasing VEGF levels.
- Norepinephrine has been shown to upregulate VEGF in adipose tissue, in ovarian cancer cell lines and in multiple myeloma cell lines.[1,2,3]

[1] Fredriksson JM, Lindquist JM, Bronnikov GE, et al. Norepinephrine induces vascular endothelial growth factor gene expression in brown adipocytes through a β-adrenoreceptor/cAMP/protein kinase-A pathway involving Src but independently of ERK1/2. J. Biol. Chem. 2000;275(18):13802–13811.
[2] Lutgendorf SK, Cole S, Costanzo E, et al. Stress-related mediators stimulate vascular endothelial growth factor secretion by two ovarian cancer cell lines. Clin. Cancer Res. 2003;9(12):4514–4521.
[3] Yang E, Donovan EL, Benson DM, Glaser R. VEGF is differentially regulated in multiple myeloma-derived cell lines by norepinephrine. Brain Behav. Immun. 2008;22:318–322.

Dopamine and Cancer

- Under chronic stress, dopamine levels are lower due to decreased release of dopamine.[1,2]
- In blood vessels, dopamine inhibits norepinephrine release.

[1] Puglisi-Allegra S, Imperato A, Angelucci L, et al. Acute stress induces time-dependent responses in dopamine mesolimbic system. Brain Res. 1991;554(1–2):217–222.
[2] Imperato A, Angelucci L, Casolini P, et al. Repeated stressful experiences differently affect limbic dopamine release during and following stress. Brain Res. 1992;577(2):194–199.

Depression and Cancer

- *Dopamine inhibits* VEGF-induced *angiogenesis* by suppressing VEGFR-2 phosphorylation.[1,2,3]

[1] Basu S, Sarkar C, Chakroborty D, et al. Ablation of peripheral dopaminergic nerves stimulates malignant tumor growth by inducing vascular permeability factor/vascular endothelial growth factor-mediated angiogenesis. Cancer Res. 2004;64:5551–5555.
[2] Chakroborty D, Sarkar C, Mitra RB, et al. Depleted dopamine in gastric cancer tissues: dopamine treatment retards growth of gastric cancer by inhibiting angiogenesis. Clin. Cancer Res. 2004;10(13):4349–4356.
[3] Sarkar C, Chakroborty D, Chowdhury UR, et al. Dopamine increases the efficacy of anticancer drugs in breast and colon cancer preclinical models. Clin. Cancer Res. 2008;14(8):2502–2510.

Depression and Cancer

- *Dopamine inhibits tumor growth* by suppressing the actions of VEGF on both tumor endothelial cells and bone marrow-derived endothelial progenitor cells.[1]

[1] Chakroborty D, Sarkar C, Basu B, et al. Catecholamines regulate tumor angiogenesis. Cancer Res. 2009;69(9):3727–3730.

ACE (Adverse Childhood Events) Study[1]

- Studied the effects of childhood trauma (Adverse Childhood Events) on 17,337 adults.
  - 10 categories of trauma were studied:
    - Physical abuse
    - Sexual abuse
    - Emotional abuse
    - Physical neglect
    - Emotional neglect
    - Exposure to domestic violence
    - Household substance abuse
    - Household mental illness
    - Parental separation or divorce
    - Incarcerated household member
  - The number of categories of these adverse childhood experiences was then compared to measures of adult risk behavior, health status, and disease.

[1] Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults: The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med* 1998;14(4)

ACE Study[1]

- Persons who had experienced four or more categories of trauma, compared to those who had experienced none, had a 4- to 12-fold increased health risk for alcoholism, drug abuse, depression, and suicide attempt.
- The more types of trauma, the higher the risks for ischemic heart disease, cancer, chronic lung disease, skeletal fractures, and liver disease.

[1] Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults: The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med* 1998;14(4)

ACE Study[1]

- BUT WHY???

STRESS!!!

[1] Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults: The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med* 1998;14(4)

Stress and Bad Habits

- Certain bad habits – particularly those that can affect your body's level of stress hormones and neurotransmitters – are increased under times of stress.

Harbor Holistic COUNSELING

Stress and Bad Habits

- For example, eating increases dopamine (the “happy” neurotransmitter in the brain), so this is why people often turn to food when stressed.
- Many drugs such as amphetamines (meth) and cocaine can lower the stress response and make the user feel better, which is likely why many trauma sufferers use drugs.

Mental Health and Cancer

- The results of 165 studies indicate that stress-related emotions like depression, hopelessness, helplessness, etc are associated with higher cancer incidence in initially healthy populations
- 330 studies noted poorer survival in cancer patients with negative emotions
- 53 studies found higher cancer mortality

[1] Chida Y, Hamer M, Wardle J, et al. Do stress-related psychosocial factors contribute to cancer incidence and survival? Nat. Clin. Pract. Oncol. 2008;5(8):466–475

Mental Health and Cancer

- Stressful life experiences are related to poorer cancer survival and higher mortality
- Stress-prone personality or unfavorable coping styles and negative emotional responses or poor quality of life were related to higher cancer incidence, poorer cancer survival and higher cancer mortality.
- Psychosocial factors are associated with a higher incidence of lung cancer and poorer survival in patients with breast, lung, head and neck, hepatobiliary, and lymphoid or hematopoietic cancers.

[1] Chida Y, Hamer M, Wardle J, et al. Do stress-related psychosocial factors contribute to cancer incidence and survival? Nat. Clin. Pract. Oncol. 2008;5(8):466–475

Harbor Holistic COUNSELING

Mental Health and Cancer

- Sustained negative moods (like helplessness, hopelessness and depression) may provide the strongest links to cancer progression.[1-4]
- This might be because …
  - They do not seek treatment when they become ill
  - They give up prematurely
  - They fail to adhere to therapy
  - They engage in risky behaviors such as drug use
  - They do not maintain a healthy lifestyle

[1] Everson SA, Goldberg DE, Kaplan GA, et al. Hopelessness and risk of mortality and incidence of myocardial infarction and cancer. Psychosom. Med. 1996;58(2):113–121.
[2] Stommel M, Given BA, Given CW. Depression and functional status as predictors of death among cancer patients. Cancer. 2002;94(10):2719–2727.
[3] Watson M, Haviland JS, Greer S, et al. Influence of psychological response on survival in breast cancer: a population-based cohort study. Lancet. 1999;354(9187):1331–1336.
[4] Buccheri G. Depressive reactions to lung cancer are common and often followed by a poor outcome. Eur. Respir. J. 1998;11(1):173–178.

Mental Health and Cancer

- Cancer patients with previous emotional problems face a 2.6 times greater hazard of dying than patients without prior problems over 19 months after diagnosis.

[1] Stommel M, Given BA, Given CW. Depression and functional status as predictors of death among cancer patients. Cancer. 2002;94(10):2719–2727.

Mental Health and Cancer

- Social isolation has been linked with increased rates of cancer mortality.[1]
  - 25% overall increased risk of cancer mortality
  - 39% increased risk of cancer mortality in women

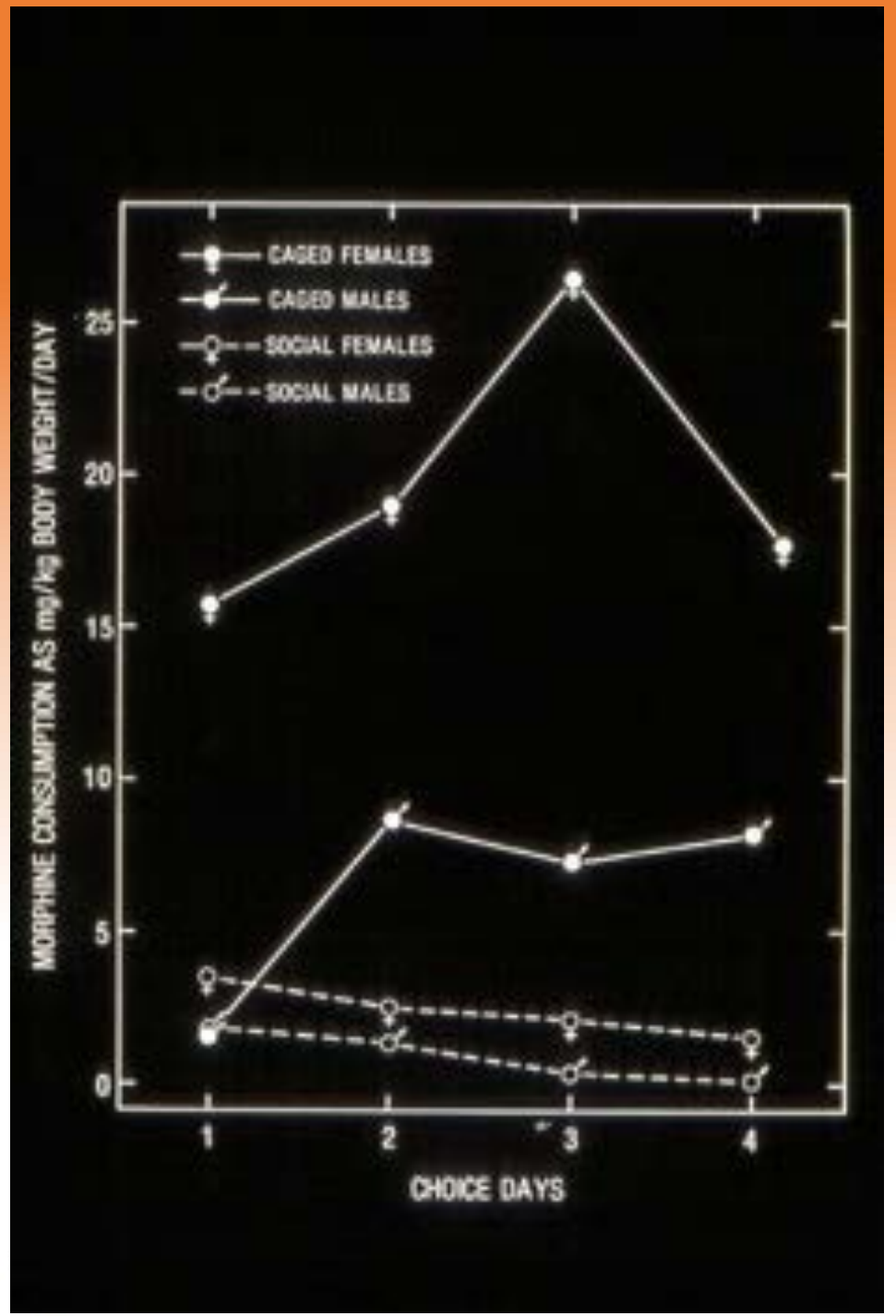
[1] Fleisch MA, Illescas AH, Hohl BC, Llanos AA. Relationships between social isolation, neighborhood poverty, and cancer mortality in a population-based study of US adults. *PLOS ONE*. 2017 Mar 8;12(3):e0173370. doi: 10.1371/journal.pone.0173370.

Rat Park Study

- Rats were isolated in cages or put into “rat park”.
  - Rat Park had lots of rats living together, allowing for socialization and mating, with exercise wheels and balls to play with and plenty of room.

[1] Alexander, B.K., Coambs, R.B., and Hadaway, P.F. (1978). "The effect of housing and gender on morphine self-administration in rats," *Psychopharmacology*, Vol 58, 175–179.

Rat Park Study



[1] Alexander, B.K., Coambs, R.B., and Hadaway, P.F. (1978). "The effect of housing and gender on morphine self-administration in rats," *Psychopharmacology*, Vol 58, 175–179.

In Summary…

The following stress-related factors have been linked to worse cancer outcomes, including increased recurrence, decreased survival and increased risk of death:

- ↑Epinephrine
- ↑ Norepinephrine
- ↑ Cortisol
- ↑ Angiogenesis

The following factors have been linked to better cancer outcomes:

- ↑Dopamine
- ↑ Social Support

Harbor Holistic COUNSELING

How to Manage Stress

Factors Influencing Your Ability to Handle Stress

- Adequate social support
- Your nutritional status
- Emotional well-being
- Overall health and fitness levels
- The amount of sleep and rest you get

Harbor Holistic Counseling

How to Lower Stress Levels

- Build strong relationships and social supports. Social support and stress reduction are associated with lower cortisol levels.[1]
- High levels of social support have been linked to improved clinical outcomes in cancer patients.[2-4]

[1] Moreno-Smith M, Lutgendorf SK, Sood AK. Impact of stress on cancer metastasis. *Future Oncol*. 2010;6(12):1863-81.
[2] Funch DP, Marshall J. The role of stress, social support and age in survival from breast cancer. J. Psychosom. Res. 1983;27:77–83. [PubMed]
[3] Marshall JR, Funch DP. Social environment and breast cancer. A cohort analysis of patient survival. Cancer. 1983;52(8):1546–1550. [PubMed]
[4] Maunsell E, Brisson J, Deschenes L. Social support and survival among women with breast cancer. Cancer. 1995;76(4):631–637. [PubMed]

Eat an “Epigenetic Diet”

- The following foods have been shown to likely contribute to positive epigenetic alterations and possibly reverse abnormal epigenetic states:
  - Green tea
  - Grapes
  - Peanuts
  - Mulberries
  - Cranberries
  - Blueberries
  - Turmeric
  - Curry
  - Soy Beans
  - Fava Beans
  - Broccoli
  - Cabbage
  - Kale
  - Watercress
  - Brazilian nuts
  - Chicken & meat*
  - Garlic
  - Beans
  - Grains
  - Fortified breakfast cereals
  - Pastas
  - Green vegetables
  - Coffee
  - Cashews
  - Tomatoes
  - Parsley
  - Milk Thistle
  - Rosemary

Hardy TM, Tollefsbol TO. Epigenetic diet: impact on the epigenome and cancer. *Epigenomics*. 2011;3(4):503-18.

* Have selenium, but chicken and meat have been associated with heart disease and cancer, so best to get selenium from Brazil nuts.

How to Lower Stress Levels

- Get help
  - Find a counselor or psychologist in your area, ideally one who specializes in your situation (health-related stress, marital strife, family issues, work issues, etc)
- Get group support
  - There are many support groups for all kinds of issues. It can be very comforting to meet other people who are going or have gone through the same thing(s) you are facing. Such people can provide insight and help that others won't be able to give.

How to Lower Stress Levels

- Get plenty of exercise
  - Get out in nature – walk in the park
  - “Ground” yourself by walking barefoot (or sitting or lying so your bare skin touches the ground)

How to Lower Stress Levels

- Rest your mind/Get good sleep
  - Cut back on caffeine
  - Remove distractions from your bedroom like TVs, computers, etc.
  - Go to bed at the same time each night

How to Lower Stress Levels

- Learn to meditate
- Do yoga
- Cultivate your spiritual/religious practice

Harbor Holistic
COUNSELING

Harbor Holistic
COUNSELING