Lecture 15: Psychophysiology of Stresses and Illnesses, Diseases, Health and Well-being

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Stress is a term in psychology and biology, borrowed from physics and engineering and first used in the biological context in the 1930s, which has in more recent decades become commonly used in popular parlance. It refers to the consequence of the failure of an organism — human or other animal — to respond adequately to mental, emotional, or physical demands, whether actual or imagined.

Signs of stress may be cognitive, emotional, physical, or behavioral. Signs include poor judgment, a general negative outlook, excessive worrying, moodiness, irritability, agitation, inability to relax, feeling lonely, isolated or depressed, acne, aches and pains, diarrhea or constipation, nausea, dizziness, chest pain, rapid heartbeat, eating too much or not enough, sleeping too much or not enough, social withdrawal, procrastination or neglect of responsibilities, increased alcohol, nicotine or drug consumption, and nervous habits such as pacing about, nail-biting, and neck pains.

The term stress was first employed in a biological context by the endocrinologist Hans Selye in the 1930s. He later broadened and popularized the concept to include inadequate physiological response to any demand. In his usage stress refers to a condition and stressor to the stimulus causing it. It covers a wide range of phenomena, from mild irritation to drastic dysfunction that may cause severe health breakdown.

Hans Selye

Hans Selye was born in Vienna in 1907. As early as his second year of medical school (1926), he began developing his now-famous theory of the influence of stress on people's ability to cope with and adapt to the stresses of injury and disease. He discovered that patients with a variety of ailments manifested many similar symptoms, which he ultimately attributed to their bodies' efforts to respond to the stresses of being ill. He called this collection of symptoms — this separate stress disease — stress syndrome, or the general adaptation syndrome (GAS).

He spent a lifetime in continuing research on GAS and wrote some 30 books and more than 1,500 articles on stress and related problems, including Stress Without Distress (1974) and The Stress of Life (1956). So impressive have his findings and theories been that some authorities refer to him as "the Einstein of medicine.

A physician and endocrinologist with many honorary degrees for his pioneering contributions to science, Selye also served as a professor and director of the Institute of Experimental Medicine and Surgery at the University of Montreal. More than anyone else, Selye has demonstrated the role of emotional responses in causing or combating much of the wear and tear experienced by human beings throughout their lives. He died in 1982 in Montreal, where he had spent 50 years studying the causes and consequences of stress.
In 1926, a young medical student named Hans Selye noticed that patients in the early stages of infectious diseases exhibited similar symptoms, regardless of the type of disease they had. He later observed a set of three common responses that occurred whenever any organism was injected with a toxic substance:

1. the adrenal glands enlarged,
2. the lymph nodes and other white blood cell producing organs swelled at first then shrank, and
3. bleeding appeared in the stomach and intestines.

He called these three common responses the General Adaptation Syndrome and proposed that certain changes take place within the body during stress that disrupt normal physiologic mechanisms and trigger an array of diseases. And no matter what type of organism he looked at, from rats and monkeys to humans, he noticed that physical and emotional stress induced a pattern that, if left untreated, always leads to infection, illness, disease, and eventually death.

Stage 1. Alarm Reaction: Any physical or mental trauma will trigger an immediate set of reactions that combat the stress. Because the immune system is initially depressed, normal levels of resistance are lowered, making us more susceptible to infection and disease. If the stress is not severe or long-lasting, we bounce back and recover rapidly.

Stage 2: Resistance: Eventually, sometimes rather quickly, we adapt to stress, and there's actually a tendency to become more resistant to illness and disease. Our immune system works overtime for us during this period, trying to keep up with the demands placed upon it. We become complacent about our situation and assume that we can resist the effects of stress indefinitely. Therein lies the danger. Believing that we are immune from the effects of stress, we typically fail to do anything about it.

Stage 3: Exhaustion: Because our body is not able to maintain homeostasis and the long-term resistance needed to combat stress, we invariably develop a sudden drop in our resistance level. No one experiences exactly the same resistance and tolerance to stress, but everyone's immunity at some point collapses following prolonged stress reactions. Life sustaining mechanisms slow down and sputter, organ systems begin to break down, and stress-fighting reserves finally succumb to what Selye called “diseases of adaptation.”

The General Adaptation Syndrome is thought to be the main reason why stress is such an abundant source of health problems. By changing the way our body normally functions, stress disrupts the natural balance - the homeostasis - crucial for well-being. It can also subtract years from our lives by speeding up the aging process.

Resistance is the name of the game when it comes to disease. Stress is one of the most significant factors in lowering resistance and triggering the various mechanisms involved in the disease process. By learning relaxation and stress management techniques, we can improve our overall health as well as our odds of living a disease-free life.

**Stress is not always bad**

Selye: eustress and distress

Selye published in 1975 a model dividing stress into eustress and distress. Where stress enhances function (physical or mental, such as through strength training or challenging work), it may be considered eustress. Persistent stress that is not resolved through coping or adaptation, deemed distress, may lead to anxiety or withdrawal (depression) behavior. The difference between experiences that result in eustress and those that result in distress is determined by the disparity between an experience (real or imagined) and personal expectations, and resources to cope with the stress. Alarming experiences, either real or imagined, can trigger a stress response.
Lazarus: cognitive appraisal model

Lazarus argued that, in order for a psychosocial situation to be stressful, it must be appraised as such. He argued that cognitive processes of appraisal are central in determining whether a situation is potentially threatening, constitutes a harm/loss or a challenge, or is benign. Both personal and environmental factors influence this primary appraisal, which then triggers the selection of coping processes. Problem-focused coping is directed at managing the problem, whereas emotion-focused coping processes are directed at managing the negative emotions.

Secondary appraisal refers to the evaluation of the resources available to cope with the problem, and may alter the primary appraisal. In other words, primary appraisal includes the perception of how stressful the problem is and the secondary appraisal of estimating whether one has more than or less than adequate resources to deal with the problem that affects the overall appraisal of stressfulness. Further, coping is flexible in that, in general, the individual examines the effectiveness of the coping on the situation; if it is not having the desired effect, s/he will, in general, try different strategies.

It is now well recognized that socio-economic and political problems, pollutions and securities have caused us anxiety, and stresses, both physical and mental stresses, and disturb our health and quality of life. Stresses also cause illnesses and degeneration of various body organ systems e.g. hypertension, coronary heart diseases (CHD), myocardial infarction, heart attacks, cerebro-vascular accidents (CVA), strokes, peptic ulcers, head aches, joint and back pains, diabetic mellitus type II and become risk factors for cancers and allergies etc.

Stresses and anxieties disturb brain functions, learning and memory, decision making and judgment, and working efficiencies. Stresses produce emotional and behavioral disturbances. Prolonged, chronic and severe stress may lead to depression, or emotional aggression, hostility and violence behavior. Conflicts and stresses can lead to smoking, drinking of alcohol and non-prescribed drug and narcotic uses and suicidal or homicidal.
### Causative Factors of Stresses and tension:

1. **Environmental Factors**
   - Physical, Chemical and Biological Pollutions

2. **Psycho-Social factors**
   - Adaptation to Life events
   - Deprivation or Overloading and Over Burden
   - Conflicts and Frustration

3. **Biological factors**
   - Genetic or developmental abnormalities
   - Nutritional Disturbance or Abnormal Biorhythms

4. **Personality, Behavioral patterns and Life styles:**
   - Attitude, Anxiety, Behavioral Patterns
   - e.g. Type A-Personality or Behavior

5. **Economic, Political, Security & Stability Problems**

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**Psychophysiological model of the stress response**

This acute response is not typically problematic.

*Chronically, however, it’s a different story...*

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**What is Stress?**

- **Stress**
  - the process by which we perceive and respond to certain events, called stressors, that we appraise as threatening or challenging

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**Stressful Life Events**

- **Catastrophic Events**
  - earthquakes, combat stress, floods

- **Life Changes**
  - death of a loved one, divorce, loss of job, promotion

- **Daily Hassles**
  - rush hour traffic, long lines, job stress, burnout

- **Perceived Control**
  - loss of control can increase stress hormones

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**Stress and Control**

- Animal studies of control and helplessness

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What is Stress?

- **Burnout**
  - physical, emotional and mental exhaustion brought on by persistent job-related stress
- **Coronary Heart Disease**
  - clogging of the vessels that nourish the heart muscle
  - leading cause of death in the United States

Stress and Disease

- **Psychosomatic Disease**
  - psychologically caused physical symptoms
- **Psychophysiological Illness**
  - “mind-body” illness
  - any stress-related physical illness
  - distinct from hypochondriasis – misinterpreting normal physical sensations as symptoms of a disease
The stress-illness correlation

Stress-Illness Relationship

- Preexisting physiological or psychological vulnerability
- Exposure to stress
- Physiological & psychological wear and tear
- Behavioral changes & Coping efforts
- Illness precursors, symptoms
- Illness

Stress and Depression

- 3-6 months before the onset of depression, 50%-80% of individuals experience a major life event.
- 20%-25% of people who experience a major stressful event develop depression.
- Increased stress is linked to longer duration of depression, exacerbation of symptoms, and relapse.
- Positive effect of treatment is reduced with ongoing stressful events.

Stress and Cardiovascular Disease

- Ongoing SAM activation leads to myocardial ischemia and activation of inflammatory and coagulatory responses.
- ~50% increase in CVD risk is associated with high levels of work stress.
- Traumatic events also increase CVD risk.

Stress and HIV/AIDS

- Among HIV-positive men, each additional moderately severe event increased by 50% the risk of progression to AIDS.
- Stress affects the course of viral conditions to which HIV-positive people are especially vulnerable.
Stress and Cancer

- Animal studies demonstrate a link between stress and tumor growth and metastasis.
- Prospective human studies show mixed results.
- It is likely that stress affects cancers related to antiviral immunity and hormonal activity, such as cervical cancer, hepatocarcinoma, and HIV-related cancers.

Stress & Coronary Heart Disease

- **Type A**
  - Friedman and Rosenman's term for people who are competitive, hard-driving, impatient, verbally aggressive, anger-prone
- **Type B**
  - Friedman and Rosenman's term for easygoing, relaxed people

Stress and Disease

- **Lymphocytes**
  - two types of white blood cells that are part of the body’s immune system
  - B lymphocytes form in the bone marrow and release antibodies that fight bacterial infections
  - T lymphocytes form in the thymus and, among other duties, attack cancer cells, viruses and foreign substances

- **Conditioning of immune suppression**

- **Negative emotions and health-related consequences**
  - Unhealthy behaviors (smoking, drinking, poor nutrition and sleep)
  - Heart disease
  - Immune suppression
  - Autonomic nervous system affects (headaches, hypertension)
The Stress Effect

Stress and Health:

The Signs and Symptoms of Stress:
- The Emotional Symptoms
- The Physical Symptoms
- The Behavioural Symptoms
- The Mental and Cognitive Symptoms
- Common Health Problems

The Emotional Symptoms

Anxiety  Nervousness  Worry
Depression  Anger  Irritability
Guilt  Moodiness  Loss of Enjoyment
Loneliness  Isolation  Loss of Humor
Feeling tearful
Lack of Confidence
Dissatisfaction with own life
The Physical Symptoms

Feeling Restless, Feeling uptight, Feeling Jumpy
Hypertension, Palpitation, Headache
Muscle tension in the neck and the back
Pain and ache, Poor Sleep and Insomnia
Fatigue, Lack of energy, Dry mouth
Weakness, Dizziness, Trembling
Grinding of teeth, Frequent Urination
Diarrhea or Constipation, Cramp
Butterflies in the Stomach, Faint
Loss or increasing appetite, Tinnitus

The Behavioural Symptoms

Impatience, Impulsiveness, Hyperactivity
Short temper, Aggressiveness, Violence
Become accident-prone, Avoid Difficult Situation
Increase Smoking, Alcohol abuse
Use of prescribed drugs
Use of non-prescribed, illegal drugs
Absenteeism, Poor work performance
Loss of sexual drive, Being uncooperative
Overworking, Compulsions and Obsessions

The Mental and Cognitive Symptoms

Difficulty concentrating
Frequent lapse in memory
Constant negative thinking and attitude
Hypercritical with oneself and others
Inability to make appropriate decision
Difficulty getting thing done
Increase susceptibility to oneself
Distorted ideas
Very rigid attitudes
New links to stress:

- Type 2 Diabetes mellitus
- Obesity and Metabolic syndrome
- Cancer
- Autoimmune disorders e.g. SLE
- Many skin disorders

Common Health Problems

Hypertension, and strokes

Angina pectoris, Coronary Heart Diseases, and myocardial infarction and Heart attack

Tension Headache, and Migraines

Neck and back pains, Fibromyalgia

High susceptibility to colds and flu

Stomach disorders, Irritable bowel syndromes, and ulcers

Asthma and Allergies

Skin rashes

etc..
Traumatic Experience
PTSD: Post-traumatic Stress Disorders

Stress results in release of adrenocorticotrophic hormone (ACTH) from the pituitary into the general bloodstream, which results in secretion of cortisol and other glucocorticoids from the adrenal cortex. The related compound cortisone is frequently used as a key anti-inflammatory component in drugs that treat skin rashes and in nasal sprays that treat asthma and sinusitis. Recently, scientists realized the brain also uses cortisol to suppress the immune system and reduce inflammation within the body. These corticoids involve the whole body in the organism’s response to stress and ultimately contribute to the termination of the response via inhibitory feedback.

Corticosteroids
- Three classes (by effect):
  - Glucocorticoids
  - Mineralcorticoids
  - Androgenic steroids
Glucocorticoids

- Regulate fat, glucose, protein metabolism
- Catecholamine and β-adrenergic receptor synthesis
- Maintain vascular tone and cardiac contractility
- Control endothelial integrity/vascular permeability

**Glucocorticoids**

- **Cortisol**
  - Controlled by HPA axis
  - Hypothalamus ➔ CRH and arginine vasopressin in circadian rhythm (max 2-4am)
  - Anterior Pituitary ➔ ACTH
  - Adrenal cortex ➔ cortisol
  - Peak @ 8am; declines throughout day

**Mineralcorticoids**

- Regulated via renin-angiotensin system & serum potassium levels
  - Diminished GFR ➔ juxtaglomerular apparatus release of prorenin
  - Aldosterone release ➔ Na & H₂O resorption at distal tubules (K is lost)
  - Minor hyperkalemia can stimulate aldosterone secretion directly

**Adrenal Androgens**

- Controlled by ACTH
- Diurnal pattern (like cortisol)
- Significant source of androgens in females
  - Can cause signs/symptoms seen in adrenal insufficiency
The stress system is among the most important and highly preserved systems in the organism. It is located and functions in both the central nervous system (CNS) and the periphery. Several external or internal stressful stimuli or stressors in association with higher cortical functions integrate and act at the level of the hypothalamus and the brain stem to activate the stress system. The latter maintains a basal circadian tone and responds to stressors in an appropriate attempt to maintain homeostasis. The CNS components of the stress system are the corticotrophin-releasing hormone (CRH)/arginine vasopressin (AVP) and locus ceruleus-noradrenaline (LC NA)/autonomic, mainly sympathetic, neurons of the hypothalamus and brainstem, respectively. The main effectors of the stress system include CRH, AVP, propiomelanocortin-derived peptides, glucocorticoids, and the catecholamines norepinephrine and epinephrine. Adequate responsiveness of the stress system to stressors is responsible for attaining homeostasis and achieving a sense of well-being.

The adaptive or stress response depends not only on the intensity of the stressor but also on the inherent ability of the stress system to achieve and maintain an appropriate level and duration of activity.

The stress response is influenced by both genetic and developmental factors.

Nosologic disorders of homeostasis develop when there is an inappropriate level or duration response of the stress system to stressors.

Inadequate or excessive and/or too brief or prolonged stress responses can be deleterious to the organism.

The state of achieving survival at the expense of the psychologic and somatic well-being of an individual is called chronic dyshomeostasis or allostatic, or, even more to the point, cacostasis.

Cacostasis accounts for major endocrine, metabolic, autoimmune, and psychiatric disorders.

The main central nervous system (CNS) components of this system are the corticotrophin-releasing hormone (CRH)/arginine-vasopressin (AVP) and locus ceruleus-noradrenaline (LC-NA)/autonomic (mainly sympathetic) neurons of the hypothalamus and brain stem (Chrousos, 1995). These respectively regulate the peripheral activities of the hypothalamic-pituitary-adrenal (HPA) axis and the systemic/adrenomedullary sympathetic nervous systems (SNS) (Chrousos and Gold, 1992).

Activation of the HPA axis and LC-NA/autonomic system result in systemic elevations of glucocorticoids and catecholamines (Cas), which together with other products of the stress system, influence a variety of adaptive responses both at their baseline levels and/or at elevated levels which are encountered during the stress response (Elenkov et al., 1999).

The frontal lobe and the Hypothalamus control the body responses and emotions through the somatic motor system, the autonomic nervous system and the endocrine system.
During stress, cardiac output, and respiration are enhanced and blood flow is redirected to provide the highest perfusion to the brain and musculoskeletal system. The brain focuses on the perceived threat and stimulates behaviors that propel the organism to act accordingly (Habib et al., 2000).

Endocrine programs of growth and reproduction are suppressed in order to save energy; catabolism is enhanced and fuel is used to supply the brain, heart, and muscles accompanied by increases in glucose levels, heart rate, and blood pressure (Chrousos and Gold, 1992).

In addition, stress induces a state of immunomodulation particularly inhibiting innate and cellular immunity and favoring humoral immunity. In certain tissues, activation of the sympathetic system and the peripheral CRH-mast-cell-histamine axis, induces early pro-inflammatory activity, which has been referred to as neurogenic inflammation (Elenkov and Chrousos, 2002).

This new understanding helps explain some well-known, but often contradictory, effects of stress on a variety of infectious, autoimmune / inflammatory, allergic, metabolic, adaptive, and neoplastic diseases.

**ORGANIZATION OF THE STRESS SYSTEM:**
The brain circuits that initiate and maintain the stress response are the HPA axis and the SNS are the afferent limbs of the stress system, whose main function is to maintain basal and stress-related homeostasis (Chrousos and Gold, 1992; Chrousos, 1995). The central components of this system are located in the hypothalamus and the brain stem. They include the paraventricular neurons of the paraventricular nuclei (PVN) of the hypothalamus that release CRH and AVP, the CRH neurons of the paragigantocellular and parabrachial nuclei of the brain stem, and the A1, A2, A3, and A6 (locus ceruleus, LC) mostly noradrenergic (NE) cell groups of the pons and medulla (the LC-NE system) (Chrousos and Gold, 1992). Paraventricular CRH neurons project to and innervate proopiomelanocortin (POMC)-containing neurons of the central stress system in the arcuate nucleus of the hypothalamus, as well as neurons of pain control areas of the hind brain and spinal cord.

**Psychoneuroendocrinology (PNE)**

The hypothalamic-pituitary-adrenocortical (HPA) axis, neuroendocrine (NE), cholinergic (ACh), mesolimbic (DA), and GABAergic systems work in concert to elicit the hypothalamic–pituitary–adrenal (HPA) axis and to alter the release of corticotropin-releasing factor (CRF), which stimulates release of ACTH from the anterior pituitary, which in turn stimulates release of glucocorticoids from the adrenal cortex. Glucocorticoid feedback occurs at all levels of the axis.
Activation of the stress system leads to CRH-induced secretion of POMC-derived and other opioid peptides, which enhance analgesia (Chrousos, 1995). These peptides also simultaneously inhibit the activity of the stress system by suppressing CRH and NE secretion (Chrousos and Gold, 1992). CRH and AVP synergistically stimulate the secretion of corticotrophin (ACTH) hormone by the corticotroph cells of the anterior pituitary. This in turn stimulates adrenal steroidogenesis (mainly cortisol and androgens). CRH and AVP may act synergistically on other target tissues as well, both in the CNS and the periphery (Chrousos and Gold, 1992).

Every hour, the parvocellular neurons secrete two or three mostly synchronous pulses of CRH and AVP into the hypophyseal portal system. In early morning, the amplitudes of these pulses are highest, increasing the amplitude and apparent frequency of ACTH and cortisol secretory episodes (Chrousos and Gold, 1992; Chrousos, 1995). During acute stress, the amplitude of CRH and AVP pulses also increases, resulting in increases in the amplitude and apparent frequency of ACTH and cortisol pulses. In this case, the stress system recruits additional secretagogues of CRH, AVP, or ACTH, such as magnocellular AVP, and angiotensin II (Elenkov et al., 1999).

Circulating ACTH of pituitary origin is the key regulator of glucocorticoid secretion from cells of the adrenal gland’s zona fasciculata. Other hormones, including Cas, neuropeptide Y (NPY), and CRH are produced by the adrenal medulla and additional autonomic neural input to the adrenal cortex also influences glucocorticoid secretion (Elenkov et al., 1999).

The Locus Ceruleus (LC-NE) system controls stress-induced stimulation of the arousal system as well as of the systemic sympathetic and sympathoadrenal nervous systems. The SNS, which originates in nuclei within the brain stem, gives rise to preganglionic efferent fibers that leave the CNS through the thoracic and lumbar spinal nerves (“thoracolumbar system”). Although this review will not address the parasympathetic nervous system (PSNS), it should be noted that it also participates in the stress response. Thus, Barrington’s nucleus, the nucleus tractus solitarius, and the dorsal motor vagal nucleus, all components of the PSNS, control the differential activation of vagal and sacral parasympathetic efferent nerves that mediate gut responses to stress (Habib, Gold, and Chrousos, 2001). Furthermore the PSNS may facilitate or inhibit the effects of the SNS by respectively decreasing or increasing its activity.
The LC-NA system activates and is activated by the amygdala, which, acting in conjunction with the hippocampus and the anterior cingulate and prefrontal cortices, mediate focused attention of a perceived threat, define the affective state of the individual and regulate fear-related behaviors (Brown et al., 1982). Most of the sympathetic preganglionic fibers terminate in ganglia located in the paravertebral chains that lie on either side of the spinal column; the remaining preganglionic sympathetic neurons terminate in prevertebral ganglia, which lie in front of the vertebrae (Chrousos and Gold, 1992). From these ganglia, postganglionic sympathetic fibers run to the tissues innervated by the SNS. Most postganglionic sympathetic fibers release NE. However, subpopulations of neurons also secrete other active substances including CRH, neuropeptide Y (NPY), somatostatin, and inflammatory mediators (Chrousos and Gold, 1992). In contrast to the SNS, the main neurotransmitter that mediates the action of the PSNS is acetylcholine (Habib, Gold, and Chrousos, 2001).

The adrenal medulla contains chromaffin cells, embryologically and anatomically homologous to the sympathetic ganglia but unlike the postganglionic sympathetic nerve terminals, releases mainly epinephrine, and to a lesser extent NE in an approximate ratio of 4:1. Typical preganglionic sympathetic nerve terminals, whose main neurotransmitter is acetylcholine, innervate the chromaffin cells of the adrenal medulla (Chrousos, 1998).

Role of stress system in maintaining basal and stress-related homeostasis
1. The stress system has a baseline, circadian activity, but also responds on demand to physical and emotional stressors through CRH, glucocorticoids and Cas.
2. These substances are major regulators of behavior, metabolism, cardiovascular function and thermogenesis, and adjust these functions according to the needs of the organism.
3. The stress system integrates and responds to a great diversity of distinct circadian, neurosensory, blood-borne, and limbic signals.
4. Functionally, the CRH/AVP and LC-NE systems seem to participate in a positive, reverberating feedback loop, so that activation of one system tends to activate the others as well. This includes projections of CRH- and AVP-secreting neurons from the lateral PVN to the central sympathetic regions in the brainstem, and conversely, projections of catecholaminergic fibers from the LC-NE system, via the ascending noradrenergic bundle, to the PVN in the hypothalamus.
5. Thus, CRH and AVP stimulate norepinephrine secretion through their specific receptors, while norepinephrine stimulates CRH and AVP secretion through primarily α1-noradrenergic receptors. Autoregulatory, ultrashort negative feedback loops are also present in these neurons, with CRH and norepinephrine collateral fibers acting in an inhibitory fashion on presynaptic CRH and α2-noradrenergic receptors, respectively.
The endocrine component of the stress system

1. Glucocorticoids. Glucocorticoids, the final products of HPA axis stimulation, are pleiotropic hormones and exert their effects via ubiquitously distributed intracellular receptors.

2. The glucocorticoid receptor is a cytoplasmic protein with three major functional domains and several subdomains.

3. The nonactivated glucocorticoid receptor resides in the cytosol in the form of a hetero-oligomer with heat shock proteins and immunophilins. The carboxyterminal region binds glucocorticoid and the middle portion binds DNA with high affinity, thereby recruiting transcriptional co-activators. The amino-terminal portion of the receptor can interact with glucocorticoid-responsive genes (glucocorticoid-response elements).

4. The activated receptors also inhibit, by protein-protein interactions, several transcription factors, such as activator protein-1 (AP-1) which comprises c-jun/c-fos, and NF-kB, which are positive regulators of the transcription of several genes involved in the function and growth of nonimmune and immune cells. They also change the stability of mRNAs and, hence, the translation rate of several glucocorticoid-responsive genes and proteins.
Stress and Cognition

- Under stress, people may have difficulty thinking clearly or remaining focused on the task at hand.

- High levels of bodily arousal that characterize the alarm reaction stage can impair memory functioning and problem solving ability (example: test anxiety).

- Chronic long-term high levels of stress can be linked to neuro-degenerative disorders such as dementia and Alzheimer’s disease etc.
Clinical Features

- Slowly progressive from 2-10 years
- Normal → mild cognitive impairment (MCI) → AD
- Dementia with anterograde amnesia predominates
- Memory loss → interference with daily life → rigid, mute, incontinence & bedridden → death
- Imaging: diffused or posteriorly predominate cortical and hippocampal atrophy

PET scan using Pittsburgh Compound-B

Corticosterone Titers in Young (3-5 mos) and Aged (24-28 mos) Fischer 344 Rats, during and after 1 hr of immobilization stress

11.17 Neuronal degeneration associated with stress. The hippocampal regions between the arrow in a normal monkey (a) and a monkey subjected to stress (b) show large deficits in the number of pyramidal cells present in the striped monkey compared with the normal monkey. From Kuo et al., 1989.
Personality: Personality is the particular combination of emotional, attitudinal, and behavioral response patterns of an individual.

Factors describing individual’s personality:
- Intellectual abilities
- Motivation
- Emotional reactivity
- Attitude, belief
- Moral values
- Talent, skills etc..

Development of Personality:
Factors: Genetics + Biological Foundation
Common Experience: e.g., Culture, Gender roles, Occupation
Specific Individual Experiences: e.g., Parental roles
Personality

Psychological Viewpoints:
Social Conditions
Physical Conditions
Personality
Consistent patterns of behaviors

Personality: Characteristic patterns of behavior and modes of thinking that determine an individual’s adjustment or adaptation to the environment.
- Individual’s most striking characteristics
- Individual differences
Approaches to understanding (or theories) of Personality:

1. The Trait > Traits
2. Psychoanalytical > id, ego, superego
3. Social-learning > learned habits
4. Humanistic > Self concepts
5. Neurobiological > Specific Brain areas and functional differences between individuals
6. Genomics > Genes

Trait theory is a major approach to the study of human personality. Trait theorists are primarily interested in the measurement of traits, which can be defined as habitual patterns of behavior, thought, and emotion. According to this perspective, traits are relatively stable over time, differ across individuals (e.g., some people are outgoing whereas others are shy), and influence behavior.

Gordon Allport was an early pioneer in the study of traits, which he sometimes referred to as dispositions. In his approach, central traits are basic to an individual's personality, whereas secondary traits are more peripheral. Common traits are those recognized within a culture and may vary between cultures. Cardinal traits are those by which an individual may be strongly recognized. Since Allport's time, trait theorists have focused more on group statistics than on single individuals. Allport called these two emphases "nomothetic" and "idiographic," respectively.

There is a nearly unlimited number of potential traits that could be used to describe personality. The statistical technique of factor analysis, however, has demonstrated that particular clusters of traits reliably correlate together. Hans Eysenck has suggested that personality is reducible to three major traits. Other researchers argue that more factors are needed to adequately describe human personality. Many psychologists currently believe that five factors are sufficient.

Virtually all trait models, and even ancient Greek philosophy, include extraversion vs. introversion as a central dimension of human personality. Another prominent trait that is found in nearly all models is Neuroticism, or emotional instability.

Carl Jung, 1940 proposed to call 2 opposite traits:
- Introverts.....withdraw to himself in times of emotional stress and conflicts, shy, like to work alone.
- Extroverts.....Seek company of others, very or too sociable

Personality describes by individual’s position on a number of continuous dimensions or scale, each of which represents a trait.

- Measurable variables (Traits)
- Persisting
- Individual differences
- Personality Inventory e.g.

Minnesota Multiphasic Personality Inventory (MMPI)
Eysenck Personality Inventory (EPI)
Hans Jürgen Eysenck (March 4, 1916 – September 4, 1997) was a German-British psychologist who spent most of his career in Britain, best remembered for his work on intelligence and personality, though he worked in a wide range of areas. At the time of his death, Eysenck was the living psychologist most frequently cited in science journals.

Assessment of Traits:
1. Self report questionnaires
2. Rating scales
3. Personality profiles

Halo Effects: ..... Tendency to rate a person in favorable direction on all traits because of good impression made on one or two-trait, and conversely.

Good: - as screening devices
Bad: - as predictive or behaviour in individual case

Neurobiological --> Specific Brain areas and functional differences between individuals
Personality genetics is a scientific field that examines the relation between personality and genetics. Studies investigate the link by genetic association studies where subjects are genotyped and their personality is quantified with a personality test. Among the possible links found is, e.g., one between a polymorphism called 5-HTTLPR in the serotonin transporter gene and the personality trait neuroticism. Other genes that have been suggested to be related to personality is AVPR1A ("ruthlessness gene") and MAOA ("Warrior gene").
**Common Cardiovascular disorders:**

1. Control of blood pressure: Hypertension and Hypotension
2. Congestive Heart Failure
3. Myocardial Infarction or “Heart attack”
4. **Coronary Heart Diseases (CHD)**
   - **Angina pectoris**
5. Diseases of heart valves
7. Arrhythmia, abnormal rhythms of contraction

**Risk factors for heart diseases:**

1. Family history of heart diseases: Genetic or environment, ethnic, culture and life styles
2. Cigarette smoking (Nicotine)
3. High Blood Pressure (Hypertension)
4. High LDL, low HDL and total serum cholesterol levels
5. Physical inactivity
6. Diabetes mellitus
7. Obesity
8. **Stress and behavioural patterns:** (Type A behaviour, hostility & emotional reactivity)

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*The treadmill test is used in assessing the ability of heart patients to engage in strenuous exercise.*

*A clot in an already narrowed coronary artery can completely cut off blood flow to the heart. If blood flow is not restored quickly, 90% of the tissue fed by the blocked artery will die within 3 hours.*

*Figure 163 from “Psychological influences in sudden cardiac death.”*
Reducing Risk of CHD

- Stopping Smoking, controlling weight, and following a healthful diet.
- Reducing Hypertension.
- Lowering low-density lipoprotein serum cholesterol.
- Modifying Type A behavior.
- Exercising.

Some Behavioral Patterns related to Stresses:

**Type – A:** Coronary Heart Disease (CHD)

**Type – B:** a non-Type A pattern

**Type-C:** Cancers and Malignancies

Type A Personality or behavioral patterns:

In 1974 two cardiologist, Myer Friedman and Ray Rosenman reported in JAMA on “Type A behavior and your heart”

And in 1966 Ray Rosenman et al reported in JAMA on “Behavioral patterns that have high risks for coronary heart diseases.”
Type A Personality or Behavioral Patterns:

1. An intense sense of time urgency, tendency to race against the clock, the need to do more, and obtain more in the shortest possible time.
2. An aggressive personality that at times evolve into hostility, highly motivated, yet may lose his or her temper very easily, and a high sense of competitiveness. A desire to make contest out of everything, the inability to “Play for fun”.
3. An intense achievement motives, yet too often this “Go for it” attitude lack proper define goal.
4. Polyphasic behavior, that is the involvement in multiple, diverse tasks at the same time.
5. Conversation constantly centered around time, work, and achievement.

Table 5.1 Risk Factors for Coronary Heart Disease

<table>
<thead>
<tr>
<th>NONMODIFIABLE</th>
<th>MODIFIABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Sex</td>
<td>High low-density lipoprotein levels and low high-density lipoprotein levels</td>
</tr>
<tr>
<td>Family history</td>
<td>Cigarette smoking</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Sedentary lifestyle</td>
</tr>
<tr>
<td></td>
<td>Stress and Type A behavior</td>
</tr>
</tbody>
</table>

Figure 5.7 Incidence of hypertension as a function of stress. High-stress air traffic controllers (men working at high-traffic towers) show greater prevalence of diagnosed hypertension than do low-stress controllers (men working at low-traffic towers).

**Type B or Non-Type A:**

In contrast to Type A, the Type B behavioral pattern is characterized by low levels of competitiveness, time urgency and hostility.

They tend to be more easy going and “Philosophical about Life”

Can stop to look around or “to smell some roses”

---

**Type C (Cancers or malignancies):**

In 1955 Lawrence Le Shan reported and later in in 1977, 1986 and 1994 concluded that among major personality correlates of cancer was a severe degree of poor Self-expectation coupled with self-dislike.

-A very pessimistic outlook on life.

-Relatively “Selfless”, often display sign of great sacrifice and Self-effacement, feeling “hopeless” and “Helpless” before the onset of cancer.

-Low Self perception.

---

**Type D personality**, a concept used in the field of medical psychology, is defined as the joint tendency towards negative affectivity (e.g. worry, irritability, gloom) and social inhibition (e.g. reference and a lack of self-assurance). The letter D stands for ‘distressed’.

Individuals with a Type D personality have the tendency to experience increased negative emotions across time and situations and tend not to share these emotions with others, because of fear of rejection or disapproval. Johan Denollet, professor of Medical Psychology at Tilburg University, Tilburg, The Netherlands, developed the construct based on clinical observations in cardiac patients, empirical evidence, and existing theories of personality. The prevalence of Type D personality is 21% in the general population and ranges between 18 to 53% in cardiac patients.

Research has shown that CHD patients with a Type D personality have a worse prognosis following a myocardial infarction (MI) as compared to patients without a Type D personality. Type D is associated with a 4-fold increased risk of mortality, recurrent MI, or sudden cardiac death, independently of traditional risk factors, such as disease severity.

Type D personality can be assessed by means of a valid and reliable 14-item questionnaire, the Type D Scale (DS14). Seven items refer to negative affectivity, and seven items refer to social inhibition. People who score 10 points or more on both dimensions are classified as Type D. The DS14 can be applied in clinical practice for the risk stratification of cardiac patients.

Type D has also been addressed with respect to common somatic complaints in childhood.

---

**The Hardy Personality:**

Kobasa (1979, 1986); Kobasa and Maddi (1977) defined a broad array of personality characteristics – called “Hardiness” which differentiates people who do and do not get sick under stress.

1. Control: or belief that they can control or influence events in their lives i.e. Personal Control.

2. Commitment: or sense of purpose or involvement in the events, activities, and people in their lives.

3. Challenge: tendency to view changes as incentives or opportunities for growth rather than threat to securities.

---

**Suzanne Kobasa (1979)**

- People who can handle stress possess ‘hardiness’.
  - There are three components
  
  I. **Control** - can you control events? (See Locus of control)

  II. **Commitment** - Sense of purpose, involvement.

  III. **Challenge** - problems seen as an opportunity for personal growth.
Suzanne Kobasa (1979)

- Kobasa (1979) - High stress executives 2 groups - high illness Vs low illness. Using questionnaire, the low illness group had more hardiness.

Problems

I. People vary with their personality. Unlikely to be one type of person all of the time.

II. Only looked at white professional American men - may not be true of other groups.

III. Hardiness and social support correlate so what is attributed to hardiness could really be the effect of social support (Blaney & Ganellen, 1990).
Does Prenatal Stress Impair Coping and Regulation of Hypothalamic–Pituitary–Adrenal Axis?

MARTA WEINSTECK
Department of Pharmacology, School of Pharmacy, Hebrew University, Hadassah Medical Centre, Ein Kerem, Jerusalem, 91120, Israel

WEINSTECK, M. Does prenatal stress impair coping and regulation of hypothalamic–pituitary–adrenal axis? NEUROPSYCHOBIOLOGY (2013) 11: 101-109. — Prenatally stressed (PS) human infants and experimental animals show abnormal stress hormones and pathologic behavior. The effects of stress in utero can have long-lasting implications on the developing fetus, resulting in behavioral and physical abnormalities. Prenatal stress during pregnancy can lead to increased levels of stress hormones (CRH) and development of stress-related disorders in the offspring. PS rats have higher levels of CRH in the hypothalamic paraventricular nucleus and show endocrine and behavioral alterations similar to those observed in animals subjected to prolonged stressful environments. The results suggest that prenatal stress can lead to behavioral and physiological changes in the offspring, which may persist throughout life. This suggests that prenatal stress can have long-lasting effects on the developing fetus and may contribute to the development of stress-related disorders in humans and animals.

CONCLUSIONS
Clinical observations suggest that exposure to uncontrollable psychological stress during gestation results in changes in the behavior of the children, which include attentional deficits, hyperactivity and abnormal social behavior. Experimental data from prenatally stressed rats and mice show more fearful novelty, and exhibit an inability to cope in stressful and demanding situations. They also show dysregulation of the HPA axis, characterized by increased circulating levels of ACTH and β, which could result from decreased feedback inhibition of the release and action of CRH, which remains to be tested. The abnormalities in the HPA axis are similar to those seen in humans with endogenous depression and appear to result from a deficit in glaucocortical structures in the prefrontal and other brain regions, and of endogenous opioid and GABA/Benzodiazepine activities, that serve to normalize the activity of this axis.

Stress related Common Health Problems
Hypertension, and strokes
Angina pectoris, Coronary Heart Diseases, and myocardial infarction and Heart attack
Tension Headache, and Migraines
Neck and back pains, Fibromyalgia
High susceptibility to colds and flu
Stomach disorders, Irritable bowel syndromes, and ulcers
Asthma and Allergies
Skin rashes etc..
Barker's Hypothesis
Professor David J.P. Barker

Heart of the matter: Barker's discovery that birth weight is linked to cardiovascular disease in adulthood has launched a revolution in public health.
The thrifty phenotype hypothesis says that reduced fetal growth is strongly associated with a number of chronic conditions later in life. This increased susceptibility results from adaptations made by the fetus in an environment limited in its supply of nutrients. These chronic conditions include coronary heart disease, stroke, diabetes, and hypertension. Proponents of this idea say that in poor nutritional conditions, a pregnant woman can modify the development of her unborn child such that it will be prepared for survival in an environment in which resources are likely to be short, resulting in a thrifty phenotype (Hales & Barker, 1992).

It is sometimes called Barker's hypothesis, after David J. P. Barker, a researcher at the University of Southampton who published the theory in 1997.

It has been suggested that the thrifty phenotype is the consequence of three unlike adaptive processes:
1. maternal effects,
2. niche construction and
3. developmental plasticity, which all are influenced by the brain.

While developmental plasticity demonstrates an adaptation by the offspring, niche construction and parental effects are result of parental selections rather than offspring fitness. Therefore, the thrifty phenotype can be described as a manipulation of offspring phenotype for the benefit of maternal fitness.

The information that enters offspring phenotype during early development mirror the mother's own developmental experience and the quality of the environment during her own maturation rather than predicting the possible future environment of the offspring.

Individuals with a thrifty phenotype will have "a smaller body size, a lowered metabolic rate and a reduced level of behavioural activity... adaptations to an environment that is chronically short of food" (Bateson & Martin, 1999). Those with a thrifty phenotype who actually develop in an affluent environment may be more prone to metabolic disorders, such as obesity and type II diabetes, whereas those who have received a positive maternal forecast will be adapted to good conditions and therefore better able to cope with rich diets. This idea (Barker, 1992) is now widely (if not universally) accepted and is a source of concern for societies undergoing a transition from sparse to better nutrition (Robinson, 2001).

New links to stress:
- Type 2 Diabetes mellitus
- Obesity
- Cancer
- Autoimmune disorders e.g. SLE
- Many skin disorders

Many human diseases in adulthood are related to growth patterns during early life, determining early-life nutrition as the underlying mechanism. The thrifty phenotype hypothesis suggests that early-life metabolic adaptations help in survival of the organism by selecting an appropriate trajectory of growth in response to environmental cues. Recently, some scientists have proposed that the thrifty phenotype prepares the organism for its likely adult environment in long term. However, environmental changes during early development may result in the selected trajectory becoming inappropriate, resulting in adverse effects on health. This paradox generates doubts about whether the thrifty phenotype is adaptive for human offspring. Thus, the thrifty phenotype should be considered as the capacity of all offspring to respond to environmental cues during early ontogenetic development.
Fetal Alcohol syndrome
Shyness, Sadness, Curiosity, Joy. Is It Nature or Nurture?

Wiring Feelings

What's happening in this simple moment?

Plenty.

THE EQ FACTOR

New brain research suggests that emotions, not IQ, may be the true measure of human intelligence.
1. Knowing one's emotions: Self-awareness—recognizing a feeling as it happens—is the keystone of emotional intelligence.

2. Managing emotions: Handling feelings so they are appropriate is an ability that builds on self-awareness.

3. Motivating oneself: Marshalling emotion in the service of a goal is essential for paying attention, for self-motivation and mastery, and for creativity.

4. Recognizing emotions in others: Empathy is the fundamental “People skill,” more attuned to what others need or want.

5. Handling relationships: The art of relationships, leadership.

PARENTAL CARE AND THE HEALTH OF OFFSPRING

The quality of family life influences the development of individual differences in vulnerability throughout life to illness. As adults, victims of childhood physical or sexual abuse are at considerably greater risk for mental illness, as well as for obesity, diabetes, and heart disease (e.g., Bifulco et al. 1990; Brown & Anderson 1993; McCollough et al. 1995; Poitras et al. 1998). Children need not be harmed to be compromised. Persistent emotional neglect, family conflict, and conditions of harsh, inconsistent discipline all serve to compromise growth (e.g., Montgomery et al. 1997) and intellectual development (Ammerman et al. 1994; Tschirgi & McBride- Chang 1995) and to increase the risk for adult obesity (Lewis & Sorenson 1994), depression, and anxiety disorders (Holmes & Robison 1987, 1988; Cutler 1995) to a level comparable to that for abuse.

Parental factors also serve to mediate the effects of environmental adversity on development. For example, the effects of poverty on emotional and cognitive development are mediated by parental factors to the extent that if such factors are controlled, there is no discernable effect of poverty on child development (Eisenberg & Elms 1975; Conger et al. 1994; McLoyd 1998). Moreover, treatment outcomes associated with early intervention programs are routinely correlated with changes in parental behavior. In cases where parental behavior proves resistant to change, treatment outcomes for the children are seriously limited.

A critical question concerns the mechanisms that mediate these enduring parental influences on the health of offspring. The relationship between early life events and health in adulthood appears to be, in part, mediated by parental influences on the development of neural systems that underlie the expression of behavioral and endocrine responses to stress (Seckl & Meaney 1994; Nemeroff 1996; Serota 1997; Francis & Meaney 1999; Francis et al. 1996; Heim et al. 2001). Physical and sexual abuse in early life, for example, increases endocrine and autonomic responses to stress in adulthood (Dellorbi et al. 1984; Heim et al. 2001). There are two critical assumptions here. First, that prolonged activation of neural and hormonal responses to stress can promote illness; second, that early environmental events influence the development of these responses. There is strong evidence in favor of both ideas.

RESPONSES TO STRESS

Stress is a risk factor for a variety of diseases, ranging from autoimmune disorders to mental illness. It is ironic that the pathways by which stressful events promote the development of such divergent forms of illness involve the same hormones that ensure survival during a period of stress (Chrousos & Gold 1992; McEwen & Stellar 1993; Miller 1998). These effects can, to some extent, be understood in terms of the normal set of adaptive responses elicited by stressors (Dallman et al. 1987, 1995; Chrousos & Gold 1992; McEwen & Stellar 1993; de Kloet et al. 1999). The increased sympathoadrenal release of catecholamines, primarily adrenaline and noradrenaline, as well as the adrenal glucocorticoids, orchestrate a move to catabolism, mobilizing fat and adverse reserves, and to treat stressors (Mendel et al. 1984; Baxter & Tyrrell 1987; Brindley & Rolland 1988, Dallman et al. 1991). The increase in circulating levels of catecholamines and glucocorticoids also promotes increased cardiovascular tone. These actions serve to increase the availability and distribution of energy substrates. Although these responses serve to meet the metabolic demands posed by the stressor, prolonged exposure to elevated levels of these “stress hormones” can promote insulin resistance, hypertension, hyperlipidemia, hypercholesterolemia, abdominal fat deposition, and an increased risk of atheroma, all of which are associated with an increased risk for heart disease (Brindley & Rolland 1989, Rosmond et al. 1990).
These findings provide an understanding of how stress can influence health. Yet the influence of stress can only be fully appreciated when we factor into the equation some appreciation of the individual’s response to stress. After all, not all individuals fall sick under conditions of stress, and questions concerning the basis for such individual differences are central to understanding the etiology of chronic disease. The hypothesis that guides research on the development of psychopathology focuses on the role of early life events in determining individual differences in vulnerability to stress. This hypothesis rests on the assumption that chronic activation of central and endocrine stress responses can promote illness (see references cited above). Thus, early life events that increase stress reactivity result in a greater vulnerability to stress-induced illness over a life span.

Summary

It is interesting that postnatal handling increases maternal LG and ABN, whereas maternal separation has precisely the opposite effect (Liu et al 1997; DD Francis & MJ Meaney, unpublished data). These findings support the long-held belief (Levine 1975, Smotherman & Bell 1980) that the effects of such early environmental manipulations are in fact mediated by alterations in maternal behavior. Together, the results of these studies suggest that the behavior of a mother toward her offspring can “program” behavioral and neuroendocrine responses to stress in childhood. These effects are associated with sustained changes in the expression of genes in brain regions that moderate responses to stress and form the basis for stable differences between individuals in stress reactivity. These findings provide a potential mechanism for the influence of parental care on vulnerability/resistance to stress-induced illness over a life span.


**Stress and Disease Connection**

- Roughly 80% of all doctor’s office visits are related to stress.
- Current research indicates that between 70% and 80% of all health-related problems are either precipitated or aggravated by emotional stress (e.g., type II diabetes, colds, flu, migraines, lupus, cancer, etc.).

**Health and Disease**

- **Frequency of accidents declines**
- **Individuals are less susceptible to colds and allergies**
- **Stress is a key factor in disease, especially if cumulative**
- **Immune system functioning decreases with normal aging**
- **Link between stress and cardiovascular disease can be indirect**
  - Stress can lead to unhealthy lifestyle choices
  - Chronic emotional stress is associated with high blood pressure, heart disease, and early death
- **Culture plays an important role in coronary disease**
  - Immigration modifies healthy practices even as genetic predispositions remain constant

**Mortality Rates**

- Chronic diseases are the main cause of death during middle adulthood
  - Heart disease
  - Cancer
  - Cerebrovascular disease
- In the 1st half of middle age, cancer claims more lives than heart disease; trend is reversed during the 2nd half of middle age
- Men have higher mortality rates than women

**HEALTH AND BEHAVIOR**

Changes in behavior and lifestyle can improve health, prevent illness, and reduce symptoms of illness. More than twenty-five years of research, clinical practice, and community-based interventions in the field of behavioral medicine have shown that behavioral changes can help people feel better physically and emotionally, improve their health status, increase their self-care skills, and improve their ability to live with chronic illness.

Behavioral interventions also can improve the effectiveness of medical interventions, can help to reduce over-utilization of the health care system, and can reduce the overall costs of care.
Focus on Research
Health and Lifestyles

In 1953, Maria Peirce and later Breed (1964) began a project to study the importance of mental health on physical health. The project was supported by the National Institute of Mental Health, which was established in 1953. The researchers were interested in how stress affects mental health and its impact on various physical health outcomes. They found that stress can lead to various physical health problems, such as heart disease and cancer.

Stress Management

Teaching the Whole Person

According to many of the world’s health organizations, stress is a major contributor to the development of chronic diseases. Stress can be caused by daily life events, such as work, relationships, or financial difficulties. People who experience chronic stress are at a higher risk of developing physical and mental health problems.

Minor Tranquilizers

If the antidepressants have a flaw, it's that they sometimes don't start working for weeks—a lifetime for the severely anxious. For this reason, many doctors recommend a gradual dose of short-acting tranquilizers such as the benzodiazepines Xanax, Valium, or Librium, to serve as a temporary bridge until the SSRIs have a chance to kick in. The downside of such drugs is that they can be highly addictive and may merely mask symptoms. For this reason, doctors will prescribe them very carefully and strictly limit refills.
Frequency With Which Adults Use Various Coping Strategies

<table>
<thead>
<tr>
<th>COPING STRATEGIES</th>
<th>FREQUENCY OF USE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diverting attention away from the problem</td>
<td>26</td>
</tr>
<tr>
<td>2. Trying to see the problem in a different light</td>
<td>24</td>
</tr>
<tr>
<td>3. Doing something to solve the problem (direct action)</td>
<td>46</td>
</tr>
<tr>
<td>4. Expressing emotion</td>
<td>25</td>
</tr>
<tr>
<td>5. Accepting the problem</td>
<td>30</td>
</tr>
<tr>
<td>6. Seeking social support</td>
<td>14</td>
</tr>
<tr>
<td>7. Doing something relaxing</td>
<td>17</td>
</tr>
<tr>
<td>8. Seeking religious comfort</td>
<td>6</td>
</tr>
<tr>
<td>9. Other</td>
<td>7</td>
</tr>
</tbody>
</table>


Antidepressants

When talk therapy doesn’t work—or needs a boost—drugs can help, especially the class of antidepressants called selective serotonin reuptake inhibitors. Prozac is the best known of these drugs, which work by preventing the brain from reabsorbing too much of the neurotransmitter serotonin, leaving more in nerve synapses and thus helping to improve mood. Another SSRIs, Paxil, was recently approved by the Food and Drug Administration specifically for the treatment of social anxiety disorder, though the others seem to work as well. A third has been approved for OCD and panic disorder. Each form of an SSRIs is subtly different—targeting specific subclasses of serotonin. And side effects—which can include dry mouth, fatigue and sexual dysfunction—will vary from person to person. A new group of antidepressants, known as serotonin-norepinephrine reuptake inhibitors, may be even more effective in treating anxiety disorders than the SSRIs are. As the name implies, the SNRIs target a second neurotransmitter called norepinephrine, which is secreted by the adrenal gland and plays a role in triggering the fight-or-flight response—thus actually increasing anxiety symptoms in many situations. However, norepinephrine also helps control emotion and stabilize mood, and, properly manipulated along with serotonin, may be able to do just that for the anxious person.

Changes in behavior, early detection of problems, and intervention could prevent death in many cases.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimated % of Deaths or Disability Prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>45%</td>
</tr>
<tr>
<td>Cancer</td>
<td>23%</td>
</tr>
<tr>
<td>Diabetes Disability</td>
<td>50%</td>
</tr>
</tbody>
</table>

Estimated % of Deaths or Disability Prevented

THE HOLISTIC APPROACH TO THE CONTROL OF STRESS

1. Techniques to Minimize the Frequency of the Stress Response
   - Social Engineering
   - Personality Engineering
2. Techniques to Minimize the Intensity of the Stress Response and Reduce Emotional Reactivity
   - Meditation
   - Biofeedback
   - Neuromuscular Relaxation Training
   - Autogenic Relaxation Training
3. Techniques to Utilize Stress and Promote Body Consciousness
   - Body Awareness Activities
   - Ego-Void Physical Exercise

Holism. The concept underlying an approach to controlling stress and tension that deals with the complete lifestyle of the individual, incorporating intervention at several levels—physical, psychological, and social—simultaneously.
Headaches

Headaches are among the most common stress-related physical ailments. Two of the most common types are:

- **Muscle-Tension Headache**: The single most frequent type of headache. Persistent stress can lead to constant contraction of shoulder, neck, forehead, and scalp muscles. Catastrophizing negative events can also bring on muscle tension headaches.

- **Migraine**: Throbbing headaches caused by wavelike firing of neurons on the brain, which creates ripples of neural activity that reach pain centers in the brain stem.

  - Sensory and motor disturbances may precede the onset of the migraine.
  - The underlying causal mechanisms of migraine are not well understood but appear to be related to changes in blood flow to the brain and subsequent imbalances of.

**Treatment of Headaches**

- Aspirin, acetaminophen, and prescription drugs are used to fight headache pain. Newer drugs combat migraines by balancing serotonin levels.

- **Relaxation Training**

- Identify triggers for attacks such as chocolate, MSG, red wine, fluorescent lights, etc.
Biofeedback systems such as this one, which records tension in the forehead muscle of a headache sufferer, allow people to monitor one or another of their subtle physiological responses in an attempt to modify that response.

The development of biofeedback in the 1960's provided behavioral medicine researchers and clinicians with a third clinically useful method of treating patients. In this case through the monitoring and altering physiological responses associated with some illnesses (Blanchard 1982). Like behavior modification and behavior analysis this technology was a powerful intervention for behavioral medicine (when used appropriately with a relevant illnesses) because it was also very objective and reliable. Biofeedback demonstrated graphically the interconnectedness of the mind and the body and how an intervention with one can impact the other. Like behavior modification and behavior analysis biofeedback was a rapidly adopted treatment intervention.
**Promoting Health**

- **Aerobic Exercise**
  - sustained exercise that increases heart and lung fitness
  - may also alleviate depression and anxiety

**Prescription Exercise Program**

**Promoting Health**

- **Biofeedback**
  - system for electronically recording, amplifying, and feeding back information regarding a subtle physiological state
  - blood pressure
  - muscle tension

**Promoting Health**

- Modifying Type A life-style can reduce recurrence of heart attacks

In the San Francisco Recurrent Coronary Prevention Project, heart attack survivors who received counseling aimed at modifying their Type A behavior suffered fewer repeat heart attacks over the ensuing years than those in the control group who received only counseling from a cardiologist.

**Prevention**

- 14% of US Gross Domestic Product is spent on health care
- 2/3 of organizations with >50 employees have health promoting programs
  - health assessments
  - fitness training
  - smoking cessation
  - stress management

**Prevention**

- Prudential’s experience with a fitness program
  - reduced sick days by 20%
  - reduced medical costs by 46%
  - saved $1.93 for every dollar spent on health care
Coping With Stress

- **Problem-focused coping** – addressing stress directly by changing the stressor or the ways we interact with it
  - E.g., talk it out with the person we are fighting with
- **Emotion-focused coping** – attempting to reduce stress by avoiding or ignoring a stressor and attending to emotional needs related to our stress reaction
  - can be healthy when we cannot change the stressor
  - can be maladaptive when we distract ourselves from addressing a problem that could be solved.

Personal Control

- **Personal control** is our sense of seeing ourselves in control of our environment.
- Psychologists study this in two ways:
  - They *correlate* peoples feelings of control with behaviors and achievements.
  - They *experiment*, by raising or lowering people’s sense of control and noting the effects.

Control, Morale, and Health

- Seligman (1975) strapped dogs in a harness and gave them electric shocks
- When later placed in another situation where they could escape the punishment by simply leaping over a hurdle, the dogs cowered and did not move
- Other dogs that were able to escape the first shocks did not act this way

Control, Morale, and Health

- **Learned helplessness** is the term for the hopelessness and passive resignation an animal or human learns when unable to avoid repeated aversive events.
  - Perceived loss of control predicts health problems.
  - Ability to control one’s environment leads to greater happiness and productivity.

Who’s at the Controls?

- Is your life out of your control? Is the world run by a few powerful people?
- Do you control your own fate? Is being a success a matter of hard work?
- **External locus of control**: the perception that chance or outside forces beyond personal control determine our fate
- **Internal locus of control**: the perception that we control our own fate

“Internals” and “Externals”

- Internals assume an internal locus of control.
  - believe they control their own destiny
  - achieve more in school and work, enjoy better health, and feel less depressed than their counterparts.
- Externals assume an external locus of control.
  - view that chance or outside forces control their fate
Self Control

**Self Control:** The ability to control impulses and delay gratification

- **Self-control is like a muscle:** Temporarily weakens after use, regains energy with rest, and grows stronger with exercise
- **Self-discipline** in one area may strengthen self-control in general and lead to a less stressed life

Is the Glass Half Full?

- **Optimism** is the anticipation of positive outcomes
- **Pessimism** is the anticipation of negative outcomes
- Optimists tend to have better health, and may live longer
- Success requires enough optimism to provide hope, and enough pessimism to keep us on our toes

Social Support

- Feeling liked and encouraged by friends and family promotes both happiness and health.
- Social support can calm the cardiovascular system and foster stronger immune functioning.
- Both good and bad habits can travel quickly among networks of friends.

Finding Meaning

- Those with a strong sense of meaning for a purpose for which to live, strong values, and a sense of self-worth.
- Those who find meaning in a tragic event have fewer adverse health effects and lower rates of depression.

Managing Stress Effects

- Sometimes we cannot avoid experiencing stress.
- What can we do to manage it?
  - Regular Aerobic exercise
  - Relaxation
  - Mind-fullness and Meditation
  - Spirituality
- Social support
- Good nutrition
- Time-management skills
- Clear communication
- Modify behavioral pattern or changing life styles

Aerobic Exercise

- **Aerobic exercise,** sustained activity that increases heart and lung fitness, may reduce stress, depression and anxiety
- Study: mildly depressed women improved more with exercise than with relaxation exercises
Relaxation: Lifestyle Modification

- Study with Type A heart attack survivors: a control group was given advice about medications, diet, and exercise.
- A second group was given this advice PLUS guidance in modifying their lifestyle—Walking, laughing, eating slowly

Relaxation: Meditation

- Relaxation procedures can provide relief from headaches, high blood pressure, anxiety, and insomnia.
- The relaxation response:
  - Sit quietly in a comfortable position. Close your eyes. Relax your muscles, starting with your feet and moving slowly upward. Breathe slowly, and on the exhale focus on a word, phrase or prayer. Repeat for 10-20 minutes.
- Meditation enhances activity in the left frontal lobe, associated with positive emotions. It also improves immune functioning.

Spirituality

- The faith factor: Religiously active people tend to live longer

Possible explanations for the Faith Factor?

- Religiously active people tend to have healthier life-styles.
  - less alcohol, dietary fat, and smoking
- Belonging to a faith community is to have access to a support network.
  - Religion encourages marriage, another predictor of health and longevity
- Religion promotes positive emotion, optimism, a stable worldview, and relaxed meditation.
- These factors correlate with participation in religious activities, not necessarily with strength of belief.

What Accounts for the Faith Factor?

- Some qualities and influences can help us flourish by making us emotionally and physically stronger:
  - A sense of control
  - Optimistic outlook
  - Healthy habits
  - Social support
  - Relaxation
  - A sense of meaning
  - Spirituality

How to Flourish

- Healthy behaviors (less smoking, drinking)
- Social support (faith community, marriage)
- Better health (less immune system suppression and fewer stress hormones; greater longevity)
- Positive emotions—hope, optimism, coherence (less stress, anxiety)
Rest, Relax and Recreation

Exercise

Aerobic exercise and depression. Mildly depressed college students who participated in an aerobic exercise program showed markedly reduced depression scores compared to those who participated in a treatment of relaxation exercises or received no treatment.

Behavioral Therapy

When the brain sets anxiety alarms ringing, our first inclination is to find the off switch. Behavioral scientists take the opposite approach. They want you to get so accustomed to the noise that you don’t hear it anymore. The standard behavioral treatment for such anxiety conditions as phobias, obsessive-compulsive disorder and panic disorder is to expose patients to a tiny bit of the very thing that causes them anxiety, ratcheting up the exposure over a number of sessions until the brain habituates to the fear. A patient suffering from a blood phobia, for example, might first be shown a picture of a syringe, then a real syringe, then a vial of blood and so on up the anxiety ladder until there are no more rungs to climb. There is a risk that if treatments is cut short (before the patient has become inured to the anxiety triggers), the anxious feelings could be exacerbated. But done right, behavioral therapy can bring relief from specific phobias in as little as two or three sessions. Social anxiety takes somewhat longer, and OCD may take a good deal longer still.

Cognitive Therapy

Rather than expect patients to embrace anxiety, cognitive therapists encourage them to use the power of the mind to reason through it. First popularized in the 1960s, cognitive therapy teaches people who are anxious or depressed to reconfigure their view of the world and develop a more realistic perspective on the risks or obstacles they face. Patients suffering from social-anxiety disorder, for example, might see a group of people whispering at a party and assume the gossip is about them. A cognitive therapist would teach them to rethink that assumption. Some behavioral therapists question cognitive techniques, arguing — not without some justification — that a brain that was so receptive to reason wouldn’t be all that anxious in the first place. Cognitive therapists dispute that idea, though some have begun incorporating behavior-modification techniques into their treatment.

Exercise

Before turning to drugs or talk therapy, many people prefer to try to bring their anxiety under control on their own. Unlike most emotional or physical conditions, anxiety disorders respond well to such self-medication — provided you know how to administer the treatment. One of the most effective techniques is simple exercise. It’s no accident that a good workout or a brisk walk can take the edge off even the most acute anxiety. Scientists once believed the effect to be due to the release of natural opioids known as endorphins, but new research has called this into question. Regardless, working out regularly — most days of the week, if possible for at least 30 minutes or so — may well help recalibrate the anxious brain.
Emotional Skills and Intelligence

1. Knowing one’s emotions: Self-awareness—recognizing a feeling as it happens—is the keystone of emotional intelligence.
2. Managing emotions: Handling feelings so they are appropriate is an ability that builds on self-awareness.
3. Motivating oneself: Marshalling emotion in the service of a goal is essential for paying attention, for self-motivation and mastery, and for creativity.
4. Recognizing emotions in others: Empathy is the fundamental “People skill”, more attuned to what others need or want.
5. Handling relationships: The art of relationships, leadership.

Alternative Treatments

One of the most popular self-treatments is yoga, which is both a form of exercise and a way to quiet the mind by focusing attention on breathing. Indeed, even without yoga, breathing exercises can help quell an anxiety episode, if only by slowing a racing heart and lengthening the short, shallow breaths of a panic attack. Many anxiety sufferers have found relief through meditation or massage — even just a 10-min. foot treatment. For those willing to travel a little farther from the mainstream, there’s aromatherapy (enthusiasts recommend rose and lavender scents), guided imagery (a form of directed meditation used with some success by people recovering from cancer and open-heart surgery) and acupuncture.

Lifestyle Changes

If all else fails, go back to basics and by cleaning up your lifestyle. For starters, you can cut back or eliminate the use of sugar, caffeine, nicotine, alcohol and any recreational drugs you may be taking. Are you eating right and getting enough sleep and leisure time? Finally, if your job or the place you live is making you and us, you might consider moving to a less stressful environment or finding a different line of work.
ayurveda

Ayurveda is an ancient system of traditional healing rooted in India. It is one of the oldest systems of medicine still practiced today. The word ayurveda means “science of life” or “knowledge of life.” Ayurveda recognizes that the body, mind, and spirit are interconnected. A person’s health is determined by the balance of three doshas: vata, pitta, and kapha. Each person has a unique combination of these doshas, and maintaining balance is key to good health.

Ayurveda uses a variety of treatments, including herbal medicine, dietary recommendations, massage, and meditation. It emphasizes the importance of living in harmony with nature and understanding the body’s unique constitution to prevent illness.

herbalism

Herbalism is the study and practice of using plants and other natural substances for medicinal purposes. Herbs have been used for thousands of years to treat a wide range of conditions, from common colds to chronic diseases.

Herbal medicine can be taken in many forms, including teas, tinctures, capsules, and extracts. Herbalists often combine different herbs to create a formula tailored to the individual needs of each patient. Herbal medicine is generally considered to be safe, but it’s important to consult with a qualified herbalist or healthcare provider before using any herbal remedies, especially if you are pregnant or have a chronic illness.

homeopathy

Homeopathy is a system of alternative medicine developed by Samuel Hahnemann in the early 19th century. It is based on the principle that “like cures like.” In other words, a substance that causes symptoms in a healthy person can be used to treat those same symptoms in a sick person.

Homeopathic remedies are made from plant, mineral, and animal materials that are diluted andsuccinized to create a very weak solution. These remedies are given in small doses and are supposed to stimulate the body’s natural healing process. Homeopathy is generally considered safe, but it’s important to discuss any homeopathic treatments with your healthcare provider before starting them.

massage

Massage is a form of therapy that involves the manipulation of the body tissue to improve blood flow, reduce stress, and promote relaxation. There are many types of massage, including Swedish, deep tissue, and lymphatic massage.

Massage can be beneficial for a variety of reasons. It can help reduce pain and stiffness, improve circulation, and increase flexibility. Massage can also be relaxing and help reduce stress. It’s important to discuss any massage treatments with your healthcare provider before starting them, especially if you have a chronic illness or are pregnant.
Entertaining: Good Health and Relationships

We all have a fundamental need for stable and caring relationships. Having a confidante doesn’t just save your sanity—it can safeguard your health.

Research shows that women’s immune systems suffer when they aren’t well connected with friends. That makes you less able to fight off infections and disease.

Communicative lies at the heart of good relationships. As many of modern life is with the development of so many technologies for global

ตรีศึกษา (Triple Education)

ปัญญา (Wisdom)

การรับรู้ (Perception)

การเรียนรู้ (Learning)

พฤติกรรม (Behaviour)

ความจำ (Memory)

อารมณ์ (Emotion)

ศีล-วินัย (Disciplines)

สมาธิ (Concentration)

N. Kotchabhakdi

Meditation

How Foods Fight Cancer

How Foods Fight Cancer

How Foods Fight Cancer

How Foods Fight Cancer

How Foods Fight Cancer
**PROLOGUE**

Life is largely a process of adaptation to the circumstances in which we exist. A perennial give-and-take has been going on between living matter and its inanimate surroundings, between one living being and another, ever since the dawn of life in the prehistoric oceans. The secret of health and happiness lies in successful adjustment to the ever-changing conditions on this globe; the penalties for failure in this great process of adaptation are disease and unhappiness. (Selye, 1956, p. vii)

**Overview.**
1. It has been almost 50 years since the publication of the classic book by Hans Selye (1956) on stress, adaptation, and disease.
2. In his formulation of the general adaptation syndrome, the role of the autonomic and endocrine systems on stress-related disease processes was highlighted. These two physiological systems continue to be the major focus of contemporary research aimed at understanding the health consequences of stress.
3. The emergence of psychoneuroimmunology (PNI) as a discipline in the early 1970s has resulted in the immune system becoming a third major physiological perspective, which links stress to health outcomes.
4. However, we now have a more detailed understanding of how these major stress systems are coordinated during threats and their implications for health.
5. The major aim is to provide a detailed overview of the links between stress and illness with an emphasis on underlying physiological and stress component processes.

**Historical background.**
1. In his model of the general adaptation syndrome (GAS), Selye found that animals exposed to more chronic stress seemed to go through a distinct sequence of behavioral and physiological changes.
2. Initially, in what he termed the alarm stage, the SNS dominated. As more coping attempts were initiated (i.e., the resistance phase), the release of glucocorticoids (e.g., cortisol) from the hypothalamic-pituitary-adrenal (HPA) axis became important.
3. The effects of glucocorticoids are broad and include increased glucose metabolism, increased lipolysis, and inhibition of immune processes (Munck, Guyre, & Holbrook, 1986). Although the immunosuppressive effects of cortisol were not anticipated by the GAS, the HPA axis was given special status by Selye as he suggested coping attempts that failed to terminate a stressor could result in exhaustion and compromise health.
4. Although more contemporary views of stress, physiological regulation, and disease (e.g., allostatic) have been proposed and are presently favored, these prior perspectives provided important initial frameworks linking stress to physical health. The legacy of these perspectives is also evident in that a focus on the SNS and HPA axes continues to dominate contemporary research on stress and health.
5. However, the emergence of PNI has resulted in the immune system as a third major physiological perspective for researchers interested in health and disease. More important is the fact that extensive interactions exist among the autonomic, neuroendocrine, and immune systems. Evidence for such interactions is starting to pave the way for a more integrated and complete view of how stress might influence health.

**THE CONCEPTUALIZATION OF STRESS.**
1. The concept of stress is often used ubiquitously in the research literature to refer to either acute or chronic strains. The focus of researchers has historically emphasized stress as a stimulus (stressor), a response (biological changes), or a transactional process in which perceptions of stress are emphasized (Lazarus & Folkman, 1984).
2. A classic distinction is also usually drawn between more acute (or time-limited) versus chronic (long-term) stressors. Chronic stress is generally regarded as being more consequential for health and usually results from long-term exposure to stressors.
3. However, chronic stress may also be a result of lasting perceptions of stress that are driven by ruminative thinking (Baum, O’Keeffe, & Davidson, 1990). Thus, chronic stress may be defined as long-term exposure, lasting perceptions, or both (e.g., caregiving for a family member with Alzheimer’s disease).
4. Although the time course and associated perception of stress have traditionally been emphasized in past research, more recent models are attempting to separate component processes associated with stress. This “new look” is important because a strict focus on general perceptions of stress does less to elucidate the precise mechanisms operating to influence health outcomes.

Cacioppo & Berntson have argued that stress may have at least four health-related components:
1. exposure,
2. reactivity,
3. recovery, and
4. restoration.

Exposure refers to the number of stressors that an individual experiences; reactivity refers to the strength of an individual’s physiological reaction to any given event; and recovery refers to how long it takes an individual to return to “baseline” following stressful events. A unique aspect of this perspective is on restoration, which focuses on anabolic processes that refresh or repair the organism, because stress may directly impede our ability to perform these functions (e.g., disturbed sleep and impaired wound healing).
A simplified conceptual model based on the framework of Cacioppo & Berntson is presented in Figure 26.1.

1. Accordingly, stress exposure may be either acute or chronic and influence reactivity.
2. Stress reactivity may then lead to differential stress recovery, and some evidence suggests these processes are separable (Linden, Stossel, & Maurice, 1996).
3. Stress reactivity, recovery, and exposure may also have effects on restorative processes such as sleep and wound healing.
4. It is also predicted that these restorative processes may in turn influence stress reactivity and recovery, especially over time as insufficient restoration may be associated with changes in the set-point and response characteristics of physiological systems (Sterling & Eyer, 1988; Eipol, McLewen, & Ickovics, 1998).
5. These stress components may ultimately influence health depending on the disease context (i.e., development or exacerbation of disease). Of course, disease morbidity also entails significant psychological, behavioral, and social adjustments that can in turn be associated with greater stress exposure (Nicassio & Smith, 1995).
6. Although there are conceptual issues related to these stress components that will be discussed later (e.g., independence of components and time course), it provides a broad and potentially unique means for evaluating and organizing current research linking stress to health outcomes.

**Evidence linking stress to cardiovascular disease.**

1. The overall evidence linking stress to cardiovascular disease appears strong (Krantz et al., 2000; Linden, Stossel, & Maurice, 1996; Rozanski, Blumenthal & Kaplan, 1999; Schneideman et al., 2001; Smith & Ruiz, 2002).
2. In a comprehensive review, Rozanski and colleagues (1999) found that exposure to both acute and chronic stress (especially work stress) was associated with an increased risk for morbidity and mortality from cardiovascular disease.
3. Moreover, interventions explicitly aimed at decreasing stress appear to be effective in reducing cardiovascular mortality (Dusseldorp et al., 1999; Krantz et al., 2000; Linden, Stossel, & Maurice, 1996).
4. Because of the pathophysiology of CAD, there are at least two ways that stress may influence cardiovascular outcomes. The influence of stress on health may be due to effects on either the development or the exacerbation of CAD in clinical patients. Importantly, research suggests that stress may play a role in both processes, although the putative physiological mechanisms appear to differ.
5. Animal studies clearly suggest a role for stress in the development of cardiovascular disease (Manuck, Kaplan, & Clarkson, 1983). In one study from an important program of research, Manuck, Kaplan, & Clarkson (1983) examined monkeys that were high or low in heart rate reactivity to stress. The monkeys were then placed in unstable, stressful environments in which they had to reestablish their dominance. Results revealed that monkeys who were high in heart rate reactivity had greater coronary atherosclerosis upon necropsy. These results have been replicated, are eliminated by β-adrenergic blockade, and exacerbated by other risk factors such as an atherogenic diet (Kaplan et al., 1987). These data are consistent with other animal models such as the borderline hypertensive rat that develops elevated blood pressure following exposure to chronic stress (Ganders & Leaster, 1992).

1. Hypertension is another leading cardiovascular disorder and is a condition of elevated blood pressure (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg).
2. However, there is also increasing appreciation of the health relevance of blood pressure previously labeled as “normal.”
3. Recent guidelines suggest that both SBP between 120–139 mmHg or DBP between 80–89 mmHg be considered “prehypertension” (American Heart Association, 2004).
4. In about 5% to 10% of cases, the cause of high blood pressure can be determined and is labeled secondary hypertension (e.g., kidney problems).
5. However, in the vast majority of cases the cause of elevated blood pressure is unknown and is labeled essential or primary hypertension.
6. Because of the heightened workload within the cardiovascular system, as well as the increased pressure in various organ systems, the consequences of hypertension can be kidney damage and increased risk of MI, stroke, and heart failure.

**STRESS AND CARDIOVASCULAR DISEASE:** Background information.

1. Cardiovascular disease is a broad term used to cover several diseases of the cardiovascular system, including coronary artery disease (CAD) and hypertension.
2. It is by far the leading cause of death in the United States and most industrialized countries (American Heart Association, 2004). In fact, it accounts for about as many deaths as the next six leading causes of death combined. It is estimated that if all major forms of cardiovascular disease were eliminated, life expectancy would be raised by about seven years.
3. This stands in comparison to a life expectancy gain of three years if all forms of cancer were eliminated (American Heart Association, 2004).
4. CAD is a condition in which the coronary arteries become narrowed, and ultimately results in decreased blood flow to the heart. The pathological change in the coronary arteries is due to a process called atherosclerosis, which is a progressive buildup of fatty deposits within the arterial walls.
5. This buildup is not a passive process that simply occurs with the passage of time. Recent research suggests that inflammation (e.g., macrophage activity or cytokine release) may play a key role in the progression of CAD (Libby, 2002; Ross, 1999). The end result of this process is the formation of arterial lesions and narrowing of the arteries. These processes increase the chance that a blood clot will form thereby increasing the risk of blocking the arterial passage. Although most people think of CAD as occurring in older adults, it is important to note that this atherogenic process starts very early.
6. For instance, the beginnings of arterial plaque can be found in children, while some young adults already show evidence of advanced lesions. Of course, only when the disease is in its later stages (as is often the case with older adults) does it result in clinical symptoms. Thus, CAD is generally considered a disease with a long-term developmental history.
Potential mechanisms linking stress to cardiovascular disease.

1. Overall, strong evidence is available linking stress to the development and course of cardiovascular disease.

2. One limitation, however, is that less direct evidence is available in these studies on the mechanisms responsible for such links. Furthermore, stress in these studies has usually been operationalized in its aggregate or as general perception. As a result, the more precise stress-related components that might be operating are unclear.

3. There is, however, a relatively large literature linking stress to more "intermediate" cardiovascular endpoints such as reactivity, ambulatory blood pressure (ABP), or noninvasive imaging of carotid/coronary arteries. Such research can help clarify the conceptual role of stress in the development and exacerbation of cardiovascular disease.

4. One model linking stress to cardiovascular disease is represented by the reactivity hypothesis (Krantz & Manuck, 1984). According to this perspective, individuals or situations characterized by high levels of cardiovascular reactivity (usually indexed by blood pressure or heart rate) may be related to higher risk for the development and exacerbation of cardiovascular disease. Research linking reactivity to cardiovascular disease is still ongoing, but current evidence is consistent with this hypothesis.

5. For instance, relatively high levels of reactivity prospectively predict increased blood pressure in adolescents (Matthews, Woodall, & Allen, 1993) and middle-aged adults (Light et al., 1992; Matthews, Woodall, & Allen, 1993). A recent review of this literature found evidence consistent with the reactivity hypothesis, although exceptions were evident (Treiber et al., 2003).

Cancer is a disease of the cells which is characterized by unrestricted cell growth and proliferation that usually forms a malignant tumor or neoplasm. Although there are more than 200 varieties of cancers in many different organs of the human body, the majorities of cancers are of four types:

1. **Carcinomas**: malignant neoplasm of skin and epithelial cells, 85% of cancers are carcinomas

2. **Lymphomas**: cancers of lymphatic system

3. **Sarcomas**: malignant neoplasm of muscle, bones and connective tissues

4. **Leukemias**: cancers of blood forming cells
An important characteristic of cancer cells is that they do not adhere to each other as strongly as normal cells do. As a result, they may separate, and spread to invade other parts of the body, through the tissue, the blood vessels and lymphatic system. This migration is called metastasis, and the new neoplasms are also known as metastases.

Cancer is the second most frequent cause of death in the USA and developed or industrialized countries. Each year cancer takes more than 500,000 lives, and over 1.1 million new cases are diagnosed. About half of the individuals who develop cancer can expect to live for at least 5 years.

Cancer

• Cancer is the number one killer of women in the United States and the number two killer of men.
• Cancer is a disease characterized by the development of abnormal, or mutant cells that may take root anywhere in the body. Cancer cells are normally destroyed by our immune system, but people who have an impaired immune system (as a result of physical or psychological factors) are more likely to develop tumors.

What cause cancers?
1. Genetic factors: Onco-genes, protective genes
2. Environmental factors
   2.1 Radiation, repeated & chronic physical injuries
   2.2 Chemical carcinogens, hormones and toxins
   2.3 Biological agents e.g. Virus, bacteria, fungus, parasites
3. Behaviour and Life styles e.g.
   smoking, alcohol drinking, chronic stress, depression, Type “C” behavior

Cancer Risk Factors
• Obesity
• High fat intake
• Diets low in fiber
• Depression
• Stress

Cancer Prevention
• Modify diet by reducing fat and increasing intake of fruits and vegetables. Tomatoes, broccoli, cauliflower, and cabbage appear to be helpful.
• Have regular medical checkups
• If living with cancer, maintain hope and a fighting spirit.
Standard treatment for cancers:
1. Surgical removal of tumors
2. Chemotherapy
3. Radiation therapy
4. Immunotherapy

Behavioral and Psychological therapy for cancer patients:
- Cognitive Behavioral stress Management
- Relaxation training
- Systematic desensitization
- Progressive muscular relaxation and imagery before and during chemotherapy
- Psycho-social supports
- Exercise, aerobic exercise
- Nutritional, Diets, antioxidants, anticancer food supplements
- Mental Imaging Exercise, “Fighting Spirit”
- Improving Self esteem, Self-satisfaction

Conceptualization of stress
- Dynamic state of threatened or perceived threatened homeostasis
- Activation of primary stress systems
  - Hypothalamic-pituitary-adrenal axis (HPA)
  - Sympathetic nervous system (SNS)
- Principal stress hormones
  - Catecholamines
  - Glucocorticoids

Scientific scope of RFA

Exposure to chronic stress promotes tumor growth and angiogenesis
- Use of mouse host-human tumor hybrid model
- First experimental evidence that behavioral stressors can enhance pathogenesis of ovarian carcinoma in vivo
- Neuroendocrine stress response affects the growth and activity of malignant tissue through hormone receptors expressed by tumor cells

Exposure to chronic stress: Ovarian carcinoma growth in vivo

Thaker et al., (2006)
Thaker et al., (2006)
Stress effects on ovarian carcinoma growth in vivo

- Experimental results demonstrate that chronic exposure to stress and to social isolation result in enhanced tumor growth.

- Two molecular mechanisms identified:
  1. Stress regulation: Catecholamine signaling via beta-adrenergic receptors
  2. Tumor biology: Up-regulated angiogenesis

Propranolol counteracts the effects of chronic stress

- Mean Tumor Weight and Mean Tumor Nodules graphs showing the effects of control, placebo, and propranolol on tumor weight and nodules.

Adapted from Thaker et al., (2006)

Effects of chronic stress on angiogenesis

- Image showing newly formed blood vessels in Matrigel with labeled nuclei and endothelial cells.

Thaker et al., (2006)

Effect of VEGF-R inhibition on HeyA8-injected mice

- Graph showing tumor weight and number of nodules for PBS, PBS+daily stress, PTK787, and PTK787+daily stress groups.

Thaker et al., (2008)

Stress effects on ovarian carcinoma growth in vivo

- Experimental results demonstrate that chronic exposure to stress and to social isolation result in enhanced tumor growth and progression.

- Two molecular mechanisms identified:
  1. Stress regulation: Catecholamine signaling via beta-adrenergic receptors
  2. Tumor biology: Up-regulated angiogenesis
Historical perspective: Stress and cancer

- Clinical observations
- Epidemiological associations inconsistent
  - More consistent associations for disease progression than for disease incidence
- Early experimental and clinical studies
  - Virally induced tumors in experimental animal models
  - Role of immune response

Potential Research Topics

- Determine which tumor types and tumor genomes are sensitive to the physiologic stress response (PSR)
- Determine which endocrine and neurobiological molecules mediate effects of stressors on tumor biology
- Characterize specific aspects of tumor biology that are affected by the PSR
- Understand the biological influence of the PSR on the cancer continuum and during the perioperative period, treatment, and progression free survival
- Identify molecular pathways by which behavioral or pharmacological interventions can protect against the deleterious effects of the PSR on tumor biology

Contemporary perspective: Stress and cancer

- Emerging focus on:
  - Biochemical mediators of stress, rather than the subjective experience of stress
  - Assessing relationships within the tumor and its microenvironment, rather than the periphery
- Substantial support in experimental animal models
  - Recent observations in rigorous experimental designs:
    - Validated animal models and stressor paradigms with translational relevance

STRESS AND CANCER: Background information.

1. Perhaps no diagnosis strikes more fear in people than that of cancer. Cancer is the second leading cause of death in the United States and over 1.3 million new cancer cases are expected to be diagnosed in 2004.
2. In fact, one of every three individuals is predicted to be afflicted by cancer at some point in their lives (American Cancer Society, 2004).
3. Cancer is a broad term used to describe many different diseases that are characterized by the uncontrolled growth and spread of abnormal cells (Abbás & Lichtman, 2003).
4. A key to cancer appears to lie in the DNA. Cells can be observed to undergo genetic changes that directs cell development and growth. However, carcinogens can cause damage to cells with subsequent changes in their DNA. In some cases, the body is able to repair such damage to DNA or the cell dies off before it replicates.
5. However, in the case of cancer, uncontrolled replication of such cells leads to tumors that can eventually result in death if not detected and treated. Cancerous tumors can also metastasize and spread cancerous cells to different parts of the body via blood or lymph.
6. There is no one cause of cancer and many factors seem to play a role in its initial development and progression. Research clearly suggests the importance of genetics in the risk for some forms of cancer (e.g., BRCA II gene for breast and ovarian cancer). Also important are carcinogens that include chemical factors and ionizing radiation that may damage cells and increase cancer risk. However, some of the main factors implicated in the development of cancer are behavioral or lifestyle in nature. These lifestyle factors include smoking, excessive alcohol consumption, diet, and sun exposure. In fact, several types of cancer could be almost completely eliminated (lung cancer by not smoking) or significantly reduced (skin cancer with the use of sunscreen) just by altering one’s behavior (American Cancer Society, 2004).

The processes described above refer collectively to three postulated stages of cancer immuno-editing:

1. elimination,
2. equilibrium, and
3. escape (Dunn et al., 2002).

Elimination coincides with the initial concept of immunosurveillance and T-cells, along with the production of interferon-γ, appear critical for the detection and elimination of immunogenic tumors. In the equilibrium stage, tumors with less immunogenicity survive elimination and are at equilibrium with the immune system.

At this stage, immune processes invoked by T-lymphocytes and interferon-γ can keep the tumor in check but not eliminate it. However, mutating variants of these tumor cells are constantly arising and may carry mutations that make them even more resistant to immune processes (e.g., loss of MHC molecules, interferon-γ insensitivity). Finally, the phase of escape corresponds to resulting tumors that are much less immunogenic and can thus grow in an immuno-competent individual.

This later stage of escape usually corresponds to clinically diagnosed malignant disease, and the immune system is less able to control it as a result of earlier selection processes. Although the concept of immuno-editing is still being refined, it provides a broad, developmental framework for interpreting prior research.
Evidence linking stress to cancer.
1. The overall evidence linking stress to cancer outcomes is controversial. Animal models provide a stronger case for stress influencing some types of cancer (Fox, 1998; Sklar & Solomon, 1983).
2. However, human studies have provided inconsistent findings linking stress to overall cancer outcomes (e.g., Cooper, Davies-Cooper, & Faragher, 1986; see review by Fox, 1998).
3. As noted by others (e.g., Cohen & Herbert, 1996; Kiecolt-Glaser & Glaser, 1995), the evidence linking stress to cancer is complex and several issues are in need of greater consideration.
4. First, past research has tended to focus on all cancers combined, or failed to consider the stage of cancer potentially impacted by stress. This is important because some cancers are more deadly than others (e.g., pancreatic cancer). It has further been suggested that psychosocial factors such as stress are less likely to influence survival from cancer in later stages of the disease (Kiecolt-Glaser & Glaser, 1995).
5. These points would suggest that studies examining certain types of cancers might provide a stronger test of the role of stress in the development of cancer. Of such studies most have focused on breast cancer. In a meta-analysis, McKenna, Zaven, Com, and Rounds (1999) did find evidence of an association between stress and the development of breast cancer. Although the number of studies were not large (16 for separation/loss and 12 for stressful life events), significant stress effects on breast cancer development were found with overall mean effect sizes not moderated by various methodological factors such as type of control group and sample size.

Potential mechanisms linking stress to cancer.
1. The overall evidence linking stress to cancer development and survival is controversial (Fox, 1998). Studies that focus on specific cancers show some promise (Andersen, Kiecolt-Glaser, & Glaser, 1994; McKenna et al., 1999).
2. In retrospect, these inconsistent results are not surprising given that modulation of the immune system is one of the primary proposed mechanisms linking stress to cancer, and the effectiveness of such immune processes may be dependent on the type of cancer (Abbas & Lichtman, 2003). The concept of immune system involvement in cancer is also undergoing development (Dunn et al., 2002). The emerging concept of cancer immune-editing suggests that stress may only be weakly associated with cancer outcomes later in the clinical course of disease. At this later “escape” stage, tumors with less immunogenicity have been selected and inflammatory cytokines may already have made them resistant to immune processes (Dunn et al., 2002).
3. In such cases, stress-induced modulation of immune function may evidence little association with the development of cancer. This shift highlights more generally the importance of modeling stress effects across the full course of cancer. In theory, by suppressing the immune system (e.g., interferon-γ production), chronic stress may hasten the progression through stages of cancer immune-editing. Of course, some cancers are more deadly than others (e.g., pancreatic cancer) and this complexity would also need to be considered in modeling the time course of stress effects on cancer outcomes. Importantly, stress does appear to be related to early processes that in theory should be related to the development of cancer.

1. Although there are studies that have failed to find a link between stressful life events and breast cancer development (e.g., Kiviat et al., 1994), there is some evidence that increased stress exposure may be important to consider.
2. In the Finnish Twin Cohort study, a comprehensive assessment of stressful life events was obtained for the five years preceding a biomarker assessment (Lilberg et al., 2003). During a 15-year follow up, the experience of five major life events predicted the incidence of breast cancer even after statistically controlling for social class, smoking, alcohol use, and exercise patterns. Further examination of the data suggested a cumulative effect of stress on breast cancer development as the number of life events increased.
3. There is also controversy about whether stress can influence subsequent survival following a cancer diagnosis (Fox, 1998).
4. The strongest evidence for a link between stress and the course of cancer comes from intervention studies (Fawzy & Fawzy, 1998). Although the number of studies is not large, these interventions usually include an educational or stress management component and appear to have beneficial influence on health outcomes (Baum & Posluszny, 1999).
5. In one well-known intervention, Fawzy and colleagues (1993) evaluated the effects of a six-week structured group intervention that provided education, problem-solving skills, stress management, and social support to cancer patients. Importantly, a six-year follow up revealed that only 9% of individuals in the structured group intervention had died compared to 29% of individuals in the no-intervention condition.

1. Damaged cells may become cancerous following changes to their DNA. However, the cell is usually repaired or it dies off before it replicates (i.e., apoptosis).
2. There is a small literature indicating that stress may influence both of these processes. In studies of medical students during high stress (i.e., exams), apoposis of blood leukocytes in response to gamma irradiation is impaired.
3. In addition, rats exposed to rotational stress showed lower levels of a DNA repair enzyme in response to carcinogens (Glaser et al., 1985).
4. These findings highlight the potential role of stress exposure, stress reactivity, and stress restoration in early biological events related to cancer development.
5. Evidence linking stress to direct changes in immune function may also serve as the basis for understanding the development and course of cancer.
6. The elimination phase of cancer immuno-editing is characterized by immune processes that actively prevent and eliminate tumors (Dunn et al., 2002).
7. Importantly, there is strong evidence indicating that stress can influence aspects of both innate and adaptive immunity (Segrestrom & Miller, 2004). However, it is clear that the chronicity of the stressor is one important dimension to consider.
8. Studies modeling how short-term laboratory stress (three minutes to half hour) influences aspects of immunity most often increase in cytotoxic T-cells, NK cells, NK cell activity, and decreases in the proliferative response to the mitogens PHA and Con A (Cacioppo et al., 1995; Matthews et al. 1995). These changes appear short-term, reflect changes in cell trafficking, and are mediated by activation of the SNS (Bachman et al., 1995).

1. Stress has also been directly linked to decreases in immunity in cancer patients and hence may theoretically play a role in disease progression depending on the stage and time course of disease (Kiecolt-Glaser & Glaser, 1995).
2. In one study, investigators examined if perceptions of cancer-related stress had an influence on immune measures following surgical treatment (Andersen et al., 1998).
3. Cancer-related stress in these patients had uniform effects on immunity as it was related to lower NK cell activity, proliferative responses to mitogens, NK cell activation via interferon-γ, and T-cell proliferation to antibody (Ab) directed at the T-cell receptor. This study is consistent with the results of interventions suggesting that stress reduction may improve immune function in cancer patients, and has potential beneficial influences on survival (Fawzy et al., 1993). It is important to note, however, that direct evidence is still needed suggesting immune-related mediation of such effects (Cohen & Herbert, 1996), as well as the components of stress that might be impacted by such interventions.
4. One critically important pathway linking chronic stress to changes in immunity is through neuroendocrine mechanisms. Cells of the immune system (e.g., lymphocytes) have functional receptors for endocrine hormones, which provide a mechanism by which stress may influence immunity (Sanders et al., 2001).
5. It is now evident that immune responses vary for a variety of hormones including EPI, norepinephrine (NE), ACTH, cortisol, opioids, growth hormone, prolactin, and estrogen that provide a pharmacological basis for neuromodulation (Sanders et al., 2001).
1. Although the SNS is clearly involved in short-term changes in immunity, the longer-term consequences of SNS activation may also be significant. Sympathetic nerve fibers innervate both primary and secondary lymphoid organs (Felton et al., 1987), and provide a direct mechanism by which the SNS may influence aspects of immunity.

2. Destruction of lymphoid sympathetic fibers via treatment with 6-hydroxydopamine appears to potentiate immune responses to antigen. These observations have led some to argue that the SNS exerts a tonic inhibitory influence on lymphoid immune processes. In a sustained program of research, Ben-Eliyahu and Shalit (2001) have found that stress decreases NK cell activity and increases tumor growth.

3. These effects appear mediated by the SNS because ß-adrenergic blockade or adrenal de-medulation eliminated these stress-induced effects, whereas ß-adrenergic agonists mimicked the effects of stress on tumor growth.

4. Another pathway of interest is through an opioid mechanism because stress has been linked to activation of the opioid system (Wang et al., 2002). In vivo studies suggest that infusion of morphine or implantation of morphine pellets decreases splenic NK cell activity and the proliferative response to mitogens (Bayer et al., 1990; Shavit et al., 1986).

5. These effects appear partially eliminated by opioid antagonists (Bayer et al., 1990), with activation of the SNS and HPA as two potential indirect mechanisms also responsible for such effects (Feinstein, Dykstra, & Sibley, 1983; Freier & Fuchs, 1994). Consistent with the role of opioid hormones on immune processes and tumor growth, fentanyl (an opioid analgesic) was associated with a suppression of NK cell activity and decreased resistance to tumor metastasis in rats (Shavit et al., 2004).

1. The three major hormonal pathways linking stress to immune processes include activation of the HPA, SNS, and opioid systems.

2. Of these, much focus has been placed on hormones of the HPA, such as cortisol, given its theoretical role in chronic stress processes (Selye, 1956).

3. The major influence of HPA hormones on immune processes appears inhibitory (Munck, Guyre, & Holbrook, 1984). For instance, glucocorticoids inhibit aspects of antigen presentation (Baus et al., 1996) and pre-incubation of PBLs with glucocorticoids tend to decrease the proliferative response to mitogens as well as NKCA (Holbrook, Cox, & Horner, 1983; Wiegers et al., 1993). Many of these effects were blocked by the specific glucocorticoid receptor antagonist RU-486 (e.g., Wiegers et al., 1993).

4. HPA hormones may indirectly suppress in vivo cellular immune function in at least two ways. Central administration of CRH reliably decreases the proliferative response to mitogens (Johnson et al., 1994) and splenic NK cell activity.

5. Although central CRH activates the HPA axis, it also activates the ANS and the influence of central CRH on splenic NK cell activity appears mediated by activation of the ANS (Irwin et al., 1989). HPA hormones also appear to modulate cytokine production (Munck, Guyre, & Holbrook, 1984). The cytokines interferon-γ and IL-2 enhance the cytolytic activity of NK cells and cytotoxic T-cells, and appear to play an important role in the elimination phase of cancer immuno-editing (Dunn et al., 2002). Importantly, HPA hormones, such as ACTH, appear to inhibit the synthesis of both interferon-γ and IL-2 (Krya, Wang, Stea, & Gallo 1984; Kelso & Munck, Guyre, & Holbrook, 1984).

1. The data linking stress to immune function highlights the potential role for stress-reduction interventions in enhancing aspects of immune function, with potential beneficial influences on cancer-related processes.

2. One cognitive-behavioral stress management intervention in early stage breast cancer patients found decreases in cortisol (Cruess et al., 2000), a finding mediated by changes in patients’ perceptions of benefit finding.

3. In general, interventions in chronically stressed populations such as cancer patients appear to have beneficial influences on immunity (Fawzy et al., 1993; Lutgendorf et al., 1997). However, little evidence exists suggesting that stress management interventions can increase immunity in healthy, non-stressed populations (Epel, 2001).

4. The link between chronic stress and immune processes potentially highlights the role of stress reactivity, exposure, recovery, and restoration on cancer outcomes. Very little research has separated out the effects of these stress component processes on cancer outcomes, especially in regards to stress recovery.

STRESS AND INFECTION DISAESES: Background information.

1. Although mortality as a result of infectious diseases has declined in industrialized countries, it nevertheless remains an important cause of morbidity and mortality.

2. More specifically, the emergence of HIV has highlighted the importance of understanding links between stress and infectious disease processes.

3. According to recent statistics, over 20 million people have died worldwide since the start of the epidemic in the early 1980s and an additional 40 million individuals are now living with HIV or AIDS (UNAIDS/WHO, 2004). With no known cure, it is clear that HIV and AIDS will continue to be a significant worldwide health problem.

4. It is also important to note that infectious diseases such as influenza, even in industrialized countries, are an important cause of mortality in older adults (Effros & Walford, 1987).

5. In addition, tuberculosis (TB) was responsible for an estimated 2 million deaths in 2002 and the incidence of new infections continues to pose major health risks in many countries (WHO, 2004).

6. The immune system plays an important role in the control of such infectious diseases. However, the specific effector mechanisms responsible for protection depend on the type of challenge (Abbas & Lichtman, 2003). Protection against virions and bacteria begins with innate immunity to prevent them from entering the host (e.g., skin, mucous membranes). Innate immune processes such as complement activation, macrophage activity, and inflammation provide further protection once pathogens enter the host.

7. For instance, some extracellular bacteria have features in their cell walls (e.g., LPS in gram-negative bacteria) that activate the alternative complement pathway that in turn can destroy the bacteria. Macrophages and NK cells may also play important roles in innate immunity because they are able to phagocytize some pathogens once they enter the host.
1. Once the pathogen begins replicating inside the body, the adaptive immune response becomes the important mechanism for resolution of these infections.

2. For extracellular pathogens such as some bacteria, the primary arm of adaptive immunity is humoral. Humoral immunity refers to the activity of B-cells that replicate and produce Ab specific to the pathogen.

3. Antibodies can facilitate the elimination of extracellular pathogens by neutralizing them and their toxins, marking them for destruction, or both (e.g., opsonization). Helper T-cells (i.e., TH2 subset) facilitate this process by aiding in the clonal expansion of B-cells.

4. However, viruses and some bacteria (e.g., TB) are intracellular pathogens and the resolution of these infections is primarily T-cell mediated via the cellular arm of adaptive immunity (Abbás & Lichtman, 2003).

5. Cytotoxic T-cells recognize viral antigen in the context of MHC class I molecules and can directly lyse infected cells. In addition, helper T-cells (i.e., TH1 subset) aid in the clonal expansion of cytotoxic T-cells and secrete cytokines (i.e., IL-2, interferon-γ) that enhance NK (kiss or phagocytosis of infected cells. Helper T-cells may also stimulate B-cells to produce Ab.

6. Antibodies and complements may then directly lyse infected cells or opsonize them for subsequent killing.

Evidence linking stress to infectious diseases.

1. The overall evidence linking stress to infectious diseases appears strong (Baum & Posluszny, 1999; Cohen & Williamson, 1991; Kiecolt-Glaser et al., 2002).

2. There have been two general approaches to examining the links between stress and infectious diseases. One approach has been to link stress to naturally occurring infections. Recent studies suggest that life stress, and chronic stress in particular, is related to increased susceptibility to infectious disease (Deyck, Short, & Vitaliani, 1999; Kiecolt-Glaser et al., 1993). For instance, caring for a family member with schizophrenia was related to the risk of developing an infectious disease (Deyck, Short, & Vitaliani, 1999).

3. Results of this study showed that patient symptoms during acute exacerbation of schizophrenia, but not more stable symptoms, was related to risk for infections in caregivers. In the context of long-term stress, these data suggest that exposure to less predictable sources of stress may be particularly important to consider.

4. Although the above data are consistent with the role of stress in the risk for infections, a more controlled approach has been to expose consenting adults to a viral challenge.

5. Recent studies, which improved on the methodological limitations of prior research, provide strong evidence for a link between stress and susceptibility to infectious diseases (Cohen et al., 1998). In one study that examined different types of stressors prior to challenge, consenting adults were inoculated with the common cold virus and quarantined for five days (Cohen et al., 1998).

6. Only stressors lasting over one month were associated with increased risk for verified colds. Of these, chronic interpersonal and work stressors were primarily responsible for the effects of chronic stress on infections. These effects were independent of pre-challenge Ab status, demographic factors, personality processes, and various health practices. In another study, these investigators also reported the combination of high life stress and high cortisol responses to acute laboratory stress predicted an increase in verified upper respiratory illnesses (Cohen et al., 2002).

Importantly, there is strong evidence from both animal and human studies that stress can result in reactivation of latent viruses. The exposed individual is infected for life, but the cellular immune response is usually successful at keeping the virus in check. However, individuals with compromised cellular immune processes (e.g., HIV+ populations or patients on immuno-suppressive therapies) may experience reactivation of one or more of these latent viruses.

1. One virus of particular interest is HIV, which is found in blood, semen, vaginal fluids, and breast milk of infected individuals at biologically relevant quantities. Upon entering the body, it infects cells possessing specific surface molecules (e.g., CD4+ cells).

2. One of the important cells infected and destroyed by HIV is the helper T-cell. Helper T-cells are absolutely essential to coordinate both the cellular and humoral arms of adaptive immunity. By depleting helper T-cells, HIV cuts off the ability of the immune system to effectively fight against foreign invaders.

3. Although the body mounts a vigorous immune response, the virus can reside in a "latent stage" that can last for years. During this phase, HIV may be diminished in blood, but disease progression continues in lymphoid organs.

4. Ultimately, HIV infection can result in the destruction of this important cell line and the subsequent development of AIDS which is a condition in which the body's immune system eventually loses its ability to fight off foreign invaders (Abbás & Lichtman, 2003).

5. As a result, the infected person is at risk for morbidity and mortality from pathogens that a healthy person would normally have no trouble fighting off. Although no cure is presently available, recent biomedical advances have successfully extended the lives of HIV+ individuals (Kelly et al., 1998).

6. Although significant challenges exist (e.g., ability of HIV to mutate because of encoding errors), vaccines against HIV are now being evaluated in several large clinical trials and remains a high priority for biomedical research.
1. However, evidence was found for an association between stress and lower NK cell counts and NK cell activity in HIV+ populations. Although the links between stress and NK cell function were consistent with poorer immune regulation of HIV, the lack of findings for CD4+ cells was unexpected.

2. However, some researchers have argued that more long-term studies were needed in order to examine how stress is related to the entire course of disease. In one such study, Leserman and colleagues (1999) followed a sample of HIV+ individuals for up to seven and a half years.

3. In their study, 37% of the sample had progressed to AIDS. Importantly, faster progression to AIDS was predicted by a total index of stressful events (i.e., number and severity). Although more research is needed, there is recent preliminary evidence linking stress to the progression of HIV infection (see Cole & Kemeny, 2001, Kopinski, Stoff, & Rauch, 2004).

4. In the context of HIV it is also important to discuss how stress may influence exposure to HIV infection (Baum & Picouzay, 1999). This is salient because the primary route of HIV infection is behavioral in nature (Kelly et al., 1993).

5. Stress is linked to changes in health behaviors, including alcohol and drug use (Testa & Collins, 1997). The use of alcohol and illegal drugs may in turn increase risky sexual behavior through processes such as dis-inhibition and facilitation of sexual arousal (McCarty, Diamond, & Kaye, 1982; O’Keefe, Nesselho, Kendall, & Baum, 1990).

6. Thus, stress appears to influence behavioral factors that may place individuals at risk for HIV infection.

1. Studies examining the links between stress and vaccination provide a promising paradigm for understanding more specific biological mechanisms because increased Ab titers to such vaccines are related to lower risk for infection (Center for Disease Control, 1996).

2. Importantly, stress predicts lower Ab production in response to influenza (Kiecolt-Glaser et al., 1996; Miller et al., 2004; Vedhara et al., 1999). However, R (Lubanyi et al., 1993; Glaser et al., 1992), meningingi C (Burns et al., 2002), and Pneumococcal Pneumonia vaccinations (Glaser et al., 2000).

3. One preliminary study also found that a stress-management intervention was associated with higher serum cortisol in response to vaccination compared to nonintervention caregivers, although there was no evidence that changes in stress perceptions mediated such differences (Vedhara et al., 2001). The studies linking stress to Ab titers following vaccination clearly implicate the humoral arm of adaptive immunity as an important mechanism linking stress to infectious disease susceptibility.

4. One question, however, relates to the kinetics of the Ab response and the phase in which stress may influence susceptibility to disease.

5. In one of the only studies that we know of to examine this question, Miller and colleagues (2004) examined daily assessments of stress and its association to Ab production to an influenza vaccination in healthy participants. Daily levels of stress were followed for three days prior to and ten days post-vaccination. Results of this intriguing study found that stress prior to and on the day of the vaccination was not related to subsequent Ab production. However, from the third day post-vaccination, daily stress was associated with less Ab production, with the strongest independent effect evident on the tenth day post-vaccination (Miller et al., 2004). Of course, the findings regarding the kinetics of the susceptible period need to be considered in light of the healthy population because these patterns may change as a function of an individual’s immune status (e.g., caregivers).

1. Although many studies have examined cortisol levels at one point, or in some cases averaged over an extended period of time, some research suggests the importance of modeling repeated exposure to cortisol. Such studies would be consistent with the role of stress exposure in these disease processes.

2. In vitro studies suggest that cortisol can reactivate latent EBV (Glaser et al., 1995), the kinetics of such changes were recently tested by Cacioppo et al. (2002).

3. These researchers incubated latently infected cells in varying concentrations of desamethasone (DEX) (i.e., 10, 5, 10, 5 M to 10, 5 Meverry 24 hours for three days). The different concentrations of DEX were thought to model the in vivo effects of pulsatile cortisol changes that are likely to occur with acute stressors. Control cells were incubated with media only, or a single concentration of DEX for three days.

4. Replicating prior research, it was found that the control media alone resulted in only a small (2–3%) percentage of EBV antigen positive cells, while single concentrations of DEX were associated with greater reactivation of EBV as measured by antigen positive cells after three days (5.63%–8.06%).

5. However, varying the concentration of DEX over three days resulted in a threefold or greater increase in EBV antigen positive cells.

6. These results are consistent with the notion that pulsatile changes in P因子 hormones, which covary with repeated exposure to stress, may have greater health consequences than tonic levels of these hormones.

1. In an attempt to model biological mechanisms, several studies have examined neuroendocrine processes responsible for some of these stress-induced vaccination effects.

2. Cortisol is a prime candidate given its general immunosuppressive effects (Muneck, Guyre, & Holbrook, 1984). In the case of Ab production following vaccination, one study found little evidence that changes in cortisol were responsible for such differences in healthy participants (Miller et al., 2004).

3. However, a study looking at the chronic stress of caregiving found associations between stress, cortisol, and Ab titers that were consistent with mediation (Vedhara et al., 1999). In addition, Cacioppo and colleagues (1998) reported that cortisol reactivity to acute psychological stress predicted a decline in the T-cell response to an influenza vaccination in older adults. These data suggest that cortisol may play a relatively larger role in stress-induced immune changes during chronic stress or in populations with more compromised immune systems.

4. Animal models may provide a stronger test of neuroendocrine mediation because of the increased experimental control and more detailed assessments that can be obtained. In a murine model of influenza infection, restraint stress was associated with a virus-specific decrease in IL-2, IL-10, and interferon-γ production (Dobb et al., 1996).

5. These effects were blocked by the glucocorticoid blocker RU-486. It should be noted that although hormones of the HPA axis appear important, there are other hormonal pathways that need to be considered. For instance, in one study stress was linked to a poorer Ab response to a novel antigen in rats (Shao et al., 2003). However, significant correlations were only found between Ab titers and norepinephrine levels (r = -.56) but not corticosterone levels. Sheridan et al. (1998) also reported that the effects of restraint stress on lymphocyte trafficking and cytokine responses in virus-infected rats were mediated by activation of the HPA axis. However, the decreased cytotoxic T-cell response to stress was not influenced by treatment with RU-486 but by α-2-adrenergic blockade, which suggests a sympathetic mechanism for this effect.

1. Promising evidence for mechanism also exists regarding the neuroendocrine pathways potentially responsible for the links between stress and HIV infections (Kopinski, Stoff, & Rauch, 2004).

2. In vitro studies suggest that incubation of HIV infected cells with glucocorticoids can increase viral load in some cell lines (Markham et al., 1986). In work using a primate model of HIV infection (simian immunodeficiency virus, or SIV), Capitanio, Mendoza, Lerche, and Mason (1998) examined the influence of social stress on various outcomes. Results revealed that infected animals in stressful (unstable) social groups had lower basal cortisol and shorter survival. The investigators speculated that the lower baseline cortisol levels might indicate a dysregulation of the HPA axis as often seen with posttraumatic stress patients (e.g., Yehuda et al., 1990).

4. Research also suggests the importance of considering other neuroendocrine processes in HIV+ individuals. As reviewed earlier, both SNS and opioid processes appear to inhibit aspects of immune function and increase progression. In vitro studies suggest that NE can increase HIV replication, an effect that appeared mediated by a α-2-adrenergic mechanism (Cole et al., 1998). Similar in vitro effects of opioid hormones (e.g., morphine) on HIV replication have been found (Li et al., 2003).

5. Moreover, opioids appear to increase macrophage susceptibility to infection, possibly by up-regulating CCR5 receptor expression which is an important coreceptor for HIV infection (Li et al., 2003).
1. In terms of component stress processes, very little evidence exists on the role of stress recovery on immune mediated disease processes. However, there is evidence indicating that restorative processes may play a major role in stress-induced susceptibility to infectious disease.

2. Although critical data are just appearing, researchers suggest that the important role of sleep in immune function (Irwin, 2002). Even acute stress predicts decreased objective (e.g., rapid eye movement count) and subjective (e.g., sleep quality) aspects of sleep (German et al., 2003; Morin, rodrique, & Ivers, 2003).

3. In one study, Lange and colleagues (2003) examined if sleep deprivation (i.e., 36 hours) following a Hepatitis A vaccination influenced subsequent Ab responses. Results showed that the immediate effects of sleep deprivation resulted in a delayed and reduced release of growth hormone, prolactin, and dopamine.

4. Sleep deprivation started to have an effect on the primary immune response about 14 days after vaccination and became larger up to 28 days post-vaccination. The authors speculate that early immune processes related to IL-2 production, a cytokine that enhances both T- and B-cell differentiation, may have been responsible for these effects.

5. Importantly, several studies have now shown that sleep disturbances mediate the effects of stress on aspects of immunity for more chronically stressed participants (Cruess et al., 2003; Hall et al., 1998; Ironson et al., 1997). Bereaved participants (Hall et al., 1998), and HIV-infected patients (Cruess et al., 2003). For instance, researchers examined the impact of Hurricane Andrew's one to four months after the disaster. The stress of Hurricane Andrew was associated with posttraumatic symptoms that in turn were related to lower NK cell activity. Importantly, the onset of new sleep problems statistically mediated the post-traumatic symptoms – NK cell activity relationship.

6. The role of immune processes in cardiovascular disease.

1. Traditionally, the immune system was thought to be involved in the development and progression of cardiovascular disease (CVD). The immune system is known to play a role in the development and progression of CVD by initiating and perpetuating inflammation and tissue injury.

2. Cardiovascular disease can be exacerbated by smoking, obesity, diabetes, and hypertension. These risk factors can trigger inflammation, which can lead to the development of atherosclerosis.

3. Atherosclerosis is a condition in which the walls of the arteries become inflamed and thickened, leading to the formation of plaques. These plaques can rupture, causing blood to flow into the surrounding tissue, leading to the formation of clots.

4. The immune system plays a critical role in the development of atherosclerosis. The immune system identifies and responds to foreign substances, such as lipids and lipoproteins, that are present in the bloodstream.

5. Once these substances enter the bloodstream, they can become trapped in the walls of the arteries, leading to the formation of plaques. This process can be further exacerbated by the production of inflammatory cytokines, which can promote the growth and development of plaques.

6. The immune system can also respond to infections, such as pneumonia. This response can further exacerbate inflammation and tissue injury, leading to the development of atherosclerosis.

7. In addition to systemic inflammation, the immune system can also respond to local injury, such as plaque rupture. This response can promote the development of new plaques and the formation of new blood clots, leading to the development of acute coronary syndromes and heart attacks.

8. Therefore, the immune system plays a critical role in the development and progression of cardiovascular disease. By understanding the role of the immune system in CVD, researchers can develop new strategies to prevent and treat this deadly disease.
1. Stress-induced cytokine production may be mediated by the release of neuroendocrine hormones that influence cytokine release and macrophage-TCF function more generally (Sanders et al., 2001).

2. However, it is important to note that inflammatory cytokines are not just produced from cells of the immune system (Papanicolaou et al., 1998). For instance, IL-6 is produced by bone marrow stromal cells, epithelial cells, Smooth Muscle Cells, and cells of the anterior pituitary (Papanicolaou et al., 1998). When released, such cytokines can cause an increase in adhesion molecules that promote the migration of monocytes and T-lymphocytes as a characteristic of early endothelial dysfunction.

3. Moreover, Bosch and colleagues (2003a) found that acute psychological stress was associated with a selective increase in T-cells that express chemokine receptors. These changes were most pronounced in high cardiac sympathetic responders and further highlighted the importance of a more integrative analysis of stress effects across systems. Illustrative steps in which stress can influence inflammation and cardiovascular disease risk are provided in Figure 26.2. Stress-induced cytokine release can influence early inflammatory processes that are related to cardiovascular disease. Cytokine release during stress may also influence cardiovascular disease processes as the lesion advances.

4. The cytokine macrophage colocalization (CMC) hypothesis proposes that development of the foam cell as it can augment scavenger receptor expression on macrophages (Libby, 2002). M-CSF, as well as IL-1 and TNF-α, can also increase the binding of LDL to vessel walls, and up-regulate the LDL-receptor gene (Libby, 2002). At later stages of the lesion, plaque disruption can be influenced by cytokines (Libby, 2002). Activated T-cells produce monokines that can decrease collagen production by SMC. Cytokines such as IL-1 TNF can increase the production of the protein metalloproteinase that in turn can degrade the fibrous cap of advanced lesions (Papanicolaou et al., 1999). The result is a weaker fibrous cap that is susceptible to rupture due to factors such as increased hemodynamic stress (Libby, 2001).

1. An additional pathway by which stress-induced inflammatory cytokine release can influence cardiovascular disease is via the subsequent release of acute-phase proteins (Papanicolaou et al., 1998).

2. IL-6 is a potent stimulator of CRP and fibrogenesis from the liver. CRP has received much recent attention as it has been shown in a number of large prospective studies to predict future coronary risk, even in participants with normal levels of cholesterol (Libby, 2002). Although CRP can be thought of as a clinical marker of inflammatory processes, recent research is showing that CRP may play a direct pro-inflammatory role in the atherogenic process (Kreiss et al., 2004; Verma, Smitko, & Yeh, 2004).

3. For instance, CRP may decrease nitric oxide production and increase cytokine production (Verma, Smitko, & Yeh, 2004). These factors can regulate adhesion molecules and increase monocyte recruitment (Kreiss et al., 2004; Verma, Smitko, & Yeh, 2004).

4. Although the release of CRP via IL-6 seems to be an important factor in inflammation and cardiovascular disease, connections between these factors are still under investigation (Ridker et al., 2000).

5. The more precise mechanisms responsible for cytokine release during stress, and its implications for health more generally, are actively being investigated (Black & Garbutt, 2007; Kiochi Glaser et al., 2002).

6. One cytokine of recent interest is IL-6 given its diverse physiological role in inflammation as well as the adaptive immune response (Hawkley et al., in press; Kiochi Glaser et al., 2002). IL-6 predicts a range of health problems including cardiovascular disease, diabetes, osteoporosis, and some autoimmune disorders (Papanicolaou et al., 1998).

Figure 26.2. The potential role of stress-related immune processes in cardiovascular disease.

1. The links between stress, IL-6, and other health-relevant physiological changes are starting to be understood.

2. A key first step in this process appears to be stress-induced changes in SNS processes (Papanicolaou et al., 1998). Both stress and SNS agonists increase the production of IL-6 (Soszyński et al., 1996), and 82-adrenergic blockade eliminates these effects (Soszyński et al., 1996; van Gool et al., 1990).

3. Importantly, the mechanism of action appears to be central 82-adrenergic receptors as agonist more selective to such central processes (e.g., L-propranolol), but not more peripheral processes reduce the stress-induced increase in IL-6 (Soszyński et al., 1996).

4. Following SNS release, IL-6 is a potent stimulator of the HPA axis (Papanicolaou et al., 1998; Webster et al., 1998).

5. Administration of IL-6 is associated with an increase in glucocorticoids that can occur through a CRH-dependent or independent mechanism (Karigiannis et al., 2004).

6. For instance, Böth, Vot, and Muglia (2000) found IL-6 receptors on both parietal and cortical arterial cells. These investigators also found that knock out mice deficient in IL-6 produced less corticosterone during stress.

7. However, knock out mice deficient in both CRH and IL-6 produced the lowest levels of corticosterone (also see Karigiannis et al., 2004).

8. Under normal conditions, the subsequent increase in glucocorticoids serves as a negative feedback mechanism to down-regulate the inflammatory response (Papanicolaou et al., 1998). However, high levels of stress can decrease the sensitivity of immune cells to the inhibitory effects of glucocorticoids (Miller, Cohen, & Ritchey, 2002; Stark et al., 2001).

9. One mechanism by which this effect may be mediated is that glucocorticoids can directly modulate important isoforms of glucocorticoid receptors on cytokine producing cells (Webster et al., 2001).

1. Although IL-6 can influence the release of CRH, there is good evidence that the links between IL-6 and CRH are bidirectional. CRH plays an important role in the in vivo and in vivo regulation of IL-6 (Webster et al., 1998). Inhibition of HSP70 reduced macrophages with CRH leads to an increase in inflammatory cytokines, including IL-6 (Agapitov et al., 2002).

2. Similar findings were demonstrated in vivo in mice given cornflour (a CRH receptor antagonist with both central and peripheral effects) showed decreased inflammatory cytokine responses to LPS.

3. Moreover, the biological significance of these CRH-induced processes was shown in transplantation experiments (Xiong et al., 1998). LPS activates monocyte CRH by upregulating the CRH receptor in monocytes. These findings suggest that CRH may play a direct pro-inflammatory role in the atherosclerotic process.

4. Despite links between stress and inflammation, there are several complexities in these associations that require further discussion.

5. First, although evidence does exist on the pro-inflammatory influences of IL-6 (e.g., via induction of CRP, see Verma, Smitko, & Yeh, 2004), the ability of IL-6 to activate the HPA axis suggests that it may also have important anti-inflammatory properties. In fact, Hawkley and colleagues (in press) have argued that the primary function of IL-6 may be anti-inflammatory.

6. Consistent with this view, IL-6 in itself does not appear to upregulate inflammatory mediators (e.g., prostaglandins) or the expression of adhesion molecules (Barton, 1997).

7. IL-6 can also down regulate the synthesis of pro-inflammatory cytokines (i.e., IL-1, TNF-α), and enhance the synthesis of IL-10 and the soluble TNF receptor factor p55 (Tigges et al., 1999). IL-6 knockout mice also produced higher levels of TNF-α in response to endotoxin challenge, and administration of IL-6 in these knockout mice eliminated the observed differences in TNF-α production (Ong et al., 1998). These IL-6 knockout mice also had a 50% lower survival rate in response to endotoxin challenge. Interestingly, levels of TNF-α were not different in the IL-6 knockout mice suggesting that IL-6 could not compensate for the deficiency in IL-6 (Tigges et al., 1998). As a result of existing data, Hawkley and colleagues caution researchers in interpreting the results of correlational studies because it is possible that elevated levels of IL-6 may be co-activated in an attempt to control inflammation. Future research will be necessary to determine the disease-relevant contexts in which IL-6 has pro- or anti-inflammatory effects.
1. A second complexity related to links between stress and inflammation that requires increased attention relates to the conditions under which normal control points can be disrupted (Hawley et al., in press).

2. One important control mechanism is activation of the HPA axis that tends to suppress immunity (Munck, Guyre, & Holbrook, 1984).

3. However, chronic stress can also lead to a state of glucocorticoid resistance (Miller, Cohen & Ritchey, 2002; Hawley et al.). For instance, pro-inflammatory cytokines such as TNF-α can modulate important isoforms of glucocorticoid receptors on cytokine producing cells (Webster et al., 2002).

4. The cytokine macrophage migration inhibitory factor (MIF) is also receiving attention as an important mechanism of glucocorticoid resistance (Hawley et al.). MIF is a pro-inflammatory cytokine that is released from the anterior pituitary, as well as from macrophages during glucocorticoid release (reviews by Baugh & Donnelly, 2005; Hawley et al., in press). It has been shown to override the suppressive effects of glucocorticoids and may control the “set-point” of the inflammatory response (e.g., via modulation of NF-κB activity).

5. These are promising integrating mechanisms linking stress to health outcomes may involve the

CNS coordination of the stress response.

1. Evidence for coordinated central pathways involved in the stress response provides further impetus for a more integrative view of the association between stress and health.

2. The central pathways involved in the stress response are complex and moderated by a number of factors including the duration of exposure, prior experience, and the social environment.

3. These moderational influences are not surprising given the role of multiple brain structures (e.g., hippocampus, amygdala) with reciprocal connections that are crucial to interpreting, responding to, and receiving feedback about potential threats (Chrousos, this volume, Dunn & Berridge, 1990; Gray, 1993). However, there are identifiable brain structures and pathways that appear critically important in the coordinated stress response.

4. One promising integrating mechanism linking stress to health outcomes may involve the activation and release of central CRH (Dunn & Berridge, 1990). Central administration of CRH mimics many of the physiological and behavioral states seen during stress. For instance, central CRH activates both the ANS and HPA axis (Irwin et al., 1989) and stimulates the release of endorphins (River et al., 1982). Increased CRH in brain regions involved in emotional responses, such as the amygdala, paraventricular nucleus, locus coeruleus, and cortex, mediate many behavioral responses to stress (Dunn & Berridge, 1990).

5. These include increased freezing behavior (Swigiel, Takashaki, & Kalin, 1993), decreased appetitive behavior (Krahn et al., 1986), decreased sexual behavior (Srinath Singh et al., 1983), increased grooming behavior (Holahan, Kalin, & Kelty, 1997), and an enhanced startle response (Lee & Davis, 1997). In fact, the CRH receptor antagonist antalarmin attenuates both biological and behavioral responses during stress (Habib et al., 2000).

Multilevel analyses of stress and health.

1. A more integrative view of stress and health will also need to consider diverse but complementary levels of analyses. Although most of the emphasis has been on biological mechanisms, understanding stress effects on disease may require similar attention to the social, personologic, psychological, and behavioral levels of analyses (Cacioppo & Bernston, 1992). In many cases, these different functional levels are embedded; hence, processes at more macrolevels can influence the more microlevels and vice versa (Cacioppo & Bernston, 1992).

2. Integrative research on the mechanisms linking stress to health across functional levels of analyses is in its infancy. However, the prior literature does provide some data on these processes.

3. At a more macrolevel of analysis, there is evidence that social stressors may be particularly important sources of stress explaining variations in health outcomes (e.g., Keelott-Glaser et al., 1996; Padgett et al., 1998). For instance, Padgett and colleagues (1998) exposed silently infected HSV rats to either social stress (i.e., social group reorganization) or physical stress (i.e., restraint stress).

4. Results revealed that only social stress was associated with significant reactivation of HSV (i.e., over 40% of socially stressed animals). These findings are consistent with research indicating that social stressors appear to be related to large and lasting effects on mood (Boiler et al., 1989) and immunity in humans (Cohen et al., 1998) and nonhuman primates (Coe, 1993).
1. **There are also potential personality factors that may influence the links between stress and health.**

2. Personality factors such as neuroticism are linked to greater subjective stress and hence may be responsible for the results of stress on some health outcomes (Bolger & Eckenrode, 1991).

3. Cohen and colleagues (1998) reported that self-esteem and the big-five personality factors could not account for the effects of stress on susceptibility to the common cold. However, a likely role for personality factors is in the moderation of stress-induced health processes.

4. **Prime candidates for examination include trait hostility and optimism that appear to influence physiological processes and health related outcomes (Scheier & Bridges, 1995; Smith & Gallo, 2001).**

5. Stress has been linked to changes in health behaviors such as exercise and alcohol consumption (Ng & Jeffrey, 2003). Therefore, it is also important to evaluate the effects of health behaviors as pathways responsible for the effects of stress on health outcomes. In most of the studies detailed earlier, health behaviors including exercise and alcohol did not explain much of the variance in the effects of stress on health (Cohen et al., 1998; Kiecolt-Glaser et al., 1995, 1996).

6. However, it is clear that stress influences health behaviors, and health behaviors are tied to similar physiological processes that are linked to health risks (Kiecolt-Glaser et al., 2002). Better measurement and conceptualization of health behaviors in light of more integrative mechanisms may allow a clearer test of their mediational role in explaining links between stress and health.

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**CONCLUSIONS**

1. **We have reviewed evidence linking stress to illness. These diseases include the leading causes of morbidity and mortality: cardiovascular disease, cancer, and infectious illnesses.**

2. There was strong evidence linking stress to cardiovascular and infectious diseases. The literature linking stress to cancer was controversial, but future research guided by the emerging concept of cancer immuno-editing may prove informative.

3. Importantly, impressive evidence exists on the biological mechanisms potentially linking stress to these disease processes. Of these, immune processes (e.g., inflammation) appear to play a critical role across these diseases and, along with an examination of CNS processes, may provide the impetus for an integrative approach to the study of stress and health.

4. The time is ripe for such an approach. Research that elucidates the complex links outlined in this paper at different functional levels of analyses may play a crucial role in helping us better understand, in Selye's (1956) words, the “secrets of health and happiness” and the “penalties for failure in this great process of adaptation.”

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1. One discussion that bears on these different levels of analyses involves the stress components reviewed in this part. These components linking stress to health include exposure, reactivity, recovery, and restoration (Cacioppo & Berntson). Of these components, relatively little research exists on stress recovery, especially in regards to immune-mediated disease processes.

2. Although the components of stress reactivity and stress exposure were often confounded, there was good evidence for links to disease outcomes, with interactive effects apparent when modeling both processes (e.g., Cohen et al., 2002).

3. Research on chronic stress and sleep disturbances also highlights the potential direct role of reactivity and exposure on restorative processes (Figure 26.1). Beyond this, little empirical evidence exists in these studies on how these stress components may have cascading or reciprocal effects as depicted in Figure 26.1.

4. Future research will need to take a more integrative approach to modeling these stress components and clarify their related (mediated), independent, or interactive effects on disease processes.

5. Of these components, restorative processes are particularly interesting given their potential unique association with health outcomes. Indeed, preliminary evidence exists linking restorative processes such as sleep and wound healing to health-related stress outcomes (Irwin, 2002; Kiecolt-Glaser et al., 1998).

6. Although the concept of restorative processes is promising, several questions will be important for future research to address. One question relates to what indices or outcomes are most relevant to restorative processes.

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1. **Restoration is linked to anabolic (energy conserving) processes and a number of potential indicators seem relevant such as growth hormone release and PNS processes (see Hawkley & Cacioppo, 2004).**

2. Integrating measurement and conceptual issues related to restorative processes at different functional levels would provide more guidance to future research.

3. A second question concerns the balance of anabolic to catabolic processes that is health relevant (Epel et al., 1998). Anabolic processes play an important role in physiological regulation, but direct research on how it counteracts harmful catabolic processes is needed.

4. A final, related question is how anabolic and catabolic processes unfold over time in ways that are health relevant.

5. Epel and colleagues (1998) have argued that one process relates to having sufficient time following catabolic processes to recuperate. In general, research on restorative processes as they relate to stress and health is just beginning, but process questions will soon begin to take on added importance.

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Thank you for your attention and participation

With all best wishes,