Workshop Report

Stress:
Putting the Brain Back Into Medicine

An Interdisciplinary Workshop of the
INTERNATIONAL LONGEVITY CENTER–USA

Sponsored by
International Longevity Center-USA
Institute for the Study of Aging
Canyon Ranch
Canyon Ranch Institute
Alliance for Health & the Future

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The International Longevity Center-USA (ILC-USA) is a not-for-profit, nonpartisan research, education, and policy organization whose mission is to help individuals and societies address longevity and population aging in positive and productive ways, and to highlight older people's productivity and contributions to their families and society as a whole.

The organization is part of a multinational research and education consortium and includes centers in the United States, Japan, Great Britain, France, the Dominican Republic, India, Sub-Saharan Africa, and Argentina. These centers work both autonomously and collaboratively to study how greater life expectancy and increased proportions of older people impact nations around the world.

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Executive Summary

Throughout the life course stress plays a major role in health and disease. Although it has long been known that the brain orchestrates the many ways that the body responds to these experiences, a gap exists between health care providers who focus on what is going on from the neck up and those who focus only from the neck down. Fortunately, as we gain greater understanding of the interrelationship between the central nervous system and various bodily functions through the interconnections of the nervous, endocrine, immune, and musculoskeletal systems, opportunities are increasing to breach this chasm.

The impact of stress on the body, classically understood as the "fight or flight response," has profound significance for both health and disease. The stress response to a threatening situation begins in the cerebral cortex, hippocampus, and amygdala, the latter two playing specific roles in learning, memory and emotions. Significantly, the amygdala and prefrontal cortex have links to fear, anxiety, and stress. Of particular importance is the effect of stress on the brain itself, with stress playing a significant role in regulating the structures of the central nervous system. Cortisol is one of the key mediators and quells the body's inflammatory responses to stressful situations.

Under acute conditions stress is protective, but when the body is activated chronically stress can cause damage and accelerate disease. Two important new concepts have emerged that differentiate between the body's adaptive response to acute stress (allostasis) and the wear and tear associated with chronic stress (allostatic load). The body creates allostasis by an intricately organized system of communication that links the brain, the endocrine system (chiefly the adrenal glands), and the immune system. Through allostasis the body attempts to remain stable in the face of changes and to provide enough energy to cope with any challenge. Wear and tear from overuse or the body's insufficient management of allostasis results in allostatic load. Over the course of a lifetime the body responds repeatedly to stressful events, and some allostatic load is nearly inevitable.

Contemporary neuroscience has afforded us a new understanding of the brain's plasticity, that is, its ability to repair or replace neurons when damaged or destroyed, as well as its capacity to protect itself in the face of repeated stress.

Evidence to support the association between brain function and health includes research findings on the continual transfer of information between the systems that make up the autonomic nervous system, the sympathetic system, and the parasympathetic system. The sympathetic nervous system reacts to stress by accelerating the heart rate, constricting blood vessels, and raising blood pressure. The parasympathetic system, on the other hand, slows the heart rate, increases intestinal and gland activity, and relaxes sphincter muscles.

Understanding the impact of stress upon various bodily systems leads to a connection between stress, cardiovascular health, and gastrointestinal health, as well as to the immune system.

Furthermore, brain-gut interactions play an important role in health and disease, but the precise role of gut signaling to the brain in health and disease currently is a research frontier. Common, everyday language is illustrative of the interrelationship of the central nervous system and the gut. For example, we refer to "butterflies in the stomach" or "gut feelings," reflecting an intuitive understanding of the brain-gut connection.

It is essential to view stress and allostatic load in the context of human social organization, which has a strong influence on health. Socioeconomic status, most commonly measured using some combination of information about education, occupation, and income, has a strong and persistent association with health and behavior. Poor people with fewer opportunities for higher education and increased income are more likely to experience chronic hazards and stress. Practices and policies that attempt to address stress and allostatic load must consider the social environment.

Further research and policy directions are needed.

- We need to continue to improve the battery of surrogate markers that can be thought of as an expansion of the cholesterol and blood pressure screening concept but that tap into a wider range of interacting body systems and may thus be better predictors of disease risk.
- Because depression and anxiety disorders, which are widely underdiagnosed and undertreated, are risk factors for a number of medical conditions, two of the simplest and most useful screening instruments are brief assessments for depression and anxiety, followed by referrals for treatment with psychotherapy, pharmacotherapy, or lifestyle change. Cognitive behavioral therapy and physical exercise have both been shown to be effective in the treatment of mild to moderate depression and anxiety disorders.
- A healthy regimen of diet, exercise, and effective stress management can prevent or substantially reduce many of our most common diseases, such as heart disease, diabetes, and high blood pressure. Practical instruction in the specifics of healthy eating, exercise, and stress management can help people sustain healthy lifestyles.
- Individuals at lower socioeconomic levels, who have less access to quality health care, health education, health clubs, and healthy foods, will have more obstacles to making and sustaining lifestyle change. Therefore, on a societal and governmental level, efforts must be made to disseminate health education information and provide greater access to resources that support healthy lifestyles. Many of the most powerful lifestyle habits, such as walking, eating smaller portions, or practicing a relaxation technique, involve little or no expense. The key to practicing them is education about their benefit and how to do them properly.
- Collaborations with the food industry are needed to promote the production of foods with less sugar and saturated fat content and the use of smaller portions.

Direct policy recommendations:

- Encourage private philanthropic support of studies that bridge the relationship between mind and body.
- Further expand the National Institutes of Health effort through extramural funding by setting up a specific unit of health administrators whose task and responsibility would be to help build the field of mind and body and stress.
- Establish a trans-NIH committee on stress (allostatic load) particularly involving the neurology, mental health, aging, and heart institutes but others as well to strengthen the trans-NIH intramural research and encourage support for the extramural program.
- Introduce into the medical, nursing, social work, and allied health curriculum attention to the interrelationships between social economic, mental, and biological factors.
- Expand human performance and longitudinal studies.
- Continue to build measures of allostatic load and stress.

- Bring clear attention to the role of the socio-economic status and human health.
- Study the economic benefits that derive from the integration of social, behavioral, and biological factors in medicine.
- Pay particular attention to evolving neuroscience, including brain-gut relationships.
- Establish a national effort to transform American lifestyles.
- Clarify and expand the definition of allostatic load as a means to quantify the cumulative toll exerted on the body over time in its efforts to adapt to life experience.
- Examine the role of allostatic load upon cognitive health.
- Study both preventative and therapeutic interventions that derive from new knowledge of the role of stress.
- Transform and translate key information derived from putting the brain back into medicine into the broad health care enterprise. This integration would have many social and economic benefits and advance quality of life.

Stress:
Putting the Brain Back Into Medicine

INTRODUCTION

Good or bad health often begins in the brain. Through this organ of conscious thought we make decisions that support or damage our health. Behind the scenes, the brain orchestrates the myriad ways in which the body responds to experience—through the interconnections of the nervous, endocrine, and immune systems.

Doctors have always known that many illnesses, too, begin in the brain. Some studies show that up to 70 percent of visits to primary care providers are for what turn out to be "psychological" complaints. But due to the structure of the medical care system and insurance-related restrictions—as well as a doctor's obligation to treat whatever medical illness exists—these complaints are not always adequately addressed.

This gap takes the form of a divide between those care providers who focus only from the neck down and those who look only from the neck up. Modern biomedicine, for example, is deeply invested in efforts to understand the machinery of the body from organ to cell to molecular events and how these are regulated by gene expression. It is a powerful strategy but most often ignores the vital input of social context, life events, and emotions. Thus, it often fails to take into account our heads, and the functioning of our mind and brain.

On the other side of the divide, those who emphasize the importance of mind and brain, of social and psychological realities, do not always attend to the rest of the body. The wondrous achievements of neuroscience, linking mind and brain in many aspects of mental functioning, have mostly ignored how the brain impacts bodily functioning in ways that can help or harm.

This isolation of views from only the neck up or neck down must be breached. Such is the goal of putting the brain back into biomedicine and the need to study the consequences of stress from both vantage points: psychology and physiology. In the doctor's office, most primary care physicians already deal with stress-related issues to the best of their abilities. Addressing psychological problems through a team approach is a cornerstone of care in some specialties, such as geriatrics.

The "classic" geriatric patient suffers from multiple, complex, interacting, physical, social, and emotional problems. Such a patient is ordinarily far more challenging than a young patient. For example, a 78-year-old woman hospitalized with congestive heart failure, which is the most common reason for hospitalization of older persons, may be "successfully" treated but she has lost functional capacity and morale in the hospital. She is fearful that she might never leave the hospital. But her doctors, nurses, and other staff have never gauged her fears or taken them into account. She has lost her appetite, but no one has time to sit with her at mealtime, so she eats alone and feels depressed. She loses muscle function, for no one on staff has the time to ambulate her. In short, no connections are being made between this woman's head and her body.

The purpose of this workshop report is to encourage more widespread integration of the two points

of view. Bearing this in mind, we will describe the role of the brain regions involved in learning, memory, and decision-making, then move on to look at the interactions between the brain and the various physiological systems traditionally treated in medical practice.

BRAIN STRUCTURE AND FUNCTION IN RELATION TO STRESS AND COPING BEHAVIORS

Importance of the cerebral cortex, hippocampus, and amygdala

Conscious thought in all of its aspects—sensory processing, motor control, decision-making, and consciousness itself—is made possible by the cerebral cortex. A thin outer covering consisting of folds (known as *sulci* and *gyri*) that separate it into identifiable lobes and regions, the cortex is actually one continuous sheet that, if laid out on a table, would cover several square feet. Classical terminology divides this sheet of cerebral cortex into two major categories: the *neocortex*, a complex structure divided into dozens of regions each with a different function, and the *allorcortex*, which includes an important nexus of memory known as the hippocampus and surrounding structures. A related brain area is the *amygdala*; this seat of memory and emotion, though not itself part of the cortex, is intricately linked to certain regions of the cortex, including the hippocampus. These interconnections play crucial roles in stress, memory, and stress-related illness.

Neocortex

Accounting for more than 90 percent of the total cerebral cortex in humans, the neocortex is the ultimate example of variation on a theme. This structure comprises six layers that are specialized for output and input to and from various other areas of the brain. A few dozen cell types populate virtually all neocortical areas. However, each layer's unique pattern, the types of cells represented, the combination of inputs and outputs, and synaptic organization actually vary substantially across the cortical surface, such that dozens of identifiable, distinct cortical regions exist, each dedicated to a given function. A key cell type is the *pyramidal cell*, so called because of the pyramidlike shape of its cell body. These neurons send out branches, called *dendrites*, and each dendrite is studded with hundreds of spines, each one receiving an incoming signal—providing an extraordinary capacity to integrate information from multiple sources.

While many brain regions send nerve signals to the cortex, the two most important types of projections are inputs from the *thalamus*, which handle sensory information, and inputs from other parts of the cortex, which connect functionally linked areas and form broad, distributed systems well suited to complex information processing. In the neocortex, the two extremes of regional specialization are the primary sensory areas (such as the primary visual cortex), which are highly specialized to receive the initial sensory input from the thalamus, and the primary motor cortex, which directly drives the motor centers of the brain stem and spinal cord. In rodents, these two areas represent the majority of the neocortex.

In the more complex human brain, however, much of the neocortex is the so-called association cortex. Association cortex can be linked to one of the individual senses, such as vision, or can receive many convergent inputs, allowing color, shape, movement, sound, and smell to come together into a cohesive and vivid perception—a playground scene, for example. The neocortex also uses its associative abilities to map sensory fields not only of the outside world but also of the body. The sensory inputs from the thalamus establish these maps in the primary sensory cortices, and they are sustained through multiple links within the cortex to more advanced association regions. For the visual system alone, there are dozens of dedicated cortical regions, each with its own map of the

visual world, in synchrony with other maps of other interconnected regions.

One of the most advanced regions of association cortex is the prefrontal cortex, which not only receives many different levels of input but also creates and sustains internal models of reality. The prefrontal cortex differs from other types of cortices in a fundamental way. As one might imagine, a region such as the primary visual cortex is hard-wired in the adult, so that the visual world remains stable. The prefrontal cortex, however, is highly "plastic," able to reconfigure the connections between neurons (known as synapses) to accommodate new memories, new rules, and new plans of action. In nonhuman primates and humans, this plasticity in the prefrontal cortex is critically important for learned behaviors, providing for such "executive" functions as working memory, planning, response inhibition, and temporal structuring of behavior. Unfortunately, the extraordinary capabilities of the prefrontal cortex make it uniquely vulnerable to aging, decreased estrogen levels, Alzheimer's disease, and probably schizophrenia.

The final type of cortex, the *limbic* cortex, receives input from many different cortical areas, including the prefrontal areas, and is strongly interconnected with the classical limbic structures involved with memory and emotion, such as the temporal lobe, the hippocampus, and amygdala. A key component of the limbic cortex for the current discussion is the anterior cingulate cortex, which is involved in emotional processes and visceral functions, and, according to recent data, is a region affected by stress (Radley et al., 2004).

Hippocampus

The hippocampus is critically important for the formation of new memories, particularly what is referred to as declarative memory (memory for facts) and episodic memory, the memory of life's events in time and space. If you can remember when something happened by visualizing, for instance, the apartment you lived in at the time, the hippocampus is at work. In order to form such memories, the hippocampus must have access to highly processed neocortical information. However, it receives such information indirectly. Association and limbic neocortical regions send convergent projections to the regions surrounding the hippocampus (e.g., *entorhinal* cortex), which then funnel such information into the hippocampus. Information flows through the hippocampal subregions in what is referred to as the *trisynaptic loop*, a series of excitatory projections through the hippocampus. While the trisynaptic loop is critically important for formation of certain memories, the storage, retrieval, and use of such memories become more reliant on the neocortex, in keeping with the flow of information back out of the hippocampus to the same neocortical areas that fed into the hippocampus through the entorhinal cortex.

Amygdala

While the amygdala is not a component of the cerebral cortex, it is strongly interconnected with the neocortex, as well as several other brain regions. The amygdala is a collection of clusters of nerve cells, so-called nuclei that have connections with each other and with other brain regions. For example, the lateral amygdala is the nucleus most directly linked to the neocortex, receiving from and projecting to sensory association regions (such as the *auditory association* cortex); it also connects with the *anterior cingulate* cortex, involved with fear and anxiety, and the orbital frontal regions, associated with social behavior. The lateral amygdala also receives thalamic inputs and appears to be the key site for fear conditioning. In contrast, the central nucleus is directly connected to centers in the hypothalamus and brain stem that control involuntary responses from the nervous system and digestive organs. Thus, the various nuclei of the amygdala work in concert to both provide emotional tone to sensory input and environmental influences, as well as to link the cortical

components of such behaviors to the centers that control many involuntary responses.

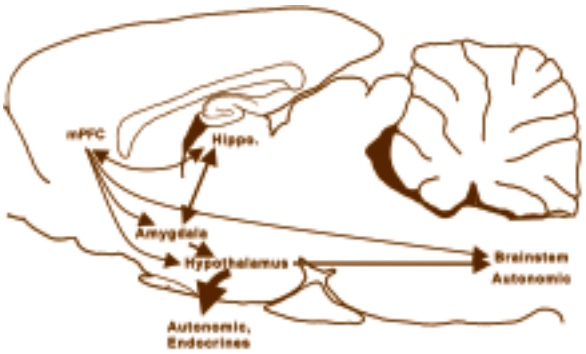
The amygdala plays a critical role in learning, particularly with respect to the emotional components of learning. Interestingly, these regions are also responsive to shifts in circulating hormone levels—sex hormones such as estrogen, and stress hormones such as glucocorticoids, produced by the adrenal glands. This link reinforces the notion that the hippocampus, amygdala, prefrontal cortex, and anterior cingulate cortex participate in a complex system that responds over an extended time frame to endocrine status—modifying behavior, learning, and response to future events. These modifications in neural circuitry are manifested even on the level of the synapse. However, some of these long-term synaptic alterations may underlie less desirable forms of learning, such as post-traumatic stress disorder (PTSD) or anxiety disorders. Chronic stress is known to cause neuron death and decrease dendritic branching in the hippocampus. Recent research shows a similar effect of chronic stress in the anterior cingulate cortex, suggesting that neocortical circuits, too, are profoundly affected by stress (Radley et al. 2004).

HOW THE BRAIN AND BODY RESPOND TO STRESS

The fight or flight response

"Stress" can be anything that causes the brain to activate the defenses—the nervous system and the hormonal and immune responses—that provide immediate protection and help the body adapt to the challenge in the longer term. For the stress, or fight or flight response to be successful, several things have to happen at once. The heart rate and blood pressure increase to provide oxygen to the muscles that will bring about fight or flight. The immune system gets ready to deal with any infection that might result from injury, and the brain is geared up to remember important features of danger as well as to be vigilant. Additional energy supplies are mobilized from storage in the liver. When the stressful situation is over, the emergency response system is shut off, and ongoing processes, such as growth and digestion (which have been temporarily suspended), are restored.

How the Brain and Body Respond to Stress



Role of the hypothalamus in controlling the mediators of the stress response

The stress response to a threatening situation begins in the amygdala, hippocampus, and cerebral cortex when an event is perceived as potentially dangerous. This information is rapidly transmitted to an area of the brain called the hypothalamus. This pea-sized structure influences the heart, the liver, the immune system, and digestive organs through a fast, hard-wired link of neural circuits—the so-called autonomic nervous system—consisting of the sympathetic and parasympathetic components. The sympathetic component uses the stress hormone epinephrine (better know as adrenalin) and the related neurotransmitter norepinephrine (or noradrenalin), whereas the parasympathetic component uses the neurotransmitter acetylcholine.

Indeed, it is important to realize that, besides the adrenal gland and sympathetic and parasympathetic nervous systems, there are other systems involved in stress, including the immune and metabolic systems. Moreover, the chemical messengers involved in the

stress response include not only adrenalin, noradrenalin, and acetylcholine, but also neurotransmitters like glutamate that are released from nerve terminals when neurons are activated; the "hormones" of the immune system, the *cytokines*, and *chemokines*; the hormones *prolactin* and *oxytocin*; and the metabolic hormones, such as *insulin* and *leptin*, a hormone produced by fat. The release of many of these chemicals has effects, both positive and negative, on the release of the other chemicals; hence the "stress-responsive system" operates like a nonlinear network. The adrenal hormone *cortisol* is an important player in this network of stress mediators, and its release is also controlled by the hypothalamus.

Key role of cortisol as a mediator of the stress response

Through a slower relay, the hypothalamus secretes hormones into the bloodstream, controlling the pituitary gland and the rest of the endocrine system. Key players in the endocrine exchange are the adrenal glands, which secrete adrenalin as well as the other chief stress hormone, cortisol. One of cortisol's jobs is to keep a gentle restraint on the immune system, along with the parasympathetic nervous system. Moreover, cortisol also affects many organs throughout the body, including the brain itself. The hypothalamus, in its turn, receives information from many of the same brain areas that play important roles in the stress response, especially the amygdala, the hippocampus, and the prefrontal cortex.

Each of these brain regions contributes to the behavioral and physiological response to major stressful events as well as the minor hassles of daily life. The central nucleus of the amygdala activates autonomic and neuroendocrine stress responses and freezing behavior, while the basal nucleus of the amygdala stimulates active coping (fight or flight) behaviors. The prefrontal cortex controls decision-making, such as the simple decision to interrupt ongoing behavior and do something different. It's also important in the "extinction" of fear—the active learning process by which a person or animal determines that something is no longer a threat. The prefrontal cortex receives important input from the amygdala. The hippocampus participates in spatial as well as declarative and episodic learning, and it is essential for "contextual" memory, such as remembering where you were and what you were doing when something important happened. The hippocampus is connected to both the amygdala and the prefrontal cortex; all three structures influence the hypothalamus when something stressful happens.

The stress response contributes to memory, immune function, and metabolism in ways that are protective and adaptive—in the short term (McEwen 1998; 2003; McEwen and Lasley 2002). However, as we shall discuss below, repeated stress can have damaging effects, in part because the very same physiological mechanisms that help protect the body in the short run become mismanaged and/or overused. One of the organs most vulnerable to overuse of the stress response system is, perhaps surprisingly, the brain itself. This is because in addition to initiating the fight or flight response, the brain receives input from many of the other circuits that are involved.

After a person or animal has mobilized to deal with a challenge, through either fight or flight, the branch of the *autonomic nervous system* known as the *parasympathetic nervous system* (discussed in greater detail shortly) sounds the "all clear" and restores the normal, everyday bodily processes back to functional status. At the same time, another shutoff mechanism is activated—the switching off of the slower second relay of hormones throughout the bloodstream. This mechanism is located in the hippocampus and is brought about by one of the stress hormones, cortisol itself, which participates in a negative feedback loop and thereby shuts off its own production. The hippocampus is rich in cortisol receptors, partly to make this shutoff feature possible and partly for another reason.

From an evolutionary standpoint, the last but not least component of the fight or flight response is the ability to deal with the situation if it ever happens again. Thus a stressful event carries an extra emotional charge that sharpens the memories associated with it. Working together, the amygdala and hippocampus provide what are sometimes called "flashbulb" memories. If you think of something in your life that had particular emotional resonance, the feelings associated with that memory come from the amygdala, whereas the context—the where, when, and how—are the work of the hippocampus. Memories of stressful events are seared into the hippocampus by cortisol, acting on its receptors in that part of the brain.

The dangers of chronic stress: allostasis versus allostatic load

When the stress response is not shut off or when it remains activated due to chronic stress or internal anxiety, the same chemical mediators that are so important for adaptation become involved in effects that are damaging to the body and contribute to such conditions as immune suppression, obesity, and diabetes, hardening of the arteries and hypertension (McEwen 1998; 2003; McEwen and Lasley 2002). This paradox has led to the introduction of two new terms: *allostasis* and *allostatic load*. Allostasis (meaning "achieving stability through change") refers to the active, adaptive response of the body that maintains homeostasis through the actions of the stress mediators discussed above. Allostatic load refers to the wear and tear from the overuse or inefficient management of allostasis, i.e., the almost inevitable impact on the body of responding repeatedly to stressful events. These two terms help to clarify ambiguities in the terms *stress* and *homeostasis* (for discussion, see McEwen and Wingfield 2003).

The nonlinear nature of the stress mediator network and the involvement of many mediators and body systems make it imperative to measure multiple body systems in order to assess allostatic load. The need to make measurements as noninvasive and inexpensive as possible has necessitated the development of a battery of measures that have been validated in a number of epidemiological studies. These are surrogate markers, like cholesterol, of risk for later disease, and their use and interpretation is patterned after the cholesterol screening. The difference is that the battery taps into multiple interacting systems.

In the original allostatic load battery, overnight urinary cortisol and catecholamines were assessed along with plasma levels of total and HDL cholesterol, glycosylated hemoglobin, DHEA, systolic and diastolic blood pressure and waist hip ratio as a measure of abdominal fat accumulation. These measures had been obtained in the MacArthur Successful Aging study and represented a good approximation of some of the surrogate markers for age—related risk for cardiovascular and metabolic diseases (McEwen and Seeman 1999). In the current CARDIA study, overnight urinary cortisol and catecholamines are being assessed longitudinally along with total and HDL cholesterol, glycosylated hemoglobin, IL 6, CRP and fibrinogen, waist hip ratio, systolic and diastolic blood pressure, and high-frequency heart-rate variability. Moreover, six saliva samples are taken over one day to assess the diurnal pattern of cortisol secretion.

There is nothing magical about the selected measures. They are a pragmatic solution to balance cost, relative noninvasiveness, and the need to tap into multiple systems. As a result, there is a need to further improve and test the allostatic load battery.

HOW STRESS AFFECTS THE BRAIN

Stress and stress hormones affect the structure and function of the brain regions that mediate the interpretation of what is stressful, namely, the hippocampus, amygdala, and prefrontal cortex. In so doing, they bias how the brain responds to stress. In the restraint stress model in rats, this bias

occurs because repeated stress impairs hippocampal-dependent declarative and spatial memory while enhancing fear and aggression (McEwen and Chattarji 2004).

The hippocampus as a target of stress and stress hormones

Studies with animal models have shown that cortisol and the "excitatory" neurotransmitters in the brain (those, like glutamate, that increase activity of neurons) play key roles in learning tasks that involve the hippocampus, such as spatial navigation (Otzil et al. 2001; Pugh et al. 1997). However, repeated stressful experiences can impair these functions, in part because the very same adaptive mechanisms begin to have different effects when chronically overactivated (McEwen 1998). For example, the overactivity of stress hormones in the blood, and excitatory neurotransmitters in the brain, suppresses the production of new cells in a part of the hippocampus known as the *dentate gyrus*. The birth of new neurons, called *neurogenesis*, is considered an ongoing and essential aspect of brain health; it is critically important in learning, memory, and perhaps even mood. Excess hormones and excitatory neurotransmitters can also reduce dendritic branching in parts of the hippocampus and prefrontal cortex, whereas chronic stress causes neurons in the amygdala to increase dendritic branching (McEwen 1999; Sousa et al. 2000; Wellman 2001; Vyas et al. 2002). These changes are accompanied by impaired cognitive function and increased fear and anxiety.

Yet, underlying these changes are indications that the brain is attempting to protect itself, in spite of the fact that it may also become more vulnerable to permanent damage as a result of repeated stress. In a model of chronic stress in rodents, restraining the rats for brief periods for 21 days impairs their performance on cognitive tasks that involve the hippocampus (Luine et al. 1994; Conrad et al. 1996). This same treatment enhances amygdala-dependent unlearned fear and fear conditioning (Conrad et al. 1999), which are consistent with the opposite effects of stress on hippocampal and amygdala structures. Taken together, the animal studies suggest that chronic overexposure to stress undermines memory and mental performance while increasing the load of anxiety.

Animal studies show that psychosocial stress (competitive, hostile, or unstable social environments) suppresses neurogenesis and causes dendritic shrinkage in key hippocampal neurons (Gould et al. 1997; Magarinos et al. 1996; Czeh et al. 2001); one of these stress models, the tree shrew, is considered to be a model of human depressive illness (Van Kampen et al. 2002). In humans, some studies of major depression and other mood- and anxiety-related psychiatric disorders show loss of hippocampal volume and enlargement of the amygdala (McEwen 2003; Sheline 2003). Studies in the tree shrew have shown that treatment with antidepressant, antiseizure, and mood stabilizing drugs prevents stress-induced hippocampal structural changes (Magarinos et al. 1996; Czeh et al. 2001; van der Hart et al. 2002). Besides reduced neurogenesis in the dentate gyrus, evidence shows that the cell bodies of existing neurons in the hippocampus become smaller, which is consistent with reduced size of the dendritic tree (Stockmeier et al. 2002). Such structural changes seem likely to play a major role in the volume loss in the human hippocampus and the related effects on cognitive function and mood (Sheline 2003).

The amygdala/prefrontal cortex links to fear, anxiety, and stress

In addition to the amygdala and hippocampus, the medial prefrontal cortex (mPFC) is affected by chronic stress, showing reduced dendritic branching (Radley et al. 2004). This may exacerbate the effects of stress by reducing the prefrontal control of many functions, such as decision-making, working memory, and the extinction of learned fear. Recent work has shown that the mPFC plays a critical role in

safety learning. Damage to the mPFC prevents animals from learning that a tone once paired with shock is no longer dangerous, a process called extinction of fear. Neurons in the mPFC increase their responses to tones after extinction (Milad and Quirk 2002), in effect signaling that the tone will not be followed by shock. This signal reaches the amygdala, where it inhibits central nucleus output neurons (Quirk et al. 2003; Rosenkranz et al. 2003), thereby preventing the expression of fear memories stored in the amygdala. In fact, mimicking this safety signal with electrical stimulation of mPFC reduces conditioned fear (Milad et al. 2004)

From a clinical perspective, these findings suggest that deficits in mPFC function would be associated with high levels of fear and anxiety. In support of this idea, people with depression and post-traumatic stress disorder (PTSD) have a smaller mPFC (Bremner et al. 2002; Rauch et al. 2003) and reduced prefrontal control over the amygdala (Bremner 2002; Shin et al. 2004). People with PTSD also have a smaller hippocampus (Gilbertson et al. 2002). Therefore, stress could trigger a vicious cycle characterized by increased activity in the amygdala and decreased prefrontal and hippocampal function, the result of which would be increased anxiety and increased stress. Future approaches to breaking this cycle may include augmenting mPFC function, either pharmacologically (Walker et al. 2002), physiologically (Cohen et al. 2004), or through cognitive control (Hariri et al. 2003). In the last decade, a type of cognitive therapy called *eye movement desensitization and reprocessing* (EMDR) has been widely used and demonstrated to be effective in the treatment of PTSD. In an unpublished study reported in *Psychiatric News*, Bessel van der Kolk observed changes in brain function that accompanied decreases in anxiety in PTSD patients after treatment with EMDR therapy. Specifically, after a series of EMDR therapy sessions, brain scans of PTSD sufferers showed increased activation in the frontal lobes and cortex.

EVIDENCE FOR ASSOCIATIONS BETWEEN BRAIN FUNCTION AND HEALTH

Outputs from the amygdala work through the neuroendocrine and autonomic nervous systems to affect many other systems in the body. The activity of the autonomic nervous system—in particular the balance between parasympathetic and sympathetic activity—is especially important for the health of the cardiovascular and immune systems.

Autonomic imbalance

There is growing evidence for the role of the autonomic nervous system (ANS) in a wide range of diseases. The ANS is generally conceived to have two major branches: the sympathetic system, associated with energy mobilization, and the parasympathetic system, associated with ongoing vegetative and restorative functions. Normally the activity of these branches is in dynamic balance. For example, there is a well-documented circadian rhythm in which sympathetic activity is higher during daytime hours and parasympathetic activity increases at night. The ANS can fluctuate on other levels as well, allowing the activity of the two branches to respond rapidly to changing environmental demands.

An organism's ability to adapt to its environment by being itself able to change has replaced the older concept of homeostasis—maintaining stability by staying the same. More modern conceptions hold that stability, adaptability, and health are maintained through a dynamic relationship between cells, organs, and biological systems (Friedman and Thayer 1998a, 1998b; Thayer and Friedman 1997; Thayer and Lane 2000). In this model there are multiple points of stability and a dynamic organization of resources to meet the demands of a specific situation, using up as little energy as possible. For example, in healthy individuals, average heart rate (HR) is greater during the day, when energy demand is higher, than at night, when energy demand is lower. People who lack this circadian variability—whose hearts beat in rigid regularity

24 hours a day—are more prone to many kinds of illness and even early death (Lipsitz and Goldberger 1992; Peng et al. 1994).

A lack of flexibility in the ANS also has ill effects. For example, when the sympathetic branch of the system has the upper hand for too long, pathological conditions can result—even death, if the situation goes on for too long (for review see Thayer and Lane, in press).

Imbalance in the ANS takes its toll most immediately on the heart. The heart is innervated by both branches—stimulated by the sympathetic nervous system and slowed down by the parasympathetic (Jose and Collison 1970). When at rest, the restorative influences of the parasympathetic nervous system predominate—a feature that neatly favors energy conservation. This dynamic balance is actually measurable in a person's heart rate, which, in addition to being slower at night, has a similar built-in variability from one beat to the next. Again, people with decreased heart-rate variability (HRV) are at increased risk of death, and HRV has been proposed as a marker for disease (Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology 1996).

Resting heart rate can be used as a rough indicator of autonomic balance, and several large studies have shown that risk of death from all causes—including such noncardiovascular ones as cancer—increases in tandem with resting heart rate (see Habib 1999 for review). This association of heart rate with all-cause mortality is independent of gender and ethnicity, and shows a threefold increase in mortality in persons with a heart rate over 90 beats per minute compared to those with heart rates of less than 60 beats per minute.

The explanation lies in an elegant mechanism sometimes known as the *vagal brake*. The parasympathetic nervous system exerts its calming, restorative influences through the vagus nerve (actually a fairly complex network of nerves), which, among other responsibilities, slows down heart rate. When the heart beats more slowly as part of normal beat-to-beat variability, the vagus nerve is in control—the vagal brake is on. In healthy people, when a minor change in the environment requires a slight mobilization of energy—if you're reading a book and the doorbell rings, for example—the vagal brake comes off and the heart rate increases a notch. People with unvarying heart rates, in whom the vagal brake does not function optimally, are not able to meet minor demands by taking off the brakes. They have to floor the accelerator, so to speak, by engaging the full emergency resources of the sympathetic nervous system, stimulating the heart again and again.

This sort of imbalance, in which the sympathetic nervous system has the upper hand, is associated with a wide range of abnormalities that lead to heart disease and death (Brook and Julius 2000). But there are also links with disorders less obviously connected to the heart. For example, decreased heart-rate variability is associated with diabetes mellitus—often preceding the onset of diseases as measured by standard clinical tests (Ziegler et al. 2001).

Autonomic imbalance may be a common pathway to increased illness and death from a host of other conditions, especially those in which the immune system goes awry. The healthy fight or flight response mobilizes the immune system, partly by increasing small molecules known as *cytokines*. When there is an injury, or the possibility of injury, the infection-fighting cells move out of the bloodstream and attach themselves to blood vessel junctions throughout the body—their battle stations, so to speak—to be ready to fight infection. If an actual injury occurs, the blood cells summon additional forces by sending out so called pro-inflammatory cytokines. When the infection has

been contained, other messengers, called anti-inflammatory cytokines, are sent out to call off the alarm.

Immune dysfunction in the form of unnecessary, damaging inflammation has been implicated in a wide range of conditions associated with aging—including cardiovascular disease, diabetes, osteoporosis, arthritis, Alzheimer's disease, periodontal disease, and certain types of cancers, as well as declines in muscle strength and increased frailty and disability (Ershler and Keller 2000; Kiecolt-Glaser et al. 2002). The common mechanism seems to involve excess proinflammatory cytokines, such as interleukin 1 and 6 and tumor necrosis factor. The connection to stress lies, once again, in the balance of the ANS. Increased activity of the parasympathetic branch and elevated levels of its chief neurotransmitter, acetylcholine, have been shown to slow down the production of proinflammatory cytokines that can lead to disease; on the other hand, frequent activation of the sympathetic nervous system can increase production of these potentially damaging messengers (Das 2000; Maier and Watkins 1998; Tracey 2002). Thus, autonomic imbalance may be a final common pathway to increased morbidity and mortality from a host of conditions and diseases.

The idea that less measurable factors, such as negative emotional states and dispositions, or personality, may be linked to disease and ill health is not new (Sternberg 1997). For example, anxiety, depression, and hostility have all been shown to be associated with ill health. Several recent reviews provide strong evidence supporting this connection (Friedman and Thayer 1998b; Kiecolt-Glaser et al. 2002; Krantz and McCeney 2002; Musselman et al. 1998; Rozanski et al. 1999; Verrier and Mittleman 2000). All of these reviews implicate altered autonomic function and decreased parasympathetic activity as a key player.

An additional pathway between psychosocial stressors and ill health is an indirect one, in which stressful external conditions lead to poor lifestyle choices that in turn undermine health—such as lack of physical activity and the abuse of tobacco, alcohol, and drugs. Sedentary lifestyle and substance abuse are both associated with autonomic imbalance and decreased parasympathetic tone (Ingjaldsson et al. 2003; Nabors-Oberg et al. 2002; Reed et al. 1999; Rossy and Thayer 1998; Weise et al. 1986). In fact, the therapeutic effectiveness of smoking cessation, reduced alcohol consumption, and increased physical activity rest in part on their ability to restore autonomic balance and increase parasympathetic tone.

In sum, autonomic imbalance, and decreased parasympathetic tone in particular, may be the final common pathway linking negative affective states and dispositions, including the indirect effects via poor lifestyle choices, to numerous diseases and conditions associated with aging as well as increased morbidity and mortality.

Cardiovascular health and disease

The last 30 years have witnessed a remarkable increase in our awareness of how closely the brain and heart (and its blood vessels) are intertwined. Concurrent advances in neuroscience, psychological science, and epidemiology have established the brain's widespread control of the cardiovascular system—showing that "psychology" can be a powerful risk factor for heart disease and identifying the relevant behavioral treatments. Once these advances are widely recognized and translated into controlled intervention studies, the brain will be a central figure in cardiovascular medicine.

Neuroscientists have established that the cardiovascular system is functionally well integrated with the central nervous system, not a separate, autonomous entity. Early views separating the two were based on observations that the cardiovascular system can function in the absence of neural input. Furthermore, the autonomic nervous system, which is connected to the heart and vasculature, was previously considered to be governed by

lower brain stem structures and to be effective only in emergency situations, for example, in response to a frightening situation. Extensive research in animals and corroborating research in humans have updated this concept. We now know that the brain receives significant information about the state of the cardiovascular system and that brain stem nuclei, acting on the ANS, make adjustments based on this information. Midbrain structures and areas of the cortex, including the medial prefrontal, also receive this information and are now known to control brain stem mechanisms (see reviews, Verberne and Owens 1998; Armour and Ardell 1990). Brain-imaging techniques have verified much of the functional neuroanatomy of these cardiovascular control systems in humans (Critchley et al. 2003; Gianaros et al. 2004)

Behavioral scientists and epidemiologists have established that certain patterns of behavior, stress reactions, and forms of mental illness increase the risk that a person will develop cardiovascular disease. Early work suggested that a pattern of competitive, hostile, impatient behavior (the Type A behavior pattern) created a risk factor for heart disease; current work continues to support this view (reviewed in Treiber et al. 2003; Rozanski et al. 2001). Relatedly, cardiovascular reactions to behavioral challenges predict subsequent hypertension as well as atherosclerosis development. Mental depression and an associated decrease in beat-to-beat variability of the heartbeat also have been clearly related to cardiovascular disease (Carney and Freedland 2003; Carney et al. 2001). In short, the brain control of the cardiovascular systems appears to have implications for disease. Cardiovascular disease also has clear effects on brain function. This is most notable for stroke, but relatively mild hypertension now appears to alter the brain's function during mental tasks. Anatomically, heart failure is associated with loss of gray matter within the brain (Woo et al. 2003).

The promise that these cardiovascular brain linkages may be exploited to combat heart disease and promote cardiovascular health has not yet been fully realized. An impressive array of individualized and public health–oriented behavioral changes, stress management, and relaxation/health enhancement techniques have been developed and applied in short-term studies to patients and individuals at risk for cardiovascular disease (Orleans 2000). However, the beneficial effects remain largely untested in large scale randomized clinical trials and, when tried, have not been uniformly successful (Rozanski et al. 2001; Davies et al. 2004). Perhaps this is not surprising given the complexity of the central nervous system and our rather primitive knowledge of its basic operation. However, the brain is a key player in cardiovascular disease but a poorly understood player. A focus on its role in the development and treatment of cardiovascular disease is overdue.

Immune system response

The immune system consists of mobile, infection-fighting cells (called T, B, and accessory cells), distributed in key locations to defend the body against the invasion of pathogens. All immunocytes originate in the bone marrow, but T cells develop their mature functions in the thymus gland, whereas B cells probably receive their "education" within the bone marrow itself, at least within mammals. Both of these educative regions are referred to as primary immune tissue. Once educated, immunocytes move about the body in the bloodstream and lymph vessels, residing for periods of time in secondary tissues such as lymph nodes and spleen and in tertiary immune tissues such as the gut, the skin, and the brain. Primary, secondary, and tertiary immune responses are innervated by parasympathetic, sympathetic, and sensory nerves. Immunocytes are, at some times in their lives, able to respond to many neurotransmitters and other chemical messengers and to virtually every hormone in the body, and they move about in the body as needed to fight an infection or heal a wound.

One such chemical messenger, *calcitonin gene–related peptide* (CGRP), is locally produced in the thymus and other tissues, including the brain. CGRP appears to act as a regional regulator of immune responses. In the thymus it suppresses activation of T cells and promotes their exit from the thymus when mature, or "educated." Expressed in the brain in instances of brain damage, CGRP is one of a series of molecules that may serve to keep the immune system "quiet." When someone suffers brain or spinal cord injury, much of the resulting disability comes from so-called secondary damage, brought about by excessive inflammatory reactions. CGRP and its partners may help keep this damage to a minimum.

Stress hormones such as cortisol and epinephrine help send immune cells to places where they are needed (a phenomenon known as trafficking), and, along with the sympathetic and parasympathetic nervous system, regulate the acute-phase response to an infection or wound. In a simplistic overview, the sympathetic nervous system, with epinephrine as its messenger, enhances the production of proinflammatory cytokines, whereas the parasympathetic nervous system has anti-inflammatory effects, at least in part by enhancing the production of anti-inflammatory cytokines that inhibit and otherwise modulate the inflammatory cytokine response. Cortisol is also well known for its anti-inflammatory actions—as anyone who has been treated for poison ivy can attest—and for its ability to shift the immune response toward the production of antibodies and away from a more immediate inflammatory response.

GASTROINTESTINAL FUNCTION AND THE BRAIN

Unique importance of the gut in mood and affective state

The unique relationship between the brain and the digestive organs collectively known as the *gut* has been recognized by the lay public and by practitioners of healing traditions going back to ancient times—long before the recent scientific interest in brain-gut interaction. This close relationship is reflected in colloquial expressions like "gut feelings," often associating the gut with negative emotional experiences, in commonly held beliefs that a heavy meal may impair our ability to think and cause bad dreams, and in the widely held concept that stress causes "butterflies" in the stomach (Mayer et al. 2000). Hippocratic medicine implicated the secretions from the liver in the mood (melancholy, for example, was ascribed to black bile), and traditional Chinese medicine postulates close relationships between mood states and energy flow in different viscera (such as liver chi deficiency or spleen chi stagnation) (Tan et al. 2004). Only within the last hundred years has the close relationship of the brain and the digestive system become the focus of increasing scientific investigation. From the Russian school of corticovisceral interactions in the early parts of the twentieth century to the current concept of brain-gut interactions, there has been continuous progress toward a better understanding of the two way interactions between brain and gut in health and disease (Anonymous 1, 2000).

Gut feelings and "visceral" reactions merit attention: The gut is one of the most important interfaces an organism has with its environment. It is unquestionably the largest. Whereas, in humans, the spread-out cerebral cortex would cover several square feet, the gut, if stretched out and ironed flat, would cover an entire football field. The gut has its own nervous system and hormone producing cells, as well its own immune system. Furthermore, its lumen contains an impressive array of bacteria. These systems function semiautonomously and are intricately linked to their counterparts in the body and brain.

Stress and gastrointestinal disease

Scientific interest in brain-gut interactions derives in large part from the well-known fact that stressful

events can trigger or aggravate some of the most common chronic disorders of the digestive system, including functional GI disorders, inflammatory bowel disease, gastroesophageal reflux disease (GERD—sometimes known as heartburn) and peptic ulcer disease. The observation that stressful events precede symptom exacerbation is based on several well-designed surveys in patients with functional GI disorders (Drossman et al. 2002). In addition, acute, life-threatening stress episodes in adult life (rape, post-traumatic stress syndrome) are an important risk factor in the development of such disorders. Finally, early life stress in the form of abuse can make victims more likely to develop functional GI disorders and inflammatory bowel disease later in life (Mayer 2000).

In the case of peptic ulcers, recent focus on the roles of bacteria (*Heliobacter pylori*) and nonsteroidal anti-inflammatory drugs (NSAIDs) has nearly abolished interest in the role of stress. Nevertheless, considerable evidence indicates that such a role does exist (Levenstein et al. 1999). Bacterial infection itself does not necessarily lead to ulcers; more than 80 percent of *H. pylori*–infected individuals never develop an ulcer. The majority of people who take NSAIDs never develop ulcers; in people with peptic ulcers unrelated to NSAID use, at least 10 percent are not infected with *H. pylori* (Peterson and Graham 1997). It is intriguing to speculate that certain life stressors may determine which *H. pylori* positive individuals actually develop an ulcer, and which patients develop the more general symptoms of dyspepsia instead, without an ulcer.

The epidemiological evidence to support a causal relationship between life events and disease activity in heartburn is less conclusive. The primary information about a role of stressful life events comes from a population-based survey, in which 64 percent of patients indicated that stress increased their symptoms (Anonymous 2, 1988). These results may be complicated by the fact that anxious patients exposed to long periods of stress are more likely to notice stress-induced symptom exacerbation.

The brain-gut axis The association of stressful life events with various chronic GI disorders is an obvious consequence of the close interactions between the brain and the GI tract. However, the evolving understanding of brain-gut interactions suggests a much wider role of these interactions in health and disease.

An organism's response to stress is generated by a network of integrative brain structures, such as the paraventricular nucleus (PVN) of the hypothalamus and the amygdala. These structures receive information about the general state of the body via a network of neural "microphones" in the digestive tract and throughout the body; they also receive input from cortical structures including the medial prefrontal and anterior cingulated cortices, both of which are involved in stress and emotion (Bandler et al. 2000). This same integrative network sends outgoing signals to the pituitary and other endocrine locations, which in turn mediate the neuroendocrine and autonomic output to the body including the GI tract. The parallel outputs of this central circuitry have been referred to as the "emotional motor system" (EMS) (Anonymous 3, 1996). The EMS is activated in response to disturbances in both the internal and external environment, and generates responses of the ANS, the endocrine response, the brain's pain control system, and other pathways.

One important chemical mediator of the stress response in general, and of stress-induced GI changes in particular, is corticotropin releasing factor (CRF) and probably other unknown molecules located in certain neurons of the PVN, the amygdala, and a few other areas (Valentino et al. 1999). Central injection of CRF can reproduce behavioral and gastrointestinal responses similar to those seen in acute psychological stress. When CRF-mediated responses are inhibited by molecules that block the substance (Tache et al. 2004), or in experimental

animals missing the gene, a decrease in the animal's response to stress results (Timpl et al. 1998).

The two-way interactions between the various outputs of the EMS and GI function are unique compared to such interactions with other visceral organs. Besides its well-characterized role in food processing and assimilation, the GI tract has other functions, unrelated to nutrition, that are incompletely understood.

For example, between the layers of the gut is the enteric nervous system (also referred to as the little brain, or the second brain (Gershon 1998), a set of neurons equaling in number those of the spinal cord. The enteric nervous system is considered the third branch of the autonomic nervous system, which regulates and integrates essential gut functions, such as motility, secretion, and mucosal blood flow.

Contained within the gut's lining is a large number of so-called enterochromaffine cells. These cells secrete neurotransmitters and other chemical messengers to nearby neurons—in fact, enterochromaffine cells may be considered the largest endocrine organ in the body. These cells help regulate a wide range of functions, including peristaltic activity, satiety, and food intake. Since enterochromaffine cells contain 95 percent of the body's serotonin, one may speculate that they are also involved in the modulation of mood, sleep, and pain, possibly by modulating the activity of vagal-afferent pathways reaching the brain.

The gut's inner layers also contain a large number of immune cells, the so-called gut-associated immune system, which is influenced by neuroendocrine signals and by the autonomic nervous system (Mowat et al. 2004). Exposure of gut immune cells early in life to antigens may play an important role in the development of a healthy immune response and in the development of various autoimmune disorders later in life. It has been suggested that the reduced exposure of children growing up in Western societies to bacterial and parasitic antigens may have consequences for the responsiveness of the adult immune system, predisposing them to the development of such autoimmune disorders as inflammatory bowel disease.

Finally, the gut contains an elaborate system made up of microorganisms referred to as the microflora. When viewed together the microflora make up an additional "organ" larger than the liver. These microorganisms secrete chemicals to communicate with each other, as well as with cells lining the gut (Shanahan 2002).

These signals may play a role in preventing inflammation of the gut wall, as well as in the development of malignancies. Therapeutic attempts to increase the number of the beneficial microorganisms have been used to treat a variety of gastrointestinal disorders, such as inflammatory bowel disease.

Taken together, these four elements of the gut's neuroendocrine immune system all provide information to the central nervous system via nerves that may be important in regulating mood and other mental processes (Craig 2002). For example, vagal afferents from the GI tract are likely to play a prominent role in pain modulation, immune activity, and interactions between the brain's emotional and cognitive centers (Tracey 2002).

In summary, brain-gut interactions play an important but incompletely understood role in health and disease. While stress-related disorders of GI function are well known, the precise role of gut signaling to the brain in health and disease has become a new frontier in research with potential implications for a wide range of medical and psychiatric conditions.

The importance of socioeconomic status

Socioeconomic status (SES), which is most commonly measured using some combination of information about education, occupation, and income, has

a strong and persistent association with health and behavior (Duncan et al. 1998). Thus, exposure to stressful life events might be particularly relevant in understanding disparities in both health and cognitive outcomes (McCloyd 1998; Lupien et al. 2000). Besides stressful life events, the daily lives of people will differ across income and education and result in different levels of ongoing stress, as well as differences in lifestyle that include diet, exercise, tobacco use, and many other factors that also influence health via many of the same pathways that are activated by stress. Many of these effects begin early in life.

Stressful experience has been extensively shown to affect brain development at many levels of organization, from molecules to neural systems (Lupien et al. 2000; Greenough et al. 1987; Rosenzweig and Bennett 1996; McEwen 2001). Thus, differences in stress that are associated with SES differences may lead to differences in human brain development and subsequent health and behavioral outcomes. Evidence for this has been provided by the fact that children growing up in low socioeconomic environments have higher salivary levels of cortisol by age 6, relative to their higher SES peers (Lupien et al. 2000). Furthermore, this biological marker of stress is associated both with maternal depression and with family income, suggesting that access to resources and stress are intertwined, and themselves associated with mental health and disease. Children who grow up in lower SES environments are in fact exposed to numerous emotional, cognitive, and physiological stressors that are risk factors for negative developmental outcomes, including family violence and instability, decreased access to academic resources, and lower quality air and water (Evans 2004).

Genetic predisposition may play a role, based on the studies by Caspi and coworkers that show a difference in risk for adult antisocial behavior from childhood abuse related to different alleles of the enzyme monoamine oxidase A, which metabolizes biogenic amines (Caspi et al. 2002). At the same time, adversity in the home and living environment has been shown to be associated with increased body mass and blood pressure by age 9 (Evans 2003). Moreover, childhood SES leaves a lasting mark on metabolism, physical activity, and health of the teeth, among other effects that are not erased by upward or downward mobility later in life (Poulton et al. 2002).

In addition to its associations with health, SES has long been known to be associated with cognitive development; parallels with the development of language skills are particularly strong (Whitehurst 1997; Noble et al. 2005). Access to good quality health care is influenced by literacy levels—so much so that the Organization for Economic and Cooperative Development cites, as one of its three broad priorities for action in improving global health care, the reduction of widespread inequities in literacy, education, and the distribution of income (Bennett 2003).

Although not all factors that mediate the relationship between SES and academic achievement are necessarily related to an individual's experiences, evidence from a variety of sources indicates that at least part of the SES gap in cognitive performance is attributable to childhood environment (Capron and Duyme 1990; Duncan et al. 1994; Ramey and Ramey 1998; Jackson et al. 2000). Importantly, it has been shown that the proportions of IQ attributable to genes and environment differ across SES (Turkheimer et al. 2003). Specifically, in lower SES families 60 percent of the variance in IQ is accounted for by environmental factors, whereas the contribution of genes is close to zero; in affluent families, the result is almost exactly the reverse. Further, children in lower SES neighborhoods are at an increased risk for emotional and behavioral problems above and beyond any genetic risk, suggesting a direct link between neighborhoods and child mental health (Caspi et al. 2000).

This suggests that academic difficulties that occur in an environment with limited access to resources may be quite different—in terms of both development and response to intervention—from those that arise despite plentiful access to resources. The use of neuroimaging could potentially help to tease such effects apart, extending our knowledge beyond the limitations of behavioral data. Preliminary evidence of such a possibility comes from data that suggest that higher SES children who struggle with reading show greater evidence of a neurobiological marker of reading disabilities than do lower SES children who demonstrate the same difficulties but whose impairments are presumably more likely to be rooted in differences in the literacy environment (Eckert et al. 2001).

HOW CAN WE INTERVENE TO TREAT STRESS-RELATED DISORDERS?

Many of the common diseases of modern life such as cardiovascular diseases and disorders related to overweight and physical inactivity are largely preventable, or at least can be significantly attenuated, with changes in behavior and lifestyle, and thereby contribute to reducing health care and insurance costs. Because stress plays a significant role in determining the lifestyles and behaviors that cause these problems, stress reduction programs are an increasingly important component of preventative health care.

The reactions to stressful events, i.e., allostasis leading to allostatic load, begin in the brain, and the nervous system controls not only the autonomic and neuroendocrine responses but also the health-promoting and health-damaging behaviors and the emotions, memories, and decision-making capabilities that determine which behaviors are chosen.

The ultimate goal of studying the many levels of response to stress is, of course, to keep the fight or flight response on our side and to avoid the imbalances that lead to disease. This cannot be done simply by addressing one system at a time; rather, the multiple mediators of stress and allostasis must be considered in relation to many systems of the body that are all affected in parallel. This is important because the systems that help us adapt to stressors, such as hormones and the autonomic nervous system, can also contribute to mental disorders when not functioning properly. Thus, it is important to consider how they can be kept in balance so that they turn on when needed and turn off again when no longer needed. In maintaining an optimal response, two areas are most important: physical and mental fitness and a healthy diet.

The influence of fitness and diet

Fitness In recent years a substantial body of research has addressed the relationship between fitness, cognition, and brain function and structure. Research with nonhuman animals has shown that fitness training increases levels of key neurochemicals that improve plasticity and neuronal survival, such as brain-derived neurotrophin factor (BDNF) (Neeper et al. 1995), insulinlike growth factor 1 (IGF 1) (Carro et al. 2001), and serotonin (Blomstrand et al. 1989), as well as reduced corticosteroid levels (Cameron and McKay 1999). Other studies have reported that fitness interventions increase the development of new capillaries, presumably to support increased neuronal activity, in rodents (Black et al. 1990; Isaacs et al. 1992) and primates (Rhyu et al. 2003). Indeed, this added vasculature has been shown to be functional: Rats that exercise on an activity wheel have both a greater resting blood flow and a greater "reserve capacity" in response to increased oxygen demand compared with those not allowed to exercise (Swain et al. 2003). Finally, there have been a number of recent demonstrations of enhanced learning and memory (Anderson et al. 2000; van Praag et al. 1999a) and neurogenesis with fitness training (van Praag et al. 1999b; Rhodes et al. 2003; Trejo et al. 2001).

Until recently, human studies have primarily examined the influence of fitness training on selective aspects of perception, cognition, and motor function. Prospective epidemiological studies have found that older adults with higher fitness levels at baseline assessments tend to have better cognition and reduced incidence of Alzheimer's dementia five to eight years later (Laurin et al. 2001; Yaffe et al. 2001). In a recent meta-analysis of randomized clinical trials of fitness training effects on cognition, Colcombe and Kramer (2003) reported that while fitness training has a positive effect on a broad array of cognitive processes, the greatest benefits showed up in executive control processes such as working memory, interference control, planning, and scheduling that are supported in large part by frontal and prefrontal regions of cortex. A number of other variables were uncovered. Fitness effects were larger for studies that had a greater proportion of female participants, when aerobic training was combined with strength- and flexibility-training protocols and with longer training protocols. An important question for future research concerns the biological mechanisms underlying these effects.

Several recent studies have also examined fitness differences and fitness training effects on human brain function using magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) techniques. Colcombe et al. (2003) reported that older adults who were fit displayed reduced declines in cortical volume in frontal, parietal, and temporal cortices. Furthermore, this reduction in decline was larger in adults older than 65 years as compared to younger (55 to 65 years or older) study participants. Similar patterns of cortical volume effects have recently been observed in a randomized clinical fitness training trial. Increases in the efficiency of cortical circuits that support attentional function (the ability to selectively focus on some information and ignore task irrelevant information) have also recently been reported in both a cross-sectional and randomized clinical trial study of fitness effects on brain function (Colcombe et al. 2004).

Exercise is an extremely effective treatment for mild to moderate depression, equaling the therapeutic efficacy of antidepressants, with fewer negative side effects and greater long-term compliance. It also tends to improve sleep quality and quantity. The antidepressant and sleep-enhancing benefits of vigorous exercise may contribute to the overall beneficial effect of exercise on cognitive function.

In summary, an increasing body of data in recent years indicates improvements in cognition, brain structure, and function with improvements in fitness. Future studies will be necessary to extend this research to determine the relationship between other lifestyle factors (social activities, nutrition, intellectual engagement, etc.) and fitness in promoting successful aging.

Diet Clinical trial evidence suggests that losing 7 percent of body weight and maintaining 30-60 minutes of physical activity per day may lead to reductions in the incidence of chronic disease. Unfortunately, even these modest goals require intensive efforts and a high degree of personal commitment as well as support from others. Crucial to success for many individuals are education about the benefits of weight loss and fitness, and education and training in proper nutrition and exercise strategies.

Analysis of reported behaviors from the Diabetes Prevention Program highlighted the need to teach "dietary restraint skills," as well as strategies to reduce "binge eating" and "fantasizing about favorite foods" (Delahanty et al. 2002). Furthermore, evidence suggests a number of behavioral strategies to be effective, such as self-monitoring and stress management. For instance, keeping a

food diary and periodic weigh-ins are significant predictors of success at weight loss. Stress-reducing interventions such as cognitive behavioral therapy and guided imagery have also been helpful in restructuring thoughts and behavior related to food intake, body image, and self-care. In one pilot study done at Canyon Ranch, participants in an employee weight-loss program who listened regularly to a guided-imagery cassette tape for weight loss lost almost twice as much weight as participants who listened to a music tape without guided imagery.

An imbalance between the brain's "executive" control and its reward and hunger systems may override a person's efforts to restrain food intake. People under chronic stress have been demonstrated to gain weight over time; in addition, the dietary restraint so necessary for successful weight loss may itself be a source of psychological distress. Compounding this problem is evidence that those who most need to make dietary changes for health reasons may have lower cognitive resources with which to cope with the demand. Both obesity (Elias et al. 2003) and impaired glucose tolerance (Convit et al. 2003) have been associated with lower cognitive performance, while Del Parigi and colleagues (2004) have demonstrated that both the obese and "recovered obese" (obese individuals who lose weight) show similar hyper reactivity of emotional neural centers in response to food stimuli. It appears that the ongoing battle being fought out between the prefrontal cortex and the amygdala may result in poor dietary choices, which abound in our food-rich environment.

Strategies for improving allostasis and reducing allostatic load

We now turn to a discussion of how several key systems can be treated using strategies that emphasize physical and mental fitness and diet.

Immune system modulation/inflammation So far, the best way to keep the immune system in balance seems to be through indirect measures. One is to optimize the day-night rhythms of the autonomic nervous system and cortisol secretion, and to improve the parasympathetic nervous system's control—since all of these systems influence immune activity. Once again, increasing exercise (during the day) is the most productive step anyone can take. Exercise can improve parasympathetic tone (Levy et al. 1998) and can help guarantee a good night's sleep. Improving restorative sleep for sleep-deprived individuals may also keep the immune response in balance. Meditation and other types of mindfulness training may also be useful, but these have not been extensively and rigorously tested for their long-term effects.

Heart-rate variability (HRV) taps into the parasympathetic/sympathetic balance, which affects not only cardiovascular function but also the balance of inflammatory and anti-inflammatory cytokines. Reduced HRV is a useful index in certain psychiatric conditions (e.g., depression) and indicates potential risk for heart attack and stroke. The relationship of HRV to inflammation has not been extensively studied because the two fields—inflammation and cardiovascular—are only now beginning to communicate because of the realization that cardiovascular disease (CVD) has an inflammatory component.

Specific mind-body techniques have been developed to enhance HRV. Through biofeedback training, for instance, individuals can observe on a computer screen the beat-to-beat changes in their heart rate and learn to increase their HRV by modulating their breathing and shifting their emotional state with positive imagery. With continued practice of these techniques, HRV enhancement is maintained outside of the biofeedback office.

Inflammation is also linked, through specific biochemical pathways, to the pattern of nerve cell damage known as oxidative stress, a hallmark of

various disorders including diabetes, cardiovascular disease, and Alzheimer's disease. Proinflammatory processes feed forward to exacerbate the generation of the free radicals that damage membranes and DNA (Clark and Valente 2004). This vicious cycle is exacerbated by glucose (Leehey et al. 2005) and by stress (Bierhaus et al. 2003), and it is an important factor in disorders such as diabetes (Bierhaus et al. 2001). There are several ways to interfere with this vicious cycle: For example, agents that enhance parasympathetic activity via activation of the cholinergic system agents (Borovikova et al. 2000) are useful in quelling inflammation, and antioxidants such as vitamins E and C are also useful in quenching free radicals and reactive oxygen species that are linked to oxidative stress. But both of these treatments are dangerous if they are too drastic, and they must be used in moderation. This is because each is tapping into an interacting network of mediators, not a linear sequence of cause and effect. This means that pharmacological treatments must not be so harsh as to distort the network and cause excessive changes in other mediators that may lead to unwanted side effects.

Exercise and diet It is entirely possible to correct undesirable neural responses to stress by simply increasing physical activity. Exercise is an effective treatment for depression (Blumenthal et al. 1999), improves parasympathetic tone (Levy et al. 1998), and may improve cognitive function (Colcombe et al. 2004). These benefits may also make exercise the best remedy against overeating—it is a logical assumption, though untested formally, that individuals with high cardiovascular fitness are less likely to increase food intake in response to stressful circumstances. In one study, college students who binged were instructed to take a walk every time they had a craving for a snack. Students in this group ate significantly less snack food and lost more weight than a matched group of control subjects who were not given such instructions.

Although stress management or cognitive therapy should be helpful for people whose chief coping mechanism is food, little long-term data exist to confirm this proposition. Alternatively, it may be best to recognize the limitations of individual prefrontal control over the amygdala/stress responses and to concentrate on providing an ideal dietary environment. Academic and medical professionals, the food industry, and retailers could play a paramount role in creating products and environments that help consumers eat wisely for weight loss and maintenance. These could range from products with clear guidance on caloric and fat content to products that make eating a satisfying experience while maintaining the overall healthiness of the diet. However, all these concepts are based on an understanding of behavior, and with future advances in our understanding of the brain's impact on food choices, we may even discover how abnormal neural responses to food can be blunted by novel dietary strategies and formulations. Therefore, we may eventually be able to identify the role of the brain in eating behaviors.

Changing behavior A growing body of literature documents the positive impact that behavioral interventions can have on health. The following are some examples of randomized, controlled trials that showed statistically significant outcomes of behavioral health interventions:

1. Strain et al. (1991) studied hip fracture patients undergoing postoperative rehabilitation in a nursing home. The intervention group received, in addition to the normal rehabilitation program, psychiatric evaluation and treatment as well as consultation with the family regarding return to the home environment. The length of hospital stay was reduced by several days with significant savings in costs.
2. Many studies have examined the role of the emotions in serious illness. In one study, 60 patients in the early stages of breast cancer

were invited to write about their experience with the illness. One group wrote down their deepest feelings regarding breast cancer, one wrote only constructive thoughts and feelings, and the third wrote the facts of their experience. Compared with the facts-only patients at three months, the patients who described their emotions reported significantly decreased physical symptoms; the groups detailing their emotions and their positive thoughts had significantly fewer medical appointments for cancer-related medical problems than the patients who concentrated on the facts (Stanton et al. 2002).

3. Fawzy et al. (1993) found that patients with malignant melanoma undergoing a six-week psychiatric group intervention were able to reduce stress, enhancing their coping skills. Patients who did not undergo group counseling had more recurrence of cancer and a s tatistically significant greater rate of death than experimental patients. Higher levels of baseline distress, as well as baseline coping and enhancement of active coping behaviors over time, were predictive of lower rates of recurrence and death. Fawzy et al. (2003) conducted a follow-up study of the foremen-tioned cancer survivors and found that, while the overall effect had weakened, participation in the intervention was still predictive of increased survival.

4. In a group of HIV 1 patients, Goodkin et al. (2001) reported that bereavement support group therapy, in addition to reducing psychological distress, helped reduce levels of the HIV virus in the blood (in conjunction with reliable antiretroviral medication).

5. In a study that matched 22 CHD patients for hostility and age, Gidron et al. (1999) showed that participants in an intervention designed to reduce hostility had significantly lower diastolic blood pressure and lower self-reported hostility than a control group that received information only, both immediately and two months postintervention.

6. Davidson et al. (2003) showed that an eight-week mindfulness meditation program significantly affected brain and immune function in a work environment of healthy employees. Study results showed significant increases in antibody levels in response to influenza vaccine among subjects in the meditation group compared with those in the wait-list control group.

7. Williams and Schneiderman (2002) performed a major review of research over the last two decades and concluded that behavioral therapy modifies disease outcome via psychosocial factors. That is, psychosocial interventions can influence subclinical markers of disease along with clinical outcomes in organic diseases, e.g., behavioral interventions can lower risk factors such as caloric and fat intake, smoking, and alcohol consumption. Such interventions can also reduce physical risk factors such as body mass index and cholesterol levels, and biological characteristics including altered endocrine, cardiovascular, autonomic, and immune system responses.

8. Mendes de Leon et al. (1991) analyzed the Recurrent Coronary Preventive Project to demonstrate that the addition of "Type A counseling" to standard cardiac counseling resulted in significant reductions in Type A behavior and in a 44 percent reduction in subsequent heart attacks. Furthermore, the intervention resulted in significant decreases in depression and anger and marginally significant gains in social support and well-being,

9. Turner-Cobb et al. (2000) found that greater quality of social support was associated with lower cortisol concentrations in women with

metastatic breast cancer, which was indicative of healthier neuroendocrine functioning. The study intervention involved group therapy on emotional adjustment and health. In this connection, Seeman et al. (2002) found that having three or more social ties reduces the allostatic load score in both men and women. Thus, promoting social networks is a potential way of reducing the impact of chronic stress.

Importance of recognizing socioeconomic status

A number of randomized controlled trials have shown that intervention has the potential to narrow the health and achievement gap noted across SES. Results have been promising for interventions related directly to improving a family's economic situation. In some studies, assistance has been provided in relocating families from public housing to higher SES neighborhoods. In general, children who move to less impoverished neighborhoods have not only higher academic achievement, but also better physical and mental health (Leventhal and Brooks-Gunn 2003). Furthermore, a recent prospective study showed that following a family income supplement that raised children out of poverty, the incidence of childhood psychiatric disease decreased relative to children whose families did not receive the supplement (Costello et al. 2003). Educational interventions directed at low-income families have also been largely successful. For instance, the IQ of low SES children who have participated in intensive early education is between one-half and one full standard deviation higher than control groups of low SES (Ramey and Ramey 1998). Although critics often conclude that the benefits of early intervention wane shortly after the program ends (Haskins 1989), other studies have shown sustained (Brooks-Gunn et al. 1994) and cost-effective (Barnett 1998) effects. Perhaps the key is to intervene with more precision. This can be accomplished by more precisely measuring the outcome, with educational curricula targeting the particular outcomes, such as language development, that are most strongly associated with SES differences (Noble et al. 2005.

Furthermore, by combining neuroanatomical information with traditional measures of achievement, we might one day be able to design interventions that are more appropriately targeted to an individual child's needs in ways that simple behavioral measures alone could not elucidate. Improved access to resources may reduce stress and improve academic circumstances, which together would be likely to decrease SES-related health disparities.

CONCLUSION AND SYNTHESIS: RESEARCH AND POLICY DIRECTIONS

Stress is an unavoidable feature of the human experience throughout the life course. Throughout human history there has been broad awareness of the connections between the mind and body and intimations of a role for stress. Yet, the modern professionalization of medicine and its scientific underpinnings have tended toward separation both in the academic preparation of health care practitioners, which carries on into their active practice, and in scientific and scholarly pursuits.

Stress plays a major role in health and disease from infancy to old age. It lays the stage or triggers disease and disability. Yet, biomedicine has become highly specialized and technical, and we often miss the forest for the trees by not seeing how behavior and experiences and other aspects of brain function are reciprocally connected to body functions over the life course.

Neuroscience has an enormous contribution to make to the study of stress since the nervous system interprets what is stressful and controls the behavioral, autonomic, endocrine, and immune responses to stressors. And stress has both good and bad sides—the body defends itself acutely, and yet the same response that defends can become pathophysiological when there is chronic stress.

We need to educate medical professionals and the public in the behavioral neuroscience and integrative physiology that illuminates our current understanding of brain-body communication because this provides a broader perspective in which to understand the progression toward certain common diseases and to evaluate intervention strategies. Ideally, the intervention strategies would include a seamless array of behavioral and lifestyle interventions, as well as pharmacological means and osteopathic and other procedures such as, but not limited to, acupuncture and yoga or meditation, but, unlike what is done now, they would be based on a growing appreciation of neuroscience and physiology, where we still have a rudimentary understanding of topics such as positive outlook and meaning and purpose in life, which need to be translated into physiology. Moreover, the interventions would be based upon an appreciation of how genes and experience interact over the life course to alter vulnerability to disease. Hence, interventions should start as early as possible.

Thus, the time has come for unification, that is, for putting the brain back into medicine and exploring the new and advancing disciplines from the behavioral sciences, epidemiology, neuroscience, genetics, endocrinology, immunology, geriatrics, and beyond, which together can bridge this unfortunate gap—unfortunate because it has such adverse effects both upon our understanding of the human condition and our efforts to be of assistance. However, before this can happen, more intensive research and discussion of a number of important issues are crucial.

Some research directions:

1. In relation to the concept of allostatic load, we need to continue to improve the battery of surrogate markers that can be thought of as an expansion of the cholesterol and blood pressure–screening concept but that tap into a wider range of interacting body systems and may thus be better predictors of disease risk. As noted above, the allostatic load concept recognizes that mediators operate as a nonlinear network, e.g., cortisol, autonomic, inflammatory cytokines, metabolic hormones, etc. Validation of such a battery may require the equivalent of another Framingham study, although ongoing research in large studies such as CARDIA and NHANES is providing some of the necessary validation as to the predictive value of such a battery.
2. If the allostatic load markers are used to assess the health status of people, as is done at Canyon Ranch and in many similar health programs, as well as in doctors offices using cholesterol and blood pressure screening, what are the intervention tools that are available? As a basis for further investigation, two of the simplest and most useful screening instruments are brief assessments for depression and anxiety. Using brief eight-question assessments, individuals suffering from depression or anxiety disorders can be identified and referred for treatment with psychotherapy, pharmacotherapy, or lifestyle change. As noted above, cognitive behavioral therapy and physical exercise have both been shown to be effective in the treatment of mild to moderate depression and anxiety disorders. Moreover, depression and anxiety disorders, which are widely underdiagnosed and undertreated, are risk factors for a number of medical conditions.

Lifestyle change How much can we do with diet and exercise? Many of our most common diseases, such as heart disease, diabetes, and high blood pressure, can be prevented or substantially attenuated through a healthy regimen of diet, exercise, and effective stress management. Maintaining these lifestyle practices is sustainable if individuals are given sufficient education about their value for disease prevention and practical instruction in the specifics of healthy eating, exercise, and stress management.

Ongoing individual or group support in maintaining these habits is invaluable for many individuals, but we need to determine how sustainable they are and how applicable they may be to different SES levels. Programs at places such as Canyon Ranch are wonderful if one can afford them; however, even with these programs, returning to normal life is a different matter and old habits are likely to return. Obviously, individuals at lower socioeconomic levels, who have less access to quality health care, health education, health clubs, and healthy foods, will have more obstacles to making and sustaining lifestyle change. Therefore, on a societal and governmental level, efforts must be made to disseminate health education information and provide greater access to resources that support healthy lifestyles. For instance, health information and lifestyle change programs can be offered to individuals at low or no cost in schools, community centers, and religious institutions. Municipalities can create bike paths and bike lanes, and make indoor space available in schools and malls for exercise in inclement weather. Many of the most powerful lifestyle habits, such as walking, eating smaller portions, or practicing a relaxation technique, involve little or no expense. The key to practicing them is education about their benefit and how to do them properly.

Food industry Can better foods (small portions, less sugar and saturated-fat content, palatable) be developed, and can the food and beverage industry be brought into a synergy to do this? What about affordability? Governmental regulation of food industry advertising, similar to regulations limiting advertising of alcohol and cigarettes, would help to diminish one of the most powerful societal contributors to obesity, diabetes, and heart disease. *At the same time, it may be more effective to work with the food and beverage industries to produce healthier products.*

Pharmacological Most people would rather improve their health with a pill, and yet every pharmacological agent has side effects, e.g., statins, aspirin, ibuprofen, diabetes drugs, antioxidants, tranquilizers, antidepressants. Side effects must be recognized, and consumers must be warned more clearly of the risks but also apprised of the potential benefits.

Besides diet, exercise, and social support, other complementary treatments, such as osteopathic procedures, acupuncture, yoga, behavioral and psychotherapy have their place in individual lifestyles. Yet, the jury is still out as to their effectiveness when one uses accepted methods for evaluating treatments. These evaluations need to be conducted, although it is important to note that numerous studies have demonstrated the efficacy of behavioral interventions such as cognitive behavioral therapy, EMDR, mindfulness-based stress reduction, and guided imagery in the treatment of conditions such as anxiety, depression, PTSD, and chronic pain. There is evidence that patients who make use of behavioral treatments subsequently require less treatment for medical conditions and have shorter hospital stays when they do suffer serious medical illness.

In order to facilitate the progress of the rejuvenated field of mind-body medicine, there are a number of specific policy recommendations.

1. Encourage private philanthropic support of studies that bridge the relationship between mind and body.
2. Further expand the National Institutes of Health effort through extramural funding by setting up a specific unit of health administrators whose task and responsibility would be to help build the field of mind and body and stress.
3. Establish a trans-NIH committee on stress (allostatic load) particularly involving the neurology, mental health, aging, and heart institutes and others to strengthen the trans-NIH intramural research and encourage support for the extramural program.

4. Introduce into the medical, nursing, social work, allied health curriculum attention to the interrelationships between social economic, mental, and biological factors, in short, bringing the brain back into medicine.
5. Expand human performance and longitudinal studies.
6. Continue to build measures of allostatic load and stress.
7. Bring clear attention to the role of the socioeconomic status and disparities upon human health.
8. Study the economic benefits that derive from the integration of social, behavioral, and biological factors in medicine.
9. Pay particular attention to evolving neuroscience including brain-gut relationships.
10. Establish a national effort to transform American lifestyles.
11. Clarify and expand the definition of allostatic load as a means to quantify the cumulative toll exerted on the body over time in its efforts to adapt to life experience.
12. Examine the role of allostatic load upon cognitive health.
13. Study both preventative and therapeutic interventions that derive from new knowledge of the role of stress.
14. Transform and translate key information derived from putting the brain back into medicine into the broad health care enterprise. This integration would have many social and economic benefits and would advance quality of life.

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