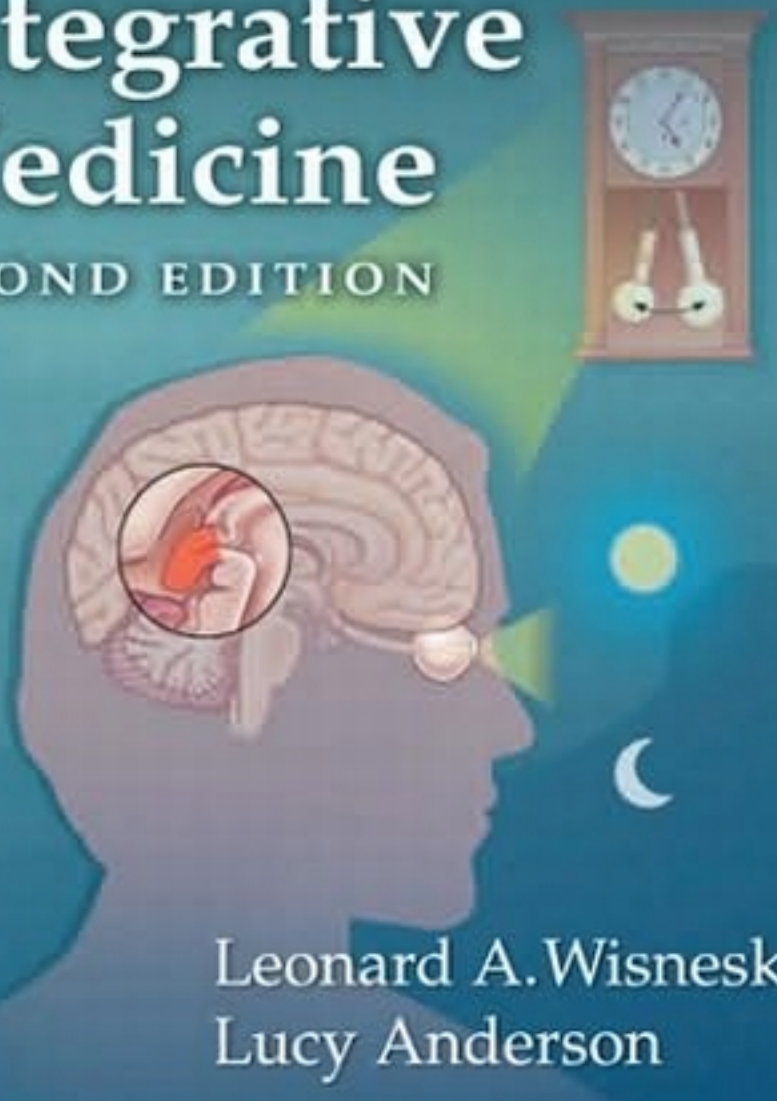
The Scientific Basis of Integrative Medicine

SECOND EDITION



Leonard A. Wisneski
Lucy Anderson

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Dedication

To my loving and supportive wife, Judith, who renews my enthusiasm for life each and every day; to my daughters, Amy and Hope, who have given me the opportunity to parent two wonderful souls and are a constant reminder of the eternal youth within my being—especially celebrating the birth of my delightful grandchildren, Brendan and Kai; and to my brother Harris, who, from a young age, taught me the meaning of diligence, scholarship, and love of knowledge.

In loving memory of my mother, Faye, who taught me the meaning of love and true service.

L.A. Wisneski

For Nicholas Anderson, who already understands so much about humanity, and for Anne Anderson, who taught me loving kindness.

In loving memory of Lila Anderson, whose insights and invaluable guidance are woven through these pages.

L. Anderson

Table of Contents

Foreword to First Edition

Welcome to this exciting and much-needed textbook in the field of integrative medicine. It may change your view of disease and conventional medicine.

The revolutions of the past two decades in molecular biology and molecular genetics have done an outstanding job of informing physicians and scientists of the molecules, DNA, RNA, peptides, enzymes, proteins, and other components that comprise the human body. We now understand how, and to a great degree, which hormones, neurotransmitters, cytokines, and antibodies are produced in various states of health and disease.

To a great extent, we biomedical types remain isolated within narrow areas of knowledge and often think only about our own disciplines and subdisciplines. We have accumulated facts and figures about our chosen fields at a mind-numbing pace, and we have excelled at using this information to develop treatments and procedures that are largely directed at treating the symptoms manifested by full-blown pathologies. *The Scientific Basis of Integrative Medicine* goes a considerable distance in providing physicians and biomedical researchers with the opportunity to reassemble all those disparate molecules and biological mechanisms into a logical, integrated whole from which a real understanding of the causes of disease may arise. This is particularly true for grasping the perturbations in normal physiology that lead to the difficult-to-manage chronic diseases—persistent conditions that do not respond to the usual armamentarium of pharmaceuticals or invasive procedures so that the only sanity-saving measure is to refer the patient to the next subspecialist who is no better equipped than we are to provide relief to the patient.

Len Wisneski and Lucy Anderson's approach in this text is to connect those seemingly separate biological systems to give us a rational roadmap to use to locate the underlying mechanisms of many multifaceted disease processes. In so doing, they make it more likely that practitioners and healers will understand better what the primary targets of their treatment modalities should be and what the relationship of each disorder is to the others. In other words, the content of these chapters allows us to identify the sources of a number of cascading pathologic events and how they magnify underlying disease processes.

The authors educate us using a conversational, patient-centered approach that is not overly preachy or dogmatic. Their extensive documentation of scientific studies and their results lend credibility to their interpretation of their findings and conclusions. The first four chapters provide a strong scientific foundation for our understanding of human physiology, psychoneuroimmunology, stress, and relaxation. The last two chapters open our minds to the less organic and corporeal realm of our existence and health as influenced by our environment. At the very least, we might all heed this advice to listen to and respect the desire of those patients who wish to invoke spiritual aspects in the healing process.

Len Wisneski, a practicing MD, also sets an example by showing us that it is indeed all right to collaborate with healers from other backgrounds and traditions,

especially when the greater goal of the best possible outcome for the patients is achieved (rather than protecting the sanctity and exclusiveness of the MD club).

In summary, this book achieves the following three major goals: (1) It shows us how the body's organs and cells are not isolated systems, but work together in an integrated fashion to maintain our health; (2) it explains how many diseases arise as a result of stressors that perturb homeostasis and that addressing these initial stressors is necessary for healing to occur; and (3) it opens our minds to consider energetic healing modalities that heretofore were taboo in the Western medical establishment.

Read, enjoy, and expand your healing horizons.

Michael D. Lumpkin, Ph.D.
Chairman and Professor of Physiology & Biophysics
Georgetown University School of Medicine

Foreword to Second Edition

Twenty years ago, when I first began teaching, writing textbooks, and organizing educational conferences on what was then labeled *complementary/alternative medicine* (CAM), I found Dr. Len Wisneski, who was practicing (in my own hometown of Bethesda, Maryland) what I was preaching around the country. My hometown sits in the shadows of the big, high temple of biomedically oriented science, the National Institutes of Health (NIH). Len Wisneski was already casting light within those shadows.

As a physician–anthropologist in my early career at the University of Pennsylvania Museum in Philadelphia and the National Museum of Health and Medicine in Washington, D.C., I sought clues for innovative approaches to health and healing (beyond the biomedical paradigm) in Southeast Asia, China, the Amazon, and elsewhere. Then, one day, I looked in my own backyard and found practitioners of ancient ethnomedical traditions and contemporary healing all around me. They were often just under the radar screen; foremost among them was Len Wisneski. [Len soon got onto the radar screen with the first edition of this book.] There suddenly appeared opportunities here at home to draw on the ancient knowledge and wisdom of how the body heals and how it can maintain a healthy balance.

But understanding CAM/integrative medicine is not just about rediscovering ancient knowledge beyond the biomedical paradigm and the accepted boundaries of contemporary Western biomedical science. Rather, as per the opening statement of my own textbook, first published in 1995 and now entering its fourth edition,[1] what we need in medicine is not less *science* but more *sciences*. Understanding CAM/integrative medicine does not at all require suspending belief in accepted medical science (as incorrectly posited by its critics), but opening our eyes to the abundance of science from biology, physiology, physics, and the social sciences to which contemporary medicine has still not caught up or caught on.

Thus, Len Wisneski and Lucy Anderson bring to bear the sciences of psychoneuroimmunology, the stress response, the functions of heretofore incompletely understood endocrine glands, and the bioenergy that surrounds us. They have written a true textbook of physiology—the physiology of the mind–body connection.

As such, for this book, as for the human body, the whole is greater than the sum of its parts. Len continues to shine the light, no longer from the shadows of the NIH in Bethesda, but from his 9,000-foot peak in Colorado. Shine on.

Marc S. Micozzi, M.D., Ph.D.
Adjunct Professor of Physiology & Biophysics
Georgetown University School of Medicine

REFERENCE

1. Micozzi, M.S., 2009. *Fundamentals of complementary and alternative medicine*, 4th ed. St. Louis: Elsevier Health Sciences.

Preface

We have expanded the second edition to include three new chapters and to report on remarkable research advances in the fields of neuroscience and psychoneuroimmunology. In Chapter 3, we introduce the concept of the mind–gene connection—a segment of chromosomes known as the telomere. Fascinating studies reveal that stress and disease have a bearing on telomere length. While the much-publicized implications of telomere length and longevity remain controversial, once again, the association between stress and ill health is uncontested. Also in Chapter 3 is a discussion of the subiculum, a small structure located within the hippocampal formation, which appears to be an important "switch" that helps to regulate and synchronize memory and the stress response's impact on memory. Finally, Chapter 3 reviews the embodiment theory, which evaluates mental and emotional reactions from the "body" perspective. It illustrates that relationships between the mind and body that are based on mental and emotional perceptions actually are dependent upon memories involving posture as well as on motor and visual sensory input.

We neglected to include a very important discipline in the first edition: naturopathic medicine (see Chapter 5). Our apologies, particularly as this important profession forms the philosophical and intellectual scaffolding for the integrative practitioner, regardless of discipline.

There are several diagnostic and therapeutic devices now utilized by integrative medical practitioners. Dr. Bernard Williams, with great expertise in this area, has written Chapter 7, which discusses the science behind some of these devices and reviews potential clinical applications. We neither endorse nor do not endorse the efficacy of these devices, but rather feel that it is important to present to our readership the status of the science in this field. Similarly, in the energy modalities chapter of the first edition, we discussed laser acupuncture and conventional laser use. In the second edition, we enlisted the help of Dr. Nelson Marquina to bring the reader up to date on laser therapy. Dr. Marquina, who invented several therapeutic lasers, wrote Chapter 8, which describes state-of-the-art laser therapy and its clinical applications.

The basis for an understanding of any scientific discipline, including integrative medicine, begins with education. Chapter 9, entitled "The Four Pillars and Two Guideposts for the Healing Professions™," is in many ways a policy document. Yet, it offers Wisneski's personal perspectives and professional stance on how a comprehensive education for the healthcare professional should be designed to prepare physicians for the twenty-first century.

Chapter 11 covers some new research on neuroplasticity, that is, the brain's ability to reorganize and change based on new information and ideas that each individual encounters. Intriguing evidence is presented that neuroplasticity, as assessed by alterations in an electroencephalogram (EEG), occurs in experienced practitioners of meditation.

In summary, it has been a pleasure to present new material in the form of the chapters and sections noted above. Research into the scientific basis of integrative medicine is growing at a heartening rate. We hope that you thoroughly enjoy the second edition of our textbook, and that, most importantly, it spurs you to practice, research, or simply live out the wisdom presented here, which was derived from many before us who had the courage to bring creativity to the discipline of medical science.

Len Wisneski
Lucy Anderson

Acknowledgments

We are forever grateful to Lesley Carmack and Lila Anderson whose wisdom and profound understanding of subtle energy compelled us to write about the physiology of spirituality.

Deepest thanks to Judith Homer Wisneski who helped in numerous practical ways and whose gentle stillness supported us both.

To our outstanding medical illustrator, Rob Flewell, CMI, whose courage to conceptualize new medical drawings, technical excellence, and witty sense of humor delighted us no end—all of which has carried on to the second edition.

Our gratitude to Dr. William Tiller for reviewing sections of Chapter 11 and ensuring that our layperson's interpretation of physics was, indeed, accurate, as well as to Dr. Richard Wurtman at MIT and Dr. Raphael Mechoulam at Hebrew University in Israel for taking the time to share their insight and knowledge of endogenous ligands, which we feel are critical to the human relaxation system. We would like to thank Dr. Elmer Green, the father of biofeedback and a remarkable scientist, who is willing to think outside the boundaries of conventional medicine. He was one of the first researchers to scientifically study healing and spirituality.

We have the honor and privilege of two guest authors for the second edition. Chapter 7, "Energy Medicine: Focus on Nonthermal Electromagnetic Therapies" was written by Bernard O. Williams, Ph.D. who is president of the Center for Environmental Energy Medicine Studies at Kansas University in Lawrence, Kansas. He has authored numerous books and professional articles and has demonstrated great expertise in the field of energy medicine.

Nelson Marquina, Ph.D., D.C. wrote Chapter 8, "Energy Medicine: Focus on Lasers." Dr. Marquina is the president of USA Laser Biotech, Inc. and is the inventor of several therapeutic lasers. He is associate professor of biophysics at Virginia State University. Dr. Marquina is an educator and inventor with more than 25 years experience in information systems, statistical analysis, and bioelectrical devices.

We gratefully thank them for their excellent contributions.

For this, the second edition of *The Scientific Basis of Integrative Medicine*, we extend our gratitude to Beth Clay, who developed the initial framework for the Four Pillars and Two Guideposts, and to Mel Warriner, who assisted Len in formulating the Four Pillar concept while on retreat in the woods of West Virginia. We also acknowledge and thank Dr. Clyde Jensen for his expert assistance in guiding Len to crystallize the Four Pillars philosophy into reality at the University of Sint Eustatius School of Medicine. We also gratefully acknowledge Steven Grantowitz for his excellent assistance in improving our knowledge of prevailing and cutting-edge technologies that can be applied to medical education. We extend our thanks and appreciation to Amy Grantowitz for her excellent editorial assistance. Finally, thank you to Courtney Errico and Hope Wisneski for their assistance with editing the manuscript.

At the Taylor & Francis Group, we thank Barbara Ellen Norwitz, our editor, and project coordinator Jill Jurgensen for their indispensable guidance. We also would like to thank Iris Fahrer for her excellent services as project editor.

We gratefully acknowledge the scholarship and diligence of the vast number of scientists and clinicians upon whose research this book is based. In particular, we want to pay tribute to those individuals who have had the courage to explore new frontiers of medical science.

Disclaimer

Although all of the stories that are included in this book are true and based on factual situations, some information and identifying details have been changed to protect the identity of the individuals described. The purpose of this book is to educate. The authors and publisher shall have neither responsibility nor liability to any person or entity with respect to any loss, damage, or injury caused or alleged to be caused directly or indirectly by the information contained in this book. The information presented herein is in no way intended as a substitute for medical counseling and treatment.

Leonard A. Wisneski
Lucy Anderson

Introduction

BEYOND THE MIND–BODY CONNECTION

The most divine art is that of healing; it must occupy itself with the soul as well as the body.

Pythagoras, fifth century BCE

In 1978, Steven, a strapping 40-year-old, appeared at my office for a physical examination. He looked and felt vibrant, but came at his wife's urging. Steve had a very low hematocrit—an indication of serious disease. An endoscopic exam revealed extensive gastric carcinoma. A subsequent operation confirmed that Steve was studded with cancer throughout his abdomen and into the surrounding lymph nodes. Then, as now, there was no definitive treatment, especially for such an advanced cancer.

In the recovery room, beset with fear, Steve asked, "Lenny, how long do I have to live?" His eyes were wide and his pupils were dilated; he was frantically pumping adrenaline. Steve was hanging on my every word. I did the old vaudeville routine, "How long do you want?" "Ten years," he said. "You got it," I replied. And he did get it. Steve again got sick in the winter of 1987 and died within 6 months. Steve not only went into remission for years, but he was healthy and vital until months before he died.

This incident with Steve profoundly altered my perspective on practicing medicine and my beliefs about the nature of the healing process, particularly regarding the power of the mind to heal. Consequently, for over 20 years now, I have engaged in the study of psychoneuroimmunology (PNI) or, as I prefer to call it, *integral physiology*. Integral physiology has to do with the synthesis of conventional physiology and how our individual psyches (i.e., mind, emotions, and spirituality) interact with the world around us to induce positive or detrimental changes in our bodies. In a broader sense, the concept applies to the health of society as a whole.

In the past two decades, biomedical research has changed our understanding of body systems. It is now known that there is a complex network of feedback, mediation, and modulation among the central and autonomic nervous systems, the endocrine system, the immune system, and the stress system. These systems, which were previously considered pristinely independent, in fact, interact on myriad levels. PNI is concerned with the various interactions among these body systems and provides the underpinnings of a scientific explanation for what is commonly referred to as the mind–body connection.

In 1964, George Freeman Solomon wrote "Emotions, Immunity, and Disease: A Speculative Theoretical Integration." In this paper, Solomon first used the term *psychoimmunology* and introduced the concept of a medical link between our emotions and immune systems (Solomon, 1964). In 1975, Robert Ader expanded on Solomon's work and coined the term *psychoneuroimmunology*. During that same year, Ader and his colleagues published the startling results of their research on the conditioned

immune response in a rat population (Ader and Cohen, 1975). The rats in the experimental group were injected with cyclophosphamide (an immunosuppressive agent) while simultaneously being given drinking water flavored with saccharin. The rats were later given only the saccharin-flavored water, but no cyclophosphamide. To the researchers' surprise (not to mention the rest of the medical community), the rats continued to evidence immune suppression. This was the first documented example of Pavlovian conditioning of the immune response.

In Ader's groundbreaking research, he used a pharmaceutical agent to induce the conditioned immune response. Subsequent studies have expanded on the theory to include investigations of conditioning stimuli that are neither physical nor chemical, but are instead cognitive (e.g., perceptions, thoughts, or emotional states). What has been learned is that these cognitive stimuli can just as easily mediate changes in the immune system. Two examples:

- Lymphocyte activity in men is diminished immediately following the death of a spouse from breast cancer (Schleifer et al., 1983).
- A study of 75 medical students showed a significant reduction in natural killer-cell activity during final examinations as compared with the previous month (Kiecolt-Glaser et al., 1984).

Twenty years later, *Lancet* published a study by Ader and Cohen (1975) that concludes with the following statement: "The association between stressful life experiences and changes in immune function do not establish a causal link between stress, immune function, and disease. This chain of events has not been definitively established." In this book, we will illustrate that the integration among body systems and that causal link can now be established. The first few chapters of the book will cover this information in some detail.

What are the practical implications of the understanding that a mind–body system exists? It is a summons to bring holism to the practice of medicine; to do away with the unbalanced cold logic of clinical dispassion; and to bring to medical treatment the balance of nurturing, caring, and empathy as well as to instill hope, when appropriate. Over 100 years ago, the dean of the Johns Hopkins University School of Medicine, Sir William Osler, said that the care of the patient with tuberculosis has more to do with what is in the head than what is in the chest. Somehow, in all our enthusiasm for scientific precision and methodology, we have lost sight of that important message. And, in doing so, we have lost sight of the art and heart of medicine, of the healing process, and of the mystery of life itself.

In this book, we first establish the scientific basis for the mind–body connection and begin to understand why Steve lived only as long as his requested time. We will learn that stories like Steve's are not all that unusual and begin to understand how this can happen. We will document the puissant interactions of the endocrine, immune, nervous, and stress systems that can so profoundly influence our lives. Once this information is clearly established, we will turn our attention to issues beyond the mind–body connection and examine what it is that the dimension of spirituality (i.e., that which informs, but transcends the five senses) can add to healing. We will look at issues such as hope and faith and what they have to do with healing. If we are

more emotionally present with our patients, can we influence their healing process or outcome? What does deeply caring or loving have to do with health and healing—not only in patients' lives, but also in the lives of those called to the healing profession?

If Western medicine is to have a truly cohesive physiological system, it must incorporate a unified theory that can account for the existence of energy fields within—as well as outside—of the human body. This book looks at how various forms of energy (e.g., light, sound, electromagnetism, and prayer) translate into chemical and electrical signals that orchestrate our physical health. Some of these forms of energy can be called "subtle energy," that is, types of energy that typically are not detectable by the five senses or current scientific instrumentation. Integral physiology serves as a bridge between Western medical knowledge and the equally valuable, but less well-recognized, Eastern systems of medicine. Eastern medical concepts concern endogenous energy systems, such as Qi or life force that, according to Chinese medicine, flow throughout the body. A clear understanding of these issues will usher in a new form of medicine. I call it integral medicine because it combines important Western biological knowledge with forms of healing that incorporate the mental and emotional, if not the spiritual, capacities of humans to heal.

Jeff Levin writes the following in the last paragraphs of his book, *God, Faith, and Health*:

> I believe that a new generalist perspective, which is on the rise, will be based on something akin to a "unified field theory" of the determinants of health and healing. This perspective will not be grounded principally in genetics and molecular biology, as the mainstream medical research establishment presumes. Instead, it will be founded on an integrated, body–mind–spirit perspective—a view of all sentient life as part of a continuous bioenergetic spectrum, or to use a metaphor borrowed from author Ken Wilber, a "spectrum of consciousness." This will be the next era or historical epoch of Western medicine. (Levin, 2001)

In the final chapters of this book, we introduce a paradigm that we called "integral physiology," curiously, a schematic much akin to Levin's "unified field theory," which presents an integrated perspective of healthcare. It takes us on a pilgrimage well beyond the mind–body connection and research in the field of PNI—it brings the subtle-energy dimension into the mix. The bridge that we are constructing between Eastern and Western medical knowledge is like a Rosetta Stone of integral physiology. In Chapter 11, we use the image of the Rosetta Stone of ancient Egypt as an allegory for deciphering the pieces of information that incorporate the physical, mental, emotional, and spiritual aspects of our lives and of our health. Someday, we will have the scientific means to prove the principles inherent to a system of medical treatment that incorporates a fully integral physiology and the technology to employ it to benefit physical, emotional, and spiritual health. And someday, research on human subtle energy will be the next exciting frontier in medicine.

The fragility of life confronts us, often personally and certainly existentially. We have been inspired to give this book a deeper voice, a voice that neither of us thought would be expressed here, but, rather, in the future. We were wrong. It is clearly time to begin to describe the power and importance of the spiritual in overall health and

in the healing process. In the final chapter (Chapter 11), we present some initial blueprints for construction of a "bridge" that will connect science and spirituality, leading medicine toward a fully integrated view of physiology.

While this book addresses many technical issues, it is not intended solely for the physician, but also for the interested healthcare practitioner. The technical parts are necessary to responsibly convey the contributions that Western medicine has offered to the deciphering of our "Rosetta Stone." We would encourage the nonphysician reader not to get too bogged down in understanding every technical aspect or physiological explanation. Such readers can later return to the text to work on the more purely scientific understanding. The overriding message will be apparent, even if the medical details are not entirely understood. And to the physician, we encourage you to read it all. Although you might be familiar with, for example, the pineal gland or the neuroendocrinology of the stress response, topics are presented here from a new viewpoint and emerge to convey a candidly innovative perspective of healing.

Please note that throughout the book when the text states "I" or "my," it is intended to designate author Len Wisneski's voice and opinions.

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About the Authors

Leonard A. Wisneski, M.D., FACP is clinical professor of medicine at George Washington University Medical Center and adjunct faculty in the Department of Physiology and Biophysics at Georgetown University where he was a founding member of the Complementary and Alternative Medicine Curriculum Planning Committee. He serves on the Board of Directors of the Integrated Healthcare Policy Consortium, an organization driving public policy to ensure all Americans access to safe, high quality, integrated healthcare.

Dr. Wisneski's past accomplishments include serving as vice chairman of the National Institutes of Health (NIH) Consensus Panel on Acupuncture and chairman of the NIH Advisory Board on Frontier Sciences at the University of Connecticut. He holds fellowship positions in the American College of Physicians, the American College of Nutrition, and The American Institute of Stress. He served on the board of the American Holistic Medical Association and was president of the International Society for the Study of Subtle Energies and Energy Medicine. He has published more than 30 scientific articles.

Combining his knowledge with an intense passion for innovation in healthcare delivery and the quest to develop pathways toward the attainment of optimal vitality, Dr. Wisneski is a leader in the field of health and healing. In 1999, Dr. Wisneski co-founded and served as the regional president and medical director of American WholeHealth, an integrated, multi-practitioner center devoted to fostering individuals in the achievement of health and life goals. His medical practice in endocrinology and integrative medicine, spanning three decades, embodies the true meaning of integral medicine — an optimal synthesis of conventional and alternative medicine practiced with a whole person approach delivered with reverence and humanism. He also served in the role of medical director and chief medical editor for Integrative Medicine Communications, a publishing company that produced textbooks and newsletters devoted to this new field of medicine.

Dr. Wisneski graduated from Thomas Jefferson Medical College and performed his postgraduate training in the field of internal medicine and endocrinology in the George Washington University healthcare system, where he served as chief medical resident in internal medicine. From 1977 until 1997, Dr. Wisneski was the corporate medical director of Marriott International, Inc., and director of medical education at Holy Cross Hospital in Silver Spring, Maryland, an affiliate of George Washington University Medical School and Children's National Medical Center.

Lucy Anderson is a medical author, editor, and journalist. She has researched and written medical and mental health conference reports, reviews, monographs, newsletters, Continuing Medical Education reports, and biomedical corporate training materials. She wrote numerous articles for *The Integrative Medicine Consult* newsletter, including monthly reviews of both the allopathic and complementary treatment issues of designated medical conditions. Since 2002, she has been the content editor for the American Epilepsy Society's journal, *Epilepsy Currents*. Her nonmedical publication includes *Taking Charge* (Bantam Books, 1976). Lucy has a BA from Stanford University and a master's degree in social work (MSW) from the University of California, Berkeley.

1 A Review of Classic Physiological Systems

INTRODUCTION

In this chapter, we will examine body systems that permit our mind and emotions to interact or communicate with the environment and, thus, to induce positive or detrimental physiological changes. The classic body systems that we will address are the nervous system (including the enteric system), the endocrine system, and the immune system. However, in addition to these classic body systems, we suggest that there are two other fundamental human body systems: the stress system and the relaxation system. The stress system will be introduced in this chapter and covered more thoroughly in Chapter 3. The relaxation system (see Chapter 4) will be presented for the first time in a medical text. It is necessary to acquire a general understanding of each system in order to grasp how the systems interact to influence the mind–body connection. Right away, we see that it is almost impossible to describe any one system in an isolated manner.

Each of these systems is ultimately a conduit for energy communication. What do we mean by that? Think about how you hear. The speaker's larynx vibrates and sets forth a wave of air molecules, which impinge upon your tympanic membrane. The molecules are converted to mechanical energy by three little bones (i.e., the malleus, incus, and stapes) in your ear. Next, electrical energy is produced and transmitted across your cortex where it is understood as intelligible sound in the temporal lobe. Likewise, you look at the person who is speaking, but actually what you are seeing is light energy impinging upon the cerebral cortex (i.e., the brain), allowing you to interpret movements within time. In both instances, there is no material/material interaction. It is purely energy.

Energy communications similarly affect our emotions. We realize the implications of energy communication as we think about our relationships. How we feel in relationship to others accounts for the majority of the physiological reactivity that we experience. This may be most dramatically experienced when a harmonious relationship is disrupted by a major altercation. Simply being in the same room with that individual evokes an energy tension. As with our hearing or seeing, any emotional tension is transmitted by the body's systems. Some types of energy communication can be quite subtle, such as the transmission of "energy" that occurs with intercessory prayer (i.e., praying for others' well-being). Dr. Larry Dossey's commentary on a recent intercessory prayer study included the following thought-provoking statement: "We should be cautious in calling events miraculous or mystical because the subsequent course of history may reveal that these terms reflect little more than our own ignorance" (Dossey, 2000). We will review extensively the topic of energy medicine in Chapters 6 through 8. As we look at the technical aspects of the electrical and chemical functioning of

the various body systems, it will be useful to keep in mind that there are also types of energy transmission, such as prayer, that are less well understood, but now have scientific studies confirming their impact on humans.

SECTION 1: THE NERVOUS SYSTEM

The nervous system is lightning fast, but it has a very poor memory. It serves as the Paul Revere of our bodies. It indicates, largely through electrical signals, that there is incoming information. The nervous system transmits information to the proper part of the brain to be assimilated and then sends it back out to the particular portion of the body it intends to influence. The nervous system has two main divisions: the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS consists of the brain and the spinal cord. The PNS is comprised of the somatic nervous system and the autonomic nervous system (ANS), and the latter is further divided into the sympathetic and parasympathetic systems. The neuron is the basic unit of communication in the nervous system. Several of the structures of the brain that we will review here are also integral parts of the endocrine system. The enteric nervous system (ENS), which is reviewed later in this chapter, is a more recently identified system, and it involves the nervous system of the gut.

The heart also is currently being studied as another nervous system. It is known that upper chambers of the heart, called the atria, secrete a hormone called atrial natriuretic hormone, which decreases blood pressure and volume. The field related to systems interaction and the heart is called cardioneuroimmunology. I would speculate that in the coming few years, researchers will find that the heart does have its own nervous and immune systems.

The Central Nervous System

The Brain

We begin with an overview of the anatomy of the brain. The brain weighs approximately 3 pounds and contains about 100 billion neurons, which ultimately means enormous possible conduits of energy. The brain is supported by bone and meninges, which are connective tissue membranes.

The cerebrospinal fluid (CSF) is the clear, extracellular fluid that surrounds the entire brain and the spinal cord as well as filling the cavities (ventricles) within the brain. Most people have less than a cupful of CSF. It is secreted by tissue that lies within the ventricles. One of the crucial functions of the CSF is to protect the brain from injury. The brain literally floats in the CSF, which also minimizes compression of the spinal cord by its own weight. CSF nourishes the brain and provides an avenue for waste removal (waste returns to the blood via sinuses). Because the CSF is replaced numerous times each day, it provides a steady mechanism for frequently flushing out the CNS (Travis, 1999). The CSF carries messages that affect the endocrine, immune, and stress systems (see Chapter 2, Systems Integration).

While the CSF can exchange particles with the blood and can then pass these substances along to the neurons, the cells that make up the blood–brain barrier require

that all bloodborne substances pass through them before entering the brain. The blood–brain barrier is quite a strict gatekeeper, permitting mostly healthy substances to reach the brain. Plasma proteins, for example, happily are invited in. However, there is another route by which particles enter the brain: lipid solubility. Natural lipid soluble substances (e.g., dietary components or vitamins), as well as some drugs (e.g., morphine), enter the brain by this pathway. The complications and diseases stemming from such substances are well known.

The Hemispheres

The right cerebral hemisphere responds primarily to signals from the left side of the body. The right side of the brain largely involves nonverbal processes, such as music or mathematics. It is concerned with more abstract thinking, loose associations, three-dimensional forms, insight, and imagination. This is the artistic part of us. The left cerebral hemisphere responds primarily to signals from the right side of the body. The left hemisphere largely is concerned with verbal or rational processes, such as spoken or written language and logic. However, each of the cerebral hemispheres functions separately, and depending upon your line of work, you may use one side of your brain a great deal more than the other.

If we slice the brain open, there is a large strip of material that connects the two hemispheres. It is called the corpus callosum, which is very rich in myelinated (promotes fast moving messages) nerve fibers (approximately 200 million to 300 million axons). Its job is to transmit information from one hemisphere to the other so that the hemispheres can communicate with one another.

Using one hemisphere at the expense of the other does not allow us to experience our full capabilities. What we need to learn to do is to dance on the corpus callosum. We need to learn to be centered between both brains. We need to learn to use our minds, combining both hemispheres in a dual brain mode, in a whole brain mode, in a holistic manner. Dancing on the corpus callosum is the way to gain more harmony in our lives.

The Lobes

The brain is divided by deep fissures into the right and left hemispheres. Each hemisphere is then divided into four lobes: frontal, parietal, temporal, and occipital (see Figure 1.1). Each of the lobes has discrete functions attributed to it, but there is a great deal of systems interaction within a lobe. For example, the temporal lobe, which involves musical activity, must interact with the parietal lobe, which involves mathematical ability, in order to perform a piece of music. Furthermore, a lobe does not perform entirely the same function in each hemisphere or side of the brain. For example, the portion of the frontal lobe that is most involved in speech articulation lies predominantly only in the left hemisphere.

Following is a brief description of each of the four lobes and their primary functions.

- **Frontal Lobe**: The frontal lobe takes up one-third of the hemispheric surface of the brain. The frontal lobe has a lot to do with personality and how you basically think. It is involved with rationalization and inhibitions. It is the portion of the mind that allows us to plan and order things in a

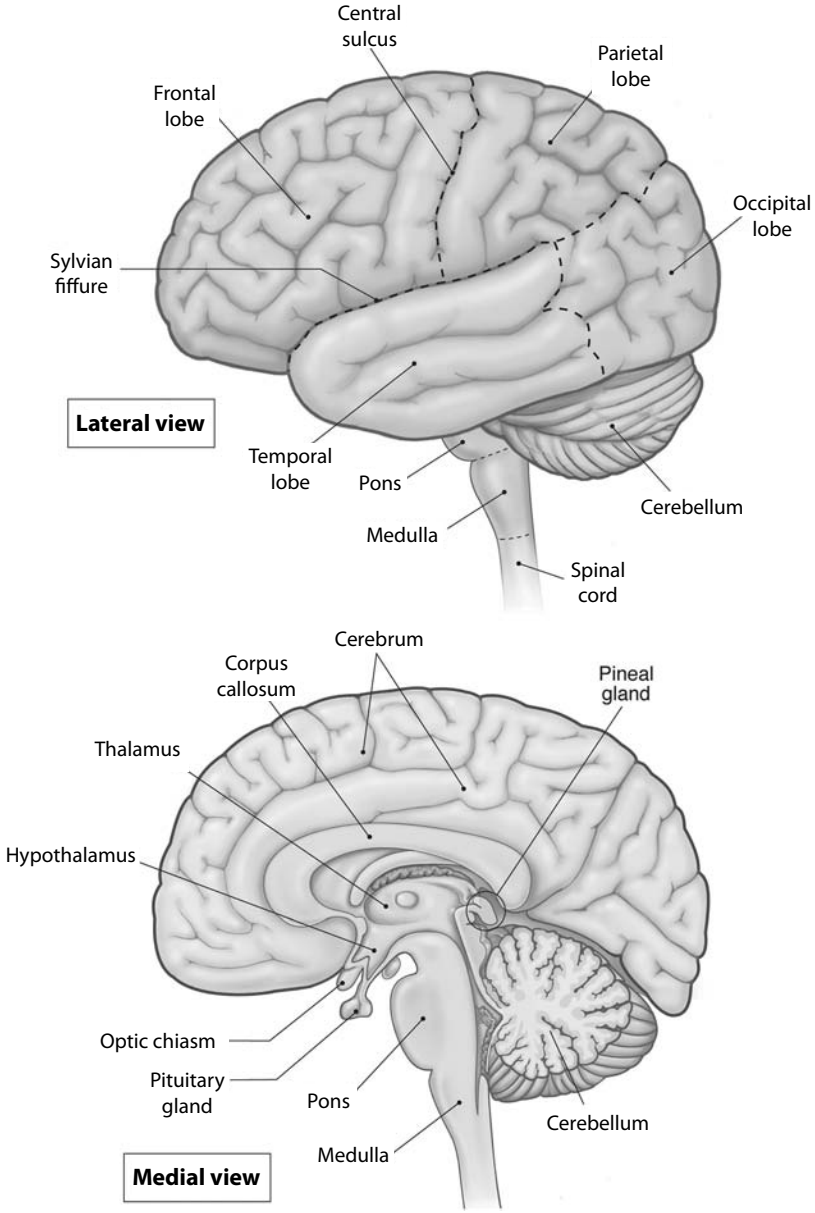

FIGURE 1.1 Lateral and medial views of the brain.

timely sequence. As mentioned, it is the center for articulation, but it also controls muscle contraction and discrete body movements from within the somatomotor cortex.

- **Parietal Lobe**: The parietal lobe is centrally located at the upper rear portion of the two hemispheres, although it is basically impossible to

delineate its precise boundaries. The parietal lobe assimilates incoming information from any of the five senses. It houses the somatosensory cortex, or primary sensory area, where all ascending somatosensory pathways (mainly from the skin and joints) terminate. Nerve pulses related to touch, pressure, heat, cold, and pain travel from the site of the sensation and are processed in the somatosensory cortex.

- **Occipital Lobe**: The occipital lobe, which houses the primary visual cortex, records information about light and receives information from the visual receptors of the eye. The occipital lobe is capable of associative memory and for memory of what you have seen. However, damage to the lobe can cause loss of vision in all or part of the visual field. It is the most intensely studied portion of the brain.
- **Temporal Lobe**: The temporal lobe, which is located near each temple, houses the auditory cortex, our processing center for hearing. The lobe is responsible for memory processes and complex associations related to things that you have seen. Some portions of the temporal lobe influence emotional behavior. The temporal lobe is also involved in the integration of multiple sensory functions (e.g., speech, vision, and touch) that can influence some of our more artistic qualities, such as remembering songs and things of that nature.

The Hindbrain

The cerebellum and brainstem are found in the hindbrain. The cerebellum is the CEO of the nervous system, modulating the entire system. It is crucial for the unconscious coordination of movements, maintenance of equilibrium, integration of skeletal muscle activity, and quality of muscle tone. The brainstem, which is attached to the cerebellum, includes the pons and the medulla. The brainstem connects the cerebral hemispheres with the spinal cord, carrying information that has been processed by the brain to the rest of the body.

The reticular formation is a network of interneurons extending the length of the brainstem and into the midbrain, taking in information carried by sensory, motor, and visceral pathways. It filters out repetitive stimuli and helps to maintain alertness. Motor portions of the reticular formation are involved in maintaining muscle tone and coordinating skeletal muscle activity. Neurons from the reticular formation make up the reticular activating system (RAS). This is a very interesting system because it is the core of consciousness. The ascending midbrain portion of the RAS extends to the hypothalamus and then to the thalamus. Directly or indirectly, it receives information from and is stimulated by every major somatic and sensory pathway. It modulates the level of cortical activity (by a gating mechanism that enhances or diminishes neuronal activation) and, therefore, the level of consciousness (Goetz and Pappert, 1999).

The Midbrain

The midbrain is the most superior portion of the brainstem. It houses the superior colliculi, which hold visual reflex centers, and the inferior colliculi, which contain

auditory reflex centers. These reflex centers involve responses, such as blinking in response to a bright light or startling in response to a loud noise.

The Forebrain

The forebrain is undoubtedly the most highly developed region of the brain. It includes two olfactory lobes (relating to the sense of smell): the cerebrum and the limbic system. The limbic system, which is housed in the insula cortex, is comprised of the thalamus, hypothalamus, pituitary gland, the pineal, the amygdala, the hippocampus, and the subiculum—to name a few structures. Much of the forebrain also is integrally involved with the endocrine system.

The cerebral cortex or cerebrum covers both of the hemispheres and is made up of gray matter and unmyelinated nerve fibers that are capable of receiving, encoding, and processing information. The cerebrum integrates sensory input and motor responses. It is responsible for higher mental functions, visceral functions, behavioral reactions, perception, and some types of motor activity.

The thalamus, which also is gray matter, is one of the main regulators of sensory input (except for the sense of smell) from different areas of the body to the cerebrum. It is thought to be the place in the CNS at which sensations are first consciously experienced. The thalamus then channels the neuronal input to the appropriate area of the cortex, where it will be interpreted and processed. The thalamus is the pacemaker for the rhythmicity in the cerebral cortex, which is seen on an electroencephalogram (EEG) as recurring waves that are similar in morphology and duration based on the frequency of the rhythm (see Chapter 1 "We Are on the Planet Like a Work of Art" for further discussion).

The hypothalamus is a very small area of the brain, about the size of a walnut, and weighs about 4 grams. It is an incredibly powerful command center and relay station. It monitors internal organs, including the endocrine system and the visceral nervous system. It is actually a link between the nervous and endocrine systems because it regulates the hormonal secretions of the pituitary, the adrenal cortex, the gonads, and the thyroid either by direct or indirect hormonal stimulation. It regulates the adrenal medulla by direct neural stimulation. The hypothalamus regulates thirst, hunger, body temperature, sexual activity, and emotional behavior as well as allergic and immune responses. It relays sensory messages, such as pain, and governs many autonomic functions so that you do not have to think about breathing or regulating your temperature or your blood flow. You can just relax and read your book because you are on automatic pilot with the hypothalamus.

The hypothalamus contains several highly specialized nuclei. In the hypothalamus, there is a structure called the suprachiasmatic nucleus. It is a very small structure, which is composed of approximately 10,000 neurons. Destruction of this nucleus eliminates the body's ability to maintain its circadian rhythm (i.e., daily changes in physiological processes, such as sleep patterns) or biological clock.

If you take one of these human nuclei from the suprachiasmatic nucleus and put it in a petri dish, it will exhibit its own independent electrical firing. This firing can continue for several weeks in the dish. But what is really interesting is that it maintains a circadian rhythm, with a periodicity that never deviates more than tiny amounts from the 24-hour cycle (Hastings, 1998). The suprachiasmatic nucleus is our

biological clock. If we take one of us, put us in total isolation, the suprachiasmatic nucleus will keep going. We really do not entirely understand it. There is a whole field of chronobiology that has been developed over the past 20 years. It concerns our circadian rhythms and biological clock. We will be discussing this more in Chapter 10, which covers the pineal gland.

The pituitary gland, which is about the size of a pea, hangs on a stalk from the hypothalamus and is controlled by the hypothalamus. Medical students have always been taught that the pituitary gland is the "master gland," but it really is not the master gland. The pituitary stores hormones and secretes them according to instructions given by the hypothalamus. That is not a master gland. The pituitary and the hypothalamus combined are, however, a major neural–endocrine control center.

Until about 240 million years ago, vertebrates had a third eye on the top of their head. Lampreys still have one just beneath the skin. This third eye was historically a photosensitive organ, and today it appears in a modified form as the pineal gland, still with photosensitive qualities. Ancient literature refers to the third eye, the pineal gland, as the seat of wisdom or light, which, as we will see in the latter chapters of the book, would make sense.

The pineal gland is the "master gland," and in the chapter on the pineal gland (Chapter 10), we will explain in great detail why it is our master gland. The pineal gland lies on top of the third ventricle posterior to the corpus callosum. It weighs about 100 to 150 mg and is 7 mm in length and 5 mm in width. Its name derives from the Latin word *pinea*, or pinecone, because of its cone-shaped appearance. The pineal gland is an external and internal transducer of energy. It regulates neuroendocrine functions, transfers environmental information to the appropriate internal structures, and helps to regulate the immune system. It modulates the circadian rhythm, keeping our biological clock in balance.

The limbic system is an amazing system. As depicted in Figure 1.2, it surrounds the hypothalamus. Consisting of scattered but interconnected regions of gray matter, it is our emotional brain. It receives all incoming sensory input and is capable of output to motor, endocrine, and visceral systems. The limbic system is also central to our memory, and as we will see, emotion and memory are integrally related. The limbic system is made up of various processes, including the cingulate gyrus, fornix, and mamillary body. But the processes that we will concern ourselves with here are those of the amygdala, the hippocampus, and the subiculum as well as the thalamus and hypothalamus, which we just reviewed.

The amygdala, which means "almond" after its shape, is our center for incoming sensory input for fear, rage, aggression, and sexual feelings. What happens if you were asked, for instance, to give a lecture? If you were afraid of speaking in front of a lot of people, your adrenal gland would be producing both cortisone and adrenaline. (Adrenaline is an older but still commonly used term for epinephrine; however, most research and many physicians now refer to it as epinephrine.) Increased cortisone and adrenaline production would cause you to start sweating, your heart would be beating fast, and perhaps your voice would go into soprano once in awhile. You would probably get exhausted within 40 minutes, or maybe less. On the other hand, you might really enjoy public speaking and remain quite calm. The amygdala says: "Audience, audience in front of you, everyone is looking at you." It then looks to

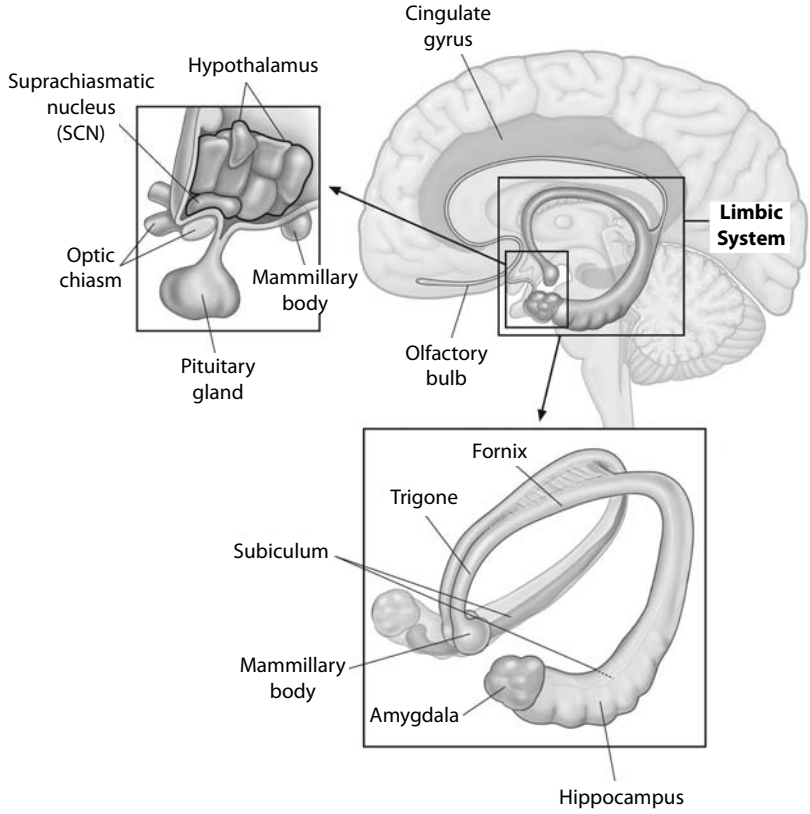

FIGURE 1.2 The limbic system and the hypothalamus.

the hippocampus to see if there is a trauma memory pattern. If so, a fear response, or what was initially described by Walter Cannon in 1914 as the "fight or flight" response, is triggered (Cannon, 1914). It is, therefore, the amygdala that determines whether or not there should be a fear or stress response and, if necessary, activates the nervous system's response via projections that link it directly with the fight-or-flight response center.

Research on the amygdala shows that there is severe impairment in the recognition of fear with patients whose amygdala has been destroyed. Studies reveal that the amygdala is involved in gaze direction and interpretation of facial expressions (Adolphs et al., 1994; Allman and Brothers, 1994). Scientists at the University of Wisconsin at Madison are carrying out research on the amygdala to learn about its association with negative emotions. They place wire meshes, which are capable of registering the electrical activity of 128 different brain sites, on the heads of subjects. The subjects are then shown a variety of pictures. Results of magnetic resonance imaging (MRI) of the brain demonstrate that our right prefrontal cortex governs negative or inhibiting feelings and that the left prefrontal cortex governs positive, more extrovert-type emotions (Robbins, 2000). There is evidence that this prefrontal

portion of the brain has a memory for the representation of elementary positive and negative emotions (Davidson and Irwin, 1999). Subjects who are depressed show deficits that include both the brain's inability to allow positive emotion to dominate as a response to outside stimuli as well as an inability of the left side to turn off the fear messages from the amygdala.

Children who are depressed produce the same results of right and left frontal cortex variation as well as difficulty with processing the correct affective face as it is presented to them in pictures (Davidson and Slagter, 2000). This research indicates that the young brain is perhaps more vulnerable to the detrimental effects of severe stress than the adult brain.

When a person becomes chronically stressed, and often depressed, the left frontal cortex becomes incapable of turning off the amygdala's fear response to just about anything. This pattern of reaction inevitably brings hopelessness and despair to the individual. Furthermore, it could well be the physiological setup of the fear conditioning that occurs in posttraumatic stress disorder (Yehuda, 2000; Baker et al., 1997). Notably, the prefrontal cortex dominance pattern also is associated with the health of the immune system. Individuals who have greater right-side activity and more negative affect have lower levels of natural killer (NK) cell activity at baseline than their counterparts with predominant left-sided prefrontal cortexes. (NK cells will be discussed later in this chapter in Section 4 on the immune system.) These individuals have greater decreases in their NK levels during exam periods, and they do not show as great an increase in NK activity after exposure to positive film clips than those with greater left prefrontal cortex activity (Davidson et al., 1999).

The hippocampus, which means "sea horse" after its shape, lies just next to the amygdala. Its job is to remember. What is crucial to understanding the whole theory of integral physiology is to bear in mind that the hippocampus is a huge filing cabinet for your personal memories. In particular, it stores memories that are associated with trauma and deeply imprints them in the memory. Since the first edition of this book, we have learned about a small, rarely discussed structure called the subiculum, which along with the dentate gyrus and Ammon's horn, is considered to be part of the hippocampal formation. It is located between the Cornu Ammonis 1 (CA1) area of the hippocampal formation and the entorhinal cortex of the parahippocampal region. As will be discussed further in Chapter 3 on stress, the subiculum principally serves as an interface for memory and other types of information processing between the hippocampus and the neocortex.

This is very new data. Encoded traumatic memories are very hard to change because they crystallize. It takes a lot of work to change them, and this is the key, in my mind, to the healing process. It is possible, however, to erase traumatic memories or to override them with the cognitive functions of the higher-ordered brain. We will revisit this topic in later chapters.

The Peripheral Nervous System (PNS)

The PNS comprises 31 pairs of spinal nerves and 12 pairs of cranial nerves leading into and out of the spinal cord and the brain. The afferent (sensory) division of the PNS carries impulses to the CNS and the efferent (motor) division carries impulses

away from the CNS. The efferent division of the PNS consists of the somatic nervous system and the ANS.

The Somatic Nervous System

The somatic nervous system (sometimes called the voluntary nervous system) involves the transport of information from the CNS to the skeletal muscle. It is concerned with motor pathways and our external world. This is the fast-moving part of the PNS.

The Autonomic Nervous System

The ANS is a network that synthesizes visceral (i.e., internal organs or their covering, especially those of the abdomen), humoral (i.e., elements, such as antibodies), and environmental information. This synthesis permits it to establish an integrated autonomic, neuroendocrine, and behavioral response to external and internal stimuli. Nerves branch out at each segment of the spinal cord to innervate the various visceral motor organs (see Figure 1.3). Autonomic means self-regulating, so these organs are all capable of functioning without our conscious thought. Mostly, that is what happens; the ANS just hums along by itself. However, we are capable of consciously altering certain visceral responses, such as heartbeat rate.

The ANS connects the CNS with numerous motor organs: the smooth muscles (i.e., not the skeletal muscles) of the heart, gastrointestinal system, and the blood vessels as well as the adrenal, pancreas, and salivary glands. These are sometimes referred to as visceral or effector organs. What is less well known is that the ANS is also wired into the thymus, spleen, bone marrow, lymph nodes, and to the enteric nervous system. Curiously, all of these structures are a part of the immune system. What we are seeing here are new pathways, new tracks by which information may be conveyed and by which systems may communicate with one another.

There are two divisions of the ANS: the sympathetic, which leads to arousal, and the parasympathetic, which calms the body. The sympathetic nerves can cause the release of adrenaline (i.e., epinephrine), a hormone that is involved in the "fight or flight" response in our bodies. The amazing cacophony of intricate neural wiring that will respond to stimuli in the sympathetic nervous system is all regulated by that little walnut-sized hypothalamus. The PNS is set into motion by neurons in the midbrain, pons, and medulla via the vagus nerve (the major parasympathetic nerve), which allows the message to travel through the body.

The Enteric Nervous System

In 1917, Ulrich Trendelenburg, a German scientist, first introduced the term peristaltic reflex after illustrating this reflex with a segment of a guinea pig's gut, which he had isolated in an organ bath. If you tried to perform the same experiment with a heart vessel, no peristaltic reflexive action would occur, so this was an amazing finding. Trendelenburg showed that the gut has a nervous system all its own, yet his work somehow was lost from scientific practice and study. Then in 1921, an Englishman named J. N. Langley published his renowned book *The Autonomic Nervous System*. Although, until the past 10 years or so, medical students have rarely been given this information. Langley stated that there were three divisions of the ANS: the sympathetic, the

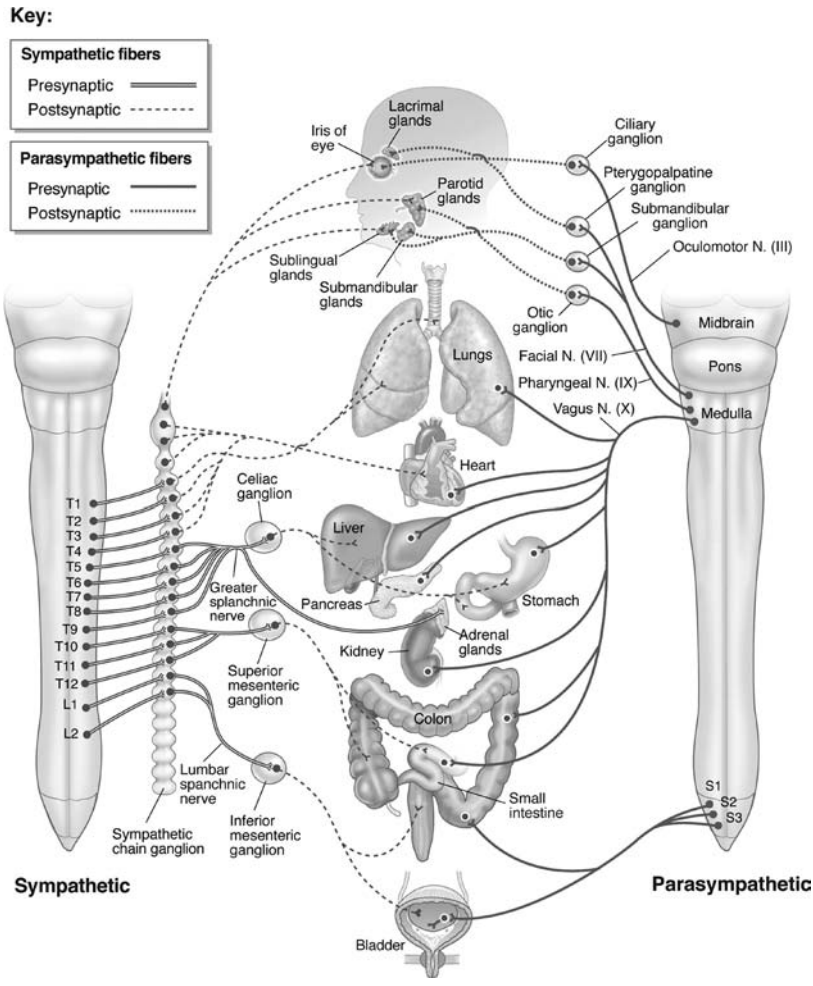

FIGURE 1.3 The autonomic nervous system (ANS).

parasympathetic, and the enteric, which are located on the walls of the gut. His opinion that the enteric system was a third division was based on his discoveries that the majority of enteric nerve cells received no direct connection or innervation from the brain or the spinal cord, in contrast to the rest of the PNS. Perhaps because of the rush of excitement resulting from the discovery of neurotransmitters, all of Langley's work was disregarded, and the neurons of the enteric system were considered simply to be part of the postganglionic parasympathetic system, which it is, but only in a relatively minor way. However, all of this information was recently brought to light by a physician, Dr. Michael Gershon, in his book *The Second Brain* (Gershon, 1998).

The enteric system, which contains approximately the same 100 billion neurons as does the spinal cord, closely resembles the CNS in its functioning (Goyal and

Hirano, 1996). However, it has sensory receptors that can pick up information without any assistance from the CNS and then can activate a set of nerves that it alone controls. But the CNS does maintain contact with the enteric system via a network of sympathetic and parasympathetic fibers, allowing the ENS to integrate information into its own "brain" that comes from the CNS.

The scientific community adheres to the premise that there are two neurotransmitters that run the parasympathetic system: acetylcholine and norepinephrine. Stemming back to work begun in the 1950s, Gershon postulated that serotonin, previously considered only a CNS neurotransmitter, was also an enteric neurotransmitter. In 1981, his colleagues, not being able to deny the results of their own research, finally accepted this fact. Since that time, Gershon and others have determined that serotonin, in addition to being an enteric system neurotransmitter, is also a signaling molecule that is secreted by specialized, nonnerve cells in the gut lining. Serotonin works within the mucosa to stimulate sensory nerves that carry out peristaltic and secretory reflexes. The ENS is now known to contain at least seven different receptors that respond to serotonin (Gershon, 1998).

In addition to serotonin, there are numerous other neurotransmitters that have been identified from enteric neurons. The ENS also secretes neuropeptides identical to those secreted by the neurons in the brain, including norepinephrine, acetylcholine, endorphins, enkephalins, substance P, somatostatin, and vasoactive intestinal polypeptide (VIP). These various ENS neurotransmitters have discrete functions (Goyal and Hirano, 1996).

All of this is very interesting when you consider how we refer to our "gut feelings." One day when I was a college student, I was walking through town. I sensed a gang of boys approaching behind me. I sensed it because I felt it in the pit of my stomach. When I turned around, sure enough, a group of kids were coming after me. Similarly, when I do rounds in the hospital, I might say to a nurse or another doctor that I have a gut feeling that the patient in bed number 4 is not going to make it. I literally feel it in my gut. When we talk about our gut feelings, it is my contention that we are actually referring to our intuition (a far less acceptable term to use in the medical setting). Our gut has a brain of its own that seemingly can facilitate or collaborate with our mind or our intuition.

As a result of the work of Gershon and others, the scientific community is beginning to understand that medical problems in the enteric system may actually be localized there (i.e., as a result of heredity or other reasons) and not just a result of "nerves." In other words, the theory that the brain is responsible for all enteric abnormalities no longer holds water. Acceptance of this premise has opened the way to research and discoveries on treatment for gastrointestinal diseases, such as irritable bowel syndrome.

The Triune Brain

In the first edition of this book, we discussed Paul MacLean's theory of the triune brain (MacLean, 1985). We wrote of his theory that the forebrain of humans anatomically and chemically has common features with reptiles, early mammals, and late mammals (see Figure 1.4). MacLean explains that in the evolutionary transition

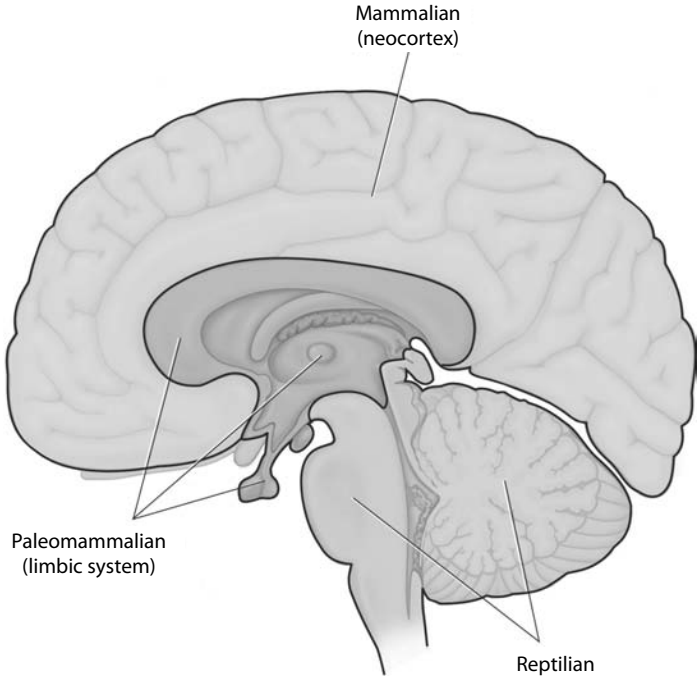

FIGURE 1.4 The triune brain.

from reptiles to mammals, there were three key developmental factors: (1) nursing, in conjunction with maternal care; (2) auditory communication, for maintaining maternal–offspring contact; and (3) play. These developmental changes, he theorized, correlated with the evolutionary development of the thalamocingulate division of the limbic system, which does not appear in reptiles and which concerns emotion. In support of this theory, other researchers conducted an experiment that involved damage to the limbic, thalamic, and cingulate portion of female rat brains by seizure-inducing injections of lithium and pilocarpine. After giving birth, the injected rats displayed a complete absence of maternal behavior, supporting MacLean's triune theory that those brain portions are critical to the development of emotion (Peredery et al., 1992).

The first of our triune brains, then, has to do with our reptilian nature, which is controlled by the brainstem. The reptilian response to a stimulus is different from the fright one might experience before giving a lecture. It is more like the experience of stepping on a nail. You don't calmly say, "I perceive I just stepped on a nail. Perhaps it would be good to lift my foot now." No. It is a rapid, automatic response, generally accompanied by an expletive. There are long reflex arcs through the brainstem that convey the information. So, even before you feel the nail, the information is transmitted up to the brain. Think about how reptiles react. They do not reflect; they are not worried about feelings. They simply react. This is the reptilian brain.

The development of the thalamocingulate division of the limbic system is our second and mammalian brain. This is the brain that is concerned with feelings and emotions and is much like that of our pet dogs or cats. Pets exhibit emotions—they feel good, they purr, they bark, they get angry. They just put out their feelings. However, pets have absolutely no sense of time, no sense of prioritized thinking, and no ability to dream of the future. Therefore, animals are not really subject to the acculturation processes that humans are.

The third brain is the human brain, which is affiliated with the limbic system, but controlled by the prefrontal neocortex. MacLean saw the human brain as key to the development of familial acculturation. The human brain is capable of higher cognitive processes, of perceiving time, and of pondering the spiritual self.

So these are the three brains: the reptilian, the mammalian, and the human brain. The triune brain is sometimes inaccurately described as simply an evolutionary process culminating in the human brain. However, our brains should more correctly be thought of as a dynamic interaction of the evolutionary trends of the three. Richard Davidson, PhD, at the University of Wisconsin, Madison states: "We now know that emotion is not all subcortical, and thought or cognition is not all cortical … that there are certain subcortical areas that are absolutely critical for what we think of as cognitive function" (Davidson, 2005). Further, we each employ all three of our brains in the course of a day. As we develop as individuals, we have the daunting task of effectively integrating our so-called three minds.

Neurons and Neurotransmitters

There are two interconnected modalities that the brain uses to communicate with the outside world as well as with the rest of the body: chemical and electrical. Electrical impulses, carried by neurons, move information to various locations, but they communicate with each other in a chemical language via neurotransmitters. In Section 2, entitled "The Endocrine System," we will review more fully the chemical, or hormonal, modes of communication.

As already mentioned, the neuron is the basic unit of communication or information processing in the nervous system. A neuron or nerve cell is made up of a cell body, dendrites, and an axon. Dendrites increase the available area for a neuron to receive incoming information. The axon is typically the structure by which the cell sends out information. A nerve is a cluster of processes (mostly axons) from many neurons. The axon is wrapped in a fatty coating called a myelin sheath, which is like a coat of insulation that preserves electrical impulses. It allows the impulses to traverse down the nerve in a rapid and smooth fashion. The sympathetic nervous system is myelinated, and the parasympathetic is unmyelinated. Multiple sclerosis, for instance, occurs when the myelin sheath is disturbed or destroyed, preventing the electrical impulses from being transmitted properly.

There are three types of neurons: sensory (which send information to the CNS), motor (which relay information away from the CNS to muscles or glands), and interneurons (which are situated between a sensory and a motor neuron and help to integrate information). For example, receptors in the eye that are sensitive to light are linked to sensory neurons that can relay the information to the CNS. After processing

this information, if the brain determines that a motor response is needed, it sends the message via the motor neurons, and your body moves.

When a neuron is at rest, there is a steady voltage difference across its plasma membrane. This is called the resting potential. When the neuron receives a strong enough signal, an action potential is created. This is a get-up-and-go message, causing a brief reversal in voltage across the plasma membrane. Action potentials arise and move rapidly along sensory and motor neurons because of the myelin sheath.

Each neuron has an input or presynaptic zone and an output or postsynaptic zone. When the action potential reaches the postsynaptic output zone, it either just stops or it may release a neurotransmitter that passes the message along. Neurotransmitters are substances released on excitation from a presynaptic neuron of the CNS or PNS. They can be either excitatory, causing the receiving neuron to continue passing the electrical impulse, or inhibitory, stopping the chain of electrical firings. The neurotransmitter "jumps" between the axon terminal of the presynaptic neuron to the receptor molecules located on the postsynaptic neuron to pass along information. The region of communication between two neurons is called a synapse, which is illustrated in Figure 1.5.

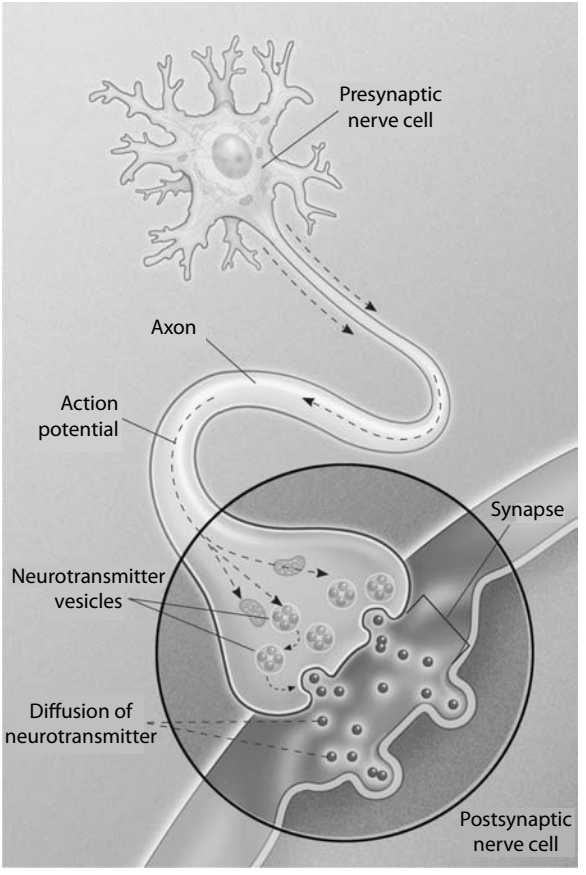

FIGURE 1.5 Synapse.

A signal coming from the CNS to any skeletal muscle takes a nonstop route. A signal coming from the CNS to an ANS organ passes the message along via nerve cell bodies called ganglions. The first nerve cell is called the preganglionic nerve, and the second nerve to receive the message is called the postganglionic nerve. The neurotransmitter for sympathetic and parasympathetic preganglionic and for the parasympathetic postganglionic neurons is acetylcholine. The neurotransmitter for sympathetic postganglionic neurons is norepinephrine. The postganglionic nerve carries the message along to the outlying effector organs. Thus, sending messages to the ANS is a little like playing "telephone" as a kid: The message might get there intact, but it might get changed along the way.

Do you ever wonder if your neurons can be replaced? Is there such a thing as neurogenesis? When I was in medical school, we were taught that humans were born with something like 100 billion neurons, and when any one neuron died, that was the end. Recently, Fred Gage, from the Salk Institute for Biological Studies in La Jolla, California, and his colleagues in Sweden have shown that neurons can be produced in the adult human being, not just the child, which completely blows a major theory. The neurons Gage researched were produced in the dentate gyrus of the hippocampus. The rate of proliferation was not high, about 500 new neurons a day, but they did have the morphologic and phenotypic characteristics of neurons (Eriksson et al., 1998). Although the biological significance of this neurogenesis is yet to be fully determined, it is very interesting to keep in mind for later when we talk about the healing response because, as you will remember, the hippocampus is the center of traumatic memory.

Neurotransmitters can bind with receptor proteins on the membrane of a neuron, a muscle (this is called the neuromuscular junction), or a gland, and as we said, they can excite or inhibit them. (See Table 1.1 for a list of neurotransmitters.) Some of these substances (e.g., norepinephrine, epinephrine, dopamine, and serotonin) are also released directly into the bloodstream, and then they are considered hormones (see Section 2 on the endocrine system in this chapter).

In medical school, I learned that one neuron was capable of secreting only one neurotransmitter. That made it very easy to pass my physiology test. Today's medical students do not have it so easy because it is now known that one neuron can secrete several neurotransmitters.

Neuromodulators can make the postsynaptic neuron more sensitive or less sensitive to the neurotransmitter that is present. Endorphins, which are naturally occurring substances in our body, are important neuromodulators because they are powerful painkillers.

Your Thoughts and CNS Neurotransmitters

It is my contention that the brain is capable of secreting any hormone it so chooses, at any given point in time. We are just beginning to understand this phenomenon. It is also my opinion that cortical activity, which means a thought, produces a series of hormones (neuropeptides) that flood into other portions of the brain, frequently the limbic system. The limbic system is asking, "Do I see anything I want to pick up

TABLE 1.1
Neurotransmitters

Class I:
Acetylcholine (ACh)
Class II: Amines
Norepinephrine, epinephrine, dopamine, serotonin, and histamine
Class III: Amino acids
Inhibitory: glycine and γ-aminobutyric acid (GABA)
Excitatory: aspartate and glutamate
Class IV: Polypeptides—there are over 60 peptides, some are listed here:

A. Hypothalamic: corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), somatostatin (growth hormone), growth-hormone-releasing hormone (GRH), and gonadotropin-releasing hormone (GnRH)
B. Pituitary peptides: adrenocorticotropic hormone (ACTH), β-endorphin, vasopressin, oxytocin, and α-melanocyte-stimulating hormone
C. Peptides that act on the gut and brain: enkephalins, substance P, cholecystokinin (CCK), vasoactive intestinal polypeptide (VIP), insulin, glucagon, and neurotensin
D. Peptides from various other tissues: angiotensin II, bradykinin
E. Lipids: anandamide, sn-2 arachidonylglycerol (2-AG), noladin ether

here? Do I have any receptors that fit?" And, if a receptor does fit, there is a response throughout the body.

A field of research called psychoendocrinology is concerned with hormones and the behavioral effects attributed to them. Neuropeptides are any of the molecules composed of short chains of peptides (e.g., endorphins, enkephalins, and vasopressin) that are found in the brain tissue. Typically, they localize in axon terminals at synapses. Peptides are small proteins. Neuro means they come from neurons. Neuropeptides are a type of neurotransmitter, but some function as hormones. Neuropeptides that function as hormones produce chemical signals instead of electrical signals. These hormones can communicate with another structure or another system. For instance, when we think a particular thought, receptors in the limbic system (the limbic system is rich in receptors) affect numerous functions, including sexual behavior, sleep, temperature regulation, breathing, blood pressure, addiction, habituation, memory, and learning. Influenced by thoughts, the brain secretes and releases neuropeptides. The core limbic structures, long considered the emotional center of the brain, are infused with receptors, not only for opioids, such as endorphins and enkephalins, but also for the majority of the neuropeptides. The neuropeptides are secreted when you have a thought process that impinges on this limbic system. If there are receptors in the limbic system for these particular hormones, there will be an alteration of the response.

Neuropeptides can alter or influence behavior and physiological function. For example, calcitonin, a neuropeptide produced in the CNS, is typically thought of as being produced in the thyroid gland. But it is also produced in the brain (Rizzo and Goltzman, 1981; van Houten et al., 1982). What is it doing in the brain? Recent

research has shown that there is a whole calcitonin-based system for pain relief that is similar to the endorphins (e.g., Ormazabal et al., 2001; Xu et al., 2000; Yamazaki et al., 1999). It has been there for millions of years, and we are just discovering it.

Another example of a neuropeptide that has significant behavioral impact is DDAVP (desmopressin acetate), which is a synthetic version of a hormone called antidiuretic hormone (ADH) or vasopressin. ADH is a major stress hormone, secreted by the anterior pituitary during physical stress. For example, you go wandering in the desert and it is a hot day, and you forgot your water bottle. But, you do not care and continue to walk. The thirst mechanism exclaims, "Oh my, what are you doing?" and the pituitary begins to release ADH. Your kidneys get the message loud and clear: "Hold on to your water!" (The kidney tubules reabsorb the water so that less is lost as urine.) ADH is a major stress hormone that keeps you going until you get to the next oasis. ADH also helps you remember, "Do not do this again!" So it also enhances memory.

Experiments with DDAVP have been conducted. Male subjects treated with DDAVP demonstrated better memory than control subjects, but the hormone has no effect on women (Beckwith et al., 1984). Male subjects who were given 60 μg of DDAVP by nasal inhaler had enhanced recall of narrative passages (Beckwith et al., 1987). However, in other DDAVP research, low-verbal subjects had greater improvement in immediate memory, and high-verbal subjects had increased delayed memory, demonstrating that the impact of vasopressin on memory relates not only to gender but to individual verbal ability as well (Till and Beckwith, 1985).

Your Thoughts and Immune Cells

The nerve cells in the brain are capable of instigating an immune response. Not long ago, any medical doctor would have disagreed with that statement. We will devote all of Chapter 2 to understanding this and other system integration issues. The important concept to grasp now is that these very cells that we have elaborated are secreting hormones and, consequently, allowing communication across major systems.

We Are on the Planet Like a Work of Art

There are basically three directions of information transmission to the command center, which is our hypothalamus. Moving via chemical and electrical pathways, our thoughts go to the hypothalamus from the cortex; our emotional reactions go to the hypothalamus from the limbic system; and, as described, our states of awareness go to the hypothalamus from the reticular formation.

I want to digress briefly to convey a belief that is very important to me. If someone has been meditating, maybe for 10 years, he or she begins to get a sense of eternity, a sense of accepting the fact that we are on the planet like a work of art. We are like flowers—we are seeded, we grow, we blossom, and part of life is that we start to refold, and then we are gone. That is the way it is; that is the way it has always been. When we deeply understand this truth, there is a sense of serenity that comes to our lives. This, I think, is going to be the key to future research in consciousness and awareness, and how it interfaces with physiology. I think that research will increasingly show that when our higher awareness center (i.e., the reticular formation) is

capable of affecting input into the hypothalamus, it will not only override our fear system (i.e., the amygdala), but our thoughts as well. And when the reticular formation becomes the command center, everything settles down into a state of physiologic relaxation, healing, and harmony.

So, input to the hypothalamus is via the cortex for thoughts, the limbic system for emotions, and the reticular formation for "states of awareness or levels of consciousness." (I put this in quotes because it is not proven yet.) We will let the hypothalamus worry about which one to listen to. Another route to experiencing higher states of consciousness comes by working on quieting our state of mind, using a technique that I call limbic therapy. Limbic therapy begins with an understanding of brain waves. Brain waves are the fluctuations of electrical potential in the brain. They appear in different patterns, depending upon how much electrical current is emanating from the nerve cells.

When brain patterns are recorded on an EEG, the brain waves characteristically resonate between 14 and about 40 cycles per second. One cycle per second is called a hertz (Hz). Figure 1.6 depicts the appearance of various EEG brain waves and correlates them with their common states of awareness. States of awareness in which you are fully alert and in which there is intense activity of the nervous system are called *beta*. In the beta state, your brain waves have a frequency of 13 to 24 Hz. The *alpha* state, from 8 to 12 Hz, includes normal waking hours and when you are in a relaxed state of mind. You are able to be alert, but you are also very restful. You are not ruminating over memories of things you have to do, things you may not want to do, or arguments you may have had. Neither are you feeling very hungry because that brings you back into beta. It is a feeling of restful peace. *Theta*, which is 4 to 7 Hz, is a state between wake and sleep that is called hypnagogia. Theta also is involved in some nonrelaxation actions, such as learning, memory, and acquisition of information. Until recently, it was thought that meditation occurs exclusively during alpha and more rarely during theta states. However, as discussed in Chapter 11, at least for meditations that focus on compassion for others and possibly during other types of meditation, it is now known the mind emits *gamma* waves (25 to 42 Hz). A person demonstrating predominant *delta* (< 4 Hz) wave activity is in deep sleep, a coma, or has significant brain pathology. Certain factors, including illness, drugs, and meditation can alter one's wavelength state.

It is my theory that theta is a state of mind in which the healing of old emotional traumas may occur, which is why I call it limbic therapy. It is a state that allows us to get into the traumatic memories that have been encoded in the hippocampus and either greatly decrease their impact or actually erase them. We will be revisiting this issue many times.

In the next section, we will take a look at the endocrine system.

Essential Points

- An understanding of the parts of the brain will aid you in understanding much of the rest of the book.
- The pineal, and not the pituitary, is the master gland.
- The amygdala is our fear center.
- The hippocampus encodes and crystallizes memories, with the help of the subiculum.

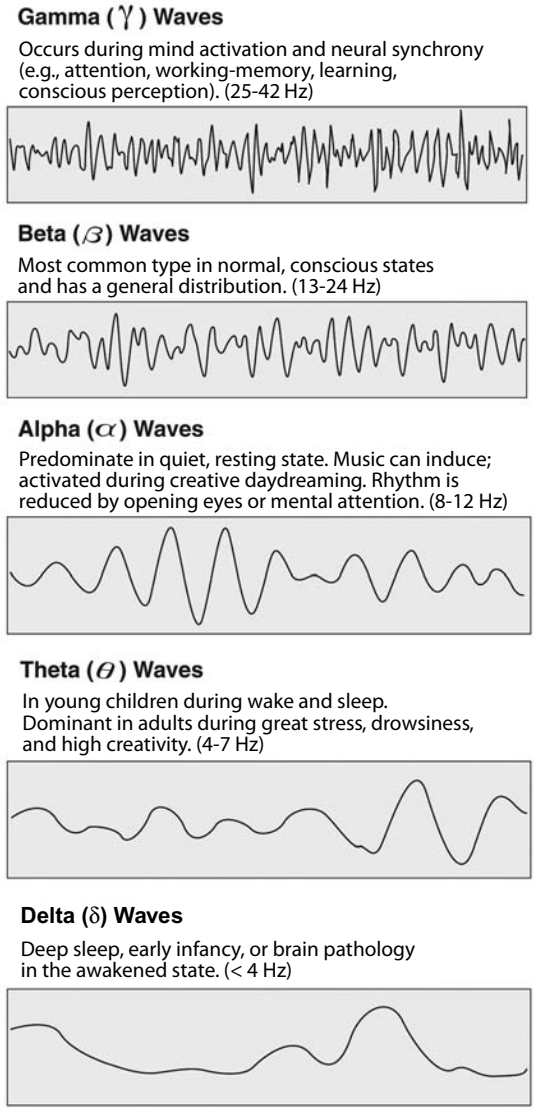

FIGURE 1.6 Brain waves.

- The gut has a brain of its own.
- The triune brain theory challenges us with the daunting task of integrating our reptilian, mammalian, and human brains.
- The neuron is the nervous system's basic unit of communication. Neurotransmitters facilitate this communication.
- Neuropeptides can have behavioral effects, and thoughts can influence the health of the immune system.

SECTION 2: THE ENDOCRINE SYSTEM

The endocrine system is a system of internal structures that secrete hormones (mostly into the bloodstream) to regulate metabolism and perform myriad other bodily functions. The endocrine system is not as zippy as the nervous system. It turns an electrical signal into the elaboration of a single hormone or of several hormones, which then travel to various places in the body, communicating and directing physiological activity. The glands of the endocrine system include the pituitary, hypothalamus, thyroid, parathyroid, pancreas, adrenals, gonads (ovaries and testes), thymus, and the pineal gland (see Figure 1.7). In addition, there are various other organs with hormonal functions that are not technically considered to be endocrine glands, such as the previously discussed enteric system. In the first half of the twentieth century,

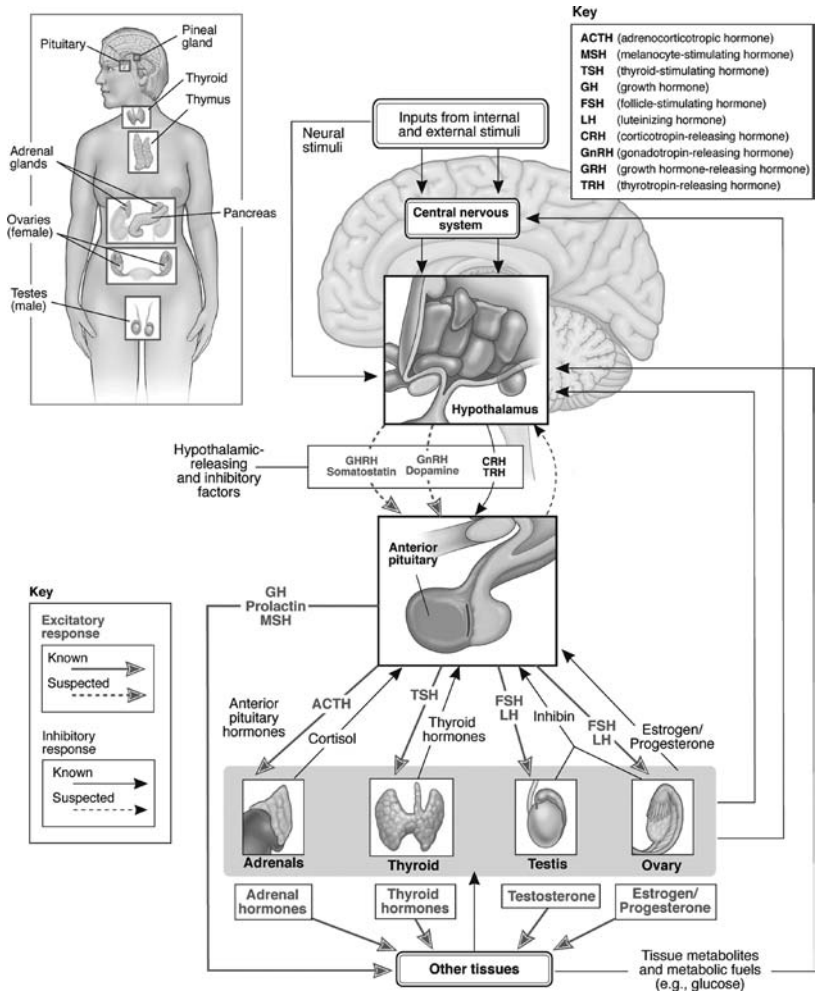

FIGURE 1.7 Overview of endocrine glands and hormonal pathways.

scientists did not think of the brain as an endocrine organ. After nearly 15 years of work, two researchers, Roger Guillemin and Andrew V. Schally, identified the first hypothalamic secretion of hormones. In 1977, they both won the Nobel Prize for their efforts. Scientists continue to discover new hormones and neurotransmitters.

Hormones and Their Properties

Hormones are the mode of communication for the endocrine system, and they include various types of proteins as well as steroids. For a hormone to have an effect, the cell must have a receptor site specific to that hormone. If the hormone does not exactly fit into the receptor (which is similar to the paradigm of a triangle fitting into a triangle or a circle into a circle), the hormone has absolutely no effect on that cell. Not every cell has a receptor for every hormone, although many cells have receptor sites for more than one hormone. Sometimes the receptors for a given hormone are predominantly localized on one organ, but increasingly, receptors for such hormones are being found in other organs as well as the brain.

The body produces its hormones or neurotransmitters, which are referred to as endogenous ligands. However, different pharmaceutical agents and other exogenous substances also fit into a receptor. These are important terms with which to be familiar. In some instances, the drug mimics the endogenous ligand; in other instances, it can produce a much stronger or different reaction. When either a drug or an endogenous ligand produces a known effect, it is called an agonist. When a drug or endogenous ligand exhibits the ability to block a receptor, it is called an antagonist. A reverse or inverse agonist is a drug or endogenous ligand that produces symptoms opposite to those that are known. Sometimes one receptor can interact with all three types of ligands. In Chapter 4, which addresses the relaxation system, you will read about the benzodiazepine receptor that accepts all three types of ligands. Keep in mind that multiple receptors also may be activated by the same ligand via a number of mechanisms. Different ligands for the same receptor probably elicit diverse magnitudes of response and use several signaling pathways under varied conditions (Pauwels, 2000).

Peptide hormones consist of proteins (e.g., insulin), glycoproteins (e.g., luteinizing hormone), peptides (e.g., oxytocin), or amines (e.g., epinephrine, formerly called adrenaline). The interaction between the hormone and the receptor activates an enzyme, called adenyl cyclase, within the cell. The adenyl cyclase diffuses into the cytoplasm and, through chemical reactions, produces cyclic adenosine monophosphate (cAMP). The cAMP brings about the reaction that is attributed to the hormone. It is the energy source—a little like filling the car with gas so that it can run. This process is quite rapid and is far more rapid than that of steroid hormones.

Hormone molecules that are steroids (e.g., cortisol) act on receptors that are located within the cell membrane. Steroid hormones are synthesized from cholesterol and are lipid or fat soluble, which as you will recall, means that they do not have to cross the blood–brain barrier. They diffuse through the cell membrane to receptors that affect designated genes within the DNA. This event instigates messenger RNA (mRNA) synthesis within the cytoplasm. The mRNA then synthesizes proteins. It is these proteins that produce cAMP and bring about the reaction that is attributed to the hormone.

Another type of hormone is the group of eicosanoid hormones (e.g., prostaglandins, thromboxanes, leukotrienes, C30 hydroxy fatty acids, and lipoxins), which are a family of oxygenated fatty acids. They are transported through the bloodstream like endocrine hormones and act locally. The eicosanoids are derived from arachidonic acid, an essential fatty acid, and have short half-lives. Each locally acting hormone system mainly affects the tissue from which it is produced. We will be discussing a class of arachidonic acid hormones, called the cannabinoids, in Chapter 4, which covers relaxation. They are the endogenous ligands that fit into the same receptors as the exogenous substance of tetrahydrocannabinol (THC) or marijuana. In addition, lymphocytes produce a type of hormone called cytokines. These are not classic hormones. We will review them in Section 4 on the immune system.

Hormonal messages are not always passed via the classic means of release of neurotransmitter and acceptance by receptor. These chemical messengers may also communicate in more localized ways (see Figure 1.8). For instance, when some messengers are diffused into the interstitial fluid, that is, the fluid between two neurons, they latch onto receptors on neighboring cells. This is called paracrine communication. Autocrine communication occurs when cells secrete hormones that bind to the same cell that secreted it. This may sound like a minor point. Indeed, you may even be thinking, "Well, that doesn't sound too significant because, after all, the powerful neuropeptides are the important hormones." Wrong. As we will see in the next

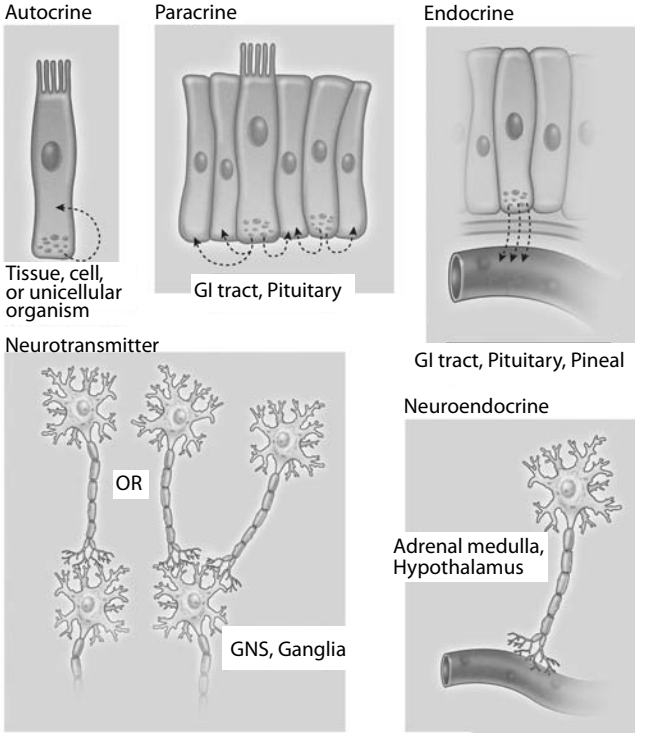

FIGURE 1.8 Transmission of endocrine messages.

chapter, what occurs by paracrine and autocrine communication is eminently important to the overall function of the organism.

We will now review each of the organs of the endocrine system.

The Pituitary Gland

The pituitary gland, which is about the size of a pea, has been called the master gland because it produces hormones that regulate the activity and function of other endocrine glands. Even by the 1950s, scientists knew that the pituitary was not a master gland, but the myth persists today. It influences numerous metabolic processes, including growth. The posterior pituitary stores and secretes hormones that are synthesized by the hypothalamus (see Table 1.2). It secretes vasopressin (or arginine vasopressin [VAP]), which is frequently referred to as ADH because one of its major physiological effects is retention of water by the kidneys, as we discussed previously. It conserves water for the body's use. The synthesis of ADH or VAP is controlled by the hypothalamus. Very importantly, VAP also potentiates the release of adrenocorticotropic hormone (ACTH) by the hypothalamus, which would serve to enhance the stress response. The posterior pituitary also secretes oxytocin, which acts on the uterus and affects milk ejection during lactation. New research shows that oxytocin is a significant factor in the stress response of women, but not for men. It buffers the fight-or-flight response in women, encouraging instead a desire to tend children and gather with other women. We will review this research in Chapter 3 on stress.

Neurons secreting posterior pituitary hormones do so directly into blood vessels in the posterior pituitary, and they are then transported to the target tissue. This is in contrast to the anterior pituitary, which primarily secretes hormones on instruction from the hypothalamus (circulating hormones can also influence the anterior pituitary). These hormones then influence other glands, such as the thyroid, adrenals, and gonads. The pituitary is also influenced by autocrine and paracrine signals arising from its own cells. These signals, called cytokines, will be reviewed in Chapter 2. The anterior pituitary secretes six hormones (see Table 1.3), three glycoproteins, and three polypeptides.

Briefly, LH and FSH are involved in reproduction, and TSH acts on the thyroid. PRL affects the mammary glands and is most important for lactation. In Chapter 2, Systems Integration, we will see that prolactin is a modulator of the immune system, stimulating the proliferation of cytokines. GH affects protein synthesis and cell division, and as the name implies, it is critical for growth, especially of the cartilage and bone. Finally, ACTH facilitates the release of adrenal steroid hormones (see section on adrenal glands) by stimulating receptor sites in the adrenal cortex. ACTH is particularly important for controlling cortisol secretion. You will learn more about

TABLE 1.2
Hormones of the Posterior Pituitary

Antidiuretic hormone (ADH) or vasopressin (VAP)	Conserves water, modulates ACTH release
Oxytocin	Produces lactation, reduces stress in women

TABLE 1.3
Hormones of the Anterior Pituitary

Three Glycoproteins	
Luteinizing hormone (LH)	Gametogenesis; production of male and female hormones
Thyroid-stimulating hormone (TSH)	Stimulates the thyroid gland; stimulates production of thyroid hormone by the thyroid gland
Follicle-stimulating hormone (FSH)	Stimulates the production of eggs or ova in females and sperm in males; also stimulates the ovary to produce estrogen
Three Polypeptides	
Adrenocorticotropic hormone (ACTH)	Stimulates secretion of adrenal steroid hormones, including cortisol; stimulates the adrenal gland
Growth hormone (GH)	Affects protein synthesis and cell division; critical for growth, especially of the cartilage and bone
Prolactin (PRL)	Affects the mammary glands, lactation; stimulates the proliferation of cytokines

ACTH and cortisol in Section 3 on the stress system, and it will be revisited in Chapter 3.

Pro-Opiomelanocortin (POMC) and the Pituitary

There are a number of peptide proteins that are produced both by the nervous system and by the pituitary that derive from a big, primordial hormone called pro-opiomelanocortin (POMC). POMC is made in a variety of tissues, including the brain, lymphocytes, and the anterior and posterior pituitary. POMC is a precursor peptide that weighs 31,000 daltons and has 265 amino acids. In the mid-1970s, opiate receptors were discovered, and it was learned that some of the endogenous opioid ligands (hormones, in this instance), such as β-endorphins, are present within the POMC molecule. In addition to β-endorphins, ACTH, lipoproteins, and melanocyte-stimulating hormone (MSH) are all synthesized from POMC. All of these peptides possess behavioral effects, and many are involved in the stress response, including ACTH, β-endorphin, and enkephalins (see more in Section 3 on the stress system).

Hypothalamus

The hypothalamus releases and inhibits hormones that are carried via vessels from the hypothalamus to the pituitary. It is the structure from which tropic hormones (i.e., hormones that cause secretion of other hormones) approach, influence, and stimulate various tissues. This is also the pathway by which other endocrine glands can exert their own feedback control on the hormones that the pituitary and hypothalamus secrete. The hypothalamus is our control center, integrating the chemical input from the CNS, the CSF, and from the general circulation. The hormones of the hypothalamus are listed in Table 1.4.

TABLE 1.4
Hormones of the Hypothalamus

Corticotropin-releasing hormone (CRH)	Stimulates the secretion of corticotropin, which is a hormone that tells the pituitary to secrete ACTH during stress; in addition to the hypothalamus, it is present in the limbic system, cortex, adrenal medulla, pancreas, gut, and placenta
Thyrotropin-releasing hormone (TRH)	Stimulates the release of thyrotropin from the anterior pituitary, which stimulates and sustains hormonal secretions from the thyroid
Growth-hormone-releasing hormone (GRH)	Stimulates the secretion of growth hormone from the pituitary
Somatostatin (or growth-hormone-inhibiting hormone)	Inhibits the release of numerous hormones, including GH, thyrotropin, corticotropin, insulin, glucagon, gastrin, and secretin
Gonadotropin-releasing hormone (GnRH)	Regulates the growth and function of the ovaries and testes; it stimulates the secretion of FSH and LH from the pituitary
Prolactin-inhibiting hormone (dopamine)	Is released to stop prolactin secretion, which stimulates milk production in a woman after giving birth

Thyroid

The thyroid gland produces thyroid hormones (i.e., thyroxine and triodothyronine), which require iodine for synthesis and cannot be produced in adequate amounts without it. Thyroid hormones stimulate cells to consume oxygen; increases the rate of cell metabolism (i.e., the rate that cells release energy from carbohydrates); regulates lipid, protein, and carbohydrate metabolism; stimulates bodily heat production; and is essential for normal growth. The functions of the thyroid are controlled by TSH secretion from the pituitary, and a balance in thyroid hormone level is necessary for proper development and to maintain health. The hypothalamus and pituitary are involved in a direct inhibitory feedback loop that adjusts the rate of thyroid secretion to keep it at a balanced level. The thyroid gland also produces calcitonin, a hormone that lowers calcium levels in the blood by inhibiting bone resorption (i.e., inhibits calcium from leaving the bone and increases calcium excretion in the urine). Calcitonin decreases the amount of calcium that the intestines absorb; as mentioned, it modulates pain perception in the brain (see, e.g., Ormazabal et al., 2001; Xu et al., 2000; Yamazaki et al., 1999). Calcitonin is probably going to prove to be one of the most important antiaging hormones; however, the research is not yet there to illustrate this theory definitively (Kalu, 1984; Yamaga et al., 2001).

Parathyroid

The parathyroid glands are four small glands located behind the thyroid gland. Special cells, called chief cells, in the parathyroid secrete parathyroid hormone (PTH), which is involved in calcium and phosphate metabolism. PTH is the major regulator of blood calcium levels and performs actions opposite to calcitonin. PTH activates vitamin D

to maintain a constant level of calcium in the blood. This is necessary for nerve and muscle function, blood coagulation, and formation of bone and teeth.

Pancreas

The pancreas is an organ that has both exocrine and endocrine capabilities. The exocrine portion produces digestive enzymes. The endocrine portion involves the secretion of insulin, glucagon, and somatostatin. Insulin is important for metabolism and regulates glucose by lowering it. If there is more glucose than can be used by the body, it is converted by insulin to glycogen. Glycogen resides in the liver and muscle cells. Insulin facilitates storage of triglycerides in adipose tissue. Glucagon, like insulin, is important for metabolism and regulates blood glucose by raising it. A normal blood glucose level is essential, as it is the energy source for the entire nervous system. Somatostatin helps regulate carbohydrate metabolism and inhibits the release of numerous hormones, including insulin.

Adrenals

The adrenal glands are our stress glands. There are two adrenal glands, one resting atop each kidney. The adrenal glands act like brake liners. When the rubber hits the road, when you start getting stressed, it is the stress hormones that go into action to keep your body in a somewhat resilient state. The adrenal gland consists of two endocrine organs: the adrenal medulla and the adrenal cortex. The hypothalamus communicates with the adrenal medulla via an electrical route and with the adrenal cortex via a hormonal route (Table 1.5).

TABLE 1.5
Hormones of the Adrenal Cortex (Corticosteroids)

Mineralocorticoids	Aldosterone, which regulates mineral electrolytes, thus maintaining blood volume and pressure and facilitating nerve impulse conduction and muscle contraction
Glucocorticoids	Cortisol and corticosterone, which break down proteins and convert them to glucose; cortisol ensures that the glucose in the bloodstream is adequate to meet the needs of the brain; during stress, it reduces glucose delivery to some parts of the body, slowing the uptake of glucose from the blood and using it for tissues like skeletal muscles, with the brain always being supplied first; glucocorticoids also break down fat that can be used for energy; the effect of these hormones is long lasting, as they are removed slowly from body tissue
Androgenic steroids	Two androgens (the synthetic version is the well-known anabolic steroids)—dehydroepiandrosterone (DHEA) and androstenedione (which can be converted to testosterone)—and small amounts of estrogen

The main hormonal secretions of the adrenal medulla are the catecholamines, primarily epinephrine, but also norepinephrine. Epinephrine and norepinephrine (which also act as neurotransmitters) are secreted during stress. The result is a multiorgan response. Epinephrine is a vasodilator, causing increased heart rate and force of myocardial contraction, dilation of the smooth muscles of blood vessels, and elevation of the level of available sugars and fatty acids in the blood, which gives immediate energy reserves for the fight-or-flight response. While both hormones increase alertness, epinephrine evokes anxiety and fear. Norepinephrine is a vasoconstrictor that affects brain regions concerned with emotions (it is found in elevated amounts in depressed persons), dreaming and awaking, control of food intake, and regulation of body temperature.

Gonads

The gonads are the testes in males and the ovaries in females. In both sexes, they have two functions, which is gametogenesis (creation of germ cells) and the production of sex hormones. The main feminizing sex hormones are the estrogens, and the main masculinizing hormones are the androgens, particularly testosterone. Gametogenesis is dependent upon hormonal secretions of GnRH from the hypothalamus as well as LH and FSH from the anterior pituitary.

Thymus

The thymus has the appearance of a lymph node and lies behind the breastbone. The thymus is crucial to the immune system because it is the location where white blood cells, called lymphocytes, undergo important steps in maturation and, consequently, become T lymphocytes. The thymus is the master trainer of the T lymphocyte portion of the acquired immune system. Cells of the thymus are capable of producing hormones, including thymosin, thymulin, and thymopoietin. Thymic hormones have independent neuroendocrine effects and can increase the secretion of other hormones, including ACTH, corticosterone, GH, and prolactin (Ader et al., 1991).

When I was in medical school, it was thought that the thymus atrophies some time after puberty. If you take chest x-rays, the thymus will no longer appear after childhood. Studies were performed that showed that the thymus does not atrophy. Rather, it involutes, and it takes a computed tomography (CT) scan of the chest to pick up the image (see Figure 1.9). Correlating to the involution process, there is a progressive decline in thymic hormone secretion throughout adulthood (Bellinger et al., 2001). The thymic cortex progressively shrinks because it changes from a dense tissue full of blood into fatty tissue with fewer thymocytes (i.e., mature and immature T lymphocytes found in the thymus) (Bellinger et al., 2001). When we are young, the thymus is busy educating cells in an effort to establish a strong immune system in the body. It then becomes smaller because most of its work is completed. But it is still there, ready to secrete hormones and train lymphocytes if we become quite ill and need it.

Pineal Gland

The pineal gland orchestrates both the endocrine and immune systems. It truly is the master gland, as it transmits information from the environment to our body systems

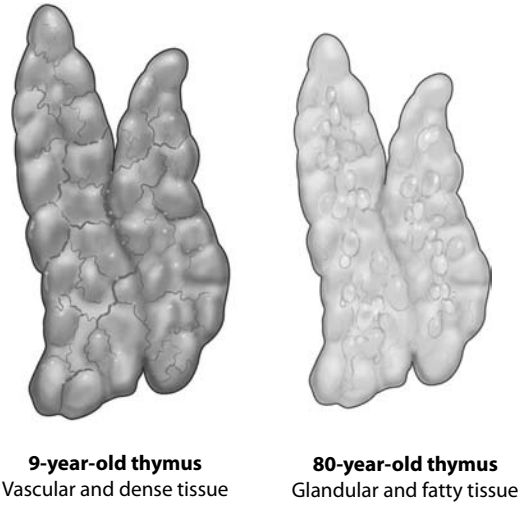

FIGURE 1.9 Thymus of a 9-year-old child and of an 80-year-old adult.

and helps us regulate ourselves with the outside world. In today's world, that can sometimes be a problem, an issue that we will address in other chapters.

The pineal gland secretes a hormone called melatonin that is crucial to our biological rhythm. The pineal is photosensitive, which means that it is influenced by light. Light stimulates the suprachiasmatic nucleus (which we will discuss in detail in Chapter 10) to tell the specialized secretory cells of the pineal gland, called pinealocytes, to slow secretion of melatonin. At night, or in the absence of light, higher levels of melatonin are secreted by the pinealocytes into the CSF, which carries it to the bloodstream and helps to promote sleep. Melatonin has various other functions, such as modulating reproductive development (by inhibiting gonadotropin-releasing hormone), influencing mood, and regulating hunger and satiety. There is a whole chapter on the pineal, so you will be learning a lot about this little gland and why it is our master gland.

The Gut

Endocrine cells in the stomach secrete the hormone gastrin, which stimulates the secretion of hydrochloric acid (HCI) into the stomach. The hormone somatostatin stops the secretion of this acid. The duodenum secretes secretin, a peptide in the lining of the small intestine that stimulates the pancreas to secrete bicarbonate, which neutralizes stomach acids, thus allowing the intestinal enzymes to function.

Receptors and Health

Ideally, the endocrine system produces a harmonious cascade of chemicals that keep our bodies humming along, fit and content. The receptors, capable of receiving an endogenous hormone may be similar or identical to those that link up with an exogenous drug. Conversely, when there is an exogenous drug that is influencing behavior,

there must be a receptor to receive it. THC, the active agent in marijuana, for example, is now known to have endogenous THC receptors in the brain and in spleen tissue. Similarly, specific receptors have been found in the brain for the chemical benzodiazepine. Benzodiazepine receptors are capable of receiving drugs, such as Librium® and Valium®, which also can influence behavior. Do pharmaceutical companies develop drugs that are the only substances that can fit into a given receptor? No. Every time there is a receptor located for an exogenous drug, there has to be an endogenous ligand that will fit into this receptor as well. Furthermore, and importantly, it is likely that there are natural (i.e., not synthetic) exogenous substances that fit into that same receptor. These natural agents, frequently, have a more favorable side-effect profile, but may take much longer to exhibit efficacy. Far fewer research dollars are designated for natural exogenous substances than pharmaceutical agents, so consequently, less is known about their pharmacokinetic properties.

In the chapter on the relaxation system (Chapter 4), we will learn more about the benzodiazepines and other hormones that facilitate our relaxation response. The existence of a relaxation system that mirrors our stress system (i.e., the fight-or-flight response) is presented for the first time.

Essential Points

- Hormones are the basic unit of communication for the endocrine system.
- The organs of the endocrine system secrete hormones that govern myriad functions.
- The same receptor can accept both endogenous ligands and exogenous substances.

SECTION 3: THE STRESS SYSTEM

Now that we have reviewed both the nervous and endocrine systems, we can begin to understand the contribution to and integration of these two systems in the stress response. We will also see that stress has a powerful role in instigation and modulation of the immune system. This discussion is a preview of the next chapter on systems interactions, and it will make the reading of the next section on the immune system a richer experience.

As shown in Figure 1.10, the human stress system has both a neural and an endocrine pathway, which means that the same stimulus activates both systems simultaneously. When there is a stressful stimulus, the message is conveyed, via the cerebral cortex and limbic system, to the hypothalamus. The stimulus can be either physical or cognitive, including upsetting emotions, memories, or thoughts. The electrical response is faster than the chemical one, but throughout the process, the chemical highway sustains the responses.

The hypothalamus–pituitary–adrenal (HPA) axis governs the chemical highway. The HPA axis is highly sensitive to stimuli of various sorts. The hypothalamus conveys the stress message to the pituitary. The pituitary can receive that message from the hypothalamus via either a neural or an endocrine (i.e., CRH) route, or both. VAP and CRH, in a synergistic manner, potentiate the release of ACTH by the pituitary, which in turn causes

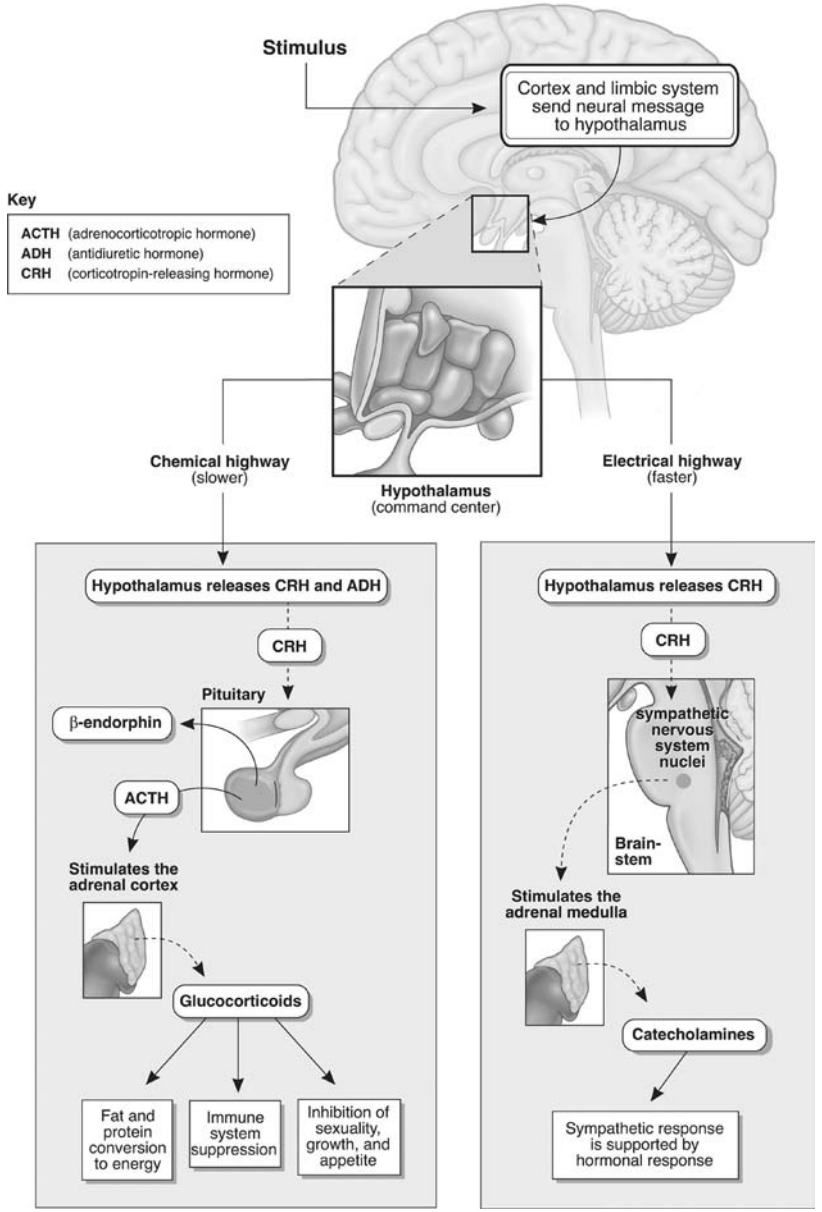

FIGURE 1.10 The human stress system.

the adrenal cortex to release corticosteroids, primarily cortisol. If you read a study performed with rodents, the hormone comparable to cortisol is called corticosterone.

Corticosteroids convert fat and protein to useable energy for the stress experience. The blood flow is diverted from organs that are not essential to the stress response and directed toward the organs and systems that are critical to the response, providing

them with the glucose, fatty acids, and oxygen necessary for effective action. This event causes the hormones related to such nonessential functions as reproduction, growth, and appetite to be inhibited. Simultaneously, endorphins are released, which reduces the experience of pain during trauma. Ideally, the stress stimulus is not harmful and is a short-term event. In such situations, the circulating cortisol inhibits further pituitary release of ACTH. The situation resolves, and the body goes back to normal. It is as if the cortisol is set at a certain thermostatic temperature, and when that temperature is reached, it switches off. However, in circumstances involving long-term stress, this feedback loop is overridden by higher cortical centers, and the stress reaction continues, which can be devastating to long-term health.

On the electrical pathway, the ANS nuclei in the brainstem receive the stress alert messages from the hypothalamus. These messages come from the brainstem nuclei via neural (i.e., electrical) signals to the ANS. The ANS controls the adrenal medulla, causing it to release epinephrine (i.e., adrenaline). Epinephrine initiates all the classic sympathetic nervous system responses (e.g., increased heart rate, blood pressure, sweat production).

The beautiful part of it all is that the same stimulus causes both of these response highways to shift into gear in tandem, allowing the body the maximal response when needed. However, this system was largely designed for the earliest humans, who frequently had to flee from or fight a predator. We modern-day humans are like cave dwellers in a three-piece suit, kicking a stress response into motion simply with our thoughts and no external stressor. Chronic stress, as we will see, has serious implications for health.

Stress and Immune System Interaction

The immune system interacts with the glucocorticoids during stress, enhancing the effects of the HPA axis. At first, the immune system rallies to face the potential harm (before modern times, stress responses typically involved physical danger, so this makes sense), but with chronic stress, the immune system often becomes depressed. Immune cells called monocytes produce other messengers called cytokines that evoke an inflammatory response. Some cytokines are potent stimulators of ACTH, so your body actually initiates the stress response when you are ill. However, in the body's continual drive toward homeostasis, the corticosteroids inhibit the inflammatory response, usually producing a net effect of mitigating immune function. During chronic stress, the ability of the negative feedback loop to decrease cortisol production can become severely impaired, resulting in serious immune dysfunction. In addition, endorphins and enkephalins inhibit ACTH, attenuating the stress response and stimulating the immune system, creating another feedback loop. Furthermore, CRH induces lymphocytes to produce β-endorphins (Kavelaars et al., 1990). Endorphins themselves elevate antibody production, enhance natural killer cell activity, and cause analgesia (Williamson et al., 1988). In examining just this little portion of how the immune and stress systems interact, we are getting a preview of the intricate interdependence and integration of the body systems.

Essential Points

- The HPA axis governs the chemical pathway of the human stress response.
- The electrical pathway of the human stress response is responsible for initiating all the classic sympathetic nervous system responses.
- The stress system is related to each of the other major body systems.

SECTION 4: THE IMMUNE SYSTEM

The immune system is a series of dedicated glandular structures and cells whose purpose is to help recognize self from nonself. In other words, the immune system distinguishes your body from any foreign materials or invading organisms, including bacteria, viruses, cancer cells, or foreign materials (e.g., tissue transplants) (see Huston, 1997, for a general review). A molecule that is nonself or foreign is called an antigen. The immune system is the eliminator. It eliminates anything that is thought to be alien or unfamiliar to the body. It is the police patrol, called out to maintain homeostasis. The immune system has to preserve a delicate balance between mounting an aggressive response to outside invasion and not having that aggression turn against the body itself. When this process goes awry and the body loses tolerance to itself, it is called autoimmunity. In addition to skin, the immune system is typically thought of as having two divisions: the innate and the acquired immune systems. The two systems, however, are inextricably interwoven (see Delves and Roitt, 2000a, 2000b, for reviews).

As you read about the cells of the immune systems, note that there are four functions of the immune response that repeatedly occur:

1. Recognition
2. Recruitment
3. Response
4. Attenuation

These four functions will be pointed out to you. However, keep this pattern in mind as you read the entire section on immunity.

The Lymphatic System

The lymphatic system, which includes the spleen, thymus, tonsils, and various lymph nodes, supports the immune system (see Figure 1.11). The lymphatic system filters and removes foreign particles. Lymph nodes store B and T lymphocytes for activation when an antigen is present. Lymph nodes are distributed throughout the body and filter the lymph before it is sent out into the blood circulation again. They can remove bacteria, viruses, and cancerous cells. There are other cells, called macrophages that are also present in lymph nodes and contribute significantly to the immune response. Lymph is blood plasma that has filtered through capillary walls. It is called interstitial fluid until it enters the lymph capillaries, and then it is called lymph. There is a whole lymph flow system that is still somewhat enigmatic.

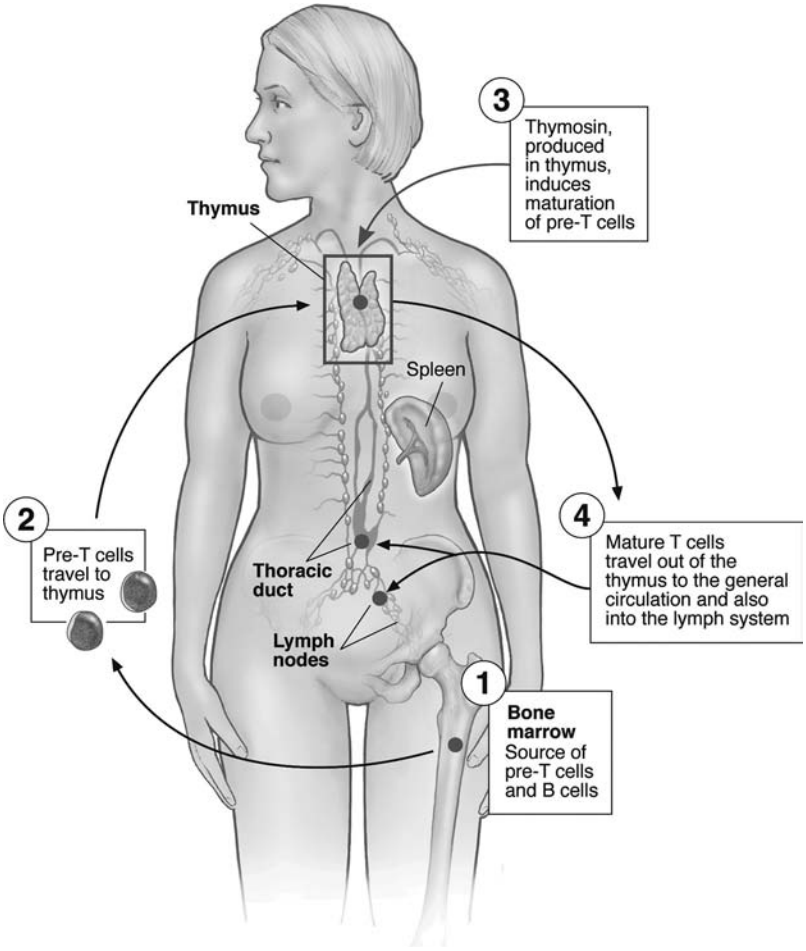

FIGURE 1.11 The lymphatic system.

The Innate Immune System

Natural or innate immunity exists from birth and is a more generalized system than the acquired system. The innate system is nonspecific to antigen and is initiated immediately. It includes skin, mucus, secretions (such as sweat and gastric acid), certain intestinal bacteria, urine, cytokines (which are capable of modulating leukocytes), leukocytes (other than B and T lymphocytes that are part of the acquired system), fever, inflammation, and other factors that prevent foreign materials from invading the body. This system destroys unwanted organisms without having to create antibodies, although sometimes it influences the production of them. The innate immune response is often activated by chemical properties inherent in the antigen.

If a foreign body invades the system, a variety of cells respond and are transported by the bloodstream, although they function primarily in tissue. Leukocytes

are white blood cells that vary in function. Some are phagocytes that are capable of consuming and destroying antigens or other types of harmful microorganisms. They simply engulf and ingest the foreign matter. Other leukocytes produce antibodies, secrete or neutralize histamine, or promote or inhibit inflammation. Leukocytes are either granulocytes (e.g., neutrophils, basophils, or eosinophils) or nongranulocytes (e.g., lymphocytes and monocytes).

Neutrophils

Neutrophils are the most common leukocyte. They play a significant role in inflammatory reactions, but only live a day or two. They are the first-response team and are capable of phagocytosis. They quickly begin an immune response, but are essentially destroyed by their effort. Neutrophils also can be harmful, contributing to tissue damage through inflammation that, for example, can worsen myocardial injury.

Basophils

Basophils are the least common of the leukocytes. Basophils contain vasoactive amines (substances that can exert a dilating effect on blood vessels and increase the permeability of small vessels), such as serotonin. They secrete histamine (which dilates blood vessels, increasing blood flow to damaged tissue) and heparin (which inhibits blood clot formation).

Eosinophils

Eosinophils are valuable because they increase during allergic reactions. They are weakly phagocytic, kill parasites, and secrete leukotrienes, prostaglandins, and some cytokines.

Monocytes

Monocytes, which are the largest of the white blood cells, are phagocytes with the capability of engulfing fairly large particles. Antigens have receptors that the monocyte can recognize (this is the recognition phase). The monocytes literally eat up the foreign material. Monocytes are formed in bone marrow and then circulate in the bloodstream.

Macrophages

Macrophages are monocytes that are found in tissue and are thought to stay with you for most of your life. Macrophages are primordial looking, amoeba-like structures. They circulate for about 40 hours and then lodge in tissue and increase in phagocytic activity and, thus, in size. They are present in the liver and spleen, where they phagocytize invading organisms before tissue damage occurs, and in the lymph nodes, where they cleanse the lymph. They come into areas of damaged tissue and help clean up the mess by devouring bacteria and cellular debris. They restore homeostasis. Furthermore, while it is digesting, believe me, does it remember! Macrophages can remember thousands of antigens and can respond very quickly if this type of bacteria dares to enter the system again. They mediate nonspecific antigen destruction, eliminating tumor and bacteria cells in the absence of an antibody, but they can also have receptors for antibodies. Sometimes

the macrophage presents a portion of partially digested antigen to B or T lymphocytes and alerts them to the situation. In this case, they are called antigen-presenting cells.

Osteoclasts

Osteoclasts evolve from macrophages that have gathered in the bone marrow. Osteoclasts are involved in the resorption and removal of bone. This slow, lumbering cell may hang out in the bone until the brain calls it into circulation. It actually may be another method of cellular communication, a Paul Revere if you will, albeit a somewhat slow one.

Microglia

Microglia are cells whose job it is to make sure that no foreign invader protein gets into the nervous system. They become mobile and literally start eating up invading cells (and, therefore, are phagocytes). Microglia are fundamental to the removal of dead neurons, proliferating and then removing the dead cells (Streit and Kincaid-Colton, 1995). They are fundamental in the maintenance of homeostasis.

Cytokines

Cytokines are nonantibody proteins that are secreted by various immune cells when an antigen is present. Cytokines are intercellular mediators that influence and sometimes regulate immune responses and even the production of other cytokines. Monocytes, macrophages, neutrophils, T lymphocytes, and natural killer cells all produce cytokines (Table 1.6).

IL-6 is a cytokine that is secreted during active inflammation and chronic stress and will be further reviewed in Chapter 3. The secretion of IL-1 by a macrophage, upon exposure to an antigen, causes T lymphocyte activation (this is the response phase). Once activated, the T lymphocyte secretes another interleukin, IL-2, in response to both the message from IL-1 as well as to the stimulation from the antigen itself. IL-2 is capable of further stimulating the proliferation of T lymphocyte cells (this is the recruitment phase). The attenuation phase concludes the immune

TABLE 1.6
Cytokines

Interleukins (IL)	A family of cytokines that stimulates T lymphocytes and alters various immune responses; some of the interleukins interact with the endocrine and nervous systems
Interferon (INF)	Cytokines that adhere to virally infected cells, providing a line of defense
Tumor necrosis factor (TNF)	Cytokines produced by macrophages and T lymphocytes during an acute inflammatory response; they are capable of stimulating interferon production

response. It is caused by secretion of hormones, such as cortisol, which have the capability to suppress the active immune response.

IL-1 does some very interesting things in addition to inducing T-cell proliferation. It incites slow-wave sleep, inhibits food intake, and mediates fever (Krueger et al., 1987; Rothwell, 1989, 1991). Furthermore, when challenges to the immune system increase HPA activity levels, both IL-1 and IL-2 stimulate the release of the stress hormone ACTH from the pituitary, which stimulates cortisol secretion (Bernton et al., 1987; Fágárásan and Axelrod, 1990; Lotze et al., 1985). We will discuss this issue in more detail in Chapter 2, Systems Integration.

So, the two cytokines, IL-1 and IL-2, stimulate a hormone from the pituitary gland. This was groundbreaking information—information that immunologists and endocrinologists found astounding, as it did not fit conventional knowledge. However, it had me dancing with glee because it was solid medical evidence of what I (as well as colleagues) had intuited about systems interaction. This was the first example of physiological systems truly interacting with one another. I will show you other examples, but this is the first.

Natural Killer (NK) Cells

Natural killer (NK) cells are large, granular lymphocytes that locate and destroy viruses and cells that spontaneously become malignant. They function without prior sensitization to, or recognition of, the antigens. The NK cell's most significant effect is in preventing primitive cancers from metastasizing. NK cells originate in the bone marrow. They are crucial to the body's natural resistance and are instigated early in host defense. The NK cell's effectiveness is enhanced by the presence of INF-γ. In almost every person, the sheer number of NK cells is adequate. Problems occur when the cells become weak and incapable of destroying tumor cells. Therefore, NK cells are measured by their activity or function level. A variety of stress-related factors and diseases can reduce their activity level. Figure 1.12 demonstrates the various routes by which immune information is conveyed.

Researchers have shown that creative visualization and relaxation training can cause the activity level of NK cells to increase. In one study, 10 patients with metastatic cancer who were given both relaxation and imagery training showed increased immune response (Gruber et al., 1993). In another study, 45 subjects aged 60 to 88 were given relaxation training and demonstrated increased ability to destroy herpes cells (Kiecolt-Glaser et al., 1984). The effect did not appear with subjects who were assigned to social contact groups instead of the relaxation group. So, what we are seeing here is that the immune system is capable of getting stronger simply by the action of our thoughts.

The Acquired Immune System

Acquired immunity is more specific and occurs when an antigen enters the body. There are two types of lymphocytes or immune cells involved in acquired immunity: B lymphocytes and T lymphocytes. The cell-mediated immune response, which defends against virus, fungi, protozoa, cancerous cells, tissue transplants

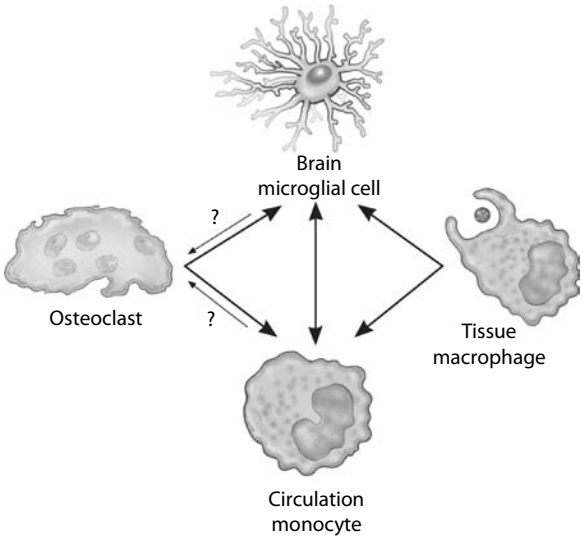

FIGURE 1.12 Information circulation.

and functions in allergic reactions, involves T lymphocytes. The humoral immune response, which defends against bacteria and toxins, involves the secretion of antibodies by plasma cells that are derived from B lymphocytes. During fetal development, the cells that migrate to the thymus to mature are the T lymphocytes, whereas B lymphocytes mature in the bone marrow (B for bone and T for thymus, according to their sites of maturity). In spite of the reduction in size in the thymus during puberty, T lymphocytes continue to develop in the thymus throughout life. Both T and B lymphocytes develop receptors specific to each type of antigen encountered and can retain a memory for them.

Cell-Mediated Immunity and T Lymphocytes

T lymphocytes are not involved in the production of antibodies. The process of maturation of T lymphocytes to functional cells is a complex, hormonally guided process of rigorous selection (Vacchio et al., 1998). The thymus gland is the main regulator and the schooling site for T lymphocytes; this is referred to as thymic education. After maturing in the thymus, T lymphocytes enter the circulation and are distributed throughout the lymphatic system, but are found most abundantly in the lymph nodes. The T lymphocyte is the most prevalent lymphocyte, accounting for approximately 70 to 80% of lymphocytes circulating in the body.

T lymphocytes differentiate into five distinct varieties:

1. Cytotoxic T cells, which are capable of destroying virus-infected or foreign cells.
2. Killer T cells, which recognize and obliterate specific antigens. They look for their target antigen and, like smart bombs, they blast a hole in the cell membrane. The cell essentially explodes and the contents are lost.

3. Helper T cells, which prepare the antigen so that it is easier for the B cells to destroy them. They also assist in T-cell maturation.
4. Suppressor T cells, which suppress the immune response of both T and B cells when the antigen is destroyed. They act by suppressing the helper cells or by inhibiting activated lymphocytes.
5. Memory T cells, which have the capacity to remember previous exposure to an antigen and, thus, to hasten the immune response. They reside in the lymphatic system until called into action. This is called the secondary immune response.

To mount a fight on an infectious agent, macrophages and other cells present antigens to T lymphocytes that have not been activated. At the same time, the antigen-stimulated macrophage releases IL-1, which stimulates helper T-cell activity. The helper T cell then releases IL-2, which stimulates T lymphocyte proliferation and, subsequently, cytotoxic T-cell proliferation. It is the cytotoxic T cells that do the job of destroying the intruder. T cells that do not attach to macrophages eventually die by apoptosis, or programmed cellular death. Only about 5% of all T cells reach maturity. This is called the primary immune response.

Humoral Immunity and B Lymphocytes

The primary function of B lymphocytes is to fight invasion by producing antibodies rather than by directly attacking the antigen itself, as do T cells. They are considered a humoral response because B cells are mostly stored in the lymphatic system. A macrophage presents a portion of partially digested antigen to the B lymphocyte, and the antigen attaches to receptors on the surface of the macrophage. B lymphocytes and helper T cells that bear receptors specific to that antigen become activated by the antigen-presenting macrophage. As with cell-mediated immunity, helper T cells release IL-1, but also secrete a B-cell growth factor that causes the B lymphocyte to begin to rapidly divide. The B cell then releases antibodies specific to the offending antigen, which tags the antigen for destruction by other components that are present in the immune system. The rapid division of B lymphocytes results in differentiation into plasma cells and memory B cells.

When a B cell encounters an offending antigen, it transforms into a plasma cell, which secretes substances called immunoglobulins (IgG, IgA, IgM, IgD, and IgE). These are antibodies. They bind to the pathogen and, along with other immune system components, inactivate it. IgG is the most common, comprising 75 to 85% of the total serum immunoglobulin. Typically, a blood test is used to measure these antibodies, but IgA, for example, is produced in and can be measured from saliva. Memory B cells are a type of memory cell with the capacity to remember previous exposure to an antigen and, thus, to hasten the immune response upon a subsequent encounter. Both memory B cells and memory T cells are efficient immune response cells. The cells are stored in the lymphatic tissue, waiting for a returning invader. Vaccines permit an initial, relatively mild exposure to an antigen, but they result in storage of the memory cells that can later prevent the illness.

Essential Points

- Recognition, recruitment, response, and attenuation are the basis of all immune responses.
- Monocytes and macrophages are cells important to both the innate and acquired immune systems. They are phagocytes and an important first line of defense. They also prepare antigens for destruction by both B and T lymphocytes.
- Natural killer cells are important for locating and destroying viruses and cells that spontaneously become malignant.
- Memory B and T cells provide a qualitatively and quantitatively superior secondary immune response.

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2 Systems Integration
Psychoneuroimmunology

Even the ignorant know that man has a heart and lungs, brain and stomach; but he thinks that each of these organs are separate and independent things that have nothing to do with each other.

Paracelsus, 1493–1541
Swiss physician

It has become abundantly clear that there are probably no organ systems or homeostatic defense mechanisms that are not, in vivo, subject to the influence of interactions between behavioral and physiological events.

Ader, Felten, Cohen, 1990
Pioneers in the field of psychoneuroimmunology

INTRODUCTION

It was only in the latter half of the twentieth century that researchers teased apart the molecular and cellular basis of the immune system, began to understand the genetics of immunity, and elucidated patterns of interaction with antigen-presenting cells. All the material that we presented to you in Chapter 1 regarding the immune system took years of research to amass. Currently, the frontier in medical scientific exploration involves the interface between such detailed understanding of cells and the examination of how one body system interacts with others to communicate vital information. This is the field of psychoneuroimmunology (PNI). Researchers studying cells of the immune system, for example, are finding that they have receptors for hormones of the endocrine system and neuropeptides of the nervous system (e.g., there are receptors in the lymphocyte for β-endorphins, enkephalins, somatostatin, and adrenocorticotropic hormone [ACTH], among others). These are the groundbreaking findings of the past 20 years, giving medical research a wholly new perspective. And it quickly gets more complicated than that: The endocrine hormones actually modulate the response of the immune cells, for example, ACTH depresses the immune response and insulin stimulates it (Besedovsky and del Rey, 1996). Moreover, an antigen must stimulate a lymphocyte before the resting lymphocyte evidences a detectable receptor for insulin (Helderman and Strom, 1978). In other words, the lymphocyte does not even reveal that it has a receptor for insulin until it is faced with an antigen. Such results provide a glimpse of the complexity of systems integration.

Some investigators and scientists who write about the immune system are still resistant to incorporating discussion of systems interaction, which is evidenced by the fact that recently written, standard medical textbooks describe the immune system as an autonomous entity, entirely ignoring information about systems integration. In

looking at the history of medicine, there has been a propensity among the medical community to separate and simplify everything in the body. Yet, research has shown that neither cellular functions nor body systems are pristinely discrete units, as previously taught. Rather, they are intricately woven and cannot be separated. Upon close examination, a picture of the physiological systems as a harmonious network arises, and a clear, seminal pattern of the scientific bases of the mind–body connection becomes evident.

In spite of considerable capacity for self-regulation, the immune system can be modulated by endocrine and neural activity, and it can just as easily influence endocrine, neural, stress, and other behavioral functions (Ader et al., 1990). We will begin by reviewing numerous studies of functional and cellular interactions among the body systems. There are interactions between each of the classic body systems and the stress system as well. However, we will cover these issues in the chapter on stress (Chapter 3) and not here. The implications of systems integration for human disease will then be discussed and sometimes speculated upon. This chapter is not designed to be a comprehensive overview of the field of PNI. In fact, there are important areas of research, such as gene expression, cancer, and human immunodeficiency virus (HIV), which we have consciously chosen not to include. The extensive bibliography will help you to explore further on your own. Our intention is to give the reader a sense of the sheer wonder of the body's intricate ability for systems interaction and to illustrate that this ubiquitous design reinforces the body's primary objective of maintaining homeostasis, which promotes self-regulation, and thus, self-healing.

DEFINITIONS

As we investigate systems integration, we will learn that immune cells secrete and have receptors for molecules that, up to now, exclusively have been called hormones, neurotransmitters, or neuropeptides. The researchers who many years ago designated what was and was not a hormone never imagined that an immune cell could secrete a "hormone." What do we call a substance that is secreted by an immune cell, but is classically thought of as a hormone? It is important to recognize that we are now faced with terms whose meanings no longer fit their designated definition. In Chapter 1, we made every effort to define these terms by their classic or traditional terminology. It is beyond our interest and scope in this book to attempt to create new definitions (although it is our contention that they are needed), so we have chosen to use these words in their classic descriptive sense as we peruse the frontiers of medicine.

The following is a list of chemicals of communication:

- Hormones
- Neurotransmitters
- Growth factors
- Neuropeptides
- Protein ligands
- Cytokines

NEUROPEPTIDES: WHEN IMMUNE CELLS SECRETE HORMONES

Research concerning the interface between the nervous and endocrine systems falls largely into two categories. First, studies show that various neurons can have receptors for both hormones and neurotransmitters (i.e., both types of messengers can connect to a receptor site on the exact same neuron). This is a radical change in the understanding of transmitters. Second, investigations have revealed that many classic hormones behave like a neurotransmitter, that is, they are not only released from endocrine tissue, but from nerve cells as well. We call these *neuropeptides* to create a distinction. Therefore, hormones can be found in the brain of humans and various other mammals, functioning both as hormonal and electrical transmitters.

Neuropeptides and classic neurotransmitters can coexist in the same neuron. It seems that this coexistence promotes discrete behavioral effects. For example, the functional interactions between a neuropeptide, called galanin, and the classic neurotransmitter, acetylcholine, appear to be related to memory inhibition, and there is some suggestion that the mitigation of this interaction may benefit those suffering from various types of dementia (Crawley, 1990).

Table 2.1 lists the numerous hormones (neuropeptides) that are found in the brain. Some have been discovered by chemical means, others by immunological studies. Most of these neuropeptides previously were thought to be localized only in discrete areas of one of the three classically defined body systems and not in the brain. The list of neuropeptides is so numerous that there are undoubtedly some that we have left out, and with equal assuredness, there are others that will be discovered in the near future. I reiterate; it is my contention that the brain is capable of secreting any hormone produced by the body, as needed, and that it is only a matter of time before this is determined scientifically.

The implications of the nervous and endocrine systems sharing transmitters are enormous and set the stage for significant interactions with the immune and stress systems. Think about it. The body houses an efficient organization not only for the nervous system to communicate with the hormones of the endocrine system, or vice versa, but also, as we shall review, for the immune and stress systems to influence and be influenced by the nervous and endocrine systems.

CONDITIONED IMMUNE RESPONSES

Research elucidating the interactions between the nervous and immune systems began with studies on conditioned responses of the immune system. As mentioned in the Introduction of this book, in 1975, Robert Ader and his colleagues published research on the conditioned immune response in a rat population. If you recall, the rats in the experimental group were injected with cyclophosphamide (an immunosuppressive agent) and given drinking water flavored with saccharin. Rats later given only the saccharin-flavored water nevertheless continued to evidence reduced immune responses. Similarly, over a hundred years ago, Sir William Osler, the notable physician from Johns Hopkins, describes a patient having an asthma attack after smelling an artificial rose. Although the effects of such conditioning were experientially familiar to physicians, Ader's experiment was the first scientific proof of Pavlovian conditioning of the immune response (see Cohen et al., 1994, for a review).

TABLE 2.1
Neuropeptides Found in the Brain

Hypothalamic-Releasing Hormones	Gastrointestinal Hormones
Corticotropin-releasing hormone (CRH)	Gastrin
	VIP
Thyroid-releasing hormone (TRH)	Cholecystokinin (CCK)
	Substance P
Growth-hormone-releasing hormone (GRH)	Insulin
	Glucagon
Somatostatin	Motilin
	Pancreatic polypeptide
Gonadotropin-releasing hormone (GnRH)	
Prolactin-inhibiting hormone (dopamine)	
Beacon[a]	
Anterior Pituitary Hormones	**Growth Factors**
Luteinizing hormone (LH)	Insulin-like growth factor II (IGF II)
α-melanocyte-stimulating hormone (α-MSH)	Fibroblast growth factor (FGF)
	Endothelial cell growth factor
Thyroid-stimulating hormone (TSH)	
Follicle-stimulating hormone (FSH)	
Growth hormone (GH)	
Prolactin (PRL)	
Adrenocorticotropic hormone (ACTH)	
Posterior Pituitary Hormones	**Others**
Vasopressin (also called antidiuretic hormone [ADH])	Carosine
	Sleep peptide (S)
Oxytocin	Calcitonin gene-related peptide (CGRP)
Neurophasin(s)	Neuropeptide Y
	Thymosin
Opioid Hormones	
Dynorphin	Cardionatriuretic peptide (also called atrial natriuretic peptide)
β-endorphin	Angiotensin II
Met-enkephalin	Bombesin
Leu-enkephalin	Bradykinin

[a] A recently discovered neuropeptide involved in the control of energy balance in the hypothalamus.

Source[a]: Collier et al., *Diabetes*, 49 (11), 1766–1771, 2000.

Ader's research opened the way to a plethora of studies that illustrate the conditioning of immune suppression and to some that define immune enhancement as well. Conditioned immune enhancement, like suppression, has now been illustrated with the use of the same chemical, cyclophosphamide, as well as by a variety of

other stimuli, including taste and smell (Bovbjerg et al., 1987). However, much of the earlier research on conditioning involved studies of immune suppression. Many of these studies showed that an aversive stimulus can induce glucocorticoid elevation and immune suppression. It is clear that the hypothalamic–pituitary–adrenal (HPA) axis is a predominant pathway for neuromodulation of the immune system, which will be elaborated later in this chapter. Ader's work also revealed that antibodies can increase simply by using an antigen as the unconditioned stimulus, postulating that it is the interaction between the immune and neuroendocrine systems that mediates the conditioned response (Ader et al., 1993). All of this research suggests that behavior itself is the regulator of immune function (Ader, 1990; Reichlin, 1993).

Figure 2.1 summarizes some of the systems interaction that you will read about throughout this chapter.

THE IMMUNE SYSTEM AS A SENSORY ORGAN

Introduction

Many neurotransmitters and their receptors, previously thought to be located only in the brain, have been found in the immune system (Reichlin, 1993). Conversely, accumulated research shows that any immune function can occur in the brain. Think about how amazing that statement is; our immune system is fully expressed in the home of our thoughts and emotions. When the central nervous system (CNS) receives cognitive stimuli that are relevant to the immune system, it conveys that information by hormonal pathways to receptors on immune cells, causing immunological changes. For example, γ-aminobutyric acid (GABA) receptors (GABA being the primary inhibitory neurotransmitter) and benzodiazepine receptors (benzodiazepines being powerful antianxiety molecules), typically thought of as being housed in the brain, have been discovered on immune cells and actually modulate the actions of the immune system (Song and Leonard, 2000). This is the physical basis for the mind's impact on the development of disease—a primary example of the mind–body connection.

The nervous system communicates with the immune system via sympathetic fibers coming from and going to the brain. The fibers innervate the primary (i.e., bone marrow, thymus) and secondary (i.e., spleen, lymph nodes) immune organs and include noradrenergic (i.e., bearing receptors for norepinephrine), cholinergic (i.e., bearing receptors for acetylcholine), and peptidergic (i.e., bearing receptors for neuropeptides) nerve fibers (Ackerman et al., 1991; Bellinger et al., 1990; Felten and Felten, 1991). Neurotransmitters typically must be activated by the immune system before passing on their message.

So, how does the brain receive and respond to chemical and electrical information from the immune system? The CNS is capable of modulating the immune system from within the CNS itself (e.g., microglia have phagocytic functions in the brain). However, modulation predominantly occurs via peripheral immune stimuli affecting the autonomic nervous system (ANS). The information received involves messages about the general type and level of intensity of the intruder, not information about the specific antigen. In other words, the immune system alone detects an antigen, virus, or bacteria. It then lets the central and peripheral nervous systems in on the news,

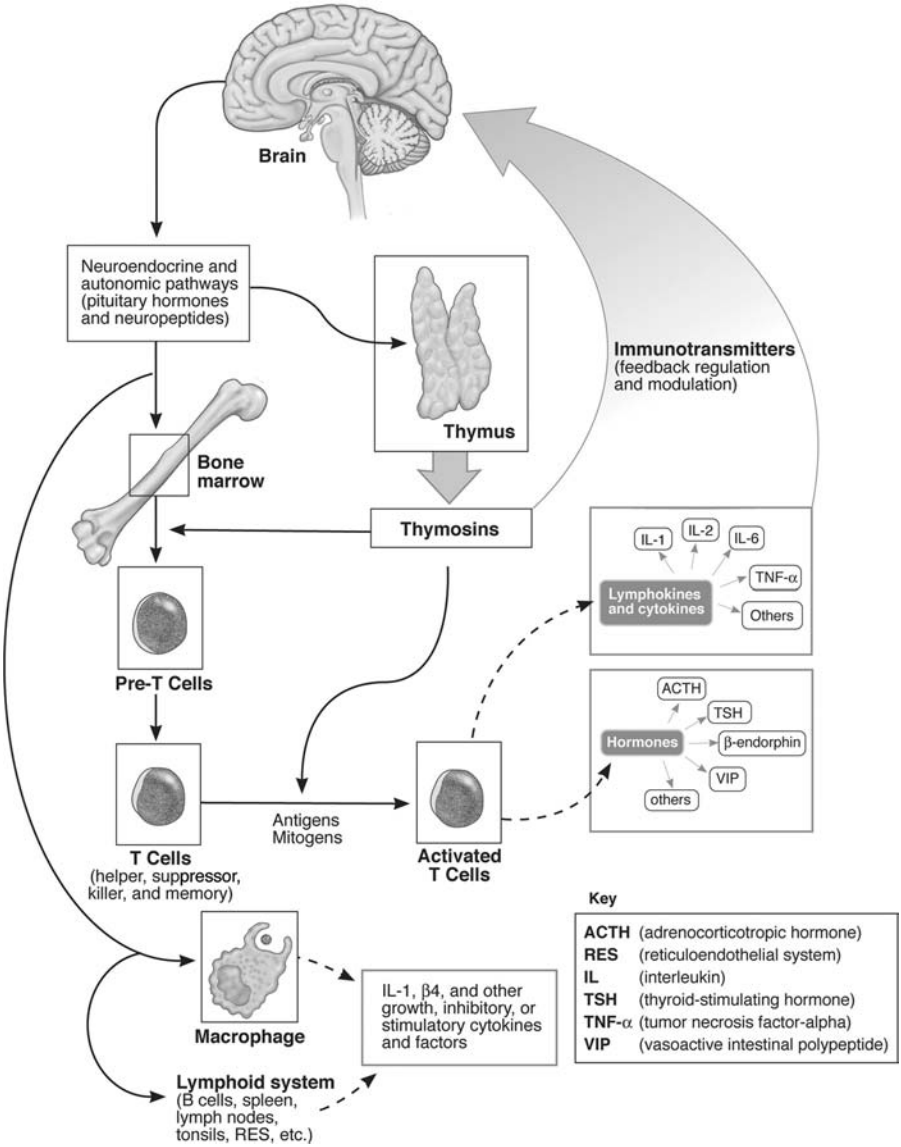

FIGURE 2.1 Interactions among the three classic body systems.

by way of its own mediators as well as via neuroendocrine mediators. The immune system's activation of the CNS most likely involves the older brain structures, such as the limbic system, and follows discrete neuronal pathways (Besedovsky and del Rey, 1991).

Interestingly, the immune stimulus (e.g., virus, bacteria) must reach an, as yet undetermined, but apparent threshold before it is capable of activating the CNS. The

CNS then can generate neuroendocrine peripheral effects. There is, in fact, an interactional and functional relationship between the two systems. For example, when secreted from the sympathetic nerves, epinephrine and norepinephrine generally suppress the immune system, but both have distinct immune enhancing effects in the CNS, potentiated by the immune system's own cytokines, interleuken (IL)-1 and -2 (Zalcman et al., 1994). Based on these findings, researchers have designated the immune system a sensory organ for its ability to obtain, process, and then dispatch information to the CNS (Besedovsky et al., 1983a; Blalock, 1984, 1988).

One of the greatest examples of the interdependency of the nervous and immune systems came out of pioneering work begun in the late 1970s, which was performed by Hugo Besedovsky and his colleagues in Germany. They determined that neuronal firing rates increased in the hypothalamus during peak antibody response to an immunization, with a corresponding decrease of norepinephrine content in the hypothalamus. Norepinephrine also showed a time-dependent decrease in the spleens of mice following immunization as well as after antigen challenge (Besedovsky et al., 1977, 1979a/b, 1983a/b, 1985). Ten years later, a pattern of increased firing rate corresponding to antibody production was ascertained by another investigator as well (Saphier et al., 1987).

Any alteration in neuroendocrine factors, whether local or systemic, can markedly alter the immune activity (Felten et al., 1991, 1993; Madden et al., 1994, 1995; Stanisz et al., 1986; Strom et al., 1972; and many more). Given the mobile nature of immune cells, messages can reach the immune system by nerves in the vicinity of the target immune cells or via the circulation (i.e., local or systemic influences) (Felten and Felten, 1991). The first evidence that immune/brain communication causes a peripheral response was the observation that glucocorticoid levels increase when the HPA axis is activated (Besedovsky et al., 1975). This systemic change results in immune system adjustments, which we will discuss in detail in the chapter on stress (Chapter 3). Likewise, local synthesis and secretion of neuropeptides by immune cells are important for subtler adjustments in the maintenance of immune homeostasis. (See a full discussion on pituitary-like hormones later in this chapter.)

Research eventually focused on the precise modulating activities of the neuropeptides as they affect immune cell function and of the immune cells on neuroendocrine tissue and organs. Bear in mind that the body systems are sharing receptors for multiple possible combinations of immune, endocrine, stress, and/or nervous system factors that can be elaborated either within or between one another. We will now take a look at a few of these modulating molecules.

Cytokines as Immunological Messengers

Cytokines are nonantibody proteins that function like hormones and can trigger further cytokine and hormonal secretions. Cytokines are the immune system's own mediators and are capable of modulating the immune system in a localized manner. For example, IL-1 stimulates itself as well as tumor necrosis factor (TNF), IL-2, and IL-6 and results in immune modulation (Dinarello et al., 1987, 1989; Le and Vilcek, 1987). In addition, cytokines are the principal mediators of communication between the immune and neuroendocrine systems, which also results in immune system

modulation, particularly regarding inflammation and infection. The immune system has receptors for foreign stimuli, such as antigen, virus, or bacteria, which, as mentioned, the CNS is incapable of recognizing on its own. However, the immune system can communicate the presence of such stimuli through cytokine immunological messengers (Bulloch, 1985). Upon CNS recognition of the cytokine, the information is converted to neuroendocrine signals, resulting in chemical messages being sent back to the immune system, with ensuing physiological changes.

By and large, the cytokines (and their receptors) that are found in the nervous system are localized to the brain. While most research has been performed on rodents, TNF and interferon-γ (INF-γ) have been found in human brain tissue and IL-1 in human hypothalamus, human thyroid, and ovary tissue as well (Breder et al., 1988; Hurwitz et al., 1992; Svenson et al., 1991; Tada et al., 1994). Detailed analysis shows that different cytokines have discrete portions of the brain that they are capable of stimulating: dopamine in the striatum, prefrontal cortex, and hippocampus; serotonin predominantly in the hippocampus; and tryptophan accumulating in a more diffuse fashion in the CNS (Besedovsky and del Rey, 1996, 2001). The effect of having cytokines localized in the brain is that they are capable of influencing neuroendocrine production. Among the first cytokines found to have hormonal function were INF, which increases glucocorticoid production, and IL-1, which increases hypothalamic secretion of corticotropin-releasing hormone (CRH) (Blalock and Harp, 1981; Tsagarakis et al., 1989). However, now we know that cytokines are responsible for numerous neuroendocrine alterations (see partial list in Table 2.2).

The activated immune system sends both humoral and neural messages to the brain that there is some type of intruder (antigen, virus, or bacteria) present in the body (Besedovsky and del Rey, 2001). Upon CNS recognition of the cytokine, the brain converts the information to neuroendocrine signals, resulting in chemical messages being sent back to the immune system. The CNS response to the cytokine message either affects distinct neuroendocrine functions that are under the control of the CNS (e.g., stimulating the HPA axis), or it promotes behavioral properties of peripheral cytokines (e.g., fever) (Brown et al., 1991; Dantzer et al., 1998; Linthorst et al., 1995). The hypothalamus, hippocampus, and the pituitary of the CNS, as well as the sympathetic nerve terminals of the peripheral nervous system, are the primary sites at which communication occurs (Scarborough, 1990).

Another route for cytokine modulation in the CNS is via immune cells themselves (Fontana et al., 1982; Frei et al., 1989, 1992). Activated immune cells are capable of permeating the blood–brain barrier and secreting cytokine mediators. This interaction is distinct from the cytokines independently traveling to the CNS. Studies show that these brainborne cytokines can influence peripheral neuroendocrine functions and influence behavioral effects, particularly those associated with the hypothalamus and hippocampus (Kent et al., 1992; Pitossi et al., 1997). These actions probably help maintain homeostasis by modulating the interaction of the systems during antigen challenge.

Moreover, fascinating research shows that IL-1, IL-2, IL-6, TNF-α, and INF-γ all cause pituitary-like hormones to be secreted by immune cells in a localized autocrine- and paracrine-type manner (Carr and Blalock, 1991). This news is

TABLE 2.2
Effects of Various Cytokines on the Body

Cytokine	Species	Effect
		Thyroid (*in vivo*)
IL-1β	Rat	Decrease free T4 (first 2–4 days); decrease plasma total T4 and T4 binding the whole week; depending on dose, decrease plasma TSH and impaired TSH responsiveness to TRH
IL-1α	Mouse	Decrease serum T4 due to inhibition of release; thyroid *in vitro* unresponsive to TSH; increase pituitary TSH 22 and 31 days after treatment
TNF-α	Rat	Decrease T4; decrease binding of T4 in plasma caused by reduction of T4 binding prealbumin; no effect on basal or TRH-stimulated TSH levels
TNF-α	Mouse	Decrease rT3; increase T3 T4 ratio; decrease T3 and T4 responses to TSH
TNF-α	Human	Decrease T3 and TSH; increase rT3; no effect on T4 and free T4
		Hypothalamus–Pituitary Axis (*in vivo*)
IL-1β	Mouse	Increase ACTH
IL-1α	Mouse	Increase ACTH
IL-1α	Rat	Increase ACTH
IL-1β	Rat	Increase ACTH; increase vasopressin
IL-6	Mouse	Increase ACTH
IL-6	Rat	Increase ACTH; increase CRH
TNF-α	Rat	Increase ACTH
TNF-α	Human	Increase LH; no change in FSH
		Adrenal Gland (*in vitro*)
IL-1	Human	Increase cortisol (more effect with monocyte supernatant)
IL-1	Bovine	Increase cortisol (mediated by PG)
IL-1	Rat	Increase corticosterone (mediated by PG)
IL-2	Rat	Increase corticosterone (mediated by PG) (effect only with rat IL-2, not with human IL-2)
IL-6	Rat	Increase corticosterone (mediated by PG)
TNF-α	Human, fetal	Decrease cortisol; shift to androgen production
INF-γ	Human, fetal	Increase mRNA insulin-like growth factor II

(*Continued*)

astounding, and the implications for modulation and integration of systems are profound. These lymphocyte-derived, pituitary-like hormones actually modulate subtle adjustments in pituitary hormone secretions (Schwartz, 2000). For example, IL-1 regulates anterior pituitary cell growth, while IL-2 and IL-6 inhibit

TABLE 2.2
Effects of Various Cytokines on the Body (Continued)

Cytokine	Species	Effect
		CNS (*in vivo*)
IL-1α,β	Mouse	Increase cerebral concentration MHPG (largest in hypothalamus, medial division); increase Trp throughout the brain
IL-2	Mouse	Increase NE turnover in hypothalamus and DA turnover in prefrontal cortex, but not 5-HT

Note: IL = interleukin; TNF = tumor necrosis factor; INF = interferon; TSH = thyroid-stimulating hormone; TRH = thyroid-releasing hormone; ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; LH = luteinizing hormone; FSH = follicle-stimulating hormone; PG = prostaglandin; MHPG = 3-methoxy 4-hydroxy-phenylglycol; Trp = tryptophan; NE = norepinephrine; DA = dopamine; 5-HT = 5-hydroxytryptamine.

Source: Besedovsky, H.O. and del Rey, A., *Endocrine Rev*., 17 (1), 64–102, 1996.

normal growth yet encourage tumor growth (Arzt et al., 1998). As in the other aspects of the immune–neuroendocrine bidirectional communication, we see that cytokines play an enormously important role in system homeostasis during immune challenges.

Neuroendocrine Hormones as Immunological Messengers

There are numerous neuroendocrine hormones that have receptors on and that are produced by immune cells (Reichlin, 1993). In other words, stimulated lymphocytes produce neuropeptides to modulate their own immunity (Smith and Blalock, 1981). In fact, lymphocytes secrete numerous types of hormones, including ACTH and endorphins (Blalock and Smith, 1980); substance P (Weinstock et al., 1988); vasoactive intestinal polypeptide (VIP) (Cutz et al., 1978); thyroid-stimulating hormone (TSH) (Smith et al., 1983); prolactin (Hiestand et al., 1986); growth hormone (GH) (Weigent et al., 1988); and others (Bost, 1988). This was one of the first major findings in immune–neuroendocrine research—that lymphocytes secrete and have receptors for hormones. That is pretty dramatic information. Table 2.3 is a chart of some of the neuropeptides that are produced in the immune system.

We will next briefly review the ways in which some of the neuroendocrine hormones can affect immune function.

Pro-Opiomelanocortin (POMC) Molecules

You will recall from the endocrine section in Chapter 1 that the POMC molecule is made in a variety of tissues, including the lymphocytes, the brain, and the anterior and posterior pituitary. Studies in the area of immune–neuroendocrine interactions

TABLE 2.3
Neuropeptide Receptors on Cells

Neuropeptide	Immune Cell Carrying the Receptor
β-Endorphin	B and T lymphocytes, natural killer cell (NK)
Enkephalin	B lymphocytes
Somatostatin	Mononuclear lymphocyte, mast cell, neutrophil
VIP	Mononuclear lymphocyte, mast cell

Source: Adapted from Blalock, J.E., *Physiolog. Rev.*, 69 (1), 1–32, 1989.

began with the POMC-derived peptides. Enormously significant were the findings that leukocytes (after antigen stimulation) secreted ACTH and endorphins that were identical to pituitary ACTH and endorphin (Blalock and Smith, 1980; Smith and Blalock, 1981). CRH actually encourages leukocytes to secrete ACTH and endorphins—molecules that are typically secreted during a stress response. In addition to β-endorphins and ACTH, lipoproteins and melanocyte-stimulating hormone (MSH) have receptors on and are secreted by lymphocytes.

ACTH

ACTH is capable of several types of immunomodulatory activities, and there is much evidence for bidirectional communication of this hormone. It decreases antibody production by B lymphocytes and INF-γ synthesis by T lymphocytes (Weigent et al., 1990). Its ability to suppress immune function via glucocorticoid stimulation will be discussed later in this chapter.

Enkephalins and Endorphins

Enkephalins and endorphins help regulate the immune system. In 1979, T lymphocytes were shown to have receptors for enkephalins (Wybran et al., 1979). This was astounding news. Enkephalins are now known to increase NK cell activity levels and IL-2 production in humans, which stimulates T-lymphocyte proliferation and B-cell production of immunoglobulins for a specific antigen (Faith et al., 1987; Weigent et al., 1990; Wybran et al., 1987). Receptors for endorphins were first located on virus-infected leukocytes (Blalock and Smith, 1980). Endorphins can either potentiate or inhibit lymphocyte proliferation. Both opioids increase NK cell activity levels, suppress antibody production, and stimulate cytotoxic T lymphocytes (Weigent et al., 1990). Furthermore, both endorphin and enkephalin secretion during stress contribute to an immunomodulating function, inhibiting ACTH (which attenuates the stress response) and, thus, stimulating the immune system (Morgan et al., 1990).

Generally, α-endorphin and the enkephalins (to a lesser extent) inhibit antibody production, and β- and γ-endorphins increase antibody production. Some of the opioid–lymphocyte interaction occurs in a localized manner within lymphoid tissues. Therefore, it is probable that the endogenous opioids complete a circuit, linking

the immune with the nervous and endocrine systems as well as acting independently within each system (Smith et al., 1987).

α-MSH

α-MSH has complex behavioral and immune effects. It is associated with control of food intake, the regulation of skin pigmentation, protection against microbes, and the modulation of inflammation. It is secreted from the pituitary gland and from human immune cells. α-MSH is a powerful anti-inflammatory agent. It acts both by modulating inflammatory mediators, such as cytokines, and at peripheral inflammatory receptors. α-MSH increases during an immune response, but generally decreases with age. Individuals capable of producing greater amounts of α-MSH will have significantly less disease progression. It may be that pharmacological use of α-MSH can help alleviate inflammatory diseases in the future (Catania et al., 2000a, 2000b; Ichiyama et al., 1999; Lipton and Catania, 1998).

Other Immune Messenger Molecules

- GH stimulates NK cell activity levels, augments antibody synthesis, and increases the proliferation of cytotoxic T lymphocytes, generally enhancing immune responses (Kelley, 1989, 1990). Curiously, it may also be involved with aging (Kelley, 1991; Pierpaoli et al., 1969).
- VIP inhibits T-cell proliferation and migration, alters antibody production, and reduces NK cell activity levels (Bellinger et al., 1990; Stanisz et al., 1986).
- Nerve growth factor (NGF), required for the maintenance of sensory and sympathetic neurons, enhances the secretion of IL-2, thus promoting T-lymphocyte proliferation and B-cell production of immunoglobulins for a specific antigen (Thorpe et al., 1990).
- Substance P stimulates T-cell and antibody proliferation as well as stimulating mast cells and basophils to release histamine.
- TSH enhances antibody production (Bellinger et al., 1990; Weigent et al., 1990).
- Somatostatin inhibits T-cell formation (Bellinger et al., 1990; Weigent et al., 1990).
- Prolactin appears to inhibit NK activity (Matera et al., 1990).
- Insulin enhances the proliferation and differentiation of antigen-stimulated T cells (DeBenedette and Snow, 1990).

Table 2.4 summarizes this information.

THYMUS AND PINEAL GLANDS: FACILITATORS OF BIDIRECTIONAL COMMUNICATION

So, the immune and neuroendocrine systems share signaling molecules, primarily neuropeptides and cytokines, which promote communication within and between

TABLE 2.4
Messenger Molecules and their Immune Actions

Hormone	Immune Action
Growth hormone	↑ NK cell activity and cytotoxic T lymphocytes
Vasoactive intestinal polypeptide	↓ NK cell activity and T-cell proliferation
Nerve growth factor	↑ IL-2 and thus ↑ B and T lymphocytes
Substance P	↑ B- and T-lymphocyte proliferation
Thyroid-stimulating hormone	↑ Antibody production
Somatostatin	↓ T-cell formation
Prolactin	↓ NK cell activity
Insulin	↑ Antigen-stimulated, T-lymphocyte proliferation

Key: ↑ Stimulate, ↓ Inhibit

systems. We will now take a look at the thymus and pineal glands as organs that have major roles as facilitators of immune and neuroendocrine communication.

Thymus Gland

In addition to its role as the master trainer of the immune system, the thymus is also a very active endocrine gland. It is capable of secreting various hormones and is influenced by neurotransmitter secretions, resulting in actions that both regulate the immune system and impact on other body systems. Incorporated on this gland there is actually an integration of all three classic systems.

Thymic hormones regulate IL-2 production, which then aids in the maturation of thymocytes and the presence of IL-2 receptors on mature T-cells. This effect appears to be synergistic with IL-1 (Hadden et al., 1991). In addition, numerous hormones produced within the thymus are classically thought of as pituitary hormones (e.g., GH, prolactin, ACTH, luteinizing hormone [LH], and others). I cannot emphasize enough the importance of such findings. It has forced us to alter our whole concept of how the body functions. These thymic hormones have paracrine–autocrine actions, which serve to regulate immune action and influence neuroendocrine functions that affect the regulation of the HPA axis (Savino et al., 1998). Glucocorticoids play a particularly interesting role in T-lymphocyte development. At high concentrations, they induce thymocyte apoptosis, but at lower concentrations, they actually potentiate thymocyte maturation (Vacchio et al., 1998). We will come back to this point when we look at the role that glucocorticoids play in stress (see Chapter 3, which covers the stress system).

Sympathetic noradrenergic innervation of the thymus is well established both from animal and human studies, and norepinephrine is the primary hormone affecting the thymus (Ackerman et al., 1991; Bellinger et al., 1988, 2001a; Bulloch and Pomerantz, 1984). There is evidence that norepinephrine regulates lymphocyte entry and exit of immune organs in general and with the thymus in particular (Madden, 2001; Wiedmeier et al., 1987). Moreover, changes in noradrenergic innervation occur with aging (Madden, 2001). As the thymic cortex progressively alters in composition with

age, noradrenergic innervation becomes denser and norepinephrine increases, possibly playing a role in immune regulation (Bellinger et al., 2001b). An aging thymus contributes to decreased efficacy of the immune system because of a reduction in secretion of thymic hormones and fewer T lymphocytes capable of functioning at full competency. It also affects B-cell efficacy, possibly because there are fewer helper T cells to prepare the antigen for the B cells. Both decreased T- and B-lymphocyte function subsequently result in fewer cytokines, such as IL-1, which in turn, is important for inducing T-cell proliferation—a web of interacting molecules.

Pineal Gland

The pineal gland is eminently important to systems integration; in fact, it is my contention that the pineal gland, not the pituitary, is the master gland (see Chapter 10 on the pineal gland). The pineal gland is to the endocrine system what the cerebellum is to the nervous system—the root of orchestration and modulation. Its hormonal products affect all of the classic body systems. It is the primary neuroendocrine energy transducer, which means that its sensory receptors are capable of receiving environmental stimuli and converting them into action potentials capable of communicating with the brain. In short, the pineal can take one form of energy and transform it into another. The most well-studied environmental energy transduction involving the pineal gland is the transformation of light–dark sensory information into the modulation that we call the circadian rhythm and into the production of the hormone, melatonin. This one hormone is capable of regulating myriad endocrine and immune functions.

Pineal innervation is supplied by the sympathetic nervous system as well as by fibers coming directly from the brain. Nerve endings typically are found in proximity to the specialized secretory cells of the pineal gland, called pinealocytes, which are the cells that elaborate melatonin. The primary neurotransmitter is norepinephrine, which acts on β-adrenergic receptors on the pinealocyte membrane. However, some researchers describe the pineal gland as having numerous types of receptors (Ebadi and Govitrapong, 1986). The neuronal pathways are connected to the hypothalamus and, in particular, its suprachiasmatic nucleus (the home of our biological clock). This ebb and flow of melatonin provides us with the circadian rhythm governing our daily sleep cycles and the seasonal cycles of many animals.

Melatonin has been shown to stimulate immune function and reduce the deleterious effects of stress. It fits into its own receptor, but also into the benzodiazepine receptor. Notably, the immune-boosting effects of melatonin appear to be mediated by opioid agonists. These opioid agonists arise when melatonin stimulates T-lymphocyte helper cells that have already been stimulated by an antigen (Maestroni and Conti, 1991). And with sheer wonder at the complexity of it all, this is what we call systems integration.

EXAMPLES OF SYSTEMS INTEGRATION

One of the best ways to understand systems integration is to take a couple of examples and play it out, uncovering the network of connections and interweavings. We have chosen the stress–immune system and the neural, immune, and endocrine

factors that contribute to intercellular communication in the anterior pituitary as two examples to bring alive for you the countless ways in which the systems interact.

First Example: HPA Axis and the Immune System

It was Hans Selye, in 1936, who first showed that adverse stimuli (e.g., stress, fear) activate the HPA axis (Selye, 1936). Selye was the first to recognize the common, nonspecific aspects of disease. At the time, pathologists were concerned with defining the discrete components of each disease (e.g., what bacteria or virus caused the disease). Selye observed that no matter what the specific disease, there is a collective set of signs and symptoms affecting patients and lowering their immunity. Today researchers continue to uncover the neuroendocrine actions that Selye observed.

In 1977, Hugo Besedovsky, a researcher in the field of neuroendocrine and immune system interactions, hypothesized that in order for neuroendocrine cells to modulate immune cells, the immune cells must be capable of informing neuroendocrine structures about their functional state. Besedovsky believed that an immune–neuroendocrine network existed, which he postulated was based on the existence of a bidirectional, afferent–efferent pathway between the immune and neuroendocrine structures (Besedovsky and Sorkin, 1977). Besedovsky proposed that glucocorticoids are responsible for preserving the specificity of immune reactions because they prevented immune overactivity, that is, autoimmunity or an allergic response. Scientific evidence supports Besedovsky's theory, and the interactions between the HPA axis and the immune system now have been elucidated.

As we have already discussed, the immune system is a sensory receptor organ that sends information to CNS-controlled structures, via the cytokines, and that the information received by the brain is not antigen-specific, but rather involves messages about the general type and level of intensity of the intruder (Besedovsky et al., 1983a; Blalock, 1984). Activated CNS structures, such as the hippocampus and hypothalamus, then cause neuroendocrine immune peripheral effects, attesting to the fact that either direct or indirect brain stimulation has occurred (Besedovsky and del Rey, 1991).

Prior to the discovery that lymphocytes can secrete and have receptors for POMC peptides, there were already studies showing that the immune system stimulates the HPA axis. As mentioned, most illuminating was the finding that when the immune system reaches a given threshold in response to an antigen, it causes the HPA axis to stimulate the adrenal cortex to release glucocorticoids (Besedovsky et al., 1975). However, some researchers feel that the lymphocyte-derived ACTH is not the same as that secreted by the pituitary. Studies show that lymphocyte-derived ACTH is incapable of increasing the secretion of corticosterone from the adrenal cortex of animals (Dunn et al., 1987; Olsen et al., 1992). However, both of these studies were performed on hypophysectomized (i.e., the pituitary gland is removed) rats or mice, possibly rendering their adrenal glands powerless to make such a response. Many other experiments, both *in vitro* and *in vivo*, demonstrate that antigen-stimulated lymphocytes do indeed increase either or both ACTH and glucocorticoid levels, sometimes mediated by cytokines (Besedovsky et al., 1981; del Rey et al., 1998). Further research showed that the lymphocyte-derived ACTH and endorphins are virtually identical in

both composition and function to the same pituitary hormones (Blalock et al., 1985; Blalock and Smith, 1985). The increased glucocorticoid levels may serve the purpose of increasing glucose levels and allowing the individual to have sufficient energy to respond to the antigenic insult, but, as we will see, it is also integrally involved in an immune–neuroendocrine network, subtly tuning the body's homeostasis.

As previously reviewed, research on the immune system has revealed that cytokines stimulate the pituitary to release the POMC-derived peptides (ACTH) and β-endorphin, which means that the immune system has the ability to directly stimulate the HPA response (Bernton et al., 1991; del Rey et al., 1987). There is still controversy as to whether CRH is an obligatory precursor or whether cytokines can directly affect ACTH and glucocorticoid secretion (Besedovsky et al., 1986; Kehrer et al., 1988; Milenkovic et al., 1989; Naitoh et al., 1988; Uehara et al., 1987). Nevertheless, current thinking is that the cytokine, IL-1, is the primary mediator of increased glucocorticoid levels induced by virus, although IL-1 does not modify the activity of other stress hormones to nearly the same extent (Berkenbosch et al., 1989; Besedovsky et al., 1986). Other cytokines (e.g., IL-1, IL-2, IL-6, INF, and TNF-α) also are capable of initiating secretion of CRH, ACTH, or glucocorticoids and causing HPA axis activation (Karanth and McCann, 1991 [IL-2]); (Naitoh et al., 1988; Späth-Schwalbe et al., 1994 [IL-6]); (Holsboer et al., 1988 [INF]); (Milenkovic et al.,1989; Sharp et al., 1989 [TNF]). However, IL-1 appears to be a more potent stimulator of glucocorticoids (Besedovsky and del Rey, 1991). It is my contention that further research will reveal increasingly more information on the effects of the other cytokines and their role in immune system homeostasis. For example, IL-6 is stimulated by IL-1 and subsequently inhibited by glucocorticoids (Schöbitz et al., 1993; Spangelo et al., 1991a, 1991b). Undoubtedly, there is much ahead of us to learn in this field of investigation.

One important feature of immune–neuroendocrine research is the finding that a threshold in immune response had to be met before the HPA was activated. Below this threshold, the immune system appears to work somewhat autonomously. At the time of peak immune response, the HPA axis is initiated, and activated leukocytes and cytokines increase the level of glucocorticoids circulating in the blood, which subsequently initiates an immunosuppressive effect (Besedovsky et al., 1975, 1985). So, the instigation of the HPA axis response occurs only when its immunomodulating effect is necessary. Cytokines provide a feedback circuit that ameliorates over-responsiveness (which can cause autoimmunity) because virtually all aspects of the immune system are inhibited by cortisol (Besedovsky and del Rey, 2001; Sternberg et al., 1989). A feedback loop that has the net result of bolstering the immune system occurs when cortisol reaches levels that cause ACTH to decrease (and eventually lower cortisol levels). For instance, immunoglobulins (Ig)M, IgG, and IgA are increased in the spleen of mice when glucocorticoids are decreased (del Rey et al., 1984). It appears that both glucocorticoids and cytokines are active modulators of the immune system.

Furthermore, little-known studies reveal intricate and discrete modulating capacities for glucocorticoids and cytokines. For example, lymphocytes with lower antigen affinity are more likely to be destroyed by glucocorticoids, possibly a mechanism to control over-responsiveness (Besedovsky et al., 1981). In contrast, glucocorticoids

in initial stages of the immune response actually enhance antibody production, contrary to its typical immune-suppressing actions (Besedovsky et al., 1979b). Finally, as mentioned, cytokine stimulation causes immune cells to produce pituitary-like peptides. Each of these actions is an example of the immune system fine-tuning itself for optimal operation.

Activation of the stress response during injury or illness, paradoxically, causes immune suppression and is an effective way to control its overexpression. When glucocorticoids cannot ameliorate the immune response, the result may be autoimmune disease (Reichlin, 1993). Conversely, if the immune mediators are unchecked, perpetual glucocorticoid secretion would result in serious if not catastrophic immune suppression. The bidirectional communication between the immune and neuroendocrine systems is undoubtedly one of the most crucial to the body's homeostasis and self-regulation. Researchers Carr and Blalock call integration of the immune and neuroendocrine systems a "bidirectional pathway of intersystem communication" (Carr and Blalock, 1991). Immune organs are innervated; cytokines and other immune neuropeptides send messages to the brain; the messages are heard by both the neuroendocrine and immune systems … this is systems integration.

Second Example: Intercellular Communication in the Anterior Pituitary

As we have already reviewed, IL-1, IL-2, IL-6, TNF-α, and INF-γ directly affect the pituitary gland, and immune cells secrete pituitary-like hormones following cytokine stimulation. These cytokines influence cell function (i.e., regulate the secretion of pituitary hormones) and cell growth via autocrine and paracrine actions (Arzt and Stalla, 1996; Arzt et al., 1999; Carr and Blalock, 1991). Recent studies, which are not only engaging, but are undoubtedly pioneering a new field of integral medicine, reveal a variety of pituitary factors (other than the classic hormones) that act as messengers with distinct paracrine- and autocrine-type actions within the pituitary gland. Autocrine or paracrine actions occur at high concentrations or in a persistent fashion, chronically exposing the target cell. There is substantial evidence that novel pituitary-like hormones subtly adjust and modulate the classic pituitary gland hormones, thus affecting both function and cell growth (Renner et al., 1996; Schwartz, 2000). While any one of these various modulators would have an insignificant impact on pituitary secretions, unbelievably, their overall influence is significant to an integrated hormonal response and affects pituitary homeostasis. The impact of the subtle adjustments is still not entirely understood. A survey of all known anterior pituitary communicators is available (see Schwartz, 2000) as well as reviews of various specific messengers (Arzt et al., 1998, 1999; Denef and Van Bael, 1998; Ganong, 1993; Houben and Denef, 1994; Ray and Melmed, 1997). Therefore, to demonstrate the theory, we have chosen to review two of these locally acting messengers (i.e., factors that act as an intrapituitary signal): galanin and α-MSH.

Galanin

One of the most interesting anterior pituitary paracrine messengers is galanin, classically thought of as a polypeptide neurotransmitter in the hypothalamus and pituitary and as a hormone that influences smooth-muscle contraction in the gut (not exactly

your most frequently discussed hormone). Galanin is synthesized and secreted in the anterior pituitary and influences intrapituitary hormonal activity, particularly of prolactin, which stimulates lymphocytes to secrete cytokines (Schwartz, 2000). Recent research indicates that it mediates the paracrine-induced effect of estrogen secretion by cells that secrete prolactin (Wynick et al., 1993). Estrogens, in turn, modulate galanin, with estradiol significantly increasing its secretion (Hammond et al., 1997; Wynick et al., 1993). Galanin decreases prolactin and GH levels, while estrogen increases galanin secretion (Cai et al., 1998 [prolactin]; Schwartz and Cherney, 1992 [GH]; Wynick et al., 1993 [estrogen]). Both galanin and estradiol decrease ACTH secretion, possibly modulating the HPA response (Cimini, 1996). Finally, galanin is implicated in the stimulation of LH secretion that is induced by GnRH—both related to sexual function (Todd et al., 1998). Sufficiently confused? The idea here is that a little-known hormone significantly influences pituitary secretions, which affect sexual and growth functions as well as modulating the stress and immune responses. We have to begin to let go of our ideas that the major hormones are the only ones that have a notable impact on systems regulation.

α-MSH

Our second example of a paracrine messenger that affects the pituitary in a totally novel manner is α-MSH. The classic hormone α-MSH is synthesized and secreted by anterior pituitary cells. The actions of the novel immune-cell-secreted, pituitary-derived α-MSH are different and distinct from the well-known classic endocrine effects. The pituitary-derived α-MSH hormone stimulates secretion of prolactin (which is also synthesized in the anterior pituitary) by paracrine action. The secretion of the prolactin is significant enough to then elevate thyrotropin-releasing hormone (TRH) and adenosine triphosphate (ATP) (Schwartz, 2000). TRH stimulates the release of thyrotropin (which helps stimulate and sustain hormonal secretions from the thyroid) from the anterior pituitary. ATP is an enzyme that is capable of producing high amounts of chemical energy for the body and, thus, is crucial as the source of energy for many physiological functions, from muscle contraction to metabolism. Just to add one more layer of interaction, recall that we just learned that immune-cell-secreted, pituitary-derived galanin decreases prolactin and, here, that α-MSH increases it. The intricacy of interaction is staggering.

Perhaps these paracrine pituitary-like messengers can be seen as the archetypal "feminine" aspect of the body system, or as Eastern philosophers would call it, the yin. Historically discovered first were the powerful, strong system modulators, such as the hypothalamic hormones that inhibit or potentiate the systemically influential hormones of the pituitary. These may be thought of as representing the archetypal "male" energy, or yang. Currently, the subtle modulators, such as those acting as intrapituitary signals, are beginning to be discovered and acknowledged for their importance to overall body functioning. Their physiological significance and power is in the ability to interact and integrate. It is an accumulation of subtle effects, rather than the more expressive impact of the strong system modulators. Both are fundamentally important to system homeostasis.

INTEGRATION: THE POTENTIAL FOR HARMONY

We are just beginning to understand systems integration. Chemical and electrical transmitters, once thought to have limited and discrete functions, are found to have significant impacts on one another, often interchanging functional roles. Although studies bringing to light specifics such as the fact that lymphocytes have receptors for and secrete neuropeptides are of enormous significance to medical science, I speculate that the intricacy in systems interaction that will be revealed in the coming decade will be far more astounding. Now that scientists have discovered the functional modulators that have the most dynamic influence on the body, increasingly subtler ones are being detected. We have approached this stranger from a distance, but are now beginning to draw nearer and get an impression of some of the detailed features.

In Chapter 1, we learned that the HPA axis is connected to a memory system for stress and trauma. We can now begin to speculate that the immune system too has a memory beyond that specific-to-antigen memory. In this chapter, we have seen that the same sites (e.g., the hippocampus and hypothalamus) that are recognized as crucial for memory functions for stress are also fundamentally important in the immune–neuroendocrine bidirectional communication pathway. These sites are both important transfer stations for cytokines, the all-important interceding messengers. The ubiquitous and intricate array of electrical and chemical routes of communication that are already known to make up the immune response is a compelling indication that there could be a memory for the emotional or behavioral components of illness. It is my contention that we will eventually learn that there is consciousness, therefore the potential for memory, in every living cell—in the nucleus and chromatin of every living cell.

What are some of the practical implications of understanding that our bodies are integrated networks? We know that illness and psychosocial factors, such as stress, bereavement, or divorce, can change or deplete immune performance and alter neuroendocrine function. In the next chapter on stress, we will review diverse situations in which people are at significantly greater risk for illness (e.g., relatives of Alzheimer's patients; medical students taking exams; individuals experiencing bereavement, especially men). The impact of these events on one's health is more fully understood from the perspective of systems integration, as discussed in this chapter.

An analogy can be made between the body and a transportation department. There are passengers traveling from one destination to another. There are managers concerned with tracking the arrival and departure of these passengers and their luggage. There are separate discrete events transpiring, yet there is also an interconnectedness that ideally allows for an overall efficient management. Our bodies have the capacity to function in a similar manner, with separate, yet fully interactive, parts maintaining homeostasis. There is a harmony whose sum is greater than the parts—in other words, there is integral physiology. This statement reflects the ancient concept of Taoism: "If you want to be whole, let yourself be partial.… If you want to become full, let yourself be empty. If you want to be reborn, let yourself die. If you want to be given everything, give everything up." We are approaching a time when the scientific knowledge of the intricate interrelationships of every cell as well as the integration of

the classic body systems will come to be seen as the most profound reflection of the subtle energies that interconnect all beings.

> *The practice of medicine they split up into separate parts, each doctor being responsible for the treatment of only one disease. There are, in consequence, innumerable doctors, some specializing in diseases of the eyes, others of the head, others of the teeth, others of the stomach, and so on; while others, again, deal with the troubles which cannot be exactly localized.*
>
> **Herodotus, 484–424 BCE, Histories**
> *Greek historian, considered "The Father of History"*

ESSENTIAL POINTS

- We are now faced with terms whose meanings no longer fit their designated definitions.
- The nervous and endocrine systems share neurotransmitters.
- The brain is capable of both receiving and responding to chemical and electrical information from the immune system.
- The immune system is called a sensory organ because it can obtain, process, and then dispatch information to the CNS.
- Cytokines are the principal mediators of communication between the immune and neuroendocrine systems.
- Receptors have been located in the lymphocyte for β-endorphin, the enkephalins, somatostatin, substance P, VIP, GH, TSH, ACTH, and others.
- Lymphocytes secrete neuropeptides.
- Thymic hormones can influence neuroendocrine functions in ways that affect the regulation of the HPA axis.
- The pineal gland is the master gland. Its hormonal products affect all of the classic body systems.
- There is a bidirectional, afferent–efferent pathway between the immune and neuroendocrine systems, promoting homeostasis.
- Cytokines stimulate the pituitary to release the POMC-derived peptides, ACTH and β-endorphin, making the immune system capable of directly affecting the stimulation of the HPA response.
- At high concentrations, glucocorticoids induce thymocyte apoptosis, but at lower concentrations, they actually potentiate thymocyte maturation.
- Integral physiology is a seamless integration of the classic body systems, which now must incorporate the impact of thoughts, emotions, and beliefs on the nervous system.

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ADDITIONAL RESOURCES

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3 The Stress System

A merry heart doeth a man good, while a broken spirit drieth the bones.

King Solomon
Proverbs

A BRIEF HISTORY

We begin the chapter on stress by returning to the work of Hans Selye, who is rightly known as the "father of stress." The story begins when, as a medical student in Czechoslovakia in the 1920s, Selye observed that patients at the hospital in which he worked appeared to have a fairly common set of symptoms, regardless of their specific diagnosis. This was a significant deviation from the thinking of the time, which postulated that discrete agents caused disease and that symptoms are restricted to that specific disease. Selye, knowing that there would be no support for his theory, did not pursue it, but neither did he forget it.

Then, in 1936 at McGill University in Montréal, where Selye was working as a research physician, he conducted an experiment that would forever change our understanding of medicine. The experiment involved frequently injecting rats with a putative placental hormone (which he never succeeded in purifying). After days of constant abuse from repeated injections, the rats developed gastric ulcers, enlarged adrenals, and involuted thymuses—all the signs that we now associate with a stress reaction. However, much to Selye's astonishment, the rats that had been subjected to the same protocol, but were injected with saline instead of the putative hormone, had the identical set of symptoms. Experiments using other types of stressors yielded the same results, giving Selye the explanation for the common symptoms he had seen in the patients at the hospital in Czechoslovakia. Selye called this nonspecific reaction to disease *the stress response*, and he expanded this concept to include a response to all types of stress, whether or not the stress was of a physiological or psychological origin.

In the subsequent 10 years, Selye developed his ideas on stress and eventually published a paper delineating his comprehensive theory of stress, called the general adaptation syndrome (Figure 3.1) (Selye, 1949). Selye understood that this nonspecific response was hormonally triggered and involved the hypothalamic–pituitary–adrenal (HPA) axis. As his work proceeded, he unraveled the relationship between glucocorticoids and the inflammatory response and was the first to recognize the importance of glucocorticoids in the stress response. Selye then outlined the relationship between stress and disease, expounding on the various potential malfunctions of the general adaptation syndrome. He determined that adrenocorticotropic hormone (ACTH) and cortisol were related to the suppression of inflammation and

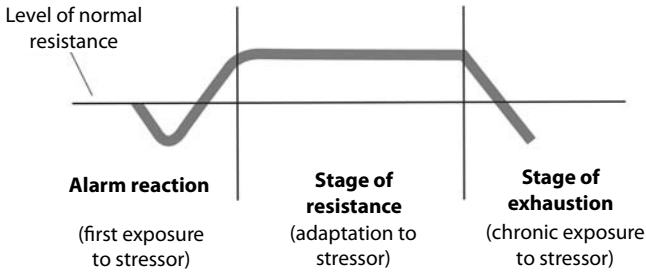

FIGURE 3.1 Selye's general adaptation syndrome.

determined that either an excess or deficiency of these and other hormones could cause a "derailment" in the adaptation response (Selye, 1949; Selye, 1955). Far more is now known about the cellular and systems interactions involved in the stress response. Nonetheless, as one peruses the literature, it is always Selye's work against which theory or accuracy is measured. Selye's discovery that the neuroendocrine and immune systems interact during stress, disease, and injury arguably makes him the father of the field of psychoneuroimmunology (PNI) as well.

Prior to Selye's work, the physiologist Walter Cannon was the person to actually introduce the use of the word *stress*. Cannon borrowed the term de facto from physics and applied it to the phenomenon of the organism reaching a breaking point in which homeostasis cannot be maintained. He also adopted use of the word *strain* from physics, which is intended to include the concept of elasticity. Strain is an important concept, and later in this chapter, we will discuss the differences between stress and strain as they apply to our daily lives. Cannon also coined the term homeostasis, which is the harmonious equilibrium of myriad factors that permit the body to maintain a steady state of health. He pioneered the roles of epinephrine/norepinephrine and the sympathetic nervous system in the stress response and described an adaptive stress reaction that he called "fight or flight," which we now know as the stress response (Cannon, 1914). Given that researchers only recently have unequivocally agreed that stress is a contributing cause to disease, it seems amazing that it has been almost a century since Cannon recognized that both physical and emotional factors can disrupt the body's homeostasis (Cannon, 1914; Chrousos and Gold, 1992).

Against this backdrop, Selye began his pioneering work, confronted by a skeptical medical community that largely relegated his findings to the psychological professionals. Emotional issues had no place in medicine. After all, physicians were beginning to find cures to discrete diseases and to tease apart the molecular underpinnings of the immune system.

WHAT IS STRESS?

Selye's research gave us information about the chemical pathway, and Cannon's work gave us the outline of the electrical pathway of the stress response. Each investigator recognized that stress is a departure from homeostasis. Selye's concept of the adaptation response, which now is referred to as a stress response, is the body's constant

TABLE 3.1
Selye's Stress Response Theory

Selye's Signs of Stress	The Stress Response
Adrenal hypertrophy	Increased blood pressure
Thymus involution	Increased pulse rate
Spleen involution	Elaboration of stress hormones
Lymph node involution	Increased muscle tension
Reduced lymphocyte count	Rapid, shallow respiration

effort to right any physical or mental stressor, maintaining physiological, mental, and emotional harmony or homeostasis (Table 3.1). Stress, therefore, is the absence of homeostasis or an imbalance in the harmonious workings of the organism, which results in the body's concerted effort to reestablish that balance. If the organism is incapable of reestablishing the homeostasis, typically the consequence is disease. In humans, activation of the chemical stress pathway (glucocorticoids) tends to be associated with depression, whereas activation of the electrical stress pathway (epinephrine) more frequently is correlated with anxiety (Sapolsky, 1994).

With illness comes symptoms that are both specific to the disease, but also those that are the nonspecific symptoms that Selye first observed in the 1920s. Selye labeled protracted or chronic stress, such as that seen in seriously ill patients, *the stress syndrome*. You will recall the discussion in Chapter 2 regarding the immune system reaching a given threshold in response to an antigen before it stimulates the HPA axis (Besedovsky et al., 1975). Similarly, an individual's level of stress must qualitatively and quantitatively reach a given (but as yet undetermined) threshold before the stress syndrome develops. Today it is recognized that the stress syndrome is not limited to the physically ill, but occurs as well in chronically emotionally stressed individuals, such as caregivers of Alzheimer's patients, as well as numerous people affected by the stress of work, financial concern, divorce, or bereavement.

Selye believed that some types of stress actually could be advantageous and pleasantly stimulating. This theory has been affirmed by numerous studies in the subsequent 60 years. Interestingly, the physiological basis for this beneficial low-grade stress has now been established. While studies show that glucocorticoids that are secreted in a prolonged manner, as a result of chronic stress, induce apoptosis of thymocytes during the maturation process, recent research indicates that there is actually immune enhancement, via the promotion of T-cell development, when glucocorticoids are secreted in small amounts (Munck and Guyre, 1991; Vacchio et al., 1998). Once again, there is an undetermined set point at which glucocorticoids become detrimental to the body's homeostasis.

Several studies have established this set point in number of days for a given protocol (McEwen, 1998; Munck and Guyre, 1991). The conversion to a harmful response after that given number of days is quite consistent. In this chapter, we will discuss the physiological underpinnings of chronic stress in order to understand why it can be so destructive and then review the patterns of behavior that can induce such a

response. Memory, which plays a significant role in the perpetuation of stress, will also be discussed. We humans are capable of worrying ourselves sick, and as we will see, we actually are capable of worrying ourselves to death.

THE STRESS RESPONSE

Underlying the stress syndrome are changes that are associated with both the electrical and chemical stress response. The stress response is designed to empower the gazelle fleeing the lion on the savanna; in other words, it is the fight-or-flight response (Figure 3.2). Let us quickly review what was covered in Chapters 1 and 2. The stressful stimulus causes the hypothalamus to secrete corticotropin-releasing hormone (CRH) and antidiuretic hormone (ADH). CRH stimulates the release of ACTH from the pituitary, which in turn causes the adrenal cortex to release corticosteroids, primarily the glucocorticoid, cortisol. Meanwhile, the autonomic nervous system (ANS) stimulates the adrenal medulla to release epinephrine (adrenaline), which initiates all the classic sympathetic nervous system responses, such as increased heart rate, blood pressure, and respiratory rates. Release of these adrenal medulla hormones also results in increased arousal and anxiety (Figure 3.3).

The glucocorticoids, epinephrine, and norepinephrine all can inhibit insulin secretion, which results in the conversion of stored protein and fat to useable energy for exertion (the hormone glucagon also helps do this). So, when stress occurs, the stored energy becomes usable glucose and free fatty acids that enter the blood stream for quick energy use. The energy conversion is complemented by increased depth of respiration in the wings, which increases the available oxygen supply. The circulating blood directs the oxygen and glucose to the specific organs and muscles essential

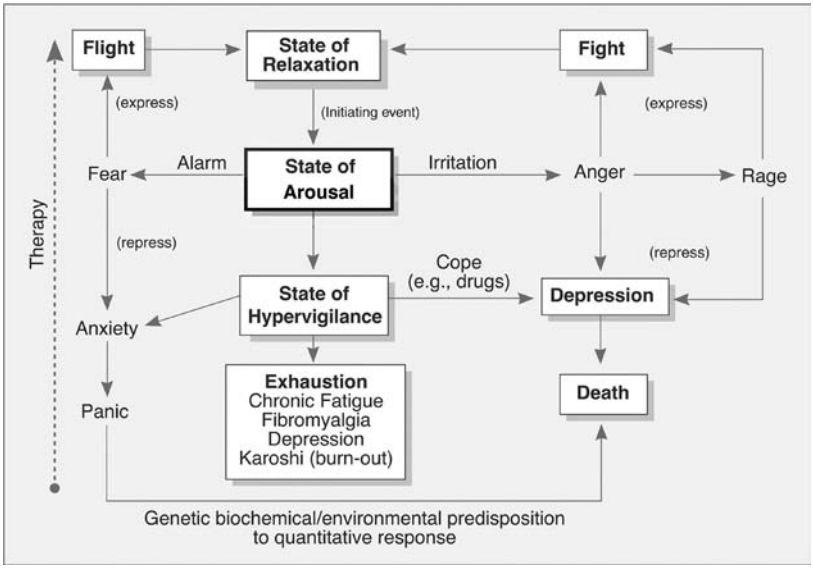

FIGURE 3.2 Clinical stress response.

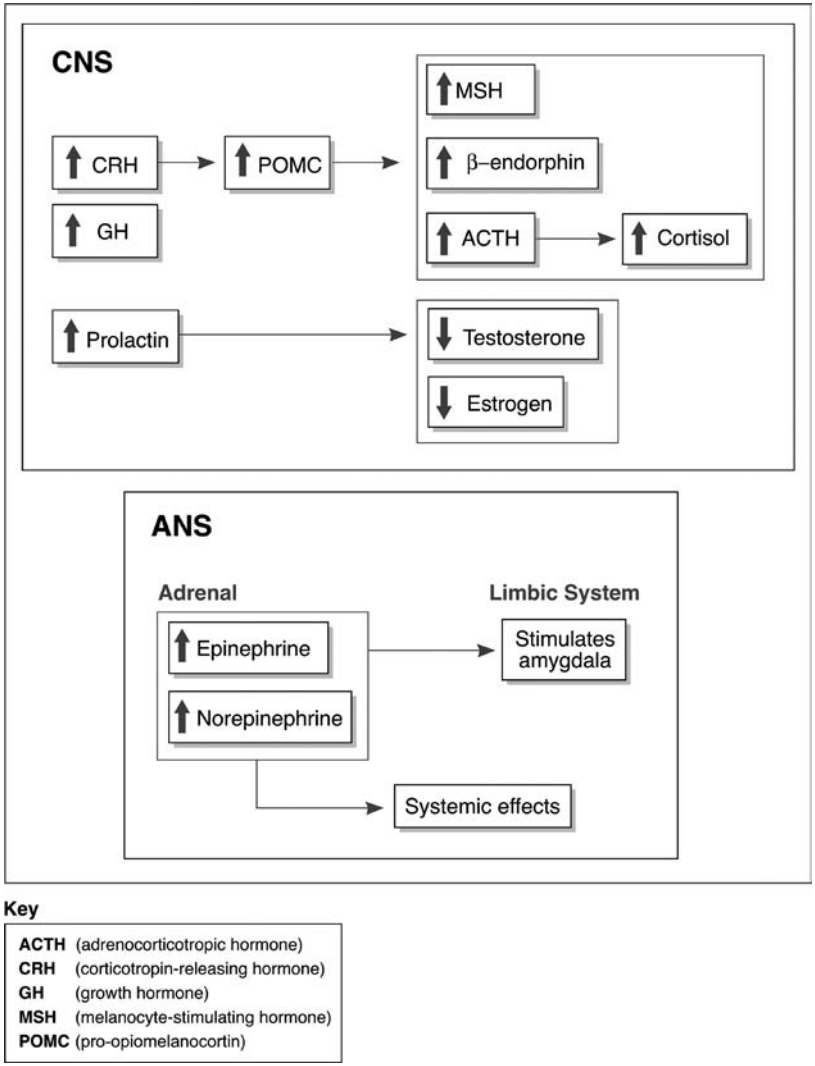

FIGURE 3.3 Endocrine stress response.

for physical exertion and avoids those that are not absolutely necessary for survival. This is how the 110-pound woman is able to lift the family van off of her husband trapped beneath. Hormones related to functions that are nonessential to goals of acute stress, such as reproduction (prolactin, luteinizing hormone, follicle-stimulating hormone), appetite (insulin), and vigilant immune system function, are inhibited. Simultaneously, endorphins, which are strong analgesics, are released.

Keep in mind that the electrical pathway (which also includes hormones) responds to a stressor immediately, whereas the hormonal response is slower, but more sustained. While glucocorticoids and epinephrine are the dynamos of the stress response,

in this chapter we will cover other molecules that influence or sustain the stress response in subtler ways. Having now learned so much about systems interaction, you will not be surprised to hear that the lines between what we called the chemical (CRH/ACTH/cortisol) and electrical (ANS/epinephrine) pathways are not pristinely separated. For example, norepinephrine stimulates the hypothalamus to secrete CRH, which helps to instigate the stress response of the sympathetic nervous system, stimulating the secretions of both epinephrine and norepinephrine (Cunningham et al., 1990; Dunn and Berridge, 1990). Furthermore, ADH, which works synergistically with CRH to stimulate ACTH, also appears to work synergistically to promote behavioral effects (e.g., memory enhancement) of the stress response (Elkabir et al., 1990; Rittmaster et al., 1987).

> I will tell you a story to illustrate the stress response. Several summers ago, I was heading down the Snake River in Wyoming and saw a herd of buffalo. I had my corncob pipe and my hat, but I did not have a gun because I do not hunt. However, I did have my camera. I figured that it would be fun to go up close to the bison. So, I did. I heard a snort. What happened next was that my body experienced a great deal of sensory input. There was rapid input into my amygdala—the fear center. It took about a half a millisecond for my amygdala to say to itself, "Connect, danger, danger!" The hormonal cascade of the stress response was initiated—first the ANS, adrenal medulla, and epinephrine, then CRH, ACTH, and the glucocorticoids. My sympathetic nervous system threw out all sorts of signals, and right after I snapped the picture that you see in Figure 3.4, I ran for my life! Never have I run that fast! I am a big guy, and I could never run a marathon. But, I ran my own marathon in Yellowstone Park that day. I got back to the car (which was across the river) in about 20 seconds, no kidding!

This is an example of the fight-or-flight HPA stress response in its classic sense. The response was clearly designed to give the body immediate energy. My endocrine system was just surging. Adrenaline (i.e., epinephrine), cortisol, and other hormones were secreted. The stored sugar and fats were flowing in my bloodstream, providing fuel for my Yellowstone Park marathon. Likewise, more blood was directed to my large muscles to enable the exertion. My respiratory rate increased, providing more oxygen for the run. My heartbeat was soaring. My blood pressure shot up. In other words, I became a temporary Superman. It didn't last, the Superman part that is. What typically follows an acute stress is sheer exhaustion.

DO WOMEN HAVE THEIR OWN DISCRETE STRESS RESPONSE?

In a well-publicized paper, Shelly Taylor and colleagues at the University of California in Los Angeles discuss their theory of a markedly different pattern of response to stress in women than in men (Taylor et al., 2000). While acknowledging that the fight-or-flight response remains the primary physiological hormonal response in both sexes, they tease out a pattern of stress response that is unique to women. They call this pattern "tend-and-befriend" and speculate that it is the female's counterpart to the infant's attachment mechanism, which has been so thoroughly examined by child development professionals. Based on both human and animal studies, Taylor et al. hypothesize that the "tend-and-befriend" pattern is mediated by a stress regulatory system composed of female reproductive hormones and endogenous opioids, but

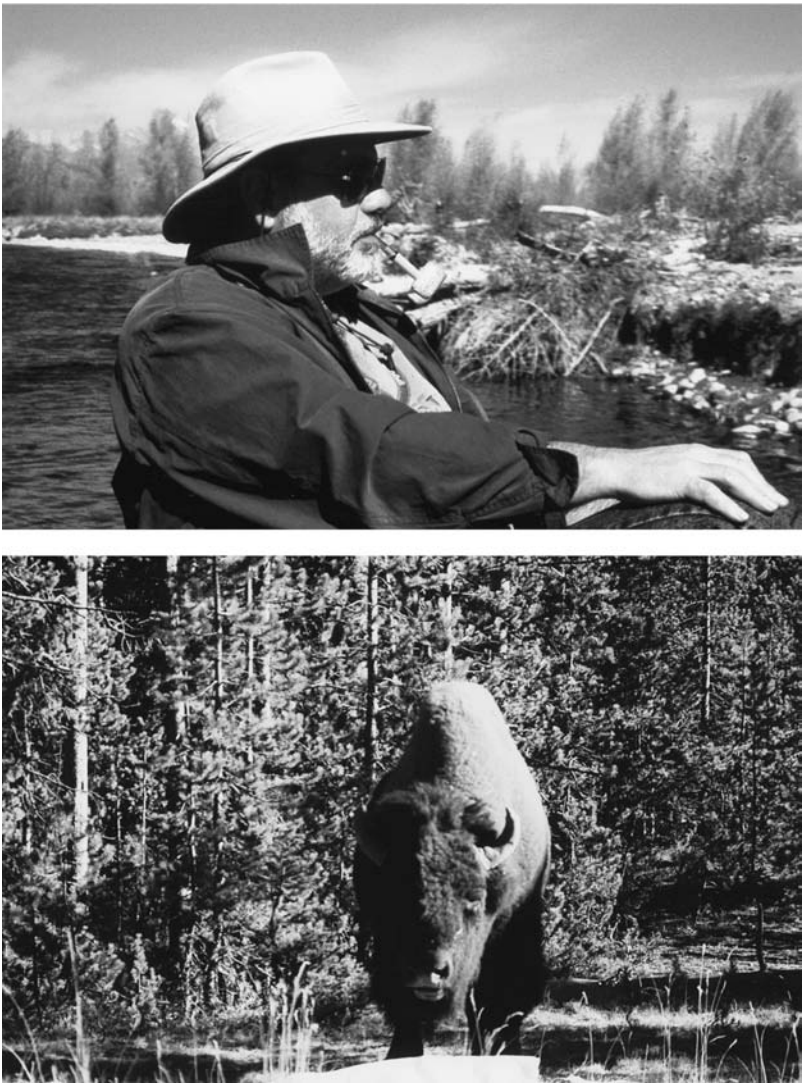

FIGURE 3.4 The buffalo story.

primarily involving the secretion of oxytocin. Taylor and colleagues cite numerous studies that demonstrate the anxiolytic properties of oxytocin, including mild sedation, decreased blood pressure, lower sensitivity to pain, and decreased glucocorticoid secretion. Furthermore, they point out that oxytocin levels increase as a response to massage and decrease with sadness. The researchers then go on to make the case that the same properties, which cause the "tend-and-befriend" pattern in response to stress and are present in the mother–infant bond, also are typical of women in various stressful situations—and are marked by a propensity to affiliate. One study that Taylor et al. cite on coping behavior found that women seek and use social support

more than men—the combined significance was beyond the $P < .0000001$ level. What is so remarkable about this theory is that the physiological response results in a hormonal cascade as well as social/emotional behavior that is a healthy response to stress. Oxytocin is essentially a relaxation hormone, which is now known to be secreted in women during stress. In the next chapter, other hormones that produce a relaxation response will be reviewed.

ALLOSTATIC LOAD

CRH is supposed to stop being secreted when the glucocorticoids reach a theoretical set point, at which time the negative feedback loop ought to do its job and shut down the secretion of glucocorticoids. While glucocorticoid suppression of the immune system is helpful, if not lifesaving in short-term situations, chronic stress can alter the feedback regulation and cause prolonged glucocorticoid secretion, which can be profoundly detrimental. The stress response was not designed to be a prolonged physiological event, but rather a relatively short sprint away from the buffalo or other ominous critter (angry humans not excluded). The symptoms that occur from chronic stress, of any etiology, correlate to those physiological changes that are induced by and supportive of the fight-or-flight response. The symptoms (e.g., weight loss, loss of sexual drive, peptic ulcers, and, of course, immune suppression, which can lead to serious illness) have become exaggerated versions of an initially adaptive response.

In 1993, researcher Bruce McEwen published his views of the complex process of the body's effort to maintain homeostasis (McEwen and Stellar, 1993). McEwen realized that the concept of a static internal system maintaining a constant homeostatic steady state was entirely unrealistic. He recognized that the body is constantly fluctuating in its effort to maintain homeostasis. McEwen used the concept of allostasis, coined by researchers Sterling and Eyer in the 1980s, to express his premise. Allostasis is defined as the "operating range" of the body or the body's ability to adjust various vital functions (e.g., HPA axis, cardiovascular, metabolic, endocrine, nervous, or immune systems) in order to reset itself to a steady state (i.e., a state of relative homeostasis) following stress of any sort. It is the ability of the body to "achieve stability through change" (McEwen, 1998). McEwen took this concept one step farther and coined the term allostatic load (graphically depicted in Figure 3.5). He defined allostatic load as the state of an organism in which "the strain on the body produced by repeated ups and downs of physiological response, as well as by the elevated activity of physiological systems under challenge, and the changes in metabolism and the impact of wear and tear on a number of organs and tissues, can predispose the organism to disease" (McEwen and Stellar, 1993). In other words, there comes a point at which the strain of accommodating the stress becomes too much, and the body can no longer handle the load. At that point, the person enters a state of chronic stress, with the accompanying physiological breakdown.

According to Larry Dossey, MD, there is something akin to allostatic load, which he calls time sickness or hurry sickness. We are victims of time sickness syndrome. Many of us are always feeling rushed, and it is a major cause of stress in our culture. It is similar to a sensory overload syndrome. You are handling all of the stress, and then there is just one more thing that happens, but it happens at the wrong time. You

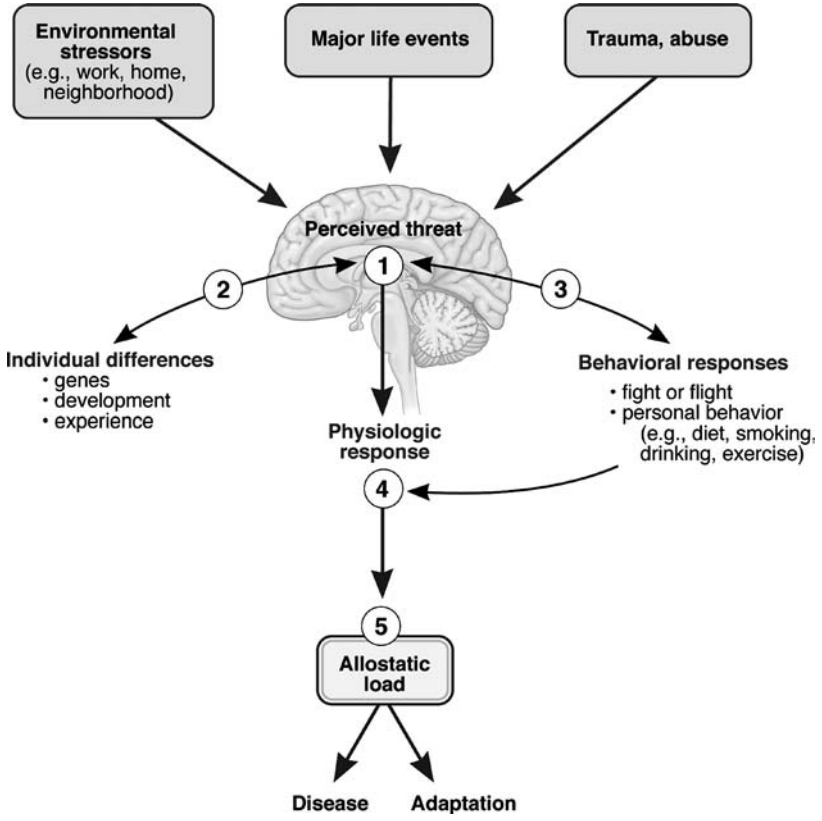

FIGURE 3.5 McEwen's allostatic load.

just crash, and your sympathetic nervous system flares. You may subsequently do or say something you might not normally do or say. Or, if you are capable of being calmer in the face of such overload, you are undoubtedly thinking thoughts that you would rather not think.

What glucocorticoids can do! Selye gave us the basics: thymic involution (reduction in size and function of the thymus), lymphopenia (decrease in proportion of blood lymphocytes), eosinopenia (decrease in eosinophils in blood), and decreased lymph node size. We now know that glucocorticoids inhibit cytokine release (essential to both T- and B-cell maturation), suppress natural killer (NK) cell activity, and promote lymphocyte apoptosis, which is programmed cellular death (Hetts, 1998; Munck and Guyre, 1991). Yet, in contrast, the acute stress response has been shown to strengthen the immune system and provide an immunological memory (McEwen, 1998). Sometimes I think of acute stress as the body's way of staying in shape, of exercising the stress aspect of our being. If we never experienced stress, we would lose our vitality and vigor for life. A muscle never used becomes useless. Recent studies, however, have provided more understanding of the extensive implications of allostatic load (McEwen, 1998, 2000c, 2000d). This basic concept of allostatic load

is an important one to keep in mind as we proceed to examine different issues that may be supportive during acute stress but maladaptive during chronic stress.

HORMONAL AND NEUROTRANSMITTER INFLUENCES ON STRESS

The major hormones and neurotransmitters of the stress system are beneficial modulators, but these same elements cause its malfunction, potentially leading to serious illness. There actually are numerous other factors that contribute to the stress–immune homeostasis, but for the most part, discussion in this section will be limited to what happens physiologically during chronic stress (see Khansari et al., 1990, for a review). Further, we will look at the role of opioids in HPA–immune interactions, determining their modulating role in both systems.

Glucocorticoids

More than 100 years ago, the physician Thomas Addison identified a condition (that later came to be known as Addison's disease) in which the adrenals secrete insufficient amounts of cortisol and the patient evidences abnormally high levels of white blood cells (leukocytosis). Based on this finding, physicians decided that glucocorticoids were immune enhancing. That concept should have been dispelled in the mid-twentieth century, when glucocorticoids were shown to have antiinflammatory properties (Hench et al., 1949). Yet, the idea that glucocorticoids stimulate the immune response persisted. Research in the latter part of the twentieth century fully established the correlation between high doses of glucocorticoids (e.g., prednisone) and suppression of the immune response, even when administered to healthy adults (Rinehart et al., 1975).

On the heels of these studies came the work of researchers, such as Hugo Besedovsky, who looked at the actions of the glucocorticoids from a systems interaction perspective and surmised that the net effect of glucocorticoids was modulatory. Besedovsky felt that the glucocorticoids prevent immune overactivity and permit specificity (e.g., magnitude, duration) of immune reactions (Besedovsky et al., 1975; Besedovsky and Sorkin, 1977; Munck et al., 1984). They are a little like the foot controlling the gas pedal. He showed that lymphocytes with lower antigen affinity are more sensitive to the effects of glucocorticoids, once again, possibly a means for controlling overresponsiveness of the immune system (Besedovsky et al., 1981).

Glucocorticoids suppress the immune system by decreasing the production of many factors that facilitate B- and T-cell proliferation, including the cytokines, β-endorphin, and insulin. Inhibition of these mediators reduces proper functioning of monocytes and macrophages (Guyre et al., 1988; Moynihan and Stevens, 2001; Munck and Guyre, 1991). High levels of glucocorticoids also reduce NK cell activity levels in mice and humans (Cox et al., 1983; Holbrook et al., 1983; Keller et al., 1991; Oya et al., 2000; Shavit, 1991). Curiously, one experiment showed that rats, who were administered corticosterone in amounts equal to those induced by inescapable tail shock, did not have antibody suppression like the shocked animals (Fleshner et al., 1998). This finding supports the argument that there is a combination of issues that contribute to the immune-suppressing effects of glucocorticoids and that we do not yet fully understand these factors.

Many physicians today are not aware that brief exposure to glucocorticoids actually enhances the immune response, but there are many studies illustrating this point. In one experiment, γ-interferon was shown to completely abolish the immune suppressive actions of glucocorticoids (Girard et al., 1987; Morganelli and Guyre, 1988). Furthermore, Allen Munck and Paul Guyre, at Dartmouth Medical School, concluded from analysis of various studies that steroids must saturate at least 50% of the glucocorticoid receptors for a minimum of 24 hours before monocyte or macrophage inhibition occurs (Munck and Guyre, 1991). The research supports Selye's premise that some stress is important. The role of glucocorticoids, both in controlling overresponsiveness of the immune system and in enhancing the immune system at low levels, are illustrations of the body seeking homeostasis. Both responses are adjustments to help lower the allostatic load, anticipative of maintaining or regaining health.

Adrenocorticotropic Hormone (ACTH)

Recall that the secretion of ACTH from the pituitary, prompted by CRH from the hypothalamus, stimulates the adrenals to secrete glucocorticoids. Fascinating research shows that during chronic stress, glucocorticoid levels remain high, while ACTH returns to normal or slightly below normal levels. In other words, the ACTH levels no longer correlate to those of the glucocorticoids (Bornstein and Chrousos, 1999). Curious! So, researchers began to try to figure out why this happens. It is well known that the adrenals atrophy if the pituitary is removed and that exogenous ACTH can reinstate normal glucocorticoid secretion. So, how can the adrenals continue to secrete high levels of cortisol during chronic stress if ACTH has all but shut down? Well, a few creative individuals, from several different countries, broke from the conventional thinking that the adrenal medulla and the adrenal cortex are two proximate glands that lack any pathway for communication. For the reader who is new to the topic, this theory might seem like the obvious. Although it is known that fetal and neonatal adrenal function occurs independently of pituitary ACTH, medical students today are still being taught that the two segments of the adrenals have nothing to do with one another (McDonald and Nathanielsz, 1998, includes a review of adrenal innervation). The finding that the adrenal medulla and cortex communicate introduced a potentially new route for mechanisms of hormonal action during chronic stress. The observations opened the way to a whole new field of research, called non-ACTH or ACTH-independent regulation of the adrenal cortex.

Chromaffin cells of the adrenal medulla extensively communicate with the steroid-producing cells of the adrenal cortex (also called adrenocortical cells) in such a manner as to elevate cortisol (Bornstein et al., 1997; Haidan et al., 1998). *In vitro* studies show that when adrenocortical cells are mixed with medulla chromaffin cells, they produce 10 times the amount of glucocorticoids as adrenocortical cells alone (Bornstein and Ehrhart-Bornstein, 2000). This means that we probably do not need ACTH to keep the cortisol pumping during stress. Several mechanisms of paracrine bidirectional communication have been proposed. First, neuropeptides and small amounts of CRH and ACTH from the adrenal medulla may influence cortisol secretion, although the effect is probably minor (Bornstein and Chrousos, 1999; Ehrhart-Bornstein et al., 1998). Second, and probably more importantly,

various immune cytokines are secreted by the adrenal cortex and may play a role in immune–adrenal regulation, which could theoretically stimulate cortisol (Bornstein and Chrousos, 1999; Bornstein and Ehrhart-Bornstein, 2000). For example, interleukin (IL)-6, during chronic but not acute stress, increases steroid production (Päth et al., 1997). And, when pituitary ACTH shuts down during chronic stress, it appears that the chromaffin cells of the medulla become potent stimulators of adrenocortical steroidogenesis via a paracrine mechanism. Recent research suggests the activation of the sympathetic nervous system and the secretion of epinephrine from chromaffin cells of the medulla as a route by which cortisol is stimulated (Haidan et al., 2000; Pignatelli et al., 1998).

Speculatively, it could be the collaboration of all three of the mechanisms mentioned that produces the effects of non-ACTH–mediated cortisol during chronic stress—or that the most salient factor has not yet been discovered. Recall from Chapter 2 that, historically speaking, the major systemically influential hormones, such as the hypothalamic and pituitary hormones, were discovered first. In recent years, subtler modulators, such as those involving paracrine and autocrine interactions, have been acknowledged for their importance to overall physiologic functioning. The significance resides in their ability to interact and integrate. It appears that research on stress has now entered a phase in which the subtler interactions of the adrenals are being elucidated as significant to prolonged stress.

Corticotropin-Releasing Hormone (CRH)

CRH, isolated from the hypothalamus in 1955, is best known for its role as the hormone released from the hypothalamus to stimulate the secretion of ACTH (see Saffran and Schaly, 1955; Taylor and Fishman, 1988; Vale et al., 1981, for a review). CRH is a very powerful hormone that is capable of affecting multiple human functions, including mood, growth, and reproduction (Chrousos, 1999; Ghizzoni et al., 1996; Gold et al., 1987; Habib et al., 2000). CRH stimulates the secretion of epinephrine from the adrenal medulla and is stimulated by norepinephrine (Pacak et al., 1995; Pacak, 2000). In fact, norepinephrine and CRH are capable of stimulating one another and appear to operate differently during acute stress than during chronic stress (Calogero et al., 1988; Kiss and Auguilera, 1992, 2000).

Intriguing research on adult male rhesus macaques using a CRH antagonist confirms just how germane CRH is to the malfunction of the HPA response. Researchers synthesized a CRH antagonist and determined the dose at which it reduced ACTH blood levels. They administered it to the monkeys who, 90 minutes later, were exposed to the acute psychosocial stress of being placed in a cage with two unfamiliar monkeys in adjacent cages, separated only by Plexiglas®. The exposure lasted for 30 minutes, and behaviors were recorded. The episode elicited symptoms of acute stress in the controls, including hitting the Plexiglas, audible teeth grinding, body tremors, grimacing, urination, and defecation. However, the rhesus macaques that were given the CRH antagonist exhibited significantly less anxiety and aggression. Blood tests showed that the monkeys given the CRH antagonist had significantly lower ACTH, cortisol, norepinephrine, and epinephrine (Habib et al., 2000).

The findings of CRH antagonist-related stress levels in macaques confirmed previous studies on rats (Webster et al., 1998). Researchers speculate that a CRH antagonist could have therapeutic potential for inflammatory conditions, sexual disorders, growth retardation, and gastrointestinal disorders. Additional research revealed that administration of the CRH antagonist did not result in adrenal atrophy—an enormously important finding if it were ever to be used as a therapeutic agent (Bornstein et al., 1998).

Opioids and Stress

Numerous studies link opioids, particularly the endorphins, to HPA stimulation of the immune system. Opioids appear to have immune-modulating characteristics, variously increasing or decreasing the immune response (see Moynihan and Stevens, 2001, for a review). Endorphins are secreted by the adrenal medulla during the stress response and are primarily associated with the reduction of pain. Leukocytes have opioid receptors specific to the opioid type. For instance, NK cell activity levels are enhanced by β-endorphin, γ-endorphin, and met-enkephalin, but not by α-endorphin or leu-enkephalin.

Endorphins have neurotransmitter properties as well as CNS involvement and, therefore, communicate back and forth between the HPA axis and the immune system about both cognitive and noncognitive stimuli (Smith et al., 1985). β-endorphin stimulation of NK cell activity can be reversed by naloxone, an opioid antagonist, which means that increased NK activity is opioid-mediated. CRH indirectly modulates the immune system by augmenting the production of β-endorphins by leukocytes and by inducing monocytes to secrete IL-1 (Carr and Blalock, 1990). IL-1 causes B cells, but not T-cells, to secrete β-endorphin, which in turn enhances the immune response (Kavelaars et al., 1990). Thus, we have another great example of systems interaction and integration.

In the 1980s, researchers made a distinction between opioid and nonopioid forms of stress. Yehuda Shavit, who began this work as a graduate student in psychology at UCLA, showed that, depending on the length and intensity of the stressor, the body responds with either an opioid-mediated or a nonopioid-mediated form of analgesia. Rats exposed to prolonged intermittent foot shock (inescapable shock) demonstrated an opioid-mediated route of analgesia (ascertained by its ability to be blocked by the opioid antagonist, naloxone). These experiments caused an "escape or avoidance learning deficit" or "learned helplessness" (Shavit, 1991). However, rats exposed to brief but continuous foot shock, given for the same cumulative amount of time, elicited a nonopioid analgesic response to a degree comparable with that of the opioid-mediated analgesia.

So, why are the two different routes of analgesia significant? Research shows a correlation between opioid-mediated analgesia and depressed NK activity levels as well as decreased tumor median survival time with tumor (Shavit et al., 1985). Similar research shows a depressed mitogen (i.e., a substance that aids lymphocyte proliferation) response can result from just one instance of intermittent foot shock. When the protocol was changed to continuous foot shock, the mitogen suppression was correlated to β-endorphin stimulation (Panerai et al., 1997). Additional research

showed that learned helplessness correlates to decreased norepinephrine and to depression (Weiss and Simson, 1988).

Although opioids, such as β-endorphin, help limit the stress response via their analgesic effects, the analgesic effect can fail when stress causes chronic activation of the HPA axis (Chrousos, 1998). One study on the effects of exercise-induced stress showed that mild exercise enhances immunity, while continuous exercise that exhausts the opioid system can result in immunosuppression (Ilyinsky et al., 1990). The fact that different stress parameters variously evoke opioid or nonopioid forms of analgesia may be one factor behind the inconsistent results found in studies on stress.

THE IMMUNE SYSTEM PREPARES FOR ACTION

During an acute stress response, the HPA stimulates the immune response and arouses immunological memory for invaders (Dhabhar and McEwen, 1996). The stress stimulus instigates a process by which leukocytes (particularly T-cells and monocytes) move from the blood stream to the walls of blood vessels, lymph nodes, or bone marrow, in preparation to mount an immune response, if there is a need to do so (Dhabhar et al., 1996). This phenomenon is evidenced by a reduction of blood leukocytes (over 50%), an increase in neutrophils (over 80%), and an increase in the number of leukocytes in other areas, particularly the skin (Dhabhar and McEwen, 1996; Dhabhar et al., 1996). Following acute stress, it appears that some of these leukocytes are retained in certain areas of the skin and that γ-interferon, as a local mediator of this enhanced skin immunity, fosters immunological memory (Dhabhar et al., 2000). However, research shows that glucocorticoids are the primary mediators of the leukocyte shift. So, in spite of overall statistics indicating the destructive aspects of glucocorticoids, again we see that they enhance the immune response in the initial stages.

The researchers describe the leukocyte migration as "battle or communication stations" for the enhancement of cell-mediated immunity, that is, T-cell immunity (Dhabhar et al., 1996). This seems to be an appropriate function from the evolutionary perspective—an individual in a fight-or-flight scenario would need to mount a rapid immune response if injury occurred during conflict. It also makes logical sense that this immune readiness would be beneficial to immune challenges, such as wounds, but would most likely exacerbate immune challenges in systemic disorders (Dhabhar and McEwen, 1996). A contrasting profile emerges of the immune response during acute versus chronic stress, as chronic stress not only causes leukocyte function to be inhibited, but also induces a decrease in the redistribution of lymphocytes from the blood to the immune compartments (Dhabhar and McEwen, 1997, 1999). Typically, an immune-enhancing effect will endure for three to five days, after which time the allostatic load becomes too great, and features of chronic stress emerge (McEwen, 1998).

APOPTOSIS

In 1972, John Foxton Ross Kerr, M.B., Ph.D., Emeritus Professor at the University of Queensland and colleagues published the groundbreaking results of their work on a new type of cell death, which they called apoptosis from the Greek for "a falling off" (Kerr et al., 1972). Apoptosis is the end result of chronic stress. It is programmed cellular death,

and it can be the programmed death of the individual. Basically, there are two ways cells die. One is an inflammatory response, called necrosis, by which cells expand and essentially burst. The contents inside of the cell, such as the cytoplasm and nuclear particles, spill out into the intercellular spaces, causing inflammation. Various roving phagocytes surround the necrotic material and ingest the debris, effectively clearing it away. Although necrosis is the process of cellular death that typically occurs with injury and some inflammatory conditions, apoptosis is the most common mechanism of cell death overall.

During apoptosis, cells shrink because the chromatin condenses and fragments the cell's contents into membrane-bound particles. The nucleus involutes, and the cell implodes, instead of exploding. As with necrosis, the dead material is phagocytized. Because the cells shrink, there is no inflammation caused by intercellular deposits as occurs with necrosis. Much of what is known about apoptosis was gleaned from a nematode worm, the *Caenorhabditis elegans*, whose genetic model of apoptosis is remarkably similar to, although far less complex than, humans. The existence of apoptosis in the nematode indicates that the process has been conserved in evolution.

Apoptosis can be called a programmed cellular death because it is genetically determined (Hetts, 1998). Tissue-specific signals elicit protein products from a gene that researchers named the CED-4 gene. CED-4 activates the CED-3 gene to instigate the process of apoptosis. Various commitment signals cause the process of apoptosis to begin, while other signals inhibit it. In other words, there are prodeath ligands, and there are antideath ligands. Research is still being conducted on various commitment signals, but let us look at one death ligand, the Fas protein, to generally explain the process. When a cytotoxic T lymphocyte binds to an antigen, it causes the elaboration of the Fas ligand (FasL). The FasL easily binds to Fas, which is a cell-surface death receptor that is found on most cells. This interaction results in apoptosis, which in this instance would cause the death of the cell. The Fas receptor is like a smart bomb; it turns on the genetic material to initiate a cascade that commits the cell to destruction.

Glucocorticoids are known to induce apoptosis, particularly in thymocytes and activated T-cells, but they also are able to rescue immune cells from apoptosis (Hetts, 1998; Planey and Litwack, 2000; Tolosa and Ashwell, 1999). Survival of activated T-cells is mediated by glucocorticoid receptors, with signaling between the T-cell antigen receptor and the glucocorticoid receptor (Jamieson and Yammoto, 2000). In addition, certain proteins (of the Bcl-2 family) may influence the lymphocytes to surrender to the apoptotic process or not (Huang and Cidlowski, 1999).

Importantly, apoptosis may be a crucial factor in the development of autoimmunity. If a cytotoxic T lymphocyte binds to a self-antigen, mistaking it for a foreign antigen, apoptosis ideally protects the body from such a defective T lymphocyte receptor (Hetts, 1998). However, when this process fails, autoimmunity occurs. For instance, if a viral antigen, whose DNA is similar to a normal cell, activates the Fas receptor, the normal cells then are marked for destruction. They are victims of friendly fire, which could be the basis of autoimmune thyroiditis or Hashimoto's thyroiditis.

As we have shown, there are prodeath ligands that trigger the apoptotic cascade in response to stress and other psychological factors. If someone went to a country abounding with occult rituals and had a curse placed on her or him, she or he might begin to believe that the ritualistic action could be fatal, and it might well be so. Death-ligand neuropeptides could cause the process of apoptosis to be instigated,

and the individual, in a most extreme case, could die. Researchers continue to study the physiological basis of the apoptotic form of psychoneuroimmunology—or what might be called the physiological basis of the voodoo response. It is also called the nocebo response or the negative response.

> I think that there is a physiological basis to the nocebo response that is very dramatic. I am no longer willing to try to withhold my passion regarding the way in which some doctors unwittingly program illness in their patients. I have seen it time and time again in my clinical practice. The physician says something akin to any of the following statements: "You have six months to live." "You have diabetes. If you don't control your blood sugar, in two years you're going to need an amputation." "Sorry, you have multiple sclerosis. That's a chronic disease; you're going to be in a wheelchair in about three months." I am concerned that some physicians do not grasp the powerful effect that their communication can have. This is an entire area of psychoneuroimmunology that warrants more study—how we communicate with our patients. Negative programming is much like implanting an emotionally destructive thought virus. I call the process "voodoo medicine." It is the antithesis of being a physician. Remember, above all, *do no harm*. Particularly with life-threatening diseases, the patients come in feeling vulnerable. In the office, they are literally physically naked, and they are emotionally naked, hanging on every word the physician says.

Are physicians doing an adequate job of helping the patient cope with the emotional aspects of their disease? This is not an issue of being willing to offer alternative or complementary medicine to a patient. It is about bringing the heart, the feeling, the caring, and the nurturing back to medicine. A physician's work ought to include trying to instill hope, while indicating that there is much that scientists just do not understand about the mystery of the healing process. Be artful, positive, a pillar of strength for your patients. Sometimes I feel like the most important thing I can do is to try to give the patient hope so that if bodily healing cannot occur, at least inner healing can.

Now, recall the story in the Introduction in the front matter of this book about Steve, who got 10 years more to live. How do you explain it? It is the opposite of the nocebo response or of programmed cellular death. We can leave it to the Great Mystery. But, we also can see that this new science is beginning to explain some of these previously unknown phenomena that many physicians, if they are honest, will admit to having seen in their clinical practices. Unfortunately, because of the acculturation of physicians to be obligate scientists, we are loath to discuss these incredibly special, sanctified experiences we have with our patients. As integral medicine and the true art of healing—which is an approach to healing the whole person: the body, mind, emotions, and spirit—becomes commonly accepted, physicians will be joyfully swapping stories of patients like Steve.

THE EFFECTS OF STRESS ON GENES: TELOMERES

What Is a Telomere?

In recent years, much research has been focused on telomeres, a 3 ft. to 5 ft. strand located at the distal end of the chromosome that resembles a fiddlehead, but functions more akin to an aglet—that protective cover at the end of a shoelace (Ben-Porath

and Weinberg, 2004; Green and Mayeux, 2006). Human telomeres are composed of a double-stranded, hexamer-shaped DNA sequence, with a 100- to 400-nucleotide protein complex. (Ben-Porath and Weinberg, 2004; Blackburn, 2005; Chan and Blackburn, 2004). The tandem DNA sequence creates a structure analogous to scaffolding, which has binding sites for proteins. These proteins have a specialized role in that they cover and protect the end of the chromosome; thus, it is said that they serve the biological function of *capping* the chromosome (Blackburn, 2005; Chan and Blackburn, 2004). Most telomeres shorten when a cell divides; however, telomeres on neurons are a notable exception to this phenomenon (Green and Mayeux, 2006). In fibroblasts, leukocytes, and various other cells that have been studied, there is a correlation between shorter telomeres and increased human age. However, as will be seen in the subsequent discussion, telomere length is a marker of a cell's biological age in respect to its ability to further divide and appears to be genetically determined; however, whether or not telomere length can be used as a biomarker of the host's ability to survive disease or predict longevity is far more questionable (Epel et al., 2004; Njajou et al., 2007).

Telomere DNA is synthesized and replicated by an enzyme, called telomerase, which is a ribonucleoprotein complex made up of an RNA template and telomerase reverse transcriptase (TERT). The short RNA template sequence (in humans, the repeats are call T2AG3) within the structure can copy that RNA into the telomere DNA. Thus, by definition, the telomerase protein enzyme is called a reverse transcriptase (Blackburn, 2005; Green and Mayeux, 2006). The key function of telomerase is to elongate telomeric DNA, arresting the shortening process anticipated with cell division by creating numerous short double-stranded repeats, synthesizing the chromosome ends (Damjanovic et al., 2007). Thus, telomere DNA caps and protects chromosomal DNA.

An image of a telomere cap akin to a cover that protects the ends of electrical wiring would be misleading, as both the protein and DNA components of telomere capping engage in a vibrant and dynamic process—they repeatedly break apart and then reassemble. Because chromosomal DNA has incomplete replication (i.e., it cannot reach the chromosome ends during each replication), DNA molecules could not maintain their length if it were not for the effects of telomerase (Blackburn, 2005). Even so, with age, telomeres of many cell types slowly, but steadily, get shorter and shorter.

When DNA breaks, various responses ensue to repair the break; capping protects telomeres from the DNA repair responses that could simultaneously harm the telomere. There needs to be several hundred nucleotide repeats capping the telomere to prevent DNA repair pathway activation (Aubert and Lansdorp, 2008). In a variety of ways, telomerase helps prevent end joining fusions not only of telomeres with a double-stranded DNA break, but also of telomeres with other telomeres—all of which provides genomic stability (Chan et al., 2003). Curiously, capping also prevents too much telomerase expression, and telomerase, itself, can make errors and miscopy (Chan et al., 2003). This action is important, as overexpression of telomerase immortalizes cells in culture, causing them to become premalignant; yet, if telomeres are not normally functioning for any number of reasons, including underexpression of telomerase, the mechanisms that repair DNA damage cannot engage (Green and

Mayeux, 2006). Thus, telomeres and telomerase are part of a critically important balancing act: a genetic homeostasis.

Yet, telomerase also seems to have a mind of its own, so to speak. Most cancer cells have high levels of telomerase, but they do not have telomeres that are unusually lengthened. Studies on the role of telomerase and cancer in human cells demonstrated that when telomerase RNA levels were knocked down, such that both the telomerase ribonucleoprotein *and* the enzymatic activity were depleted, there is a rapid decrease in the growth of cancer cells that are telomerase-positive. Most promising, this decrease in growth was not associated with telomere shortening/uncapping or with DNA damage. Thus, the investigators concluded that "telomerase participates in cell responses in ways that do not seem to involve the telomere itself" (Blackburn, 2005).

Replicative Senescence

In both Petri dishes and humans, as a telomere gets shorter and shorter, it cannot sustain its capping function, which results in cell senescence. Nearly 50 years ago it was assumed that human cells had a finite number of divisions, which was associated with an eventual failure to divide and telomere shortening. The concept likely came from experiments on cells grown in cultures in which it was observed that cell division goes through a period of rapid division (approximately 60 population doublings), then a slowing of that division, and ultimately no longer dividing at all, but not dying either; thus, it is called replicative senescence (Hayflick and Moorhead, 1961). The telomere shortens, reaching a decisive length beyond which growth is impeded or halted, as retinoblastoma and p53 pathways become activated (Gorbunova et al., 2002). This type of senescence is accompanied by changes in cell form and volume as well as modifications in gene and protein elaboration.

Many investigators thought replicative senescence and the accompanying telomere shortening were much akin to apoptosis (see previous section of this chapter). However, in 1998, Bodnar and colleagues determined that cells that they had manipulated to express telomerase not only continued to robustly divide, but also had elongated telomeres and a longer life span than cells that were cloned not to express telomerase (Bodnar et al., 1998). So, clearly the actions of replicative senescence are more complex than occur in cell termination via apoptosis. Nevertheless, cell division does trigger senescence at some point. Although the jury is still out as to whether replicative senescence contributes to aging, it is known that the breakdown of the molecular mechanisms that restricts cell division can give rise to cancer (Ben-Porath and Weinberg, 2004).

Stress-Induced Senescence?

There are other factors that can cause cells to enter a state that appears to resemble replicative senescence, particularly irradiation and oxidative damage. Triggers that cause this so-called stress-induced senescence were originally thought to shorten telomeres as a result of DNA damage. In fact, the reverse has been demonstrated:

Irradiation and oxidative stress effectively causes DNA damage at a site-specific portion of the telomere sequence (i.e., the 5' site of 5'-GGG-3') (Kawanishi and Oikawa, 2004). However, a study in which normal human fibroblasts, with and without overexpression of the human TERT (hTERT) subunit, were subjected to irradiation and oxidative stresses found that both cell types similarly went into stress-induced senescence (Gorbunova et al., 2002). The investigators concluded that the DNA damage from the irradiation and oxidative stresses actually is the signal that stimulates the premature senescence, promoting telomere shortening. Curiously, fibroblasts that were manipulated to overexpress hTERT had greater resistance to stress-induced apoptosis and necrosis, suggesting that telomerase inhibits cell death, but cannot repair the damaged DNA. Similarly, another group of researchers found that ambient oxygen shortens the lifespan of fetal and adult lung fibroblasts, as evidenced by a ratio of telomere elongation that proportionately had greater decreases when telomerase was exposed to higher (21%) oxygen levels as compared with lower (2% to 5%) levels (Forsyth et al., 2003). While not arresting growth, ongoing exposure to ambient oxygen caused oxidative damage to telomeres; however, in some cell lines, the damage could be reversed by exposure to oxygen-reducing therapies, including antioxidants, corticosteroids, and micronutrients, such as vitamin B_{12} and zinc.

However, other studies have demonstrated that chronic oxidative stress both increases telomere shortening and induces telomeric DNA damage. Oxidative stress may cause these effects by increasing the export of telomerase from the cell nucleus and to mitochondria, which cripples its ability to ameliorate telomere shortening (Ahmed et al., 2008). One study explains: "Cells that are exposed to stress in culture will respond either by entry into senescence, by apoptosis, or by a transient growth arrest; the choice among these three responses depends on the cell type, the type of stress, and the level of stress …" (Ben-Porath and Weinberg, 2004). Yet, the picture becomes more complicated when both telomere- and stress-based mechanisms appear to be inducing senescence, as occurs with oxidative stress. It seems fairly certain at this point that, in fact, both mechanisms contribute to a general stress response in which it is the uncapping of telomeres rather than their overall length that induces senescence (Ben-Porath and Weinberg, 2004). In other words, telomeres are *not* a clock-like mechanism for cell senescence (and thus for a decline in cell replication) or a mechanism to determine our place in the aging process, but rather they are part of a dynamic symphony that we can help conduct by monitoring the extrinsic and stress-related factors to which our bodies are exposed.

Telomeres: Can They Predict Longevity?

Telomere length appears to be genetically inherited. Studies do not agree on the specifics, except that there is a preponderance of evidence that telomere length is paternally inherited (Njajou et al., 2007; Unryn et al., 2005). The rate of telomere shortening slows throughout life. It is quite rapid during *in utero* development and the first decade of life, it slows down or stabilizes in the adult years, which is followed by a more gradual but also more variable telomere decline during old age (Njajou et al., 2007; Unryn et al., 2005). Interestingly, sperm cells show increasing rather than decreasing telomere length with age, so researchers investigated whether the age of

the father can affect the telomere length "in blood" of the offspring; it can (Unryn et al., 2005). Male and female children (125 random subjects) had an average of 22 more base pairs in the DNA nucleotide sequence for each year older their father was at conception, which added on as much as 20% of the length of the average telomere. There was not a significant correlation between maternal age and male or female offspring, although a trend toward the same was noted. The investigators suggest that the positive correlation between paternal age and telomere length of both male and female offspring may reveal a key underlying factor in the variability of telomere length among humans—especially if the effect can be passed on to future generations.

A subsequent study was designed to reassess mean telomere length between parents and children, but used a much larger population of 3,365 Caucasian men and women, aged 18 to 94 years, from four previously published studies: (1) the Offspring of the Framingham Heart Study, (2) the NHLBI Family Heart Study, (3) the Longitudinal Study of Aging Danish Twins, and (4) the U.K. Adult Twin Registry (Kimura et al., 2008). Similarly, this study found telomere length (in leukocytes) of adult offspring to be positively correlated with paternal age at the time of birth of the offspring; however, the finding was significant for males only in two of the subjects. While these investigators stated that the relationship between leukocyte telomere length and human lifespan has been repeatedly investigated and has yielded "conflicting results," they nonetheless state that it "is apparently a biomarker of aging and a forecaster of longevity in humans."

A study of Amish families (356 men, 551 women, aged 18 to 92 years) also observed a significant correlation between paternal mean age at conception and leukocyte telomere length of offspring, which is known to be longer in women than in men and shorter in people with age-related diseases (Njajou et al., 2007; Kimura et al., 2008). In addition, this study found that mean telomere length of leukocytes was positively correlated between the daughter's telomere length and the father's lifespan, but not the mother's (Njajou et al., 2007). The investigators write, "Our observation of a positive correlation between TL [telomere length] and lifespan ($r = 0.30$, $P = 0.1$ in 35 subjects) is unique. *In vitro* studies have revealed an association between TL and cellular lifespan, but no similar study has been carried out in humans to our knowledge." They conclude, "Our findings support the hypothesis that TL [telomere length] may be used as a biomarker of aging and survival." Thus, the researchers felt that their finding of a correlation between the daughter's telomere length and the father's lifespan in 35 subjects supported the use of telomere length as a biomarker of aging. It is possible that the study was even underpowered to draw such a finding, given the size of the subject pool.

Research on *in vivo* human telomeres tends to use white blood cell (WBC), particularly peripheral blood mononuclear cells (PBMC), which will be reviewed in the next section. As discussed in Chapter 1, there are several types of WBCs. These cells can have different mean telomere lengths (e.g., naïve cells have longer telomeres than memory cells), and cells at various stages in the lifecycle have different lengths (e.g., in adults, cells in postmitotic tissues have longer telomeres than those in proliferative tissues) (Aviv and Lansdorp, 2004). In addition, there are various factors that can influence telomere length, from increased telomerase activity that occurs as cells move through the thymus to oxidative damage, age (which exhibits significant

interindividual differences), or disease. If not controlled for, any one of these variations could confound data outcomes of a study comparing telomere length to human lifespan. It would be very valuable to have a biomarker of human aging. However, the fact that age correlates to telomere length does not necessarily make telomere length a biomarker for human longevity, as there is a complex network of actions involved (Aviv and Lansdorp, 2004).

Telomeres: Stress, Disease

Telomere length also has been proposed as a biomarker for disease risk or staging in diseases that are as disparate in their symptomology as dementia (Grodstein et al., 2008) and cardiovascular risk in patients with chronic kidney disease (Tsirpanlis, 2008). In addition, a recent study involving caregivers of Alzheimer's disease patients (compared with age- and gender-matched controls) recognizes the negative impact of chronic stress on T-cell function (as reviewed in Chapter 2), but adds that cytokines (e.g., IL-2, IL-7, and IL-15) and hormones also can positively regulate and increase telomerase activity in T-cells (Damjanovic et al., 2007). In fact, the investigators found basal telomerase activity levels in PBMC (types of WBCs that include monocytes or lymphocytes) and T-cells of caregivers were significantly higher than in controls. In other words, telomerase was doing its job of trying to compensate for the telomere shortening occurring in the caregivers. While caregivers of Alzheimer's patients had significant telomere shortening compared with controls, the rate of attrition could not be determined. As stated, it is attrition or uncapping that seems to be the factor that induces senescence. Damjanovic et al. proposed that a longitudinal trial be run to assess the relationship between telomere shortening in immune cells and chronic stress, as the underlying mechanisms remain unknown. Although these findings demonstrate that chronic stress is associated with altered T-cell function and telomere shortening, again, it cannot be extrapolated that these actions decrease the lifespan of the organism.

However, in 2004, Epel et al. claimed that for the first time they had *in vivo* evidence that psychological stress, based on both the perception and chronicity of the stress, correlated with accelerated telomere shortening, decreased levels of telomerase, and aging (Epel et al., 2004). The investigators concluded that the women (19 caretakers of a healthy child and 39 caretakers of a chronically ill child) who reported the highest levels of perceived stress also had the highest levels of telomere shortening in PBMC. They deduced that the deleterious effects of these highest levels were equivalent to a "decade of additional aging," as compared with women reporting low levels of stress. The researchers acknowledged that they could not control for the possibility that subjects who are psychologically more resistant to stress simply have longer telomere length. A murine study assessing telomere length in animals exposed to *salmonella,* in fact, did find that the mice that had long, as compared with short, WBC telomeres at the beginning of the experiment were relatively disease resistant (Ilmonen et al., 2008).

However, the Epel et al. study also reports that a higher level of oxidative stress was correlated with the increased telomere shortening. As discussed in this chapter and in Chapter 1, glucocorticoids are secreted during stress by the

adrenal glands, and, during chronic stress, the secretion becomes protracted and is detrimental to the body's homeostasis at an undetermined set point. Epel et al. as well as other more recent studies report that increased HPA-related hormones can cause oxidative damage *in vivo* (Zafir and Banu, 2009), which, as discussed, decreases telomerase expression and accelerates telomere shortening. Similarly, a study by Choi and colleagues demonstrated that when human T lymphocytes (i.e., CD4 and CD8 T-cells) are exposed to cortisol, telomerase activity is significantly downregulated, including decreased hTERT (Choi and Fauce, 2008). So, we now appear to have a pretty clear trail: Chronic stress → leads to → increased glucocorticoids → leads to → higher oxidative stress → leads to → telomere shortening and decreased telomerase expression, which may lead to telomere uncapping.

The transition from these facts to the statement that chronically stressed caregivers experience the equivalent of a "decade of additional aging" may be a stretch. In fact, Martin-Ruiz et al. tested the hypothesis that PBMC telomere length is a biomarker of aging in a large (n = 598) population-based followup of the Leiden 85-plus Study (mean baseline age = 89.8 years) and found that baseline telomere length was neither predictive of mortality or of age-related morbidity, including dementia (Martin-Ruiz et al., 2005). Thus, a causal relationship remains questionable and the more important implication may be well expressed as Choi and Fauce assert: "Although our study did not examine the long-term outcome of reduced telomerase, we have shown the converse, namely that enhanced telomerase activity retards telomere loss and extends proliferative potential of virus-specific T-cells" (Choi and Fauce, 2008). In other words, the investigators are saying that the long-term outcome of enhanced telomerase activity is a healthy immune system.

Furthermore, Epel and colleagues based their claims on studies that used averaged telomere shortening across adulthood years, ages 20 to 95. While telomere shortening has been associated with syndromes or conditions with symptoms of premature aging (e.g., dyskeratosis congenita, Werner syndrome, or Alzheimer's disease), as well as with various other disease states (e.g., cancer, neurological, cardiovascular, infectious, as well as chronic stress), there is no solid evidence that telomere shortening *causes* such diseases or expedites the aging process itself. Obviously, telomere shortening is not the only arbitrator of senescence. Thus, diseases associated with premature aging must have additional mechanisms that influence telomerase synthesis and/or coordinate a dynamic confluence of telomere and nontelomere-related actions (Green and Mayeux, 2006). In addition, as already stated, both the protein and DNA components of telomere capping are part of dynamic process. So, particularly in the instance of chronic caregiver stress (particularly if other disease-specific factors are not also in play), it is theoretically possible that the stress could be ameliorated by the resolution of the source of the stress and/or the individual's active participation in relaxation modalities and behaviors, which over time could result in telomere lengthening and increased telomerase expression.

For instance, a study of Caucasian male and female twins demonstrated that telomere length of leukocytes is increased when leisure time is spent in physical activity—possibly by as much as 88 nucleotide repeats (Cherkas et al., 2008). Similarly, a study in *Lancet Oncology* supports our contention that lifestyle changes can impact

telomere viability. The study, which was led by Dean Ornish (see Chapters 4 and 5) and included Epel, Blackburn, and Liu of the 2004 Epel et al. study, showed that three months of intensive lifestyle changes did increase telomerase activity (Ornish et al., 2008). Again, PBMC were the cells assessed; however, this study involved 30 men with low-risk prostate cancer, as determined by biopsy. Appropriately, the investigators described the finding as "a significant association rather than inferring causation." As will be elaborated in the next two chapters, such lifestyle changes in this and other studies also have been associated with decreases in low-density lipoprotein cholesterol, improved cardiovascular health, and diminished psychological distress, to name a few.

THE DISEASES WE GET FROM PROLONGED STRESS

Case Study: Roseto, Pennsylvania

Dr. Stewart Wolf studied the town of Roseto, Pennsylvania, for 28 years. There was a group of Italian immigrants from a small town in southern Italy that had moved to Roseto and, basically, they were in each other's kitchens. They were in each other's pasta and tomato sauce—butter, pasta, wine, and a lot of love. There were intermarriages among the family members, a true modern-day tribe. They lived with the feeling of being more than themselves, a feeling of being connected, a feeling of identity, and with the security that they had a place, an inherent place in life. What Wolf found in Roseto was that the incidence of heart disease and mortality was lower when compared with neighboring towns. But, unfortunately, the Roseto story has a sad ending. During the last 10 years of the study, the young people began moving out. They wanted more in life. They felt there was more out there that they did not have. Technology crept in. Some of the people did well with their lives, and instead of living on Gabriel Avenue in the center of town, they moved to a big house on top of the hill. Soon, the woman who lived in the nice house on top of the hill started complaining that nobody comes around to visit anymore. Feelings of isolation and loneliness crept in. And, with all these changes, the incidence of heart disease rose significantly. But, for so many years, these people had dietary habits that were absolutely horrific by most conventional standards, yet the incidence of myocardial infarction and cardiovascular disease was incredibly low (Wolf, 1992).

An Eastern Perspective of Stress

The emotions we feel, we feel in our bodies. We burn with anger, tremble with fear, and are choked up with sadness. Our stomachs turn with revulsion. Humans experience unpleasant emotions as unpleasant bodily sensations, and thus they feel physically distressed when emotionally distressed. According to Chinese medicine, there is a particular type of energy called shen, which is one's spiritual vitality. It may be recognized by a brilliant glow in the eyes, even of a dying person. It may be absent in a person with a relatively minor illness and is an indication of the patient's will.

Shen resides in various organs, correlating to the primary emotion that one is experiencing. For example, burning with anger is manifested by burning in the liver. When you are feeling grief, you feel it in the lungs, and sadness is felt in the heart.

When you are feeling fear, you feel it in the kidneys. So, for example, when someone is very fearful for a long period of time, often that person may go to the doctor complaining of low back pain, prostate, or menstrual disorders. If you are a physician or healthcare practitioner of any sort, you might want to pick up a book on the five Chinese elements and learn how emotions affect the different organ systems. You can watch for the clinical correlation in your practice. In six months, I think you will be surprised by what you have observed. I should not have been surprised, but I was, which was my scientific skepticism showing.

The effects of stress are numerous: physical, emotional, behavioral, and cognitive. It has become the mode in which a lot of us function. Most of the patients I see, to one degree or another, suffer from stress. It is the sign of an exhausted, unhealthy culture. Repressed emotions are a significant factor in the cause of disease. It is my feeling that we are taught to repress powerful emotions in our culture. Repression of anger, fear, and grief may lead to chronic disease, helplessness, depression, and alexithymia (i.e., the inability to verbalize one's emotions). In the next section, we will discuss memory and trauma, and the engrams that crystallize in our personalities. These engrams are repressed emotions that can cause disease. According to Chinese tradition, when you repress an emotion, it creates an energetic imbalance. This imbalance, over a long period of time, will be translated into functional pathology, like back pain.

Clinical Perspectives on Stress

A fascinating study was published in *Science* in 1983 (Ekman et al., 1983). An actor was instructed to depict various emotions through facial distortions and to poignantly express an emotion: anger, fear, sadness, happiness, surprise, and disgust. He was connected to monitors that measured several physiological parameters. The technician in the other room could guess what emotion he was showing by the physiological response seen on the monitors. For example, if he had a high skin temperature and pulse rate, the technician knew that he was angry. If his skin temperature went up, but his pulse rate was low, he was either fearful or sad, and so on. This landmark study showed a direct physiological correlation to an emotion simply performed by an actor. Recall that magnetic resonance imaging (MRI) of the brain shows that the right prefrontal cortex governs negative feelings (which would manifest on the left side of the face) and that the left prefrontal cortex governs positive emotions (manifesting on the right side of the face) (Jackson et al., 2000). Just as with our actor, something so simple as contracting a few muscles may actually alter your mood.

Approximately 25 years after Ekman's work, *embodiment theory* has brought insight to the mechanisms underpinning the actor's physiological data. Embodiment theory exerts that the relationship between mind and body in processing emotional information is neither a direct nor a linear event. Rather, it is better described as the mind's analysis of internal interactions among perceptual, motor, and body/viscera communications, thus, previous events are reexperienced while simultaneously they are integrated with present happenings (Niedenthal, 2007). Studies have shown a reciprocal relationship between how the body expresses an emotion and how that emotion is interpreted. For instance, if an individual receives positive news while the body is in a posture that is upright/shoulders back, he or she experiences more pride

than if the very same piece of news is delivered while in a slumped posture. Curiously, if an individual is shown a picture of a face expressing one emotion, such as fear, but the picture is depicting a different emotion, such as anger, in the body, there is a rapid (within less than 120 milliseconds) interpretation of the predominate emotion that is biased toward the body expression, not the facial one (Meeren et al., 2005). Conversely, while engaged in imitation of a given emotion, say disgust or joy, the appropriate corresponding muscles of the face will be activated (Niedenthal, 2007).

Thus, the body's posture actually influences the evaluation of emotional content, which means that there is a causal relationship between the body and the mind's interpretation of emotional events (Niedenthal, 2007). Functional MRI studies confirm this view. For example, relevant portions of the brain (the posterior middle temporal gyrus, in this instance) are more highly activated when a happy voice is paired with a happy face than just the voice alone (Johnstone et al., 2006). In the section in this chapter entitled New Findings on Memory and Stress: The Subiculum, we will learn that the subiculum, located in the inferomedial portion of the hippocampal formation, helps to integrate incoming information and memories with the emotional and behavioral contextual memories already acquired that make up our perspective on the world. Speculatively, the subiculum plays a key role in what scientists now call embodiment. But, why would we, in a split second, bias our interpretation of incoming emotional information toward what the physical body has to say rather than the face? While the hippocampus and prefrontal cortex are well-known sites for memory storage (see Chapters 5 and 8), it is suggested that connective tissue, called myofascia, holds emotionally laden memory patterns. Perhaps, the connections that the body provides are grosser, weightier, and are met first. Most humans take care of their need for protection, sustenance, and sleep long before they stop to consider their emotional or spiritual needs. Thus, if we are really to achieve whole health, these latter two aspects must be consciously addressed. However, like our actor in the Ekman study, if we imitate or reenact positive, caring emotions (even from the printed word), it is possible to develop empathy to the other people's concerns. In fact, one author suggests that the mimicking of each others expressions, as an unspoken empathetic facial communication, may be the reason that some couples who have been together for many years begin to physically resemble one another (Niedenthal, 2007). More information on empathy will appear in Chapter 11, when we discuss meditation and brain plasticity (i.e., the ability of the brain to reorganize based on new experiences).

There are various captivating studies showing how different types of stress can be detrimental to the body and how certain personalities are more vulnerable to particular types of stress than others. First, I want briefly to share with you an example of this in the animal world. It comes from the work of Robert Sapolsky, a neuroendocrinologist who is in Kenya researching baboons when he is not teaching at Stanford University (Sapolsky, 1990, 1994). In his study of baboons, Sapolsky initially determined that the dominant male baboon had a resting cortisol that was significantly lower than the subordinate males. Predictably, when the pecking order changed, so did the cortisol levels of the respective baboons.

Continuing his research, Sapolsky uncovered the intriguing fact that there were actually larger discrepancies in the cortisol levels between dominant males with different personality traits than there were between dominants and subordinates. Among

the personality traits that kept dominant males with a healthier cortisol profile were the ability to discriminate between a neutral and threatening action of another baboon and, in the latter situation, to be the one to control the situation by initiating a fight. Dominant baboons that lose a fight and control the situation by displacing their aggression (and perhaps frustration) on to another baboon also have relatively lower cortisol levels. As you may have guessed, the issue of control is the salient one, but it also correlates to issues of security and predictability and, in humans, to social support as well.

A researcher, Eileen Kobasa, studied corporate mentality at a large company that was undergoing a merger and cutback of employees. (Is this not somewhat akin to a group of baboons changing their pecking order?) She looked at stress patterns and found something she called hardiness (Kobasa, 1979, 1983). Similarly, I was the corporate medical director of Marriott International Inc., for 20 years, and there were people in the corporation who we called shock absorbers. We'd say: "Joe can handle that. Give him more work. Pete left? Give it to Joe. George left? Give it to Joe. He can handle it." Joe was our No. 1 shock absorber. Kobasa wanted to know what makes a shock absorber a true shock absorber, not just someone who is repressing his or her feelings. She found that the common factors were the three Cs: commitment, challenge, and control (that is control of oneself, not control of the outside environment). Kobasa writes that "high stress/low illness executives show, by comparison with high stress/high illness executives, more hardiness, that is, [they] have a stronger commitment to self, an attitude of vigorousness toward the environment, a sense of meaningfulness, and an internal locus of control" (Kobasa, 1985). These individuals manifested coherence between their internal and external environments. Remember the phrase "coherence of the internal and external environment," as it will be revisited.

A chronic state of high anxiety and vigilance is destructive to health, in part, as a result of chronic suppression of the immune system. HPA hyperfunction is correlated to heart disease, osteoporosis, depression, and age-related diseases, to name a few (Chrousos, 2000). The work of researchers, such as Soloman, Cohen, Felten, and Ader, described in previous chapters, paved the way for recognition of the interface between disease and various behavioral factors that provoke an altered immune response. In short, the immune system is depressed when one has a prolonged stress response. There are many human studies on bereavement, depression, stress of exams, space flight, sleep deprivation, loneliness, divorce, cancer, the heartbreak of herpes, helplessness, and loneliness all showing the same thing—that each type of stress leaves us more vulnerable to illness (see Biondi, 2001; Calabrese et al., 1987; Friedman et al., 1996; Glaser and Kiecolt-Glaser, 1994; Kiecolt-Glaser et al., 1987, 1988; Kiecolt-Glaser and Glaser, 1991, for reviews). The next section will review a few of these illnesses and their known correlation to stress.

ILLNESS AND STRESS

Heart

There is an increased risk of myocardial ischemia for individuals enduring either acute or chronic stress (Jiang et al., 1996; Krantz et al., 1999; Krantz et al., 2000; O'Connor et al., 2000). Over 20 years ago, researchers showed that acute mental stress in patients with coronary artery disease causes ischemia; the startling part was

that it was symptomatically silent in 83% of their subjects (Rozanski et al., 1988). More recently published studies are detailing stress-induced abnormalities, such as abnormal vasomotor response and blood flow velocity, occurring with patients suffering from coronary artery disease (Kop et al., 2001; Yeung et al., 1991). Stress has also been shown to increase platelet activation, increasing susceptibility to heart attack (Markovitz and Mathews, 1991).

The heart is affected both by stress and by depression (Januzzi et al., 2000). An article in the *Journal of the American Medical Association* (*JAMA*) showed that depression correlates to an independent and higher mortality rate. In a prospective study performed at a cardiac care unit of a university-affiliated hospital, researchers amazingly found that major depression is as much a risk factor for cardia-related mortality as a previous myocardial infarction (MI) (Frasure-Smith et al., 1993). A similar study published in *Lancet* shows that patients with postinfarction depression are at high risk for incomplete recovery in the six-month period following an acute MI compared with those patients who are not suffering from depression (Ladwig et al., 1994). More recently, research confirmed earlier findings of increased risk of mortality for those with postinfarction depression (O'Connor et al., 2000).

As mentioned in our story about the baboons, social stresses contribute to a measurable increase in stress hormones, which are damaging to the cardiovascular system. It is clear that there is a strong correlation between social stresses of various sorts and heart disease in humans. The years of studies and debate (beginning in the 1960s) about type-A personalities and myocardial infarction ended up ferreting out anger and hostility as the two most salient qualities correlated to heart disease. Researchers are indeed still finding solid correlation between anger and heart disease (Moller et al., 1999). However, Levin points out that any personality characteristic may or may not have a detrimental effect, depending upon whether it is adaptive. For example, he and his colleagues found a protective effect for type-A individuals who were not religious (Levin, 2001).

Marital status also has correlates to cardiac events. Women (but not men) in stressful marriages as well as unmarried men both are at greater risk for heart disease (Kumlin et al., 2001; Orth-Gomer et al., 2000). For the first time, hopelessness has been identified as a risk factor for hypertension in men, which we had already gleaned from our rodent studies (Everson et al., 2000).

A physician, Robert Eliot, did some very interesting research on personality and stress. He identified the common, but previously unknown, phenomenon by which individuals have normal blood pressure during an office visit, but highly elevated blood pressure when confronted with normal daily challenges. He calls these people hot reactors (Eliot and Breo, 1989). Eliot, a driven cardiologist until he suffered his own heart attack at the age of 44, asked himself, "Is any of this worth dying for?" His resounding "No!" compelled him to find ways to help others reduce stress and the risk of heart disease. Amazingly, one in five of us seemingly healthy individuals is a hot reactor.

In the late 1960s, Eliot was asked to go to NASA to determine why so many NASA employees were dying suddenly from cardiac arrest. Autopsies showed mysterious microscopic lesions, called contraction band lesions. These lesions are difficult to observe with current heart imaging techniques. Contraction band lesions are tiny ruptures in muscle fibers of the heart that cause microscopic electrical short

circuits, which can lead to ventricular fibrillation and sudden death because the heart muscle is so extensively damaged that it literally dissolves. It took Eliot and his colleagues 16 years to determine that the cause of the contraction band lesions are dose-related, continuously high levels of the catecholamine stress hormones. Contraction band lesions can, in fact, cause death in people whose arteries are patent and healthy looking. Sociologically, Eliot learned that the NASA scientists who died of sudden myocardial infarcts were frequently the highly educated astrophysicists or jet propulsion experts, whose jobs were highly specialized and not transferable to employment anywhere else in the country. Once a rocket program was completed, they were laid off and often forced to take menial jobs, such as pumping gas, in order to help feed their families. The stress was literally fatal (Eliot, 1994). Eliot devoted himself to educating people on how to prevent the development of contraction band lesions.

> A phenomenon called *karoshi*, literally death (*shi*) from overwork (*karo*), is the second leading cause of death (after cancer) in Japan, according to the Japanese Ministry of Health. Karoshi affects managers and supervisors, primarily in their 30s and 40s. These men (it seems it is exclusively men) suddenly die from stroke or heart attack—perhaps from contraction band lesions. They are forced to work 70-hour weeks, week after week, month after month. In addition, they tend to use cigarettes and alcohol to reduce their stress. The labor ministry is now granting compensation to widows of these men, while still denying the existence of karoshi. Sadly, these men simply lose their ability to function, sometimes while at work. If they are lucky enough to survive, they are taken to a specialized medical facility, called a *karoshi unit*, for physical and emotional rehabilitation, where they learn relaxation techniques and self-management skills (see Neunan and Hubbard, 1998, for a review of workplace stress).

The Common Cold

Researchers have confirmed age-old anecdotal reports that increased stress is related to catching the common cold (Cohen and Miller, 2001). One landmark study concludes that "psychological stress was associated in a dose-response manner with an increased risk of acute infectious respiratory illness" (Cohen et al., 1991).

Wound Healing

In a much-publicized study involving caretaker relatives of Alzheimer's patients, it was found that healing from a punch-biopsy wound took significantly longer—an average of nine days longer—than that of matched controls (Kiecolt-Glaser et al., 1995). Caregivers reported greater levels of perceived stress and were producing lower levels of a cytokine known to be important in wound healing than the controls. Subsequent examinations of the topic have sought to understand more fully the neuroendocrine regulation of wound healing and its clinical implications (Marucha et al., 2001).

Exam Stress

Several studies show that examination stress affects students' immune systems, resulting in increased morbidity. Students tend to get upper respiratory tract infections and

bronchitis following the stress of the exam. An important study, which occurred in 1984, involved 75 first-year medical students at The Ohio State University College of Medicine. Blood samples drawn on the first day of final examinations, compared with blood drawn a month prior, revealed declines in NK cell activity levels. Students with higher stress and loneliness scores had statistically significantly lower NK cell activity between blood samples (Kiecolt-Glaser et al., 1984). Other research shows increases in plasma cortisol and salivary norepinephrine as well as elevated antibody titers to various latent herpes viruses (Kiecolt-Glaser and Glaser, 1991; Lacey et al., 2000; McClelland et al., 1985).

Cancer

Research shows a correlation between stress and cancer incidence. There is also an association between factors such as social support, lack of control, and suppression of emotion with cancer progression and possibly survival (see Rosch, 1996; Spiegel, 2000; Turner-Cobb et al., 2001, for reviews). There are various studies on personality characteristics that are predictive of cancer. Among the earliest and better known of these studies is the work of Carolyn Biddell Thomas at Johns Hopkins University. She followed several graduating classes of medical students for up to a 30-year period. Thomas found that those students who later were diagnosed with cancer had reported (at the time of graduation) feeling a lack of a close relationship to parents (especially fathers with sons). This effect persisted even when various known risk factors, such as smoking and drinking, were controlled (Schaffer et al., 1982a; Thomas et al., 1979). Students who scored higher on a test designed to elicit levels of nervous tension and those who had fewer intellectual interests in life also were at a statistically significant greater risk of developing cancer (Schaffer et al., 1982b; Thomas and McCabe, 1980).

Another prospective study showed that women with breast cancer, who had relapses, had a 5.67-fold higher incidence of bereavement or job loss compared with controls who remained in remission (Ramirez et al., 1989). Similarly, a joint study between researchers in Sweden and UCLA's School of Public Health revealed a 5.5-fold increase in colorectal disease for individuals with severe stress in the workplace in the prior 10 years (Courtney et al., 1993). Researchers speculate that the constant stress may lead to changes in lifestyle that increase a variety of risk factors for disease.

In contrast, there are various studies showing that social support improves outlook and health of cancer patients (Bloom and Spiegel, 1984; Butler et al., 1999; Koopman et al. 1998; Schrock et al., 1999; Spiegel, 1999; Spiegel et al., 1999). One study revealed that metastatic breast cancer patients who scored higher on subscales of belonging and tangible social support on a personality inventory had lower salivary cortisol levels, which correlates to greater immune function (Turner-Cobb et al., 2000).

David Spiegel, who is at Stanford University School of Medicine, was the pioneer in finding a link between group therapy for breast cancer patients and stress reduction, improved quality of life, and possibly prolonged survival. His first published piece of research revealed that breast cancer patients who participated in a

weekly support group and used self-hypnosis for pain had a mean survival time of 36.6 months compared with 18.9 months for the control group (Spiegel et al., 1989). His later work delineates issues that undermine a patient's sense of support, which if inadequate, can have both adverse medical and emotional consequences (Spiegel, 1997, 1999; Spiegel et al., 1999). He designed a 12-week, supportive–expressive group for breast cancer patients that could be implemented effectively in community settings. Group participation reduced patients' distress by 40%, as measured by a mood disturbance scale taken before and after the 12-week session (Spiegel et al., 1999). Other studies have supported his results (Blake-Mortimer et al., 1999; Kogon et al., 1997). Similarly, researchers also have found that psychological therapy, relaxation, guided imagery, and biofeedback are correlated with both reduction of anxiety and improved immune parameters (Gruber et al., 1993; Watson et al., 1999).

Bereavement

There are numerous studies that illustrate the correlation between bereavement and a depressed immune system. Many studies show that the bereaved have a poorer lymphocyte response to an immune challenge (Bartrop et al., 1977; Schleifer et al., 1983). Epidemiological research and studies of select populations of bereaved individuals show that the alteration in immune competence actually corresponds to greater illness and even higher mortality rates. Risk of death for individuals with cancer who suffered the loss of a child is greatly increased, as is the death rate of bereaved spouses (bereaved men experience twice the incidence as bereaved women) in the 7- to 12-month period following the bereavement (Levav et al., 2000; Schaefer et al., 1995).

Divorce

The correlation between the stress of separation or divorce and immune suppression is quite well documented and results in even greater health risks than bereavement (see Kiecolt-Glaser and Glaser, 1991, for a review). Once again (like our baboons), the salient issue appears to be one of control. Individuals who initiate the separation or who do not remain attached to their ex-spouse fare better both psychologically and in regard to immune function than those who do not sever attachments (Kiecolt-Glaser et al., 1987; Kiecolt-Glaser et al., 1988).

Physicians Be Warned

Physicians are not immune to the devastating effects of stress. In 2001, *JAMA* published an article advising increased self-awareness of emotions related to the stresses of patient care (Meier et al., 2001). While couched in conservative language, "Our approach is based on the standard medical model of risk factors, signs and symptoms, differential diagnosis, and intervention," the report clearly expounds on issues that may increase "physician distress." Undoubtedly, it was an appropriate admonition. A prior survey on physician burnout indicated that 58% reported being "highly"

emotionally exhausted (Deckard et al., 1994). Women physicians appear to be more at risk of burnout than men (McMurray et al., 2000). Compared with their male counterparts, female physicians reported being more satisfied with their specialty as well as with their patient and colleague relationships ($P < .05$); however, they reported significantly less work control and were paid a mean income about $22,000 less than matched males. Once again, compared with male physicians, women physicians were 1.6 times more likely to state they had burnout ($P < .05$). Strikingly, after working an initial 40 hours, the odds of burnout increased 12 to 15% for each additional 5 hours worked per week ($P < .05$).

Stress and Aging

Not only can we acquire a variety of illnesses from stressing ourselves, we also can accelerate our aging process. Aging, by definition, includes decreased levels of circulating hormones and a decline in immune efficacy—all of which are exacerbated by stress (Friedman et al., 1996; Soloman and Benton, 1994; Soloman and Morley, 2001). One study showed that prolonged cortisol exposure in chronically stressed elderly subjects was correlated to hippocampus memory deficits (Lupien et al., 1998). Various studies support the theory that prolonged stress in the elderly, particularly when they become caregivers, carries with it an increased risk of mortality (Kiecolt-Glaser and Glaser, 1999).

Chronic stress and the overproduction of the inflammatory cytokine IL-6 have been strongly implicated in a host of age-related diseases and conditions. A summary of the conference held at the National Institutes of Health in 1998 and moderated by Dr. Dimitris Papanicolaou described IL-6 as "a potent stimulator of the hypothalamic–pituitary–adrenal axis" and stated that it is secreted during stress (Papanicolaou et al., 1998). A seminal study compared 119 men and women who were primary caregivers for a spouse who suffered dementia (included in the data were individuals who lost their spouse during the study) with 106 men and women who were noncaregivers (Kiecolt-Glaser et al., 2003). Caregivers had an increase in the average rate of IL-6 that was four times the rate of the noncaregivers. The effect persisted for years after the death of the spouse. Based on epidemiological studies on aging, the researchers predicted that the caregivers had a risk of death at around age 75 compared with age 90 for noncaregivers, the primary cause likely being the premature aging of the immune system.

Summary

Stress reduces immune competence, leaving us more susceptible to a host of diseases. Stress accelerates the impact of discordant emotions, pollution, environmental factors (e.g., chemical, electromagnetic), and personal lifestyle factors (e.g., drugs, alcohol, smoking, poor nutritional habits) on our well-being. Response to stress depends on our psychological reaction to it. As with baboons, factors such as outlets for frustration, social support, predictability and warning, a sense of control, or a perception that things are improving all help to reduce stress (Weiss, 1972).

MEMORY AND STRESS

We, cave dwellers in three-piece suits, no longer need a buffalo chasing us (or anything else so dramatic) to activate the stress response. We are fully capable of sitting quietly and arousing a stress response simply with our thoughts and memories. How can it happen that mere memories can arouse stress reactions? Negative emotional thoughts activate the stress system and interact with particular facets of the CNS that are involved in the storage of memories. These memory storage areas are significant to memory retrieval and emotional discernment of any given stress (Chrousos and Gold, 1992). To understand this phenomenon more fully we need to take a look at where and how memories are stored in our brains.

There are various sites in the brain in which short-term memories are stored. The amygdala is important because it is the short-term storage site at which contextual information acquires an emotional significance, such as fear (LeDoux, 1994, 1996). However, the cortex, particularly the prefrontal cortex, also is vital to short-term memory storage. Subjects who are depressed show deficits that include an inability of the brain to turn off the fear messages from the amygdala. This can develop into an inability to turn off the amygdala's fear response to just about anything and may be the physiological setup of the behavioral conditioning that occurs in posttraumatic stress disorder (Yehuda, 2000).

Long-term and declarative memory storage is largely the responsibility of the hippocampus. It is a center of learning as well as memory. The hippocampus creates event-dependent representations of the emotional significance and interpretation of memories, and the amygdala can regulate the encoding and the storage of these memories. However, when a memory is stimulated, the hippocampus can impact the amygdala by the way it has interpreted the event. Phelps aptly states, "Although these are independent memory systems, they act in concert when emotion meets memory" (Phelps, 2004). Information is moved from the various storage sites of short-term memories to the hippocampus for longer-term storage. Eventually, usually after about three years, the hippocampus relinquishes the storage of a memory to the neocortex (LeDoux, 1996). With Alzheimer's disease, patients preserve the oldest memories the longest because the disease is very advanced by the time it affects the neocortex.

A stressful thought is capable of causing the sympathetic nervous system to secrete norepinephrine, activating the amygdala, which in turn activates the stress response. Norepinephrine also can directly trigger the HPA axis and is an important factor in sustaining hypercortisolism during chronic stress (Wong et al., 2000). Furthermore, norepinephrine not only facilitates the movement of negatively charged memories from temporary storage in the amygdala to long-term storage in the hippocampus, but, as depicted in Figure 3.6, it strengthens the stressful memories, as they reside in the hippocampus (Habib et al., 2000). In other words, each time you have a negative experience that is similar to one that is already in storage, the traumatic aspects of the first experience will be reinforced by the subsequent stressful experience. The hippocampus even remembers relationships between stimuli (LeDoux, 1996). Norepinephrine also is the culprit in stress-related impairment of the prefrontal cortex and is associated with a decreased attention span, poor working memory, and a lack of inhibition in behavior (Birnbaum et al., 1999).

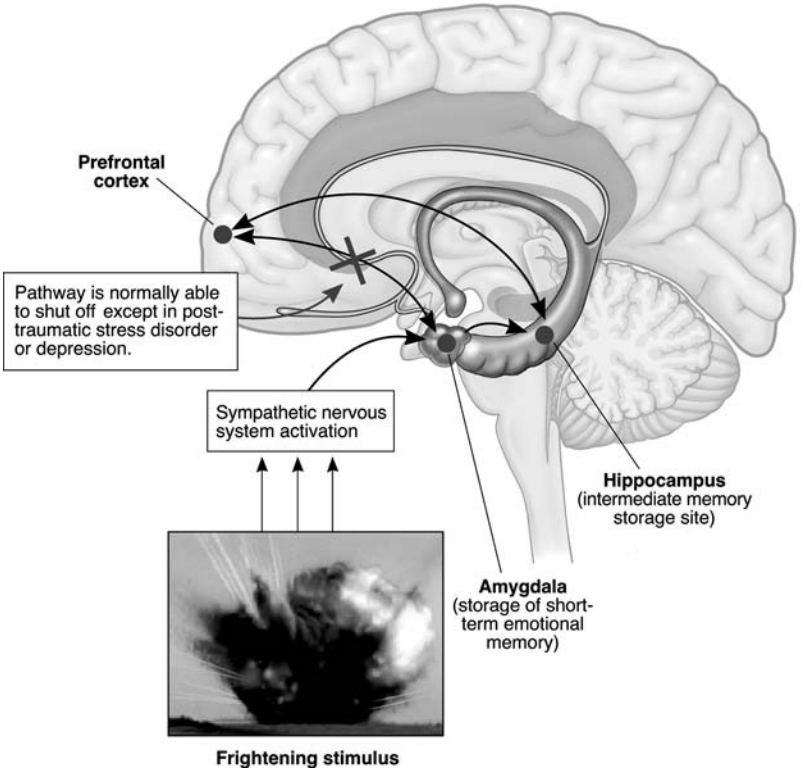

FIGURE 3.6 Diagram of the fear response.

There is a particular part of the amygdala that has β-adrenergic receptors for epinephrine as well as receptors for glucocorticoids. The activation of the epinephrine receptors is crucial to the modulation of the glucocorticoids that infuse the amygdala during stress. It has been shown that blocking the β-adrenergic receptors largely blocks the ability of glucocorticoids to promote memory storage in the hippocampus (Ferry et al., 1999; Quirarte et al., 1997). A small amount of glucocorticoids enhance memory, which is important for recall of dangerous incidents, but too much stress impairs memory.

Chronic stress can be devastating to the brain. As the brain is continuously bathed in cortisol, the hippocampus begins to atrophy, causing plasticity (McEwen, 2000b). Dendrites, which increase the available area for a neuron to receive incoming information, shorten and lose their branches. In addition, neurons in a part of the hippocampus called the dentate gyrus have a suppressed neurogenesis (McEwen, 2000a; Ohl et al., 2000). This reduces the ability of the hippocampus to perform vital functions, including those involving declarative, spatial, and contextual memory. Neurons in the hippocampus actually die because of exposure to glucocorticoids, even in a petri dish (Sapolsky, 1994). The hippocampus is the first part of the brain to be affected by glucocorticoids, which is a staggering thought when you

consider the level of lifetime exposure that many of us experience. Their insidious effects appear to increase with aging (Sapolsky et al., 1986). Estrogen, which ameliorates the deleterious effects of stress, decreases with age (particularly in women), which is of concern because aging brains of individuals who have endured chronic stress would be more affected by memory loss (McEwen, 2000c).

The destructive ramifications of glucocorticoids are reversible if the neurons are injured, but not destroyed. As discussed in the first chapter, neurogenesis can occur in the hippocampus. Therefore, healing can occur. However, recent studies point to a decrease in the size of the hippocampus with chronic stress and a correlated inhibition of hippocampus-associated types of memory (Ohl et al., 2000). One experiment, using high-resolution techniques, showed that the number of days spent in depression corresponds to the amount of hippocampal atrophy. The study was done on formerly depressed individuals so that the affects of acute stress could be eliminated (Sheline et al., 1996). Similarly, possible links with chronic stress in certain forms of dementia, such as Alzheimer's disease, are being researched (Soloman and Morley, 2001).

High levels of glucocorticoids from chronic stress desensitize the brain. Sometimes, especially when I am tired, I put on the news and, inevitably, hear about a disaster that is occurring. Instead of feelings of sorrow or compassion, I just feel numb. When you feel numb from hearing about devastation and you cannot respond, you are putting out a lot of cortisol. You are in a hypervigilant state. You can almost taste the anxiety. If you have experienced losing a loved one, you probably have experienced a feeling akin to having cotton wool in your head, you cannot put thoughts together, and feel dissociated from life events. That is the state that I believe corresponds to hypercortisolism.

Therefore, if you are experiencing stress, you are secreting norepinephrine, which alerts the hippocampus to be incredibly vigilant to stimuli and the recording of memories. The amygdala receives the incoming sensory information and checks in with the hippocampus to see if there is what traditionally has been called an engram, that is, an engrained thought pattern, associated with a traumatic memory to which the hippocampus can respond. The amygdala is scouting around to see if there is a match. It is somewhat like doing an FBI computer search for a fingerprint. If the sensory data is close, you get a hit, and the sympathetic nervous system fastens onto the incoming information. The information locks into the amygdala and hippocampus in such a manner that you carry that engram with you until you find a way or receive help to erase it. Many individuals proceed through life accumulating engrams and, consequently, becoming generally more fearful as they age. It is my contention that engrams can be minimized, or even erased, through deep introspection or professional assistance.

> When my first child was about to be born, I started acting, well, a little strange. I noticed that I was tightly gripping the car steering wheel as I drove the Washington, D.C., beltway, and I started getting feelings of impending doom. I said to myself, "I am an internal medicine resident. Hey, why am I afraid that I am going to die?" In those days, I saw myself as invincible and detached from the struggles of my patients, yet I was preoccupied with dying—from instant to instant. What was my amygdala honing in on? (Nobody knew 20 years ago what the amygdala did. Scientists thought it had something to do with angry animals because when their amygdala was taken out, they calmed down. You could even pet a lion. This is all we knew about the amygdala in

those days.) What was going on? I finally broke down and spoke to a psychiatrist friend of mine: "So, Bruce, I have a young patient who is unreasonably apprehensive about dying." Knowing me well, Bruce responded, "So, what's really the matter, Lenny?" Bruce helped me into a state of deep relaxation. I recognized that my daughter's imminent birth had evoked in me a fear of fatherhood because my father had died when I was young. I was actually programming myself to think that I was supposed to die now because I was to become a father. With Bruce's help, I understood the connection, and it was a remarkable revelation. There was a complete erasure of that particular engram for me, and I felt calm and at peace, joyfully anticipating the birth of my daughter.

Encoded traumatic memories, or engrams, are hard to change. I see them as crystallizing, but not indelible. It is possible to erase traumatic memories or to override them with higher-ordered cognitive functions, closing the loop on the system of traumatic memory (LeDoux, 1996). Understanding how engrams form is key to resolving fears. Fear underlies a good deal of our physiological derailment. The fear may be associated with traumas that go back to a time prior to language acquisition, a time void of the ability to form contextual thoughts. Engrams frequently form during childhood. Regardless, with courage and conscious awareness, erasure of the engram and healing can occur. There are various strategies that aid this process, and they will be discussed thoroughly in the chapter on relaxation therapeutic modalities (Chapter 5). But we cannot emphasize strongly enough that each of us harbors the power and the ability to understand and dissolve our long-crystallized engrams.

NEW FINDINGS ON MEMORY AND STRESS: THE SUBICULUM

In Chapter 1, we introduced you to the subiculum, a structure that runs along the length of the hippocampal formation. Not surprisingly, given its location, recent research indicates that the subiculum plays a role in memory, stress, and likely in the combination of the two experiences. In order to understand the significance of its role, we must first provide you with background information on this impressive little structure.

Communication into and out of the Subiculum

How does information pass through the subiculum? The principal subiculum afferent inputs come from two locations: (1) directly from the entorhinal cortex neurons or (2) from pyramidal neurons in the cornu ammonis 1 (which is Latin for ram's horn or Ammon's horn, reflecting the shape of the hippocampus) (CA1) region or area of the hippocampus, via the hippocampal circuit. They also begin at the entorhinal cortex, as illustrated in Figure 1.2 in Chapter 1 (Stafstrom, 2005). Input to the entorhinal cortex is largely derived from cortical association areas (i.e., not motor or sensory connections, but rather those involving higher processing of information, especially memory, attention, thought, and language) in the frontal, parietal, and temporal cortices. From the entorhinal cortex (via the perforant path), inputs proceed to the dentate granule cells (also called mossy fibers) of the dentate gyrus, which in turn synapse onto CA3 pyramidal cells. CA3 neurons innervate the CA1 cells that synapse onto the pyramidal neurons of the subiculum. Subiculum efferent outputs,

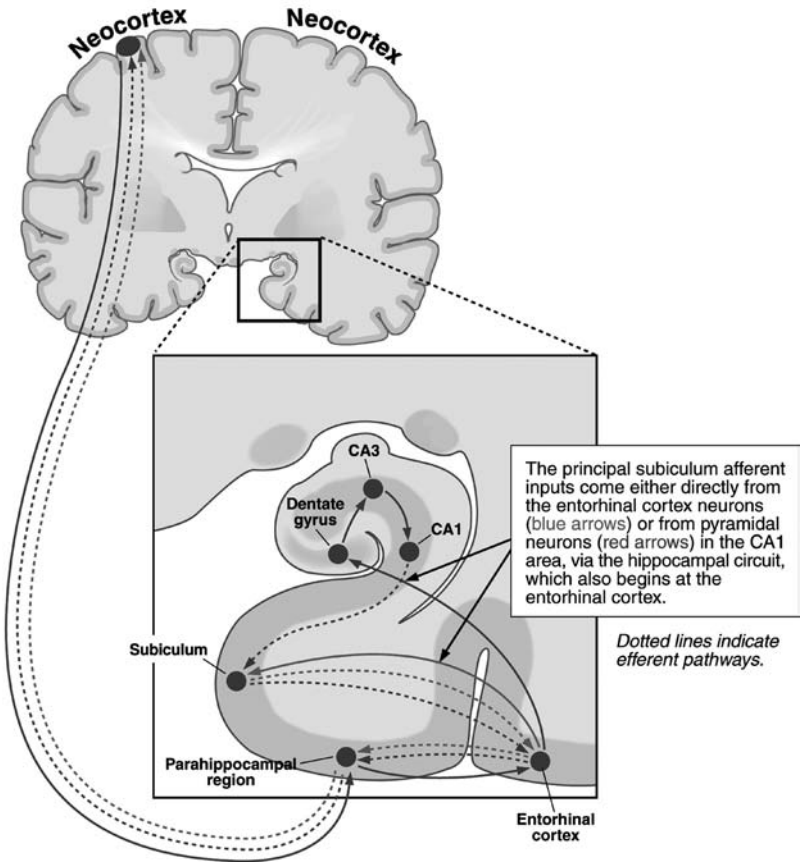

FIGURE 3.7 (See color insert following Page 160.) Afferent and efferent pathways of the subiculum.

again via the entorhinal cortex, return to the association areas, including projections to the orbitofrontal and mesial frontal cortices. This string of connections within the hippocampal formation is referred to as the *hippocampal circuit* (see Figure 3.7) and is strongly involved in the formation of memory, enabling the proper association cortical region to store the specific type of memory (Goldman, 2007). A description of the location of the subiculum is pertinent because it reveals how strategically it is placed to be a conduit and synthesizer of higher processed information.

Subicular pyramidal neurons that project to various cortical and subcortical structures are a major dispatch site for outgoing information. A key tenet of how humans learn and retain information is that the strength of the connection between two neurons can change over time (typically involving proteins and/or neurotransmitters). This is called *synaptic plasticity.* The ability to learn obviously requires the function of memory. The term, *long-term potentiation* (LTP), refers to long-lasting and stronger connections between synapses to the postsynaptic nerve cell, which

is assumed to be the mechanism underlying memory. As one investigator explains, "The formation and recall of sensory, motor, and cognitive representations require coordinated fast communication among multiple cortical areas" (Jinno et al., 2007). Thus, not only do individual synapses strengthen, but in addition, their increased vigor (i.e., synaptic plasticity) fosters a network of connections that permits memory to be multimodal. So, how does this occur?

Synaptic plasticity between the CA1 pyramidal cells and the subiculum in hippocampal slices have a frequency response that is upshifted compared with synaptic plasticity that occurs in pathway between the CA3 and CA1 areas, also called the Shaffer collateral pathway (see Figure 3.7) (Huang and Kandel, 2005). Thus, the synapses are stronger as the information enters the subiculum. The amplification of synaptic plasticity between the CA1 area and the subiculum, again, suggests that the subiculum is a key site in the acquisition of learning and memory.

Place cells are principal neurons within the hippocampal formation that are known to be excitable when an animal is orientating or navigating itself in a given space. In the CA1 and CA3 hippocampal areas, the place cells are pyramidal neurons. While place cells fire particularly strongly in the CA1 area, subicular neurons do not show the same excitability, but rather appear to be modulated by movement (O'Mara, 2005). Studies concur that the hippocampus plays a key role in mapping, spatial, and episodic learning and memory (Smith and Mizumori, 2006). Place cells figure prominently in contextual processing of episodic memories, that is, they contextually record time and place of an incident. Interestingly, hippocampal neurons appear to be able to temporally differentiate contexts, thus differentiating memory episodes (Smith and Mizumori, 2006). Declarative memories, that is, the retention of facts, are either semantic or episodic. Semantic memories are knowledge-based memories that are meaningful without the need for integration of an event and or personal experience to assign meaning, while episodic memories involve personal experiences of time, place, perception, or the emotions involved in such events. Retention and retrieval of the details of autobiographical episodic memories engage the hippocampus, regardless of how long ago they occurred, whereas semantic memories require reinforcement (Moscovitch et al., 2005). As the investigators state, "The function of the hippocampus (and possibly that of related limbic structures) is to help encode, retain, and retrieve *experiences*, no matter how long ago the events comprising the experience occurred, and no matter whether the memories are episodic or spatial" (Moscovitch et al., 2005). It is possible that the dorsal subiculum is instrumental in integrating hippocampal spatial information with cortical movement-related association area inputs from the entire body, possibly including working memory (O'Mara, 2005).

Oscillating Networks and Frequency

Studies recording subicular pyramidal neurons demonstrated that these cells have two distinct, well-known firing patterns: (1) bursting (i.e., bursts of numerous action potentials) or (2) regular firing (i.e., repeated, single action potentials, with prolonged depolarization) (Wozny et al., 2008). Within the subiculum, there are distinct differences between the LTP of bursting and regular firing cells. For instance,

the expression of LTPs in burst firing neurons is presynaptic and does not require postsynaptic calcium, while the expression of LTPs is postsynaptic in regular firing neurons and is calcium-dependent (Wozny et al., 2008). LTPs that are postsynaptic are thought to cause an increase in synaptic transmission and presynaptic LTPs to redistributed existing synaptic efficacy, thus, each firing pattern has a different functional role in processing information from the hippocampus. Furthermore, based on the type of LTP expressed, different subcortical structures are distinctly targeted and, as the synaptic firings leave the subiculum, information will be processed in different ways depending on the nature of that information (Wozny et al., 2008).

Studies on animals show that the dorsal subiculum of adult anesthetized rats have spontaneous firings, predominantly in delta (1 to 4 Hz) and theta (5 to 10 Hz) frequency bands. In this situation, transitions occur between burst firing in the delta frequency and regular firing neurons in the theta frequency that are dependent on prolonged inactivation of sodium channels (Cooper et al., 2005). Prolonged or slow inactivation is not that well understood, but likely regulates pyramidal neuron outputs. The investigators describe it as a "switch" from bursting to regular firing neurons that occurs when the voltage-gated sodium channels are inactivated in a frequency-dependent manner. Thus, output information is not just influenced by the type of LTP expressed (bursting or regular firing), but also may be determined by a switch-like, frequency-dependent mechanism that influences or even regulates network activity of hippocampal and subicular output, including working memory.

Oscillations and Coordination of Multiple Cortical Activity Patterns

Synaptic plasticity and LTPs occur between individual neurons, so how do these individual events then have a networkwide impact on stress, learning, or memory? Resonance frequency signifies the frequency at which a nucleus absorbs or emits radiofrequency, and it is the frequency at which it and its network naturally tend to oscillate. Thus, it is easier to get a molecule to vibrate at its resonant frequencies than at any other. Discussion of the elaboration of network oscillations quickly gets very complicated, so simply put, the resonance properties of neurons inform and interact with network oscillation mechanisms; importantly, network oscillations correlate to various behavioral states (Hu et al., 2002).

Local oscillators of principal cells (in this case, pyramidal cells) are linked to one another via axons, and the discharges of these interlocked cells cause interneurons to create a localized oscillatory system (Traub et al., 1996). These local oscillations foster synaptic plasticity that, in turn, produces oscillations that have a frequency and timing that optimally foster a specific behavior, such as learning/memory (Bibbig et al., 2001). Thus, cortical neurons in humans are part of behavior-dependent, phylogenetically preserved oscillating networks of various frequencies (frequencies are discussed next). These oscillating networks regulate input, facilitate synaptic plasticity and LTPs, and temporally connect neurons for long-term memory and consolidation of experiences (Buzsáki and Draguhn, 2004).

Theta Rhythms in the Hippocampus

In Chapter 1, we discussed the fact that the theta rhythm occurs during that period of deep relaxation between sleep and wake, sometimes referred to as hypnagogia. However, there are events during which theta is not associated with relaxation, but rather with learning, memory, and receiving information. Individual neurons in the hippocampal formation exhibit oscillatory activity within the theta frequency band, firing rhythmically at high rates (Jinno et al., 2007). When subicular pyramidal neurons are at a theta-frequency resonance, they contribute to the network's oscillatory function of communicating cortical association information that occur during theta-related behaviors, such as sensory encoding, exploration, REM (rapid eye movement) sleep, and various cognitive functions. Blocking synaptic transmission with glutamate or γ-aminobutyric acid (GABA) does not arrest the oscillations; however, changing the frequency by hyperpolarizing the oscillating cells or by suppressing the sodium current *will* eliminate them (Glasgow and Chapman, 2007). Therefore, network oscillations are voltage dependent and function separately from synaptic activity. Theta rhythms have been called the fingerprint of the hippocampus, and curiously, neuronal firing that occurs while words are being encoded differs depending on whether the words are later retained or forgotten.

During alert but moving behaviors, theta oscillations predominate, while during alert but quiet behaviors nontheta oscillations predominate (Anderson and O'Mara, 2003). Similarly, input to the hippocampus generally flows freely during theta frequency, and output from the subiculum does not reach the frontal lobes (Johnson, 2006). It is believed that the hippocampus integrates these inputs, creating contextual memory, that is, memory that uses expected, known experiences. Conversely, input to the hippocampus generally is restricted during nontheta frequency; however, output from the subiculum to the frontal lobes and other cortical regions generally flows freely, but it is based on the context memory *acquired during the theta frequency*. The outputs create emotional and behavioral contextual memories as well as associations for memory retrieval (Johnson, 2006). In other words, these outputs are the building blocks of our worldview, our personal reality. Not surprisingly, as we leave the childhood years, we rely increasingly on the nontheta, action mode to process much of the information and experiences encountered.

The brain also can be in an action mode, which would emphasize frontal lobe functions, or a quieter, receptive mode, each state having corresponding neuromodulators. One researcher describes the action and receptive modes, stating, "Their alternation forms a conversation with the environment" (Johnson, 2006). The subiculum regulates the receptive mode (e.g., listening, acquiring new information), which is an input mode, via cholinergic activity during hippocampal theta rhythm, and regulates the action mode (e.g., speaking) by enhancing output to the frontal lobe (Johnson, 2006). As various types of data are processed through the subiculum, tweaking of the theta-frequency resonance comes into play to integrate or synthesize the information, which likely includes disparate types of sensory input. While the frontal lobes are understood to control executive power, the ability to alternate between receptive and action modes likely occurs in the hippocampus. It has been hypothesized that hippocampal theta frequency restricts output at CA1 during the receptive

mode, hindering information from reaching the frontal lobes and, consequently, weakening their executive powers. Conversely, the action mode denotes increased CA1 excitability and communication between the hippocampus and the frontal lobes (Johnson, 2006).

Neuromodulators

So, the subiculum participates in an information processing and regulating network that switches the frequency from delta (or lower) to theta, as needed, to communicate different types of information (e.g., memory, spatial orientation, etc.). These changes, however, are induced by various neuromodulators. For instance, glutamate is a primary neuromodulator of pyramidal cells, fostering communication between various cortical regions. When hippocampal slices are exposed to prolonged low-frequency stimulation in the delta range, the neuromodulator that stimulates the change in synaptic strength is β-adrenergic (epinephrine), which as discussed in Chapter 1, is a key modulator of the sympathetic system and is critical to the fight-or-flight response (Huang and Kandel, 2005). In other words, it takes a neuromodulator with some kick to induce synaptic strengthening in the subiculum. Yet, the output information of LTPs that occurs via the switch-like, frequency-dependent mechanism is stimulated by serotonin, a key modulator of the parasympathetic system (Cooper et al., 2005). Curiously, while it takes a neuromodulator with some kick to enforce synaptic strengthening, it takes a neuromodulator to calm things down for network regulation.

Researchers also have found that long-range, fast-spiking interneurons have specialized functions that these principal pyramidal cells lack. Studies indicate that GABA, the primary inhibitory neurotransmitter, facilitates interneuron communication (Jinno et al., 2007). GABA fosters interregional temporal coordination of oscillatory timing across cortical structures, including areas specific to memory (Jinno et al., 2007). Thus, again, an inhibitory neuromodulator is utilized for network regulation. The resulting effect is that spiked timing of neurons that have these direct, long-range GABA-ergic projections between the hippocampus and cortical areas facilitate network oscillations in portions of the brain whose functions are coupled. In other words, there is a circuit that involves both the oscillating subicular pyramidal neurons and the long-range interneurons that, with the help of GABA (in addition to the underlying work of glutamate), permits the subiculum to be the coordinator of multiple functions of the brain (Jinno et al., 2007). In the healthy brain, this circuit synchronizes both sensory and thought experiences. Thus, you can see, smell, touch the rose, but you can, at the same moment, have a memory related to it—the experiences are temporally integrated.

Cortical Activity Patterns Regulating Memory and Stress

The hippocampus mediates memory consolidation and the neocortex stores declarative memories. Shifts in brain frequency, either increases or decreases, indicate that memory processes are occurring. Research has now shown that semantic memory attainment (i.e., deep encoding tasks) is associated with decreases in beta and alpha frequency bands, while nonsemantic memory achievement (i.e., shallow encoding

tasks) is associated with theta frequency (Hanslmayr et al., 2008). In fact, some investigators think that theta is like a "tag" for short-term memory (Vertes, 2005). When stress disrupts normal memory consolidation (i.e., the ability to preserve the memory of a specific event), memories get stored in the hippocampus or prefrontal cortex in a disorganized manner that makes facts relating to place, context, or time difficult, if not impossible, to retrieve (Bob and Fedor-Freybergh, 2008). The hippocampal-dependent memory impairment stemming from over exposure to cortisol alters plasticity and hinders LTP, induced in part by the amygdala (Kim et al., 2006).

The fact that both the afferent fibers into and the efferent projections out of the subiculum extend widely from or to cortical and subcortical areas, respectively, indicates that what happens in that small structure has far-reaching network influence. Recent work supports the budding theory that the subiculum actually has a dorsal/ventral separation of function, with the dorsal portion involved in processing information that relates not only to memory retrieval, but to spatial orientation/navigation and movement, features already discussed (Esclassan et al., 2009; O'Mara, 2005). Curiously, the ventral sector is implicated in the regulation and inhibition of the HPA axis and fear, via GABA-ergic neurons that inhibit the stress response. Thus, when a lesion is made in the ventral subiculum, the HPA response to stress is ameliorated (Mueller et al., 2004).

It has been proposed that the "pattern of convergence" of the inputs to subicular neurons (i.e., either coming directly from the entorhinal cortex or from CA1 area pyramidal neurons via the hippocampal circuit) influences the location of response (dorsal or ventral) of subicular neurons (O'Mara, 2005). Supporting this hypothesis, researchers demonstrated that in trace conditioning (i.e., conditioning that involves little or no temporal overlap between the conditioning stimulus [e.g., a bell] and the unconditioned stimulus [e.g., food]), the ventral part of the hippocampus is concerned with delayed fear conditioning and anxiety, while the dorsal portion processes temporal and contextual orientation (Esclassan et al., 2009). The subiculum appears to have a dual role in the stress response: on the one hand, it impressively regulates the HPA axis; on the other hand, the CA1–subicular communication can be overwhelmed by systemic stress, particularly to unconditioned stimuli (O'Mara, 2005).

Melatonin, the Subiculum, and Stress

Melatonin receptors, MT_1 and MT_2, are present in the subiculum (Musshoff et al., 2002). Using various molecules that can block these receptors (i.e., antagonists), studies demonstrate that melatonin modulates neuronal excitability by altering the neuronal firing rate in the subiculum and other portions of the hippocampus (Musshoff et al., 2002). *N*-methyl-d-aspartate (NMDA) triggers synaptic plasticity (i.e., memory and learning) by regulating calcium influx and converting electrical neurotransmitters to chemical neurotransmitters when both pre- and postsynaptic cells are active. Thus, NMDA is an excitatory neurotransmitter. In fact, it is considered an "excitotoxin" and is used to destroy brain tissue in animal studies to assess whether there is an associated behavior deficit. There is evidence that synaptic plasticity in the hippocampus may be restricted by melatonin (via the MT_2 receptor),

which subsequently melatonin-induced hyperpolarization, modulates intrinsic excitability, and reduces LTP by NMDA inhibition (Wang et al., 2005). Furthermore, in MT_2 knockout mice (i.e., mice without the MT_2 receptor), theta burst stimulation causes stable, long-term potentiation in the CA1 of hippocampus, demonstrating a role for MT_2 receptors, thus melatonin, in hippocampal synaptic plasticity and memory (Larson et al., 2006). The excitatory/inhibitory actions of these disparate neurotransmitters are simply the body's efforts toward homeostasis.

In Chapter 10 on the pineal gland, we will review the fact that there is an on/off switch in the suprachiasmatic nucleus (SCN) that abruptly changes us humans from being asleep to being awake and visa versa. The SCN is also the location of melatonin synthesis, which is entrained by light and suppressed by the lack of light. With the input of melatonin, the SCN functions via a tick–tock-like oscillating communication between the core and shell of the SCN, between the nuclei on each side, or both. Actually, this oscillating function not only manages the circadian rhythms of the sleep/wake cycle, but also for temperature, blood pressure, immune cell count, and hormones that impact entire body systems, stemming to and from the central and peripheral systems. Melatonin also is key to temporal ordering—without it cognitive, behavioral, and memory processes would not synchronously or sequentially be associated or consolidated (Bob and Fedor-Freybergh, 2008). Research on the pineal gland, melatonin, and the SCN is far more advanced than for the subiculum. In Chapter 10, we will see that, through the elaboration of melatonin, the pineal gland is the transducer of incoming information and the regulator of endogenous hormonal synthesis. So, while melatonin synchronizes the SCN, it also synchronizes the hippocampus and subiculum, largely by contributing to synaptic plasticity, long-term potentiation, and thus to memory (Bob and Fedor-Freybergh, 2008). Melatonin, via activity-dependent changes in synaptic strength, may regulate learning and memory. So, when there is a stressful event, melatonin is the mechanism underlying memory dysfunction. While emotional aspects of an event may be remembered (encoded in the amygdala), nonemotional aspects of the episode may be encoded in the hippocampus in a disorganized fashion, as mentioned, and cannot be retrieved (Bob and Fedor-Freybergh, 2008).

It is our contention that one day, details of the oscillating activity in the subiculum will be further elaborated to reveal that the so-called switch from delta (or lower frequencies) to theta is actually the switch that moves us into relaxation, via melatonin. Already MRI research on the brains of adept meditation practitioners is showing that regular meditation induces synaptic plasticity and synchronous oscillatory activity, much like the subiculum, that can significantly decrease emotionally reactive behavior. Meditation is a trainable skill, which might engage the subiculum in switching to a theta mode in the advance practitioners.

LOOKING AHEAD

Stress management involves looking at our personal needs: support, intimacy, loving, caring, recreation, relaxation, joyful creativity, as well as spiritual concerns. There are many modalities that offer relaxation techniques to reduce the impact of stress. We will review some of these in Chapter 5. The topic of spiritual "needs" is very interesting

because this is the latest area of research in psychoneuroimmunology. There are spiritual leaders, yogis, Tibetan monks, and such who are being studied physiologically. They are wonderful human beings, allowing themselves to be poked, probed, and measured to help us understand the physiological impact on the body of a person who lives a balanced existence. So, rather than calling these individuals the super-healthy, we might refer to them as the super-aware, evidencing the benefits of a tranquil lifestyle. We will closely examine the impact of spiritual awareness and development in the last chapters of the book. For now, we turn to learning about the relaxation system in Chapter 4.

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4 The Relaxation System
Theoretical Construct

The concept of total wellness recognizes that every thought, word, and behavior affects our greater health and well-being. And we, in turn, are affected not only emotionally, but also physically and spiritually.

Greg Anderson
Retired NBA basketball forward/center,
San Antonio Spurs and Atlantic Hawks

INTRODUCTION

We understand that there is darkness because we know light; we understand that there is light because we know darkness. Likewise, we know stress because we have experienced relaxation and vice versa. Hans Selye introduced us to the stress response and Herb Benson to the relaxation response, both of which, essentially, are epidemiological findings of various physiological responses to stressed or relaxed patient populations, respectively. The autonomic nervous system (ANS), our neural or electrical control center for stress and relaxation, has a sympathetic portion that responds to stress and a parasympathetic portion that is concerned with homeostasis or relaxation. The key is balance.

It is universally recognized that there is a stress system, including a set pattern of electrical and hormonal responses, varying in sequence and quality between acute and chronic reactions. We propose that the body not only possesses a stress system, but an endogenous relaxation system as well. Would the body only harbor a hormonal cascade for stress and not for relaxation? Logically, there ought to be a hormonal component to both systems. Herein we present, for the first time, evidence of an endogenous relaxation system that both hormonally counterbalances the stress response and, furthermore, integrates the physical response with mental and emotional input. We call the combination of the endogenous relaxation system and the nonphysical input, the *theta healing system*. The term was coined because the effect naturally occurs when the body is relaxed enough to allow the mind to enter a tranquil state. While we have not been able to determine the sequence of hormonal release, we have been able to substantiate our theory with reports of both hormones that induce tranquility as well as neuropeptides that are associated with deep relaxation.

Imagine with me for a moment that you are outside on a clear evening far from city lights. The sky is a rich, dark indigo blue and the stars are brilliantly luminous. You begin to realize that certain areas of the sky hold pictures with discernable images: a bear, a hunter, a crown. You see the dots of light that make up these images, light in the midst of darkness, but there are no lines to connect them. We have located many

of these dots of light that belong to the theta healing system, and an undeniable picture is beginning to emerge, but not all of the dots have been connected as of yet.

William Devane, who holds a doctorate in pharmacology from the St. Louis University Medical School, made a prodigious discovery while in the midst of completing his doctoral degree. Under the tutelage of cannabinoid researcher Allyn Howlett, Devane found and characterized the cannabinoid tetrahydrocannabinol (THC) receptor, which is the main active ingredient in marijuana, in the rat brain (Devane et al., 1988). The finding compelled Devane (and numerous others around the world) to search for the endogenous ligand for the THC receptor. An intriguing unsubstantiated story surrounds the discovery. Devane traveled to the Sri Aurobindo ashram (an ashram is a place of Hindu meditation and teaching) in India. While meditating there, he had a vision in which he foresaw that he would be the one to discover the hormone that acted on the cannabinoid receptor. The Sanskrit word for bliss is *ananda*, and Devane thought it a fitting name for the putative ligand. He surmised that the new neuropeptide would be an amide; so, long before finding it, he called the molecule anandamide, which means the amide of bliss. Devane subsequently traveled to Hebrew University in Jerusalem because he wanted to work on finding the elusive molecule with Raphael Mechoulam, the researcher who had unraveled the molecular structure of THC in the early 1970s (Mechoulam et al., 1972a, 1972b). Four years later, Devane's vision proved prophetic, and he indeed discovered anandamide. As published in *Science* in 1992, these researchers, along with several other colleagues at Hebrew University, succeeded in extracting anandamide from pig brain tissue (Devane et al., 1992).

The story of Devane's discovery of anandamide, although not verified, is reminiscent of the story of the elucidation of the structure of the benzene ring by Friedrich Kekulé in 1866. The well-known story is that Kekulé was in an extremely relaxed state, gazing into his fireplace, when he had a vision of a snake that curled into itself and bit its own tail. He then realized that the benzene structure was actually a ring, a fact that subsequently was shown to be correct. Kekulé's method of discovery, to many people, would seem unusual or creative; nonetheless, it was an insight that would revolutionize the field of chemistry. How fitting that the discovery of the relaxation neuropeptide anandamide would also occur through a vision in a state of deep relaxation.

So, can we deduce from Devane's finding that our body naturally produces a substance that instills calm? It is a far more coherent and logical theory to presume that we have an equally authoritative, but opposing, physiological system to the stress system than to assume that any relaxation response is a haphazard reaction to our mind and emotions. Evidence for the presence of a relaxation system resides, in part, in the endogenous relaxation hormones, such as anandamide, as they are the biochemical basis for a complex, interactive relaxation network. I believe ongoing scientific research in this field is a new frontier of medical science. An understanding of these transmitters of relaxation is the starting point in the elaboration of a human relaxation system. We present the rudimentary, sometimes speculative, but strongly compelling facts that point to the existence of the theta healing system. The theta healing system involves the integration of the physiological, mental/emotional, and even the spiritual aspects of our being. Furthermore, we define relaxation medicine

as any therapy that triggers the theta healing response and then elaborate some of the key components of the theta healing system. The next chapter provides an extensive review of relaxation medicine modalities. By the end of this book, you will understand how the theta healing system also is a passageway or conduit for experiences of subtle energy, referred to in Eastern systems of medicine as *Qi*.

THE HISTORY

Let us begin with a brief review of the major events in the history of relaxation medicine. Herbert Benson, who is currently an associate professor of medicine at the Mind/Body Medical Institute at Harvard Medical School, has been a pioneer in relaxation research. In the early 1970s, when Benson began studying the physiology of practitioners of transcendental meditation (TM), there were already various relaxation modalities—such as hypnosis, progressive muscle relaxation, autogenic training, and biofeedback (for an extensive review of these techniques, see the respective listing in Chapter 5 on relaxation modalities)—that were quite well known to medical science. The term relaxation response was coined in the late 1960s to refer to the general stress-reducing phenomenon resulting from meditation and similar practices.

Benson constructively exploited the term to get physicians and the general population thinking about the benefits of relaxing. He developed a four-step procedure, which he felt elicited the relaxation response (Benson, 1974, 1975). He learned that meditation and other modalities induced beneficial physiological responses. For example, subjects consumed 17% less oxygen, had lower heart and respiratory rates, and had lower blood pressure than did control subjects. Other researchers soon began confirming the physical and mental benefits of integrating relaxation techniques and conventional medicine. The salient aspects of meditation techniques were lifted and taught to patients in a manner that involved no philosophical conviction or religious belief. One notable example of this trend took place in the late 1970s with the Lifestyle Heart Trials of Dr. Dean Ornish (Ornish et al., 1983). Ornish's programs include diet, exercise, as well as a TM-type meditation. Results of a five-year Lifestyle Heart Trial (1986 to 1992), published in the *Journal of the American Medical Association*, indicate that the experimental group evidenced regression of coronary atherosclerosis at one year and had half the cardiac events of the control group (Ornish et al., 1998).

Researcher Jon Kabat-Zinn did for mindfulness meditation what Herbert Benson had done for TM. He took this, essentially Buddhist, practice and secularized it, providing meditation training for medical patients. Unlike TM, which is based on the repetitive use of a mantra, mindfulness-based meditation involves developing a keen sense of moment-to-moment awareness by observing thoughts and sensations. Kabat-Zinn taught chronic pain patients mindfulness meditation, and a four-year follow-up study indicated good compliance and significant improvement in coping with the pain (Kabat-Zinn et al., 1986). He also worked with patients with anxiety disorders and witnessed significant reduction in anxiety at a one-year follow-up (Kabat-Zinn et al., 1992). Patients learned to identify anxious thoughts as just thoughts rather than "reality." The intent of mindfulness therapy is not simply to obtain coping skills, but

to acquire a practice intended to be a way of life. Both studies indicate that there was an ongoing value to patients in having acquired the meditation skills.

While these therapeutic practices undoubtedly have benefited thousands of people, they have taught us little about the actual physiological events that occur inside the body. For instance, why is it that heart rate or blood pressure is lowered while meditating? Benson, Ornish, and Kabat-Zinn provide us with epidemiological data, that is, they give us broad pieces of information about disease and health for those who meditate as opposed to those who do not. In the previous chapter, we analyzed the major factors involved in the classic stress system. Similarly, we will now propose a system of hormones and neurotransmitters that make up the theta healing system—the first system to be introduced as a coherent system of relaxation.

ENDOGENOUS LIGANDS OF THE RELAXATION RESPONSE

The brain has its own resident neurotransmitters or endogenous ligands. Many endogenous ligands and the precise receptors for them are known; we can assume that there are many yet to be discovered. Neurotransmitters are both the messengers of our nervous system and the chemistry of our emotions. But, what happens when a drug (i.e., an exogenous substance) also fits into a receptor? In some instances, the drug mimics the endogenous ligand; in other instances, it can produce a much stronger or significantly different reaction than the natural chemical.

Drugs can work by blocking actions of neurotransmitters or by interfering with or enhancing the mechanisms associated with the receptor, such as blocking their reuptake and preventing them from doing their job. As discussed in Chapter 1, when a drug or endogenous ligand promotes a known effect, such as relaxation at a benzodiazepine receptor site, it is called an *agonist*. When a drug or endogenous ligand exhibits the ability to block a receptor, it is called an *antagonist*. Antagonists stop the known effects, which, in the case of benzodiazepine receptors, mean not permitting a reduction in anxiety. A third type of effect that may occur is sometimes referred to as a reverse or inverse agonist. This occurs when a drug or endogenous ligand actually produces an outcome that evokes symptoms opposite of those known to occur. What is quite amazing to ponder is that one receptor can interact with all three types of ligands. The communication can become more complex when multiple receptors are activated in response to an agonist. It is not only possible that different agonists for the same receptor elicit diverse magnitudes of response, but that they also select several signaling pathways (Pauwels, 2000).

When it is known that a drug produces a particular effect in humans, researchers go searching to find a receptor into which the drug fits. As soon as the receptor is located, scientists want to know what endogenous ligand fits into the receptor. For many of the hormones, such as anandamide, which are discussed in this chapter, the receptors and endogenous ligands have been located relatively recently. Bear in mind, however, that simply finding a molecule that binds to a known receptor does not establish that there is also a function for that ligand within the human body. As we discussed in the chapter on stress (Chapter 3), oxytocin is a hormone with properties that evoke a response that can be categorized as a relaxation response. In this chapter, we will cover properties of several other hormones that are putatively

relaxation ligands, including benzodiazepines and associated ligands, melatonin, the cannabinoids, and *N,N*-dimethyltryptamine.

THE BENZODIAZEPINES

Overview

We begin our discussion with a review of the benzodiazepines because so many of the relaxation hormones are purported to fit into benzodiazepine receptors or to have actions that mimic the functions of the benzodiazepines. The benzodiazepines are a class of drugs that have had enormous therapeutic impact, particularly for those individuals who have suffered from anxiety or depression. Benzodiazepines also are used for their anticonvulsant, hypnotic, and muscle-relaxing properties, and some of them are used to reduce withdrawal symptoms. They are well-known by their commercial names, such as Valium® (diazepam), Xanax® (alprazolam), Versed® (midazolam), and Librium® (chlordiazepoxide). Librium was the prototype for the benzodiazepine compounds.

The location of the benzodiazepine receptor was unknown for many years, yet it had to exist somewhere in our bodies because pharmaceutical companies had found drugs, which they called benzodiazepines, with distinctive anxiety-reducing therapeutic properties. Sure enough, in 1977, two teams of researchers simultaneously located specific benzodiazepine receptors (Braestrup and Squires, 1977; Mohler and Okada, 1977). The location of the receptor was vital to the development of the drugs. Researchers found that different types of benzodiazepines bind to the receptors with more or less potency, but the fun part was that this indeed correlated to the observed therapeutic strength of the drug—both in animals and in humans.

Each of the scientists who had located the receptor continued their research, postulating that the benzodiazepine receptors existed primarily in the central nervous system (CNS) (Braestrup and Squires, 1978a, 1978b; Mohler and Okada, 1978; Mohler et al., 1978). Since that time, it has been established that benzodiazepine receptors exist in just about every tissue of the body. They are even present on platelets and monocytes (Moingeon et al., 1984; Ruff et al., 1985). Eventually, it was determined that there are actually two types of benzodiazepine receptors. The original receptors found in the CNS currently are referred to as central receptors and the other type as peripheral receptors—a distinction that no longer is applicable in regard to physiological location.

The major difference between the two receptor types is that one potentiates the inhibitory effects of γ-aminobutyric acid (GABA) and the other does not. Recall that GABA is the primary inhibitory neurotransmitter in the CNS. Even before the central receptors were located, scientists knew that the benzodiazepines bind to the GABA receptor complex, specifically the GABA receptors located on the postsynaptic neuron (Haefely et al., 1975). The benzodiazepines increase GABA's ability to inhibit neurotransmission at the postsynaptic binding site by causing the chloride channel to open and allowing chloride to enter the second neuron. This action prevents excessive discharge by reducing the potential excitability of the postsynaptic neuron (Tallman et al., 1980). So, we journey inward and observe the flow of hormonal reactions that contribute to a calming effect.

As mentioned, when scientists know that there is a receptor, they are curious to discover which endogenous ligand also fits into the receptor. In 1983, ligands for both peripheral as well as central benzodiazepine receptors were located. The major ligand for the peripheral receptor is called diazepam-binding inhibitor (DBI) because it displaces drugs that have a high affinity for the receptor (for a review of DBI, see Guidotti et al., 1983; Papadopoulos, 1993). There are numerous ligands that have been shown to bind to the central benzodiazepine receptor. Some of the candidates that we will review include β-carboline, nicotinamide, inosine, hypoxanthine, melatonin, and cannabinoids—all potential relaxation hormones. Curiously, in addition to finding agonists and antagonists, researchers also found ligands that acted like inverse agonists, producing anxiety and convulsions, effects opposite to the benzodiazepines (Braestrup et al., 1983; Prado de Carvalho et al., 1983). Researchers continue to unravel the multifaceted relationship of various ligands to the benzodiazepine receptor and GABA complex, including receptor subunits, and seem to be endlessly discovering new ligands (Haefely et al., 1993; Rothstein et al., 1992; Teuber et al., 1999).

Benzodiazepines and the Immune System

Before surveying the putative endogenous ligands for the benzodiazepine receptor, we want to divert for a moment to share with you a little about the role of benzodiazepines in the immune system. For years, it has been known that benzodiazepine receptors are present on platelets, monocytes, and circulating lymphocytes (Moingeon et al., 1983, 1984; Ruff et al., 1985). Furthermore, a correlation between an imbalance of benzodiazepine receptor binding (both increased and decreased) and various diseases, including liver disease, brain tumor, epilepsy, heart disease, and leukemia, often has been cited (Basile et al., 1991; Ferrarese et al., 1989; Ishiguro et al., 1987; Mazzone et al., 2000; Mullen et al., 1990; Savic et al., 1988; Venturini et al., 1998).

Recall that when we experience stress, the hypothalamic–pituitary–adrenal axis (HPA) is activated. Remember that during an acute stress response, the HPA has mechanisms by which it stimulates the immune response and arouses the immunological memory. This process becomes skewed, if not destructive, when stress is attenuated. There is now evidence that the anxiety-reducing benzodiazepines play a protective role in stress-induced immune suppression, which is at least partly due to suppression of the HPA (Korneyev, 1997; Rocca et al., 1993; Zavala, 1997). Some of this effect may occur as a result of the ability of benzodiazepines to limit the production and release of corticotropin-releasing hormone (CRH) or adrenocorticotropic hormone (ACTH) (Rohrer et al., 1994; Skelton et al., 2000). Epidemiological studies support this theory. For example, research shows that diazepam modifies the immune response of rats during acute and chronic swim stress (Salman et al., 2000). This is a striking role that the benzodiazepines play in modulating the immune system—a role that we will see (later in this chapter) is also played by melatonin, the primary hormone of the pineal gland.

We now proceed with a review of some of the significant ligands, detailing their relationship to the benzodiazepines and their role in the theta healing system.

β-Carboline, Hypoxanthine, Inosine, and Nicotinamide

In 1977, when Dr. Claus Braestrup from Denmark located the benzodiazepine receptor, he did so by locating a compound, called β-carboline-3-carboxylic acid, in the urine of mentally ill patients. It was soon learned that β-carboline inhibits brain benzodiazepine receptors, and there was much speculation that some derivative of it might be an endogenous ligand for the benzodiazepine receptor (Braestrup et al., 1980). β-carboline actually has a higher affinity for the benzodiazepine receptor than do most benzodiazepines. The only problem is that the molecule that Braestrup found was not really an endogenous ligand, but an artifact of the extraction process he used to isolate it. No matter, because it turned out to be profoundly useful anyway, and soon endogenous β-carboline alkaloids were located and found to be benzodiazepine ligands (Rommelspacher et al., 1981). These alkaloids (primarily harmane and norharmane) were also shown to possess antioxidant properties (Tse et al., 1991). At first, β-carboline was recognized as an antagonist (Beer et al., 1978). However, further testing uncovered its reverse agonist properties, that is, β-carboline can in fact produce anxiety and convulsions in animals and humans (Dorow et al., 1983; Duka et al., 1987; File et al., 1985; Rommelspacher et al., 1981). Because β-carboline does not share a recognition site with diazepam, researchers very early on began to speculate that the benzodiazepine receptor must be a multicomponent complex (Hirsch, 1982). In other words, it was clear that the benzodiazepine receptor site permitted numerous, diverse types of actions at its portal.

Three other endogenous ligands for the benzodiazepine receptor were identified in the late 1970s; they are inosine, hypoxanthine, and nicotinamide (Asano and Spector, 1979; Mohler et al., 1979; Skolnick et al., 1978). Like β-carboline, they competitively bind to benzodiazepine sites, but not to other sites with similar actions, such as β-adrenergic or opiate sites. Unlike β-carboline, they bind to the benzodiazepine receptor with a low affinity. Inosine and hypoxanthine increase the inhibiting ability of diazepam, and nicotinamide was shown to potentiate the anticonvulsant properties of barbiturates typically used for epilepsy (Bourgeois et al., 1983; Marangos et al., 1981).

In addition, various other factors have been proposed as endogenous ligands of the benzodiazepine receptor, such as prostaglandins and glutamate (Asano and Ogasawara, 1982; Garthwaite et al., 1988). However, the literature is not consistent on how these various factors function or even whether they actually use the benzodiazepine/GABA receptor complex. And as mentioned, having binding properties does not mean that there is a physiological or therapeutic component. The endogenous benzodiazepine ligands appear to play a role in modulating neuronal actions, and it is my speculation that this may be the clue to their most important function (Skolnick et al., 1978).

MELATONIN

Melatonin (N-acetyl-5-methoxytryptamine) is the principal hormone of the pineal gland, and the pineal is our major transducer of neuroendocrine information. It transforms neural input into endocrine output. The pineal converts light, temperature, and

magnetic environmental information into neuroendocrine signals that influence the body's functioning, often via melatonin.

There is an intriguing piece of research on the benzodiazepines that I happened upon over 20 years ago. The researchers discovered that melatonin not only fits into its own receptor, but also into the benzodiazepine receptor (Marangos et al., 1981). We also know that both receptors are modulated by the GABA receptor (Haefely et al., 1975; Li et al., 2001; Monteleone et al., 1989). There are noteworthy similarities between the physiological characteristics of benzodiazepines and melatonin. For example, melatonin—like the benzodiazepines—reduces anxiety, is an antidepressant, and can aid insomnia. However, melatonin often ameliorates the same symptoms with far fewer side effects (Garfinkel et al., 1999; Raghavendra et al., 2000).

Diazepam can suppress melatonin-binding sites in the brain, an action that can be reversed by exogenous melatonin administration (Atsmon et al., 1996; Raghavendra et al., 2000). Furthermore, when test animals are administered melatonin or a benzodiazepine (temazepam), similar types and levels of effects (e.g., sleep induction) are elicited (Gilbert et al., 1999; Stone et al., 2000). Consequently, melatonin has been used therapeutically to facilitate benzodiazepine discontinuation with insomnia patients and to enhance the reduction of anxiety in the preoperative period (Garfinkel et al., 1999; Naguib and Samarkandi, 1999, 2000). Clearly, there appears to be a reciprocal and interactive nature between these two molecules.

Melatonin and the Immune and Stress Systems

More than 30 years ago, researchers showed that pinealectomized rodents demonstrated a depressed immune response and that melatonin is, in fact, a fundamental modulator of immune responses in normal mammals (Jankovic et al., 1970; Maestroni et al., 1989). We now know that melatonin has prophylactic functions, immune-enhancing properties, and ameliorates the immune-deteriorating effects of stress. It also plays a fundamental role in immune reactions to viral and bacterial infections.

The prophylactic functions of melatonin are particularly effective during times of stress. Immune system suppression in mice (including reduced antibody production, resistance to virus, gastric ulceration, and lower thymus weight) caused by the exogenous administration of the stress hormone corticosterone can actually be reversed by melatonin (Khan et al., 1990; Maestroni et al., 1986, 1987). The benzodiazepine receptors present on monocytes may be the avenue through which melatonin modulates the immune system (Moingeon et al., 1984; Ruff et al., 1985). Research on rodents and restraint stress reveals that the beneficial effect of melatonin is actually not dependent upon a reduction of corticosteroids, but rather occurs via melatonin's immune-enhancing capability (Maestroni and Conti, 1991). This finding is quite stunning, as it implies that melatonin functions as an ongoing immune-system support. Reinforcing this theory are several experiments showing that the antistress effects of melatonin are only seen in mice that have been primed with antigen (Maestroni et al., 1986; Pierpaoli and Maestroni, 1987). Immune-enhancing functions of melatonin also have been observed in patients with various conditions that depress the immune system, including pharmacological therapies that are typically administered for cancer treatment (Maestroni, 1993, 2001).

Just as melatonin boasts discrete immune-enhancing characteristics, certain immune products, such as γ-interferon, colony-stimulating factors, and interleukin-2 (IL-2), are in turn capable of modulating the synthesis of melatonin in the pineal (Maestroni, 1993). Here again we have one of those remarkable instances of systems interacting in a bidirectional manner reminiscent of the systems integration paradigms reviewed in Chapter 2 (Maestroni, 1999).

So, melatonin ends up being a powerful mediator of stress that works in a subtle manner, via the immune system, perhaps synergistically with the benzodiazepines. I think that this fact alone gives us pause to suspect that it plays a part in an endogenous system of relaxation hormones. Research is just beginning to show that the stress-reducing and immune-enhancing effects of melatonin are associated with a reduction in both breast and prostate cancer (see Coker, 1999, for a review). In the chapter on the pineal gland (Chapter 10), you will read more about associations between melatonin and disease.

Melatonin and Meditation

Research performed by the Maharishi University (named after the founder of TM) in Fairfield, Iowa, identifies numerous physiological associations between a regular practice of meditation and health benefits (Alexander et al., 1989). When we meditate, electroencephalogram (EEG) measurements are in the alpha–theta frequency range. The Maharishi University researchers have shown that in long-term practitioners of TM, this pattern persists during sleep (Mason et al., 1997). It is as if meditation has become part of the fabric of the lives of these individuals. In other words, there is a correlation between our physical health and the time we spend in a relaxed state of mind. Such research comes under the category of epidemiological types of studies, such as that promoted by Herb Benson and others (Benson, 1974, 1975). However, intriguingly, some newer research has shown that there is a direct correlation between meditation and our endogenous levels of melatonin.

Melatonin levels have been shown to rise during meditation and are higher in those who regularly meditate (see Figure 4.1). Researchers working with Jon Kabat-Zinn at the Stress Reduction and Relaxation Program in Worcester, Massachusetts, found that eight women who regularly practiced mindfulness meditation (graduates of or teachers at the program) had higher melatonin levels (as measured by urinary 6-sulphatoxymelatonin) than did eight female controls who did not meditate (Massion et al., 1995). Another group of researchers in Australia found that melatonin levels measured at midnight are higher immediately following a period of meditation (Tooley et al., 2000). They used experienced meditators from two different traditions, one that practiced for a half hour and the other for an hour. Both groups had significantly higher melatonin levels following their period of meditation than did the controls.

The Australian researchers reasoned that, from a physiological standpoint, it is unlikely and undesirable that meditation during the day could cause melatonin levels to rise. I think their reasoning is spurious. Although it is speculative because the research has not been performed, I think that it is reasonable to assume that daytime melatonin levels could also rise during meditation. Eyes are closed, the room is

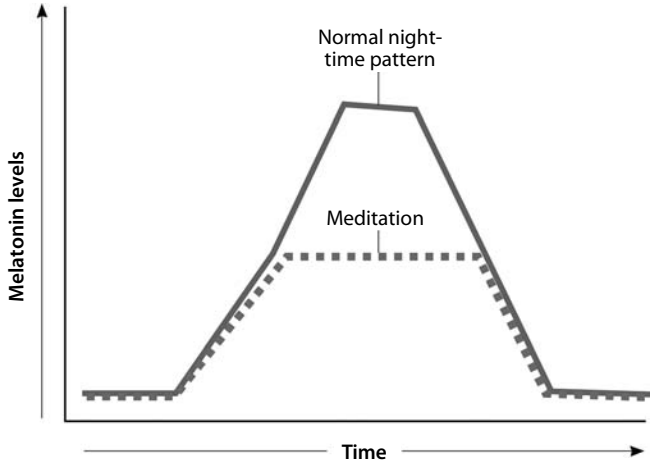

FIGURE 4.1 Meditation and levels of melatonin.

usually darkened, the body begins to relax—it seems feasible that levels could rise. For most meditators, it may only be a modest elevation. However, it is my contention that the slight increase in melatonin begins a hormonal cascade that we have chosen to call the theta healing system. In support of this premise is research that shows that the physiological parameters that occur during meditation are very different from those of subjects during eyes-closed rest (Jevning et al., 1992). So, we have fairly solid evidence that melatonin, one of our putative hormones of healing, is in fact correlated to a primary experience of relaxation.

THE CANNABINOIDS

Cannabinoid Receptors

As reviewed in the beginning of this chapter, William Devane found and characterized a cannabinoid or THC receptor in the rat brain (Devane et al., 1988). A couple of years later, researchers at the National Institute of Mental Health (NIMH) located the rat gene that encodes the THC receptor and soon learned that the receptor influences several major functional areas of the brain, including sensory, motor, cognitive, limbic, and autonomic (Matsuda et al., 1990, 1993). It was also in 1990 that cannabinoid receptors were localized in human brains. The work again occurred at the NIMH and was led by Miles Herkenham and included Ross Johnson and Lawrence Melvin, who had worked with Howlett and Devane on the original receptor study (Herkenham et al., 1990).

Studies have shown (as with the benzodiazepines) that other categories of psychoactive drugs (e.g., opiates) have no effect at these receptor sites. The NIMH researchers determined that cannabinoid receptors are most dense in the hippocampus, the cerebellum, and the outflow areas of the basal ganglia. Conversely, they are

extremely sparse in the lower brainstem areas that control the heart and respiratory function, which may likely be why high doses of THC are not lethal. We will not cover the issue here, but suffice it to say that the relationship is a complex one regarding THC and the respiratory system, with chronic use of marijuana being associated with increased symptoms for asthmatics and injury to the lungs (Calignano et al., 2000; Sarafian et al., 2001).

There are actually three receptor subtypes, designated CB1, CB1A, and CB2, for the cannabinoid receptor (see Axelrod and Felder, 1998; Felder and Glass, 1998; Matsuda, 1997, for reviews). CB1 receptors are largely expressed in the nervous system, and CB2 receptors are expressed in the lymphoid organs (Hajos et al., 2001). Sometimes different endogenous cannabinoid ligands respond in discrete ways to the CB1 and CB2 receptors. For example, anandamide suppresses norepinephrine release at the CB1 receptor, but another endogenous ligand, sn-2 arachidonylglycerol (2-AG), increases the release of norepinephrine (Kurihara et al., 2001). The CB1 receptor can exhibit the same action or function with more than one ligand, such as modulation of food intake (Di Marzo et al., 2001).

There is almost no information available regarding cannabinoid interaction with other receptor types. In 1986, a brief article was published revealing that eight of nine test subjects had elevated melatonin blood levels after smoking a 1% THC cigarette, but not after smoking a tobacco cigarette (Lissoni et al., 1986). Because the ninth subject had a very different profile with inhibition of melatonin, the researchers speculated that THC may regulate the pineal in some way. They called for more research, but it was not forthcoming. More than 10 years later, another study found that in bovine tissue, anandamide decreases 5-HT (a melatonin precursor) receptor binding, but had no effect on benzodiazepine receptor binding (Kimura et al., 1998). These scientists speculated that anandamide might be mediated via the 5-HT receptor. In 2004, we were unable to confirm any of this work, but recent work has demonstrated a role for 5-HT(3) and 5-HT(1A)—receptors in cannabinoid effects involving analgesia and 5-HT(3) in controlling emesis (Braida et al., 2007; Rácz et al., 2008; Xiong et al., 2008).

Cannabinoid Ligands

As of this writing, there are five known endogenous ligands for the cannabinoid receptor. They are referred to as endocannabinoids, as they are endogenous cannabinoids. First, anandamide, as stated, was discovered in 1992. Next, in 1995, 2-AG was identified simultaneously by Mechoulam's group in Israel and by a group in Japan led by Takayuki Sugiura. Then, the endogenous ligand, 2-arachidonoylglycerol ether, which the researchers call noladin ether, was located through the efforts of Mechoulam and colleagues in Israel (Devane et al., 1992; Hanus et al., 2001; Mechoulam et al., 1995; Sugiura et al., 1995). Finally and most recently, virodhamine and N-arachidonoyldopamine have been located, but very little has been published on either of them (Chu et al., 2003; Porter et al., 2002; Walker et al., 2002). Parenthetically, there are also numerous synthetic agonists and novel analogs that have been developed for research purposes (Hanus et al., 1999; Priller et al., 1995;

Suhara et al., 2001). We will not cover these agonists, as our work is directed toward understanding the hormones involved in the theta healing system.

Anandamide

Devane and colleagues in Israel worked for more than two years to obtain the first drop of the purified compound of anandamide (Devane et al., 1992). Devane then returned to the United States and began work at the NIMH with Julius Axelrod who, with Richard Wurtman, had been instrumental in determining the synthesis and catabolism of melatonin in the 1970s (see Chapter 10 on the pineal gland). By 1996, anandamide had been isolated from the human brain, heart, and spleen. Its minor presence in the blood and cerebrospinal fluid (CSF) led researchers to conclude that the majority of its action most likely occurs right where it is synthesized, and this insight opened the door to speculation that anandamide might participate in systems regulation (Felder et al., 1996; Piomelli et al., 2000). Furthermore, anandamide is part of a novel class of lipid neurotransmitters and, like melatonin, is highly lipophilic, which means that it easily passes in and out of cell membranes (Axelrod and Felder, 1998). The lipophilic quality makes it likely that anandamide is a neuromodulator, as it can travel in a retrograde direction as well (Devane and Axelrod, 1994; Di Marzo, 1999; Felder et al., 1996; Piomelli et al., 2000).

Along with other NIMH researchers, Devane and Axelrod continued to learn more about the anandamide ligand, confirming its role as an endogenous THC receptor ligand and establishing its similarities to exogenous THC, its predominantly inhibitory actions, and its therapeutic actions (Crawley et al., 1993; Felder et al., 1993). The therapeutic actions of anandamide include amelioration of pain, nausea produced by chemotherapeutic agents, wasting syndrome (particularly in cancer and AIDS patients), and brain damage (Di Marzo, 1999; Mechoulam, 1999; Walker et al., 1999a, 1999b). Both its ability to modulate neurotransmission and its distinct therapeutic functions are key to our theory of a theta healing system and anandamide's role in modulating the effects of stress.

2-AG

As mentioned previously, 2-AG was identified in 1995 by two research groups who isolated it from rat brain and canine intestine (Mechoulam et al., 1995; Sugiura et al., 1995). The endogenous ligand 2-AG is a unique lipid molecule that has the capability to calm neuronal function via a negative feedback system, inhibiting neurotransmission at cannabinoid receptors (Sugiura and Waku, 2000). This function is crucially important to the relaxation system because sustained activation of neurons, as we discussed in the chapter on stress (Chapter 3), is correlated to cellular exhaustion and apoptosis. The 2-AG ligand is present at 170 to 800 times the concentration of anandamide in the brain, giving rise to claims that it, and not anandamide, is the primary endogenous ligand for the cannabinoid receptor (Stella et al., 1997; Sugiura et al., 1999; Sugiura and Waku, 2000). Some researchers speculate that 2-AG and anandamide perform complementary functions. However, one of its most distinctive

functions, speeding recovery from head injury, may be exclusive to this ligand (Panikashvili et al., 2001).

Noladin Ether

Raphael Mechoulam has been involved in the identification of the three initial endogenous ligands for the cannabinoid receptor. Noladin ether, the most recently identified cannabinoid ligand, was isolated from porcine brain and binds far more strongly to the CB1 than to the CB2 receptor (Hanus et al., 2001). Little is currently known about it, but the researchers speculate that it will have a more narrow profile of activity because of its very weak binding to the CB2 receptor. In a personal communication, Dr. Mechoulam said that a few of his colleagues were rather skeptical about the compound, in part because it is an ether derivative, which is a new, unprecedented type of cannabinoid ligand. Mechoulam said that his collaborator, Lumir Hanus, successfully repeated its identification in the labs at the National Institutes of Health (NIH). "So, it's for real!" he exclaimed. So far, Mechoulam has found that noladin ether in rabbits is an excellent agent for the reduction of intraocular pressure, which is obviously a model for glaucoma, and that research on its effects on the immune system have had very encouraging preliminary results.

Functions of Cannabinoids in the Stress and Immune Systems

The available research on stress and the cannabinoids is seemingly contradictory. On the one hand, there are several reports that exogenous and endogenous cannabinoids activate the HPA axis (Hao et al., 2000; Murphy et al., 1998; Weidenfeld et al., 1994). This sets the stress response in motion, which, as we have emphasized in previous chapters, can be beneficial on a short- but not long-term basis. On the other hand, there are studies indicating that there are various antistress properties of the cannabinoids, such as ameliorating ulcers, possessing antioxidant mechanisms that modulate B-lymphocyte growth and survival, and reducing anxiety and stress-induced pain (Chen and Buck, 2000; Germano et al., 2001; Giuliani et al., 2000; Valverde et al., 2000). One interesting study looked at structural changes in the hippocampus resulting from extended cannabinoid administration. The researchers found that patterns of change looked similar to those seen with toxic damage, but opposite to that observed with chronic stress (Lawston et al., 2000).

When the CB2 receptor was identified, it was located in macrophages of the spleen (which, among other immune functions, stores lymphocytes). Subsequently, researchers learned that the CB2 receptors are expressed in far higher quantities in the peripheral blood mononuclear cells than are the CB1 receptors (Munro et al., 1993; Nong, 2001). The CB2 receptor appears to be a predominantly immune-related receptor. However, CB1 receptors were also identified as being involved in the immune system via functions of the brain (Sinha et al., 1998). While anandamide has been shown to have some immune-modulating factors, such as potentiating the release of IL-6, it is 2-AG that seems to play the larger role in the immune system (Berdyshev et al., 2001; Molina-Holgado et al., 1998). The 2-AG ligand has been shown to inhibit lymphocyte response, the formation of antioxidants, the production

of *in vitro* tumor necrosis factor, and the T- and B-cell response—all depressing the immune system (Gallily et al., 2000; Lee et al., 1995).

One of the main issues limiting the use of exogenous cannabinoids for therapeutic purposes is that they induce psychotropic side effects. Another is that exogenous THC, particularly marijuana, is associated with modulation of the immune system (including T and B lymphocytes, natural killer cells, and macrophages) in such a manner as to depress its ability to fight disease (Klein et al., 2001; Schwarz et al., 1994). While we know that cannabinoids play a role in modulating the immune response, the exact role they play remains unclear, which is evidenced by the contradictory research results that can be found (Klein et al., 2001; Lynn and Herkenham, 1994; Salzet et al., 2000; Zimmer et al., 1999). Endocannabinoids may depress the immune system via their ability to inhibit cytokine secretion or modulate inflammation, although, again, the results are conflicting (Klein et al., 2000, 2001; Salzet et al., 2000). The most promising area for therapeutic use of cannabinoids may well be as analgesics. Endocannabinoids appear to be natural modulators of pain, suppressing pain receptors at the level of the spinal cord and thalamus (Iversen and Chapman, 2002; Walker et al., 2001, 2002). Work needs to be done to cull out the factors of how and when the cannabinoids do and do not support the immune system. There is obviously a missing factor or, more likely, factors. It is possible that one kind of cannabinoid-induced reaction occurs during stress and another when the mind is calm.

Cannabinoids and the Theta Healing System

We now present further compelling medical evidence for the theta healing system. Recall from the prior benzodiazepine discussion that the benzodiazepines increase GABA's ability to inhibit neurotransmission at the postsynaptic binding site by causing the chloride channel to open, thus allowing chloride to enter the second neuron. This effect is typical of the way in which neurons pass on or inhibit a message. However, unlike the benzodiazepines, the cannabinoids work at the site of the presynaptic neurons and their actions involve calcium channels. For over a decade, it has been known that calcium can induce a retrograde inhibition at presynaptic terminals (Llano et al., 1991). The less-conventional retrograde signaling involves a message being returned to the neuron that sent it (i.e., the presynaptic neuron), and the message is: "Stop producing neurotransmitter." Consequently, the presynaptic cell causes an inhibition of the neurotransmitter at the postsynaptic neuron (Vincent and Marty, 1993). It eventually became clear that a receptor on the presynaptic cell, most likely a cannabinoid receptor, is central to the calcium channel-induced inhibition of the neurotransmitter (Sullivan, 1999; Twitchell et al., 1997). Most interestingly, these experiments were performed on the hippocampus, which is not only central to learning and memory, but is also a critical link to the limbic system, our central processing station for emotion.

Researchers named this process of retrograde inhibition of neuron activity depolarization-induced suppression of inhibition (DSI), and they determined that it not only occurs in the hippocampus, but also in the cerebellum (a part of the brain that is central to coordinated movement). They knew the mechanism and the putative receptor, but not the messenger itself. In 2001, two seminal but little-known studies

were published that identified the messenger. First, Rachel Wilson, a graduate student of Rodger Nicoll's at the University of California, San Francisco, determined that endocannabinoids are, in fact, the elusive messenger.

Activated, depolarized hippocampal neurons release the cannabinoids as postsynaptic calcium levels rise. Both the synthesis and the release of the cannabinoids are calcium dependent, which actually had been known for some time (Di Marzo et al., 1994). The cannabinoid receptor CB1 is expressed largely by GABA-mediated neurons. Wilson figured out that when the endocannabinoids, anandamide and 2-AG, are released, they send a message backward, across the synapse, to the presynaptic neuron and tell GABA to slow down (Wilson et al., 2001). It means that the cannabinoids are telling inhibitory neurons to stop inhibiting quite so much, thus, paradoxically, increasing excitation. This finding was simultaneously made by a group in Japan and published in the same month (Ohno-Shosaku et al., 2001). Wilson showed that the process occurred in a very rapid fashion in hippocampal cells, providing discrete evidence of a neuromodulatory role for the cannabinoids. As she states, "Our study represents the first identification of a physiological process mediated by endogenous brain cannabinoids."

The identification of a second physiological function mediated by cannabinoids came right on the heels of Wilson's report. Some researchers in the neurobiology department at Harvard's medical school heard that Wilson had identified the cannabinoids as the messenger in DSI. They concluded that the cannabinoids might well be the elusive retrograde messenger in a process of neuromodulation that is similar to DSI, which they named depolarization-induced suppression of excitatory inputs (DSE). Working with cerebellar Purkinje cells, researchers Antol Kreitzer and Wade Regehr determined that the DSI process of postsynaptic depolarization and the increase of calcium that causes a release of endocannabinoids, via the retrograde mechanism, can also inhibit excitatory neurons, not just the inhibitory ones that Wilson had identified (Kreitzer and Regehr, 2001a). The researchers make the point that the retrograde mechanism is important to both synaptic strength and rapid time scales. Later that year, Kreitzer and Regehr published another study that confirmed Wilson's DSI work, but went on to show that the DSI signaling mechanism functions in the cerebellum in addition to the hippocampus (Kreitzer and Regehr, 2001b). The diffusible and short-lived endocannabinoids, therefore, have a notable role in modulation of both inhibitory and excitatory neuronal communication. In fact, it ends up looking a bit like a mechanism of homeostatic regulation.

The obvious issue, given that DSI and DSE occur in hippocampal tissue, is the role of the cannabinoids in memory and learning, and by extension, of the limbic system in our emotional well-being. It is known that the exogenous cannabinoid marijuana reduces memory and learning functions. Mechoulam and colleagues emphasize that there are significant pharmacological differences between the exogenous and the endogenous cannabinoid ligands (Martin et al., 1999). It is likely that marijuana overwhelms the receptors and results in a physiological picture very different from endocannabinoids, including deficient memory processes. Is it possible that the endocannabinoids, via the subtle DSI and DSE modulations, could actually enhance memory? There is research that points in this direction. By observing a spectrum of behavior in CB1 knock-out mice (i.e., mice without the CB1 receptor), researchers in

Spain determined that activation of the CB1 receptor by endocannabinoids controls memory and learning as well as emotional behavior (Martin et al., 2002). This study is epidemiological evidence for DSI/DSE-facilitated cannabinoid modulation.

There is one other study that we want to share with you because it is related to the hippocampus. A group of scientists at the Institute of Experimental Medicine, which is part of the Hungarian Academy of Sciences, have done work on the cannabinoids (Hajos et al., 2000, 2001). They found that the gamma oscillations of the hippocampus, which are synchronous, could be reduced in amplitude by a particular CB1 receptor agonist (with the lively name of CP 55,940). The reduced amplitude occurs in a DSI/DSE manner, with activation of presynaptic CB1 receptors decreasing calcium-dependent GABA release. So, picture your hippocampus, like the pendulum of a grandfather's clock, perpetually oscillating. A little anandamide comes along and modulates the synchronicity of the hippocampus.

Another thing happens with DSI that we have not spoken about yet. When GABA inhibition is slowed, it causes long-term potentiation of glutamatergic synapses—a condition that facilitates learning. The same Hungarian group performed a similar study on the amygdala and found that the agonists (CP 55,940 plus one called WIN 55,212-2) modulate specific elements of the amygdala nuclei via the same retrograde synaptic signaling action (Katona et al., 2001). These results leave wide open the possibility that the endocannabinoids play a part in expression of emotion and, in particular, might participate in the regulation of fear (perhaps correlated to the reported symptoms of paranoia with some marijuana users). DSI can only occur when there is robust depolarization; therefore, cannabinoids probably are released only when there is a strong external stimulus. What sort of stimuli could cause an increase in the endocannabinoids? It appears that the factors could range from experiences of intense peace to significant fear.

Speculating about the Role of Cannabinoids in the Relaxation Response

So, let us translate all of this theory into the potential practical applications in human functioning. When the synchronous gamma oscillations of the hippocampus are reduced in amplitude by a CB1 receptor agonist, we surmise that the individual is in a state of deep relaxation and that cannabinoids are being secreted. Most people are in alpha and theta when they meditate or engage in any number of other of the modalities you will read about in the next chapter. Therefore, it makes logical sense that the cannabinoid ligands are potentially neuropeptides of deep relaxation. When one goes into a deeply meditative state at the alpha–theta interface, it is possible that anandamide and 2-AG are facilitating that sense of inner calm of which meditators speak. It is a balancing act, not a surging hormonal expression. However, the physiological effect may leave the individual in a state of deep and profound tranquility. The body seems to dissolve, and the mind is balanced. In Chapter 11, we will describe the neurological complement to this hormonal phenomenon. This whole area of research on DSI/DSE receptors, in my opinion, is nothing short of landmark. We now have the first biochemical verification for the physiological underpinnings, not only of relaxation medicine, but also for energy medicine, which will be discussed in Chapter 7.

N,N-DIMETHYLTRYPTAMINE (DMT)

Another possible relaxation hormone is DMT, an endogenous molecule with hallucinogenic properties that is found in the brain, urine, blood, and CSF. It can be actively transported across the blood–brain barrier. The psychedelic effects of DMT were first discovered by Stephen Szára in the mid-1950s when he injected the substance into himself. Dr. Szára started his work in Budapest and then worked at the U.S. National Institute on Drug Abuse in Washington, D.C. In 1972, Julius Axelrod, who was working at the National Institutes of Health, found DMT in human blood. In response to an antipsychedelic sentiment sweeping the country in the late 1960s, Congress passed a law in 1970 that put many of the psychedelic drugs into a legal category that highly restricted their use for research. Concerns of inducing short-term psychosis in normal volunteers, as well as the recreational use and abuse of lysergic acid diethylamide (LSD), conspired to virtually end research on psychedelic substances. This moratorium continued until 1990 when a physician, Rick Strassman, was given the go-ahead to research DMT (Strassman, 2001).

Strassman wanted to understand more about the hallucinogenic nature of DMT. He used intravenous (IV) injections on his volunteers because enzymes called monoamine oxidases (MAOs), which are plentiful in the stomach, quickly break down DMT and prevent its hallucinogenic effects from occurring. The IV route bypasses the MAOs' ability to degrade DMT. DMT is probably diffused via the CSF because MAOs could just as easily break it down in the blood. In general, the volunteers had classic stress responses to DMT (e.g., elevated blood pressure and heartbeat); a few had lasting personal or spiritual insights; while most had little obvious benefit from the DMT. Several subjects described seeing clowns, lights, colors, and encounters with other "beings." While Strassman concluded that DMT is "the spiritual molecule," he unequivocally felt that it had no therapeutic value.

Strassman reasoned that the pineal gland is the endogenous source of DMT because serotonin, a crucial precursor to DMT, has its highest concentrations in the pineal. However, serotonin is also the precursor to melatonin, and I would speculate that DMT is very closely related to melatonin because the functional manifestations have significant similarities. Strassman himself had spent years of his life researching melatonin in his quest for "a biological basis of spiritual experience." He stopped his research on melatonin, feeling it was not the "spiritual molecule," and shifted his focus to carry out the studies on DMT.

β-carboline, as previously discussed, is another possible hormone of relaxation, which also may be synthesized in the pineal and bind to l-tryptophan, a precursor similar to that of melatonin (Fekkes et al., 2001). β-carboline increases melatonin production and inhibits the MAOs from breaking down DMT (Rommelspacher, 1994). β-carboline is the reason why the DMT-active South American drink, called ayahuasca, can be ingested and still be psychoactive. The ayahuasca concoction includes plants that contain β-carboline. Drinking ayahuasca results in psychoactive effects that are of longer duration and milder intensity than those of IV-administered DMT (Riba et al., 2001). The presence of β-carboline in our bodies is important because having a hallucinogenic-type experience while we are engaged in daily functions would be extremely disruptive. In fact, there

has been a whole line of research investigating the relationship between DMT and schizophrenia. One study reported that after, but not before, ingesting ayahuasca, hallucinogenic compounds were detected in the healthy subjects' urine samples. These compounds were the same substances found in urine samples from acutely psychotic patients who were not taking any type of medication (Pomilio et al., 1999).

Most of the hard science is yet to be performed, but it makes medical and intuitive sense to me that there could be a synergistic relationship between DMT, melatonin, and possibly β-carboline, just as there is among other hormones of relaxation. Perhaps, the association is akin to the reciprocal relationship between norepinephrine and epinephrine, which organically resemble one another yet have distinct operational components. Similarly, there is a likeness between the chemical makeup of melatonin and DMT (e.g., they both appear to derive from the tryptamine molecule), and an analysis of their behavioral expression reveals some fascinating associations. However, available published medical studies on Strassman's research indicate that melatonin levels are unaffected by the IV administration of DMT (Strassman and Qualls, 1994). So, if there is a synergistic relationship, it has to be that melatonin reaches a threshold that triggers the synthesis of DMT and not the opposite, and we can be certain that the actions of endogenous DMT are far more moderate than those of any exogenous administration.

It has already been established that melatonin is secreted during meditation, even of the alpha-wave frequency. Could it be that endogenous DMT is released during deep states of meditation? Yes, I think so. The energetic similarities between melatonin and DMT beg the question of why they are found together in the pineal gland. It is my feeling that while melatonin is secreted first, DMT is released in deeper states of meditation, culminating in visions and other experiences that could be interpreted as transcendent or even hallucinogenic.

PLACEBO

We spoke about nocebo and what we call voodoo medicine in Chapter 3. Physicians, family, and friends all have the power to support or seriously hinder the patient in his or her efforts to heal. But, is there really a placebo response? Researchers Hróbjartsson and Gøtzsche from Denmark compared 114 randomized clinical trials that used both a placebo group and an untreated group and found that placebos had no greater an effect than not providing treatment (Hróbjartsson and Gøtzsche, 2001). The researchers made sweeping conclusions about there being no justification for placebos outside of their use for clinical trials. In doing so, they swept under the carpet the fact that they had found a correlation between placebo and pain and that the reviewed studies may have been too few to provide the statistical power to elucidate other such small subgroups. It did make for a dramatic, media-catching publication, however. Paradoxically, I agree, the placebo no longer exists because we now can call it psychoneuroimmunology. PNI research has demonstrated that our minds can alter the actions of hormones and neurotransmitters, potentially evoking physiological responses that result in either immune suppression (nocebo) or healing (placebo).

What are the implications? Physicians hold tremendous power for healing their patients. Helping patients to believe that some type of "healing" can happen in their lives directs the course of both the mental and physical aspects of the disease. Caregivers, families, and friends all hold similar power to support the patient and foster wholeness. Faith represents the ultimate placebo response. A placebo only works if you believe in it. As you will recall from the Introduction to this book, it kept Steve alive for 10 years.

THE THETA HEALING SYSTEM AND LIMBIC THERAPY

The research still needs to be performed, but it is my strong belief that eventually a pattern of hormonal action and interaction (much like the stress system, in which ACTH actually decreases with chronic stress, while cortisol remains elevated) will be established for a relaxation response. The known hormones already point us toward an endogenous relaxation system. I do not know whether you have taken note of it, but there is a distinct interweaving of the hormones of relaxation. The research is not yet all there, as it is for the stress response, but what is known so far is intriguing.

Let us look at how the various hormones of relaxation overlap. First, like lipophilic melatonin and the endogenous cannabinoids, DMT is able to cross the blood–brain barrier. Second, GABA, our body's most powerful inhibitory neurotransmitter, influences and/or is influenced by benzodiazepines, melatonin, and the endogenous cannabinoids. It would make sense that DMT, which potentially guides us to more profound relaxation or spiritual experiences, would not be in this group. Third, the MAOs increase melatonin levels but quickly break down DMT levels (Murphy et al., 1986; Strassman, 2001). Meanwhile, β-carboline increases melatonin production and inhibits the MAOs from breaking down DMT. Then consider that β-carboline, nicotinamide, inosine, hypoxanthine, melatonin, and the cannabinoids all share actions, if not receptors, with the benzodiazepines. Furthermore, anandamide and THC appear to be modulated via a melatonin precursor (5-HT receptor) in some unknown manner. And finally, melatonin and the benzodiazepines seem to have at least somewhat similar mechanisms of action, as they each reduce stress in a manner that is dependent upon bolstering the immune system. We do not yet have the exact hormonal sequence or the corresponding physiological repercussions that have been established for the stress system. We also do not know exactly how the various hormones contribute to the relaxation system, but it seems very likely that each are contributing members of a complex network of relaxation hormones.

Undoubtedly, the most dramatic finding is that the endogenous cannabinoid ligands have the ability to influence the relaxation system in a retrograde manner and modulate both inhibition and excitation. Not only is it the first time that we have had concrete physiological evidence of a putative relaxation hormone, but we also have evidence that the retrograde action drives the body toward an alpha–theta state, which is the frequency of meditation. We have our first confirmed picture of how the neuroendocrine system operates during relaxation. It is my contention that deep relaxation places humans within a "target zone" for the endogenous release of any of the family of neuropeptides of relaxation. The target zone is a state of alpha brain resonance, while the interface, sometimes referred to as a state of hypnagogic

reverie, is the bull's eye of the deep healing process. I like to refer to the interface as limbic therapy because the theta resonance is the "healing zone" in which traumatic and repressed memories can be neutralized.

It is noteworthy, both for DMT and the cannabinoids, that the exogenous versions, for the most part, appear to overwhelm our receptors. In Western society, we want a quick fix. If it doesn't happen immediately and powerfully, it must not be good. If a little is good, a lot must be better. While the neurons that facilitate an endogenous relaxation response can individually fire rapidly, the hormones work in retrograde and localized fashions. Slow and steady is their modus operandi, often taking years to reset our patterns of neuronal firing. Their mode of action reflects what happens to us as we try to live more peaceful lives. Sometimes it can take years to change just one aspect of your personality with which you are not pleased. A whole new set of hormonal reactions must be secreted in situations that previously caused stress, anxiety, fear, or whatever the emotion. Giving the mind and the body more time to practice relaxation, such as periods of meditation, promotes the endogenous learning of how to instigate a cascade of relaxation rather than stress hormones.

We know what chronic stress can do to the body. Have you ever wondered what prolonged relaxation—true, deep relaxation—could do for your physical health? In the chapter on stress (Chapter 3), we discussed the concept of encoded engrams, which stem from repressed or imbalanced emotions that create an energetic imbalance and may result in functional pathology. Encoded trauma and memories that promote fear or reduce our self-worth are engrams, which are very hard to change. They crystallize, but we now have a schematic of the endogenous hormonal pattern that can change them.

Experiences of deep peace, as encountered in the theta range, allow us to release the pain associated with memories (i.e., engrams) in a detached manner and permit us to make life choices with freedom rather than as slaves to our emotions. We see, from a physiological perspective, how it is possible to change one's response to the memories. I call it limbic therapy because the emotion associated with the memory, which has been encoded in the hippocampus, can actually be released. As we train our minds to observe our reactions, we can learn to mitigate our responses to stress. In the next chapter, we will review numerous techniques that can engender this state of relaxation. The braver you are in facing the night, the more stars you will be able to discern, until someday you will note a distinct, discernible pattern in the sky and will experience a peace of which mystics speak, a peace that passes understanding.

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5 The Relaxation System
Therapeutic Modalities

INTRODUCTION

This chapter presents a review of various healing modalities. The National Center for Complementary and Alternative Medicine (NCCAM), which is part of the National Institutes of Health (NIH), designates five major domains of complementary and alternative medical practices: (1) alternative medical systems, (2) mind–body interventions, (3) biologically based treatments, (4) manipulative and body-based methods, and (5) energy therapies. Each of these categories comprises numerous individual systems and treatments for which the NIH provides research support. We have chosen to organize our review by beginning with the mechanical modalities and then continuing to those that are subtler in nature, or the so-called energy therapies. However, note the correlation between our categories and those of the NIH. Techniques of healing that correspond to each category are described in our review. If after perusing the chapter, you may want to research a particular technique, the bibliography provides a variety of resources.

MECHANICAL ENERGY

The following subsections provide some examples of manual medicine or body manipulation.

Osteopathy

Andrew Taylor Still, a physician and an ordained minister, developed the diagnostic and therapeutic techniques of osteopathy after losing three of his children to cerebrospinal meningitis in 1864. Feeling that conventional medical practice was inadequate for the effective treatment of most illnesses, he introduced his concepts of osteopathy 10 years later and opened the first school of osteopathy in 1892 in Kirksville, Missouri. Still based his new methodology on the principle that the body is structurally and functionally one reciprocally interrelated system. Still felt strongly that the body has an inherent ability to repair itself and believed that the healthy body is a homeostitic unit, not a collection of functioning parts. It appears that medical science today is once again coming to terms with that fact.

Still's diagnostic techniques included an evaluation of posture, joint function, the network of myofascial tissue, as well as the respiratory and lymphatic systems. For many years, osteopathy was primarily known for the osteopathic manipulations Still developed to restore the body's homeostasis. The high-velocity, low-frequency

technique (a thrust with an audible "pop") is the best known manipulation and has been sanctioned by chiropractors as well as osteopaths. Other techniques involve palpating the skin or muscle to release muscle spasm or myofascial tissue and to permit lymphatic drainage. However, osteopathy also incorporates a spectrum of therapeutic techniques, including nutrition, physical therapy, and conventional allopathic medical modalities, such as pharmaceuticals and surgery.

A doctor of osteopathy (DO) has full medical licensing and practicing ability in the United States today. Yet, for the last 50 years or so, most DOs have divorced themselves from the classic osteopathic manipulation techniques and have largely practiced conventional medicine. It is notable that although doctor remuneration by insurance companies for the manipulation techniques are currently inadequate, there is a small group of DOs who are bringing back what is nearly a lost art of osteopathic manipulation (Magnus and Gamber, 1997). Osteopathic manipulation, coupled with the broader spectrum of osteopathic care, is currently used for numerous musculoskeletal injuries, childhood otitis media, and various respiratory conditions. Published research largely involves reviews, case studies, description of techniques, or warnings of neurological complications. The few efficacy studies that can be found appear to be quite mixed, but they do seem to be strongest for musculoskeletal conditions (Bronfort et al., 2001b; Jarski et al., 2000; Jermyn, 2001; Pratt-Harrington, 2000; Richards et al., 1999; Tettambel, 2001; Van Buskirk, 1996; Vicenzino et al., 1996; Williams, 1997).

Craniosacral Therapy

The craniosacral system involves the brain, spinal cord, and cerebrospinal fluid (CSF). In the late nineteenth century, William Garner Sutherland, who was a DO, discovered that the joints between skull bones have a small but palpable range of motion, as do all other joints throughout the body. He also discovered that the dural membranes that cover the central nervous system (CNS) have a palpable range of motion. The dura is connected to the sacral and cranial bones, where a similar range of motion can be detected. Furthermore, Sutherland determined that there is a subtle rhythm, which he termed the cranial rhythmic impulse (CRI), that is part of a physiological and mechanistic structure concerned with the body's inherent motility, called the primary respiratory mechanism (PRM). The CRI emanates throughout the body via the fascia (connective tissue) and the CSF (Magoun, 1976). The CRI cannot be detected on cadavers; it is an energetic phenomenon of life. To the skilled professional who can detect the delicate tactile impression, it is the palpable manifestation of the cyclic fluctuation (rather than circulating flow) of the CSF. It is a resonance that spreads throughout the body, meaning that the CRI that can be felt in the head occurs in conjunction with a fluctuation throughout the body. Cranial osteopathy involves gentle manipulation to the cranial area. A book published by the Sutherland Cranial Teaching Foundation explains that the therapeutic manipulations change the rate and amplitude of the fluctuation of the CSF and thus may have profound therapeutic effects (Magoun, 1976). Effects that extend to other parts of the body via the fascia often produce release of suppressed, emotionally laden memories. An energy

transfer is said to occur between the practitioner and the patient, restoring balance to physical or emotional dysfunction.

While researchers found that both the subject's and the practitioner's CRI rhythms are not related to their respective respiratory or heart rates, the CRI rate of a patient, determined by two practitioners, is generally not the same. However, one practitioner can quite consistently palpate a CRI in the same patient at a consistent rate (Hanten et al., 1998). This study, in spite of its curious findings, states that "it is possible that the perception of CSR [craniosacral rhythm] is illusory." Most of the few other scientific studies belay the authors' skeptical attitudes, and much of the literature appears to be unable to validate Sutherland's findings (Green et al., 1999; Rogers et al., 1998). One study supporting the use of craniosacral therapy proposes that the functional origin of CRI is the harmonizing of electrical signals from various body functions, particularly from signals between the sympathetic and parasympathetic systems. This palpable harmonization is an entrainment of multiple biological oscillators. The researchers go on to speculate that skilled practitioners, who are versed with centering techniques, can also entrain their bodies with the patient's, accessing the patient's CRI for therapeutic benefit (McPartland and Mein, 1997).

In the 1970s, John Upledger, DO, created craniosacral therapy based on Sutherland's discoveries. The technique is taught to a variety of healthcare professionals, from medical doctors to those performing various types of bodywork, and requires no medical licensing. Craniosacral therapy is said to be useful for the alleviation of pain from accidents, for stress-related symptoms, for sensory disorders, and to promote overall health.

Sutherland's students established the Cranial Academy to teach, research, and advance the techniques of cranial osteopathy. The academy distinguishes itself by certifying only osteopathic doctors, medical doctors, or doctors of dentistry and by requiring approved courses in cranial osteopathy. Cranial osteopathy is based on the same principles of osteopathic care, which emphasize treating the whole body and not any one symptom.

Chiropractic

Chiropractic treatment is a complementary modality with a long history of prejudice against its use. Daniel David Palmer, who restored hearing to a man by adjusting his thoracic vertebrae, developed the treatment in the 1880s. The profession was essentially legalized in 1987 when an injunction against the American Medical Association (AMA) ordered the AMA to cease its discriminatory practices against chiropractic care, a decision that the Supreme Court let stand in 1990. Chiropractic treatment involves manipulating the spine in order to correct structural imbalances, thus restoring nerve function. A misalignment in the spine is thought to cause a subluxation, which is a slight dislocation of bones within a joint. Currently, the term is used to refer to any type of vertebral blockage, but most often nerve entrapment. Chiropractors believe that such neurophysiological imbalances not only create pain in the body, but also reduce the effective functioning of the body's immune system, leaving the individual more susceptible to disease. Thus, proper alignment of the spine results in optimal health. Currently, chiropractic treatment is prescribed for a

variety of conditions, including injury, asthma, migraine and other forms of headache, and neck or back pain, with results of mixed efficacy (Balon et al., 1998; Bove and Nilsson, 1998; Bronfort et al., 2001a; Conway, 2001; Jordan et al., 1998; Meade et al., 1990; Nelson et al., 1998; Tuchin et al., 2000). While complications may occur (Stevinson et al., 2001), studies generally show distinct improvement for some types of disorders as well as a reduction in overall side effects when compared with the side effects of pharmaceuticals (Freeman and Lawlis, 2001; Nelson et al., 1998).

Massage

Massage, which appears to be as old as recorded history, is a manipulation of the soft tissues (i.e., skin, muscles, and fascia) of the body. The tissues are loosened and proper blood supply restored to these areas, resulting in a state of total body relaxation. Massage is also known to promote venous and lymphatic drainage (Freeman and Lawlis, 2001). In addition, massage benefits the muscles, skeleton, and nervous system. It affects the autonomic nervous system (ANS), which may reduce pain, support the immune system, and reduce anxiety (Chen and Chen, 1998; Cherkin et al., 2001; Zeitlin et al., 2000). Currently there are a variety of massage techniques used, but most originate from the work of Pehr Henrik Ling and his "Swedish massage" therapy. While, historically speaking, massage is considered effective for pain relief and relaxation, it is also known to elicit feelings and memories of emotional trauma. Several bodywork techniques have evolved in recent years that directly address the issue of the mind–body interface in bodywork, acknowledging the correlation between manipulation of the body and the releasing of deep emotions. Rolfing and the Trager method are just two examples of such approaches.

Rolfing®

Rolfing was named after Ida Rolf, who developed the technique of manipulating connective tissue, or fascia, to restore the body to a state of equilibrium in relationship to the Earth's gravitational forces. Her theory is based on the premise that if the body's weight transmission is in a vertical central axis, it will move more efficiently and gracefully. Treatment requires 10 sessions, each scheduled about a week apart. As the body is brought to this vertical position, it is thought that the sensations of pain that occur are the sites at which the body has stored emotional trauma. The practitioner applies sufficient force to stretch and move tissue, liberating old patterns of holding myofascial tissue and releasing emotions. The treatment can release lifelong patterns of tension. The result is often a more balanced manner of moving, which is mirrored by an increase in vitality and emotional well-being (Rolf Institute, 1976).

Trager® Method

Dr. Milton Trager developed the Trager approach to bodywork in 1927. The technique is intended to help the patient release patterns of tension held in the body. The first part of the therapy involves a treatment called *psychosocial integration*, which entails light rhythmic rocking intended to produce a pleasurable experience and meditative state called the *hookup*. The mind–body interface promotes deep relaxation and the release of old pains and improves the patient's flexibility and range

of motion. Unlike Rolfing, the focus of treatment is on the psyche of the individual rather than the physiological changes. The Trager method sees the body as a vehicle to help the psyche achieve a sense of well-being. The second part of treatment, called *mentastics*® or *mental gymnastics*, involves learning exercise movements that can be performed at home. The movements are often free-flowing or dancelike. The exercise has repetitive components that are both physically and mentally relaxing and that reinforce the work of the practitioner (Trager and Hammond, 1987).

CHEMICAL ENERGY

Pharmaceuticals

Whether plant-derived or synthetically manufactured, pharmaceuticals today are central to conventional medical treatment, but that was not always so. Two significant events occurred in the latter half of the nineteenth century that changed the course of medicine. First, the AMA successfully established state licensing laws for physicians, and by 1900 these laws had been enacted in every state. Second, medical education and practice were swept up in scientifically based laboratory research capable of identifying the causes of infectious diseases. Then, in 1910, medicine as we now know it was resolutely established with the publication of a paper, "Medical Education in the United States and Canada," by Abraham Flexner (funded by the Carnegie Foundation) espousing that all U.S. medical schools use a scientific-based curriculum or be shut down. Natural substances (e.g., herbs) continued to be used in a cause-and-effect manner until the 1930s, when researchers synthesized the first pharmaceuticals, which resulted in a process of phasing out natural substances. The entire perspective toward medicine changed from a focus on all aspects of the individual's health (i.e., mind, body, and spirit) to reductionism and a mechanistic view of the human body. While the understanding of microbes and the development of drugs that could expunge diseases that had killed thousands of people through the ages were enormous contributions to the welfare of all people, it unfortunately came at the cost of losing sight of the whole person.

Herbs

Pharmacognosy (i.e., the scientific study of the therapeutic uses of plants) is the predecessor of the modern pharmaceutical industry. Sometimes referred to as phytomedicine, the use of plants to effectively relieve ailments is an integral part of the indigenous cultures in every part of the world (e.g., aspirin, which is derived from the white willow bark [*Salix alba*], was used to relieve pain for many years before its chemical properties were understood). Attempts to assess the active ingredient of an herb are often a challenge. The difficulty arises because the plant itself may have more than one active ingredient, or its efficacy may result from the interaction of various ingredients. For more than 1,500 years, physicians have kept records of plants and their healing properties in books called *Materia Medica*. Today the most accurate and authoritative source of information on medicinal plants, both for efficacy and safety, is *The Complete German Commission E Monographs: Therapeutic*

Guide to Herbal Medicines, which was translated and published in English in 1998 (Blumenthal, 1998).

Supplements

Supplements include vitamins, minerals, amino acids, and enzymes. While the efficacy of some supplements has been scientifically tested, most decisions concerning the use of supplements are made by the consumer. Recommended dietary allowances (RDAs) of vitamins and minerals were first established in the United States in 1943. As a result, fortified foods generally ensured that the vast majority of the population would receive levels of these supplements adequate to avoid diseases, such as rickets. The RDAs originally were intended only to prevent diseases caused by gross deficiency. Health Canada and the Institute of Medicine of the Academy of Science in the United States are currently revising and replacing RDAs with dietary reference intakes (DRIs). The DRIs are based on myriad scientific studies of cellular and molecular functions of vitamins and micronutrients. These new adequacy criteria are intended to help prevent the development of chronic degenerative diseases, such as osteoporosis, which generally take decades to manifest (Institute of Medicine, 1999, 2000; McDermott, 2000; Trumbo et al., 2001). The new levels, however, neither take into account environmental or lifestyle factors that destroy vital nutrients nor consider increasing the levels in the presence of serious disease. Currently, therapeutic use of supplements is not commonly practiced by conventional physicians, which is primarily due to lack of knowledge. Therapeutic prescription of supplements largely remains in the hands of naturopaths, herbalists, or the rare physician who has knowledge of alternative medicine.

LIGHT MODALITIES

The divine light illuminates the soul of man.

Proverbs 20:27

Full-Spectrum and Bright-Light Therapy

Full-spectrum light, like sunlight, includes all wavelengths of light, from infrared to ultraviolet (UV). Bright light includes all but the UV end of the full spectrum. In 1984, Dr. Norman E. Rosenthal first defined the condition of seasonal affective disorder (SAD), and in 1985 he described the first application of bright artificial light for its treatment (Rosenthal et al., 1984, 1985). SAD appears to stem from dysfunction in secretion patterns of melatonin from the pineal gland and from abnormally low wintertime secretions of serotonin in the CNS. Research has shown that patients with SAD have abnormally delayed circadian rhythms (Sack et al., 1990). In other words, they do not secrete melatonin at the appropriate nighttime hour. Bright or full-spectrum light, but not ordinary indoor light, can advance (i.e., shift to an earlier time) the onset of nighttime melatonin production in humans. Recent research has shown that morning light treatment (administered in circadian time at 8.5 hours after

melatonin is endogenously released) is more effective than late morning or evening treatment (Terman et al., 2001). Light therapy appears to be most effective at 10,000 lux for at least 30 minutes, but takes about three weeks for therapeutic benefit to occur (Eastman et al., 1998; Terman et al., 1998). Bulbs producing bright white light, lacking the UV end of the spectrum, are sometimes used as they are just as effective for depression, but they avoid side effects of sunburn and eye damage (Lam et al., 1992). However, some technicians selling therapeutic light products claim that sunburn and eye damage is an issue created by researchers and not a side effect that their clients ever encounter. Technicians receive complaints of glare with bright light, but not with full spectrum.

Other research has indicated that infrared may be just as effective as bright light in the amelioration of SAD (Meesters, 1999). In addition to relieving depression, light therapy reduces symptoms that often accompany SAD, such as poor vision and skin irritation (Terman and Terman, 1999). Light therapy also reduces suicidal ideation, but not symptoms of bulimia nervosa, which is frequently comorbid in women with SAD (Lam et al., 2000, 2001). Michael and Jiuan Su Terman, who have been central to the research on SAD, have shown that in addition to bright light, high-density negative air ionization also appears to be effective for SAD. The National Institute of Mental Health (NIMH) is currently conducting a clinical trial to assess the efficacy of both bright light boxes and negative ion generators. There are various devices that deliver full-spectrum or bright light that are available for home use (Breiling, 1996).

Ultraviolet (UV) Therapy

The UV radiation spectrum is composed of three wavelengths: UVB (the short-wavelength spectrum of 238 to 320 nm, which can cause sunburn), UVA (the long-wavelength spectrum of 320 to 400 nm, which can produce tanning without sunburn), and UVC (a wavelength spectrum of 100 to 280 nm, which is lethal to pathogenic organisms). UV radiation does not penetrate deeply into human tissues, so the risk of injury is confined chiefly to the skin and eyes.

Until the advent of antibiotic drugs, high-mountain sunshine was an accepted and widely used form of therapy for many sufferers of tuberculosis. UV light is the primary mode by which the body receives adequate levels of active vitamin D (unless ingested), which is crucial to calcium absorption. Today UV light therapy is used for patients with atopic dermatitis, psoriasis, scleroderma, and lupus erythematosus (Asawanonda et al., 2000; Krutmann, 2000; Morita et al., 2000; Polderman et al., 2001). Sometimes UV light is used with a drug called psoralen, and the combination of treatments is highly effective for controlling psoriasis. Psoralen enhances sensitivity to light, stops division of diseased cells, binds to DNA in the skin, and sensitizes it to the effects of UVA. Various studies indicate beneficial effects of exposure to UV for the heart, including reduced blood pressure and cholesterol. While too much long-wave UV light can lead to the development of various types of skin cancer, some exposure is crucial to optimal health and should be considered as necessary as any vitamin or mineral that the body requires (Lieberman, 1991). Unfortunately, there is no definitive research on how much exposure is beneficial and how much is harmful.

Color Therapy

Color therapy uses colors to treat both physical and emotional injury. The theory holds that specific colors correlate to a particular disease or condition and can stimulate the sympathetic or parasympathetic nervous system. Colors are also believed to correlate to particular body parts, which are associated with discrete emotions (Lieberman, 1991). Colored light experienced through the retina is believed to induce states of relaxation and release of emotional trauma. Controlled studies have not been performed to the best of our knowledge. Research in the 1970s found correlation between discrete colors and mood (Jacobs and Seuss, 1975; Reeves et al., 1978). Color produces an effect on physiology and, thus, on mood.

Laser Acupuncture

Laser is an acronym for "**l**ight **a**mplification by **s**timulated **e**mission of **r**adiation." For therapeutic use, the laser acupuncture instrument is made up of only one wavelength and consists of helium and neon emissions. Laser acupuncture, also called *cold laser therapy*, is effective for wound healing, ulcers, burns, pain, including pain related to temporomandibular joints (TMJ). In a trial that compared the use of drug therapy (desmopressin) and laser acupuncture for children (n = 10) five years or older with nocturnal enuresis, 75% of the children taking the pharmaceutical were dry at six months, while 65% of those receiving laser acupuncture were dry—offering an effective, noninvasive, alternative therapy (Radmayr et al., 2001). Interestingly, one study showed that laser acupuncture of the left foot at the point called "Bladder 67" activated the cuneus corresponding to Brodmann Area 18, as detected by functional magnetic resonance imaging, while placebo stimulation had no effect (Siedentopf et al., 2002). Further research in this area is warranted and is likely to be promising. Low-energy laser beams are used to stimulate traditional acupuncture points without the use of needles. The laser is applied for 15 to 90 seconds in a continuous or a pulsed manner (Kahn, 1994; Lieberman, 1991).

Auriculotherapy

Auriculotherapy, or auricular therapy, has been used by the Chinese since antiquity and was given new life by a French physician, Paul Nogier, in the late 1940s. The theory holds that points on the ear correlate to various locations throughout the body (Chen, 1993). In its original form, traditional acupuncture needles are applied to the ears to treat pain, dyslexia, and addictions. Many practitioners in Russia apply lasers to acupuncture points on the ear to reduce pain at distal sites. While in some instances needle auricular acupuncture may be more effective than laser, laser has the benefit of being pain free and nontraumatic, particularly for children (Brockhaus and Elger, 1990; Schlager et al., 1998; Wong and Fung, 1991). Most of the research that has been conducted on the technique is related to pain reduction, including pain from cancer (Alimi et al., 2000; King et al., 1990; Lewis et al., 1990). Auriculotherapy may be effective for SAD as well as stress syndrome.

SOUND MODALITIES

Oh the sisters of mercy they are not departed or gone.
They were waiting for me when I thought that I just can't go on.
They brought me their comfort and later they brought me their song.
I hope you run into them, you who've been traveling so long.

Leonard Cohen, 1975

Music Therapy

Music therapy uses music in a controlled manner to influence the well-being of an individual with physiological or emotional symptoms. Music therapy facilitates the release of repressed emotions, reduces stress, relieves depression, and promotes relaxation. The music is selected to match the patient's state of mind and is then slowly altered to encourage a pleasurable or harmonious state of mind. Music preferred by the patient is considered the least therapeutic because it matches their depressed mood. This finding correlates with studies showing that musical entrainment is the most effective type of music therapy (see Musical Entrainment below). Studies, which sometimes involve both imagery and music therapy, have shown a decrease in blood pressure, cortisol, mood disturbance, and anxiety and pain in critical care patients, and in patients before and after surgery (McKinney et al., 1997; Salmore and Nelson, 2000; White, 2000). Similarly, sound therapy, which reproduces sounds from nature and simply singing release emotion and reduce anxiety (Dewhurst-Maddock, 1993).

Musical Entrainment

Musical entrainment occurs when two rhythms become perfectly coupled and attain the same frequency. Therapeutic musical entrainment uses music to bring the patient from one state to another healthier state. As with music therapy, the patients begin by listening to music that somewhat matches their current state of mind. The music is then altered to bring the individual to a more positive state. Some studies have shown increased β-endorphin levels resulting from musical entrainment (McKinney et al., 1997). Entrainment tapes have been used for developmental delays, stroke, anxiety, pain, and neurological problems after trauma.

Medical Resonance Therapy Music®

Medical Resonance Therapy Music was developed from the music of classical composer Peter Hübner (spelled Huebner in some English translations). Hübner has studied the natural laws of musical harmony as a means to promote healing by employing the inherent structures of music. He uses subliminal sounds to create electroencephalogram (EEG) patterns to evoke healing of a particular disease. The concept is based on the work of Pythagoras, the fifth-century BCE philosopher, astronomer, physician, mathematician, and musicologist. Pythagoras postulated that the laws of the harmony of music are the same as those governing humans. Hübner writes,

"Pythagoras believed very strongly that all natural systems could be shown to be interrelated in some concordant fashion, and coined the term *cosmos* to describe this orderly and harmonious universe." Pythagoras wrote about the ability of music to foster health by activating an internal, natural law of harmony. Hübner's intention is to tap the healing potential inherent in the naturally structured laws of music. Based on this theory, Hübner has composed various pieces of music to treat specific types of mental or physical conditions. He explains, "It is not the music that achieves the medical result—it is the inaudible harmonic information within what we can call music, which by its resonance, helps the listener's biological system." The effects of Medical Resonance Therapy Music are believed to result from a precise harmony that resonates inside the human, traveling from the ears to the brain, and then to the various organs. The harmony residing in the music is thought to stimulate a resetting of the body's biological order, gradually bringing the entire body toward rejuvenation as well as preventing potential illness. In Germany, there are approximately 22,000 pharmacies, each called a Digital Pharmacy®, that distribute listening plans structured for various medical conditions. Hübner's Medical Resonance Therapy Music is currently widely used in Germany. There is no research that has been performed on the modality, except for that produced by the company.

Bioacoustics

Bioacoustics, or life sounds, is a technique that employs both music therapy and biofeedback. It is akin to music therapy in that specific combinations of low-frequency sounds are used, and it is similar to biofeedback in that these sounds are used to elicit specific biological and emotional responses. Sharry Edwards, M.Ed., developed the technique in 1982. Voice spectral analysis is used diagnostically to interpret the complicated frequency interactions within the body and then to determine the physical and emotional health of the individual. Computerized analysis of the voice displays a graphic representation of the individual's strengths and weaknesses.

Bioacoustics claims that vocal analysis can identify the frequency equivalents of structural components, muscles, as well as biochemical and nutrient compounds within the body. Ideally, there is coherence to one's voice patterns; however, disease is said to result when the patterns become discordant.

Edwards explains that every portion of the body has a Frequency Equivalent™ that can be mathematically calculated. She asserts, "This provides the foundation for the concept that the body's ability to heal itself can originate as frequency interactions between the molecular signals of the entire body" (Bioacoustics: www.soundhealthinc.com). Sound formula sets or sound presentation, which are constructed specifically for each individual (often with the aid of objective data, such as blood pressure or temperature readings), help the patient overcome problem areas and promote structural and emotional integrity. The patient listens to the sounds in a planned sequence of sessions, which continues at home. The goal of treatment is to entrain brain waves to healthier patterns. Edwards writes: "The principles of BioAcoustics originate with the idea that the brain perceives and generates impulse patterns that can be measured as brain wave frequencies, which in turn are delivered

to the body by way of nerve pathways. The theory incorporates the assumption that these frequency impulses serve as directives that sustain structural integrity and emotional equilibrium. When these patterns are disrupted, the body seeks to reveal the imbalance by manifesting symptoms that are interpreted as disease and stress" (Edwards, 1997).

Bioacoustics is used for nutritional diagnosis, sports injury, pain management, structural problems, and tissue regeneration. Sharry Edwards and her company, Sound Health Inc., have carried out the only studies performed to date.

Tomatis

A French physician, Albert Tomatis, developed sound therapy to correct learning dysfunction and improve self-esteem. The Tomatis method is based on his finding that the larynx can emit only the harmonics that the ear can hear or, as Tomatis was fond of saying, "The voice reproduces only what the ear hears." This fact was proven at the Sorbonne in 1957 and is now known as the Tomatis effect. Tomatis determined that when we sing or speak, we condition our own ears to our own sound. He developed devices that allowed the subject to become unconsciously conditioned to new sound. Tomatis also felt that the ears affected the entire body. He claimed that when one speaks, sound "inundates and spreads over your whole body … syllable waves break and wash over you. Your entire body surface marks their progress through the skin's sensitivity, as if controlled by a keyboard that is receptive to acoustic touch." Billie Thompson, Ph.D., a certified consultant in the Tomatis method and translator of two of his books, describes the technique as "a sound stimulation and educational intervention that improves listening, language, motivation, attention, learning, self image, awareness, musical ability and appreciation, audio–vocal control, and posture" (Tomatis, 1996). The Tomatis method claims to correct poor functioning, but not organic or neural damage. Correcting the ear to function properly allows it to hear wanted sounds and to shut out unwanted sounds and to produce a more pleasant quality of voice. Tomatis felt that an impaired ability to listen can result in low self-esteem as well as slowed learning and intellectual development.

The Tomatis method is carried out in three phases. The first phase teaches a patient to hear the entire harmonic range of sound information being presented, which teaches him or her to listen better in general. The second phase allows a period of time to integrate the fuller spectrum of sound that the individual can now hear. The final phase teaches the patient to articulate the new sounds that he or she can now hear, producing a voice (speaking or singing) that is more pleasant to hear (Tomatis, 1996).

BIOELECTROMAGNETIC MODALITIES

If humans are indeed wired for God, and benefit from spirituality in the same important ways that every generation past and every generation to come will, how are we to incorporate this new fact of physiology?

Dr. Herbert Benson, 1996

We will first offer a brief review of the mechanics of electromagnetic properties to aid the understanding of the various modalities that follow. Inside the nucleus of an atom there are protons, which are positively charged, and neutrons, which are neutral and have no charge. Electrons, which are negatively charged, rotate in defined orbits around the nucleus. For a current of electricity to occur, there must be an imbalance in the ratio of electrons to protons, usually as a result of a surplus of electrons. An electrical pathway, or current, is created by a flow of electrons to a source that is positively charged (i.e., something that has a predominance of protons). This pathway is called an electrical circuit. Electrical interactions and circuits are important to our health at both the cellular and the systems levels. This is where scientific Western and Eastern theories of human physiology unmistakably intersect.

Magnetism is largely known by its properties. Its main property is a polarity that can be arranged to either attract or repel two objects. Furthermore, where there is electricity, there is magnetism, and where there is magnetism, there is electricity. Typically, when a magnetic field comes in contact with an electrical pathway, it produces an electrical current. Conversely, when there is an electrical current flowing, it will have a magnetic field that is at a 90° angle to the current. The interaction of the electrical and magnetic energy results in a 360° electromagnetic field that continues traveling (theoretically infinitely) outward, in concentric circles, at the speed of light. The track of the outward expansion is typically lost as it integrates with other more powerful electromagnetic fields. The electromagnetic field is called a force field. The earth's electromagnetic field is an example of a force field. Various human-made objects from medical devices to power lines also generate electromagnetic fields. These localized, human-made fields are generally stronger than the Earth's electromagnetic field.

Electromagnetic fields oscillate at various frequencies. Light, as we know it, is the only frequency at which electromagnetic fields are visible to most humans. Examples of low-frequency fields (i.e., oscillating at slower speeds) are radio frequency and microwave and examples of high-frequency fields (i.e., oscillating at faster speeds) are x-rays and gamma rays. Low-frequency fields are associated with levels of radiation that generally are considered safer for humans than high-frequency fields. However, recent research has brought into question the safety of long-term exposure to low-frequency fields, such as those produced by power lines. What makes electromagnetic fields harmful to humans is ionization, a process that occurs when frequencies of electromagnetic energy are high enough to dislodge electrons from the atom. Persistent exposure of the body to ionization, especially in the higher frequency range, might cause cancer or other serious diseases because of the generation of free radicals, which are harmful to tissues. So-called nonionizing forms of electromagnetic energy are used for medical purposes. As indicated below, some of them involve heat (see the section on thermal therapies) and some do not (see the section on nonthermal therapies).

Many biomedical researchers now agree that electromagnetic fields surround the body. Electricity flows through the body, with the heart registering the highest electrical activity (emitting 2.5 watts, it produces 40 to 60 times more electricity than the brain). The electrical activity of the heart and nervous system interacts and affects one

another. The heart is correlated with the highest magnetic activity as well. According to what we have just reviewed, the heart must then also be a force field that extends out in a theoretically infinite manner. In fact, this is not only true for the heart, but also for the electromagnetic field of the entire body. There are other endogenous electromagnetic fields. The brain is the next strongest, but it is hundreds of times weaker than the heart. Research performed at the Lawrence Berkeley National Laboratory (University of California/Berkeley) reveals that pulsed, nonthermal electromagnetic fields influence calcium-channel regulation and signaling in lymphocytes. The impact varies depending on lymphocyte cell status and electromagnetic field intensity (Walleczek, 1992; Walleczek and Budinger, 1992). Researchers are investigating the interaction between exogenous and endogenous electromagnetic fields and the use of various frequencies of electromagnetic energy as a conduit for healing. It is likely that some energy fields are so subtle that they cannot be detected by existing instrumentation, yet they may have significant long-term effects on our health.

Two individuals who have produced landmark work in the field of electromagnetic energy warrant mentioning. The first is Dr. Robert O. Becker, an orthopedic surgeon whose renowned work on the regeneration of salamander limbs forms the basis for the use of electromagnetic energy in medicine today (Becker and Selden, 1985). Becker determined that when a limb is amputated from a salamander, there is continuous electric current that flows from the CNS to the injured limb. He made the fascinating discovery that the electric potential at the site of injury was briefly positive, reversed to a negative potential, and then gradually drifted back to a neutral potential by the time the limb was healed. Becker demonstrated that the human body has a positive polarity that travels along a central axis and a negative polarity along the periphery. He showed that humans likewise exhibit a positive polarity at the site of injury, until healing occurs. Curiously, he also determined that there is a reversal of polarity during altered states, such as anesthesia and hypnosis. Becker, along with Charles Andrew Loockerman Bassett (Columbia University), established the efficacy of using electromagnetic energy for bone healing, and today they are credited with the widespread application of electromagnetic devices for bone healing, particularly for refractory nonunion fractures. Becker also developed theories of the analgesic effects of acupuncture, cellular capacitors for the body's electrical system, and the deleterious effects of electrical forces on the environment.

Another individual who has produced landmark work in the field of electromagnetic energy is Dr. Björn Nordenström, formerly director of diagnostic radiology at the Karolinska Institute in Stockholm, Sweden (unquestionably, the most prestigious position attainable in Sweden in this field). Nordenström is a brilliant man who developed balloon catheterization and needle biopsy techniques and who chaired the Nobel Prize committee that selects laureates for medicine. Since the mid-1960s, Nordenström has developed a revolutionary theory of the human body's electrical system and has illustrated the existence of biologically closed electrical circuits (BCEC) within the body (see Figure 5.1). While I find that there is much validity to his theory and believe that it will be an integral part of medicine of the future, his work has neither been widely accepted by the medical establishment nor replicated by colleagues. Nordenström, unfortunately, is one of those unique pioneers who is well ahead of his time and whose work is far too cutting edge for most researchers to

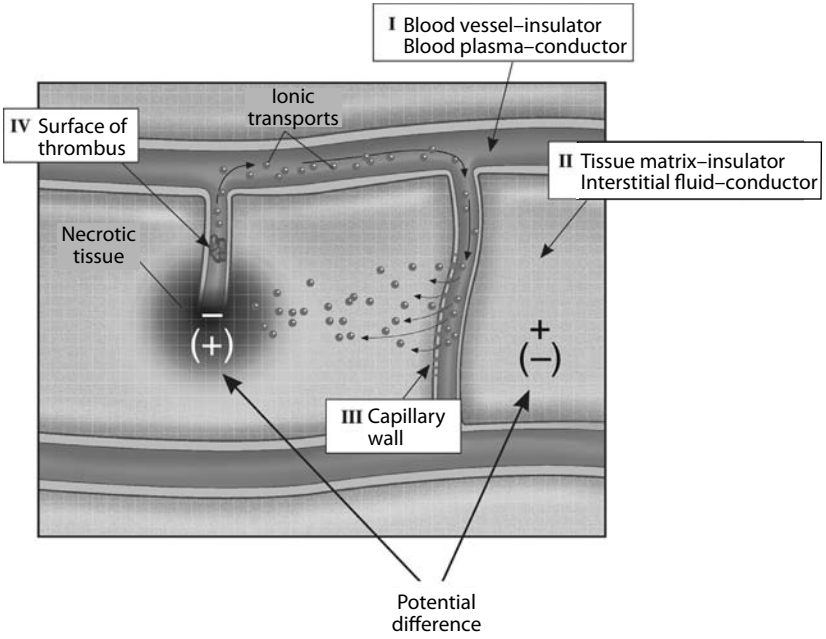


FIGURE 5.1 Biologically closed electrical circuits. (From Nordenström, B.W., *Exploring BCEC Systems*, Nordic Medical Publications, Stockholm, Sweden, 1998. With permission.)

put their time into exploring its validity. I am concerned that this milestone in electromagnetic research might be lost or obscured although I understand that clinical applications of his work have been developed in China.

Out of sheer curiosity as to why some malignant tumors had coronas around them, Nordenström discovered that when the body is injured, there is a fluctuation between positive and negative electrical currents until healing occurs. He learned that our veins and arteries act like insulated cables (whose electrical resistance is 200 times that of blood), which effectively shuttle products between injured and healthy cells. Blood and interstitial fluid serve as conductors, and enzymes serve as electrodes, which provides you all the necessary components of an electrical circuit. White blood cells (WBCs), the body's premier immune fighter, carry a negative electrical charge, so Nordenström places a positive electrode within the tumor mass to draw WBCs to the tumor. He simultaneously places a negative electrode just outside the tumor and allows the current to flow in both electrodes for about an hour. The change in the electrical fields causes an acidic-like buildup of particles to occur around the tumor. The buildup of particles prevents red blood cells and oxygen from reaching the tumor, which starves the tumor. Furthermore, Nordenström postulates that the positive electrical field forces water out of the tumor, causing swelling in the surrounding tissue and shrinkage of the tumor, further blocking blood flow to the tumor.

Nordenström's technique has been effective in treating isolated malignant tumors that are 4 cm or smaller. Much work needs to be done to design systematic studies to confirm his findings (Nordenström, 1998). It is possible that Nordenström's electrical

circuits are the elusive meridians or channels of the Chinese medical system of acupuncture. As we saw in Chapter 2, medical science now has a basic understanding of the mechanisms of action of neurotransmitters and how various drugs fit into discrete receptors to influence health and disease in the body. Similarly, we are at the threshold of understanding how internal and external electromagnetic energy influences health. It is my firm belief that the next frontier in medical research will involve an understanding of the profound effects that electromagnetic energy has on health. Someday scientists will look back upon Becker and Nordenström's work with deep appreciation for their notable professional and personal contributions to the field.

The following two sections review the major thermal and nonthermal electromagnetic therapies.

THERMAL THERAPIES

Thermal therapies are used in conventional medicine, although some of them may be considered cutting-edge therapies. However, clinical results of various types of thermal therapies for malignant unresectable hepatic tumors now exceed those for chemotherapy and radiation and are slowly becoming a standard treatment (Dodd et al., 2000). A study performed at Harvard reports on the use of magnetic resonance imaging (MRI) with thermal therapies: "The temperature sensitivity of several intrinsic parameters enables MRI to visualize and quantify the progress of ongoing thermal treatment. MRI is sensitive to thermally induced changes resulting from the therapies, giving the physician a method to determine the success or failure of the treatment" (McDannold and Jolesz, 2000). Thermal therapies also include infrared devices that provide deep-heating treatments, which are commonly used by physical therapists for relief from muscle spasms, strains, and sprains.

Laser Surgery

Laser surgery is a minimally invasive thermal therapy presently used to treat many different conditions. For example, it is used to heat small solid tumors through implanted optical fibers and eradicate the lesions with little tissue charring. One of the most promising indications for laser surgery is its use for small unresectable hepatomas, metastatic tumors, and other conventionally inoperative tumors. Laser surgery also improves the rate of being able to perform a resection on colorectal liver metastases (Shankar et al., 2001). Studies show good tumor eradication rates, low complication rates, and appear to improve survival time.

The excimer laser was approved by the U.S. Food and Drug Administration (FDA) in 1995 for corneal surgery. The more popularly known laser-assisted *in situ* keratomileusis (LASIK) involves cutting and lifting a superficial corneal flap, after which the excimer laser removes a small amount of tissue to reshape the cornea and correct refractive errors. Healing is rapid because re-epithelialization of the cornea is not needed. Laser surgery is also employed for transmyocardial revascularization, a relatively new procedure to control refractory angina. The laser creates several small channels in areas of the heart that are still viable, but where proper blood

flow is impeded. Studies show that the procedure can effectively reduce angina and increase the quality of life for patients for whom angioplasty and bypass surgery have failed to relieve symptoms. The procedure is palliative rather than curative (Jones, 2001). In addition, lasers have been used for both diabetic retinopathy and macular degeneration (Akduman and Olk, 1999; Bandello et al., 1999; Miller et al., 1999; Petrovic and Bhisitkul, 1999 [for diabetic retinopathy]; Roider et al., 1999 [for macular degeneration]).

Radio-Frequency Surgery

A phase 2 study has been completed on the efficacy of radio-frequency surgery for interstitial tissue ablation prior to surgical resection for patients with hereditary small renal tumors. A positive treatment effect was noted in 10 of the 11 lesions, and no toxicity was detected. Further evaluation is needed (Walther et al., 2000). While the technique was previously thought to be primarily palliative, a recent study showed that nearly 80% of medium (3.1 to 5.0 cm) and large (5.1 to 9.5 cm) malignant hepatocellular tumors of patients with cirrhosis or chronic hepatitis attained either complete necrosis or partial necrosis. Noninfiltrating tumors had a higher rate of necrosis than infiltrating tumors (Livraghi et al., 2000). Other studies on hepatocellular tumors have yielded similar results (e.g., Yamasaki et al., 2001). Occlusion of blood-supply and radio-frequency ablation are also effective treatments for medium to large hepatic tumors (Rossi et al., 2000). At the Mayo Clinic, physicians have performed atrioventricular node ablation using radio-frequency surgery for patients with atrial fibrillation. When there is no underlying heart disease, expected survival is equal to that of the general population, and the need for lifetime drug use is obviated (Ozcan et al., 2001). A recent study also showed radio-frequency surgery to be very effective in knee reconstruction, significantly reducing intra-articular bleeding (Camillieri et al., 2001).

Radio-Frequency Diathermy

Continuous short-wave diathermy permits the uniform elevation of temperature in deep tissue. It is used to reduce inflammation, relieve joint and muscle pain, and promote vasodilation (Goats, 1989). Pulsed short-wave diathermy is used to encourage tissue repair and reduce pain. Although some consider it a nonthermal therapy, recent research shows that as pulse repetition rates are increased, so is the temperature of the skin (Murray and Kitchen, 2000). It is also useful in the treatment of acute lesions.

Radio-Frequency Hyperthermia

Radio-frequency hyperthermia is typically used for the ablation of malignant tumors of the liver, prostate, and areas where tumors are unresectable (Falk and Issels, 2001; Hurwitz et al., 2001; Livraghi et al., 2000; Yamamoto and Tanaka, 1997). For the past 10 years, Stanford University has used the Stanford 3D hyperthermia treatment planing system, which makes use of patient-specific computer simulations to determine the best amplitude and frequency at which a tumor deep within the body should

be heated (Sullivan et al., 1993). Similar procedures are in place at Massachusetts Institute of Technology (MIT) to ensure treatment that avoids regions of the body at which high temperature treatment would be detrimental (Fenn and King, 1994). Research on rats shows that the addition of neutrophils enhances the efficacy of radio-frequency hyperthermia. Rats that were given recombinant human granulocyte colony-stimulating factor increased the antitumor response, and, conversely, an injection that decreased the rat neutrophil antibody also decreased the antitumor response (Kokura et al., 1996).

NONTHERMAL THERAPIES

In 1965, researchers Melzack and Wall introduced the "gate control theory" of pain (Melzack and Wall, 1965). This theory postulates that electrical stimulation administered at a level above the area where neurons carrying the pain information enter the spinal cord can effectively close a spinal "gate." The peripheral pain messages attempting to ascend the spinal-thalamic tract to the brain then cannot reach the brain. This theory fostered the development of surgically implanted stimulators to reduce pain. Various electrical stimulators, such as cardiac pacemakers, are implanted in the body to manage arrhythmia and other conditions. Some electrical stimulation devices, such as those described below, are designed to alter or eliminate the pain message by inducing healing at the pain site through stimulation of cutaneous nerves located at a level above the entry of the pain stimulation.

Transcutaneous Electrical Nerve Stimulation (TENS)

TENS is a modality used by many physical therapists since the early 1970s to relieve both acute and chronic pain. Dr. C. Norman Shealy developed TENS for pain management. The procedure involves attaching two electrodes to the skin. The electrodes are connected to an electricity-generating device that delivers a low-voltage current to the nerves in the vicinity of the pain. TENS works by stimulating endorphin production and by interrupting or blocking the neurological communication pathway of the pain (Kahn, 1994). It is commonly used in physical therapy, but also can be used at home. There are over 100 FDA-approved types of units available. Several studies have shown TENS to be less effective than acupuncture for pain control (e.g., Freeman and Lawlis, 2001; Lehmann et al., 1986).

Cranial Electrical Stimulation (CES)

CES uses an even lower voltage electrical current than TENS (less than 1.5 mA compared with 60 mA for TENS), and the electrodes are attached to the scalp. This very low voltage gently nudges the neuroendocrine system back into a homeostatic state, releasing the individual from a state of chronic stress and its associated diseases. CES was first called electrosleep, which is a term derived from researchers in Russia and other Eastern Bloc countries. In 1978, the FDA renamed it *cranial electrical stimulation* because the electricity is pulsed across the head. In the late 1970s, the FDA approved its use for treatment of drug addiction, as there was strong evidence

for its effectiveness in abolishing withdrawal symptoms. CES proponents have since been embroiled in controversy with the FDA for its approval for use for other conditions (Kirsch, 1999). Nonetheless, CES is used to treat depression, pain, insomnia, headache, anxiety, and depression (George et al., 1999; Kirsch, 1999). Research performed by one manufacturer showed increased levels of β-endorphins, serotonin, and melatonin as well as diminished levels of cortisol and tryptophan (Liss and Liss, 1996). Dr. Shealy (see TENS above) worked with Dr. Saul Liss, developer of the Liss Cranial Electrical Stimulator® apparatus, and determined that TENS worked more effectively with patients with comorbid depression if they were first treated with CES (Rosch, 1997).

Transcranial Magnetic Stimulation (TMS)

TMS is a noninvasive technique that uses powerful magnetic fields to alter brain activity. In one study, lateral stimulation exciting the left frontal cortex using higher frequencies (≥10 Hz) and slow (1 Hz) stimulation inhibiting the right prefrontal cortex were both shown to have antidepressant effects (George et al., 1999; Klein et al., 1999). Side effects include tension headache and seizure (never reported with low frequency, ≤1 Hz). TMS is unpleasant and painful at higher frequencies. However, it is a favorable alternative for those patients refractory to other treatment. In another study, low-frequency (1 Hz) TMS significantly reduced auditory hallucinations in schizophrenic patients. All patients remained on antipsychotic medication, but those also needing to take anticonvulsant drugs did not respond as well to the treatment (Hoffman et al., 2000).

Magnetic Biostimulation

Magnets have been used as adjuncts to acupuncture for hundreds of years, especially in China (Lawrence et al., 1998). The American public, as evidenced by millions of dollars in sales each year, has embraced the use of magnets to treat sensory and motor dysfunction. Yet, there is a striking paucity of scientific research on its effectiveness. Two small but well-designed pilot studies evidence impressive results and call for the validation of the therapy with larger, more comprehensive studies. One study involving the use of magnetic insoles (a novel approach in the history of the use of magnets) showed a 75% improvement for patients with diabetic neuropathy and a 50% improvement for those with neuropathy without diabetes (Weintraub, 1999). Other research showed strong improvement in sway and lateral stance with the use of magnetic insoles with older adults. While promising, the number of subjects in the study was too small to be definitive (Suomi and Koceja, 2001). Another study on the use of magnets for chronic pelvic pain showed that long-term use improved , but once again, the sample size was too small to reach statistical significance (Brown et al., 2000).

Qi Machine™

The Qi Machine was developed by Dr. Shizuo Inoue of Japan to provide a way to oxygenate the body without exercise-related stress or injury. Dr. Inoue researched

the correlation between levels of oxygen and health in the human body and deduced that insufficient oxygen is the main factor in most human disease. He looked to nature, particularly the undulating motions of goldfish, to develop the Qi Machine, which is placed under the ankles to rhythmically rock the legs, the spinal cord, and the muscles surrounding it, as well as the entire body, which improves efficient blood circulation. The patient is asked to relax and breathe deeply while the machine rocks the body. Up to 60% of the Qi Machine's benefits occur after the machine stops, during an approximately three-minute period in which the individual is asked to remain still. It is felt that the Qi Machine massages the internal organs, loosens fascial restrictions, moves lymph fluids, opens bronchioles, aligns the spine, and improves the immune and nervous systems. The Qi Machine is said to have psychological health benefits, including increased vitality and a sense of well-being, as the state of deep relaxation reduces chronic physical tension and mental stress. The machine is not recognized in the United States as a therapeutic appliance, but it has been certified by Japan's Medical Affairs Bureau. Its use is not recommended during pregnancy, after surgery or bone fracture, with serious bleeding or infection, or for those individuals suffering from epilepsy or heart disease. In our review, we failed to find any peer-reviewed medical studies on the Qi Machine.

Microwave Therapy

Microwave therapy has been used for 20 years, primarily in Russia and the Ukraine (see Jovanović-Ignjatić and Raković, 1999, for a review). The therapy is a nonionizing level of electromagnetic energy that is used at a nonthermal intensity, either pulsed or continuous. Microwave therapy is used for the treatment of various conditions, including asthma, bronchitis, ulcers, hepatocellular tumors, and atherosclerosis as well as for reparation of immune cells for postoperative lung cancer patients (Babak and Honcharova, 1995; Drobyshev et al., 2000; Dziublik et al., 1989; Ishikawa et al., 2000; Kuz'menko, 1998; Shevchenko, 2000; Shibata et al., 2000; Shimada et al., 1998). Studies have shown that the treatment is safe and nontoxic, and researchers have produced clear, positive results.

Pulsed Electromagnetic Field (PEMF) Therapy and Pulsed Signal Therapy (PST)

PEMF, an extremely low, nonionizing frequency of electromagnetic energy, employs pulsed electromagnetic fields, utilizing a direct current with a constantly repeating signal at a predetermined intensity and frequency. Adenosine triphosphate (ATP), the enzyme that is key to producing high amounts of chemical energy and is stored as energy for many physiological functions, is needed to heal injured cells. PEMF most likely works by amassing ATP in the region of injury by facilitating the influx of potassium into the cells (Rosch, 1997). The FDA has approved the use of PEMF for treating nonunion fractures that do not heal, muscle reeducation, and relaxation of muscle spasm (e.g., Trock, 2000). However, PEMF also is used to treat Parkinson's disease, multiple sclerosis, Tourette's syndrome, migraines, and SAD (Sandyk et al., 1991; Sandyk, 1992, 1997a, 1997b, 1998, 1999).

Like PEMF, PST is performed at a low, nonionizing frequency, but it operates by changing pulses (i.e., instead of a constantly repeating signal), which are transmitted in a programmed alternating fashion that mimics the body's natural electrical potentials. Treatment typically is for one hour. Proponents of PST feel that the damaged cells, after a relatively short period of time, do not perceive a constantly repeating stimulus, such as is used in PEMF. Beneficial effects of PST are most often reported for osteoarthritis. With osteoarthritis, the chondrocyte (a mature cartilage cell embedded in a lacuna within the cartilage matrix) can no longer receive physiological signals because of pathological changes in the matrix. PST allows the chondrocyte to receive signals in the cartilage matrix, which allows regeneration and growth of the cartilage. Similar results have been achieved with arthritic joints and tendons. Extensive studies by Richard Markoll, M.D., Ph.D., of BioMagnetic Therapy Systems in Boca Raton, Florida, and one of the leading researchers on the effects of PST, indicate that PST is also effective for tinnitus that is not responsive to other therapies. A study published in Russia followed pulse low-frequency electromagnetic field treatment for 25 patients with tinnitus that was refractory to other treatment, and the results support Markoll's findings. The study showed that noise was eliminated in two patients and reduced noticeably (by 60%) in 19 patients. The effect persisted at 6- and 12-month follow-up evaluations (Patiakina et al., 1998).

PSYCHOLOGICAL MODALITIES

Counseling

We will not review the myriad psychological therapies (e.g., Freudian, Jungian, behavioral, cognitive, etc.), as this information is well covered in numerous other sources. However, it is my contention that work on both the mind and the body is essential for full health.

Hypnotherapy

Hypnosis is a technique of deep concentration that suspends certain states of active awareness. It has been used for hundreds of years and dons a colorful history (Dossey, 2000). It is used for treatment of both psychological maladies and physical problems. Physiological parameters change in a manner consistent with other types of stress-reduction exercises (e.g., reduced respiratory rate, heart rate, and oxygen consumption). Typically hypnosis is used with some form of psychotherapy to reduce psychological or physical symptoms, including pain. Hypnosis can access memory and alter perception or mood, or increases the subject's ability to experience imagery and creativity. A willingness to participate is crucial to its success, but suggestibility does not imply compliance against one's will. However, hypnotic susceptibility has been shown to increase effectiveness of treatment, such as reducing pain (Spinhoven and ter Kuile, 2000). Dr. Milton Erickson's experiments with hypnosis in the first half of the twentieth century brought hypnosis into the realm of clinical practice. Erickson recognized the integration of the mind and body many years before psychoneuroimmunology experiments were being carried out. He saw

TABLE 5.1
Six Formulas for Evoking Relaxation Response in Major Body Systems

Formula No.	State of Mind	Perception of Body Area	Intended Effect
1	I am completely calm	My right arm is heavy	Muscular relaxation
2	I am completely calm	My right arm is warm	Vascular dilation
3	I am completely calm	My heart beats calmly and regularly	Heart function regulation
4	I am completely calm	My breathing is calm and regular…it breathes me	Breathing regulation
5	I am completely calm	My abdomen is flowingly warm	Visceral organ regulation
6	I am completely calm	My forehead is pleasantly cool	Regulation of blood flow to the head

that the unconscious mind was a rich source of information for providing physical and emotional healing. There is evidence that hypnosis is most effective when the mind is in the theta state (see Chapter 1 for information on the theta state). Today, various studies attest that hypnosis benefits relaxation and anesthesia (Ashton et al., 1995; Ashton et al., 1997; Defechereux et al., 1999).

Autogenic Training

In autogenic training, a type of self-hypnosis, the patient is taught six "formulas" to repeat in a specific pattern and then use at home. The concept that each of the formulas is tied to major bodily systems, such as the cardiovascular system and the musculature, is key to evoking a physiological relaxation response. Table 5.1 is a typical list of formulas with the corresponding area of the body that each is intended to affect.

Autogenic training is most efficacious when the patient is in the theta state (Spinhoven and ter Kuile, 2000). It has been shown to be a more effective treatment for motion sickness than intramuscular injections of promethazine. Testing at the National Aeronautics and Space Administration (NASA) showed that motion sickness tolerance was significantly increased with autogenic training. Subjects reported fewer or no symptoms at higher rotational velocities, and there was significantly less heart-rate and skin-conductance variability during motion sickness tests in the group receiving autogenic training (Cowings and Toscano, 2000). While there are plausible claims that autogenic training is effective for reducing anxiety and stress, studies to date generally are methodologically flawed and do not always use the classical autogenic training formulas (Ernst and Kanji, 2000).

Hypnagogia

Hypnagogia is an experience of psychological and physical withdrawal or relaxation at the threshold of sleep; the technique incorporates intense visual and sometimes auditory experiences. Hypnagogia, a hypnotic-like state of consciousness that

hovers between being awake and being asleep, involves a loosening of ego boundaries and a conscious participation in the experience. The technique incorporates intense visual and sometimes auditory experiences. It is the conscious experience of being in the theta state and can be intentionally prolonged to promote mental clarity and insight. Hypnagogia induces experiences that are physiologically similar to the spiritual experiences of advanced meditators, with subjects showing decreases in heart rate and oxygen consumption as well as a shift from alpha to theta on the EEG. The technique also induces experiences that are psychologically similar to those reported by advanced meditators, having the two key features of intense concentration and the dissolution of a sense of self as distinct from a sense of otherness (Mavromatis, 1987).

Meditation

Training for many types of meditation techniques is available in the United States. Meditation facilitates entry into both the alpha and theta states. These states are important for deep relaxation and stress reduction, but they also provide opportunities for profound insight. Some people can benefit from and handle the insights without outside intervention; for others, greater gain and personal growth require working with a spiritual or psychological counselor to more fully understand the issues that arise. I offer you one word of caution: Think carefully about what technique and what aspects of the technique are best for you. It is my experience that even meditation techniques that claim to have no dogma and allege only to disseminate spiritual truth are actually littered with dogmatic rules and regulations. Even rules that may have some inherent health benefits, such as not drinking alcohol, can be a dogma that binds group members in the belief that they stand on higher moral ground than those who are not part of their group. Ultimately, these individuals have missed the point, which is that all of us are part of a common energy (see Chapter 8). The meditation group becomes a way of life, perhaps even providing a false sense of security or structure in one's life instead of a serious personal inner journey. The practitioner is bound by what the leader says instead of taking the more courageous and deeper journey of an independent discovery of one's inner nature and inherent truth.

There are clear health benefits to the daily practice of meditation. As previously mentioned, meditation raises levels of melatonin and possibly anandamide. Meditation also may, very possibly, cause the rise of *N,N*-dimethyltryptamine (DMT), which is discussed in Chapter 8. Research has also shown that regular practice of meditation leads to an increased EEG-recorded alpha coherence in the frontal lobe, a significantly lower systolic blood pressure and ambulatory diastolic blood pressure, as well as long-term endocrine changes, for example, decreases in serum thyroid-stimulating hormone (TSH), growth hormone, and prolactin levels (Dillbeck and Bronson, 1981; Travis and Wallace, 1999; Wallace et al., 1983; Wenneberg et al., 1997; Werner et al., 1986). One of the most comprehensive reviews of research on the various physical effects of meditation is published by the Institute of Noetic Sciences, an organization dedicated to "the development of human consciousness through scientific inquiry" (Murphy and Donovan, 1997).

Imagery

Imagery is pervasive in our lives, occupying our thoughts and memories, providing visions during our meditation or prayer, and filling our daytime and nighttime dreams. Although imagery can seriously harm us, as occurs with the repetitive and intrusively recurring imagery that accompanies posttraumatic stress disorder, imagery also can be effective for recovery from various medical conditions, for decreasing physical pain, and for sundry emotional issues, such as the reduction of anxiety (Achterberg, 1985; Achterberg and Lawlis, 1978; Achterberg et al., 1989; Simonton and Sherman, 1998). Imagery is frequently used with other modalities, including biofeedback, hypnosis, psychotherapy, and sound or music therapy. It is a vehicle that has the potential of providing us with insights about ourselves and developing our personal and spiritual awareness. In a deeply relaxed state of mind, guided or self-directed imagery can help replace negative or destructive mental patterns with healthy images that can effectively change attitudes and behavior. One of the most prominent researchers of imagery for healing is Jeanne Achterberg, Ph.D., who has published numerous studies on the topic (Achterberg, 1985). Achterberg says, "You may think of imagery…as the way what we call 'mind' and what we call 'body' communicate" (Achterberg, 1999). Achterberg feels that imagery is a bridge between the mind and the body. Emotions and traumas, which are encoded in our bodies, are brought to a conscious state through the use of imagery.

HeartMath® Therapy

HeartMath therapy is a process of reducing stress and unwanted emotion by focusing on the heart to help restore equilibrium to the body. In the ancient literature of many religions, the heart is the site of both intuition and wisdom. HeartMath combines this physiological understanding of the wisdom of love with some very solid medical science to formulate several techniques for reducing stress in both our personal and our work lives. There is solid evidence of health benefits from using this technique, including reduced blood pressure and heart rate as well as benefits to the immune system (Childre, 1994; Childre et al., 1999).

HeartMath is based on medical evidence that the heart has a nervous system sophisticated enough to qualify as an independent "brain." The heart is capable of relaying vital information back and forth to the brain, but will not necessarily take its marching orders from the brain. Various types of information (e.g., chemical, electromagnetic) are constantly being relayed between the two organs. According to HeartMath, focusing on the heart and feelings of love or appreciation can actually shift these patterns of information and the heart's rhythms.

How does this occur? The HeartMath research team analyzed heart rate variability (HRV) and found a correlation between the HRV pattern and the emotional state of the subject, with positive emotions evidencing a coherent and ordered pattern and negative emotions displaying a random chaotic pattern. HRV is strikingly responsive to our emotions. In addition, the HeartMath research team discovered that when one person touches another person, there is transference of electromagnetic energy from the person's heart that touches to the other person's brain.

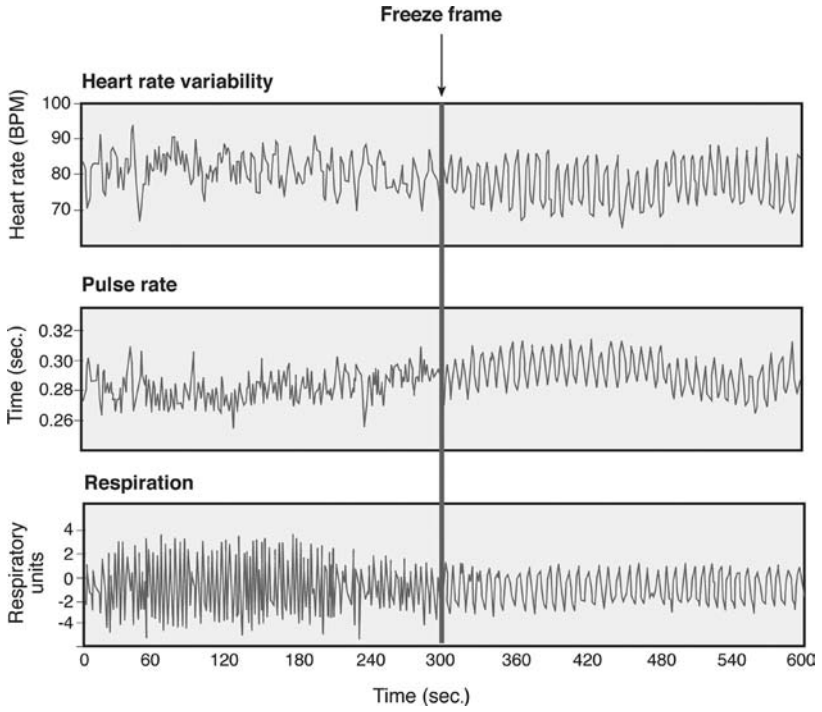


FIGURE 5.2 HeartMath entrainment.

The brain-wave pattern, as represented on an EEG, mimics the heart pattern as recorded by an electrocardiogram (EKG). This is called entrainment (Figure 5.2). So, what is occurring in our hearts is affecting those around us, whether or not we are aware of it (Childre et al., 1999).

HeartMath researchers found that a similar entrainment occurs within our own bodies. The researchers tracked patterns between the HRV and brain-wave patterns while the subjects were engaged in specific HeartMath techniques (see steps below). Our hearts and minds actually have the ability to entrain one another. Consequently, we experience a subjective sense of balance or harmony when our bodies are entrained because the body is working in harmony. This is the basis for the theory of the heart's intelligence.

There are five basic steps to the HeartMath technique:

1. Recognize that you are stressed and freeze-frame the moment, which basically means to try to stop the feeling by following the next four steps. It is a technique that allows you to stop your emotions long enough to determine how best to handle the situation.
2. Put your attention on the area around your heart and imagine that your heart is breathing; really try to feel as if your heart is breathing—in and out, in and out.
3. Shift your focus to a positive memory.

4. Using both intuition and common sense, ask your heart to help you determine a response that will minimize stress from resulting in other similar situations.
5. HeartMath says, "Listen to what your heart says in answer to your question." It should provide you with a new perspective on the issues around which you experience stress (Childre, 1994; Childre et al., 1999).

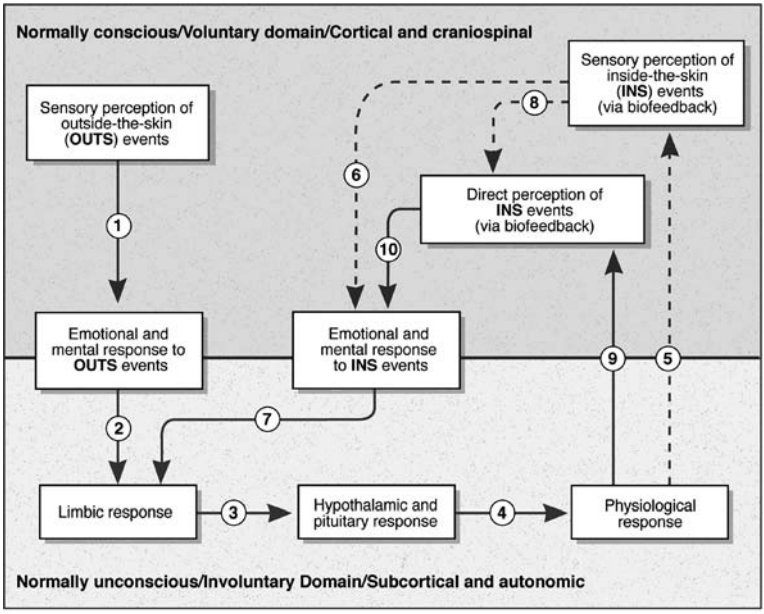
HeartMath also offers two advanced techniques, Cut-thru and Heart Lock-in. Cut-thru is designed to help release emotional issues that still remain after practicing freeze-frame. For most, undoing deeply engrained, negative patterns (e.g., those of anger, insecurity, worthlessness, guilt, etc.) will take years. Cut-thru provides a technique to reduce the impact of and eventually dissolve some of these feelings. Heart Lock-in involves focusing for a longer period of time on the cultivation of feelings of love and appreciation and on the creation of a stronger connection to the heart (Childre et al., 1999).

Instructors of HeartMath have successfully brought their techniques to major corporations and government agencies (e.g., Motorola, Shell, Hewlett Packard, and the U.S. Department of Defense). Results show increases not only in employee health and empowerment, but also in improved teamwork and increased productivity. HeartMath has also provided police officers with a tool to cope with the extremely stressful situations in which they frequently find themselves. A HeartMath police study indicates that the technique has made a significant difference in these people's lives. The research on individuals as well as in social settings reveals that focusing on our inherent heart rhythms may very well entrain our physiology to a healthier, more harmonious life (Childre et al., 1999).

Biofeedback

Beginning in the 1960s, Barbara Brown, a pioneer in the use of EEGs, was involved in research concerning the voluntary self-regulation of bodily functions that are generally considered to be part of the autonomic nervous system or ANS (Brown, 1966; Brown, 1970). The idea that subjects could voluntarily control autonomic functions was novel then. Biofeedback therapy was subsequently derived from these experiments, and as other mechanistic tools were developed that could provide bodily feedback (e.g., the EKG), they, too, were applied to the therapy of biofeedback. At a conference in 1969, which Brown sponsored for researchers involved in similar endeavors, the term *biofeedback* was first used, but some argue that it was the research scientist and widely recognized father of biofeedback, Dr. Elmer Green, who coined the word.

Elmer and his late wife, Alyce Green, who did much to promote the concept of biofeedback as a tool for learning bodily self-regulation, defined biofeedback as "the continuous monitoring, amplifying, and displaying to a person … of an ongoing internal physiological process." Figure 5.3 shows Green's schematic of the mechanism of biofeedback. The Greens also made the point that "becoming aware of normally involuntary physiological processes is linked with becoming aware of normally unconscious psychological processes" (Green and Green, 1977). The



Simplified operational diagram of "self regulation" of psychophysiological events and processes:

Biofeedback pathway

Sensory perception of OUTS events, stressful or otherwise (upper left box), leads to physiological response along **arrows 1–4.** If the physiological response is "picked up" and fed back **(arrow 5)** to a person who attempts to control the "behavior" of the feedback device, then **arrows 6 and 7** come into being, resulting in a new limbic response. This response in turn makes a change in "signals" transmitted along **arrows 3 and 4**, modifying the original physiological response. A cybernetic loop is thus completed and the dynamic equilibrium (homeostasis) of the system can be brought under voluntary control. Biofeedback practice, acting in the opposite way to drugs, increases a person's sensitivity to INS events, and **arrow 8** is eventually unnecessary because direct perception of INS events becomes adequate for maintaining self-regulation skills.

Yoga pathway

Physiological self control through classical yoga develops along the route of **arrows 7–3–4–9–10–7**, but for control of specific physiological and psychosomatic problems biofeedback training seems more efficient.

FIGURE 5.3 Elmer Green's schematic of the mechanism of biofeedback.

Greens were early advocates for performing research on the mind–body connection. To borrow from stress research, one can say that biofeedback endeavors to teach the patient to bring the body back to homeostasis by learning to perceive internal cues. Biofeedback continues to be used for relaxation or stress control (Edwards et al., 2000; Moser et al., 1997; Nakao et al., 1997; Pages et al., 2001; Weaver and McGrady, 1995; Wiesel et al., 2001). In some instances, biofeedback is used as an adjunct to conventional treatment (e.g., pharmaceuticals and physical therapy).

Various modalities are used for biofeedback, some of which are more effective for one condition than another. In each instance, the goal of therapy is that patients can eventually monitor their condition without the feedback of the modality. Perhaps the most widely used biofeedback modality today is the electromyograph (EMG), which measures muscle activity. Muscles emit an electrical charge when there is any

movement, and the EMG can measure this electrical activity. Electrodes are placed at the site of the disorder, such as on the forehead for a tension headache, and the patient learns to be aware when the muscle is engaged. Obviously, the technique is more useful when there is a distinct muscle group involved. Similarly, EEG devices, typically referred to as neurofeedback devices, are used for attention deficit disorder (ADD) in children and for fibromyalgia and other conditions. Another type of biofeedback therapy is finger-pulse biofeedback, which is accomplished by attaching an electrode to the finger. The electrode measures heart rate and blood pressure and is therefore most effective with cardiovascular ailments (e.g., hypertension and arrhythmia) and anxiety. Vascular biofeedback records thermal changes on the skin, as measured by a temperature-sensitive device, which is generally taped to the finger or toe. Low skin temperature, which occurs during stress, corresponds to a decrease in blood flow; as vessels dilate and blood flow increases, which occurs with relaxation, so does skin temperature. Thermal biofeedback is practical for Raynaud's disease, migraine headaches, hypertension, and anxiety. A final example of a biofeedback therapy is the use of sensors to train the patient in better breathing habits that encourage deeper breathing and utilize abdominal muscles. This modality is effective for respiratory conditions such as asthma, and, once again, is used for anxiety.

Art Therapy

Art therapy is an excellent modality to reveal unconscious emotions, particularly for individuals who are visually oriented and for children who do not yet have the verbal skills to articulate all that they experience. Art therapy uses various media, such as sculpture, painting, drawing, or watercolor. The technique provides an avenue for both children and adults undergoing medical procedures to express their subconscious fears, loss, pain, or other emotions. This application of art therapy is now often referred to as *medical art therapy.* Art programs established for inner-city youth, such as Artists for Humanity in Boston, provide studio art classes for urban teenagers along with staff who are trained and available to discuss personal issues.

Dance

Dance therapy, much like art therapy, is used to help the individual uncover unexpressed or blocked emotions. The modality is particularly suited to the person who is more sensate oriented, but may be inappropriate for some patients with extreme physical limitations or those who are in a weakened physical state. There is not a great deal of research available on dance and health; however, a few studies indicate that dance is effective for both physical and psychological parameters, including improvements in aerobic ability, depression, anxiety, fatigue, and tension, but not joint status for patients with rheumatoid arthritis (e.g., Noreau et al., 1995). A study of African-American and Hispanic adolescents conducted at the Stanford University Medical School indicates that a dance program coupled with a culturally sensitive health curriculum can be effective in improving health and awareness of the importance of physical exercise for this population (Flores, 1995). The long-range impact of this type of program could be significant, as cardiovascular disease is the major

cause of death among adults in both of these ethnic groups. Another intriguing study indicates a significant reduction in anxiety for students participating in a modern dance class compared with controls participating in physical education, music, or math classes (Leste and Rust, 1984).

Twyla Tharp, famed dancer, director, and choreographer, has brought the world more than 30 years of dance that expresses innovative freshness. Tharp's productions convey the infectious playfulness and vibrant inner spiritual expression from which she creates her dance. In her book *The Creative Habit: Learn It and Use It for Life*, she shares her view that dance is ultimately a spiritual statement, a declaration of the soul conveyed through movement. She advocates using dance in various healthcare settings, including hospitals and hospices. A woman who, in her life and work, has always pushed the boundaries of dance, Tharp now wants to bring that same attitude to dance as an avenue for health and well-being.

Eye Movement Desensitization and Reprocessing (EMDR)

EMDR uses a combination of clinician-directed physical stimuli (primarily a set of specific eye movements, but also hand tapping and finger clicking) coupled with mental focus. The mental focus begins first on a trauma, painful memory, or negative belief and then shifts to a positive sentiment. Francine Shapiro, who developed the technique, felt that the physical stimulation (e.g., eye movement) somehow triggers the portion of the brain involved in information processing and thus activates an inherent adaptive response that has gone awry, possibly as a result of the intensity of the trauma (Shapiro, 1995). I would speculate that the mechanism underlying EMDR involves neural pathways that connect the extraocular muscles (i.e., the muscles responsible for eye movement) with the limbic system (i.e., the area most central in processing emotion). The release of traumatic memories may be a positive therapeutic ramification of the programmed movements of EMDR. Ideally, both desensitization to the negative issue and an adaptive resolution can occur.

Neurolinguistic Programming (NLP)

In the early 1970s, John Grinder, a linguistics professor at University of California Santa Cruz, and Richard Bandler, a psychology and mathematics student at the same institution, joined forces to investigate the behavioral patterns of prominent psychotherapists of that time. What they learned is that (1) voice tone, breathing, posture, and eye movements all reveal unconscious thought patterns that correlate to emotional states, and (2) once the patterns are identified, they can be altered by reprogramming. *A Pocket Guide to NLP*, written by the NLP Comprehensive, now one of the prominent NLP training centers in the United States, describes NLP in the following words: "NLP is the study of the structure of subjective experience. NLP holds that people think and act based on their internal representations of the world and not on the world itself. Once we understand specifically how we create and maintain our inner thoughts and feelings, it is a simple matter for us to change them to more useful ones" (NLP Comprehensive, 1991). NLP is a technique that applies language and sensory processing to the thought patterns that are unhelpful to our emotional

well-being. Negative patterns of organizing and processing internal and external sensory information can be reprogrammed and replaced with healthier patterns. NLP is used for building self-esteem, eliminating phobias, developing productive relationships, and resolving conflicts in both personal and employment situations.

Humor/Laughter

Well before studies were being published on psychoneuroimmunology (PNI) and the mind–body connection, Norman Cousins, the well-known editor of *The Saturday Review*, deduced and effectively showed with his own painful, debilitating disease (ankylosing spondylitis) that laughter helps the body to heal (Cousins, 1976). Recently, Lee Berk, along with one of the fathers of PNI, Dr. David Felten, published research that confirms what Cousins had intuited … that there is significant beneficial modulation of immune parameters with laughter (Berk et al., 2001). One hour of viewing a video that causes "mirthful laughter" is correlated to increases in natural killer cell activity; immunoglobulins G, A, and M (IgG, IgA, IgM); interferon-γ; leukocytes; and granulocytes. What is perhaps the most fascinating part of this research is that many of the increased immune parameters remained elevated (as compared with baseline levels) up to 12 hours later.

Realistically, humor and laughter are adjunct therapies, yet very powerful ones. In fact, they are therapeutically so effective that major hospitals in this country and around the world permit circus clowns to perform for children in cancer and burn wards. Patch Adams, the physician and professional clown (whom Robin Williams so effectively portrayed in the movie of the same name) movingly conveys his feelings about humor: "I believe humor and love are at the core of good bedside manner, burnout prevention, and malpractice prevention, and for these alone, humor deserves a central place in a medical practice, but let us not deny its value in just raw fun. Despite my long, deep experiences with humor, I still can be brought to tears of joy over its power" (Micozzi, 2001).

Love

Dean Ornish is the physician who told heart patients all across America how to eat right, exercise, engage in social support groups, and meditate in order to reduce their likelihood of further heart disease. Health insurance companies recognized the financial benefits of his program, and now more than 40 insurance companies nationwide cover the program. In this book *Love and Survival*, Ornish then maintains that "the real epidemic in our culture is not only physical heart disease, but also what I call emotional and spiritual heart disease" (Ornish, 1998). Ornish reviews the extensive body of medical evidence showing that loneliness and isolation are detrimental to our health and increase the likelihood of premature death from any cause by two to five times. James Lynch, in his provocative book, *A Cry Unheard*, reviews similar issues and also some of the best studies on the startling impact of loneliness as a major hidden cause of heart disease, subsequent cardiac events (e.g., heart attack), and death from cardiac events (Lynch, 2000).

So, the hard scientific evidence is there: love or even meaningful social connections can keep us healthier (see Chapters 2 and 3). But, how can this happen; how can we use love and intimacy to increase our well-being? Ornish's book includes an account of his personal journey through terrors of loneliness. Through his determination to learn to be alone with himself, he discovered that he had to develop a strong sense of a separate self before being able to skillfully participate in intimate relationships. Yet, Ornish also strongly advocates group therapy for cardiac patients and others to learn to express feelings. These two seemingly disparate themes come together in an interview Ornish conducts with Jon Kabat-Zinn, Ph.D., the founder of the Stress Reduction Clinic at the University of Massachusetts Medical Center in Worcester. Kabat-Zinn speaks about finding an inner peace that is a total willingness to be at peace right now with things as they are. Think about that. It means that you can stop letting your boss get to you and perhaps even appreciate the lessons as to why he or she acts the way he or she does. It means that you can be more accepting and understanding of why your partner does not and perhaps cannot do things the way you would like them done. But, it also means that there is a deep acceptance of yourself. Kabat-Zinn concludes, "To me, that [inner peace] is synonymous with love, and synonymous with intimacy, and synonymous with the highest wisdom and courage."

Don Miguel Ruiz, a Toltec Indian from rural Mexico, has written a book called *The Mastery of Love*, which takes Ornish's discussion to a deeper level (Ruiz, 1999). Ruiz believes that mastery of self-love can transform one's life and create an awareness that allows people to open their hearts and be an expression of "Spirit, Love, and Life." He states, "The heart is in direct communication with the human soul, and when the heart speaks, even with the resistance of the head, something inside you changes; your heart opens another heart, and true love is possible." Ruiz's book is not a book of medical evidence; it is a beautiful, inspirational book about learning to love yourself as well as others so that each day can be a joyful expression of life.

Before taking a look at the healing modalities that fall into the NIH Category 5 of energy therapies (see the beginning of this chapter), we will review the pineal gland in the introduction to Chapter 6. The pineal is our master gland and the transducer and translator of external environmental information to the electrical and hormonal signals that the body is capable of reading.

NATUROPATHIC MEDICINE: NEW RESPECT FOR AN OLD PROFESSION

Soon after the first edition of *The Scientific Basis of Integrative Medicine* was published, we began receiving letters asking why we had not included a description of naturopathy or naturopathic medicine in the book. Indeed, naturopathic medicine is not an integrative *modality*—it is a system of practicing medicine that incorporates numerous modalities, many of which today are thought of as complementary and alternative medicine (CAM). The theoretical basis for naturopathic medicine extends back to the earliest indigenous doctors or healers who used herbs, food, water, fasts, and tissue manipulation to maintain health and treat ill health when needed (Bastyr, 2008a). Similarly, today's doctors of naturopathic medicine draw on current scientific knowledge, yet continue to use herbs, nutrition, exercise, and breathing as well

as other natural treatments, such as homeopathy, acupuncture, bio-resonance, colon hydrotherapy, or Ayurvedic and Chinese medical practices. However, in licensed naturopathic medical schools, conventional medicine is taught alongside these treatments, and national practice standards, peer reviews, and high-tech, progressive scientific research have been instituted.

In the United States, naturopathy was largely established by Benedict Lust, a German with degrees in both naturopathy and medicine, who was educated in hydrotherapy techniques (i.e., a wide variety of water modalities, from sitz baths to colonic irrigation) by Father Sebastian Kneipp. Kneipp requested that Lust go to the United States to train doctors in these techniques. However, in 1900, the individuals who Lust had educated in Kneipp's hydrotherapy technique decided that the practice of naturopathic medicine should include other natural healing methods, such as herbs, nutrition, exercise, psychology, homeopathy, and the manipulative therapies (National College, 2008). Lust opened the first school of naturopathic medicine in the United States in 1902 (Murray and Pizzorono, 1998). As discussed in the "pharmaceuticals" section of this chapter, 1910 was also the year in which the paper by Abraham Flexner was published for the Carnegie Foundation and changed the orientation of all U.S. medical schools, forcing them to use scientific-based curriculum or be shut down. Nonetheless, naturopathic medical education and practice thrived until the 1940s when the advent of antibiotics and other pharmaceuticals led many people to believe that a pill could cure whatever ailed you. The National College of Naturopathic Medicine, founded in 1956 by the noted naturopathic physician Dr. John Bastyr, had less than a 100 students in its early years (National College, 2008). Yet, by the 1970s, the tide had again turned, with many patients frustrated with the shortcomings of allopathic medicine. In 1978, Bastyr University was established and named after Dr. Bastyr, as he was the esteemed teacher of the founders: Drs. Les Griffith, Bill Mitchell, Joe Pizzorno, and Sheila Quinn (Bastyr, 2008b).

Six Principles of Healing

While the Latin origin of the word "doctor" means: "to teach," the Greek origin of the word for "physician" is "nature." It is commonly stated that the principles of naturopathy were first used by Hippocrates at his Hippocratic School of Medicine. Today, Hippocrates is considered the earliest predecessor of naturopathic physicians. There are *Six Principles of Healing* in naturopathic teachings (which can be found, in various forms, at the Web pages of all accredited naturopathic medical schools), one principle of which is *vis medicatrix naturae*, or "the healing power of nature," a concept derived from the teachings of Hippocrates. While the concept also stems back to earliest indigenous healers throughout the world, it continues to be a central tenant of naturopathic philosophy today. A summary of the *Six Principles of Healing* follows:

1. **Do No Harm (*Primum Non Nocere*):** The physician's actions can support or antagonize the actions of the healing power of nature. Methods designed to suppress symptoms, without removing underlying causes, are

avoided, as suppression generally interferes with self-healing. Safe and effective natural modalities are used to assist the healing process.

2. **Healing Power of Nature (*Vis Medicatrix Naturae*):** The body has the inherent ability to maintain or restore health. The healing process is facilitated by the physician who can identify and help remove obstacles to health and recovery.
3. **Identify and Treat the Causes (*Tolle Causam*):** Every illness has a cause, and the underlying cause of disease must be identified and treated for complete recovery to occur. Symptoms are not the cause of disease, but rather manifestations of the body's healing process. Thus, they can be an indication that the body is trying to defend, adapt, or heal itself from the physical, emotional, or spiritual causes of disease. Naturopathic medicine is primarily concerned with the underlying causes of disease, rather than the symptoms.
4. **Treat the Whole Person:** The physician must treat the whole person—a complex interaction of physical, mental, emotional, spiritual, genetic, environmental, social, and other factors. A harmonious functioning of all of these aspects is essential to good health, thus the naturopathic physician must develop a personalized comprehensive approach to each patient's treatment.
5. **Prevention:** The ultimate goal of naturopathic medicine is prevention, thus the study of health is important. Optimal health is accomplished through education and promotion of healthy ways of living. The patient's risk factors and hereditary susceptibility to disease are assessed, and the physician then provides appropriate preventive interventions. According to naturopathic medicine, one cannot be healthy if the living environment is unhealthy; therefore, it is the responsibility of both the physician and patient to create a healthy environment.
6. **Doctor As Teacher (*Docere*):** A cooperative, sensitive interpersonal doctor–patient relationship has inherent therapeutic value. A key objective of naturopathic medicine is to educate the patient and emphasize self-responsibility in maintaining good health, which is better accomplished when the physician is a catalyst for healthful change, empowering and motivating the patient. Although the patient, ultimately, is the one who accomplishes healing, the physician can inspire hope and offer knowledge. Thus, the physician must make a personal commitment to his/her own spiritual development.

Naturopathic Medical Education Accreditation

From the beginning, Lust wanted naturopathic medicine to be seen as a reputable profession. In the United States, a licensed naturopathic physician must attend a four-year, graduate-level naturopathic medical school. The Council on Naturopathic Medical Education is recognized by the U.S. Secretary of Education as the national accrediting agency for programs leading to the Doctor of Naturopathic Medicine or

Doctor of Naturopathy degree (Council on Naturopathic Medical Education, 2008). Accredited schools currently include:

- Bastyr University, Kenmore, Washington; accreditation granted in 1987.
- National College of Naturopathic Medicine, Portland, Oregon; accreditation granted in 1991.
- Southwest College of Naturopathic Medicine, Tempe, Arizona; accreditation granted in 1999.
- University of Bridgeport College of Naturopathic Medicine, Bridgeport, Connecticut; accreditation granted in 2006.

At the time of this writing, all but the University of Bridgeport College of Naturopathic Medicine also have been accredited to sponsor postdoctoral residency programs. In addition, on March 9, 2008 (University of Bridgeport, 2008), the National University of Health Sciences in Lombard, Illinois, was granted candidacy status by the Council on Naturopathic Medical Education, which puts its program on track for one day being accredited.

Licensing of Naturopathic Physicians

Schools of naturopathic medicine are intensive doctoral programs designed to prepare candidates for the general practice of naturopathic medicine and to pass licensing examinations, which are specifically defined by the legislation in states that license or regulate naturopathic medicine. The American Association of Naturopathic Physicians (AANP), which oversees licensing, requires that naturopathic doctoral candidates from all states graduate from a four-year, residential naturopathic medical school as well as pass extensive postdoctoral board examination (NPLEX) to receive licensing from their state (American Association of Naturopathy Physicians, 2008). Currently, 13 states (Alaska, Arizona, California, Connecticut, Hawaii, Idaho, Maine, Montana, New Hampshire, Oregon, Utah, Vermont, Washington) and the District of Columbia, and the territories of Puerto Rico and the U.S. Virgin Islands have licensing laws for naturopathic doctors. On July 2, 2009, Minnesota also will be licensed. According to the AANP, there is currently legislation that has been introduced or is pending in Iowa, Colorado, Illinois, Massachusetts, North Carolina, New York, Pennsylvania, Tennessee, Virginia, and Wisconsin. This list of state licensures is fluid; the AANP anticipates that other states will pass legislation in the coming months and years.

Naturopathic Medical Research

Bastyr University, and National College of Natural Medicine, in particular, use rigorous scientific methodology to research the efficacy of treatments that sometimes have been used for centuries, based on empirical knowledge. In 2002 and again in 2007, Bastyr University received five-year training grants from the NIH's National Center for Complementary and Alternative Medicine (NCCAM) for research projects to be performed by predoctoral and postdoctoral fellows. The 2002 funding was

the first grant to be awarded by the NIH to an institution focused on the study of complementary and alternative medicine.

To date, more than 80 research studies have been performed in the following areas:

- Cancer therapeutics
- Botanical medicine
- Cell biology
- Molecular biology
- Nutrition
- Obesity
- Mind–body medicine

In addition, in 1994, the NIH selected Bastyr University to be the national center for research on alternative treatments for HIV/AIDS. Bastyr was granted $1 million to perform the research, about which the University asserts, "This action represented the formal recognition by the federal government of the legitimacy and significance of naturopathic medicine."

Similarly, the Helfgott Research Institute at the National College of Natural Medicine was established in 2003 to conduct rigorous, high-quality research to further knowledge of natural forms of medicine (Helfgott, 2008a). Like Bastyr, the institute has received grants from NIH's NCCAM. A statement on Helfgott Institute's Web site explains: "From basic science studies to clinical trials, our goal is to find out what natural medicine therapies work, why they work, and to develop methodologies for studying modalities that don't always fall into the traditional biomedical model of research" (Helfgott, 2008b).

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ADDITIONAL RESOURCES

Acupuncture

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Bio-Electrography, available at: http://www.psy.aau.dk/bioelec/index.htm.
Council of Colleges of Acupuncture and Oriental Medicine (CCAOM); 301-313-0868; available at: http://www.ccaom.org/.
Educational Kinesiology Foundation of North America; 800-356-2109; available at: www.braingym.org.
National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM); 703-548-9004; available at: http://www.nccaom.org/.
National Sports Acupuncture Association (NSAA); 206-374-2505; available at: http://www.sportsacupuncture.com/.

Homeopathy

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QiGong

National QiGong Association, USA, (888) 815-1893, P.O. Box 252, Lakeland, MN 55043; available at: www.nqa.org.
Qigong Institute, 561 Berkeley Ave., Menlo Park, CA 94025; available at: www.qigonginstitute.org.

Rolfing

Rolf Institute of Structural Integration, The Rolfing™ Technique of Connective Tissue Manipulation, Rolf Institute, Boulder, CO, 1976.

Seasonal Affective Disorder (SAD)

Bio-Brite, Inc., 4340 East–West Hwy., Suite 401, Bethesda, MD 20814; 800-621-5483.
Light Energy Company, 1056 NW 179th Place, Seattle, WA 98177; 800-544-4826; available at: www.lightenergycompany.com.
National Institute of Mental Health (NIMH) trial; available at: http://clinicaltrials.gov.
North American Philips, 200 Franklin Square Drive, Somerset, NJ 08873; 800-752-2852; available at: www.lighting.philips.com/nam.
Ott-Light Systems, Inc., 28 Parker Way, Santa Barbara, CA 93101; 800-234-3724; available at: www.ottbiolight.com.
Weese, J.L., Harbison, S.P., Stiller, G.D., Henry, D.H., and Fisher, S.A., Neoadjuvant chemotherapy, radical resection with intraoperative radiation therapy (IORT): Improved treatment for gastric adenocarcinoma, *Surgery*, 128 (4), 564–571, 2000.

6 Energy Medicine
Cutting Edge Modalities

Does an organized energetic system that has clinical applications exist in the human body? Although biochemical and physiologic studies have provided insight into some of the biologic effects of acupuncture, acupuncture practice is based on a very different model of energy balance. This theory might or might not provide new insights to medical research, but it deserves further attention because of its potential for elucidating the basis for acupuncture.

National Institutes of Health (NIH) Consensus Statement on Acupuncture
November 1997

INTRODUCTION

In the previous chapters, we proceeded from learning about the wondrous, if not enigmatic, integration of the body's internal systems. In Chapter 10 we will learn about the profound role that the pineal gland plays in the conversion of external energy into the chemical or electrical energy of our internal physiology. These measurable paradigms are part of what has been called the human energy field. It is experienced by the body via hormones and peptides, but it interacts with other ambient fields, such as light, sound, electricity, and that of all living organisms. Research shows that our bodies are absorptive, reflective, and generative of informational energy fields. We absorb light and heat from the sun, but we also produce our own internal energy fields. Electromagnetic forces are evidenced both in Earth's atmosphere and in the binding of a discrete hormone to its appropriate receptor. Both internal and external aspects of our existence are part of the human energy field. In pondering this phenomenon, you will eventually recognize that the integration of complex systems that exist within your body is a reflection of the integration that exists between the body and all that is outside itself.

Undoubtedly, traditional Western medicine must expand its concept of healing to incorporate a human energy field, which is the foundation of Eastern medical systems, such as acupuncture. Knowledge of the existence and effects of the human energy field is the first stepping-stone on the path to understanding integral physiology, which is a new medical paradigm of integral medicine that unites the enormous contribution of Western medicine with the profound insights of Eastern systems of human energy and health. This is described in some detail in Chapter 11. Ultimately, it is my personal belief that the physical body is a biofeedback machine for the soul; a fact that I believe will eventually be borne out by reliable scientific findings.

Currently, scientists are able to measure some types of energy that the eye cannot see. Conventional medicine commonly utilizes these types of energy in its diagnostic

procedures, such as sonograms, x-rays, magnetic resonance imaging (MRIs), electrocardiograms (EKG), electroencephalograms (EEGs), and the positron emission tomography (PET) scans involved in nuclear medicine. There are various unconventional diagnostic devices that are being used to measure or evaluate subtle energy. This is an important frontier in science today, as it could finally confirm what healers and other intuitives have long experienced and known. The Motoyama machine for measuring flow in the meridians is popular in Japan. Another procedure, bioelectrography, can visualize the corona discharge of any living object. It is obtained by exposure to a high-frequency, high-voltage electromagnetic field. The image is then recorded on photographic paper or by modern video-recording equipment. The gas-discharge visualization (GDV) device and software, invented by the Russian scientist, Konstantin Korotkov (Korotkov, 2001, 2002), is currently one of the most technologically advanced bioelectrography devices. This technique is now known as evoked photon capture (EPC) or electrophotonic imaging (EPI). It takes Kirlian photography, technologically, a step farther. The device is a fast, inexpensive, and noninvasive means for the diagnostic evaluation of physiological and psychological states. Both basic and clinical research on GDV (or EPI) is currently being conducted in several countries, including the United States A two-day symposium in April 2002 at the NIH concluded that GDV bioelectrography is a promising technique that warrants further study (Francomano and Jones, 2003). Being a scientifically oriented physician, I would like to see studies performed that might reveal the potential applications of EPI (as well as other devices now being utilized in other parts of the world) for practical clinical use (see, for example, the section entitled "Brain Scans of Spiritual Experiences" in Chapter 8).

The energy that is referred to as a human energy field is also typically called subtle energy. To avoid semantic gyrations in defining terms, I simply think of subtle energies as energy that, for the typical person, is outside of the awareness provided by the five senses and is involved in the healing process. Subtle energies have to do with healing energy, divine energy, or the Chinese concept of *Qi* (pronounced *chi*), which is described as the fundamental energy of life. However, this effect is beginning to be recorded and measured. For example, it has been proposed that cells actually have receptor sites for subtle energy signals and, therefore, the "noise" recorded from brain waves on an EEG, in fact, may be the sounds of signals being transmitted to specific receptor sites (Rosch, 1994). As we will review in this chapter and the final chapter, we may look very solid, but if medicine followed the tenets of modern physics, we would realize that we are composed of informational energy fields interacting with other energy fields, some more dense, some less dense. However, subtle energies may profoundly impact our physical and emotional health.

Following is a review of various healing modalities that can be considered to be subtle energy medicine. The bibliography provides you with a variety of resources if you are interested in more information about a particular technique.

MODALITIES OF SUBTLE ENERGY MEDICINE

The solution to the riddle of space and time lies outside of space and time.

Ludwig Wittgenstein, 1974

Acupuncture

In November 1997, a panel under the auspices of the NIH convened to formulate the first consensus statement on acupuncture. The NIH consensus panel was comprised of 12 experts from various health-related fields who met for two and a half days to assess the use and effectiveness of acupuncture for a variety of medical conditions. I am honored to have served as a panelist. The panel members spent months reading hundreds of scientific articles and abstracts before attending the conference. At the conference, we listened to numerous presentations, discussed the studies that we had read, and then determined which research studies were worthy of further deliberation. The group of studies we selected as most relevant was then put to the scrutiny of the strictest scientific analysis to determine which of them were effective (NIH, 1997). The consensus statement describes promising results in the areas of adult postoperative and chemotherapy nausea and vomiting as well as for postoperative dental pain. In addition, there were several conditions for which the panel felt that acupuncture might be used as an adjunct treatment or as part of a comprehensive treatment plan, including addiction, stroke rehabilitation, headache, menstrual cramps, tennis elbow, fibromyalgia, myofascial pain, carpal tunnel syndrome, and asthma (NIH, 1997). The World Health Organization has a much longer list of recognized conditions that can be effectively treated with acupuncture. It includes the treatment of respiratory conditions, gastrointestinal illnesses, neurological and muscular disorders, as well as urinary and gynecological problems.

Acupuncture is a treatment based on traditional Chinese medicine, a system of healing that dates back thousands of years. In Chinese medicine, there is a central concept of a vital energy or life force, which is called *Qi*. Meridians are the names given to the complex pathways within our bodies along which Qi (a subtle energy) flows. Acupuncture points are specific points along the meridians at which Qi can be accessed and rebalanced. The homeostasis or balance of Qi is much like that of allostatic load in stress medicine (discussed in Chapter 3). If Qi becomes depleted or imbalanced, then physical, mental, and emotional dysfunction can occur. When there is too little or too much Qi in a given meridian or when the Qi stagnates or is blocked, physical disease can result. In the most basic terms, an acupuncture treatment consists of inserting ultrathin needles at various points on the body, known as gateways, to unblock or rebalance the flow of Qi. In fact, acupuncture techniques can encompass a very broad range of techniques for stimulating Qi, including moxibustion (the burning of the powdered leaves of mugwort [*Artemisia vulgaris*] to deliver gentle warmth), laser light, electromagnetic fields, and electrical current. Research in the 1970s and 1980s linked acupuncture analgesia to endogenous opioid peptide elaboration, particularly the endorphins. In 1995, acupuncture needles were no longer classified as "experimental" by the U.S. Food and Drug Administration (FDA).

Dick Larson, who holds a Ph.D. in acupuncture, has speculated convincingly that the myofascial tissue is the site of the elusive meridians of traditional acupuncture. Larson also effectively expresses how intertwined these meridians are with the myofascial tissue: "A disruption of the energy flow will manifest in the tissues. Conversely, a disruption in the order and balance of the tissues will ultimately manifest in the energy flow. The imbalance can start at either end of the spectrum.

Eventually the physical and the energetic will reflect each other because they are each other" (Larson, 1990).

QiGong

QiGong, which is translated as *chi* cultivation or chi function, is a healing technique that has been practiced for thousands of years in China. Qi and chi are two spellings for the same word, meaning vital force or life energy force. We have chosen to use the spelling Qi. QiGong is an aspect of the practice of Chinese medicine. Like acupuncture, it can restore disturbances in Qi. In some traditions, QiGong is solely a meditative practice, although it is best known for the exercises created by physicians of the ancient martial arts traditions of China. There is, in addition, a breathing component to the practice of QiGong, which is intended to vitalize organs and increase one's energy level. Although many techniques that involve the cultivation of Qi emphasize an underlying goal of spiritual growth, the practice of medical QiGong begins with a positive and sometimes profound impact on physical health, but can expand into mental, emotional, and spiritual development as well. It is an evolving discipline that begins with daily calisthenics and breathing exercises, resulting in comprehensive healthcare and then a refined level of personal development. QiGong has recently been the focus of reports concerning its association with the alleviation of symptoms associated with cancer and other disease, and this is the aspect of the technique that is more popularly known (Lei et al., 1991; Sancier, 1999; Wu et al., 1999). Since the 1950s, China has established "hospitals" exclusively for the treatment of disease by QiGong.

QiGong masters have been tested in Western-style scientific protocols to assess their ability to facilitate healing in people. Currently available scientific equipment (e.g., the SQUID [superconducting quantum interference device], which can measure the extremely sensitive magnetic field of the brain) measures forms of infrared, magnetic, and acoustical energy emitted from the hands of QiGong masters while practicing the technique. When a QiGong master is emitting Qi, a consistent shifting of EEG brain-wave patterns to the alpha state (7 to 14 Hz) occurs in the human or animal to which the Qi is being directed. In contrast, "fake" QiGong masters (who are actually experimental controls) are incapable of creating this change (Lee, 1999). Other research carried out in Austria illustrated that when an extremely well-trained QiGong master underwent neuromonitoring while practicing the technique, reproducible changes in transcranial Doppler sonography (e.g., stimulus-induced 40-Hz oscillations) and near-infrared spectroscopy were recorded (Litscher et al., 2001).

The QiGong healer diagnoses by passing a hand over the patient's body to scan the patient's energy field and by using acupressure to determine Qi disturbances (Jahnke, 1997). According to Richard Lee, a researcher on the effects of QiGong, QiGong masters emit infrasonic waves (a sound wave that cannot be detected by the human ear) at a range of about 70 dB (a wave intensity that is about 100 times more amplified than the infrasonic waves of a normal person) and at a frequency of 8 to 13.5 hertz, which is within the alpha range. In order for the QiGong master to be helpful, he or she must be able to produce an infrasonic amplitude and frequency of Qi that can be absorbed by the patient and, therefore, one that is biologically similar

to the waveform of the patient. Infrasonic waves are acoustically the wavelength that is the most suitable resonant frequency for human tissue, and it is known that the human body can both emit and receive infrasonic waves.

QiGong typically is practiced in three phases. In preparation, the QiGong master quiets the mind. First, the QiGong master adds Qi to the patient, which can, in the receptive patient, increase his or her energy. This procedure generates what is described as a type of energetic chaos in the patient, which allows the possibility of reordering the mind and body. I believe this experience is akin to the concept that emotional trials can potentially bring self-evaluation and growth. The shift we must make to let go of tightly held, but unhelpful, habits can feel chaotic as we pass through that phase. Second, the "bad" or "pervasive" Qi is swept out of the body. Finally, the QiGong master helps reorder the "chaos" by performing a technique called smoothing the Qi. The patient is taught movement sequences that can be independently practiced to ameliorate a specific condition or to promote general health. The technique that involves the QiGong master sending Qi is called external QiGong, while the practice of the patient independently performing movement sequences or breathing exercises is called internal QiGong.

In the United States, various research projects are being carried out on the efficacy of QiGong. An interdisciplinary team funded by the NIH is conducting a large-sample clinical study on QiGong. The study is focusing on the difficulties and unique issues that must be taken into consideration in designing a clinical trial on energy medicine. Their main objective appears to be the promotion of more scholarly and accurate information on energy healing and on QiGong in particular (Ai et al., 2001). In addition, the Dana Farber Cancer Institute's Zakim Center for Integrated Therapies in Boston is running a trial on the efficacy of QiGong (compared with aerobic exercise) as an adjunct therapy for cancer patients.

Applied Kinesiology

Applied kinesiology uses the testing of muscle strength as a diagnostic procedure to indicate the health of various bodily functions. It uses the body's subtle energy system to reveal a correlation between weaknesses in muscle groups and imbalance or disease in the body. In other words, muscle strength is used as a tool to assess the functioning of the body, not the strength of the muscles per se. Points on the body, which correspond to acupuncture points, are treated with pressure to alleviate physical ailments. George J. Goodheart, Jr., a doctor of chiropractic medicine, happened upon the finding in the mid-1960s and developed the technique by progressively identifying associations between known disease or organ impairment (i.e., from an x-ray or some other conventionally accepted test) and specific muscle weakness. He performed cranial, sacral, or muscle adjustments that he claimed relieved the patient of the conventionally identified malady. There were several specific techniques he developed to carry out this procedure. Little scientific research has been performed on the technique. Touch for Health is an offshoot of applied kinesiology. The International College for Applied Kinesiology only admits licensed doctors, while Touch for Health can be studied and practiced by anyone choosing to take the training. It has more emphasis on strengthening and balancing muscles than does

applied kinesiology. Educational kinesiology is an outgrowth of applied kinesiology that seeks to improve attention, memory, and learning.

Thought Field Therapy™ (TFT)

Thought Field Therapy, developed by Roger J. Callahan in the early 1980s, is also an offshoot of applied kinesiology (Callahan, 1985, 1995). An energy-based psychotherapy, TFT utilizes a unique interface between the techniques of applied kinesiology and the acupuncture meridian system to treat phobias, depression, and traumatic psychological problems, including highly successful outcomes with posttraumatic stress disorder. TFT is more effective for anxiety-related problems than for psychoses and has an accelerated rate of response for anxiety-related problems compared with traditional psychological therapies. Callahan felt that traumatic memories are energetically encoded within what he called thought fields, which can set off neurological and hormonal patterns of reaction. The technique uses self-applied percussion at acupuncture points (diagnosed by the therapist) and is performed in a sequence specific to the particular condition. While the patient performs the series of taps, an assessment of one's emotional or traumatic issue (what Callahan would call a perturbation in the thought field) is also performed. The tapping helps facilitate an attunement to the traumatic thought, thus allowing it to become conscious. The technique is designed to decode and release negative and bound-up energy from the thought field both by attuning to the thought field and by performing the percussive tapping. Verbal affirmations are utilized to reverse long-held psychological issues. A self-evaluation of one's current level of stress regarding the traumatic or negative issue that is being treated is used to assess treatment progress (Gallo, 1999).

Therapeutic Touch (TT)

Therapeutic Touch was developed in the early 1970s by Dolores Krieger, Ph.D., R.N. (who was then a professor of nursing at New York University) and her long-time friend and mentor, Dora Kunz, a well-respected and highly developed clairvoyant healer (Krieger, 1979). More than 20 years before the first publications on TT, Krieger had participated in a meditation group at Kunz's home at Pumpkin Hollow Farm in the Berkshires of upstate New York (now the site of many TT retreats). In 1968, Kunz introduced Krieger to Oskar Estebany, a Hungarian citizen who was renowned as a gifted hands-on healer. As a result of this encounter, the two women decided to study healers and develop a technique of therapeutic touch to facilitate healing as an art that almost anyone could learn. Krieger did postdoctoral research on the healing technique (Krieger, 1975, 1976). Early studies showing increased hemoglobin levels in patients treated with TT convinced Krieger to disseminate the concept of TT and to train nurses and others in the technique. Today TT is a widely practiced form of therapy in hospitals and other health centers (Herdtner, 2000).

TT is a contemporary healing technique of laying on of hands (although most practitioners do not actually touch the patient's body) that is based on ancient principles of Indian or Chinese concepts of life force (*prana* and *Qi*, respectively).

Krieger feels that healing is based on a transfer of this life energy, which is present in all living organisms (Quinn, 1989). The practitioner is trained both in intent and methodology. A quality of openness and willingness (i.e., intent) to heal is key to the efficacy of treatment (Heidt, 1990). After a period of centering, the practitioner places his or her hands slightly above the patient and energetically mobilizes areas of blocked energy. TT elicits a relaxation response and has been shown to be effective for degenerative arthritis, for increasing a sense of well-being and decreasing symptoms of distress in cancer patients, and for decreasing stress in hospitalized children and adults as well as in the bereaved (Eckes Peck, 1997; Giasson and Bouchard, 1998; Kramer, 1990; Lafreniere et al., 1999; Quinn, 1993). A landmark study performed on 44 male college students showed faster wound healing from skin-punch biopsy (an intentionally administered skin wound used for tissue biopsy) in subjects receiving TT compared with those who did not. Although no subject (or the administering physician) knew that TT was being performed, 13 of 23 subjects who received TT had completely healed wounds by day 16 of the study, compared with none of the control subjects (Wirth, 1992). The study was disturbing to physicians skeptical of the efficacy of TT because it was impossible to explain away the effect on methodological grounds.

A heated controversy was initiated a few years later when the *Journal of the American Medical Association* (*JAMA*) published a study run by a nine-year-old girl and her mother, a nurse who is outspoken in her bias against TT (Rosa et al., 1998). The subjects were tested under blind conditions to determine whether they could correctly identify which of their hands was closest to the investigator's hand. The vaguely described recruitment method leaves questions as to whether the practitioners were TT professionals, and the gimmicky use of "sensing" an energy field is a nonessential element in the process of performing TT. It is troubling that *JAMA* should have published this methodologically flawed fourth-grade school science project in light of the efforts being made by the NIH to bring to the forefront solid, well-designed research on complementary therapies.

Reiki

The principles that guide Reiki are somewhat similar to those of TT. Reiki was developed by Dr. Mikao Usui, a theologian and the president of the Doshisha University in Kyoto in the mid-1880s, in response to students' queries as to how sick people were healed by Jesus and other spiritual leaders. Like TT, the practitioner begins by focusing or centering him or herself on the intent for the patient's highest good. The practitioner's fingers are placed on or just above the patient's body. During a sequence of hand positions, universal life energy is said to flow from the practitioner's hands to the patient's body. The word Reiki comes from two Japanese characters: *rei*, meaning universal, source of life, air, or spirit; and *ki*, meaning life force or vital energy. The patient's energy is said to be attuned or realigned from the session. Studies support the claim that Reiki may support the immune system (e.g., significant IgA salivary elevations), invokes a sense of relaxation and reduces pain symptoms (Olson and Hanson, 1997; Wardell, 2001). However, these findings are preliminary and more research is warranted.

Polarity Therapy

Polarity Therapy is another energy medicine modality that is akin to Reiki or other touch therapies. Polarity Therapy was developed by Dr. Randolph Stone (1890–1981), who held doctorates in osteopathy, chiropractic, and naturopathy. Stone first published his findings in 1947 in a book entitled *Energy*. He felt that the unseen but empirically known polarity that is manifested in magnetic attraction and repulsion was a reflection of the relationship underlying all physical phenomena, including health. Stone, who derived many of his theories from traditional Eastern religions and medicine, believed that when energy is blocked or unbalanced, disease and other stress-related conditions can occur. He felt that the human energy field could be corrected or brought back to health by several different modalities (e.g., touch, nutrition, exercise, communication), preferably in conjunction with one another. Polarity Therapy is at the core of the treatment. An experienced practitioner places his or her hands on a particular energetic pathway, enhancing the current flowing through the patient. The shift in energy can be experienced by both the therapist and the patient. Stone liked to say, "God geometrizes," meaning that many of the energy pathways in the body form geometric shapes. Polarity Therapy also facilitates the conscious recognition of connections between the mind and the body, while supporting patients to take charge of their own lives and health. Touch, in addition to supportive verbal communication, appears to help clients build inner resources to cope with various emotional issues, even assisting the resolution of posttraumatic syndrome. As far as we have been able to determine, little to no scientific research has been performed on Polarity Therapy. Our literature search yielded one study that showed a decrease in the number of gamma rays measured in a subject's electromagnetic field as a result of receiving Polarity Therapy, but nothing on treatment efficacy (Benford et al., 1999).

Homeopathy

Dr. Samuel Hahnemann, a German physician, developed homeopathy over many years, beginning in 1790. Hahnemann coined the term homeopathy from the Greek words for similar *(omoios*) and feeling (*pathos*) because his medicine produced symptoms in healthy volunteers that were similar to the designated disease symptoms. His philosophy was "let likes be cured by likes," which he called the "principle of similars." He tested 90 substances (e.g., plants, minerals, poisons, hormones, bacteria, viruses, and many others) on himself and various volunteers. He then correlated the reaction to the disease or condition that produced the same symptoms. This was an enormous undertaking. Like the founders of TT or Reiki, Hahnemann also believed that homeopathy transferred a vital energy. Homeopathy was brought to the United States by Hans Burch Gram in 1825 and then supported by the immigration of other German homeopaths.

The problem with homeopathy for any type of molecular or chemical scientist is that the remedies are diluted (and then submitted to a process of vigorous shaking or "succussion") to an extent that supersedes Avogadro's number of molecules or theoretical setpoint (10-24). Avogadro's number is the serial dilution point beyond which even an atom of the original substance theoretically could remain in the dilution.

Some physicians are so bothered by this that they protest the efficacy of homeopathy in words such as "quackery" or "placebo." The patterns of criticism of homeopathy have actually been statistically documented (Vickers, 2000). Numerous well-designed studies can be found in support of the skeptic's view, illustrating either that homeopathy simply does not work (e.g., Ramelet et al., 2000; Vickers et al., 2001; Walach et al., 2001a) or criticizing the methodological quality of the studies (e.g., Linde et al., 2001). Recent research that leans toward findings of efficacy for homeopathic treatment generally calls for the need for larger studies to support their findings (e.g., Jacobs et al., 2001 [acute otitis media (earache) in children]; Linde and Jobste, 2000 [asthma]). However, some studies clearly have favorable results and are also well designed (e.g., Reilly et al., 1986 [hay fever]; Walach et al., 2001b [chronic headache]; Riley et al., 2001 [respiratory and ear complaints]; Berrebi et al., 2001 [lactation]; Papp et al., 1998 [Oscillococcinum®, which can decrease both symptoms and duration of flu if taken within 24 hours of onset]). The work that is most difficult to dismiss is the oft-cited and landmark study performed by researchers from the lab of Dr. Jacques Benveniste. Benveniste and colleagues took basophils (a type of white blood cell) from human blood, mixed them with the homeopathic dilution of IgE antiserum, and found that the basophils proceeded to release histamine (Davenas et al., 1988; Poitevin et al., 1988). That a solution, which according to Avogadro's theoretical setpoint should be devoid of any molecule, could cause histamine release definitely caused a stir among conventional medical scientists.

So, what is going on here? First, selecting the correct homeopathic remedy for a given individual can be a difficult undertaking, even when one utilizes a combination remedy for a specific disorder (and there is controversy about the use of combination remedies). Furthermore, it is my experience that homeopathy is a very subtle adjustment to the body. So, if the patient, for example, is being blasted with steroids for allergy relief, it is the rare individual who will feel any benefit from a homeopathic remedy at such a time. Unlike some in the field, I do not think that homeopathy is only an art or should be relegated to the status of an art. It is a fact that there are times when homeopathy distinctly works and times when it does not; therefore, we need to find out why by expanding our research efforts. Ultimately the issue is that we simply do not know the mechanism of action for homeopathy, so we cannot control for those factors that hinder the efficacy of treatment.

Did you notice that we placed homeopathy in the subtle energy section and not, for instance, next to herbs or other chemical remedies? This is because it is likely that the mechanism of action is not chemical. According to Dr. Bill Gray, author of *Homeopathy: Science or Myth?*, remedies that have been both diluted and succussed cause an alignment of molecules in water that is less compact and has regions that are more organized than the simple diffusion that occurs when a molecule is simply dropped in water. It is also known that electrical fields can create polarized groupings that cluster themselves into coherent groups and move about in the water. Therefore, at homeopathic dilutions of 10 to 7 or greater, principles of quantum electrodynamics replace simple chemistry (Gray, 2000). Beverly Rubik, Ph.D., and others have postulated that electromagnetic information from the original substance is stored in the remedy and then released once it is ingested. Rubik believes that it is theoretically feasible that biological information could be encoded into the remedy

and then could interact with endogenous electromagnetic fields, resulting in a transfer of discrete information (Rubik, 1995).

The research for this hypothesis has now been performed. Jacques Benveniste and his colleagues in France are once again leading the investigation in this area. Benveniste has shown that homeopathy's efficacy largely results from possessing a discrete electromagnetic field frequency that is transmittable to humans. He illustrated that a type of albumin (plasma albumin being the major blood plasma protein and osmotic transporter) that originates from hen's eggs (ovalbumin), once diluted and succussed, increases the cardiac flow in a guinea pig, even when there is no ovalbumin molecule present. However, he performed this experiment not with the remedy itself, but rather by using ordinary water that had been instilled with the electromagnetic digital pattern of the homeopathic ovalbumin. He recorded the "white noise" of the remedy, or what he calls "the specific electromagnetic signature," and transferred it via an oscilloscope (a device that visually displays electrical variations) into a tube with ordinary water. This indicated that the water holds the discrete subtle energy qualities of the remedy. Benveniste then cut the specific electromagnetic signature into a digital electronic file and sent it thousands of miles away via the Internet. When it was "replayed" to water (and other substances, such as plasma), the water was able to generate an effect characteristic of the original substance (Benveniste, 2000). Amazing! I find it exciting that there are now some studies available to show the impact that subtle energies have on our health. Of course, this study must be confirmed by other researchers. Yet, what this is saying is that if the remedy matches the frequency or resonance of the illness, healing could occur. We will be discussing such matters in more detail in Chapter 8, but it appears that what Hahnemann created with his principle of similars was a matching of energetic frequencies that permits healing to occur.

Healing Traditions of Indigenous Peoples

Different healing traditions have arisen from indigenous populations, such as the shamans of the Native American cultures, the kahuna healers of Hawaii, and the curanderos of Latin America. These healing traditions involve practices unique to each distinctive culture. However, underlying every healing tradition are spiritual beliefs that form the basis for both physical healing and a philosophy of life that aids the individual in his or her inner growth or emotional healing. As others have extensively written about the practices of Native Americans, we will not discuss that rich tradition. Rather, we will briefly review the less well-known practices of the Hawaiians and Latin Americans.

Kahuna

The *kahuna*, known to possess esoteric knowledge about healing and what was once called magic, were originally the spiritual teachers of Polynesia and then later of the indigenous Hawaiian people. The traditions of the ancient Hawaiian kahuna were nearly extinguished when Europeans invaded the islands in the late eighteenth century. Assuming that their knowledge was superior to that of the indigenous people, the invaders nearly caused the extinction of a tradition whose sophistication, in some

respects, was unparalleled until the latter half of the twentieth century. For example, a concept central to the kahuna practice is that an integration of the conscious and unconscious mind, which occurs with a realignment of the ego, can result in healing. This concept was not fully realized or extrapolated upon until Carl Jung's work in the first half of the twentieth century and Milton Erickson's publications in the 1960s.

The teachings and treatments of the Hawaiian kahuna are multifaceted and range from the administration of remedies to esoteric spiritual practices. Knowledge and use of native plants, as well as those brought by Polynesian settlers, is central to the treatment of common ailments (Krauss, 1981). Current research is confirming the presence of pharmacologically active components in some of the commonly used botanicals. One plant that is being actively investigated is noni (*Morinda citrifolia*). Findings of novel glycosides as well as animal studies indicating immune-enhancing white blood cell activity and tumor-destroying properties should encourage further research (Hirazumi and Furusawa, 1999; Liu et al., 2001; Wang et al., 2000). In addition to botanicals, a kahuna typically uses *kahuna lomi lomi*, a deeply relaxing, rhythmical massage; *hooponopono*, a problem-solving technique that focuses on loving communication; and the invocation of *aumakua*, one's personal guardian spirit (Horowitz, 2001).

Underlying all practical treatments and remedies is a philosophy of a way of life that encourages a deep personal growth and spiritual exploration. In a publication that directly explains the practices and teachings of the kahuna, Dr. Laura Yardley reveals a system of kahuna spiritual understanding that in many ways shares the basic philosophy of traditional Chinese medicine and Indian *Ayurveda* (Yardley, 1990). Yardley has researched the kahuna beliefs concerning both the physical body and the energetic body (e.g., vital energy or life force) as well as the reciprocal relationship between the two. Yardley reports that in the 1930s, Max Freedom Long, who devoted much of his life to researching the kahuna, uncovered the meanings of secret words used in kahuna chants and rituals. Long determined that the kahuna had an esoteric system of knowledge that emphasized a pursuit of spiritual perfection, a strong code of ethics, and a component that some call magic because it deals with phenomena that are beyond the five senses. Descriptions of the psychological workings of the conscious and unconscious mind and their relationship to the spiritual or "higher self" are prominent. Fundamental to the philosophy is that we harbor within ourselves both healing and harmful energies. It is the job of the kahuna to help keep these in balance.

Curanderos and Curanderas

Some say that the ancient practice of *curanderismo* (from the Spanish verb *curar*, meaning to heal) began with the Mayan, Aztec, and Incan folk healing traditions (Padilla et al., 2001). Other researchers ascribe its origins to the sixteenth-century Spanish conquistadors, who brought with them women, called *curanderas*, to treat the illnesses that the friars could not. The curanderas then conferred their knowledge upon the indigenous peoples of Latin America, who in turn incorporated these traditions into their own local practices (Harding, 1999). Today, the practice of curanderismo is also interwoven with prayers and rituals of Christian origin. At the center of curanderismo is the belief that the *curandera* (female) or *curandero* (male) is a conduit for divine healing and is spiritually

"chosen" to heal others. Curanderos may refer their patients to modern medical clinics and hospitals. However, they also believe that some illnesses are the result of supernatural causes, which are often confused with natural causes and cannot be treated by conventional medicine. Curanderos fault most modern medical physicians for not being capable of recognizing when supernatural causes are in play. One curandera states, "… it amazes me that Western medicine still has not realized the importance of the soul and spirit in healing" (Padilla et al., 2001). In turn, there is concern among the medical establishment that Latin Americans with serious medical conditions may not receive the care they need, turning instead to curanderos. Most curanderos would say that their work involves a supportive partnership with the patient's physician, a relationship of which few physicians ever are aware (Trotter, 2001).

Curanderismo is comprised of three different *niveles* or levels of treatment: physical, spiritual, and mental. Treatment at the physical or material nivele involves an extensive knowledge and use of herbs (*yerbera*); massage therapy skills (*sobardoras*); midwifery (*parteras*); psychological counseling (*consejeras*); and the use of rituals for supernatural cures. Perhaps the most common of these rituals is spiritual cleansing (*barrida* or *limpia*), which is performed to remove sadness, negative emotions, or physical pain. Negative energies are "swept" from the patient, typically with objects, such as a handful of herbs, an egg, or an eagle feather. Curanderos who practice at the spiritual or mental niveles have developed the ability to communicate with spirit beings and, thus, to make known the spirit world to this world. They are said to channel healing vibrations from the spirit world to patients in need of physical or emotional healing (Trotter, 2001).

Curanderismo is practiced more extensively among Latin Americans residing in the United States than generally assumed (Alegria et al., 1977; Padilla et al., 2001). One study estimated that 150 to 200 curanderos and curanderas practice in the Denver metropolitan area. The studied showed that more than 63% of the Latino population had visited one of these curanderos in the past five years (1996 to 2001) and that nearly all of the Latinos in the Denver area (91.3%) were aware of the practices of curanderos (Padilla et al., 2001). We were unable to find studies on clinical efficacy. A case report published in the *American Journal of Psychiatry* in the 1970s did claim that two cases of psychosis were successfully treated with an integration of conventional treatment and curanderismo (Kreisman, 1975).

Prayer and Spiritual Healing

Things found to be unaccountable under rigorous scientific scrutiny ought at least to suggest that science's ability to account for everything may be imperfect.

Elmer and Alyce Green, 1977

To omit the spiritual element from our medical worldview is not only narrow and arbitrary, it appears increasingly to be bad science as well.

Larry Dossey, 1995

Jeff Levin, a physician who researches the impact of prayer and spirituality on healing, examined the results of a general social survey that gathered information on

1,481 adults over a 15-year period. Levin determined that there was an 86% lifetime prevalence of some type of mystical or paranormal experience among these individuals. That is a large majority, which means that a lot of us are keeping these experiences to ourselves. Larry Dossey, who for years has advocated the power of prayer, tells the story of a woman who came to speak to him after nearly everyone had left the hall where he had just given a lecture. She had had cancer that resolved without medical intervention. She lamented that nobody wanted to hear her story and that people with experiences like hers are never interviewed on *Oprah* (Dossey, 1993). Discussion of mystical or healing experiences frightens most of us, makes us feel uncomfortable, and appears to strike extreme discomfort in the hearts of the vast majority of physicians. Levin says that his favorite closed-minded comment from a physician came from a peer-reviewed scientific journal in which the physician is quoted as saying, "This is the kind of thing I would not believe even if it existed" (Levin, 2001).

What is it that makes so many people react with such skepticism to the possibility that there is a spiritual or subtle energy that exists outside the realm of the typical experience of the five senses? The truth is that all humans have insecurities, and physicians are constantly faced with the ultimate source of that insecurity, which is the fear of death and what may or may not follow that moment. In the United States, this fear has been escalated by the terrorist attacks of September 11, 2001. As the insightful physician, Andrew Newberg, states, "In its tireless quest to identify and resolve any threat that can potentially harm us, the mind had discovered the one alarming apprehension that can't be resolved by any means—the sobering understanding that everyone dies" (Newberg et al., 2001). It has taken me many years to realize that needless suffering, and not death, is the real enemy of the practicing physician. I have been a witness to numerous stories and experiences—totally unexplainable in everyday terms—that patients have related as they journeyed through an illness. The scientist in me is becoming much more aware of the mystery of life and the fact that there are phenomena that exist and are quite "real," but not yet explainable in scientific terms.

It is now well documented that prayer, spirituality, and religious experiences can have an impact on both our physical and mental well-being. The research has received both unreasonable criticism (as addressed above) and some valid criticism regarding methodological problems. Even the best-designed studies leave some troubling questions about the impact of prayer and spirituality on health. For example, in Levin's review of the general social survey, he curiously found that mystical experiences (i.e., an intrinsically religious experience) were reported more often by those who were not a part of any organized religion, even after controlling for other possible factors (Levin, 2001). And, we cited another work of Levin's in which he explains that the intrinsically religious are 20% more likely to have experiences of "absorption" or states of altered consciousness than the extrinsically religious (i.e., those who are part of an organized religion). Furthermore, Dr. Harold Koenig, a psychiatrist and researcher in the Department of Psychiatry at Duke University's Medical Center and a preeminent scientist in the field of religion and health, has shown a correlation in elderly depressed patients between rate of time to remission and intrinsic religiosity, but not in church attendance or private religious activities (Koenig et al., 1998).

We have reviewed studies indicating that, for example, loneliness increases the mortality rate in patients with heart disease or that social support increases survival time of women with breast cancer. So, is going to church just a positive source of socializing with associated health effects? Yes, I think this is fully possible. But, what is truly exciting and needs to be more fully researched are those intrinsically religious individuals. What are they doing and what lessons do they have for the rest of us?

There is a body of literature that deals with the specific health advantages that are associated with spending time in meditation or prayer. A number of studies, for instance, have looked at the health-related benefits of practicing transcendental meditation (TM). TM is a meditative practice that is done twice a day for 20 minutes and has been shown to calm the mind, as evidenced by increased alpha-wave activity on EEG. There are also reports—verified by lower lipid peroxide levels—that practice of TM decreases blood pressure, improves hemodynamic functioning, and reduces free radical activity (Barnes et al., 1999; Schneider et al., 1998). It is now well known that a number of psychological and psychosocial interventions can affect immune function and the course of a disease (see Simonton and Sherman, 1998, and Spiegel et al., 1998, for reviews).

Moreover, there are now a handful of studies that cover the issue of religion or spirituality and immune function (Koenig, 2000). The first of these studies, which examined the relationship between frequency of religious service attendance and plasma interleukin-6 (IL-6) levels in 1,718 elderly adults, was performed by Harold Koenig. Koenig found that individuals who attended religious services were 42% (when controlled for other health variables) less likely to have high IL-6 levels (high is defined as >5 pg/mL) than those who did not attend (Koenig et al., 1997). High IL-6 has been correlated to cancer, heart disease, arthritis, and other conditions. IL-6 is also a classic marker of emotional and physical stress. This is only speculative, but perhaps the lack of a religious or spiritual belief system increases one's stress level and, thus, correlates to increased disease, as we discussed in Chapter 3.

Numerous studies have investigated the efficacy of prayer in ameliorating disease in other people. This type of prayer is called intercessory prayer, which means praying for others' well-being by asking God's help in the patient's recovery. Dr. Daniel J. Benor has compiled one of the more extensive reviews of the literature on intercessory prayer in his book, *Healing Research*, which covers more than 150 studies on healing (some of which were first published in *Complementary Medical Research*). Subjects of healing included everything from live plants and yeast in a test tube to humans with a variety of diseases. Benor found that more than half of the experiments resulted in positive effects (Benor, 1992). John Astin, while at the University of Maryland School of Medicine, performed a meta-analysis of 23 trials involving 2,774 patients. He has concluded that while the methodology in many of the studies is poor, the fact that 57% of the trials showed a positive treatment response warrants further research on the topic (Abbot et al., 2001; Astin et al., 2000; Helm et al., 2000; Mackenzie et al., 2000; Meisenhelder and Chandler, 2000; Wiesendanger et al., 2001).

The study that introduced the subject of intercessory prayer to physicians in this country was conducted by a cardiologist, Randolph Byrd, and was published in the *Southern Medical Journal* (Byrd, 1998). Dr. Byrd carried out a well-designed,

randomized, double-blind trial that caused many physicians some serious intellectual challenges, to say the least. The results unequivocally showed the benefits of intercessory prayer in the recovery of cardiac patients, and it was not possible to reasonably criticize the study on methodological grounds. Briefly, Byrd randomly assigned 393 patients from the cardiac care unit of a hospital in San Francisco to either a Protestant or Catholic Christian with a history of active devotional life who would regularly pray for the patients or to a control group that was not appointed to pray for the patients. Neither patients nor staff knew to which group the patient was assigned. Patients who had received prayer had statistically fewer complications during the course of their hospital stay. A second, similar study involving 990 cardiac patients was published in *Archives of Internal Medicine* (Harris, 1999). Both studies showed that while intercessory prayer did not shorten length of hospital stay, it did significantly decrease the course-of-treatment scores. Patients receiving prayers had fewer complications, such as pneumonia, cardiopulmonary arrest, or congestive heart failure. What is remarkable in the 1999 study is that consent forms were avoided, and patients in the study had no knowledge of being participants. In other words, the intercessory prayer was effective, even when the patient was unaware of its occurrence.

Two factors are not controlled for in either of these well-designed studies. The first is that the researchers did not know whether any of the subjects or the controls were already being prayed for by others outside of the study. Perhaps, some of the subjects were getting double doses of prayer or, perhaps, a control subject had a church whose members were keeping constant vigil. Trying to control for how many people are praying for a given patient, however, would never pass an ethics committee. The second factor is who is doing the praying. I believe that Therapeutic Touch, healing, or intercessory prayer are all acquired skills, which, like any skill, can be improved with training and use. It also is possible that some of us are born with a predisposition to these skills (as is true for many vocational or avocational choices in life), but I am convinced that we all harbor the potential. I believe that prayers are good not only for those for whom we pray, but are also good for those who do the praying. Furthermore, I have often wondered what might be the result of a study in which the friends and relatives of a sick person (e.g., a cardiac patient) agreed to spend just 10 minutes a day thinking loving thoughts about that individual—not praying, just thinking loving thoughts. Could this also influence recovery parameters? I think so. While research seems to indicate that some people might be better conduits of healing energy than others, this theory treads on unknown ground. Oral tradition, literature, and perhaps an experience that has somehow touched your own life give testimony to powerful incidences of spontaneous healing and the efficacy of prayer, even from those who do not consider themselves religious.

Russell Targ, physicist and cofounder of Stanford Research Institute (SRI) at Stanford University, reviewed several of the studies mentioned here plus a study that he performed with Fred Sicher. To fully appreciate this study, it is important to understand the distinction between intercessory prayer and distant healing. Distant healing means that someone who is physically remote from the patient is projecting healing energy to that person. The Sicher–Targ study was a double-blind, randomized trial of patients with AIDS who were being treated with triple-drug therapy.

Subjects were assigned either to receive 10 weeks of distant healing or to a control group. After six months, a blind review of medical charts showed significantly fewer AIDS-related illnesses and fewer hospitalizations in the group that received the distant healing (Sicher et al., 1998). Targ points out that their study took one-tenth the number of patients to achieve statistical significance as compared with the other major studies that had been performed. He attributed the positive results of the study to the fact that the study used only individuals with five years or more of healing experience (Targ and Katra, 2001). Apparently, well-intentioned people without skill and training in distant healing may not be capable of producing the same effect.

The most frequently cited study that is critical of the research on intercessory prayer and distant healing was performed by Sloan and colleagues at Columbia University (Sloan et al., 1999). They cite issues such as not controlling for confounding variables, covariates, and multiple comparisons as typically occurring in research on intercessory prayer and distant healing. Sloan also is critical of the prayer research because it has uncovered conflicting findings, such as the fact that church attendance and lower mortality are predominantly associated with women, not men. I do not see this as a flaw in research findings, but rather an interesting fact. Could this be related to the intrinsic/extrinsic practice of religion of which Levin writes? Or, could it be that women are more effectively hardwired for spiritual experiences?

Sloan, however, makes good points in addressing the need to clearly define what is meant by religious or spiritual activity if we are to subject these topics to conventional research. His concerns about the ethics of discussing issues of spirituality with a patient and not imposing one's own beliefs are valid, but this should not be interpreted as permission to deny patients access to such involvement in their healthcare. Certainly, the rule of thumb should be that the patient's spiritual orientation is respected above all else. It is imperative that the physician or healthcare professional honor the patient's wishes, even in determining whether to enter into or avoid a discussion of spirituality or religion. Sensitivity to the patient's needs and desires is paramount in any discussion of this nature.

If the patient chooses to enter into dialogue, the physician can facilitate the patient's effort to clarify issues and provide a forum in which to verbalize the deep emotions that arise during serious illness. The physician needs to appreciate the sacred ground upon which this discussion is held and to have respect for the patient's viewpoints. The most important words to remember in this type of discussion are sensitivity, respect, and appropriateness. Over the years, I have found this type of discussion to be immensely rewarding for both the patient and myself. However, it requires a completely different set of skills from the patient interviewing process that I was taught in medical school. Harvard Medical School, as well as numerous other medical schools, now offers courses on how to discuss topics of spirituality and religion with patients. The George Washington University Medical School has formed The George Washington Institute for Spirituality and Health with the objective of fostering research on health and spirituality as well as developing programs that address spirituality in both medical education and clinical care.

Sloan, himself, cites a 1996 poll of 1,000 adults in the United States showing that 79% of the respondents feel that spiritual faith can help people recover from disease. So, if you are a doctor who is uncomfortable talking about such matters, could

you be harming your patient's recovery by not allowing that person at least to feel permitted to discuss his or her spirituality? It is a difficult question, but one for all physicians to consider. It is my opinion that even as we pursue the science of healing, we must continue to practice the art of healing. While methodological problems will persist as we determine how best to explore this new area for medical application, the answers will be forthcoming by incorporating spirituality into practice, not by keeping it out. There is no doubt in my mind that if physicians are capable of being an emotionally, if not spiritually, caring presence, our patients will fare better no matter what the physical outcome may be. When we present ourselves to our patients as intellectual technicians, there is little room for a truly healing relationship.

So, let us go out on a limb a bit here and ask, "What are the possible mechanisms of action for intercessory prayer, spiritual healing, or distant healing?" It has been proposed that such healing may occur as a result of activating a healing bioenergy, a subtle energy as we have called it. In this paradigm, spiritual healing occurs because the healer is capable of taking energy from the subtle energy realm, using her or his body as a conduit, and then emitting the subtle energy to the ill person, literally giving it to that person. If the ill person is open to receiving it, she or he may benefit physically, emotionally, and spiritually. It is a type of entrainment of subtle energy to a resonance that the patient can access and use to her or his benefit. One can also focus the same kind of healing energy on oneself.

Is there any evidence for such a hypothesis? Yes, actually there is a fair amount. First, there is a principle in physics called nonlocality that was proposed by physicist Dr. David Bohm, who felt that there was an error with quantum physics. He believed that particles at the subquantum level, as we know them, ceased to be separated from one another. Therefore, theoretically, a connection between two seemingly separated entities is maintained. In 1964, a physicist, Dr. John Stewart Bell, mathematically proved Bohm's hypothesis, which has come to be known as Bell's theorem. However, the technology was not available to conclusively prove the theorem until 1982, when French physicists at the Institute of Optics at the University of Paris developed the technology and succeeded in proving the theorem (Talbot, 1991). Bell figured out that if two particles that have interacted are sent in different directions (imagine, for instance, a particle of light), they maintain a connection to each other such that what happens to one particle affects the other one, no matter how far apart. So, essentially, our view that objects are separated by space and time is a human experience, perhaps a human illusion, but certainly not an ultimate reality. Why does Western medicine never take this fact into account? Dr. Jeff Levin, who notes medicine's envy of physics, states it well: "While nonlocality is fast becoming old news to a generation of physicists, biomedical science has not yet caught on.… The fact is that allopathic medicine is not even being true to its own envy; the physics to which it clings has been outdated for most of the twentieth century" (Levin, 2001).

Dr. Larry Dossey writes about three eras in Western medicine. According to Dossey, the first is the era of "materialistic medicine" and the second is the era of mind–body medicine ushered in by research on psychoneuroimmunology (PNI). The third era, Dossey says, is "nonlocal" and holds "that the mind is not confined to points in space and time." He states that in the third era, "minds are viewed as spread through space and time … and that human consciousness is unbounded—and, if

unbounded, then some aspect of the human psyche must be unified" (Dossey, 1993). So, between current knowledge in physics and Dossey's vision of a third era in medicine, the theoretical groundwork has been laid to acknowledge the existence of prayerful energy that could "travel" from one person to another. In fact, what physics perhaps is telling us is that it does not have to go anywhere; it just has to be effectively directed. Several researchers have scientifically investigated healing phenomena.

Elmer Green (yes, the same father of biofeedback) and his wife, Alyce, have performed some fascinating research on intuitives and distant healers at the Menninger Clinic in Topeka, Kansas, where he directed the psychophysiology laboratory. The Greens used an apparatus developed for biofeedback of the theta state and trained themselves and others to remain in the theta state without falling asleep. They learned that hypnogogic insights occur in this state, and it appears that it may be the mind state in which information beyond the knowledge of five senses is acquired. In their book, *Beyond Biofeedback*, the Greens recount numerous stories of people who have intuitive abilities and extraordinary capacities to control body regulation (Green and Green, 1977). Elmer Green also worked with well-known healer Mietek Wirkus. In a copper-walled room, designed to avoid electrical or magnetic influences, electrical emissions were measured from Wirkus as he performed distant healing. Electrical surges as high as 80 volts were emitted from Wirkus as he healed. Wirkus says that he is aware of emitting a charge, which corresponds to these recorded peaks.

Dr. William Tiller of the Department of Material Science and Engineering at Stanford University and a preeminent scientist on the structure of matter has done work similar to Green's. The following is his description of what happens when a healer is healing (Tiller, 1994).

> When a healer emits pulses of subtle energy (not directly observable because they function at levels beyond space-time), a pulse of magnetic vector potential appears at the periphery of this 4-space via interaction between subtle level substance and physical level substance. This magnetic vector potential pulse, in turn, creates an electrical field in the body in the vicinity of the pulse, which acts on the electrodes of the tissue fluids to cause electrical charge separation and, thus, electrical dipole formation. This electrical dipole inside the body of the healer manifests outside the body as a large electrical voltage pulse at an electrode connected to the ear. The body voltage represents a substantial energy effect triggered by the conscious intent of the healer acting through organized subtle/physical body mechanisms.

Tiller writes scientifically, but what he has to say speaks to the theoretical workings of prayer and a transfer of energy. In the quotation above, he reports on a scientific experiment that he has performed, showing the very specific exchange of electrical current that occurs as the healer performs his or her work. In this same article, Tiller also says that he thinks that as spirit increases in dense matter (i.e., as we allow ourselves the experience of the spiritual or subtle energy), so does consciousness. So, as we permit spiritual experiences to be more a part of our lives, our bodies (dense matter) are infused with more consciousness. Tiller believes that with implied intentionality, or what others call "will," "focused attention," or "awareness," we can open our hearts to allow "spirit substance to enter the body." Consciousness comes in through opening the heart and is important because it activates the imprinting of patterns on both our emotions and on the etheric or spiritual energy surrounding

our bodies. The pattern of emotion can allow the etheric or spiritual to enter and affect the physical body, activating hormones, neurons, and more. As Tiller explains, "Consciousness initiated the process, but various levels of energy/matter stuff cooperated to materialize the effect" (Tiller, 1994). So, as our bodies undergo what Tiller calls "structural refinement," we are capable of effectively sending healing energy as well as receiving it to our benefit.

Another piece of research that supports the idea that prayer is a transference of energy is Russell Targ's work at SRI. For years, the Central Intelligence Agency (CIA) funded Targ and his colleagues to perform secret research to learn how information is acquired psychically (also called remote viewing) and then use psychics to obtain information about the Soviet Union. I know this must sound like a Tom Clancy novel, but it was in 1972, at the height of the Cold War, and it truly is factual. Targ has conducted numerous experiments that confirm, far beyond chance, the existence of psychically procured information. Targ's work showed that people are capable of learning rather quickly how to do remote viewing and then, with practice, learn to distinguish between what he calls the psychic signal and other mental information, such as memory or imagination (Targ and Katra, 2001).

Targ admits that the physics behind what permits intuitive acquisition of knowledge is not yet understood, but what is clear from all the research is that time, in this realm of acquiring information, does not correspond to our sense of time. An intuitive can just as easily describe something in the near future as in the present. Targ notes that the Eastern philosophers have, for thousands of years, said that human perception of separation, or what could be called singularity, is an illusion. In an interesting paper, Dr. Edward Garbacz has laid out a theoretical, but sound, comparison between the main facets of Taoist philosophy and modern physics. While his descriptions of Taoism are stronger than those of physics, he makes some interesting comparisons. Garbacz describes of the yin–yang aspect of Taoism as "the qualitative representation of polarity, or the relationship of opposite but related constituents … the immutable duality, mutuality, and balance between events, actions, and individuals; indeed, within or between any and all phenomena" (Garbacz and Marshall, 2001). All of this certainly sounds consistent with Bell's theorem to me. We will discuss this topic in more detail in Chapter 11.

I sometimes work with Lesley Carmack, who is an intuitive practitioner. One patient of mine, Sam, who is a 30-year-old successful architect, came to my office with a fever and elevated white blood cell count. A standard digital rectal examination indicated severe prostatitis. Lesley, with no more than the patient's name, told me that there were hot spots not only in his pelvis, but in his neck as well. I had seen no evidence of a throat or thyroid problem. Trusting her, I ordered a blood thyroid hormone level, which came back quite elevated—a finding consistent with hyperthyroidism. Further examination revealed that Sam had a rare form of thyroiditis called *Savoie's syndrome*, also called *silent thyroiditis* because of its lack of presentation of thyroid tenderness. If it were not for Lesley's intuitive reading, I never would have investigated for a thyroid disorder or have been able to assist Sam in such a comprehensive manner. Since that time, I have had the opportunity to share numerous, complex cases with Lesley. The information that Lesley has given to me has greatly enhanced my ability to treat these patients. I do not pretend to understand the physiological mechanisms underlying

Lesley's intuitive observations, but I have come to fully believe in her ability to make accurate observations—repeatedly.

Stories like these may make us uncomfortable, and we try to dismiss them as simply not scientifically possible or as anecdotal. Remember that, according to Levin, 86% of us experience these "anecdotal" events. Such experiences, however, can require living with a profound duality, a foot in two worlds. Oddly, it requires a solid groundedness in this realm of linear time and separation of objects to effectively operate in the world outside of singularity and time and then to "come back" again. In indigenous cultures, I believe that it was the shaman who held this duality for the whole community. He or she was the one who could move gracefully between the two worlds and bring understanding of the spiritual world back to the community. Experiences of subtle energy can be frightening to some people, as if they are experiencing a little piece of death from which they might not come back. Perhaps, it is also frightening because our culture views people who have these experiences as being a little addled. Yet, the majority of intrinsically religious persons appear to have a higher level of emotional and mental stability (Levin, 2001). The issues are made more complex by the fact that so little research has been done to understand what happens as people enter healing or intuitive states. In this country, such phenomena are spoken of dubiously or woven into ghost stories by children at slumber parties. It is my contention that it is far more valuable to support research in this area than to reject the phenomenon outright—the need to reject perhaps originating from the discomfort within us. The art of medicine is still a mystery. Those in the medical field need to embrace empiric observations even if, as yet, there is no scientific context in which to hold them. Today's mystery may be tomorrow's science. So, for today, we must simply embrace the mystery.

In the last chapter of his book, *God, Faith, and Health*, Jeff Levin concludes, "According to the scientific evidence presented in this book, the new era of medicine is no longer hypothetical. Research findings suggest that we are on the verge of a medical revolution.… The emerging medical model postulates that body, mind, and something beyond mind—call it 'spirit'—work together to promote health, prevent illness, and produce healing" (Levin, 2001). These words are an excellent segue to a more detailed discussion of subtle energies in Chapter 11. Ultimately, I think you will see that we are spiritual beings having a human experience, and not predominantly human beings occasionally having spiritual experiences.

The most beautiful thing we can experience is the mysterious. It is the source of all true art and science. He to whom this emotion is a stranger, who can no longer pause to wonder and stand rapt in awe, is as good as dead—his eyes are closed. This insight into the mystery of life, coupled though it be with fear, has also given rise to religion. To know that what is impenetrable to us really exists, manifesting itself as the highest wisdom and the most radiant beauty, which our dull faculties can comprehend only in their most primitive forms—this knowledge, this feeling, is at the center of true religiousness. In this sense and in this sense only, I belong to the ranks of devoutly religious men.

Albert Einstein, 1950

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7 Energy Medicine
Focus on Nonthermal Electromagnetic Therapies

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OPEN RESEARCH AND DEVELOPMENT

In the previous chapter, a range of cutting-edge energy modalities were briefly reviewed. In this chapter, some of the nonthermal bioelectromagnetic treatments, such as microwave therapy, pulsed electromagnetic field therapy (PEMF), and pulsed signal therapy (PST), will be examined in greater depth. However, here the nonthermal electromagnetic therapies will be approached as a subfield of energy medicine.

ASSESSING EFFICACY OF ELECTROMAGNETIC THERAPIES

There is no single underlying theory connecting electromagnetics to physiology that is widely accepted. Research on the effects of externally applied electromagnetic forces has proceeded in a piecemeal manner. Research from conventional biochemistry has focused on investigations of possible cellular mechanisms, while clinical trials have concentrated on treatment for conditions already defined from the biochemical medical perspective. European developments in naturopathic and homeopathic medicine have evolved a range of therapeutic approaches using electrostimulation; however, the conventional medical community has rejected the possibility of these approaches, assuming no biochemical mechanisms could be affected by such weak electrical processes. Innovations and evidence are accumulating in conventional medicine and biophysics that increase the plausibility of electrotherapeutics that use very subtle effects. Differences in national cultures and stark contrasts among research and therapeutic traditions have kept these communities of practice separated and continue to create tasks for translation and interpretation of knowledge for those wanting to engage in both the study and practice of electrotherapeutics. Integrative medicine can bridge these very different worlds, fostering understanding between them.

Integrative medical practice is often held up to inappropriate standards. The assumed gold standard for evidence-based medicine, the randomized controlled trial (RCT), is actually appropriate for only a small part of medicine (Institute of

Medicine, 2005). About 15% of conventional therapeutic practice can and should be evaluated with RCTs. A single, variable question, such as the efficacy of a drug, can be evaluated with an RCT, while surgeries are a prime example of therapies that cannot be evaluated using RCTs. It is widely accepted that the skill of the surgeons are major factors in clinical results. Similarly, with the highly personalized and individual approach of many integrative medical practices, the skill and influence of the practitioner may be accepted as a major factor in the healing process. The goal of having objective, well-defined study endpoints in RCTs leads to a focus on health outcomes (e.g., mortality, tumor shrinkage, or change in a measurable physiological parameter, such as temperature or blood pressure). An exclusive focus on objective endpoints can miss or ignore other effects, such as subjective symptoms (e.g., pain, fatigue, and cognitive function) or general well being.

A report on appropriate research methods for alternative medicine, from the National Academy of Sciences Institute of Medicine (NAS IOM), emphasized the distinction between efficacy and effectiveness (Institute of Medicine, 2005). Efficacy refers to what a treatment can do under ideal circumstances; effectiveness indicates what a treatment does do in routine daily use. An RCT provides information about efficacy in the statistical majority of a population. Effectiveness addresses clinical results in everyday use, for particular individuals. Efficacy does not equal effectiveness. Studies of efficacy may ignore the results of those individuals who have negative outcomes far different from the majority of the study population. The NAS IOM report has clear recommendations for research methods appropriate to the medical practice being studied and details the difficulties of research on complex conditions and similarly complex treatments.

Conventional medicine, based in biochemistry, is typically interested in cause-and-effect relationships between underlying mechanisms of illness, treatments designed to alter those mechanisms, and the observed results for the patient. Linear cause-and-effect approaches usually try to identify the simplest possible causal models (i.e., the fewest explanatory variables and the simplest relationships among those variables) that can account for the observed effects. These methods have been highly successful for medicine in acute conditions and for diseases caused by microorganisms, when individual causes can be objectified and eliminated or repaired immediately. This approach is less successful with chronic diseases.

Alternative medical approaches may use more complex systems models, with multiple factors and multiple levels of highly interactive and iterative relationships, rather than linear causal connections. Research methods can be developed that describe interactive and multiplicative processes, (i.e., the effects of one variable depend on the presence or value of one or more other variables). An example of one such method is *recursive partitioning*, which uses statistical models specifically designed to identify interactive effects of large numbers of causal factors acting simultaneously (Institute of Medicine, 2005).

In some complementary medical modalities (e.g., traditional Chinese medicine or homeopathy) there is no such thing as a standard treatment or dose. Individualization of therapy to a unique combination of patient characteristics is a core concept. Studying clinical outcomes is the only way to evaluate such complex systems of interaction, and the descriptions of the treatments and patients must be rich enough

to capture salient dynamics. By definition and theory, these treatments cannot be standardized in the same way in which drug treatments are standardized by substance, dose, and route and timing of administration. Randomized controlled trials, using isolated variables, are not appropriate for clinical assessments of such highly individualized treatments (Institute of Medicine, 2005). Nonetheless, effectiveness studies can be conducted on individualized therapies using practical clinical trials (Tunis et al., 2003).

Controversy attends integrative medical investigations because different research and clinical traditions begin from very different worldviews and assumptions. For instance, Western biochemistry focuses on specific molecular processes at the level of the cell, while acupuncture focuses on balancing large-scale energetic flows among the body's subsystems. A detailed and full critique of the widely varied approaches in integrative medicine is beyond the scope of this present discussion. Here, some biochemical and biophysical theories that suggest quite subtle energetic processes are present in the body will be surveyed—beyond the dynamics expected from biochemistry at states of thermodynamic equilibrium.

Biochemistry is based on an understanding of the flow of energy that drives chemical reactions. When applied to chemistry, thermodynamics (literally meaning the power of heat) uses statistical descriptions of the behavior of large ensembles of molecules to predict the behavior of chemical syntheses. Physical properties of molecules can be combined to express internal energy, and thermodynamic potentials are used to describe the conditions necessary for equilibrium and spontaneous processes. Thus, thermodynamics describes how cellular biochemical systems respond to changes in their surroundings.

New models in biophysics emphasize cooperative electrical activity of highly ordered ensembles of elements, at all scales of physiology: cells, tissues, organs, organ systems, as well as the whole body. These new insights can form theoretical bridges between some of the different medical traditions. For instance, acupuncture and homeopathy have plausible electromagnetic modes of action when viewed from the perspective of these new biochemical and biophysical models. After surveying these theoretical constructs, we will look further at some clinical applications of electromagnetic devices that claim to be using these subtle energetic processes for therapeutic benefit.

CONVENTIONAL ELECTROTHERAPY: USING RELATIVELY HIGH CURRENTS

In conventional medicine, electrotherapy is used primarily for iontophoresis, neuromuscular stimulation, or tissue heating (Robertson et al., 2006). In iontophoresis, direct current (DC) pushes therapeutically beneficial ions through the skin barrier with safe, DC densities that are less than 0.5 milliAmps/cm^2 cathode currents and less than 1.0 mA /cm^2 at the anode (Robertson et al., 2006). For nerve and muscle stimulation, alternating current (AC) is used in the frequency range from 1 to 10 kHz, to promote tissue healing or for pain relief. Stimulus voltages are typically in the range of 10 to 100 V, and currents range from 10 to 100 mA, supplied from electrodes

in contact with the skin. Within the broad range of stimulus frequencies, the most commonly used nerve and muscle stimulation is with AC frequencies in the 4 kHz range. Sports medicine and training applications use AC frequencies in the 2.5 kHz range for muscle strengthening (Robertson et al., 2006). AC frequencies in the radio shortwave and microwave ranges are used to produce deep-tissue diathermy, heating by induced currents. Clinical diathermy devices in the radio shortwave band typically use 27.12 MHz. Microwave diathermy that uses 2,450 MHz, 915 MHz, and 434 MHz are approved for medical use in Europe, Australia, and New Zealand. In the United States, only 2,450 MHz and 915 MHz are approved for medical applications (Robertson et al., 2006).

Current flow in diathermy involves complex processes, so patient observations of perceived heating and the rates of applied power are used to guide these therapies. AC current in tissue causes charged particles to oscillate. As the oscillations decay, kinetic energy is distributed among surrounding molecules, increasing their motion—which is heat. The rise in tissue temperature depends on the specific absorption rate of the AC current energy. More heat will be produced in tissue that conducts more easily, making the specific absorption rate greater. Diathermy is effective for heating deep muscle tissue because current flows more easily in muscle than in fat. The fundamental frequency often is delivered in pulses, which are more effective for producing charged particle oscillation. The power applied during therapy is thus a combination of pulse amplitude, duration, and frequency. Typical peak pulse amplitudes range from 100 to 1000 watts, in pulse durations of 25 to 400 msec and with the average power in the current delivered to the patient being a few watts (McMeeken and Stillman, 2002).

SUBTLE BIOCHEMISTRY

Laboratory research with animals and *in vitro* cell and tissue cultures have shown a wide array of important effects caused by weak static magnetic or alternating electromagnetic fields. The effects appear at various physiological levels: changes in cell proliferation, alterations in membrane structure and function, changes in nucleic acids, protein phosphorylation, and adenosine triphosphate (ATP) synthesis; they also can have very global effects, such as entrainment of brain rhythms and conditioned brain responses by imposed fields (Bassett, 1994; Smith, 1994; Adey, 2004). Electromagnetic field signals far too weak to cause heating can mimic heat stress, activating DNA production of two specific heat shock proteins, HSP70 and HSP27 (Blank and Goodman, 2004; Leszczynski et al., 2003). Because this stress response can be triggered by both heat and weak electromagnetic fields, the thermal and nonthermal thresholds can be directly compared. The thermal specific absorption rate to trigger HSP70 production is ~10^{-1} W/kg, while the nonthermal electromagnetic field specific absorption rate is ~10^{-12} W/kg—many orders of magnitude less than the heat stress (Blank and Goodman, 2004; Markov, 2006).

According to biochemical tenets of conventional medicine, weak electromagnetic signals are not expected to interact with metabolic processes because the thermodynamics of biochemistry seem to require that thermal noise in the tissues would swamp such weak signals. In contrast to these expectations, acupuncture and homeopathy expect extremely weak signals to have profound effects for shifting physiological

processes. The mechanisms of action for some models of acupuncture, described later in this chapter, include the minute electrical potentials of a few milliamperes provided by bimetallic battery potentials in the needles.

Large Effects by Very Weak Electromagnetic Fields

There is a stark contrast between the amounts of energy commonly used in conventional electrotherapy and the energy that produces some curiously subtle effects. In laboratory research and in some clinical devices, very low-power electromagnetic fields are used to change physiological processes. Chapter 5 briefly described microwave therapy in Russia and Ukraine. For a wide range of conditions, benefits have been shown from stimulation in the 50 to 70 Ghz microwave spectrum, using low intensities ranging from a few mW/cm^2 down to a few $\mu\mu W/cm^2$, when applied at acupuncture points associated with the effected organ systems. The small area of the stimulation makes the total power applied miniscule, when compared to a process like microwave diathermy.

Biological effects of very weak electromagnetic fields also are found in laboratory research. Early research conducted in W. Ross Adey's laboratory, identified cellular processes in which specific frequencies produced maximum effects (Adey, 1981, 1988). This work was confirmed in other laboratories (Bawin et al., 1975; Bawin and Adey, 1976; Blackman et al., 1979). Cossarizza et al. (1989) observed that when lymphocytes from aged humans are exposed to pulsed magnetic fields, they recover immune loss that occurs with aging. Autoimmune destabilizing reactions have been stimulated in rats by weak microwave radiation at 2,375 MHz, with field strengths of about 500 mW/cm^2 (Smith, 1994). In additional studies, yeast cell growth showed a resonant harmonic response from weak microwave radiation in the region of 42 GHz. Exposure to continuous microwave radiation, with a power flux density of a few mW/cm^2, produced exponential growth rates having a fine-grained frequency response effect, at a harmonic periodicity of 8 MHz. Furthermore, extremely low frequencies (i.e., at 3kHz and below), applied directly at very weak field strengths or as imposed amplitude modulation on radio frequency carrier waves, had an effect on neuroblastoma cells in culture, brain biochemistry, and (electroencephalogram) EEG in these animals; the effects depend on very specific signal characteristics (Smith, 1994).

Applied weak fields can have strengths approximating the Earth's magnetic field, which is about 50 μT or 5 G. The energy available from these fields is much smaller than the characteristic energies of chemical reactions and much less than would be conventionally expected to induce motion in charged particles with molecular masses. In laboratory studies, the parameters of these fields—frequency, amplitude, waveform, and duration of application—have been shown to be very specific to the observed effects.

Recognition of physiological sensitivities to *exogenous* electromagnetic fields arose from observing interaction with internal, *endogenous* electrical processes. An example of endogenous electrical control processes is the piezoelectric properties of bone that employs electromechanical control to determine which cells become osteoclasts or osteoblasts. The piezoelectric forces induced by walking and mechanical support direct continual remodeling of bone to provide optimal structures, by regulating cellular processes with electrical effects (Marino and Becker, 1970).

Currents of injury were observed early in the nineteenth century. Robert Becker's profound work in the twentieth century, on the role of electrical currents in growth, regeneration, and repair, is now well accepted, although he was initially castigated for pursuing fanciful theory (Becker, 1972, 1974; Becker and Seldon, 1985). Today, bone repair stimulated by electrical currents—in older practice, using electrodes inserted directly into the injury, and in newer less invasive procedures, using induction of electrical microcurrents by magnetic fields—is common practice for fractures with delayed unions (Lavine et al., 1972; Basset et al., 1974).

Detailed clinical research in orthopedic biophysical stimulation has identified specific cellular processes responding to particular forces. Osteogenic activity can be promoted by selective pathways at the cell membrane depending on the physical forces applied:

1. Voltage-gated calcium channels by capacitive coupling
2. Intracellular calcium stores with inductive coupling
3. Inositol phosphate by mechanical stimulation

As these models of cellular action continue to develop, therapy modalities and doses can be refined and directed toward particular situations (Brighton et al., 2001; Cardossi and Trania, 2004; Ryaby, 2004).

Electromagnetic processes in the skeletal system have been extensively characterized. Basic research on cells in cultures, animals, and clinical studies have refined specific information for frequency, amplitude, waveform, orientation, and exposure required to activate specific processes in specific cells (Bassett, 1989). Processes prompted by bioelectromagnetic signals have been identified in cascades of interactions taking place from the cell surface into the cytoplasm and on into the cell nucleus and genes, where selective transcriptional and translational effects have been identified (Brighton et al., 1979).

Although soft tissue healing of chronic wounds supported by electrical currents has been extensively studied, therapeutic applications are not yet widely used (Cukjati and Savrin, 2004). Endogenous wound-induced electric fields guide the cellular movements that close wounds. Externally applied electrical fields can affect orientation, migration, and proliferation of cells with key roles in healing, such as fibroclasts and keratinocytes. DC stimulation with current ranging from 0.2 to 1 mA have been demonstrated to accelerate wound healing when the positive electrode is present on the wound surface and the negative electrode is on the adjacent healthy skin. Negative electrode positioning on the wound surface has antimicrobial effects and is useful in initial stages of treatment.

When low-frequency pulsed electric currents are applied locally, both electrodes are positioned on surrounding healthy skin. Quite distant locations also can be used for promoting wound healing. Most research has used locations on spinal cord or acupuncture points. Pulse amplitudes are set just below visible titanic contraction (i.e., just below continuous contraction) of surrounding muscles. Pulsed low-frequency current increases partial oxygen tension ($p0_2$) around the wound, so benefits appear to derive from improved microcirculation. It has been inferred that stimulation promotes capillary growth. DC does not appear to effect $p0_2$, so the mechanisms of benefit are assumed to be different (Cukjati and Savrin, 2004).

Candidate Sites for Weak Electromagnetic Field Interactions

Various components of cells may be potential sites for interaction with low-power, nonthermal and nonionizing energy: intracellular structures (e.g., microtubules), various specific proteins and chromophores, mitochondria, the nucleus, cell membranes, intracellular membranes, processes in charged ion populations, and global processes involving the entire cell (Kitchen and Dyson, 2002).

- The constituent elements of cellular microtubules are electrically polarized dimers with the internal ends negatively charged relative to the surface. The microtubule cylinders can produce piezoelectric and electropiezo effects, responding selectively to resonant frequencies.
- Chromophores, such as melanin, nucleic acids, and various proteins, can absorb specific wavelengths of electromagnetic radiation in the visible, infrared, and ultraviolet ranges of the spectrum. This stored energy can then be passed to other molecules, used in biochemical processes, or degraded into waste heat.
- Mitochondria may respond to specific wavelengths of red laser light, which is absorbed by components of the respiratory chain within the mitochondria, leading to changes in the redox status of the mitochondria and cytoplasm, altered membrane permeability, and consequent changes in transport of ions across the cell wall (Karu, 1988). Smith has suggested that frequencies in the infrared not absorbed by mitochondrial cytochromes can be absorbed by cytochromic constituents of the cell membrane, effecting direct changes in calcium ion flux at these sites (Smith, 1991a, 1991b).
- Some candidates for electromagnetic field interactions in the nucleus have been suggested. Hiskenkamp and Takahashi proposed that pulsed magnetic fields can directly impact DNA synthesis and transcription (Hiskenkamp et al., 1978; Takahashi et al., 1986). Adey suggested that such effects were more likely mediated by secondary messengers, such as cAMP and Ca2+ ions, from influences at the cell membrane (Adey, 1988). DNA expression of HSP70 and HSP27 demonstrates that nuclear processes can be affected (Blank and Goodman, 2004, Leszczynski, 2003). Goodman and colleagues have repeatedly reported electromagnetic-induced genomic changes, particularly the expression of heat shock stress proteins, using both pulsed magnetic fields and sinusoidal magnetic fields (Goodman et al., 1983; Goodman and Blank, 2002). It remains to be seen whether the gene expressions are a direct effect or are mediated by other dynamics.
- Proteins can have conformational changes from interaction with an oscillating electromagnetic field, that is, if the frequency and power of the field match the kinetic character of the reactions. With protein processes in the cell membrane, such changes can induce pumping effects, transporting substances across the membrane, such as with triggers for ATP synthesis (Tsong, 1989; Westerhoff et al., 1986; Astumian et al., 1987).

- Organelles are surrounded with membranes that have electrical characteristics similar to the cell plasma membrane, and analogous effects may occur at these intracellular membranes, modifying the activity of the organelles.
- Ion populations are present in both intracellular and extracellular fluids. The movement of sodium, potassium, and calcium ions drive important functions in cell regulation. Ions respond to electromagnetic field oscillations. Movement in response to field effects can modify the ion distribution, changing cell activity (Frohlich, 1988).

CANDIDATE MECHANISMS FOR WEAK ELECTROMAGNETIC FIELD INTERACTIONS

W. Ross Adey's research group was among the earliest to focus on the cell membrane as a site of interaction with pulsed magnetic fields at particular frequencies, amplitudes, and waveforms. Adey proposed that specific magnetic field effects at the membrane could enhance communications with hormones, antibodies, and neurotransmitters. He demonstrated that an initially weak trigger could have prompt, large amplification by enhancing membrane communication processes. Further, amplitude or pulse modulations of frequencies in the radio frequency and microwave spectrum trigger cellular effects, while the same frequencies will simply pass transparently through tissue as an unmodulated carrier wave (Adey, 1981, 1988).

As mentioned, based on the concept of thermal noise, a number of physicists and physical chemists have rejected the possibility that static and low-frequency magnetic fields can cause biological effects (Muchsam and Pilla, 1996; Pilla et al., 1997; Zhadin, 1998). Bianco and Chiabrera provided an elegant explanation for thermal noise appearing to drown out any weak electromagnetic signals. Using the Lorentz–Langevin model, they clearly showed that the force applied by a magnetic field on a charge moving outside the binding site is negligible when compared to the background Brownian motion and it would then seem that such applied forces should have no significant effect on binding or transport at a cell membrane (Bianco and Chiabrera, 1992). The modeling by Bianco and Chiabrera does not, however, exclude other possible mechanisms for weak signal effects because the field interactions need not be outside the molecular binding sites. Some interesting work using calmodium shows calcium bound in the molecule to exhibit hopping between two energy states—driven by the noise (Markov, 2007; Pilla et al., 1997). Physicists and some engineers have continued to propose microthermal, rather than nonthermal processes for the biological membrane effects (Astumian et al., 1995; Barnes, 1996), but Adey and others argue that thermal processes cannot account for the specificity of frequency, amplitude, waveform, and time duration requirements (Adey, 2004; Markov, 2006).

Process Control and Magnetosomes

Binhi and Rubin (2007) recently have criticized assumptions of the so-called thermal threshold or thermal noise paradox. They reject the assumptions that electromagnetic field effects must be power processes. They propose that signals controlling magnetic

resonance conditions influence the probability that a process will proceed rather than acting with the power of an either/or trigger. By modifying the electromagnet environment, subtle signals may shift the tendencies for cellular activities, rather than turning such activities on or off. Binhi and Rubin also offer magnetosomes, biological structures that are sensitive to magnetic flux, as another candidate for a mechanism of biological sensitivity to very weak magnetic forces. Magnetite crystals are present in many organisms. Bacteria use magnetosomes for orientation in the magnetic environment, and some bird species navigate using the Earth's magnetic field, possibly relying on magnetosomes. Magnetite crystals are present in human brain tissue, estimated at concentrations of 10^8 crystals per gram (Kirschvink et al., 1992). Alternatively, Dobson provided an estimate of about 50ng/g (Dobson, 2002).

Stochastic Resonance

Noise is the underlying problem in any attempt to explain biological and clinical responses of human tissues to weak electromagnetic fields. Even for models using triggering signals, rather than power-driving models, the signal-to-noise ratio governs the signal detection at the molecular/cellular/tissue target in the presence of thermal noise. Stochastic resonance is a mechanism that provides signal amplification in a thermally noisy environment. Electronic devices and living systems can detect signals that are much smaller than ambient noise. The key to understanding these processes is the nonlinear character of the systems. Noise itself plays a constructive role in detecting weak rhythmic signals. Regular, periodic signals can entrain the ambient noise, boosting the signal strength to a detectable level (Bulsara and Gammaitoni, 1996; Oschman, 2004; Wiesenfeld, 1995).

Ion Cyclotron Resonance (ICR)

As will be seen in Chapter 10, Abraham Liboff proposed that ion cyclotron resonance (ICR) is a possible mechanism for the frequency-tuning effects discovered by Adey's group and others (Liboff, 1985, 2003). The Lorentz force influences ions that are moving in a stable magnetic field—the Earth's magnetic field in this case. Energy is transferred to the charged particle, as the ion begins to revolve in a circular or orbital cycle at right angles to the steady magnetic field. This cyclotron resonance allows magnetic fields applied at very low strength to act in concert with the Earth's magnetic field, producing significant biological effects by enhancing movement of important ions, such as sodium, potassium, and calcium, across cell membranes. Other laboratories have confirmed cellular responses to cyclotron resonance conditions for specific ions (Oschman, 2004). From laboratory studies of nonbiological solutions, Del Giudice and his colleagues proposed that coherent quantum domains in water clusters allow ions to move within the interstices between water coherence domains without collisions among themselves, thus, achieving cyclotron resonance by following classical orbits in the magnetic fields (Del Giudice et al., 2002). Without collisions, the energy loss of thermal noise is avoided. Liboff reports observation of this type of resonance not only in bone, but also in rat behavior, diatom motility, calcium uptake in cell culture, neurite outgrowth, and plant growth as well as in other organisms (Liboff, 2003).

Ion Parametric Resonance

To resolve the thermal noise problems in the ICR model, Lednev formulated an ion parametric resonance. In this quantum approach, an ion in the binding site of a macromolecule is considered as a charged harmonic oscillator. Lednev proposed that the presence of a static magnetic field could split the energy level of the bound ion into two sublevels with amplitudes corresponding to electromagnetic frequencies in the infrared band (Lednev, 1991). The ion parametric resonance model was sharply criticized by Adair (1992), but was further developed throughout the 1990s (Adair, 1992; Blanchard and Blackman, 1994; Blackman et al., 1995; Engstrom, 1996).

Biomolecular Resonance Signaling

Communication and regulation by molecular ligands and hormones have been assumed to require direct molecule-to-molecule interaction. Jacques Benveniste and his colleagues have demonstrated that communication and regulation processes can happen when only the electronic signatures of the regulating molecules are provided, with no direct molecular contact, and even without the actual physical presence of the regulating molecule.

As described in Chapter 6, Jacques Benveniste and his laboratory coworkers caused a great controversy when they demonstrated that a homeopathic dilution of IgE antiserum could trigger degranulation of white blood cell basophils, even though the solution was diluted so far that Avogradro's number should assure that it was devoid of any molecule of the original IgE antiserum (Benveniste, 2004). These high dilution experiments have been independently replicated by six laboratories, and one of the labs performed the replication twice. Benveniste's team turned their attention to how water might interact with molecules to preserve and convey some active principle, when prepared according to homeopathic methods (e.g., classical homeopathic remedies are always protected from exposure to sunlight). They demonstrated that the active effects of such high dilutions could be erased by applying oscillating magnetic fields. Benveniste and colleagues then succeeded in transferring biological information to water using electronic amplification of recorded electromagnetic signatures from specific molecules (Benveniste, 2004).

Earlier, Emilio del Giudice, also had suggested that the electromagnetic information of a substance can be transduced into the surrounding water molecules by affecting the fields produced by large clusters of molecules. Thus, when the substance is diluted out, the information is retained in the water. In his view, "the homeopathic remedy works only if it is meaningful to the array of previously existing signals in the organism; otherwise it is washed out" (Del Giudice et al., 1983).

One of Benveniste's early research models demonstrated that electronically transmitted resonant molecular signals could have the same effect on isolated guinea pig heart tissue as would occur if the tissue were directly infused with molecules of the regulating hormone. This work is conceptually similar to some of Ewa Lindstrom's work on T-cell response to low-intensity, extremely low frequency magnetic fields which will be discussed in Chapter 10.

Benveniste's team also developed an antigen–antibody precipitation test that can remotely detect an antigen or groups of antigens; they demonstrated the effects of digitally recorded heparin signals on plasma and fibrinogen clotting. The researchers suggest these techniques demonstrate that biological molecules can communicate like a radio set tuned to resonate with specific other molecules. This communication takes place through the water molecules that surround all biological molecules. Rather than being randomly in motion, the water is highly ordered and may have an amplifying role. Some of Benveniste's data indicate that the signal is emitted by the molecules, but finally is conveyed by water. Thus, biological molecules are similar to the strings of a violin that do not create music without the resonating wooden body. The surrounding water, like the wooden walls of the violin's body, provides resonant amplification. The fact that molecules emit specific frequencies has been known for decades. The same energetic processes that are the basis of molecular spectroscopy also appear to produce aggregate signatures, oscillating in frequencies comparabl to sound that can form resonant communication between interacting molecules (Benveniste, 2004).

The conventional expectation has been that the three-dimensional shape of a ligand matches a receptor embedded in a cell membrane, and physical proximity of the ligand induces a change in the conformation of the receptor, which in turn triggers a cascade of events prompting cell function. Benveniste's proposal suggests the ligand proximity to a receptor structure favors co-resonance of ligand–receptor specific electromagnetic signals and, furthermore, that resonance amplifies molecular conformational changes at all steps of the cascade inducing cell function.

Free Radical Delay Effects

W. Ross Adey has championed even very short-lived free radicals as the basis of specific electromagnetic field interactions with high-frequency microwaves in the gigahertz range. Although the brief lifetime of a free radical is about a nanosecond, imposed magnetic fields may delay the period for finding molecular partners with the required matching electron spins. These delays could influence the rates or amount of product in chemical reactions (McLauchlan and Steiner, 1994). McLauchlan suggested that these electron spin-correlated free radical pairings could provide a mechanism for biosensitivities at extremely low magnetic field levels (McLauchlan, 1992). These interactions are complex and incompletely understood. Lander has emphasized that future work on free radical signaling may join classic intracellular and intercellular messengers, to reveal "a fabric of communications that has evolved to yield exquisite specificity" (Lander, 1997). Free radicals, having been implicated in pathologies of oxidative stress, may be messengers and mediators in key cellular functions (Adey, 2004).

OPEN SYSTEMS DYNAMICS

Standard biochemical models cannot explain the behavior of all the regulation and control processes in physiology because of the extraordinary properties of biological tissues, such as the extremely high capability for electrical polarization at cell

membranes, the high degrees of cooperativity (which imply very low degrees of freedom), and yet a very high flexibility of response. Cooperativity is the interaction process by which binding of a ligand to one site on a macromolecule influences binding at subsequent sites; it can even cause a conformational change in one subunit of a protein to be transmitted to all others. These cooperative effects could be expected to reduce the degrees of freedom (i.e., the possible number of different molecular interactions) for molecules. Yet, biochemical regulation processes exhibit wide ranges of fine-grained control. Similarly, simple equilibrium physics is insufficient to characterize the more subtle metabolic processes, such as electromagnetic wave propagation in living tissues or large-scale biological rhythms.

Standard biochemical models assume the molecular interactions in cell metabolic and reproduction cycles are happening in a thermodynamic equilibrium. For example, metabolic processes in a cell, involving large populations of molecules, interacting primarily through chemical binding relations with their valence electrons, can be adequately modeled with the statistical methods of thermodynamics. However, the high sensitivity of some metabolic processes, often modified by a single molecule, cannot be described using classical thermodynamics.

Herbert Frohlich's mathematical modeling demonstrated that classic electrodynamics under the conditions of thermodynamic equilibrium could not explain the order in living systems (Frohlich, 1968). As an alternative, he treated the biological communications and regulation processes as open systems with continued energy available, moving the cellular communication and regulation systems away from thermal equilibrium and allowing stable, coherent states of oscillation with high efficiencies. Using this approach, Frohlich's model suggests that cell membranes amplify microwaves in a narrow frequency band, providing long-range coherent oscillations with stable phase relations (Wu, 1994). The potential polarities and dimensions of cell membranes suggest sufficient oscillating field strengths for relatively long-range interactive coupling. Cell membranes can develop electrical potential of about 100 mA across a thickness of about 10^{-6} cm, giving a field strength of about 10^5 V/cm—an enormous potential, which approximates the breakthrough strength of an electrical field in air. Possible physical oscillating movements of the membranes at these dimensions would produce optical phonons in the upper microwave region of 10^{11} to 10^{12} Hz. Frohlich indicated that evidence for his theory could be found in Russian studies showing that coherent microwaves (in the middle of this range) effected genetic processes in bacteria and bone marrow cells in mice, with very selective sensitivity to specific frequencies at very low power. Attempts at systematic investigation of these effects, using yeast cell growth rate as the laboratory model, have not provided consistent results, so Frohlich's theory is still considered unproven (Popp, 1994).

Both classical thermodyamics and nonequilibrium representations are useful, but each shows different aspects of the processes being studied. Using an analogy of shifting between high-temperature and low-temperature physics, Fritz Popp illustrated the differences in perspectives between the random, stochastic processes that are assumed to exist at thermodynamic equilibrium and nonlinear processes that are expected when an open system is far from thermodynamic equilibrium, with possible sudden changes of state. Often, the best insulators at high temperatures become

the best superconductors below a critical temperature. Biochemical concepts of ligand-receptor binding, with the lock and key principle, are very simplified outlines of the quantum electrodynamics. Which perspective is most appropriate to provide accurate details to investigate particular processes remains an open question. The choice of approach determines the results that can be obtained and the applicability and validity of the models (Popp, 1994).

NONLINEAR MODELS

In recent decades, high-speed, reiterative computation has enabled the development of nonlinear mathematical models, usually subsumed under the label of "deterministic chaos" or simply "chaotic models." These methods allow simple equations to describe very complex behaviors that might have been expressed less concisely in earlier stochastic methods. The chaotic models can provide descriptions of complex biological behavior in terms of regulating principles—an alternative to descriptions of component mechanisms.

Coherent Biophotonic Regulation

Biophotons are ultraweak light emissions from biological systems. All living cells of plants and animals emit biophotons, which cannot be seen by the naked eye, but can be measured by using photomultipliers. These very weak light emissions are an expression of the functional state of the living organism. For example, cancer cells and healthy cells of the same type show typical differences in biophoton emission (Bischof, 1995). Research on biophotonics was initiated in the 1970s by Fritz Popp and frequently is associated with the International Institute of Biophysics in Neuss, Germany. The institute actually is a worldwide network of biologists, chemists, medical researchers, physicists, and other scientists working at more than 20 different universities and government research institutes.

The biophoton theory proposes that light is stored in the DNA molecules of cell nuclei, and a dynamic web of light is constantly released and absorbed by the DNA, communicating among cell organelles, cells, tissues, and organs within the body. Investigators suggest that this biophotonic web is the organism's main communication network and the principal regulating system for all life processes. Morphogenesis, growth, differentiation, and regeneration are explained by the structuring and regulating activity of the coherent biophoton field. Normally the biophotons remain within the cell, coordinating activities and constantly exchanged between molecules through resonant linkages. The holographic biophoton field of the brain, the nervous system, and perhaps even of the whole organism was proposed as the basis of memory and other consciousness phenomena by neurophysiologist Karl Pribram and others (Bischof, 1995). The consciousness-like coherence properties of the biophoton field also may relate to electromagnetic properties of the physical vacuum, in which no particles of matter are present, but vast potential energy produces spontaneous creation and annihilation of virtual particle pairs. If these spontaneous events are coherent, rather than random, the coherence is proposed to provide an interface

for the processes of physiology with the nonphysical realms of mind, psyche, and consciousness (Bischof, 1995).

Fritz Popp and his colleagues suggest that massively coherent, resonating biophotonic communication lies at the core of metabolic regulation and also might provide a substrate for species interindividual electromagnetic communication (Mei, 1994; Popp et al., 1994). Very specific investigations of particular theoretical mechanisms, such as Stochastic Resonance, or Ion Cyclotron Resonance, or Frohlich's coherent states of oscillation, may fail to grasp interactive or cumulative effects. It is useful and necessary to look at various effects of different frequencies, but it would be a mistake to think that the frequency domains work independently. Multiple frequencies can manifest synergies produced by mode coupling effects across the entire electromagnetic spectrum.

Systematically examining interactions between electromagnetic fields and living systems is exceedingly difficult because of the many parameters that define the processes:

1. Location of the field in relation to the biological system
2. Whether the electric or the magnetic component of the field is acting to produce the effects
3. Field amplitudes
4. Frequency spectrum
5. Timing and waveforms
6. Field gradients and directions of polarization

A small change in any of these parameters may dramatically alter the biological effects. As Fritz Popp has expressed it: "Living systems may be playing an unimaginably huge concert of all the modes, creating a completely new category of phenomena, outside classical electrodynamics" (Popp, 1994).

Cellular Ensembles Whispering Together

Ross Adey also proposed that some response mechanisms may be found in highly cooperative properties of populations of elements, rather than in a single detector mechanism (Adey, 2004). Recognizing the wide ranges of electromagnetic effects and the panoply of possible mechanisms, Adey used discoveries of aggregated signal detection processes in sensory physiology and of so-called *quorum sensing* in bacterial colonies to hypothesize about the mechanisms of intercommunicating cellular ensembles. Pathogenic bacteria, long thought to operate independently, are now understood to exhibit communication through a process that recognizes the number of colony members, waiting for a population threshold before releasing toxins. These quorum-sensing systems demonstrate that combinations of interacting processes can form a concert of harmonious communication (Erickson et al., 2002). Adey envisioned ensembles of cell populations "cooperatively whispering together in intercellular communication and organized hierarchically at atomic and molecular levels." Given nanosecond scale processes of free radical interactions with magnetic fields, this subtle symphony may extend all the way down to the quantum zero point field (Adey, 2004). Thus, the level of subtle processes begins to approach the scale of William Tiller's investigations described in Chapters 6 and 11.

Disequilibrium Conditions Permit Tissue Response

Numerous animal and *in vitro* studies as well as clinical experience suggest the initial conditions of the electromagnetic field-sensitive targets determine whether a physiologically meaningful bio-effect will be achieved. For example, when a broken bone receives treatment with PEMF, the surrounding soft tissues receive the same dose as the fracture site; however, a physiologically important response occurs only in the injured bone tissue, while changes in the soft tissue have not been observed. This phenomenon is crucially important, as it indicates that magnetic fields are more effective when the tissue is out of equilibrium. The finding may mean that experiments with healthy volunteers (i.e., a stable system) reduce the manifestation of therapeutic response compared with patients who are victims of injury or disease.

Therapy Designed from Ion Resonance

Within a few years of Liboff's formulation of the ICR mechanism, the theory was used to design stimulators for repair of bone nonunions (Diebert et al., 1994). This ICR application is fundamentally different from other PEMF therapies. With ICR techniques, the magnetic signal is applied as a sine wave and is thought to interact with the Earth's magnetic field; thus, the emphasis shifts away from intensity to the specific resonant frequencies. Two ICR devices are approved for use by the U.S. Food and Drug Administration (FDA): one for the treatment of bone nonunions and the second for spinal fusion following back surgery.

As noted in Chapter 5, PEMF methods approved for orthopedic therapies also are used to treat a wide range of conditions, including Parkinson's disease, multiple sclerosis, Tourette's syndrome, migraines, and seasonal affective disorder (SAD). Wider application of PEMF or ICR devices is impeded by FDA rules that require clinical trials and approvals on an indication-by-indication basis. In the United States, the industry for these devices is inhibited by the expense of meeting requirements that would allow application in additional conditions—even in orthopedics, for which clinical evidence has demonstrated efficacy with osteoarthritis, osteonecrosis, osteochondritis dessecans, osteogenesis imperfects, and osteoporosis. A wider range of applications for PEMF and ICR devices is approved by other countries, with strict standards for safety and efficacy that are based on sound clinical studies (Trock et al., 1993, 1994). FDA approval processes have frustrated introduction of these techniques into the United States. Basic research and clinical data have been published to support wider use, if the regulatory climate changes (Oschman, 2004). Later in this chapter, the SEQEX, an ICR-based system that claims benefits in a broad range of treatment, will be reviewed.

EVIDENCE OF TISSUE COORDINATION AND COMMUNICATIONS

Insights from Cancer Detection

Recent decades have seen advances in cancer tumor detection using electrical and electronic properties of tissue. This work was adumbrated early in the twentieth century; however, progress was slow until recent years. Fricke and Morse identified differences

in impedance and capacitance between normal tissue, benign tissue tumors, and malignant tumors (Fricke and Morse, 1926). Harold Saxon Burr and his colleagues at Yale studied the character of detailed changes in the electrical potential across the surface of tumors induced in mice. They noted an initial hyperelectrical inflammatory response, a return to normal, followed by hypoelectrical activity (Burr et al., 1940). Further work by Burr demonstrated that skin voltage measurements could identify a variety of physiological states, such as cancer, wound healing, central nervous system activity, drug use, sleep, and reproductive and developmental cycles (Brewitt, 1996).

During the same period that Burr was pursuing the electrical character of physiological processes, Albert Szent-Gyorgi was deriving principles of electronic biology from observations that proteins act like semiconductors (Szent-Gyorgi, 1941). Initially, his view was opposed, but over the next few decades most biological molecules were found to have properties of semiconductors (Rosenberg and Postow, 1969). More recently, Swarup and his colleagues found that electrical conductivity of tumors showed very specific differences when measured at radio frequencies between 104 Hz and 108 Hz. At 104 to 106 Hz, tumor conductivity was lower than normal tissue, while at 106 to 108 Hz the tumor conductivity was higher than normal tissue (Swarup et al., 1991). When measured directly on the tumors, conductivities were 6 to 7.5 times higher than normal (Oschman, 2004; Smith et al., 1986).

Cuzick and colleagues described a noninvasive electropotential test based on Burr's original observations that tumors present electrical disturbances that can extend to the skin surface (Cuzick, 1998b). Compared with normal cells, rapidly proliferating and transforming cells have electrically depolarized cell membranes. A sensor array placed in the region of a suspected lesion monitors the depolarization processes. A multicenter study of the method was organized at eight breast cancer centers in five European countries. Tests were performed on 661 patients scheduled for biopsy. Electropotential measures showed 55% specificity and 90% sensitivity for palpable lesions (Cuzick, 1998a; Oschman, 2004).

An alternative approach called the T-Scan, which measures electrical impedance, achieved FDA approval as an adjunct to mammography after an international multicenter trial was performed. The T-Scan transmits low-level electrical signals into the body, and induced electric fields are monitored by a noninvasive probe placed on the breast (Oschman, 2004). Proprietary algorithms measure across several frequencies and display real-time capacitance and conductivity images of the breast. Malignant tissue has different electrical properties from normal tissue because of differences in water and electrolyte content, changes in membrane permeability, and differences in packing density and orientation of cells (Scholz and Anderson, 2000). An improved and simplified model is now suitable for use in a physician's office. The T-Scan 2000ED (ED for early detection) can detect tumors smaller than one centimeter, which is considered a survival threshold (Michaelson et al., 2002). The method is effective for women with dense breast tissue, painless, and in contrast with other techniques, has no harmful radiation.

Nordenström's Biologically Closed Electric Circuits (BCEC)

One of the early independent explorers of electrical processes in living tissue is Dr. Björn Nordenström. He hypothesized intrinsic electrical pathways in the body,

the most prominent being the vascular network. Blood vessel walls act as cable insulation and the circulating blood is the low-resistance, current-carrying medium. Nordenström successfully treated malignant tumors with DC. As discussed in Chapter 5, inspired by observation of curious corona patterns surrounding pulmonary malignancies and pulmonary granulomas in radiographs of lung tissue, Nordenström performed a series of experiments in the 1950s, demonstrating that fluctuations in electrical potential within lung masses could alter the fluid dynamics in the extracellular water. From this foundation, he evolved his concept of biologically closed electrical circuits (BCEC), demonstrating that corrective electrical stimulation can intervene in very subtle electrical disorders. Nordenström revealed that significant electrical potentials are generated by organs and that potentials of this magnitude lead to formation of fibrous tissue at electrical interfaces, suggesting that organ capsules and other fibrous structures, such as pleura and peritoneum, are formed by BCEC processes (Rosch and Nordenström, 2004).

Nordenström identified specific BCEC, such as the vascular closed circuit (VCC), the vascular–interstitial closed circuit (VICC), and the vascular–interstitial–neuromuscular circuit (VINMC) (Nordenström and Nordenström, 2004). The VCC is composed of blood vessels. The walls of blood vessels have 150 to 200 times more electrical resistance than blood plasma, so blood vessels are relatively insulated conducting cables for the transport of charged ions and have multiple loops. Externally applied magnetic fields can induce ionic current flows in the loops. The VICC is formed in the capillaries by electrical interactions between conducting blood plasma in the vessels and interstitial fluids in the tissues outside the capillaries. The VICC can be activated by several processes, such as metabolic activity that produces physiological disturbances in homeostasis or a working muscle that generates metabolites that make it more electropositive in comparison with blood. In addition, the field gradient between muscle and blood promotes ion exchange via the VICC, transferring waste products to the blood. The presence of the waste products in the blood signals the heart and respiratory muscles to increase their activity, thus helping respire the waste and rebalance the system.

VINMCs develop at junctions with conductive media, such as the content of urinary or glandular ducts and the exoplasm of nerves. VINMC interface with VICC at neuromuscular connections, as blood vessels and interstitial fluid make contact at open membrane channels on the axons. In these circuits, the conductive capacities of the vessels are much larger than the axon channels, so axon potentials also activate the vascular branches of the channels. Nordenström proposed that these circuits are a basic mechanism of evolutionary biological development.

Spontaneously occurring electrical positive polarity in injured tissue attracts blood platelets and leukocytes, both of which carry a surplus of fixed electronegative surface charges. The electro aggregation of platelets can promote thrombosis of capillaries surrounding an injury site. Positively charged diseased tissue also can attract leukocytes with this process. According to Nordenström's theory, electrical communications in the body can be compared with circuits driven by batteries. However, unlike batteries, which maintain a consistent polarity, the accumulated driving charges in healthy BCEC constantly oscillate between positive and negative. As a malignant tumor grows, its inner cells are cut off from the circulatory system and slowly perish.

This cell death produces chemical changes and production of positive electrical potential in the tumor compared to adjacent tissues. Using measurements with electrode inserted into the tumor tissue and surrounding normal tissue, Nordenström found that the visual coronas in x-rays were produced by this electropositive phase of the tumor growth. Spikes appeared on the surface of the tumor and water moved into the surrounding tissue, dehydrating the tumor and forming radiating structures. Running current into the tumor could amplify and prolong the electropositive phase and trigger a variety of tumor-fighting effects, including attracting leukocytes and producing acid at the center of the tumor. Using refinements of these principles, Nordenström evolved effective electrical treatments for metastatic lung tumors and breast cancers, and his concepts have been further developed in treatments of a variety of tumors.

Nordenström introduced his methods into China in 1987, and collaborations led by Dr. Xin Yu-ling have extended the treatment methods into many Chinese hospitals. By the late 1990s, over 6,000 patients with various kinds of tumors had been treated. Instead of inserting an anode in the tumor and a cathode in normal tissue, as Nordenström had done, the Chinese researchers placed both anodes and cathodes in the tumors. Using currents of 40 to 100 mA at 6 to 8 V, the Chinese studies propose that tumor cell destruction results from electrolysis, electrophoresis, and electroosmosis effects. The cathodes concentrate Na^+, K^+, and H^+ ions, while the anodes concentrate Cl^- ions. Hydration and acidity increase at the cathode, and dehydration and alkalinity increase at the anode. A review of this Chinese work, and similar methods by Dr. Chung-Kwang Chou, at the City of Hope Medical Center, in Duarte, California, were reviewed in a special issue of *Bioelectromagnetics*, guest edited by Dr. Chou (Chou, 1997a: Chou et al., 1997b; Li et al., 1997; Xin et al., 1997).

Acupuncture Electric Circuits

As Dr. Björn Nordenström extended his concepts of BCEC, he eventually came to believe that his communications processes were the same as the Chinese concept of *Qi* that flows through the organ systems; he suggested that the subtle energy of Qi is also the basis of useful information appearing in the corona of Kirlian images.

Acupuncture is at least partly an electromagnetic phenomenon. Transmission of ionic charge between two acupuncture points has been demonstrated (Mussat, 1974). Acupuncture needles with one metal for the shaft and a different metal for the handle form tiny batteries. Some schools of acupuncture use additional electrical stimulation applied to the needles. From an electrical perspective, each organ in the body is a like a battery contained in a sac of electrolytes, with a positive potential on the surface of the sac that is the aggregate result of electrical processes in the tissues of the organ. The normal functions of an organ can be expected to generate stronger and smoother electrical effects than an organ in distress or disorder. Electrical current and ionic flows are postulated to move along the fascia, providing electrical connections from the organs to the skin surface.

Acupuncture channels are located between muscle groups (Figure 7.1), while acupuncture points are located in depressions between the muscles, providing access to the underlying connective fascia tissue. Acupuncture points form interconnecting nodes in connective tissues among all of the circulatory and regulatory

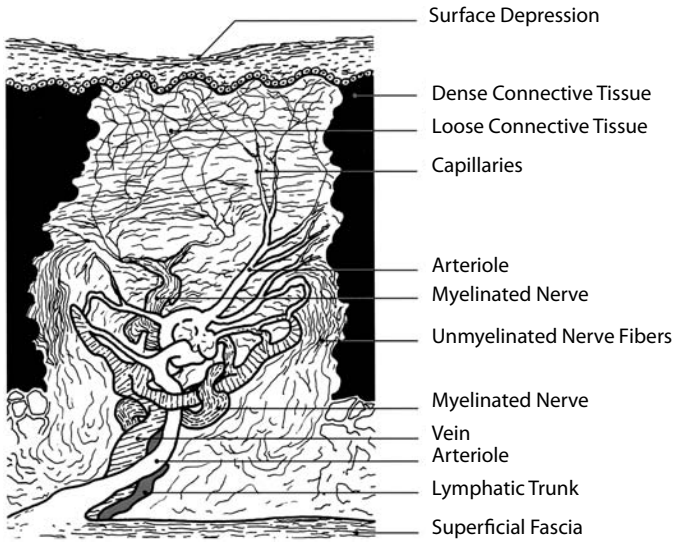

FIGURE 7.1 Anatomy of an acupuncture point. (From Helms, J.M., *Acupuncture Energetics; A Clinical Approach for Physicians,* Medical Acupuncture Publisher, Berkeley, CA, 1995. With permission.)

body systems. Each point is situated below the skin in a tube of connective tissue that is less dense than the sheath of denser, and electrically less conductive, tissue that surrounds it. At the core of this tube is a bundle of fluid vessels composed of a lymphatic trunk, entwined with an arteriole and an associated vein. The bundle of vessels creates a passage between the skin and the deeper tissues. The walls of the vessels are thin compared with their large diameters. The vessels are surrounded by webs of unmyelinated cholinergic nerve fibers from the autonomic nervous system. Other myelinated nerves weave in close proximity with the blood and lymph vessels but are not entangled with them. From a mechanical perspective, the column is an elastic system that absorbs jolts and pressure. The vascular bundle also provides interaction between the vasomotor system and temperature regulation (Helms, 1995; Auzeich, 1984; Bossy and Sambuc, 1989; Senelar, 1979; Terral, 1988).

Most, but not every acupuncture point has this structure. Senelar and Auzeich found that 80% of the points examined showed this combination (Senelar and Auzeich, 1989). Heine described this columnar arrangement in similar terms, emphasizing the high-speed electrical transmission functions of the proteoglycans in the loose connective tissues that pass through the fascia with the vessels and nerves. The proteoglycan network responds to electromagnetic and magnetic stimuli, easily depolarizing, and transmitting these electrical potentials over long distances as chain reactions in tissue matrix (Heine, 1988a, 1988b, 1990).

A modern acupuncture needle is made with a steel shaft and a handle of a dissimilar metal—copper, silver, bronze or an alloy, wound around the upper half to one quarter of the shaft. Three different electrical phenomena arise when an acupuncture needle is inserted in the tissue. A thermoelectric potential develops along the shaft

because of a temperature gradient. The tip in the tissue becomes warmer than the handle, and the larger surface area of the handle prolongs this effect by acting as a radiator in contact with air. The tip of the needle develops a positive potential via the Seebeck effect of the temperature gradient. A thermoelectric Seebeck effect causes current flow between two dissimilar metals, if there is a temperature difference at their junction. This electrode effect is also augmented by bimetallic microbattery potentials, developed at the interface of the steel shaft and the dissimilar metal of the handle (Helms, 1995).

The positive potential at the needle tip attracts negatively charged ions from the interstitial medium, until a saturation equilibrium is established. At body temperature and typical room temperature, a needle can develop current of 2 to 3 μA After insertion, it will take 10 to 15 minutes to reach an ionic saturation equilibrium in the tissue around the needle tip. This procedure results in a neutral needling technique, which is used for the acupuncture therapeutic actions of dispersing excess energy or drawing energy toward the needle as part of a combined pattern of inserted needles.

Heating the handle or manually rotating the needle changes the inserted tip to a negative electrical potential, attracting positive ions in the interstitial medium. A heated or manipulated needle can develop currents of 10 to 15 μA, which would take 60 to 90 minutes to reach saturation equilibrium. Needles are not usually left inserted for that long. The negative tip potential is used to tonify, increasing the electron flow into the acupuncture point and supplementing the activity in the channel. A useful needle pattern may combine tonifying at one point with neutral needling at a point further along the channel to help attract the flow of energy. Repeating this process by next tonifying the needle that was originally neutral and inserting a new neutral needle farther along the channel, allows the therapy to direct tonic flow in a specific direction along the channel (Helms, 1995).

Connecting additional electrical stimulation to acupuncture needles is used to tonify, add energy to depleted organ systems, or strengthen the flow in a channel when the intent is to disperse congested or inflamed areas, especially for pain analgesia (Helms, 1995). Two specific analgesia mechanisms have been identified with different electrostimulation methods. Low-frequency/high-intensity stimulation is in the range of 2 to 4 Hz, at 10 or more mA. This method particularly activates high-threshold (but also some low-threshold) skin and muscle afferent nerves and produces analgesic effects that develop slowly, are generated through the body, and continue after the stimulation has ceased. High-frequency/low-intensity stimulation uses frequencies greater than 70 Hz and current less than 10 mA, which produces analgesia that develops quickly, is localized to the region of stimulation, and ceases when the stimulation ends. Low-frequency/high-intensity analgesia is dependent on endorphins, while high-frequency/low-intensity is not, but rather is mediated by the monoamine neurotransmitters, serotonin and norepinephrine (Helms, 1995).

Oschman's Living Matrix Model

James Oschman proposes that highly conductive fluids in the circulatory system and various extracellular fluids can form virtual antennas for externally applied electromagnetic fields, adding that semiconducting molecular ensembles in the tissues

mediate these subtle and significant regulatory actions. The human body is composed of an interconnected fibrous matrix that extends throughout the body at all levels. Connective tissues with semiconductor properties join bones, tendons, ligaments, cartilage, and fascia. Proteins in the supporting structures of organs and glands also are part of this web of connective tissues. Individual cells interconnect with the larger scale matrix through transmembrane proteins, such as the integrins. Through these transmembrane processes, the larger scales of the matrix are continuous with the cytoskeleton of the cells, connecting all the way into the nuclear matrix of the cell. Oschman calls this interconnecting web the *living matrix* (Oschman, 2000, 2003).

Following the lead of Dr. Mae-Wan Ho, author and noted biophysicist, Oschman points to the liquid crystalline capabilities of the component arrays of the connective matrix—especially of collagen, which makes up 70% of connective tissues and, thus, is the most abundant protein in the animal kingdom. Collagens have dielectric and conductive properties that make them very sensitive to mechanical pressures, pH, ionic composition, and electromagnetic fields. The electrical properties are related to the water molecules bound in and around the collagen triple helix. Nuclear magnetic resonance studies and Fourier transform infrared spectroscopy have both provided evidence of three populations of water molecules associated with collagen. Interstitial water is very tightly bound within the collagen triple helix and strongly interacts with peptide bonds of the polypeptide chains. Bound water is the more loosely structured water cylinder on the surface of the triple helix. Free water fills the spaces between the fibrils and between the fibers. A layer of water four or five molecules deep separates neighboring triple helices. The biological water is integral to the liquid crystallinity of collagens and other composites, such as the extracellular matrix, cell membrane, and cytoplasm (Ho, 1999).

The ordered network of water molecules, connected by hydrogen bonds (hydrogen atom protons without their electrons are positive electric charges) and interspersed in the collagen matrix, is important because it supports proton rapid jump conduction. Jump conduction is self-conduction and is much faster than ordinary electrical conduction or nerve fiber conduction because it does not require net movement of the charged particle itself. Jump conduction passes rapidly down a line of relatively static, hydrogen-bonded water molecules. Models of jump conduction imply that signal conductivity along fibers is 100 times faster than conductivity across the fiber.

The highly ordered structure of collagen liquid crystal fibers creates the high-efficiency intercommunication. The characteristic orientation of these fibers is related to mechanical stress and strains that impact the tissue and may be crucial to communication. The water network surrounding the connective tissues is linked to ordered hydrogen-bonded water in the ion channels of the cell membrane, providing a direct electrical link between distant signals and the intracellular matrix of individual cells. Any mechanical deformations of the protein-bound water network will result in electrical disturbances that, in turn, result in mechanical effects. Proton jump conduction likely provides a much better intercommunication system than the much slower nervous system. Ho proposes that the particular role of the nervous system *is* to slow down intercommunication. Animals lacking a nervous system are

sensitive to the environment, and humans often manifest capabilities for hypersensitive, rapid response in emergencies. There is a body consciousness that is prior to the brain consciousness of the nervous system. Ho proposes that a body consciousness, with all aspects of consciousness (i.e., sentience, intercommunication, and memory), is distributed throughout the entire body, and brain consciousness is embedded in and coupled to body consciousness (Ho, 1998, 1999; Ho and Knight, 1998).

Liboff's Electrogenomic Vector Field

Abraham Liboff proposes to reform the current understanding of physiology, moving away from the usual emphasis on biochemistry and seeing the body as fundamentally electrical. He uses recent magnetic and electromagnetic therapeutic innovations in neurology to map a topological scale of electrical actions in living processes. Neuroelectromagnetic therapies can be categorized into three groups: disruptive, gross, and subtle (Jenrow and Liboff, 2004). Disruptive action is large-scale intervention, exemplified by electroshock therapy, and also by a newer magnetic method of inducing electrical current into deep brain tissue, such as occurs with repetitive transcranial magnetic stimulation. These magnetic induction methods do not induce convulsions, but do disrupt electrical brain activities sufficiently to prompt repatterning of neural activity, similar to recovery from electroconvulsive therapy. Cardiac pacemakers are an example of gross action therapies; they apply electromagnetic signals to mimic or recreate endogenous physiologic signals that have gone awry. The subtle category of action involves signal strengths that were typically assumed to be too small for coupling with physiological processes. As mentioned, based on the noise of random thermal vibrations in molecules, conventional biophysics sets lower limits for physiological effects from external electric or magnetic phenomena. Yet, observations persist that apparently subthreshold electromagnetic processes do interact with physiological events.

Liboff observes that most researchers investigating this issue are constrained by the assumptions of biochemistry. He writes, "If a certain voltage with a certain waveshape can enhance serotonin levels or increase the expression of heat shock protein, this becomes an end in itself. Rare indeed is the physiologist who inquires as to why this happens.… It matters little how these signals do the trick. Electromagnetism merely serves to transform the therapy into the familiar language of biochemistry. The medical community, the pharmaceutical industry, the funding agencies, and the healthcare providers have all been weaned on this language, and, because they are uncomfortable with electromagnetism, they are content to see the results phrased in terms of hormones, cytokines, and membrane receptors" (Liboff, 2004). Liboff proposes an alternate way to interpret subtle physiological effects—viewing the living system as an electromagnetic entity and, thus, *expecting* to find physiological response to electromagnetic phenomena. The hormonal and enzymatic effects occur, but are associated with changes in the systems' electromagnetism.

A slight deviation from Liboff's conjecture, that chemical articulation ought to be seen as a sidelight, would be to view hormonal and enzymatic expression as the milieu in which electromagnetic communications, regulation, and control exists and expresses itself. This combination still validates the important effects

of electromagnetic signals, but also recognizes that molecules provide the internal physical environment and constitute the building blocks of the body substance. In this modified version of Liboff's proposal, molecular activities are what the electromagnetic signals are regulating.

Liboff forcefully sets aside biochemistry, to break the conceptual hold it has on the basic assumptions about mechanisms in medicine, and to refocus on the electromagnetic effects as central. He emphasizes that even when we look at life as made of molecules, electromagnetism is the force that produces life. He points to the way electromagnetism forms the hierarchies that physically constitute a living being—a sequence of increasingly complex systems, with each step governed by electromagnetic force: electrons, hadrons, atoms, molecules, polymers, organelles, cells, tissues, organs, organisms.

Liboff suggests that the focus on cell biology and biochemistry should be reduced because the foundation of both bodily structures and systems is electromagnetic forces that give rise to a complex electromagnetic field unique to each organism. The total field of any living organism stems from all its constituent electrodynamic activities and has vast regularities—resulting from ontogenic and phylogenetic history. Thus, each human being has regularities in the totality of our electromagnetic symphony, relating us to our species and all that came before. Liboff asserts that the electromagnetic field of a living organism is a manifestation of the potential in the genome, which he calls the electrogenomic field. The field grows with us, is modified by changes in the developing embryo and by maturation following birth, and also reflects traumatic changes from wounds during life. The practical and theoretic advantage of this concept is mathematical: A field can be described as a vector, that is, a summation of a complex panoply of forces, and is the consequence of the source's distribution of current density and charge density. Living organisms possess highly organized systems—arranged in a manner to sustain survival through adaptive interactions with the environment. With death, the electromagnetic field of the system, these distributions of charge and current, are no longer viable. Life, itself, is an expression of the electromagnetic field.

Liboff focuses on the field of the entire organism, not only on the electrical characteristics of particular components, therefore emphasizing that the charged field acts as a template for restoring the system to its normal state. Considering human life as an expression of an electromagnetic field presents electromagnetic medicine in a new light. The endogenous electromagnetic field can be altered with the application of external electromagnetic fields. Liboff states, "Once we admit to the possibility that the gestalt of the body's physiologic state—homeostasis, metabolic turnover, respiration, enzymatic rates—is no more than an intertwined system that can be represented by a single electromagnetic field vector, then we are also admitting to the fact that this intrinsic field and, therefore, its corresponding physiological state will be changed by imposing a new applied field. Needless to point out, the change can either be beneficial in the form of a therapeutic signal to repair that which has gone awry, or it can be harmful, as an unwanted deviation from the normal resting state. Therefore, the formulation of this field also subsumes the problem of electromagnetic pollution, and likely, the question of electrosensitivity as well. There should be

no question among those making use of electric or magnetic therapies that humans can react negatively to the imposition of electromagnetic fields that act to distort the body's normal electromagnetic field" (Liboff, 2004). Here, Liboff is proposing that the electrogenomic field is not merely associated with the living system, but may itself be an ultimate biologic representation of the system. Postulating a distinct electromagnetic field for every organism suggests that this representation may be more mathematically accessible than cataloging the myriad particular attributes of the system, and perhaps a fertile mathematical transformation can relate the field to the genome.

Homeodynamics

When an organism is not in equilibrium, such as during growth and development or when recovering from injury, functional electric current emanates from large areas of the system and joins vast collections of cells—a system that is more than the sum of its parts (Becker and Selden, 1985). Applied external voltages and magnetically induced currents can stimulate specific physiological responses, again with enormous numbers of component cells acting in concert. A practical working theory for these phenomena is an intrinsic electrical field woven throughout the fabric of the system. Particular components may be a focus of interest for specific physiological processes; however, the hypothesis that homeostasis stems from broad-field interactions of all body systems is more likely accurate and is currently referred to as homeodynamics (Yates, 1994, 2008).

Beverly Rubik similarly has used the concept of homeodynamics to describe her theory of a *biofield*: "… it is now recognized that there is no single or ultimate homeostatic balance point in biologic systems because they are self-organizing systems, with many more possibilities than a single steady state…. Homeodynamics takes into account the many modes of dynamic behavior exhibited by living processes in an ever-changing lifeline of the organism" (Rubik, 2002).

In addition to feedback control, many factors effect the transaction of information in humans. The homeodynamic perspective emerges from a view of the body as a self-organizing, open system, with many nonlinear processes. Communication and control in the body's dynamic adaptations to changing external and internal environments are better modeled by chaotic mathematics and nonequilibrium thermodynamics, rather than by stochastic models at thermodynamic equilibrium (Yates, 1994, 2008; Rose, 2005; Lloyd et al., 2001; Miller, 2003; Aon et al., 2004).

If every living organism can be described by an electromagnetic field vector, then pathologies, abnormalities, and traumas will manifest as deviations from the normal field; thus, within limits, the deviations will be compensated for by the homeodynamic properties and principles of the system. Liboff notes that the impact of bioelectromagnetic therapy and other types of energy medicine treatments are unusually subtle. He stipulates that he has not yet seen convincing proof that all these subtleties are necessarily linked, but proposes that his field theory would provide a good working premise to explore energy medicine (Liboff, 2004).

Liboff's electrogenomic field is not limited to the physical space occupied by the body, but rather extends into surrounding space. Extension of the electrical field

beyond the body suggests the potential for direct electromagnetic communication between individuals. Signal intensity for such communication might be adequately provided by frequency-specific amplification modalities. A physiological broadcasting or receiving transducer would require coherent signal detection. For a possible candidate transceiver, Liboff points to the work on g oscillations in the brain, which may play a role in learning and information processing. These g oscillations arise from millions of neuronal elements all oscillating in phase (Singer, 1993).

Imaging Homeodynamics

In recent years, the increase in instrument power and sophistication has permitted the visualization of body energy beyond the boundary of the skin. Superconducting quantum interference devices, or SQUID, routinely detect magnetic signals from the brain, heart, and other endogenous current sources. Chapter 6 presents the finding that SQUID measurements have demonstrated energetic effects emanating from the hands of QiGong Masters. This and similar technologies have focused on particular subsystems of the body; however, an application of multi-instrument computerized tomography potentially might be capable of synthesizing subsystem measurements into a representation of Liboff's electrogenomic composite field vector. In a review of progress in magnetoencephalography (MEG), an imaging technique that measures magnetic fields produced by electrical activity in the brain, Ioannides, a leader in the field of magnetic field imaging, concluded that: "a noninvasive and truly functional imaging capability of the brain and body is within reach" (Ioannides, 1994). Although the precise way to achieve this integration is unclear, Ioannides suggests that combining information from regular and functional magnetic resonance imaging, positron emission tomography, MEG, and EEG would surely contribute to studies of the mind. Similarly, James Oschman proposes that recent developments in electrical impedance tomography assessments of the electronic properties of living matter may soon be capable of visualizing human energy (IEEE, 2002, Oschman, 2004). As mentioned, later in this chapter, two additional innovations in bioelectrical impedance assessments, the SEQEX and EIS systems, will be reviewed.

Liboff's electrogenomic field vector might seem to be incapable of computation, but useful approximations could provide a practical research tool. When you combine Ioannides' suggestion (which assumes conventional notions of the role of neurology) with Mae-Wan Ho's proposal that a body consciousness resides in the lightening fast communication that occurs via the connective tissues (with the brain consciousness being an embedded system of the larger body consciousness), an integrative picture of the entire physiology is created. A system that could dynamically compute and visually render all these layers of physiological processes would show these nested interactions provide homeodynamic balance. Visualizing even partial aspects of subtle whole body communications and control processes could be useful for holistic understanding of health. For instance, later in this chapter Konstantin Korotkov's imaging system, the Gas Discharge Visualization (GDV) device currently known as Electrophotonic Imaging (EPI) will be reviewed. The EPI device uses the evoked photon capture technique and takes data from only the fingertips, yet provides information about the energetic flow and balance throughout the body (Korotkov, 2002).

SUBTLE ELECTROMAGNETIC ASSESSMENTS AND THERAPIES

Some of the data on electromagnetic mechanisms of action gained from laboratory studies have subsequently been used to design therapeutic devices. Previously, orthopedic treatment based on Liboff's ion cyclotron resonance model and cancer screening with the T-Scan were delineated. In this section, subtle or low-emission electromagnetic devices designed to assess and treat disease will be presented. Similarly many of these devices also stemmed from insights gained from investigative research.

Low-Energy Emission Therapy (LEET)

Low-energy emission therapy (LEET) treats both sleep and anxiety disorders using a small, battery-powered device that provides stimulation at low amplitudes (using an electronically conducting mouthpiece that is in direct contact with the oral mucosa) and modulates electromagnetic fields in the hypothalamic–pituitary region of the brain. The LEET device emits a carrier frequency of 27.12 MHz and can be modulated to specific frequencies between 0.1 and 300 Hz. Studies have validated efficacy and safety for sleep and anxiety disorders. Double-blind insomnia trials at multiple sleep research centers have demonstrated significant increases in sleep time and more normalized sleep patterns in patients with chronic insomnia (Lebet et al., 1996; Pasche et al., 1996). Long-term follow-up found continued benefit, no adverse side effects, and no addictive tendencies (Pasche and Barbault, 2004).

LEET was developed by Symtonic S.A. in Lausanne, Switzerland. The stimulation device uses specific, proprietary clusters of modulation frequencies shown to have therapeutic effects for sleep as well as a different set of frequencies that benefit patients with anxiety. LEET delivers levels of absorbed electromagnetic energy in the brain that are approximately 100 to 1,000 times lower than those generated by handheld cellular phones. Retrospective assessments of more than 400 patients treated with LEET over several years did not indicate any increased risk for either cancer or cardiovascular disease. The only noticeable side effect reported in several studies was increased dreaming (Pasche and Barbault, 2004).

Electroacupuncture, Electrodermal Screening, and Bioresonance Therapies

Various medical practices, particularly acupuncture and homeopathy, have developed their own electrical devices for health assessment and treatments based on the assumption that electrical signals are inherent in the body, independent of the particulars of biochemical bonding energies and cellular biophysics. Electroacupuncture systems are based on measuring electrical conductance at acupuncture points. Eventually, some electroacupuncture systems evolved into electrodermal screening (EDS). Using electronic signals claimed to be derived from homeopathic remedies, allergens, and pathogens, EDS measures the body's electrical responses to these tiny electrical stimuli, selecting appropriate remedies based on the patterns of the responses. Bioresonance therapy (BRT) goes a step farther and presents

electromagnetic signals themselves as the appropriate remedies, replacing pharmaceuticals or homeopathic remedies with electromagnetic stimulation. The stimulation may be delivered through electrodes in contact with the skin, or by pulsed magnetic fields that penetrate into the body, inducing electrical potentials deep into the tissues. In some forms of BRT, the therapeutic signals are derived from the body's endogenous electronic signals and modified by the measured responses to stimulation. The bioresonance approach is rooted in the assumption that control processes gone awry can be corrected by modifying endogenous signals, via appropriate application of external stimulation.

Many devices currently in the market claim to use EDS-type methods, but do not provide adequate engineering descriptions of the systems to confirm their assertions. Signal processing methods are treated as proprietary design secrets and only anecdotal testimonials support the efficacy and effectiveness of the therapies. While some proprietary devices do provide useful clinical studies, research standards vary widely among these disparate medical cultures.

Devices for Assessing Bioelectric Phenomena

The electromagnetic properties of human skin have been studied throughout the twentieth century, with the intention of learning more about the body's electrical characteristics and patterns of function. Some of this early work culminated in the electrocardiogram (ECG), electromyogram, and EEG instruments—important tools in modern medical technology.

The second half of the twentieth century saw the development of many electromagnetic devices for assessment and therapy based on the energetic models of Chinese medicine, particularly the theory of the flow of Qi throughout the body via a network of meridians (Reichmanis et al., 1975; Reichmanis and Becker, 1978). There is more than a 60-year tradition of measuring variation in electrical conductance at acupuncture points in order to assess health and to plan therapeutic treatment. This approach has resulted in techniques for electromagnetically stimulating the body either with skin-contact electrodes or pulsed magnetic fields to induce microcurrents in the tissues or to send signals into proposed sites of metabolic regulation. Some of the procedures developed have not been thoroughly described in the literature, again claiming the designs and methods are proprietary. Published research on recent device developments and therapies would be useful and bring credibility to the field.

Electrical Measurements in Acupuncture

Beginning in the 1950s, several lines of research emerged to study the electrical behavior of skin at acupuncture points. Points of high conductivity were found to correlate well with the points and meridians of classical Chinese acupuncture. By the early 1970s, there was consensus that an electrical resistance of ~5×10^4 ohms exists between any two acupuncture points, and the value increases by a factor of two to three times during sleep. With emotional excitement, the points increase in diameter (revealed by the conductivity area); similarly, the relative conductivity changes strongly during hypnosis (Tiller, 1973).

In Japan, Nakatani used a 12 V DC device, called the Neurometer, to identify lines of conductivity that he called *Ryodoraku*. Current versions of Nakatani's Neurometer may use 21 V potentials (Nakatani, 1956; Nakatani and Yamashita, 1977; Ahn and Martinsen, 2007). In France, Niboyet, Bratu, and Brunet also studied the properties of these high conductivity points (Niboyet, 1958; Bratu, 1960; Brunet, 1960). Later, Bosy and Rabischong, also working in France, confirmed Niboyet's work (Bossy, 1971; Bossy et al., 1975; Rabischong et al., 1975). Similar research was accomplished in China (Zhang et al., 1958; Zeng et al., 1958; Zhu, 1981). Electrodermal scanning has seen extensive practice and research in Taiwan (Tsuei, 1995, 1996; Tsuei et al., 1992-1993; Tsuei et al., 1996).

This body of work forms the basis for using point-locating devices in acupuncture practice, often using electromagnetic stimulation for therapy, and for the development of a wide range of instruments that are claimed to provide complex health assessments. However, the work has been viewed with considerable skepticism in the conventional biomedical community (Royal and Royal, 1991). Some of this opposition stems from differing scientific assumptions (such as those examined in this chapter) and disagreements regarding possible mechanisms responsible for observed electrical phenomena.

Furthermore, there are considerable difficulties associated with obtaining precise electrical readings from the skin. Some recent work has focused on issues of fine-grained measurement reliability and electrode design, in an endeavor to increase precision and reliability (Colbert et al., 2004; Pearson et al., 2007; Ahn and Martinsen, 2007). Many factors are widely acknowledged to contribute to variation in electrical measures of skin tissue. The stratum corneum provides the main resistance to current flow, so methods of measurement must be capable of maintaining consistent, uniform conditions across sites tested (e.g., avoiding breaks or lesions in the skin). Sweat ducts act as shunts for ionic currents; consequently, sweat gland density is a source of variation. Electrode polarization can introduce extraneous capacitance at the electrode–skin interface. Using higher frequencies and larger electrodes can reduce electrode polarization, yet some electrodes must be small to be correctly placed. The material from which the electrode is made affects electrode polarization, and nonpolarizing material is required for measuring impedance. Electrode geometry determines the current path, and current density is greatest with more convex surfaces and with smaller electrodes. The contact environment affects electrode polarization and skin resistance. Dry electrodes require constant pressure and higher current frequencies, while wet electrodes require constant area maintained with the skin. For example, the area of skin contact with a wet electrode could vary if the angle of the surface contact varies. Electrode arrangements determine current depth, with short distances between electrodes passing current through the superficial skin layers and greater distance increasing the current flow through deeper layers (Ahn and Martinsen, 2007).

Popular acupuncture diagnostic machines often use low-voltage DC with microampere currents that are induced by potentials applied in the range of 1 to 12 V. Therapeutic electroacupuncture routinely uses much higher current levels (e.g., perhaps several milliamperes, at 2 to 100 Hz, versus 200 μA for the most intense diagnostic device, the Ryodoraku Neurometer). Many diagnostic devices compute

impedance during current flow. Impedance is the total opposition to current flow, including both resistance and reactance. In biological tissue, an applied electrical potential induces two major effects: (1) charged particles are mobilized in respond to the field potentials and (2) stationary particles become polarized. Both of these effects contribute to impedance. Moving particles encounter resistance, and stationary materials experience reactance, with components, such as membranes and proteins, becoming polarized in a manner similar to dielectric material between plates of a capacitor. Reactance is composed of both inductance and capacitance, but inductance is usually assumed not to play a significant role in biological systems.

With AC applications, the relative contribution to total impedance by resistance and reactive capacitance is dependent upon frequency. Following Ohm's law, resistance is directly proportional to voltage, regardless of frequency. Capacitance, however, is directly related to frequency, so lower frequency alternating currents create a greater role for capacitance in the total impedance. In biological tissue, polarization of molecules at low AC frequencies makes capacitance a larger component of total impedance, while higher AC frequencies induce less capacitance, making resistance the major component of total impedance. With DC, the biological molecules become polarized over time and currents may cease to travel though the tissue. Resistance to ion travel is the main component of total impedance, so resistance is often used to represent the impedance in a DC system.

Bioimpedance measures are obtained when an *exogenous* electrical potential is applied to a biological organism. Bioelectricity is a broader concept and includes measures of electrical currents associated with bodily function—in other words, *endogenous* currents. Biological systems have properties that make them different from electrical circuits that are composed of more simple and uniform materials. Electrons are the carriers of current in electrical circuits, while ions transport current in biological materials. Tissues are extremely complex, with heterogeneous materials at multiple spatial scales that have interfacial and frequency-dependent effects that cannot be well modeled by conventional electrical circuit components, such as capacitors and resistors. Many parameters are nonlinear, with values varying depending on intensities, frequencies, and waveforms. For example, at AC frequencies above 1 MHz, ionic flow greatly diminishes because ion movement entails too much inertia to adjust to rapid change in potential current direction. Biological systems are open systems, not as easily isolated as electric circuits. Emotion, perspiration, movement, and respiration can dramatically affect the reliability of electrodermal measurements (Ahn and Martinsen, 2007).

William Tiller, working in the Department of Material Science and Engineering at Stanford University, explored the electrical behavior of skin and concluded that careful measures can provide a great deal of information. The electrical measurement with probes of specific design is not limited solely to the properties of surface effects, such as sweat, which tend to dominate measurements of galvanic skin response. The evolving dielectric constant provides information on both the moisture and electrolyte properties of the tissue. Changes can be observed in both deep tissue or "bulk" properties in the response to high frequencies and in surface properties in response to low frequencies. Small changes can be distinguished in single components of

complex circuits in the tissues (Tiller, 1989). By the 1980s, three main modalities had emerged in the assessment of acupuncture points using electrical conductance measures: Hiroshi Motoyama's **A**pparatus for measuring the functions of the **M**eridians and corresponding **I**nternal organs (AMI), Reinhold Voll's Dermatron, and Helmut Schimmel's Segment Electrograph—a description of each follows.

Motoyama's AMI

Hiroshi Motoyama's original AMI device used an electrode probe at the Jing or Well points, which are located at the ends of meridians on fingers and toes. A 9 V potential develops between a large electrode at the contralateral wrist and each of the 28 Jing points, when the points are individually probed. The assessments record the initial current, the final current, and the waveform. Comparison of all these measures, computation of standard deviations, and data on the differences between right and left side provide the basis for outcome evaluation. Values that are too high suggest excited states, often indicating disease onset; values that are too low often indicate a chronic disease condition (Motoyama, 1975, 1981).

Motoyama's newest AMI uses reference electrodes on each wrist and each leg that sequentially administer 3 V potentials with 256 msec square wave pulses to each Jing point. The initial parameter or response current is designated BP, the "before polarization" current and is recorded during the first 1 or 2 μsec after current is applied. As dielectric elements in the tissues polarize, current flow decreases exponentially until it reaches a minimum steady-state current, usually within about 200 μsec. This steady-state current is designated AP "after polarization," which is the second parameter. The third parameter is the total electric charge that is mobilized during the polarization process, designated "IQ" for total charge in Coulombs, which reflects the electrical capacity of the basal membranes and other dielectric elements in the tissues (Nagayama and Motoyama, 2006). Extensive clinical studies have investigated AMI assessments across a wide range of disease conditions (Motoyama, 1997, 1999, 2001).

In a recent AMI study, the electrical properties along the lung meridian demonstrated appropriate laterality in patients with unilateral pulmonary tuberculosis. The IQ value along the lung meridian was excessive on the side unaffected (or less severely affected) by the tuberculosis, compared to the tuberculosis affected side before chemotherapy. The IQ of the unaffected side decreased to the same level as the affected side, two months after the start of chemotherapy, when most of the patients had demonstrated improvement. An interpretation offered for this combination of observations is that it was no longer necessary for the unaffected lung to support the affected one via Qi flow. During antituberculosis chemotherapy, transient drug-induced hepatitis appears in some patients. In most cases, the transient liver dysfunction improves spontaneously without discontinuation of chemotherapy. In patients who developed transient hepatitis as the antituberculosis chemotherapy proceeded, IQ and BP currents along the liver meridian decreased, at the onset of the drug-induced hepatitis (Nagayama and Motoyama, 2007).

Electroacupuncture According to Voll (EAV)

Beginning in 1953, Reinhold Voll, a German physician, began to use electrical conductance measures for health assessment based on both Chinese acupuncture and

homeopathic methods (Voll, 1975, 1977). Voll was following the lead of Walter Schmidt who had observed that acupuncture points associated with an organ already known to be diseased exhibited greater resistance to electric current than points associated with a healthy organ. Voll established standards for healthy electrical flows by measuring classic acupuncture points, one by one, on healthy school age children. These conductance values were then compared with adults in various states of ill health, evolving normal and abnormal values. Using healthy children as the norm for comparison to disease in adults may seem spurious, but it was Voll's initial normative research protocol.

Although his understanding and use of meridians was generally in agreement with Chinese tradition, over the ensuing decades, Voll identified new meridians, new measuring points, and new functions of existing points. His new measuring points relate to joints, skin, fibrous and fatty tissues, serous membranes, both central and autonomic nervous systems, the lymphatic system, capillary circulation, and allergic reactions not known to Chinese medicine (Voll, 1983).

Voll's primary assessment instrument is the Dermatron, manufactured by Pitterling Electronic in Munich, which charges a test point on the skin with ~8 to 10 μA at ~1 V. The probe electrode is a 3 mm diameter brass ball that is placed on acupuncture points in turn. The large cylindrical reference electrode is held in the patient's opposite hand to complete the electric circuit. The meter on the instrument records the skin's electrical conductance. The meter scale is calibrated to read 50 for normal and >50 to defined irritation, with the degree of irritation increasing with larger values. A reading <50 is defined as a degenerative condition, with greater degeneration with lower readings.

A more important observation is the indicator drop (I.D.), which specifies decreases from the maximum initial value, over time. The I.D. usually occurs within one to three seconds. A retarded I.D. is suggestive of an incipient functional disturbance, and the time period over which the decrease occurs indicates the intensity and scope of the pathology. The interval of the I.D. is usually 10 to 20 seconds, when the initial measurement value is about 50. If the value drops to 30, the time interval for the drop is 20 to 30 seconds, but is greater than 30 to 60 seconds if the value drops to 20 or less (Tiller, 1989).

Tiller's Assessments of the Dermatron

The Dermatron also is used for therapeutic purposes by applying constant current impulses in the range from 0.8 to 10 Hz to a specific acupuncture point or set of points. A sawtooth-shaped current pulse is employed to induce sedation, bring the reading down to 50 using a voltage ranging from 1.5 to 2 V at ~20 to 30 μW total power. To produce a tonic effect, bringing the reading up to 50, a negative amplitude sawtooth-shaped current pulse is applied when only small changes are needed. When large changes are needed, an AC current pulse of ~50 msec duration at 1 to 10 Hz is applied to the acupuncture point. For such large tonification, the voltage is in the 60 to 400 V range at ~60 to 100 μW total power (Tiller, 1989).

Changing pressure or the angle of the probe at the acupuncture point changes the meter readings. Various acupuncture point probe devices have demonstrated that a spring-loaded design equalizes this pressure and produces more uniform measures

(Colbert et al., 2004). From his laboratory investigations of electrodermal screening, William Tiller concluded that the instrument's variance, affected by physical parameters of the probe contact with the skin, is either fortunate or unfortunate, depending on your point of view. Tiller determined that the practitioner may unconsciously produce a conductance meter reading influenced by subtle information, potentially present only in the practitioner's subliminal awareness. Turning the machine around so that the practitioner cannot see the meter produces two important results: (1) in contrast to measures taken with visible readings, repeated measures give inconsistent results when the meter reading is not visible, and (2) the diagnostic success of the practitioner is appreciably reduced. Using a spring-loaded probe produces consistent pressure at the acupuncture point, which is less influenced by the practitioner's pressure, yielding repeated measures that are more consistent, but still providing less diagnostic value than when the meter reading is visible to the practitioner. It is Tiller's contention that a skilled practitioner, whose subtle intuitions are at play in the application of the tool, can use electrodermal screening more effectively (Tiller, 1997).

Tiller's judgment flies in the face of a mechanistic worldview, a view that assumes a diagnostic instrument should accomplish objective measures, independent of the subjective action of the practitioner. In a technology incorporating Chinese acupuncture, this is an ironic puzzle—given the subtle, subjective skills at play in the acupuncture practitioner's art of manually palpating—both for detecting sensitive or active points and for the 12 classical pulses. In acupuncture practice, the fingers are used to press on points to explore for tenderness or ache, which identifies active points for use in organizing needle insertion patterns. The skill of the practitioner also requires subtle observations, with varying finger pressures to observe the behavior of the 12 pulses. Six pulses are observed at each wrist, felt by using the index, middle, and ring fingers, pressing only lightly to observe the first three pulses and then pressing more deeply, to feel the second set of three pulses. Tiller suggested that if a technological instrument can augment traditional acupuncture assessments, then we should perhaps expect these methods to also enroll subtle, subjective dynamics.

Schimmel's Segment Electrograph: Vega Testing

The Vegetative Reflect Test, or VEGA, system of electrodermal testing was developed by Helmut W. Schimmel, a student of Reinhold Voll. Schimmel's first system was the segment electrograph, which consolidated measurements into anatomical regions (Grieshaber and Schimmel, 1982). The eventual computerized version of Schimmel's methods was called computerized segmental electrography, or SEG (Heim and Schimmel, 1989). The Vega test provided a consolidation of the assessment, using fewer test points and more simple indications of response to electromagnetic signals from materials inserted into the testing circuits.

Use of the Voll Dermatron required measuring a very large number of points. A simplified form of EAV, called *Biolelektronischen Funktions und Regulations Diagnostik*, eventually was developed and used a much smaller array of point measurements for diagnosis (Pflaum, 1979; Breier, 1982). Schimmel's segment electrograph further consolidated measurements onto aggregate regions and rendered the data from the measures into curves displayed on strip chart recording, analogous to early ECG and EEG outputs.

Schimmel's first segment electrograph used a series of electrodes grouped in the fashion of a target, to conduct 13 Hz voltage impulses into selected skin segments, divided into eight anatomical sections (i.e., left and right subdivisions of four quadrants: head, thorax, abdomen, and pelvis). Stimulation of the tissue in a segment used alternately negative and positive 13 Hz sawtooth voltage pulses, each pulse lasting 18 seconds. After the 36-second period, with the applied voltage set to 0, the reaction or response current in the form of a reverse polarity current flow, would be recorded for 26 seconds, with a new cycle of stimulation beginning after a 2 second pause (Tiller, 1989).

Diagnostic information is derived from various features. For instance, the current pulse during stimulation can shift, above normal for hyperfunction or below normal for subfunction. The shape of the current trace during the stimulation cycle also provides data: A normal trace is slightly curved, with the drop amplitude forming a centripetal signal 1 to 2 mm long, while a subfunctioning condition would have a shortening or absence in the centripetal drop signal, with the curve transformed toward rectangular. Schimmel interpreted the effect as energy rigidity combined with decreased energy flow. Hyperfunctioning conditions showed increased trace angles above 35^0, with corresponding lengthening of the centripetal drop signal. This form of trace was interpreted as rising energy flow and increasing inflammation and oxidation. Similarly, the magnitude and shape of the response current waveform offers diagnostic information: (1) normal reverse current, (2) weak reverse current, interpreted as energy deficiency, or (3) strong reverse current, thought to be an abnormal tissue reaction with energy surplus. In all the current traces, the wave shape provided subtle variations, which were given discrete interpretations concerning body or organ condition (Tiller, 1982).

The interpretation of functional health was then derived from the electrical conductance behavior depicted in the curves of the charts. As Schimmel's methods evolved, he shifted the emphasis to assessing the body's response to electromagnetic signals from materials: allergens, toxins, homeopathic remedies, and nosodes. Now calling his method the Autonomic Resonance Test (ART), he used only one skin contact to measure the response to large numbers of materials, in turn (Schimmel, 1997). To assess the effects of materials, vials containing the allergens, toxins, or remedies are electrically included into the probing circuits, and the character of the fluctuations in the conductance measures are used to interpret the potential for benefit or adverse effects. Similar to the work by Benveniste and his colleagues, this assessment method assumes that materials produce electrical signal patterns that are involved in physiological effects.

Electrodermal Screening (EDS)

The most controversial aspect of the EAV or EDS assessments has been the claim by Schimmel and others that electromagnetic signals from toxins or homeopathic remedies can be introduced into the testing circuits to evaluate the individual person's responses. Ludwig claims to have measured and compared a large number of the extremely low frequencies in homeopathic remedies using a spectrum analyzer sensitive to the millihertz range (Ludwig, 1987). Similarly, signals from allergens and nosodes

(i.e., pathological tissues prepared as homeopathic dilutions) are introduced into the testing circuits, and responses from the patient's various subsystems are assessed (Schimmel, 1985, 1991; Schimmel and Penzer, 1996; Zoll, 1992). In this approach, homeopathic, nutritional, and herbal materials each have a characteristic electromagnetic signature. The changes in electrodermal measures reflect the body's interaction with these substances and are purported to show the homeodynamic regulation.

EAV-guided allergy therapy has been claimed to provide benefit in clinical studies (Kail, 2001). Disputes centering on allergy testing have often been the focus for criticism and regulatory action against EDS devices and practitioners (Jeremic and Leung, 2004; Wuthrich et al., 2006). Defenders of EDS assert that electrical evaluations may not always conform to laboratory bioassays because energetic problems can be precursors to histological changes and that symptoms may be secondary to the energetic root cause. These possibilities are consistent with classical acupuncture assessment and treatment techniques. The research assumptions and methods can be critiqued on all sides of these disputes and each needs to be carefully considered. As the Institute of Medicine of the U.S. National Academy of Sciences observed in a report on researching alternative medicine, the presumption that one standard of assessment is optimal for all types of modalities and therapies being investigated, is inappropriate (Institute of Medicine, 2005).

Research on the electromagnetic therapies often is published by a German medical society, Gesellschaft der Ärzte für Erfahrungsheilkunde e.V. The Gesellschaft is an association formed to foster alliance between homeopathic and naturopathic physicians. Often cited simply as *Erfahrungsheilkunde*, or again simply as *Acta medica empirica*, the full masthead name of the journal is: *Erfahrungsheilkunde, Acta medica empirica: Zeitschrift für die ärztliche Praxis.* Erfahrungsheilkunde can be translated as "healing experience," and an empirical approach to clinical practice is the shared tradition in this community, consistent with the roots of homeopathy and natural medicine.

THERAPIES: BIORESONANCE THERAPY

Morell's MORA-Therapy

In a period of time parallel with Schimmel's SEG, Franz Morell set about using a patient's homeodynamic signals to rebalance diseased conditions. The MORA system draws on a patient's own pathological electromagnetic oscillations to dampen and extinguish the disregulation with negative feedback because electronic filtering theoretically separates healthy signals from dysfunctional signals (Morell, 1987, 1990). Morell's idea is to cancel the dysfunctional signals by phase shifting the frequency of the signals 180° and then feeding them back to the body. Signals considered healthy also are fed back to the body, amplified but without any phase shift. The system was developed with Morell's son-in-law, Eric Rasche, an electrical engineer, and named the MORA-Therapy Unit (MOrell + RAsche = MORA).

The original device used handheld electrodes or foot-contact electrodes for both signal acquisition and feedback after processing. The current model, the Super MORA, applies handheld electrode probes to the acupuncture Jing points to provide

the signal feedback. The Super MORA performs electrodermal testing of various homeopathic remedies, allergens, and possibly the patient's own body fluids or tissues; the substances are placed in metal cups and current in measuring circuits is passed through the metal containers. The modality is supposed to introduce the electromagnetic signatures of the materials into the probe circuit. Therapeutic output from the device can also be "magnetically imprinted" into a homeopathic tincture or ointment. Claims that clinical studies have shown that MORA-Therapy, prior to an EAV assessment (taken by a Dermatron or similar device capable of measuring an indicator drop by the Voll method), can reduce pathological readings by 80% have not been corroborated by formal, independent evaluations.

Brügeman's BICOM and MULTICOM

Hans Brügeman claims to have coined the term "BioResonance Therapy" in 1987 (Brügemann, 1993a). Crediting Morell with the principles of therapy using "the patient's own oscillations," Brügeman wanted a descriptive and generic term for his own version. His device, BICOM, is derived from the term BIo-COMmunication and also is referred to as "ultrafine bioenergy" for the information signals used in these diagnostic and therapeutic techniques (Brügemann, 1993b). "Ultrafine" means extremely subtle in the physical sphere, but qualitatively highly effective in the biological sphere.

At the core of this technology is the naturopathic concept of "endogenous regulatory forces," which postulates that all diseases and their preconditions are caused by pathological electromagnetic oscillations (Brügemann, 1993a). Theoretically, pathological electromagnetic oscillations are active alongside the healthy oscillations in the body of every patient, and the body falls ill if the dynamic equilibrium can no longer be maintained by counter-regulation. The electromagnetic oscillation or biosignals of a patient contain all the information that is necessary for therapy, when the signals are properly sorted and decoded.

BICOM electrodes, used on the palms of the hands or soles of the feet, are constructed of several layers, including a layer of magnetic foil that is designed to detect signals not just from the skin surface, but also from deeper tissues. When a second, similar electrode is connected to output signals, the complex magnetic fluctuations in the electrode again induce signals into deeper tissues, while the electrical potentials in the signal are disbursed along the skin surface. Magnetic fields will penetrate into the tissues, but the electrical potentials move onto the skin. Brügeman asserts that electronic filters in the system sort out harmonious from disharmonious signals in the body, with the therapy signals presented to the patient through the second, output BICOM electrode. The harmonious frequencies are positively fed back, and the disharmonious frequencies are inverted and fed back. Endogenous regulatory signals shift from interacting with the feedback and are returned to the BICOM through the input electrode. This feedback loop continues in real time and is expected eventually to "extinguish" the pathological signals.

Brügeman subsequently introduced MULTICOM therapy, which adds signals from the environment that theoretically resonate with the body in beneficial modes. MULTICOM is based on the theory that the body is an open system that

uses environment stimuli to instill homeodynamic regulation (Köhler, 1993b, 1994). Multiple harmonics of colored light, therapeutic tones, oscillating harmonics from precious stones and minerals, and especially regular cyclic variations in the Schumann waves are all part of MULTICOM therapy. Schumann waves are the continuous standing electromagnetic waves that encircle the Earth, oscillating at approximately 8 cycles per second. These waves are formed in the resonant cavity between the Earth's surface and the charged particle layer of the ionosphere. Lightning discharges are continuously present somewhere on the planet. The broadband frequencies of lightning discharges include the wavelengths that are harmonically reinforced at approximately 8 cycles per second. This frequency fluctuates slightly, as the ionosphere approaches closer to the Earth's surface or recedes, depending on pressures from the solar wind. MULTICOM therapy claims to include stimulating variations in approximately the 8-cycle per second frequency, to restore a natural harmonic stimulation that the natural environment would normally provide, but which may be disrupted by electrical equipment in our industrialized society (Köhler, 1993b).

The proposition that negative feedback created by phase shifting the frequency of a signal produced in complex physiological processes appears too simplistic, if not implausible. There are many degrees of freedom in such a complex system, so destructive interference merely from a frequency phase shift seems unlikely because various other aspects of the signals will also vary, such as amplitude, so the precise matching needed for destructive interference would not happen. The MORA supposedly amplifies healthy signals and creates a phase shift "inversion" of pathological signals. The BICOM system uses both amplification and amplitude attenuation in combination with frequency "inversion." Varying all of these aspects of the signal may increase the prospect for harmonic resonant interactions. Such prospects are based on the expectation that biological systems create complex, yet stable electromagnetic signals.

Again, proponents claim therapeutic benefit from each of these methods (Ludwig, 1988a; Keymer et al., 1996, 2004; Will, 2000). A series of papers detailing clinical trials, *in vitro* biophysical studies, and retrospective studies from medical practice is available from Brügemann's company, Regumed Regulative Medizintechnik GmbH (Regumed, 2007). Frequent colloquia presenting research and therapeutic techniques have been convened over the past 20 years. The BICOM training program is DIN ISO 9002 and EN 46002 certified. The International Standards Organization (ISO) provides this standard for quality assurance in medical device manufacturing. The DIN designation is the German version of the international standard. The European Medical Device Directive EN 46002 includes the requirements of ISO 9002, with additional requirements. Brügemann maintains 4,500 practitioners are using the BICOM, including general practitioners, ophthalmologists, chiropractors, surgeons, dermatologists, internal specialists, gynecologists, orthodontists, neurologists, orthopedic surgeons, pediatricians, specialists in sports medicine, urologists, veterinarians, and dentists. A major limitation to the scientific credibility of these devices results from developers and manufacturers who keep the signal processing methodology hidden as proprietary industrial secrets. However, some careful clinical and laboratory research has been accomplished with these methods.

These therapeutic activities are far too broad to detail concisely what is known about efficacy or lack of efficacy. The respective research communities exchange information in the form of reports describing clinical effects and effectiveness, rather than providing the controlled trials carefully designed to evaluate efficacy that U.S. medical research strategies promote as the core of evidence-based medicine. As previously discussed, controlled trial studies of efficacy are not necessarily appropriate approaches to these complex therapeutic systems (Institute of Medicine. 2005). In addition, understanding what findings have been determined is further complicated by differences in medical cultures—both in national cultures as well as in medical traditions, such as naturopathic or homeopathic or Chinese or Aryuvedic systems.

Bodo Köhler has published detailed work assessing Brügemann's BICOM bioresonance treatments. His work provides a good example of how difficult communication and controversy attends these studies because he used assessment methods that are little known in conventional medicine (Köhler, 1993a). Before looking at Köhler's study of the BICOM, it is necessary to explain his investigative methods. Köhler's research protocol used subtle assessments based on Alfred Pischinger's ground regulation system: blood chemistry and electrolyte balance shifts, lymphocyte activation, and release of a triple-conjugated, unsaturated, fatty acid derivative identified by Pischinger in the 1970s as "monocyte factor" or "factor M," because it initiates the macrophage stage of the immune response. Pischinger's system of humoral and histological observations is based on a complex set of reactions in the stress response. The usual triggering event in Pischinger's diagnostic is skin puncture, either for blood draws or for acupuncture. An elaborate cascade of metabolic and immunological responses is assessed to gain detailed diagnostic information particular to an individual patient. Curiously, asymmetric responses can be observed between the two sides of the body, which may be analogous to asymmetries observable in Chinese medicine. In some conditions, blood sedimentation rates in a sample from the cubital vein on the right arm may vary from a sample taken at the same time from the left arm. The fact that some conditions will manifest differences in blood sedimentation rates, in samples taken at the same time from opposite sides of the body, is an example of the vast distance between expectations in conventional physiological assessment and Pischinger's ground regulation principles (Pischinger, 2007).

Alfred Pischinger, with his students and colleagues in Vienna, along with W. H. Hauss and G. Junge-Hulsing at the University of Munster, and Hartmut Heine at the University of Witten/Herdecke, have continued a long-standing Austrian medical tradition, focused on the extracellular matrix (i.e., the connective tissue and body fluids that provide the environment for cellular processes). The matrix regulation system manages the nutrition of the cells and the removal of their waste products and is part of all inflammatory and immune processes. Building on a long medical tradition that focused on the fluid microcirculations that nourish the cells, Pischinger added the regulatory functions of the hormonal and autonomic nervous system, to establish what the Germans call *ground regulation*. The recent English translation of the 10th edition of Pischinger's medical text may help spread awareness of these methods. James Oschman wrote a foreword to the English translation. Oschman's "living matrix" model shares many aspects of the ground regulation model, especially regulation by electrical signals (Oschman, 2007).

The extracellular matrix system can react locally or generally. Various stimuli set off similar types of reactions in the nonspecific part of the matrix regulation system. A key diagnostic principle uses fine-grained observations of both the immediate and longer range responses to stresses. Electrical and chemical responses in the matrix regulation system have been characterized by detailed observations of the cascades of responses to puncturing the skin. These reaction-measurement observations are used to gauge the effects of noxious substances and chronic stress on the matrix system, specific for each particular person. Successes in treating chronic diseases have resulted from understanding the reaction processes of the matrix regulation system, and attending to the individual stress factors that maintain the disease state, combinations particular to every single patient.

Using concepts unique to this school of medicine, Pischinger and his colleagues have described how disturbances in matrix regulation can compromise homeostasis, eventually causing depletion and organ failure, conditions identified as regulatory rigidity, regulatory paralysis, and regulatory disintegration. This approach provides details of inflammatory processes that are missing in most conventional medical explanations (Pischinger, 2007).

Köhler performed detailed assessments of bioresonance treatment on a small number of patients with a variety of conditions to identify useful, observable measured changes in physiological effects (Köhler, 1993a). Subjects were given four-minute treatments weekly, for four to six weeks, and assessed before and immediately after treatment and again at three-day intervals after each treatment. In a group of 22 patients, the evaluations generated 3,000 measurements, including bilateral blood sedimentation rates, electrolyte determination, and complete blood count. Therapy was specific to the conditions for each patient. Subjects were included with neurodermatitis, allergic conditions (e.g., bronchial asthma and food allergies), and various problems considered "interference field processes," such as sinusitis and ovarian inflammatory conditions. Interference field processes are associated with lateral differences in blood sedimentation rates. The lateral differences were initially as high as 50% in patients with interference field stresses. Bilateral blood sedimentation rates equalized after the first treatment. The higher rates decreased to equal the lower initial contralateral rates. Electrolyte shifts were observed immediately within the four-minute treatments, but cellular processes progressed more slowly. On the third or fourth day of observations, significant proliferation in lymphocyte numbers was observed (up to 140%), demonstrating immunostimulation from the therapies. The upward trend of lymphocytes persisted through the four to six-week periods of treatment. For most patients, leukocyte counts were not changed during the treatment periods, which was interpreted as evidence that no adverse effects occurred.

Köhler's study found clinical symptomatic improvements, and modifications to the ground regulation from the bioresonance therapy showed improvement across most of the markers observed. Köhler assessed a range of conditions, including skin conditions (e.g., neurodermatitis, allergic diseases), bronchial asthma, and food allergies, and conditions considered "interference field processes" in Pischinger's ground regulation diagnostics. The rapid reactions in the observed effects, especially an immediate equalization in blood sedimentation rates, convinced Köhler that

"the energy phenomena must play a quite decisive role and take place *before* the cellular changes, or induce them" (Köhler, 1993a).

Lednyiczky's Hippocampus Lenyo and Cell-Comm Devices

During the late 1990s, Gabor Lednyiczky and his colleagues at the Hippocampus Research Institute in Budapest, Hungary, accomplished a series of studies assessing possible mechanisms for the interactions of endogenous and environmental electromagnetic signals, using Brügeman's BICOM and a system of their own design, the Cerebellum Multifunction Medical Instrument (CMMI) (Lednyiczky, 1996a; Lednyiczky et al., 1996b, 1998; Zhalko-Tytarenko et al., 1996). Various subcellular and cellular processes were measured under bioresonance conditions. In all reactions, the most pronounced alterations occur within particular frequency ranges (the windowing effect). A decrease in tumor growth and number of metastases was observed in sarcoma-bearing mice, treated *in vivo*. Treatment of sarcoma cell cultures *in vitro* that were subsequently injected into mice did not result in any antitumor effects. The finding was interpreted to suggest that the antitumor effect of bioresonance treatment results from the activation of endogenous antitumor mechanisms in mice, rather than from any direct influence on the tumor cells (Lednyiczky et al., 1996c).

Lednyiczky's hippocampal treatment devices use a variation on the MORA signal inversion methods. A simple inversion of phase should not cancel a signal by destructive interference because of the complex processes underlying the waveforms (Hippocampus BRT Ltd., 2007). The Hippocampus approach involves modulating all the wave parameters (i.e., frequency, amplitude, and phase) of the signal sets presented to the body. The purpose for modulating all of the wave parameters is to find a harmonic resonance with regulation signals that have gotten offset to a stable but disadvantageous mode. Bioresonance stimulation should help reset these regulation signals into a health mode. The Hippocampus Cell-Comm, or Cellular-Communication, comprises any of the hippocampus devices that use the patient's own endogenous signals, modified and fed back through the system to the body, in a manner similar to the MORA and BICOMM methods, but with various repeated modulations of all the wave parameters (i.e., frequency, amplitude, and phase) intended to find a supportive resonance with disharmonious regulation signals, and coax these back to a healthy robust setting.

These modified endogenous signals are combined with combinations of robust, healthy signals also generated by the system, chosen for their particular benefits. The stimulating signals are placed into various therapeutic combinations, appropriate for various treatment conditions. The Hippocampus library of 1,700 signal sets represents robust, healthy electromagnetic processes. These healthy signals were derived from clinical experience with bioresonance assessment and therapy. The healthy signals can be selected to support healing for particular organs or tissues, and for specific processes, such as wound healing or recovery from fatigue. Specific signal sets are provided to stimulate particular meridians in the Chinese medical model. The signal frequencies range from 0.5 Hz to 2 MHz. The physiological target is the extracellular fluid in the tissues, where the cells are "whispering together" to maintain

harmonious tissue and organ function. Signals in this extracellular fluid domain communicate with processes inside the cells through normal membrane activities. Therapy is presented based on clinical assessments using primarily naturopathic, homeopathic, and Eastern medical approaches, along with Alfred Pischinger's ground regulation methods.

A similar device, the Hippocampus Lenyo, does not measure the patient's own signals, but presents the healthy signal sets from the Hippocampus signal library, as a form of electromagnetic tonic. A pulsed magnetic field, approximately the same strength as the Earth's magnetic field, stimulates the body with various combinations of signals, using an antenna woven through a full body-length pad. During stimulation, all the waveform parameters are modulated around the central waveforms, moving the signal away from and back to the healthy norm. The expectation is that resonant harmonics will be established with pathological signals that are deviating from the healthy normal, and the disharmonious signals will be supported to return to a healthy robust form by the amplified healthy signals. The magnetic stimulation is expected to reharmonize the symphony being played by the body's orchestra, quite literally a form of electromagnetic tonic.

Binder's ONDAMED®

In the 1970s, Rolf Binder worked with Franz Morrell and Eric Rasche on the MORA. By the late 1980s, as Wolfgang Ludwig's associate, Binder helped develop the Indumed system, which is a magnetic stimulator system that applies therapeutic magnetic pulses that, theoretically, mimic and reinforce natural environmental signals, including the Schumann resonance and cyclic geomagnetic fluctuations related to specific geologic minerals (Ludwig et al., 1968; Ludwig, 1988b, 1999; AMS Ltd., 2007).

The ONDAMED® GmbH device was developed in 1994 by Binder and was designed to communicate with both cellular activity and metabolic regulation. In Latin, *Onda* means "wave" and *med* is understood as *ars medicina*, or the "arts of medicine," thus ONDAMED stands for "medicine wave." Adopting a central concept of stagnation from Eastern medicine, Binder anticipated that particular signals would move stagnant blockages; in addition, it is supposed to facilitate fluid movement in the tissues as well as improve lymphatic processes, metabolism, and immune function. In clinical practice, it can be used alone, but most often is used to support combined and integrated treatments.

Unlike the MORA or Ludwig's Indumed, which use localized electrodes to present combinations of endogenous signals with preselected signals, Binder's ONDAMED applies therapeutic signals to the entire body, searching for dominant resonant frequencies. When dominant frequencies are found, a hand-held stimulator is used to identify the primary locations for treatment focus. The intention is to restore the body's regulatory functions by dissolving interference fields associated with inflammatory processes, scar tissue, and chronic depletions. Frequencies range from 0.1 to 32,000 Hz in 173 preset programs that have bundled frequency patterns, preset time, and preset intensity. Magnetic field strength ranges from .5 to 50 mT. A large collection of frequencies associated with microscopic pathogens can be used to test affected organs. To screen the interaction with stagnant functions, the ONDAMED requires that a practitioner monitor the vascular autonomic signal (VAS), which is a

physiological response of the neurovascular system to information brought into the energy field of the body. The VAS is manually sensed with the practitioners thumb, as pulse changes on the wall of the radial artery (Nogier, 1983; ONDAMED, 2007).

Classic acupuncture possesses a rich vocabulary of descriptors to characterize the feel of pulses, providing variations far more subtle than merely counting the rate of impulses (Kuriyama, 1999). In classic acupuncture pulse assessments, the practitioner applies fingers to the radial arteries of both wrists, with both slight and deeper pressure, to monitor 12 major organ systems. The subtle sensations of the VAS pulse are interpreted using the thumb, laid along the radial artery, carefully noting pulse changes when a needle is brought close to a specific acupuncture point or the patient holds a potential allergen or medicine. The various shifts in the pulse that are noted may include changes in tempo, strength, or wave-shape shifting patterns, which are more subtle changes in how the impulse arises and falls away (Nogier, 1983). Paul Nogier (see Chapter 5) developed the VAS assessment as an offshoot of his auricular acupuncture techniques. Nogier found that he could evaluate the therapeutic usefulness of specific points on the ear by bringing a needle close to an acupuncture point but not touching it, yet feeling changes in the VAS. While the VAS may appear to be a very subjective assessment method, it is widely used in practice and has demonstrated consistency (Nogier, 1983; Rouxeville, 2000; Klowersa, 2000).

A clinical assessment of the reliability and validity of the VAS as a diagnostic tool in treatment for chronic pain found an 84% consistency between two mappings of the important acupuncture points for treatment, performed 10 minutes apart. Validity of the points selected was demonstrated by immediate pain reduction in 85% of the 35 study participants, with an average pain reduction for all participants of 2.7 points on a 0 to 10 visual analog scale. In a one-week follow-up, pain assessments still averaged 2.2 points below the initial pain levels (Agnes, 2002).

Binder combines monitoring of the VAS into the ONDAMED treatment protocols to dynamically read the body's response to stimulations during a therapy session. Using an applicator loop that rests on the collarbone and surrounds the neck, a patient is stimulated by frequency ranges that increase in preset steps, while the VAS is monitored at the radial artery, using the practitioner's thumb. A spike in the VAS indicates that the patient has a resonant frequency at that particular time. After identifying a dominant resonant frequency, the handheld area applicator is moved across various regions of the body, while the VAS continues to be monitored. Congested areas or chronically depleted areas are identified by changes in the VAS. Such areas can be further investigated for disease etiology and treated with appropriate therapeutic routines offered by the ONDAMED system (ONDAMED, 2007). In a clinical study of 27 patients with a wide range of chronic conditions, 90% experienced significant pain relief with 2 to 12 ONDAMED treatments (Schroeter, 2005). Most of these people had been on pain medication for many years. Further clinical studies have been announced, but have not yet appeared in the literature (ONDAMED, 2007).

Bioelectric Frequency Analysis: EnerMed

The EnerMed is a small personal magnetic stimulator, approximately the size of a man's wristwatch. Extremely low-frequency and extremely weak-pulsed magnetic

fields are presented to the body when the device is worn next to the skin. The EnerMed has been described as a pacemaker for the brain and has been demonstrated to be effective for symptom relief with migraine headaches and multiple sclerosis (Lappin, 2004). Both migraine and MS exhibit irregular nerve cell firing patterns. The pulsed magnetic stimulation at specific frequencies is thought to support brain self-regulation, by exciting under-active neural networks and reducing hyperactive ones. The device is presumed to restore the body's natural balance.

The treatment frequencies embedded in square wave pulses of the device are chosen specifically for each person, based on the proprietary system Bioelectric Frequency Analysis (BFA), created by Energy Medicine Developments Inc. (Energy Medicine Developments, 2007). During analysis, patients wear a headset, centered over the crown of the head, with a piezoelectric crystal designed to detect subtle bioelectromagnetic signals. The person sits quietly with eyes open during the scan. Clinical assessments have identified areas of low amplitude in the bioelectric output that relate to specific medical conditions. These signals are generated by the brain, but are not simply EEG signals. In a small sample of individuals selected for their purported ability to transmit healing energy, the BFA signals coming from the heart area were registered at a distance of 12 inches (Acosta-Urquidi et al., 1998).

The signals picked up by the BFA are decomposed, taken into pieces, to reveal their underlying, simpler components, using a Fourier transform and a power spectrum analysis. A Fourier transform can take apart complicated signals, revealing combinations of simpler waveforms—in other words, exposing combinations of frequencies and amplitudes that create the more complex signal. A power spectrum analysis can then identify which of these more simple waves are most powerful and which are very weak. The system displays the 16 lowest amplitude signals in the frequency spectrum ranging from 0.5 to 25 Hz. After three scans, each lasting approximately four minutes, the operator reviews the results and selects frequencies that are consistently low in amplitude. With multiple sclerosis, the treatment frequencies are typically limited to the 4 to 13 Hz range, based on improvements in clinical experience with these patients (Lappin et al., 2003a).

Treatment involves wearing an EnerMed, the small, pulsing electromagnetic device for up to 24 hours a day. The device is programmed to emit pulsed electromagnetic signals 1 to 25 times per second. Each pulse is a 1 msec square waveform. A programmable chip allows up to 16 frequencies to be programmed into one device. With a device programmed for multiple frequencies, each frequency is pulsed for 13 seconds in turn, and the sequence is repeated continuously. Because of the automatic cycling, there is a tradeoff between the number of frequencies that are programmed into the stimulator and the amount of time any one frequency can be presented.

A very weak, 50 to 100 mG magnetic field (approximately equal to the Earth's magnetic field) is generated by a 3 V battery driving current through a solenoid coil. The pulsing field is polarized with one side of the device positive and the other negative. The negative side (the north-seeking pole of the magnetic field) is worn next to the body. During treatment, the patient wears the stimulator secured to the skin with hypoallergenic tape and located over the brachial plexus (i.e., the large nerve bundle just below the clavicle). Other than occasional mild drowsiness and vivid dreams, no other negative side effects have been reported.

The EnerMed is currently approved for sale in Canada. It is not, at this time, approved for sale in the United States. Double-blind, placebo-controlled studies required to obtain FDA approval are proceeding (Lappin, 1998, 1999; Lappin et al., 2003a, 2003b). Research with placebo devices and blinding is possible because the pulsing field cannot be felt. A multisite, double-blind, placebo controlled, crossover trial of 117 patients with clinically confirmed multiple sclerosis showed improvements in fatigue and significantly greater overall quality of life outcomes with the active device (Lappin et al., 2003a). There were no significant improvements for bladder control or a disability composite of measures taken from the MSPS (MS Performance Scale) and benefits for spasticity had mixed results. Each subject received four weeks of the active and placebo treatment separated by a two-week washout period. The clinical effects were small, but consistent with previous studies showing symptom relief from PEMF stimulation (Lappin et al., 2003a). Previous studies, using more weeks of treatment, showed greater benefit for the physical symptoms (Richards, 1997).

Quantum Resonance System (QRS)

The Quantron Salut, a Quantum Resonance System (QRS), was developed by E. G. Fischer, with various collaborators at universities in Germany and Austria, based on clinical studies from a half-dozen European university hospitals (Fischer, 1996b). A German patent, DE 4122718, was issued in 1991, for the sawtooth waveform of the stimulator. The QRS is based on the concept of a symphony of signals in the body, with QRS stimulations combining with the body's own signals for energy transfer by field resonance. The device generally has a tonic approach, with predesigned stimulation routines. Recommendations for using specific stimulation sets are given for various disorders and for supporting various organ systems and physiological structures. Over a 20-year development, various unpublished research reports have proposed theories on the mechanism of action underlying the QRS (Fischer, 1996a). Effects on cellular transmembrane ion exchange are considered to be an experimentally proven mechanism (Turk et al., 2001; Wagner, 1995; Kokoschinegg and Fischer, 1996; Pelka, 2001). G.E. Fischer explicated the theoretical basis of the technique (Fischer 1996b).

QRS works with extremely weak field strengths between 1.5 to 15 μT. As mentioned, the Earth's field strength is far greater, at approximately 50 μT. The system pulse cycle is based on three main frequency components: (1) 200 Hz intended to improve blood flow and metabolism, (2) 23 Hz to neutralize the body from "electromagnetic smog" thought to be produced by the 50 Hz AC frequency of European electric power circuits, and (3) 3 Hz (EEG delta wave) to rehabilitate the body and brain or improve deep sleep. Many additional frequencies included in the QRS signal are intended to cover the spectrum of cell signals. The concept of electromagnetic smog perhaps could be better described as electromagnetic noise. Various transient current effects arise in wires that deliver AC electrical power and are induced by power fluctuations as devices draw varying power from the wires. The transient frequencies radiate into spaces near the wiring and theoretically can interact with the

body. Thus, these noisy radiations are considered to be a form of electromagnetic pollution in the environment analogous to chemical air pollution or smog.

The QRS system comes with a control unit, body length mat applicator, and a pillow applicator, although the mat is the usual application. Through an antenna in the mat, signals from the control unit generate a field expanding about three feet in all directions, so the entire body is immersed in the field stimulation. The pillow is for localized therapy to arms, legs, back, and can be used for full body stimulation while traveling. The controller has 10 settings, each an automatic program, which runs for eight minutes. Every two minutes the polarity of the sawtooth magnetic field signals reverses. The change of direction prevents the body from accommodating to the external stimulation and improves response.

In research and clinical trials, more than 10,000 patients were treated with no side effects. Proponents of QRS assert that it is an ideal adjunctive therapy to support homeopathic treatments, nutritional supplements, chemotherapy, drugs, acupuncture, massage, and other modalities; a wide range of benefits is claimed for this technique (Turk et al., 2001; Wagner et al., 1995; Kokoschinegg and Fischer, 1996; Pelka, 2001). QRS has been demonstrated to accelerate bone fracture healing, initiate mending in nonhealing fractures, increase bone density in osteoporosis, and relieve associated pain symptoms (Turk et al., 2001). The time needed for such healing may range from several weeks to many months. QRS also relaxes muscle and affects deeper breathing and relaxation. Endorphin release is stimulated, which benefits patients suffering from depression. Furthermore, Wagner and his colleagues reported therapeutic benefit for patients with diseases of the locomotive system, and Kokoschinegg and Fischer demonstrated clinical benefits as an adjunct to conventional treatment of rheumatic diseases (Wagner et al. 1995; Kokoschinegg and Fischer, 1996).

The manufacturer claims that QRS normalizes the blood pH and viscosity, improving circulation. Within the first two minutes of application, QRS has been shown to regulate blood pressure, lowering high blood pressure and raising low blood pressure. A finger-tip monitor assessing capillary vessels shows increased blood flow, usually with a temperature increase of 2 to 3.5° C. Thus, QRS is an effective aid for people with arteriosclerosis. After the blood pressure stabilization in the first two minutes of stimulation, nothing remarkable happens with blood pressure during the remaining six minutes of a tonic treatment (QRS, 2007).

Blood chemistry values take about four weeks to change. Partial oxygen pressure normalizes at that time and then increases above normal; pH normalizes in three to six weeks. Cholesterol improves over three to four months, sometimes longer. The calcium and magnesium mirror takes four to six months to improve significantly (QRS, 2007).

A Slovenian assessment study is provided at the Singapore equipment distributor's Web site (Pelka, 2001). This is a report on a randomized, double-blind, placebo controlled study at the General Hospital in Maribor, Slovenia, using the QRS Salut 1, with 71 patients suffering from osteoarthritis of the knees. Statistically robust improvement was seen from QRS treatment based on the Knee Society Score knee joint ratings for physical movement, pain, and sensitivity reduction as well as for physiological and blood chemistry assays. Systolic blood pressure improved significantly after six

weeks and, compared to placebo, remained stable for a further four weeks without therapy. After six weeks highly significant improvement was seen in blood sedimentation rates, and reduction in C-reactive protein and P-fibrinogen (Pelka, 2001).

Ion Cyclotron Resonance (ICR) Therapy: The SEQEX

Devices based on Abraham Liboff's theory of ion cyclotron resonance were first used in orthopedic therapy. The Italian SEQEX system uses complex arrays of magnetic fields that vary in intensity, frequency, and form, to deliver a broad range of therapeutic stimulation. The device allows the therapist to program 30 forms of complex waves, varying the field intensities to a maximum of 1 G, changing frequencies from 1 to 80 Hz, with period adjustable pauses and automatic inversion of the field's polarity every two minutes to counteract the body's accommodation to the stimuli (SEQEX—SISTEMI, 2007).

The SEQEX was developed by SISTEMI (Italian Society of Seqex Electro Medical and Innovative Technologies). As mentioned, Emilio Del Giudice and his colleagues were the first to propose that ion cyclotron resonance occurs within coherent quantum domains in clustered water (Del Giudice et al., 2002). Earlier the Del Giudice research group suggested that coherent dynamics in water was a possible explanation for biological membrane formation (Del Giudice and Preparata, 1994; Del Giudice et al., 2000). With ICR, as previously stated, ions move in the interstices between water coherence domains without collisions among themselves—if the interaction between two magnetic fields is tuned to the particular ions. Del Giudice's theory of ICR is used as the basis of SEQEX techniques, and Del Giudice and his colleagues outline specific neurotherapy methods (Tiengo et al., 2002).

Nicola Del Giudice, Emilio's brother, is a homeopathic physician who has served as president of the Italian Homeopathy Foundation. The Del Giudice brothers have developed their theories of homeopathic medicine based on the quantum coherent water domains (Del Giudice and Del Giudice, 1999). Nicola Del Giudice developed a synergetic relationship between SEQEX therapy and homeopathic medicine.

Again, using an antenna embedded in a mattress pad to manage the signals applied to the body, the SEQEX uses proprietary software programs to control the therapeutic magnetic signals in a feedback process, determined by continuous whole-body impedance measurements, bringing the individual into a greater state of well-being across several predetermined health parameters, termed "wellness factors." Some principles and techniques of whole body electrical impedance assessments are discussed in the next section. SEQEX therapy is designed to reactivate homeostatic balance by improving ionic exchanges. A broad range of applications are claimed to benefit from this therapy, including metabolic, endocrine, neurologic, and immunosuppressive pathologies; osteoarticular pathologies and microcirculation problems; posttrauma recovery and rehabilitation support; pre- and postsurgical treatments; and sports medicine applications.

The benefits claimed for this therapy are not yet documented by published clinical trials. Various unpublished clinical reports have circulated among physicians using the SEQEX. For example, in a small study available on the SEQEX company Web site, Grasso and Buttalo (in the Department of Clinical Neurosurgery at the University of Brescia) have documented neurotherapy benefits in both peripheral and

central nerve trauma (e.g. improvements in cervical disc herniated by trauma and carpal tunnel repetitive stress injuries), improvement in motor function in cases of myelopathy with moderate hemiparesis, and complete recovery from moderate brain trauma (Grasso and Buttalo, nd).

MEASURING ELECTROPHYSIOLOGY AND SYSTEMS ENERGY

Electro Interstitial Scan (EIS)

The electro interstitial scan (EIS) system provides a functional body evaluation using DC plethysmography, which can estimate the volume of interstitial fluids in the body using bioimpedance, by measuring electric current flow and resistance through the body (L.D. Technology, 2007). Based on the calculation of fluid volumes, differences in current flow in various body segments are interpreted to evaluate variation in constituents of the fluids. The EIS is not intended to diagnose specific diseases, but can be used for screening dysfunctions that may be associated with diseases. EIS measurement offers new complementary data on physiological tissue parameters, as well as on biochemical values and the acid base balance measured in the interstitial fluid, at little cost, very rapidly, and noninvasively. EIS measurement offers new complementary data by assessing physiological tissue parameters, including oxygen consumption, pH, blood pressure and flow, blood viscosity, tissue water content, neuronal excitability, bone density, and mitochondrial activity, a range of biochemical values and the acid base balance measured in the extracellular interstitial fluids. The EIS can be used as a therapeutic follow-up to track these readings and provide a picture of therapy progress.

EIS computes tissue physiology parameters by interpreting measured current flows and resistance. The original models for these evaluations are based on a large clinical database in Russia. The algorithms for deriving these data have been evaluated in clinical studies at Botkin Hospital and Marfino Medical Center in Moscow, St. Louis Hospital in Paris, the Gustave Roussy Institute, and in a study on attention deficit hyperactivity disorder (ADHD) in the clinic of Dr. Caudal Frederique in Dijon, France. The clinical findings are provided at the manufacturer's Web site (L.D. Technology, 2007). The original investigations at Botkin Hospital established the reference database of subjects for the body bioimpedance model, and markers for a range of disease conditions (e.g., hypertension, arrhythmia, angina, diabetes types I and II, hepatitis, circulatory problems, spastic colitis, gastritis, pancreatitis, chronic bronchitis, asthma, and others). The studies at Marfino validated the values of the interstitial ion models, the fat mass estimation technique, and statistical estimation of blood biochemical measures (i.e., atherogenic index, glucose, urea, creatinine, and triglycerides). The St. Louis Hospital study validated the modeling for stress measurement and catecholamine levels. Further studies at Botkin established screening and follow-up measures for hypothyroid, atherosclerosis, and unipolar depression. The study at Dr. Caudal Frederique's clinic validated markers for ADHD in children and estimation of dopamine levels. The manufacturer claims an 89% sensitivity and 84% specificity in the assessments (L.D. Technology, 2007). No follow-up on validation studies have yet appeared in the journal literature.

Six electrodes are used to measure conductance: one on the sole of each foot, one on the palm of each hand, and one on each side of the forehead, just above the eyebrows. In various combinations, acting alternately as cathode or anode, each pair of the six electrodes can assess 22 interior domains in the body. Flowing current from one electrode to the other provides selective measurement of impedance through specific regions and systems of the body. A full scan takes only two minutes.

The EIS uses 1.28 V DC to assess the bioelectric impedance, by measuring variations in current flow. The impedance, a dynamic measure of variation in electrical resistance, ranges between 11 kOhms and 390 kOhms, with a precision of +/–5 Ohms. By using DC, the system assesses only the interstitial extracellular fluids. Most bioelectric impedance methods use AC across a widely varying range of current, frequency, and voltage. Most of these systems are used to estimate body/fat ratios by measuring total body water. Studies of AC bioelectric impedance systems, operating at 50 MHz or higher, show that these high-frequency currents flow nonselectively through both intracellular and extracellular spaces; and thus, they provide relatively nonspecific information about the physical properties and chemical composition of total body water.

Cells act as electrical capacitors because of the electrical potential at the cell membranes and can effectively oppose the passage of a weak DC. DC flows primarily through the extracellular interstitial fluids surrounding the cells, and primarily outside the bloodstream and lymphatic systems. Any substance passing between cells and the bloodstream must traverse the interstitial space. Acting as a metabolic conduit, the ionic content and dynamic response conditions of the interstitial fluid reflect the physiology and any pathology of nearby cells.

EIS computes biochemical values from the interstitial fluid, with estimations of Ca+, Mg, Na+, Cl–, K+, phosphates, iron, triglycerides, urea, uric acid, glucose, and an atherogenic quotient, represents the disproportionate lipoprotein ratios between low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Hormonal assessment includes values for: thyroid-stimulating hormone, follicle-stimulating hormone, dehydroepiandrosterone, cortisol, aldosterone, adrenomedullary, testosterone or estradiol, insulin, parathyroid hormone, triiodothyronine, antidiuretic hormone, and adrenocorticotropic hormone. By segmenting the body into 22 compartments, the EIS can evaluate each organ system and identify functional risks across respiratory, digestive, immunological, renal/urogenital, neuromuscular, cardiovascular, endocrine, neurological, and general metabolic risk categories.

The system displays a model of the body with the evaluations rendered in detailed, color-coded displays for each organ system. The interpretation of EIS data requires knowledge of physiology, the subject's clinical context, and a consideration of variables that can modify the results. An EIS outcome with no abnormal values does not necessarily mean that the patient is healthy, it only indicates there are no physiological tissue parameter disorders or abnormal interstitial biochemical values.

Electrophotonic Imaging (EPI): Imaging the Human Energy Field

The electrophotonic imaging (EPI) technique, also known as the evoked photon capture (EPC) technique or the gas discharge visualization (GDV) technique is a computerized refinement of Kirlian imaging, using video recording rather than photographic

film. This innovation provides stability, reproducibility, and reliability that were missing with the early photographic emulsion methods. For durations ranging from 0.1 to 10 sec, a train of square wave, 3 to 5 msec electrical impulses, using a fundamental oscillating frequency of 10^3 Hz and amplitudes of 3 to 6 kV, are applied to the test subject. With humans, the stimulus is applied to the fingertips. Under these impulses, the subject produces a burst of electron emissions and optical radiation in the visual and ultraviolet range. These particles and photons initiate electron–ion cascades, giving rise to a sliding gas discharge. A sliding gas discharge is a miniature lightning storm, and the sliding ionic cascade serves to amplify the optical radiation. The spatial distribution of the discharge is registered by a charge coupled device video camera and written into bit-mapped image or video files, for mathematical analysis by computer software (Korotkov and Korotkin, 2001). The EPI system was formerly called a Gas Discharge Visualization (GDV) device (see Chapter 6), thus it is referred to here as the EPI/GDV camera. The EPI/GDV provides a set of software programs that allows observation of the corona discharge images in real time, storage in either bit-mapped image files or video files, image filtration, calculation of a range of image parameters, and diagramming complex parameter distributions.

Television capture of the image glow shows that the emission centers repeatedly appear from the same points on the skin for each individual person. The outburst current may result from the transport of electrons within structural complexes of skin or other tissue, which suggests the possible connection to acupuncture points and the meridian system. Useful clinical information is obtained with the EPI, assigning sectors around each finger tip to organ and functional subsystems, based originally on *Su Jok*, a school of Korean hand acupuncture. Sector assignments have been modified through clinical experience, first by Peter Mandel's empirical qualitative observations in Germany and refined further by mathematical analysis using the EPI/GDV in clinical observations during developmental research in Russia.

Reliable correlations between GDV indications and conventional clinical diagnoses have been demonstrated in a wide range of physical and psychological conditions, including musculoskeletal and bronchiopulmonary pathologies (Alexandrova et al., 2003; Mamedov et al., 2007), gastrointestinal pathologies requiring surgery (Polushin et al, 2004), infectious pathologies (Bolehan et al., 2006), monitoring patient response to chemotherapy in oncology (Gagua et al., 2006), psychological problems of anxiety and neuroticism (Dobson and O'Keeffe, 2007). In addition, it has been used to identify positive traits, such as personality dimensions of openness and agreeableness (Dobson, 2002) and monitoring relief from emotional distress during short-term therapy (Dobson and O'Keeffe, 2007; Sergeev et al., 2004).

EPI/GDV assessment provides quantitative measures of relative energy of the physiologic systems, biologic stress level, and overall vitality. Increasing numbers of clinical studies show that outcome data from EPI correlate with conditions characterized using standard medical diagnostics as well as assessment methods used in a wide range of complementary medicine. For example, postsurgery recovery progress correlates with EPI parameters as does independent diagnostic measures of psychophysical reserves in athletes, even directly characterizing their actual psychomotor potential (Korotkov, 2004a). EPI/GDV data also show a strong correlation with acupuncture electroconductance measurement effects (Rizzo-Roberts, 2002).

EPI is well characterized in the physical processes by which it captures and analyzes data (Korotkov and Korotkin, 2001; Korotkov 2002). EPI assessment methods can be understood using quantum biophysical models of entropy and information flows, as a main reservoir of free energy in biological processes occurs in electron-excited states of complex molecular systems (Korotkov et al., 2004b). This quantum model supports an argument that EPI techniques may provide indirect judgment about the level of energy resources at the molecular level in structure–protein complexes.

EPI may provide a first approximation to an observation of Liboff's electrogenomic composite field vector. Perhaps, EPI techniques can be combined with data from other innovative assessment methods, such as magnetoencephalography and the EIS, to approach Ioannides' proposal for "a noninvasive and truly functional imaging capability of the brain and body" (Ioannides, 1994).

OPEN RESEARCH AND DEVELOPMENT

The proliferation of electromagnetic devices claiming to have a cure for just about everything, comes all too often without any revelation of the engineering and too few open clinical studies. In addition, part of an effective research agenda for integrative medicine must be to find bridges across some of the deep differences in diagnostic and treatment assumptions among medical systems. As the U.S. National Institute of Medicine recommended, appropriate research protocols must be developed that do not try to collapse all medical evaluation into a one-size-fits-all simplification (Institute of Medicine, 2005). This is especially true for treatments that focus on the particular conditions of individuals, and medical systems that expect continuing dynamic change, as with Eastern medicine.

Innovations and evidence are accumulating in conventional medicine and biophysics that increase the plausibility of electrotherapeutics using very subtle effects. This chapter has surveyed biochemical and biophysical theories that suggest quite subtle energetic processes are present in the body—subtle energetic processes that are far beyond the dynamics expected from conventional biochemistry. New models in biophysics emphasize global and cooperative electrical activity, in highly ordered ensembles of elements, at all scales of physiology. These insights are forming theoretical bridges between what were formerly widely different medical traditions. For instance, when viewed with these new biochemical and biophysical models, acupuncture and homeopathy have plausible electromagnetic modes of action, and even controversial electromagnetic therapies, such as bioresonance, begin to fit into an integrated image of regulation and communication in the body.

Proper diagnosis of medical problems and an understanding of biophysical mechanisms pertinent to electromagnetic interaction with injured/diseased tissues continue to be important domains for research and therapeutic innovation. Design of sophisticated treatment protocols and appropriate choices of clinical outcomes should facilitate successful therapy. Such innovation requires joint efforts of engineers, biophysicists, biologists, and medical practitioners to further extend the energetic understanding of health and vitality.

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ADDITIONAL RESOURCES

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8 Energy Medicine
Focus on Lasers

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Are not the rays of light very small bodies emitted from shining substances?

Isaac Newton, *Opticks*

Lasers, the outcome of elegant physical theory and extensive experimentation, have become a vitally important tool for research in physics, chemistry, biology, and medicine. Lasers also are used extensively in everyday life, from reading barcodes to playing DVD recordings, and in industry, where they have diverse applications, such as in metal cutting tools, optical communications, and printing.

In conventional medicine, surgical lasers are designed to convert laser energy into thermal energy for ablative heat on diseased tissue. Using the same technology, but altering the laser parameters, biostimulative lasers are designed to convert laser energy into bioelectronic energy and, then, into biochemical energy for cellular utilization, such as enzyme production, cellular division, and cell membrane repair. This chapter focuses on the biophysics of lasers and applications for pain relief, reduction of inflammation, energy medicine, and accelerated tissue healing. To orient the reader, a brief background on the physics and biophysics of lasers is provided below.

THE ELECTROMAGNETIC SPECTRUM AND LIGHT

All these 50 years of conscious brooding have brought me no nearer to the answer to the question: "What are light quanta"? Nowadays every Tom, Dick and Harry thinks he knows it, but he is mistaken.

Albert Einstein, *Centenary Volume*

The radiation emitted by the sun, household light bulbs, cell phones, radar devices, and x-rays, is called electromagnetic (EM) radiation; it is a form of energy consisting of photons. Photons are the basic units, or quanta, of light. It can be useful to consider photons as particles, like tiny BB pellets, speeding through the vacuum of light at about 186,000 miles per second, that is, at about 1 foot per billionth of a second (i.e., per nanosecond). Sometimes, however, it is more instructive to think of photons as tiny waves, similar to sound waves. Photon waves consist both of an electric and a

magnetic aspect or field—hence, the name EM wave. As waves, EM radiation has an important parameter: the wavelength, which is the length from one crest of the wave to the next. The types of photons of interest in healthcare and medicine have extremely small wavelengths and are usually stated in billionths of a meter (i.e., in nanometers).

From a historical perspective, the photon has been at the heart of physics since Isaac Newton first postulated his corpuscular theory that light consists of tiny particles, which was published in 1704 in his famous book, *Opticks* (Hecht, 2002). About 25 years earlier, in 1679, Christiaan Huygens presented his theory that light consists of waves. Many years later in the mid-nineteenth century, James Clerk Maxwell showed that light, like waves through the ether of water, is an EM wave and travels as a wave (Smith and King, 2001). In 1905, Max Planck proposed his quantum theory of light whereby light takes the form of a discrete bundle, known as a quantum or photon (Smith and King, 2001). Today, according to the standard model of particle physics, photons are particles (i.e., bosons, named after Bose) that are fundamental to the mediation of EM forces that act between other quantum particles, in all types of matter. Thus, the photon currently is considered a messenger particle for EM forces, and as mentioned, is the fundamental quantum unit of EM energy. In essence, photons are discrete matter-waves and are the smallest bundle of light or luminescent energy; they are stable (without charge and without mass) elementary particles that exist only at the speed of approximately 186,000 miles per second. EM, in the form of light, is absorbed and emitted in photons. That much has been confirmed and is well established, but the question of whether or not light is really a stream of photons is far from settled (Kidd et al., 1989).

The most significant mechanism responsible for the natural emission and absorption of light occurs when electrons are confined within atoms. Electrons surrounding the massive positive nucleus of each atom constitute a tenuous charge cloud. Most of the chemical and optical characteristics of matter are determined by the electrons on the atom's outer layer. Even though it is not completely clear what occurs internally when an atom radiates, it is known with some certainty that light is emitted during readjustments in the outer charge distribution of the electron cloud. In any case, this mechanism is ultimately the predominant source of light in the universe (Hecht, 2002).

The spectrum of EM radiation that follows the laws of optics (i.e., the optical field) includes wavelengths between 1 and 1,000,000 nanometers (nm) (Hecht, 2002). The portion of the spectrum that corresponds to visible light has wavelengths roughly between 400 and 800 nm. The spectrum of infrared is divided into four wavelength regions: near-infrared, between 800 and 2,000 nm; mid-infrared, between 2,000 and 10,000 nm; far-infrared, between 10,000 and 100,000 nm; and very far-infrared between 100,000 and 1,000,000 nm. Both infrared and ultraviolet (wavelengths between 1 and 400 nm) adhere to the optical laws, just as visible light does. The term light, as used in this chapter, has a specific meaning that may not correspond to the general usage of the word. It refers to visible (i.e., violet, blue, green, yellow, orange, red), near-infrared, and ultraviolet radiations. Light between 400 to 1,000 nm is used for healthcare and energy medicine applications (Tunér and Hode, 2002; Pöntinen, 1992).

EM radiation not only comes in a broad range of wavelengths, but also of frequencies, which is the number of waves per second, although in a vacuum all EM radiation travels at the same speed. Despite the fact that different regions of the spectrum

have different names, such as radio waves, microwaves, infrared, or x-ray, there is only one entity, one essence of the EM wave (Hecht, 2002). EM waves are the most ubiquitous entities in the universe. The significance of EM waves is of utmost importance not just to laser biostimulation and energy medicine, but to understanding life itself (Burr, 1972), because life evolved from a world composed of light EM waves. Thus, it ought to follow that there are many interactions between biological systems and light EM waves (Jagger, 1967).

Today, living systems are thought to be governed mainly by EM interactions, with photons as the interacting particles. Each interaction between molecules, macromolecules, or living cells is basically EM energy, governed by photons (Klima, 2000; Popp et al., 1992). Physical EM interactions are fundamental to biology and medicine. Physicists distinguish between four interactions in nature: gravitational, strong force, weak force, and EM interactions. EM interactions are responsible for the structure and behavior of atoms, molecules, macromolecules (e.g., many proteins), and cells. Therefore, the human organism is mainly an EM system (Burr, 1972; Marino, 1988). For this reason, EM therapies that use devices such as lasers (of appropriate wavelength and power density) can have a remarkable impact on regulation of living processes.

What Is a Laser and How Does It Work?

In 1917, Albert Einstein established the physical principle of Light Amplification by Stimulated Emission of Radiation (LASER). Today, the word laser is used instead of the acronym LASER. A laser is any device that projects radiation of the light spectrum, producing a beam of light of concentrated energy. The photons emitted from a laser have two key properties: (1) wavelengths that are very close (monochromatic light) and (2) coherence, which means that photon EM waves are synchronized with each other. It is commonly thought that lasers emit parallel beams of high intensity. Laser light does not need to be parallel or particularly strong. These two characteristics are, however, important for industrial and surgical lasers—properties that can make them harmful to the eye and tissues.

High-energy photons from surgical lasers focus and are absorbed in small volumes of living tissue; they have the power to cauterize, coagulate, and destroy tissue, sectioning it with minimum necrosis of the wound edges and with minimum bleeding in the surgical field, even in highly vascular tissue. Surgical effects occur when the light energy emitted by the laser exceeds the target tissue's ability to safely absorb the photons, and, therefore, the excess energy is rapidly converted into a destructive level of heat.

Nonsurgical, tissue-stimulating laser devices, with reduced power outputs relative to lasers used in surgery, are labeled "biostimulation lasers," "therapeutic lasers," and sometimes, "cold lasers." Biostimulation lasers, as opposed to surgical lasers, are used mostly for pain relief and tissue healing or repair. The therapeutic effects of lasers also are obtained by the way in which the tissue absorbs laser radiation. Tissue absorption depends on the wavelength of the beam itself and the ability of the laser instrument to deliver an adequate amount of energy to reach the target tissue at clinically effective levels.

How Do Lasers Work?

Photons develop when electron clouds, circulating around the atomic nucleus, change their course. Normally this action happens when extra energy is applied to the atom. The simplest atom is hydrogen, which has one electron cloud moving around the nucleus in an orbit. Atomic orbits or shells are labeled K, L, M, N, and O. The electron residing in orbit K, which is closest to the nucleus, provides the ground energy level for the hydrogen atom, while O has the highest energy level. Extra energy is needed to move an electron to a higher shell and can result from a variety of actions, including heat oscillation, atom or electron collision, chemical reactions, and incoming photons. The extra energy absorbed generates excited electrons and, therefore, an atom in a higher energy level. In most substances, excited electrons can maintain their new orbits for only a very short time, returning to their original form (i.e., their normal orbits) in steps, thus releasing energy as photons.

The ground energy level for an atom is called E_1. If an atom absorbs a photon, released from an electron changing shells, the atom moves to a higher energy level (E_2). Depending on the photon's energy, the atom could move to energy levels E_3, E_4, or higher. As the atom returns to a lower energy level, it emits the previously absorbed energy, as a photon. Thus, light energy (or EM energy, in general) that is absorbed or emitted as it moves the atom from one energy level to another is contained in a packet of energy called the photon. A photon released from an atom has a wavelength that is inversely proportional to the atom's energy release. For example, if an atom's energy drops from E_2 to E_1, then the energy released by the atom is $E_{2\text{-}1} = E_2 - E_1$. Therefore, the larger the electron's *jump* (it does not physically jump; it simply disappears in one orbit and appears in another) in an atom, the shorter the wavelength of the emitted photon. Electron jumps occurring from higher to lower energy levels during emission generally occur randomly, and the photons emitted in this process do not have a relationship with one another (i.e., incoherent light). Such a collection of emitted photons is called spontaneous emission. This type of emission is given off by ordinary light sources, such as household light bulbs or light-emitting diodes (LEDs).

A different type of emission, called stimulated emission, was first described by Albert Einstein in 1917. Stimulated emission occurs only when photons of a specific energy are absorbed by an atom that is already in an excited state (i.e., at an energy level higher than its ground state E_1), causing (or stimulating) the excited atom to drop to a lower energy level. In the process of the energy drop, the atom gives up a photon with a direction, wavelength, and an "in sync" (in phase) that is identical to the one that caused the stimulated emission in the first place. It is this stimulated emission, as opposed to spontaneous emission, that lies at the heart of the amplification of light by laser action—thus, the acronym: Light Amplification by Stimulated Emission of Radiation. In other words, a laser is a device that fosters the production of many excited atoms by means of an energy source (or pumping process), such as electrical current from a battery, in a manner that permits photons, generated from the stimulated emission, to be absorbed by other excited atoms. Thus, a chain reaction of photons is generated (via stimulated emissions, also called population

inversion) that all share the same properties of wavelength, coherence, and direction (Pascu, 2000).

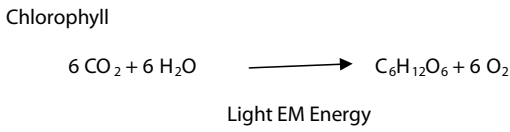
An important historical note: In early 1950, prior to the invention of the laser, a device was in use that emitted microwave photons (rather than light photons); it was called MASER for Microwave Amplification of Stimulated Emission of Radiation. The maser was developed simultaneously by Charles Townes in the United States and by Alexandr Prokhorov and Nikolai Basov in the Union of Soviet Socialist Republics (USSR); all three investigators shared the 1964 Nobel Prize in Physics for their work (Hecht, 2002). Almost immediately after the development of the maser, speculation arose as to whether or not the same technique could be extended to the optical region of the EM spectrum. In 1957, Gordon Gould, as a doctoral student under Charles Townes at Columbia University, used his knowledge of optical pumping to advance the MASER technology, coined the term laser, and designed the first laser as an optical resonator, which is a parallel arrangement of two highly reflective mirrors that produces a very fine, continuous beam (Gould, 1974; Francoeur, 2008). In 1958, Townes and Arthur Schawlow set forth the general physical conditions that would have to be met to create a laser (Karu, 2007). In 1960, Theodore Maiman, an electrical engineer at Hughes Aircraft, announced the first successful operation of an optical maser or laser, using a ruby crystal that produces red EM radiation at 694.3 nm from chromium ions. Thus, an understanding of the essential effect of simulated, coherent emission of radiation from excited atoms, precisely in phase and in the same direction, permitted the development of both the maser and the laser.

Absorption of Electromagnetic Radiation

Biophotonics or photobiology is concerned with the interaction of light with living organisms, from cells to tissues to *in vivo* live specimens (including human beings). Photochemistry and photophysics deal with the interactions of matter, in general, but most of the knowledge in these fields relates to inanimate matter (Prasad, 2003). Albert Einstein's major discovery in 1905 was in the area of photophysics, with the photoelectric effect paving the way for a revolution in optics that germinated a half-century later with the invention of the laser by Theodore Maiman. The field of biophotonics has progressed to the point that researchers are developing models to explain and demonstrate cell-to-cell communication with photons rather than chemistry (Chang et al., 1998).

Each type of laser emits light at a very specific wavelength band in the EM spectrum and is designed to interact with the specific type of tissue intended to be irradiated. In particular, lasers affect chromophores present in the tissue; chromophores are any intrinsic or extrinsic substance able to absorb EM radiation. Listed among the endogenous chromophores include: water, hemoglobin, nucleic acid, and proteins. Exogenous chromophores include porphyrins and hematoporphyrins, which are injected into the organism. These agents are described as photosensitizers because they fix themselves to the tissue, making it photosensitive at a specific wavelength. Photosynthesis is an example of a naturally occurring photochemical reaction, in which photons are absorbed by the chromophore chlorophyll, eventually converting

light energy into adenosine triphosphate (ATP). The process is illustrated by the chemical reaction:



In photosynthesis, carbon dioxide and water, through a series of reactions, are converted to glucose and oxygen. In the process, one electron of the chromophore, chlorophyll, absorbs light EM energy and becomes transformed into chemical energy by a process of photophorylation, which converts adenosine diphosphate (ADP) into ATP (Chang, 2000). Photosynthesis is thermodynamically a highly unfavorable chemical reaction, as it requires the energy provided by the EM radiation from light.

Another illustrative example of a chromophore-based physiological mechanism involves vision. Like photosynthesis, the first step in vision is absorption of light EM energy. The chromophore that absorbs visible light is vitamin A aldehyde, or retinal. Retinal is associated with the protein opsin to produce rhodopsin and iodopsin. EM absorption of visible photons induce molecular transformations of *cis* to *trans* in the rhodopsin and iodopsin, which provide the energetic resources to produce depolarization of rods and cone cells in the retina (Chang, 2000).

The level of tissue penetration of a laser beam depends on the optical characteristics of the laser beam as well as on the concentration and depth of the chromophores. Chromophores absorb light at different percentages, according to the wavelength. For instance, water absorbs almost 100% of the laser irradiation at the 10-600 nm wavelength, which is the wavelength of the CO_2 gas laser that is used in surgical applications. However, most chromophores in human tissue absorb light within the visible spectrum. Proteins and nucleic acids absorb ultraviolet rays with wavelengths between 200 and 350 nm. Lasers, such as excimer lasers, that emit at ultraviolet wavelengths, penetrate less than 1 millimeter and, therefore, are ideal for certain surgical interventions on the eye surface.

Radiation in the spectrum between 400 and 600 nm is mostly absorbed by melanin in the skin. In the infrared spectrum, water is the main chromophore. Fortunately, there exists a narrow band in the light spectrum for which water is not a highly efficient chromophore, thereby allowing light energy to penetrate tissue that is rich in water content, such as the capillary bed. This narrow band (approximately from 600 nm to 1,200 nm) is the so-called therapeutic window; most biostimulation lasers on the market today have wavelengths within this therapeutic window. However, the level of tissue penetration (referred to as the penetration index) is not the same throughout the therapeutic window. In fact, lasers in the 600 to 730 nm wavelength have less tissue penetration than lasers in the 800 to 950 nm range. The tissue penetrating capacity of a laser is greatly determined by the power and wavelength of the device, in a manner not unlike standard radiography equipment.

Laser energy, when absorbed by cells, gets converted either into heat or biochemical energy. Different wavelengths affect the conversion in different proportions. One wavelength (e.g., 1,064 nm) will interact with soft tissue in such a way that it is optimally

converted into heat for an ablative effect, while another wavelength (e.g., 2,400 nm) will more effectively interact with hard tissue, such as bone. In both surgical applications, the amount of light energy that gets converted into biochemical energy is the minimum, which ensures maximum ablative efficiency. To guarantee that the necessary energy per pulse is delivered into tissue, the clinician controls the pulse duration and pulse emission power.

Thus, surgical lasers maximize heat production in tissue for ablation. In contrast, biostimulative lasers emit photons with wavelengths and pulse energies that can maximize both bioelectronic and biochemical energy yet minimize ablative effects. Biostimulative lasers that have the best tissue penetration emit photons with pulse energies that are short in duration (e.g., 200 ns) and very high power (>40 W). To avoid the ablative effects of high-power lasers, pulsing beams with power levels that move from very low to extremely high peak levels are used. These lasers are called pulsed lasers. These High Intensity Light Treatment, or HILT, lasers deliver light energy deep into tissues with no risk of tissue damage from heat.

The biophysical process of laser absorption into cells of the soft or hard tissue is identical, except that with a suitable selection of wavelength and pulse energies, virtually all laser energy can be converted into bioelectronic and biochemical energy, thus avoiding tissue damage by heating. This photonic to electronic conversion occurs in the mitochondria of cells via the enzyme, cytochrome c oxidase, which is one of the main intracellular chromophores. Cytochrome c oxidase is a large membrane protein of considerable complexity that catalyzes the final step in the mitochondrial respiratory chain (i.e., in the transfer of electrons to molecular oxygen causing its chemical reduction into water) (Karu, 2007).

ATP, discussed previously, is the universal energy molecule for all cells in the human body. Normally, cells produce ATP by transporting fatty acids and glucose into the cells to drive the ATP synthetase. Photons of biostimulative wavelength lasers can directly drive ATP synthetase and thereby, accelerate ATP production inside the cell's mitochondria. These biostimulative photons energize the mitochondrial cytochrome c oxidase, which in turn activates ATP synthetase and production of ATP. Since more than 90% of all energy coupling in human beings involves redox reactions in the mitochondria, the physiological result is that cells absorbing the laser light have the capacity to function at a higher energetic level to repair tissue, reduce inflammation, and provide pain relief (Simunovic, 2000).

The Importance of Laser Power

Irradiance is the amount of light illuminating a surface. Another way of defining irradiance is by: the average amount of energy per unit area, per unit time—a description of a type of surface brilliance. In the past, physicists generally used the term *intensity* to mean the flow of energy per unit area, per unit time; the term has been slowly replaced by *irradiance*. The irradiance density, energy density, or irradiance dose is measured in joules per treated square centimeter (j/cm^2). The time rate of the flow of radiant energy is referred to as the optical power or radiant flux, which is measured in watts. A way of thinking of the power of a laser beam is by the rate at which the beam delivers the optical energy, thus, a laser with high power is delivering

the optical energy faster than a laser with low power. Power is the ratio of energy and time. Energy, which is measured in joules, is the amount of light delivered to the tissue over the treatment time. The energy of a laser beam (joules) is equal to the beam's power (watts), multiplied by the number of seconds the beam is delivering energy (treatment time). Therefore, a laser with more power (watts) can deliver the same amount of energy (joules) in less time. Radiant flux density is obtained by dividing the radiant flux (i.e., power) by the area of the treated tissue. Radiant flux density (power density) and the irradiance dose (energy density) are the most important parameters in determining the clinical effectiveness of a laser (Pontinen, 1992; Tunér and Hode, 2002). In a review of the research literature of studies that produced negative results with laser therapy, too low a dose was the single most significant factor in treatment failure (Tunér and Hode, 1998; Schindl et al., 2000).

As stated, light energy is measured in joules and the treated surface area in cm^2, thus, a dose (energy density) is the amount of light energy delivered to a given unit area during a treatment session. Energy density is defined as the energy radiated on a 1-cm^2 surface (measured in j/cm^2). Likewise, power density, which is another way of saying light intensity, light concentration, or irradiance, is the amount of power (watts) delivered to 1 cm^2 of tissue area and is determined by the size of the treatment applicator and the emitted power. The larger the applicator surface, the lower the power density because the treated area is larger. Likewise, the lower the power of the device, the lower also the power density because the beam is not as intense.

The penetration capacity of an emitted light is defined as the distance at which radiation intensity is reduced by 50% of the initial radiation. For example, if radiation of any given wavelength penetrates the skin by 5 mm, at this depth the intensity of the laser beam has been reduced by 50% of the initial value. Penetrating photons produce scattering—a deviation from the original path of light. The wider the scattering is, the smaller the quantity of light energy that reaches the target tissue to be treated. Increasing the length of the wavelength diminishes the effects of scattering. Thus, a laser beam with a wavelength of 910 nm will penetrate farther into tissue than a laser beam of the same power with a 830 nm wavelength. Maximum scattering occurs in the ultraviolet spectrum (i.e., an EM wave with short wavelength) and minimum scattering for the infrared light (i.e., an EM wave with longer wavelength). The tissue penetrating capacity of a laser is greatly determined by the power and wavelength of the device, in a manner not unlike standard radiography equipment.

The first law of photochemistry (and photophysics) states that light must be absorbed for photochemistry (or photophysics) to occur (Smith, 2005). As Kendric Smith states, this is a simple concept, but it is the basis for performing clinical experiments correctly. Phototherapeutic effects from laser beams are mostly initiated by photochemistry in the cell's mitochondria. Therefore, unless the laser photons are absorbed by a cell, no photochemistry (or photophysics) actions will occur in the cell or, hence, at the tissue and organism levels. Similarly, no photobiological effects will be observed—no matter how long the laser beam irradiates the tissue.

Because therapeutic lasers typically have wavelengths within the therapeutic window, they meet the first requirement for efficacy: delivery of light energy into the tissue with no, or minimal, tissue heating. The second requirement for efficacy is that the laser device has the power and energy density to deliver the light energy to the target

tissue such that it produces the desired therapeutic effects. Currently, some nonsurgical lasers can produce beams with peak powers as high as 250 watts, which are able to penetrate tissues, such as muscle and bone, and are therefore, no longer considered low-level. Therapeutic lasers with high peak powers are able to deliver energy density of sufficient level to achieve clinical effects in deep tissues and organs.

Laser Emission: Continuous or Pulsed

In general, lasers function either in a continuous or pulsed mode. In the continuous mode, they unceasingly emit light for the entire predetermined time period, at a fixed level of power. Although they lack the high-peak power of a pulsed laser, most continuous lasers can be made to flash a number of times per second, simulating pulse-like rhythms by rapidly interrupting the flow of light, as occurs in turning a light switch on and off. Because of the important distinctions between continuous and pulsed lasers, this pulsed action is more aptly termed modulated or chopped emission, so that it is not confused with actual pulsed laser devices.

In the pulsed mode, biostimulation lasers emit a radiation impulse that has high amplitude or intensity, but the duration of the impulse is extremely short, typically from 50 to 200 nsec. Pulsed lasers, as the name implies, produce a high-power impulse for each pulse, which is the mechanism that drives the light energy to the target tissue. Even though the pulse peaks at a high-power level, there are no thermal effects to the tissue because of the extremely short duration of each pulse. High peak powers coupled with short pulse durations produce average powers that are not ablative. A typical pulsed biostimulation laser may have peak powers of 40 to 100 W, but maintain average power densities at safe levels of under 0.5 W/cm^2. The peak power of a pulsed laser is typically much higher than its average pulse power by factor of 100s. By using pulsed lasers, it is possible to more effectively drive light energy into the tissue using a level of power that can be even lower than that used with a continuous laser device.

Pulsed and continuous lasers that have same average power (watts) deliver the same amount of energy (joules); however, the treatment time with pulsed lasers is shorter (about 50% shorter) and can target deeper tissues, such as intervertebral discs, abdominal organs, and brain structures (Tunér and Hode, 2002). Depth of tissue penetration is important to meet the first law of photobiology and photophysics described previously. Continuous wave lasers are appropriate whenever high depth of tissue penetration is not necessary, such as in cosmetic applications and laser acupuncture. An advantage of continuous wave lasers is that they are less expensive to manufacture than pulsed lasers.

How Much Laser Energy Is Necessary for Effective Treatment?

Most laser devices used for therapeutic treatment are the continuous type, with mechanical or electrical switching devices to simulate pulses by repetitive flashing. The average power and peak power of these devices are basically the same, as they do not produce peak impulses of light energy. In actuality, higher flashing rates (modulation) correlate with lower average emitted power with continuous laser devices—the opposite of what is intended.

Research reported by Tunér and Hode (2002) in the book, *Laser Therapy: Scientific Background*, demonstrated that the optimum amount of energy density (dose) necessary to obtain therapeutic effects should be in the range of 0.5 to 6 j/cm^2. To estimate the energy needed to reach the target tissue, the depth of the tissue or organ to be treated and the composition of the layers of tissue between the laser applicator and the target tissue must be factored.

LASER LIGHT: EFFECTS AT THE PHYSICAL LEVEL AND BEYOND

Matter is really light imprisoned by gravity.

Max Planck
1918 Nobel Laureate in Physics

The clinical efficacy of laser therapy is based on the synergistic effects of multiple factors, such as increased blood flow and lymphatic drainage, edema reduction, activation of T-suppressor cells, transient inhibition of T-helper cells, cell-membrane activation that results in prostaglandin changes, and release of mediators, such as endorphins and growth factors (Simunovic, 2000; Karu, 1998). Most of the original research reports on the mechanisms and efficacy of biostimulation lasers were published in Hungarian, Russian, French, Spanish, or Italian. Recently, many more research reports and journal articles are published in English. Yet, the breath and depth of that research remain largely unknown to conventional medical practitioners in the United States. Biostimulation laser technology is continually improving, providing deeper tissue penetration, higher power densities, and reliable technologies to achieve better clinical outcomes. The trend has been to increase power density and dose because these factors produce better clinical outcomes.

Therapeutic Effects of Lasers

Traditional applications of biostimulation lasers have been focused on pain relief, reduction of inflammation, and tissue healing (Simunovic, 2000). With inflammation, the normal resting potential of C nerve fibers is decreased, leading to hypersensitivity and chronic pain (Miserendino and Pick, 1995). Studies have shown the ability of laser treatment to restore sodium pump action and maintain the negative resting potential of neuronal membranes, thus reducing pain and inflammation. Laser EM radiation of whole blood (blood irradiation) and directly into organs and glands has significantly impacted the treatment of diverse conditions, including asthma, cancer pain, climacteric disorders, diabetic angiopathies, dental hypersensitivity, periodontitis, drug resistant forms of schizophrenia, glaucoma, hepatitis, herpes zoster, infertility, ischemic heart conditions, nerve and muscle regeneration, occlusive vascular diseases, osteoporosis, pneumonia, prostatitis, pyelonephritis, and rheumatoid arthritis (Tunér and Hode, 2002). For cosmetic applications, the U.S. Food and Drug Administration has already cleared lasers for hair growth treatments, reduction of bone fractures, and cellulite reduction.

Lasers applied to traditional acupuncture points have been successfully used to treat diverse conditions, such as addictions, depression, hypertension, migraine-type headaches, atypical odontalgia, attention deficit disorders, allergies, poststroke

pain, and many others. As discussed in Chapters 6 and 11, Qi is the vital energy that permeates all animate and inanimate matter, according to Chinese medicine. Historically, light has been understood to be a correlate of Qi. Ancient QiGong texts speak of the benefits of the body absorbing light energy from the sun, moon, and stars and that the body radiates varying degrees and qualities of light, depending on the individual's health and consciousness (Prosak, 2001). In the past three decades, traditional Western researchers have confirmed that EM energy is a vital nutrient for all life. All living cells emit, absorb, and store EM energy in the form of light. Light is an organizational and communication system for cells, tissues, and organs, within the entire body (Chang et al., 1998).

There are excellent publications presenting details of the scientific basis for laser phototherapy and extensive treatment protocols (Tunér and Hode, 2003; Simunovic, 2000; Miserendino and Pick, 1995; Brugnera et al., 2006; Karu, 2007; Pöntinen, 1992). The following list of findings summarizes key information on laser phototherapy with emphasis on applications to pain relief, inflammation reduction, tissue healing, and laser acupuncture.

- Opioid peptides seem to be responsible for the analgesic effect of laser phototherapy (Benedicenti et al., 1984). His research group found that laser treatment with a pulsed laser (904 nm) could increase β-endorphin levels in cerebrospinal fluid.
- Zhong's research group has shown that nalorphine reverses the major part of analgesia from irradiation with a helium–neon (He–Ne) red laser light (Zhong et al., 1989).
- Airaksinen treated 36 subjects with bilateral chronic neck and shoulder pain with a He–Ne laser only on one side of the subject's body. The pressure pain threshold increased significantly in the nontreated side, although the increase was higher on the treated side (Airaksinen et al., 1989).
- Milani treated 13 low back pain patients by directly irradiating the affected lumbar dorsal branches of the sensory nerves, using a fiber optic cable inserted through a 4-cm cannula. After a total of 12 treatments, with 3 treatments per week, 11 patients had resolution of the symptoms (Milani, 1985).
- Palma demonstrated total block of prostaglandin E1 and bradykinin and partial block of thromboxane with He–Ne laser irradiation (Palma, 1991).
- Martinasso and coworkers demonstrated the effects of pulsed phototherapy laser (910 nm) on bone regeneration, including bone proliferation and formation in human osteoblast-like cells, MG-63 (Martinasso et al., 2007). Bone production was evaluated by determining the expression of osteocalcin and alkaline phosphatase, which are both proteins involved in calcium nodule formation.
- Simunovic reported successful wound healing among 87% of 328 patients and 73% of 279 patients with diabetic or vascular ulcers, respectively (Simunovic, 2000). The follow-up period ranged from 7 months up to 12 years. The youngest patient treated was 75 years of age, and the power densities used were between 1 and 20 j/cm^2.

- Bradley and coworkers conducted a double-blind clinical trial involving 30 female patients who had temporomandibular joint disorder, with pain lasting for more than six months (Bradley et al., 2000). Their results, obtained with three treatment sessions, demonstrated that a dose of 100 j/cm^2 was superior to placebo or a dose of 20 j/cm^2.
- Atypical facial pain is a difficult problem to treat and is characterized by constant pain, which may follow dental extraction (phantom tooth pain). Bradley and coworkers treated 15 patients with atypical facial pain, using laserpuncture on Stomach 5 ipsilaterally and Stomach 2 contralaterally, at 120 j/cm^2 over the involved trigeminal nerve ending (Bradley et al., 2000).
- Pöntinen reported success in using lasers to stimulate acupuncture points as a noninvasive and low-risk alternative to using needles (Pöntinen, 2000). The highest success in treating pain conditions with laserpuncture was obtained with doses in the range of 1–2 j/acupuncture point in a skin contact mode. Unsuccessful results were obtained using less than 1 j/acupuncture point.
- Obata treated 89 patients at all joints presenting with inflammatory signals, until pain relief was observed in all joints (Obata, 1990). He reported significant effects on erythrocyte sedimentation rate, Lansbury's index, and correlations between synovial scintigraphy and clinical effects.
- Pavlova reported that lasers are capable of reducing the free radical oxidative chain reaction inherent in the effects of radiation therapy (Pavlova et al., 1996).
- Lievens treated 10 patients presenting with crural ulcers, with a pulsed laser, daily for three months (Lievens, 1992). He reported significant reduction in pain, wound surface, and inflammatory symptoms.
- Mikhailov treated 42 patients with autoimmune thyroiditis for 10 sessions, using an 890-nm laser over the thymus projection zones, left axillary vascular junction, and thyroid gland (Mikhailov, 1999). He reported significant reduction in thyroid gland size and facial edema.
- Bernal reported 100% success rate in treating facial paralysis, using He–Ne and pulsed lasers; however, to achieve the high efficacy rate, the treatment had to be initiated within two days of the nerve injury (Bernal, 1993).
- Rochkind implanted embryonal spinal cord nerve cells in completely transected spinal cords of 22 adult rats (Rochkind et al., 2002). Fifteen of these rats were additionally treated with 780-nm laser, 30 minutes daily for 14 days. Among the laser-treated rats, 11 showed different degrees of leg movement and gait performance, while 6 of the 7 control rats remained completely paralyzed.

Light, Color, and Electromagnetic Waves

This chapter introduced the concepts of lasers as a specific form of light and that light is a form of EM radiation. Thus, lasers are devices that can deliver specific forms

of EM radiation. These EM radiations induce changes into the body, as described in the previous section.

The term *light*, denoting visible light, is conventionally used interchangeably with the term *color.* Color is not a property of light itself, but a manifestation of the electrochemical sensing system composed of the eyes, nerves, and brain. To complicate things, a beam of red light, say 660 nm, overlapping a beam of green light of 450 nm wavelength will result in the perception of yellow light, even though no photons with wavelengths in the yellow band are present; thus, humans see color with the brain, not just with the eyes. As discussed previously, the shorter the wavelength of an EM wave, the greater is the photon energy, which then correlates to the spectrum of colors. Different colors appear in the visible light spectrum because they have EM waves with different wavelengths. Otherwise, they are exactly the same entities: EM waves. The human body responds differently to EM waves with different parameters. In other words, EM waves have different effects (resonance) on the human body, depending on their parameters.

Dr. Peter Mandel, a German naturopath, is the inventor of Esogetics (**eso**teric ener**getics**), which includes a technique that uses EM radiation, corresponding to different colors on acupuncture points, to do what he refers to as balance the flow of life energy in the meridians. The therapy is called *colorpuncture.* To quote Dr. Mandel: "We who are imprisoned in matter have to bring our 'I' out of matter and darkness and into the light. On the level of the spiritual world we humans, in our wholeness, are light beings." In numerous cases, documented by Kirlian photographs, colorpuncture has demonstrated the potency of colored light for psychosomatic healing and personal transformation (Dass and Croke, 1996).

LET THERE BE LIGHT

But, the deeper reality is something beyond either mind or matter …

David Bohm, 1917–1994
Quantum Physicist

New theories in physics and many discoveries concerning light have brought about a renaissance in philosophical thinking. The discovery of quantum physics should have led to quantum biology, but the field is little understood or practiced in conventional medicine today. Instead, molecular biology, in which the building stones of life and life's processes are studied, is the field that attempts to find solutions to healthcare problems. Quantum physics and its logical extension, quantum biology, suggest that EM energy in general, and light in particular, ought to be a key focus of attention for resolving many of today's healthcare problems. This chapter focused on biostimulation lasers, which are either visible or infrared. EM waves with wavelengths other than visible and infrared, such as ultraviolet, also have a place in healing, even though not used in lasers (Douglass, 2003). For instance, as early as 1923, before the era of antibiotics, Emmet Knott demonstrated that blood irradiation with ultraviolet light could destroy infectious organisms and successfully treated septicemia (Knott, 1948). Knott was the first to develop ultraviolet blood irradiation

into a working therapy with demonstrated dosage, method of application, therapeutic effect, and safety procedures (Dillon, 1998).

This chapter focused on light absorbed by human tissues and organs for the purpose of healing, but light is also emitted by "living" cells as biophotons at different wavelengths (Ho, 1998). These biophotons are not associated with specific organelles and are strongly correlated with cell cycles and other functional states of cells and organisms; they respond to many external stimuli or stresses. Fritz Popp and coworkers discovered that photons are held in a coherent state in the organism and when stimulated, are emitted coherently, like very weak tunable lasers (Popp et al., 1992). Biophotons include EM radiation below the visible range, passing through microwave and radio frequencies to the extremely low frequency end of the spectrum. In fact, Popp has demonstrated that cell-to-cell communication exists via EM radiation, which occurs much faster than with biochemical production and diffusion (Ho et al., 1994).

As discussed, lasers are devices to deliver light as EM radiation into living cells, tissues, and organs for healing purposes. Cells emit EM radiation at different wavelengths with very low amplitudes. Tissues and organisms, therefore, are large collections of tiny coherent emitters and receivers of EM radiation creating a harmonious ensemble of frequencies covering about 72 octaves (Ho, 1998). Integrative medical doctors listen to this bio-orchestra with new electronic devices, such as Gas Discharge Visualization instruments, for out-of-tune symphonies and reestablish harmony and cadence using EM generating devices, including lasers. It was the famous physicist, Albert Einstein, who captured the essential message of this chapter when he asserted that ultimately human beings are just frozen light—his famous formula mathematically connects all forms of energy, especially light, with matter.

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9 The Four Pillars and Two Guideposts for the Healing Professions™

INTRODUCTION

It often is said that the practice of medicine is as much an art as a science. To meet the needs of twenty-first century healthcare, medical schools must shepherd students through their education in a manner that will prepare them to accept fully the mantle of responsibility that the title Doctor of Medicine confers, which today involves far more than the mastery of scientific principles. Yes, medical education must provide a solid foundation in the basic and clinical sciences. However, that foundation is no longer sufficient to be a competent and effective doctor. Increasingly, patients are looking for physicians who are willing to address all aspects of the tapestry of healing: the body, the mind, the emotions, and the spirit. While curricula for medical schools have never been static (i.e., as transitions in science, policy, and patient needs occur, education curricula adjust), it is my contention that the time has come to institute a comprehensive transformation in medical education, reforming it both to incorporate the critical needs of the global medical community and to institute a vital advancement in the theory and practice of healthcare—reinstating the art and heart of medicine.

In this chapter, the distinguishing characteristics necessary for a high-quality medical education in the twenty-first century are evaluated. I call them The Four Pillars and Two Guideposts for the Healing Professions. They are discussed below:

The Four Pillars

1. Integrative collaborative care
2. Cultural competence
3. Clinical sensitivity
4. Technological innovation

The Two Guideposts

1. Increased services to the underserved
3. Decrease the brain drain of healthcare professionals

The Four Pillars and Two Guideposts set the stage for a much-needed revitalization and compass correction to medical education. While the issues discussed are

couched in terms of physician education, they can and should apply to the education curricula of all healing professions. As mentioned in Chapter 5, the Latin origin of the word "doctor" means: "to teach." It is still possible to restore the true meaning of the label, advancing the dialogue across constituencies and improving the quality of education for future physicians. Training students to provide a standard of care that addresses not only healthcare needs but also respects cultural mores and practices as well as religious or philosophical belief systems, will foster healing with reverence and humanism to patients in the United States and in every part of the globe.

The Four Pillars and Two Guideposts are not intended to be a static or definitive resolution to current issues in medical education, but rather the opening of a dialogue—a dialogue with various constituencies and experts in the field of medicine who can contribute solutions and foster a transformation in how health professionals of the future are educated. The outcome will be a global standard of education for the medical profession and global expectations for comprehensive care and patients' rights. We can no longer afford to focus only on healthcare in the United States, but rather must accept the reality that we have become a global community and require a global plan for healthcare.

Advancing Medical Education Curriculum

Much discussion has taken place regarding the need to bring together the organizations and individuals to choreograph the future direction of medical education in the United States and around the world. Until recently, medical education was compartmentalized on national or regional scales. According to a report published by the Association of American Medical Colleges (AAMC) entitled *Educating Doctors to Provide High Quality Medical Care*: "Medical education in the United States must undergo significant change in order to better prepare physicians for the nation's rapidly evolving health care needs" (AAMC, 2004). The report identifies opportunities for improving physician education during three distinct phases: medical school, residency training, and continuing medical education, suggesting that even doctors with many years of practice behind them must improve their sensitivity and skills for the changing needs of global healthcare. Mayo Medical School goes a step farther, stating in their M.D. Program Curriculum Overview: "Growing physician interest in healing wisdom from other cultures brings still more change to our medical curriculum and we welcome this growth. MMS [Mayo Medical School] is committed to educating physicians to be fluent in many healthcare traditions, and to be fully prepared for the possibility of a global medical practice" (Mayo Medical School, 2008).

The physician with many years of experience may ask why participate in continuing education on globalization of medical practice. Yet, all it takes is one very ill patient returning home from an international trip, to readily understand the necessity. As an article published in the *Lancet* in 2001 states: "Globalisation is accelerating and is forcing us all to realise that we cannot isolate ourselves from international issues.… The interconnectedness of the world and the implications it has for all became very real.… From the horror of the HIV/AIDS pandemic to the increasing rates of refugees and migrants; from the controversy over global pharmaceutical patents to the health implications of the World Trade Organisation; the issues of the day all affect

the work of a doctor. It is no longer enough for medical curricula to teach about national medicine; our new doctors want, and need, more" (Bateman, 2001).

As globalization became more apparent, particularly since 9/11, medical students have led the charge to transform medical education curricula to one that is international. The International Federation of Medical Students' Associations (IFMSA) is an independent, nongovernmental, nonpolitical organization that functions throughout the world; the group's expressed mission is "to offer future physicians a comprehensive introduction to global health issues. Through our programming and opportunities, we develop culturally sensitive students of medicine, intent on influencing the transnational inequalities that shape the health of our planet" (IFMSA, 2008). IFMSA's Standing Committee On Medical Education (SCOME) asserts: "We question that students educated in a so-called traditional curriculum are able to face the needs of healthcare in a modern society." One of their partner organizations, the World Federation for Medical Education, has initiated a project to develop international standards in basic medical education. According to IFMSA, the project seeks "to stimulate medical schools to formulate their own plans for change and for quality improvement in accordance with international recommendations" (World Federation for Medical Education, 2008).

In 2004, the Institute of Medicine published a report, *Improving Medical Education: Enhancing the Behavioral and Social Science Content of Medical School Curricula*, which identified 20 priority topics within 6 key domains that they recommended that medical schools integrate into their curriculum, over the entire four-year doctoral program. The domains include:

1. Mind–body interactions in health and disease
2. Patient behavior
3. Physician role and behavior
4. Physician–patient relationship
5. Social and cultural issues in healthcare
6. Health policy and economics (Institute of Medicine, 2008)

While admirable advances in healthcare for the United States, the report made no mention of global health issues or the need to design medical curricula that addresses globalization.

FIRST PILLAR: INTEGRATIVE COLLABORATIVE CARE

> *Medicine has two distinct purposes. The relative purpose of medicine is to relieve symptoms and to cure disease. But there is also an ultimate purpose, which extends beyond the physical realm to include the mind, heart, and spirit of every patient, and indeed of humanity as a whole.*
>
> **Dr. Jeremy Geffen** (*Geffen, 2000*)

The First Pillar, Integrative Collaborative Care, refers to a patient-centered model that endorses the active participation of several healthcare disciplines and professions. Currently, in most of the United States, patients must visit a different doctor

for each health issue they may have, thus, incidents of healthcare professionals collaborating on patient care occurs infrequently. Similarly, few academic institutions, here or abroad, have or are actively engaged in developing a medical curriculum to advance collaborative care; therefore, such efforts remain on the cutting edge of medical education.

The main obstacle to basing healthcare on principles of integrative medicine and collaborative care began at the turn of the twentieth century. As mentioned in Chapter 5, this was the period in which medical education and practice focused on laboratory research that could identify the causes of infectious diseases; by the 1930s, researchers had formulated the first pharmaceuticals, natural substances were phased out. Along with the institution of a biomedical model came a shift to a mechanistic view of the human body: the perspective of treating the whole individual—body, mind, and spirit—was soon lost in the fervor to identify new microbes and their antigens.

By 1977, G. L. Engel, a professor at the University of Rochester concluded: "The biomedical model assumes disease to be fully accounted for by deviations from the norm of measurable biological (somatic) variables. It leaves no room within its framework for the social, psychological, and behavioral dimensions of illness.… The biomedical model has thus become a cultural imperative, its limitations easily overlooked. In brief, it has now acquired the status of dogma. In science, a model is revised or abandoned when it fails to account adequately for all data. A dogma, on the other hand, requires that discrepant data be forced to fit the model or be excluded" (Engel, 1977).

Until the 1990s, medicine typically has been practiced in a hierarchal, paternalistic fashion, with the physician at the top of the hierarchy. Recognition of the important roles played by nurses, other types of health service providers, and caregivers have contributed to the development of a collaborative approach to care. Yet, as recently as 2006, the CEO of the Institute for Healthcare Improvement stated that "care that is neither patient-centered nor collaborative—is at the heart of the quality chasm'" (Berwick, 2006). One of the greatest challenges for physicians and medical students in the twenty-first century is learning to balance the immense technical aspects providing quality diagnostics and treatment with humanism and compassion in the delivery of care. Practical experiences in integrative collaborative and patient-centered care help develop the interpersonal skills that improve patient–physician–family interaction. Slowly, medical practice and education is moving beyond a simple biomedical model to a more integrative and comprehensive approach.

Components of an Integrative Collaborative Care Treatment Model

By definition, integrative collaborative medical care is an approach to treatment that involves ongoing collaboration among the required health service providers, patients, their families and caregivers, and the community. Patients are both the focal point and a full partner in the overall effort. What might be the key features to an integrative collaborative care treatment model?

Health Canada has been a leader in recognizing that successful treatment requires a collaborative effort and that collaborative care must be "a key aspect of primary

health care" (Health Canada, 2008). According to Health Canada, "Successful health care often relies on collaborative care, which requires a broad network of collaborative interactions among a variety of health service providers, patients, their families and caregivers, and the community, with patients being both the focal points and full-fledged partners of the overall effort." In describing *Interprofessional Education for Collaborative Patient-Centered Practice,* Health Canada asserts that collaborative care "will contribute to:

- Improved population health/patient care
- Improved access to health care
- Improved recruitment and retention of health care providers
- Improved patient safety and communication among health care providers
- More efficient and effective employment of health human resources
- Improved satisfaction among patients and health care providers" (Health Canada, 2008).

Health Canada is not alone in this recognition. In a 2001 publication, *Crossing the Quality Chasm: A New Health System for the 21st Century*, the U.S. Institute of Medicine (IOM) presented six key dimensions to improving the quality of healthcare. They state, "Health care should be

- Safe—avoiding injuries to patients from the care that is intended to help them.
- Effective—providing services based on scientific knowledge to all who could benefit and refraining from providing services to those not likely to benefit (avoiding underuse and overuse, respectively).
- Patient-centered—providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions.
- Timely—reducing waits and sometimes-harmful delays for both those who receive and those who give care.
- Efficient—avoiding waste, including waste of equipment, supplies, ideas, and energy.
- Equitable—providing care that does not vary in quality because of personal characteristics, such as gender, ethnicity, geographic location, and socioeconomic status" (Institute of Medicine, 2001).

Furthermore, the IOM outlines the following specific issues that will be important to incorporate into patient-centered care:

- Respect for patients' values, preferences, and expressed needs
- Coordination and integration of care
- Information, communication, and education
- Physical comfort
- Emotional support—relieving fear and anxiety
- Involvement of family and friends (Institute of Medicine, 2001)

The Need to Incorporate Integrative Collaborative Care in Medical Education

Medical School Students' Perspectives

There are a plethora of surveys in the peer-reviewed literature that evaluate the knowledge and interests of medical students toward including information on integrative therapies into their medical education curriculum. Overwhelmingly, the surveys indicate interest and desire for access to this information. A sampling follows:

- A 2006 survey of first and second year medical students at Georgetown University School of Medicine found that 91% of the students agreed that "CAM [complementary and alternative medicine] includes ideas and methods from which Western medicine could benefit," >85% granted that "knowledge about CAM is important to me as a student/future practicing health professional," and >75% wanted CAM to be included in the curriculum (Chaterji, 2007). Among all students, the most frequently indicated level of desired training for 11 of the 15 modalities was "sufficient to advise patients about use." The training was desired in the areas of acupuncture, chiropractic, herbal medicine, and nutritional supplements.
- A 2005 comparative survey gauged the interest and knowledge of CAM among first- to fifth-year medical students in Singapore (Yeo, 2005). Although only 57% of the students had some knowledge of acupuncture, a full 92% believed that CAM includes ideas and methods that could benefit conventional medicine, while 91% stated that CAM would play an important role in their future conventional medical practice. Yet, students acknowledged having very little knowledge about chiropractic medicine, osteopathic medicine, Ayurvedic medicine, homeopathic medicine or naturopathic medicine, and they possessed significantly erroneous information regarding these modalities.
- A 2005 survey performed at the Carite University Medical School of Berlin, Germany, also evaluated knowledge and interest in CAM modalities among medical students (Witt, 2006). Because of the increasing utilization of CAM therapies among patients and the lack of CAM training at Carite, a curriculum reform was instituted to provide basic knowledge about naturopathy, homeopathy, and traditional Chinese medicine, including utilization patterns, empirical research, underlying philosophies, as well as experiential and dialogical didactic techniques for each modality. Depending on the method 73% to 96% of the respondents supported the inclusion of the CAM therapies into the curriculum. Student participation and classroom atmosphere were rated as very good.

The U.S. Government Weighs In

Similarly, the U.S. government has called for integrative therapies to be incorporated into medical education curriculum. A sampling follows:

- In 1991, the U.S. Congress instructed the National Institutes of Health (NIH) to create an organization whose mandate would be to evaluate

CAM therapies—thus, the Office of Alternative Medicine (OAM) was established. Shortly after its creation, the OAM had a series of meetings with experts in the diverse fields of CAM medicine to gather information and recommendations. The resulting report, prepared for the NIH, included a recommendation that the OAM "work with directors of medical student education to develop comprehensive programs of undergraduate medical education that explore and critically evaluate the theory, clinical practice, and research implications of alternative medical approaches" (National Institutes of Health, 1991). After growing the annual budget of the OAM from $2 million to $20 million, in 1998 Congress elevated the OAM and renamed it the National Center for Complementary and Alternative Medicine (NCCAM). The NCCAM was granted autonomy and grant-making authority similar to the other centers and institutes of the NIH, and its budget was increased to $120 million.

- The Public Health Service has documented the fact that many of the leading causes of morbidity and mortality in the United States are attributable to social, behavioral, and lifestyle factors, such as tobacco use, lack of exercise, poor diet, or drug and alcohol abuse (U.S. Department of Health and Human Services, 2008A). As mentioned in Chapters 2 and 3, psychological stress is linked to a variety of adverse health outcomes, including heart disease and decreased immune system functioning, while attitude, beliefs, social support, prayer, and meditation can reduce stress and contribute to positive health outcomes.
- In 2000, Congress created the White House Commission on Complementary and Alternative Medicine Policy (WHCCAMP) to address: (1) CAM education and training for healthcare practitioners, (2) research to increase knowledge about CAM products, (3) provision of reliable and useful information on CAM, and (4) appropriate access to and delivery of CAM (WHCCAMP, 2008).

As the co-founder of the Design Principles for Health Care Renewal Working Group, which was developed during the Integrative Medicine Industry Leadership Summit in 2000, I was fortunate to be one of the experts called to testify before the WHCCAMP. Our working group asserted that as there are now many organizations involved in complementary or integrative healthcare, it was essential to develop consensus on guiding principles for integrative healthcare in the United States. These principles are a necessary part of medical education curricula as well as of in-service training programs. The Health Care Renewal Working Group addressed issues concerning the entire healthcare system—both allopathic and CAM—as well as how current allopathic and CAM systems of treatment could better interface. Our work was based on and expanded principles established in the report by the IOM, *Crossing the Quality Chasm: A New Health System for the 21st Century*, discussed in the previous section of this chapter.

The 10 draft principles that the working group identified follow in an edited form for the purposes of this book.

1. **Honor wholeness and interconnectedness in all actions:** Body, mind, spirit, community, and environment are an integral whole that cannot be separated into isolated parts. All are involved in healing. Healthcare interventions, regardless of their focus, affect the whole.
2. **Enhance the capacity for self-repair and healing:** The innate capacity for healing and the individual's personal empowerment in supporting these natural processes are fundamental considerations in all healthcare decisions.
3. **Prioritize care in accordance with a hierarchy of treatment:** Healthcare and the leveraging of resources to affect care are prioritized along diagnostic and therapeutic hierarchies that begin with education and empowerment for patients to make healthy choices. Prioritization then moves to the least invasive approaches and escalates, as necessary, to approaches linked to increased likelihood of adverse effects or higher costs. The starting point for intervention is established through clarifying, with the individual receiving care, the risks associated with foregoing or undertaking more invasive approaches. Chronology and cause are fundamental aspects of this healing order.
4. **Improve healthcare through continuously expanding the evidence base:** Healthcare is a combined art and science in which personal practices and clinical choices or services are continuously evaluated and improved based on diverse evidentiary input, including that from patients and all members of a provider team, but particularly from systematically gathered evidence of clinical experience and outcomes. Both allopathic and integrative medicine should be held to these standards; however, as novel therapies (e.g., energy modalities) are developed, new gold standards in study design may be needed.
5. **Embrace the fullness of diverse healthcare systems:** Conventional, traditional, indigenous, complementary, and alternative models of healthcare have contributions to make that tend to run along cultural lines. These diverse models potentially are of great value to one another.
6. **Partner with patients, their families, and other practitioners.** Caregivers have the potential to profoundly enhance healing and can strengthen and share accountability by supporting the informed decision making of the patients they serve. If approached as respected partners with practitioners for the optimal patient care, caregivers can effectively facilitate collaboration.
7. **Use illness and symptoms as opportunities for learning and growth:** Illness represents an opportunity in which healing and balance are possible, even when curing is not. Symptoms are guides to improving the overall (i.e., physical, emotional, and mental) health of an individual.
8. **Explore integration in one's own care:** Practitioners and administrators are most effective in understanding and delivering integrative healthcare when they follow and embrace these design principles in their own healthcare choices.

9. **Align resource investment with these healthcare principles:** Any plan to renew or revamp how healthcare payment and delivery systems are carried out must be fostered by aligning the monetary investment in resources with the kinds of principles outlined here. Whether in the public, philanthropic, or private sectors, humble willingness to work to place patients' rights and needs before personal interests, professional ambitions, or economic gain is fundamental to an improved healthcare system in the United States.
10. **Respect the time required for personal and health system change:** Interventions may be swift, but healing, habit change, and transformation take time and ongoing commitment.

The Institute of Medicine Takes a Stand

The IOM study titled, *Improving Medical Education: Enhancing the Behavioral and Social Science Content of Medical School Curricula* concluded:

> No physician's education would be complete without an understanding of the role played by behavioral and social factors in human health and disease, knowledge of the ways in which these factors can be modified, and an appreciation of how personal life experiences influence physician-patient relationships" (Institute of Medicine, 2004).

The IOM recommended that the NIH fund the development of medical school curricula in behavioral and social sciences. Recommendations included the following topics:

- Mind–body interactions in health and disease
- Patient behavior
- Physician role and behavior
- Physician–patient interactions
- Social and cultural issues in healthcare
- Health policy and economics

Integrative Collaborative Care and Integrative Medicine

An integral approach to health incorporates lifestyle, behavior, and social factors that affect personal well-being as well as the patient–physician interaction. This arena includes the relationships among cognition, emotion, personality, social relationships, and health, as presented in the discussion in Chapter 2 on the integration of bodily systems and the research on psychoneuroimmunology (PNI).

Integrative Collaborative Care: Healing Systems from Other Cultures

Integrative Collaborative Care cannot simply involve coordination among patients and caretakers; it must also extend to the incorporation of various practices and philosophies of medical care. For instance, today aspiring medical students will enter the healing profession when more than 50% of their patients likely will incorporate

healing practices originating from other cultures and philosophies. Therefore, a global perspective of the history, culture, and philosophy of numerous systems of healing as well as essential data on safety, research, and implementation must be integrated into the basic science curricula and clinical experiences of medical education. In 2006, the American Medical Association's (AMA) House of Delegates passed a resolution brought to them from medical students that included the following provision: "Our AMA will promote awareness among medical students and physicians of the wide use of complementary and alternative medicine, including its benefits, risks, and evidence of efficacy or lack thereof" (American Medical Assoc., 2006). As previously mentioned, I call such an expanded, collaborative approach "integral medicine": the next step beyond integrative medicine.

Ultimately, integral medicine promotes a multidimensional view of life and asserts that people are more than physical beings. An integral medical education must include concepts key to PNI that foster the understanding that the body systems are indeed an integral physiology and that mind, emotions, and spirituality each may impact the healing process. Hence, medical education will also need to teach students to be open-minded and tolerant rather than dismissive of a patient's philosophy and culture. The approach uses conventional models of health maintenance or restoration, while simultaneously considering the value and efficacy of adding integrative therapies, recommending changes in diet/nutrition, exercise, social interaction, or incorporating psychological and spiritual development. When applied in a sensitive, process-oriented manner, integral medicine can promote optimal health, self-awareness, happiness, and longevity—for both the patient and the physician.

Integrative Collaborative Care and Spirituality

A topic frequently avoided or overlooked in medical education is the role of spirituality—of either the patient or the healthcare provider. *Spirituality in Higher Education: A National Study of College Students' Search for Meaning and Purpose* was a study carried out by the Higher Education Research Institute at the University of California, Los Angeles, to assess the trends and patterns of spirituality and religiousness among college students. In 2004, Shannon Calderone, an editor of the project's newsletter, stated, "There remains a sizeable gap in our ability to articulate the role that the human spirit plays in health and wellness. While examining the mind–body–spirit connection is not unique to the world of medicine, formal ministering to the spiritual health of a patient has only recently found a foothold in the training of medical professionals" (Calderone, 2004). In the same newsletter, Dr. John Astin, a leader in the emerging field examining the role of religion and spirituality on health, was interviewed and stated, "… people have a sense that somehow, the way we think and feel about our lives, our perspectives, our beliefs (including spiritual)—somehow these do have an impact on how our body ultimately feels and functions … [a] reason for this enduring and now growing interest in the spirituality/health link probably also has a lot to do with the fact that confronting health issues frequently is a challenging, stressful, and disorienting experience for people whether that means confronting chronic pain or some other illness. The graver the illness, the

more people tend to question life's meaning and purpose: … What is the meaning of life and death?" (McJunkin, 2004).

The very nature of the medical environment, the joys and sorrows associated with birth and the trauma and pain associated with illness and death, are a natural conduit for spiritual inquiry. A collaborative care team, especially for patients with a terminal illness, often includes a chaplain. However, given globalization trends, physicians (as part of their continuing educational training), medical students (as a skill set focused on interpersonal dialogue with patients), and all healthcare professionals will benefit from information regarding various belief systems and how they may or may not affect patient–provider interaction and even health outcome. Because spirituality is intertwined with culture in most societies, understanding how the world's religions or a patient's personal spiritual beliefs affect the physician–patient interaction ultimately improves the interaction itself.

The Century Plant

I enjoyed a unique experience between the years 1998 and 2001 during which time I sold my solo practice of internal medicine to a venture-backed project, known as American WholeHealth. I assisted in their development of a multidisciplinary healthcare practice composed of physicians, osteopaths, chiropractors, acupuncturists, massage therapists, psychotherapists, and energy therapists (e.g., Reiki and others). We were all located under one roof, in a 10,000 square foot facility. Our goal was to deliver comprehensive care to each patient, inclusive of the physical, emotional, mental, and spiritual aspects of healing. The various healthcare practitioners conducted multidisciplinary rounds that included patients with complex groupings of disorders; we learned much from each other. The experience fostered greater depths of respect and understanding for each of our medical specialties and healing traditions, while it also assisted us in realizing the limitations of our individual disciplines. I have never witnessed such profound healing of so many patients, including several individuals with extremely complicated clinical problems for whom conventional medicine dictated a poor prognosis. In spite of all of its clinical success, this ideal multidisciplinary healthcare practice lasted only 2 years, when investors chose to close it. It is my contention that it needed another year to be able to stand on its own. Did you know that the century plant blooms but once a millennium, for one incredible night—with enormous flowers that can reach up 25 feet—then dies? Although ephemeral, I have had the honor and pleasure to witness the power and gift of collaborative integrative medicine, which I believe will be the future configuration of primary care medicine.

SECOND PILLAR: CULTURAL COMPETENCE

Defining Cultural Competence

The Second Pillar is Cultural Competence, which asserts that sensitivity and responsiveness to ethnic, social, and cultural identity are integral to effective, comprehensive healthcare. Cultural competence also promotes awareness of how age, gender, spiritual beliefs and other factors affect the interaction between physician and patient, encouraging the healthcare worker to be cognizant of terminology and presentation

of recommendations that may be tailored to promote optimal patient outcomes. As with Collaborative Care, various organizations and individuals have published their definitions of cultural competence and the components they feel are essential to its integration in medical care. Interestingly, it is not just medical professionals who have become concerned about cultural competence. Dorene J. Philpot, an attorney with offices in Indiana and Texas, defines cultural competence as it pertains to Special Education Law: "Services that are sensitive and responsive to cultural differences. Caregivers are aware of the impact of culture and possess skills to help provide services that respond appropriately to a person's unique cultural differences, including race and ethnicity, national origin, religion, age, gender, sexual orientation, or physical disability. They also adapt their skills to fit a family's values and customs" (Philpot, 2000).

In their publication, *Healthy People 2010 Progress Review*, the U.S. Department of Health and Human Services defines cultural competence as "a group of skills, attitudes, and knowledge that allows persons, organizations, and systems to work effectively with diverse racial, ethnic, and social groups." (U.S. Department of Health and Human Services, 2007). As part of a program in 2005 designed to train healthcare professionals in cultural competence, the American Association of Medical Colleges provided a statement that specifically addresses healthcare practitioners, stating, "Culturally competent health care combines the tenets of patient-centered care with an understanding of the social and cultural influences that affect the quality of health-care services and treatment. With an increasingly diverse population in the United States and strong evidence of racial and ethnic disparities in health care, it is critically important that health-care professionals are educated specifically to address issues of culture in an effective manner" (American Association of Medical Colleges, 2005). To this end, on March 23, 2005, New Jersey became the first state to institute legislation requiring cultural competency training and that pertinent issues relating to a patient's ethnicity, culture, and language be incorporated into the care plan (New Jersey, 2005).

In the current medical environment, physicians must respond to the needs of individuals whose backgrounds may differ radically from their own in terms of race, sexual orientation, cultural background, and attitude toward disability status. On their Web site, the American Medical Student Association asserts that "culture is a predominant force in shaping behavior, values and institutions. Not only do cultural differences exist, but they also impact health care delivery.… Rather than being insulted by another culture's perspective, culturally competent providers welcome collaboration and cooperation" (American Medical Student Association, 2008a). The statement is part of a program that provides definitions, resources, activities, suggestions for speakers, and other information for training and workshops in cultural competence. Teaching cultural competence provides students with an understanding and appreciation for differing cultural belief systems and views of health and illness. Thus, the cause of an illness may be attributed to organ failure by one culture, while another views it as an energy or spiritual imbalance. To unite both perspectives to the patient's benefit, decisions regarding the course of treatment must respect and take into account both traditional and integrative healing practices preferred by the patient.

Establishing trust among the physician, patient, and family members may be an essential step in getting some patients to disclose details of their condition and express a preference for including traditional or alternative healing practices, thus fostering compliance. In 2002, researcher Joanna Shapiro and colleagues at the University of California, Irvine, noted that "failure to pay attention to cultural differences can lead to misdiagnosis, lack of cooperation, poor use of health services, and patient alienation and mistrust" (Shapiro, 2002). The reality of diversity across the corporate world has spawned the development of a new profession—the diversity coach. For the healthcare professional, cultural competence is not simply about avoiding embarrassment from being ignorant of a cultural practice or custom, but, importantly, it is potentially about overcoming communication barriers and improving health outcomes.

Worldwide Efforts Toward Cultural Competence in Medical Education

Training in cultural competence is not just occurring in the United States, by any means. Policy and academic leaders around the globe have acknowledged the importance of improving medical education curricula regarding cultural and ethnic diversity. While there is a broad recognition of the need for cultural competency training, there is little evidence to support one specific teaching method or approach over another; researchers currently are assessing the efficacy of various evaluation tools. For instance, a study published in 2001, conducted by researchers at the University of Newcastle on Tyne in the United Kingdom, evaluated the perceptions of medical students regarding cultural and ethnic diversity training. While the participants had a broad awareness of multicultural issues, it was superficial at best, largely focusing on differences and stereotypical viewpoints among cultures. The authors concluded that the students' training was inadequate, yet there was willingness among the students to learn more. The investigators emphasized that the students "rarely identified that responding to people as individuals, specifically exploring their own attitudes to difference, or racism in health care might be relevant to learning about cultural and ethnic diversity," adding that "it may be important for educators to recognize the predominance of the 'difference' perspective as a common starting point for learners, so that an appropriate balance in learning can then be promoted" (Kai et al., 2001). The authors assert that if educators recognize the importance of modeling, learners benefit by seeing the efficacy, clinical relevance, and practical outcome of what they are being taught. Furthermore, Kai and colleagues demonstrated that training must be integrated across the different stages of the medical curriculum or students will "miss opportunities to build upon and reinforce earlier learning." Importantly, they noted that the postgraduate students were already less forthcoming in discussions of cultural competency than were the less experienced medical students they interviewed.

The Health Resources and Services Administration (HRSA) and the Office of Minority Health, both under the U.S. Department of Health and Human Services, have taken leadership roles regarding cultural competency in healthcare (Health Resources and Services Administration, 2005; U.S. Department of Health and Human Services, 2008b). The HRSA is working with the Centers of Excellence (COE) programs "to reduce disparity in the healthcare system by increasing the

number of underrepresented minorities working in the health field" and to increase cultural competence training for healthcare professionals. HRSA supports adaptation by COE centers of the *Principles and Recommended Standards for Cultural and Linguistic Competence Education For Health Care Professionals*, which was first published by the nonprofit organization, California Endowment, in 2003. The recommended standards are designed to assist COEs toward establishing cultural and linguistic competency in curriculum design by teaching the importance of:

- Increased awareness and understanding of the impact of cultural influences on the ability to provide good quality healthcare to patients from any ethnic background.
- Developing clinical excellence and strong therapeutic alliances with patients.
- Reducing disparities in the provision of healthcare by improving quality and cost effectiveness (U.S. Department of Health and Human Services, 2008b).

In addition, the HRSA recommends that adding cultural and linguistic competency programs to the curriculum occur incrementally. Training initially could cover a specific area of study and advance to integrated and in-depth coursework, with students expected to become sophisticated in the complexity of culture and linguistics as they impact healthcare. The recommended standards indicate the value of factual knowledge, but emphasize the need to establish "process-oriented tools" that teach the healthcare provider effective communication skills and how to develop a therapeutic alliance with patients of any background. Finally, the HRSA recommendations stress the importance of creating a "nonjudgmental, supportive environment" for cultural and linguistic competency training.

Cultural Competence Equals Patient-Centered Healthcare

Issues that are considered aspects of patient-centered cultural competence can include matters as relatively minor as handling a relaxed attitude toward appointment time to serious subjects, such as the belief that illness stems from energy imbalance. Both these types of concerns can be respectfully addressed by clinicians trained in cultural competence. A physician, writing a *Perspective* article in the *New England Journal of Medicine* described patient-centered as "including exploration, empathy, and responsiveness to patients' needs, values, and preferences" (Betancourt, 2004).

Yet, data from the U.S. Department of Health and Human Services' Office of Minority Health report on *Heart Disease and African Americans* describes African American adults not only as less likely to be diagnosed with heart disease, but also more apt to die from it (U.S. Department of Health and Human Services, 2008c). The report states: "In 2004, African American men were 30% more likely to die from heart disease, as compared to non-Hispanic white men." The disparity is staggering. Similarly, numerous reports detail gender bias in healthcare, which has improved since the 1980s when studies were run only on men, while outcomes were applied to women as well, but still does not reach equality (Schiebinger, 2003). It would be valuable to assess how many women have been told by a male physician that their

symptoms are from stress or are psychologically based. An article published in May 2008 reports that in the management of acute myocardial infarction, no evidence of a gender bias in pharmacologic therapy or revascularization was found; however, after accounting for confounders, women were 46% less likely than men to undergo investigative coronary angiography (Nguyen et al., 2008). Women and men were similarly offered the opportunity to proceed with a coronary reperfusion modality, yet men were more likely to be given coronary artery bypass grafting [OR = 0.57 (0.39–0.84)] and women percutaneous coronary intervention [OR = 1.41 (1.07–1.86)] to address this need. Assessing disease severity ameliorated the disparity in the modality selected. In the United States, issues of racial and gender bias still have not been resolved while simultaneously increasing numbers of immigrants and refuges need healthcare provided by respectful, unbiased providers.

Although the evidence is quite clear that training in cultural competence improves the attitudes and approaches taken by healthcare workers, findings on whether or not it improves disparities in healthcare quality and delivery are, at best, mixed. In order to be broadly effective in improving healthcare, it is important to shift the fundamental orientation of cultural competency education from simply learning facts pertinent to the patient's cultural, gender, or ethnic background and/or acquiring linguistic competence to instead focusing on patient-centered care in which the provider may even play an advocacy role. Koehn and colleagues have set out five skill domains to engender patient-centered care and cultural competency training that has meaningful, practical application (Koehn and Swick, 2006). The skills include analytic, emotional, creative, communicative, and functional components and are intended to "reduce health disparities among patients with multiple and diverse backgrounds, health conditions, and health care beliefs and practices." Two key goals of the training proposed by Koehn and Swick are to foster genuine respect of the patient's cultural beliefs and orientation as well as to use knowledge of cultural features or language in an analytical manner to assess overall health. In other words, cultural competence must become a skill that uses a dynamic, longitudinal overview of a patient rather than a static, list-based approach to evaluating health.

A Firsthand Lesson on the Need for Cultural Competence

For 20 years, I was the corporate medical director of Marriott International Inc., which gave me the opportunity to medically evaluate employees from various cultures around the globe. Early in my career, a Marriott employee from Asia came into my office with complaints of pain from an upper thoracic injury. At the physical examination, I noted circular bruises across the top of her back. Concerned that she may have been abused by a family member, I questioned her about the bruises. She explained that she had been treated with a Chinese remedy called "cupping" to adjust her stagnant "chi" or energy field, which she explained was the underlying source of her pain. The insensitive look I gave her, I'm now sorry to say, created a strong barrier to any meaningful communication. My awkward handling of the use of an indigenous remedy that remains very common in her culture short-circuited any hope of establishing a meaningful therapeutic relationship with this woman. Years later, while studying various modalities of Chinese medicine, I not only experienced firsthand the

beneficial techniques of cupping, but also learned about its efficacy in the amelioration of both muscle and musculoskeletal pain as well as in reducing local edema and congestion. In doing so, I recalled my patient from Asia, wishing I'd been taught cultural competence somewhere along the journey through medical training.

THIRD PILLAR: CLINICAL SENSITIVITY

The third pillar of the Four Pillars and Two Guideposts of Education for the Healing Professions is Clinical Sensitivity. The ability to express compassion in clinical interactions may be the single greatest tool for overall healing that a physician might bring to patient interactions, yet the restoration of compassion in medical care is sorely needed. Given the predominating technological climate, maintaining a balance between technological knowledge and human relations skills is essential to an effective practice. Clinical sensitivity must be both an internal and external practice for the care provider. Using a "physician know thyself" approach, medical students and physicians can learn emotional sensitivity and interpersonal communication skills that will enrich the clinical experience for both the patient and themselves. Sensitivity may well need to begin with appreciating the patient's comfort level in disclosing personal information, such as psychological state and philosophical perspectives.

Along with education in collaborative and patient-centered care, physicians require training in the appropriate display of caring and compassion. While these qualities—sometimes referred to as "the art of doctoring"—come naturally to some, many healthcare providers will need to be coached. Initially, the use of specific techniques, including simply sitting rather than standing in the patient–physician interaction, can reduce anxiety and build trust. Physicians and students benefit their patients by developing an attitude of service, better listening skills, and the ability to convey empathy with respect and caring.

Personal Stress Management

Effective physicians incorporate the key personal care skills of self-awareness and self-knowledge. From there, it is an easy segue to learning compassion. A "learn, do, teach" program that fosters a healthy lifestyle and stress management provides students with appropriate skills early in their medical education, but physicians themselves must be role models for these students. Programs that integrate self-awareness training can support students as they work through emotional responses from anger, frustration, defensiveness, to detachment that may arise in the clinical environment. Techniques taught may vary from writing about difficult patients and situations to learning meditation, yoga, or other so-called mind–body techniques that can restore emotional equilibrium in stressful situations. In addition, scientific evidence increasingly substantiates the impact of nutrition and lifestyle factors on health.

A 1982 study published in the *Journal of Medical Education*, noted, "medical school can be stressful experience for many students and that on completion of their medical education, students will enter a profession high in potential stressors." The

study evaluated a six-session program that taught students personal stress management techniques, including self-relaxation training, schedule planning, setting priorities, leisure-time planning, and cognitive modification techniques. Over the course of the program, students improved across a variety of measures (e.g., knowledge of stress, self-report inventory scores assessing stress symptoms and life-style, personal ratings of stressful situations, and their daily activity schedules) (Kelly et al., 1982).

Approximately 20 years later, an editorial published by Richard Smith in the *British Medical Journal* asks, "Why are doctors so unhappy?" and then responds, "There are probably many causes, some of them deep" (Smith, 2001). The editor states that the most obvious cause of unhappiness is that most physicians feel overworked and not sufficiently supported. The culture of the physician as the all-knowing authority figure has crumbled, providers often lead stress-filled lives, and both patients and physicians are looking for a new, more realistic "contract." Smith states: "Both patients and doctors know:

- Death, sickness, and pain are part of life,
- Medicine has limited powers, particularly to solve social problems, and is risky,
- Doctors don't know everything; they need decision making and psychological support,
- We're in this together.
- Patients can't leave problems to doctors.
- Doctors should be open about their limitations.
- Politicians should refrain from extravagant promises and concentrate on reality."

Physician–patient relationships based on these types of principles could foster a less stress-driven and more collaborative atmosphere and likely would facilitate the healing process. So, what behaviors do patients want to see in a physician? A report published in 2006 by the Mayo Clinic identifies seven ideal behavioral characteristics that patients want from their physician: confidence, empathy, humane compassion, taking a personal interest, forthrightness, respect and willingness to collaborate with the patient, as well as a conscientious, persistent thoroughness (Bendapudi et al., 2006). The seven identified characteristics are not all that unlike the proposed new contract described by Smith in 2001.

Learning Clinical Sensitivity and Expressing Empathy: A Complex Endeavor

A study published in 2007, using functional magnetic resonance imaging (*f*MRI), demonstrated portions of the brain involved in empathy (i.e., the anterior insula somatosensory cortex, periaqueducal gray, and anterior cingulate cortex) were significantly activated in a control group shown animated pictures of acupuncture needles being inserted into the mouth, hands, and feet of patients, while the same

area was not activated in physicians who practice acupuncture and were shown the same visual stimuli (Cheng et al., 2007). Rather than activating areas involved in empathy, portions of the brain involved in emotion regulation and cognitive control (i.e., the medial and superior prefrontal cortices and the temporoparietal junction) were activated in the physician group. The two groups also were asked to rate the level of pain that the needle pricks were likely causing the patients in the images. While the control group rated patient pain at approximately 7 on a 10-point scale, physicians rated it at 3. The investigators reasoned that repeated experiences of empathy could result in personal distress, possibly impairing the physician's ability to be effective. Thus, the response is an adaptive one. How then does a physician switch from this adaptive state to being empathetic enough to not appear cold or indifferent?

A study involving two in-depth, two-hour interviews (conducted between 1999 and 2002) with 50 doctors who had serious illnesses, disclosed how these physicians' attitudes toward their own patients changed after being a patient themselves (Klitzman, 2006). Klitzman, associate professor of clinical psychiatry at Columbia University, wanted to assess whether physicians who became patients gained insight into improving physician–patient relationships or improved their communication skills (particularly empathy). He intended to use the results of his investigation to advance medical education. Klitzman indicated that the physicians questioned whether empathy can be taught, yet they provided concrete techniques to build better communication with patients, such as "charting at the bedside rather than at the nursing station, acknowledging having kept patients waiting, and increasing awareness of nonverbal aspects of care." The physicians also reported increased sensitivity and empathy to patients and greater awareness of their communication skills and style. Yet, Klitzman noted that "despite their best intentions, many physicians slipped back into old patterns," particularly as a result of time pressures—taking time with a patient was seen as "bad" or "less efficient" by their colleagues. Physicians spoke of developing techniques that seemed helpful in developing an empathetic relationship, such as simply asking whether the patient had questions, even when they felt rushed or uncommunicative. The investigation shed light on the disparity between intellectual and experiential learning.

So, to protect themselves or to be an efficient (translation: cost-effective) part of a medical team, physicians shut down the portion of their brains that allows them to feel their patient's pain. Yet, patients want most to have a humane, empathetic doctor. Is it possible that physicians could be trained to turn back on empathy after times when cold objectivity is genuinely the optimal and effective avenue for both the patient and the physician? Such training needs to be developed into eLearning workshops and disseminated across the country. Just as *Collaborative Care* invites cooperative decision making and *Cultural Competence* is a more effective tool when a dynamic, longitudinal overview of a patient is taken, *Clinical Sensitivity* is best expressed by language that "adapts and responds to a patient's experience … in essence, language that heals simply explains what is happening" (Bedell et al., 2004). Vertical integration of the concepts inherent to integrative medicine, such as developing skills in compassion and promoting collaborative, patient-centered care, will not only improve medical education, but patient outcomes as well.

Communication Skills: Impacting Patient Well-Being

Physicians must convey patient diagnoses of conditions that are seriously life altering or shortening as well as terminal. These discussions are stressful for both physician and patient. Yet, the manner in which such news is delivered is particularly important, as it may affect patient attitude and health outcome. At such times, a patient is vulnerable and in need of compassion, and the physician is in need of communication skills to deliver factual information, make treatment recommendations, but also be an emotional support as the patient faces serious life choices. Students and physicians can endeavor to acquire these skills through a number of experiences, from watching the movie *Patch Adams* to volunteering in a hospice unit to having discussions about patient–physician interactions and attitudes.

Experiences as a patient, whether out of necessity or as a learning model, may be the most powerful and effective opportunity to understand the patient's perspective. Knowing how you would like to be treated by a care provider is a good starting point for learning the communication skills to treat others. Anatole Broyard, not a physician, but rather a *New York Times* book critic who wrote *Intoxicated by My Illness* while dying of prostate cancer (Broyard, 1992) expressed, "I see no reason or need for my doctor to love me—nor would I expect him to suffer with me. I wouldn't demand a lot of my doctor's time. I just wish he would *brood* on my situation for perhaps five minutes, that he would give me his whole mind just once, be *bonded* with me for a brief space, survey my soul as well as my flesh, to get at my illness, for each man is ill in his own way … I think that the doctor can keep his technical posture and still move into the human arena. The doctor can use his science as a kind of poetic vocabulary instead of using it as a piece of machinery, so that his jargon can become the jargon of a kind of poetry. I see no reason why he has to stop being a doctor and become an amateur human being. Yet many doctors systematically avoid contact." Broyard admonishes all physicians to communicate as real, compassionate, if not poetic, human beings, rather than hide behind the world of medical jargon.

A Firsthand Lesson on the Need for Clinical Sensitivity

A hospitalized patient is frightened and often feels victimized and helpless. The fact that the patient is receiving excellent care does not necessarily mitigate those negative emotions. Perhaps, the most illustrative patients are those in the cardiac care unit; many enter acute cardiac care for the first time having enjoyed prior good health and are now frightened and in need of empathy from their physicians. Even today, but certainly 40 years ago, medical education stressed intellectual knowledge and seldom addressed physician sensitivity. It is my contention that sensitivity training is imperative both for humanistic as well as medical reasons.

When I was supervising the training of medical students in the 1970s at George Washington University Medical Center, I had a few students who deeply concerned me because of their lack of empathy and an inability to understand their patients' feelings of vulnerability or frustration at being dependent upon the medical staff around them. Upon occasion, I required these students to spend time as a "patient" in the cardiac

care unit. Just like any other cardiac patient, the students had to wear a hospital gown, were isolated in a room, and hooked up to a heart monitor. They could overhear nurses speaking about them and were totally dependent on the nurses' help to use the bathroom, wash, or eat. They experienced feelings of powerlessness and dependency. Many of these students later told me that it changed their lives and their whole perspective of being a physician. They had learned the art and heart of medicine simply by becoming a patient themselves. Perhaps every person working in the healthcare field would do well to spend a day being the patient.

FOURTH PILLAR: TECHNOLOGICAL INNOVATION IN HEALTHCARE

The very nature of the practice of medicine requires that doctors learn and retain enormous amounts of data as well as possess interpersonal skills. Clearly, staying up-to-date with the ever-increasing scientific findings is equally as important as maintaining compassion and humanism in the daily interaction with patients and colleagues. The demand for outcome research as well as computerized medical records and billing require even those physicians in private clinical practice to have a comfort level with professional management software. Effective dissemination of knowledge and recordkeeping are just two examples highlighting the need for technology and technological innovation in both medical educational and the clinical environment.

State-of-the-art technical resources can augment and may one day replace traditional teaching methods. From eLearning to gaming, technology based learning has the potential to strengthen student and physician retention of facts required to teach cultural competence, practice empathetic communication skills, and provide opportunities to mature decision making in areas, such as ethics, diagnostics, and triage.

Schools of Medicine Support Technology Based Learning

Various schools of medicine and numerous hospitals across the country incorporate technology in educational and training programs. Examples include:

- Teaching anatomy through 3D computer visualization modeling, which is increasingly used in addition to or as a replacement for cadavers.
- Videotaping patient presentations or role-playing to develop interviewing skills.
- Interactive case management presentations via computerized simulations.
- Computer dummies, such as the cardiac simulator (developed by Dr. Michael S. Gordon at the Michael S. Gordon Centre for Research in Medical Education at the University of Miami) that teaches students to recognize heart murmurs.
- Virtual reality training to develop manual dexterity skills, such as an endoscopy system that combines video training and realistic force feedback.

Dr. Michael Rosenblatt at Harvard University cites significant transformations that have taken place in healthcare in recent decades—the emphasis on outpatient

care, same day surgeries, managed care, and the loss of extended patient interactions by medical students—that are in part a result of technological advances. He states, "Medicine is a highly technological field. In daily practice we need the skills to use information systems, magnetic resonance, computer tomography, and managerial algorithms. Technology is part and parcel of the medical training experience. We're just taking it farther to address the new challenges that have arisen for training inside academic medical centers" (Rosenblatt, 2008). A Harvard steering committee on the use of technology in medical education recommended that virtual reality and simulators be adopted and that a Center for Innovation in Electronic Learning be formed. The committee also proposed that the medical school develop an electronic curriculum, with links to textbooks and that technology be used to manage learning such that a student's clinical experiences could be tracked and midcourse corrections could be made.

Types of Technology Based Learning Applicable to Medical Students and Physician Education

There have been numerous advances in distance or online learning modalities in recent years. This section will briefly review some of the key innovations.

eLearning

eLearning is a term used to refer to computer-based educational or training programs. The predecessors of eLearning (e.g., computer-based learning, computer-aided instruction) were first implemented in scholastics, from elementary through the university level, in the 1980s. However, a much greater acceptance of technology in learning has occurred in the past seven years with the proliferation of broadband Internet access. High school and college teachers are making course content available online, while students are preparing and submitting coursework electronically. Communication services and research libraries, once reserved exclusively for students within the university system, now are available to the general public. Beyond traditional educational institutions, the business world also has adopted the fundamentals of eLearning to fit their needs. Corporations—including hospitals and medical schools—now are able to disseminate instructional training materials to employees or students in remote locations as easily as in-office, and training can occur at the convenience of the learner. Real-time updating of information or policies and procedures can be delivered rapidly, on an individual basis.

According to George Siemens, Founder and President of Complexive Systems Inc., eLearning is comprised of the following seven, sometimes overlapping, categories: courses, informal learning, blended learning, communities, knowledge management, networked learning, and work-based learning (Siemens, 2004). Organizing information, or *knowledge management* as Siemens calls it, can be a key challenge for businesses and organizations, including medical institutions. Thus, eLearning courses contain content that can be indexed and made available via a database—a knowledge management system. Content can be presented in a solely electronic manner or in a blended learning environment, consisting of both

online and face-to-face instruction. Online communities, such as one for an in-training workshop on physician communication skills, could potentially reflect the naturally social aspects of learning by permitting interaction among the online learners. Thus, Siemens defines learning networks as a "loose, personal coupling of communities, resources, and people" that "is the cornerstone of personal knowledge management." Individuals within learning networks can cooperate to update information and human resources.

As an alternative to traditional courses, eLearning can be used either as formal required training or as a passive informal resource. Textbooks are no longer the only source of course information. Educators at the forefront of their pedagogical fields are incorporating audio and video into Microsoft PowerPoint® and other presentations and podcasting or video podcasting lectures. The use of interactive Flash modules as well as casual games and simulations are all part of the evolution of creative instructional design.

Web 2.0 Collaborative Learning

Medical students in 2009 grew up in the digital age. In the words of Stanford University's Dr. Parvati Dev, they are "digital natives." Digital natives are active participants in Web 2.0, a paradigm that enhances Internet creativity and collaboration by shifting the focus from protected settings, such as the classroom, to networking communities, such as social networks (e.g., Facebook), blogs (e.g., Wordpress), wikis (e.g., PBwiki), tagging (e.g., del.icio.us), and mashups (e.g., Microsoft Popfly™). Thus, students currently in medical school are seeking the same opportunity for collaboration in their scholastic environments. Some educators are beginning to incorporate Web 2.0 technologies into their course content, which is gradually leading to a new wave of instructional design called eLearning 2.0. The next generation of eLearning tools likely will include more robust collaboration tools, and enhanced simulations and video games (i.e., professional educational games). Thus, comprehensive studies on the cognitive effects of educational games are on the horizon and will be necessary before more institutions allocate the substantial funding needed to develop quality games (Hirumi, 2008).

ePortfolio

An ePortfolio is a collection of digital research and original work (e.g., documents, spreadsheets, MS PowerPoint presentations, PDF files, images, blog entries, and hyperlinks) assembled and managed by the user. They are effective organizational tools for students to keep track of their coursework and are platforms for self-expression. Dynamic technologies, such as ePortfolios, will play a key role in the organization of student materials as the boundaries between traditional, brick and mortar schools and their online counterparts become greyer. One day, specific degree programs may be offered by educational institutions (or by partnerships among more than one educational institution) that allow students to select learning experiences and courses from multiple catalogs. While possibly required to attend certain classes, lectures, or labs in person, students otherwise will study at their own pace and will use a multitude of online resources to obtain the requisite materials and study aids necessary to complete the coursework successfully. ePortfolios will likely be the organizational tool uniting learner and educator.

Personal Learning Environments

Personal Learning Environment (PLE) is a new, learner-centered style of education that is slowly becoming an alternative to conventional eLearning. Unlike the current learning management systems that are institution-centric (or course-centric), PLEs include the integration of both formal and informal learning into a single experience. They involve social networks that traverse institutional boundaries and use networking protocols (e.g., peer-to-peer, Web services, syndication) to connect a range of resources within a personally managed space—putting the learner squarely in the driver's seat by setting learning goals, managing and processing information, and taking responsibility for communicating with instructors. When the student has the freedom to choose the sources of educational content, it places a premium on the quality of the content and ultimately on the creators of the content. PLEs could someday switch the focus of learning from any one institution to teachers themselves, wherever they may be located (Atwell, 2007).

Future Technology-Driven Medical School Instruction

Already programs, such as the Visible Human Project launched by the U.S. National Library of Medicine in 1989, have fostered the development of numerous educational tools, have been utilized in research, and have enhanced lifelong learning by healthcare professionals and others. In order for any format of eLearning to be effectively instituted in medical schools and hospitals, technological issues must be resolved, including higher video resolution and clarity of animation, better sound fidelity, and tools to enhance content, simulations, and gaming. The unique and compelling approaches to resolving these needs will no doubt require the brightest instructional designers. Customizing cognitive, behavioral, and social learning initiatives will enable individuals to embark on educational journeys in a manner that best suits their learning style, availability, and location.

eLearning and the Licensing Committee for Medical Education (LCME)

Despite the cornucopia of eLearning technology, the Licensing Committee for Medical Education (LCME) appears to be rejecting the acceptability of distance education, such as eLearning. In 2006, the LCME has provided the following the following statement: "Regardless of the learning format used, a medical school must be in compliance with all standards for accreditation of educational programs leading to the MD degree. The LCME has created the following core principles as a way to conceptually categorize accreditation standards relevant to distance learning. The core principles have been adapted by the LCME from the *Best Practices for Electronically Offered Degree and Certificate Programs*, a document developed by the eight regional accrediting bodies. It is expected that the core principles, and the relevant standards, will be considered by an educational program incorporating distance learning" (LCME, 2006). A review of the entire statement leaves the reader with a sense that eLearning is not in compliance with accreditation standards, a stance that seems out of step with the current explosion of Web-based and virtual learning.

TWO GUIDEPOSTS: RESOLVING GLOBAL MEDICAL ISSUES

The Two Guideposts take us a step beyond the Four Pillars to assess medical needs as a global community rather than based on individual nations. Just as global warming affects the entire planet, increasingly it will be seen that the global interdependence on resources and economic issues will similarly require that healthcare treatment and policies be viewed from a global rather than a nationalistic perspective. The Two Guideposts are focus areas that are key to beginning the process of instituting globalization of medical care.

The Two Guideposts

- Increased services to the underserved
- Decrease the brain drain of healthcare professionals

Increasing Services to the Underserved

The global shortage of healthcare professionals is broadly recognized as a serious concern. In 2006, leaders at the United Nations stated that there was an immediate need for 500,000 trained medical personnel around the world—the greatest need is for trained physicians. In the course of medical education, emphasis can be placed on the importance of providing medical care in communities and countries where there are shortages. Even among different regions within the United States, there are vast disparities regarding adequate numbers of physicians.

Number of Physicians in the United States

While on a national scale, the United States has in excess of 500 physicians per 100,000 citizens, there are areas within the country, such as rural and low-income inner city communities, where there are dramatic shortages of trained medical workers. As a means of encouraging new doctors to work in communities with physician shortages, the federal government has offered tuition assistance programs (managed by the National Health Service Corps [NHSC]) for medical students, through loan repayment and monthly stipend programs, in exchange for time spent in these localities. "The quality of doctors and the density of their distribution have been shown to correlate with positive outcomes in cardiovascular diseases. Conversely, child malnutrition has worsened with staff cutbacks during health sector reform. Cutting-edge quality improvements of health care are best initiated by workers themselves because they are in the unique position of identifying opportunities for innovation" (WHO, 2006a). In recognition of these concerns, the American Medical Student Association passed a resolution entitled "Principles Regarding Service in Underserved Areas and Service Obligations." The Association supports the concept of physicians volunteering to serve in a "geographic or specialty need" for two years and supports financial incentives to do so (American Medical Student Association, 2008b). Furthermore, the association supports increased funding for government programs in shortage areas, such as the Indian Health Services and NHSC programs, including NHSC's loan forgiveness and salary incentives. It also encourages private sector efforts for communities with physician shortages.

Healthcare Workforce Analysis

Robert Wood Johnson: Workforce experts surveyed by researchers from the Robert Wood Johnson Foundation determined that a minimally adequate number of physicians in inner cities was between 43 and 53 per 100,000 population (depending on the size and location of the community) and that an adequate level was between 59.5 and 75.7 per 100,000 (Robert Wood Johnson Foundation, 2001).

Dr. Richard Cooper: Dr. Cooper, professor of medicine and senior fellow, Leonard Davis Institute of Health Economics, University of Pennsylvania, anticipates a shortage of 200,000 physicians by 2020. In a 2007 interview on physician shortage, he stated, "… at the moment there is something between a 5 and 10% shortage, probably closer to 5%. It varies from area to area, and from specialty to specialty" (Cooper, 2007). He added, "… we are looking at a progressive increase in that number, hitting probably 20% by the next 15 or 20 years. So 5% is already a problem, people are already waiting, but when it gets to 20% they are going to really be waiting. It is going to be a big problem."

Number of Physicians Abroad

Although regions within the United States have disparities and may lack adequate numbers of physicians and other healthcare staff, the disparity in physician distribution worldwide is far more alarming than what is seen in the United States, as detailed in the following charts.

Table 9.1 is a comparison of numbers of physicians in G-8 and African nations. While among G-8 nations, the number of physicians considered essential to meet the health needs of its populace far exceeds the minimal, it falls critically short among the cited African Nations (WHO, 2008).

Millennium Development Goals

In September 2000, the heads of state of 189 countries endorsed the Millennium Declaration and its eight Millennium Development Goals. The goals were drafted as

TABLE 9.1
2000–2006 Comparison of the Number of Physicians per 10,000[a] Citizens

G-8 Nations	Physicians per 10K People	African Nations	Physicians per 10K People
Canada	19	Chad	<1
France	34	Eritrea	<1
Germany	34	Ethiopia	<1
Italy	37	Liberia	<1
Japan	21	Malawi	<1
Russia	43	Mozambique	<1
United Kingdom	23	Rwanda	<1
United States	26	Tanzania	<1

[a]Figures rounded.

part of a roadmap of achievable tasks to be accomplished by 2015 "to reduce poverty and hunger, and to tackle ill health, gender inequality, lack of education, lack of access to clean water and environmental degradation" (WHO, 2000).

The Millennium Development Goals are to:

1. Eradicate extreme poverty and hunger
2. Achieve universal primary education
3. Promote gender equality and empower women
4. Reduce child mortality
5. Improve maternal health
6. Combat HIV/AIDS, malaria, and other diseases
7. Ensure environmental sustainability
8. Developing a global partnership for development (WHO, 2000)

According to the WHO 2006 *World Health Report*, globally there were 57 countries that would not meet the Millennium Development Goals threshold for workforce density to provide enough healthcare coverage to meet essential interventions (WHO, 2006b). Based on these estimates, the 57 countries have "critical shortages equivalent to a global deficit of 2.4 million doctors, nurses, and midwives."

Decreasing the Brain Drain: Balancing the Global Distribution of Healthcare Professionals

An article, published in the *New England Journal of Medicine* in 2005, indicates that international medical graduates constitute between approximately 25% of physicians in the United States, the United Kingdom, Canada, and Australia (Mullan, 2005). The author found that international graduates largely come from India, the Philippines, Pakistan, and South Africa; meanwhile, as the report states: "Nine of the 20 countries with the highest emigration factors are in sub-Saharan Africa or the Caribbean." Consequently, in sub-Saharan Africa, a region that has 25% of the world's burden of diseases, 1.3% of all healthcare workers in the world are treating 13.8% of the world's citizens (American Public Health Association, 2006). The WHO 2006 *World Health Report* estimates that nearly a quarter of doctors from sub-Saharan countries are working in developed countries. However, there is a broad range in migration patterns, from only 3% in Cameroon to 37% from South Africa (WHO, 2006). Graduates who do not return to their homeland to practice medicine sometimes foster a so-called brain drain that can have devastating consequences, in some instances. To increase the number of physicians worldwide and to curtail the brain drain of physicians, it will be necessary to expand medical recruitment opportunities to more students around the world and encourage newly trained physicians to return to their homeland and become pillars of their communities. Educational institutions can help by ensuring that international students have the requisite knowledge to succeed in their medical training.

The 2006 WHO fact sheet titled *Migration of Health Workers*, asserts that the movement of healthcare workers to countries, such as the United States, the United

Kingdom, Canada, and Australia, has some beneficial effects, including the billions of dollars sent to the home countries by these professionals (WHO, 2006). In some low-income countries, the pattern has actually caused a decline in poverty. While a portion of trained healthcare providers do return, many others only become a drain on their homeland—the country of origin often finances the doctor or nurse's education, but it seldom reaps the benefits of it. In effect, these poor countries are subsidizing wealthy nations; yet, all the while they are in desperate need of healthcare personnel. According to the fact sheet, in countries with fragile healthcare systems, the loss of healthcare personnel can have consequences that are "measured in lives lost."

However, the *Migration of Health Workers* paper also stresses the need not only for better working conditions for international healthcare personnel, but also for improved safety protection while on the job. According to the WHO 2006 *World Health Report*, after seeking better remuneration, the main reason that healthcare workers in Cameroon, South Africa, Uganda, and Zimbabwe migrate is to work in a safer environment (WHO, 2006). In a paper entitled, *Ethical Restrictions on International Recruitment of Health Professionals to the U.S.*, the American Public Health Association set out the points that they assessed as key to ethical recruitment of physicians and other healthcare staff from around the world (American Public Health Association, 2006). While on the one hand, they recognize "the plight of health-care workers in poor countries who often work under dangerous conditions that do not meet their needs or those of their patients, and understands their frequent desire to leave their countries, and affirms the right of health workers to migrate as guaranteed them by the 1948 Universal Declaration of Human Rights, while also seeking to balance the responsibilities of health workers to the countries in which they were initially trained." On the other hand, the organization "urges U.S. health worker employers … to voluntarily adopt a code of ethics that guides their judicious management of the recruitment and employment of health professionals (including unlicensed caregivers) from developing countries; and recommends that these codes of ethics be developed in accordance with standards developed by the World Federation of Public Health Associations, the WHO, and other international bodies concerned with this issue." It is clear that medical educators and policy makers worldwide must work together to develop programs and initiatives to increase the number of adequately trained physicians and other healthcare professionals in regions where there are dramatic shortages.

CONCLUSION

The Four Pillars and Two Guideposts tender my philosophy of medical education and the future of medical practice, elucidating areas of study that must be integrated into medical education in order to develop and train students of the twenty-first century to become excellent physicians. What I have learned over three decades of being a physician and medical administrator is that medicine is as much an art as it is a science. Thus, it is vital to teach skills in humanism, such as self-confidence, empathy, meticulous communication, and selfless service—each are important determinants in the efficacy of a practicing physician, regardless of one's depth of medical knowledge (obviously, a factor of great importance as well).

The Pillar of Integrative Collaborative Care grew out of a thirst to educate myself in disciplines that were not considered part of conventional medical knowledge. From the outset, it seemed equally as important to personally experience unconventional treatments (such as chiropractic medicine, acupuncture, herbs, homeopathy, and many others), as to study them in books. I soon realized that several of these treatment approaches had the potential to benefit the health and vitality of any patient, and I wanted to integrate them into my practice. I have always held respect for the rehabilitation medicine model, in which members of various disciplines meet to discuss a patient's care. In this model, equal respect is given to the physical therapist, occupational therapist, speech therapist, or nutritionist as to the physician. Using this model, I designed my own medical practice to function in this manner, with an extensive referral network that included not only conventional medical experts, but nonconventional specialists as well. In my opinion, the patients fared much better, and an integrative medical specialty network emerged.

I had originally pursued learning about nontraditional healing practices because of an interest in medical anthropology as well as an aspiration to deliver the best possible care to my patients. Yet, a shift in attitude toward integrative modalities was simultaneously occurring across the country, culminating in a sea change of opinion. For instance, with the 1997 NIH Consensus Panel on acupuncture therapy, of which I was a member, it was clear to me that acupuncture had obtained a more solid footing in the United State.

The Pillar of Clinical Sensitivity is of paramount importance to the personal and professional health and well-being of a physician. It is a well-known fact that physicians work long hours and are faced with great challenges, both intellectual and emotional. The intellectual challenges are served best by enhancing one's depth of knowledge through continued education and by developing an excellent referral network, while the emotional trials are well met by understanding one's limits and spending time in self-reflection. As mentioned in the Clinical Sensitivity section, there are two key components to clinical sensitivity: developing self-awareness and effective, compassionate physician–patient communication. In much of traditional medical education, physicians are not taught how to face emotional challenges, so it is quite refreshing to witness the results of a training program in self-awareness being taught to every freshman medical student at Georgetown University. Such training enhances the ability of physicians to face and process the emotional roller coaster encountered on a daily basis. Working toward self-awareness, studies of ethics, spirituality, psychology, and comparative religions all are important components in the education and continuing education of a physician. In fact, a physician's communication style and choice of words can impact the health and well-being of his/her patient—a topic touched upon in Chapter 4. Studies in psychoneuroimmunology have shown how our minds can alter hormone and neurotransmitter elaboration, potentially evoking either immune suppression (nocebo) or healing (placebo). I could write volumes on this topic and cannot over-emphasize its importance in the practice of medicine.

The Pillar of Cultural Competence is an outgrowth of the pillars of Clinical Sensitivity and Integrative Collaborative Care. Respect for all humans and selfless service are the key factors to obtaining cultural competence. It is a well-known fact that U.S. physicians and healthcare insurance companies, in general, are not

meeting what ought to be an obligation to treat underprivileged populations, including cultural minorities. I have had a great deal of experience with underprivileged and minority populations over three decades of medical practice in the Washington, D.C. area and as corporate medical director of Marriott International Inc. Through experience and exploration, I came to understand that ultimately I am and must be a servant to my patients. Yet, there is an unspoken, in-bred sense of entitlement in the medical profession that must be dispelled and eliminated, if we are to improve as physicians and grow as human beings. When taking care of a patient from a different race or ethnic background than one's own, it is incumbent upon the physician to dispel his/her beliefs or prejudices and recognize the value of understanding the beliefs and prejudices of that patient, which in many cases, will be a core issue to their healing. Cultural Competence not only compels an appreciation of and respect for the societal and religious beliefs of others, but it also requires sensitivity to the fact that indigenous remedies and alternative medical systems are a familiar way of life for patients of various ethnic origins. It will become increasingly imperative that physicians are trained in Cultural Competence as globalization expands.

State-of-the-art technology, including real-time education via the Internet, archived lectures, and distant education, has brought excellent advances to medical education. Many countries other than the United States, allow these learning formats in basic medical education. I remember attending a course at Harvard University several decades ago. The course was oversubscribed; some of us were placed in another location, with access to the lectures via a television monitor. I could just as easily have attended that course from Washington, D.C., rather than having to travel to Boston! Similarly, when I gave a grand rounds lecture on Integrative Medicine at the Mayo Clinic a few years ago, the real-time lecture was televised in Arizona, Minnesota, and Florida. These two examples involved postgraduate education courses, for which Internet-based education currently is considered acceptable, while M.D. coursework still is not. I fail to understand why some of the basic medical education courses are not allowed in an eLearning format.

It is my contention that before long, medical education will have to combine residential and virtual education, as it is a well-known fact that a global physician shortage is looming. A combination of technology-based medical courses and affiliations set up at universities and hospitals local to students in both underdeveloped countries as well as right here in the United States would permit medical education to occur with minimal disruption to family and financial matters—both of which are important factors in the decision of whether or not one can feasibly apply to medical school. With innovative planning, such as eLearning coursework, doctors largely could be educated in their local communities. These individuals, ideally, then would provide needed medical care to their native communities, solving the problems elucidated in the Two Guideposts: (1) serving the underserved of the world, and (2) assisting physicians to practice in their country of origin, rather than migrating, which can leave medical care deficits in countries most in need of physicians.

In summary, the Four Pillars and Two Guideposts affirm the need for a more globally equitable system of medical care and ask physicians to increase their self-awareness and clinical compassion. Changing a system can take years to become a reality. The Four Pillars and Two Guideposts, coupled with a solid scientific-based program, are my

vision of what constitutes optimal medical education and is an ideal that every healthcare provider might strive to obtain. It is imperative that medical education provides far more than scientific information and also offers a comprehensive approach to treating patients. According to one of our revered mentors, Sir William Osler: "To be of any value, an education should prepare for life's work" (Osler, 2003). The life work of a physician involves constant study, cultivation of a reverence for humanity, a thirst to seek self-knowledge, and a dedication to the patients for whom he/she is responsible.

Albert Einstein stated, "The aim [of education] must be the training of independently acting and thinking individuals who, however, see in the service to the community their highest life achievement" (Einstein, 1936). It is incumbent upon each physician to possess a sense of responsibility to his or her own community and preferably, also to the global community, as we move toward globalization in the political, sociological, and personal aspects. Healthcare educational institutions that recognize the importance of teaching the fundamentals of the Four Pillars and Two Guideposts for the Healing Professions will better prepare students for the challenges and rewards of our rapidly changing world.

> *Reverence for human suffering and human life, for the smallest and most insignificant, must be the inviolable law to rule the world from now on. We must recognize that only a deep-seated change of heart, spreading from one man to another, can achieve such a thing in this world.*
>
> **Albert Schweitzer, 1918**

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10 The Pineal Gland
Energy Transducer

To everything there is a season and a time to every purpose under heaven … a time to be born, and a time to die.

Ecclesiastes 3:1–8

INTRODUCTION

The pineal gland is arguably both the most misunderstood and underrated endocrine gland in the human body. Until 40 years ago, almost nothing was known about the pineal; it was considered unimportant and physiologically useless. Yet, René Descartes stated that the pineal is the "seat of the soul," and Eastern religions have described the pineal as the mysterious "third eye," the seat of wisdom, or the source of inner light. Although these beliefs were based on some rudimentary knowledge of the pineal as being photosensitive, the alignment of the pineal with spirituality has, more likely than not, been a deterrent to serious scientific research, relegating the pineal to the realm of the unknowable (see Zrenner, 1985, for a history of the pineal gland).

Complicating matters further, Descartes's expression linking the pineal and the soul generally is misunderstood. The philosopher, who is undoubtedly even better known for his exclamation, "cogito ergo sum" (I think, therefore I am/exist), believed that the ability to think is irrefutable evidence that the mind exists. His dualistic philosophical system divides the universe into mutually exclusive but interacting elements of spirit/mind or God and matter. Descartes's "seat of the soul" expression stems from his belief that the pineal is the interface between the spiritual and the material worlds, which as we will explore in the final chapter of this book, may well be true.

It is my contention that the pineal is the master gland. I suspect that, by the time you finish reading this chapter, you are likely to agree with me. In this chapter and in Chapters 6 and 11, we will travel full circle—beginning with the essential neuroendocrinological aspects of the pineal that makes it our master gland and then progressing to how it may interface with "spiritual" (which will be redefined as "subtle energy" in Chapter 11) experiences, which paradoxically bring us back to fundamental principles of pineal physiology.

OVERVIEW OF THE PINEAL GLAND

Only in the past 30 to 40 years has an accurate understanding of the functions of the pineal begun to emerge. Most of this understanding has stemmed from the isolation of melatonin (*N*-acetyl-5-methoxytryptamine), the major pineal hormone

(Lerner et al., 1958). The pineal has the ability to transform neural input into endocrine output. It is the tiny but mighty gland that is our liaison to the world around us. It converts light, temperature, and magnetic environmental information into neuroendocrine signals that can change the course of the body's functioning, often via its primary hormone, melatonin. Numerous studies now have shown the pineal to be the regulator and orchestrator of many neuroendocrine- and neuroimmune-modulating functions in the body.

The pineal's most widely known function is its ability to use external light to generate an entrainment of the body to daily (circadian) and seasonal (circannual) rhythms of the sleep–wake cycle. The word circadian comes from two Latin words: *circa*, meaning around, and *dies*, meaning day. In addition to sleep–wake cycles, circadian rhythms are found in the body's metabolism, hormone levels, blood pressure, and core temperature, to name a few. The pineal and its major hormone melatonin are capable of activating and regulating major body systems, including the stress and immune systems (see Bubenik et al., 1998, for a review of clinical utilizations of melatonin). In the following pages, we cover the structure and functions of the pineal, demonstrating its role as the body's primary neuroendocrine regulator and systems integrator.

PHYSIOLOGICAL CHARACTERISTICS OF THE PINEAL GLAND

In humans, the pineal gland lies above the superior colliculi and below the splenium of the corpus callosum at the posterodorsal aspect of the third ventricle. Embryologically, it arises from the ependyma (the membrane that lines the ventricles of the brain) of the third ventricle. In some lower vertebrates, the pineal arises from the median of the dorsal wall of the thalamus. It weighs 50 to 150 mg in humans and is 7 mm in length and 5 mm in width, about the size of a pencil eraser. Its name derives from the Latin word *pinea*, or pinecone, because of its cone-shaped appearance. As mentioned in Chapter 1, 240 million years ago vertebrates literally had a third eye on the top of their head, and today some invertebrates, such as lampreys, still possess a third eye. The pineal gland in both vertebrates and invertebrates has retained its photosensitive qualities.

The pineal gland undergoes a gradual process of calcification throughout life. Calcification actually begins in childhood. By early adulthood, it can be seen on radiograph in about 53% of the population and is evident in approximately 80% of elderly individuals. Recent work comparing the degree of calcification, as measured by computed tomography, to urinary melatonin excretion shows an association between lower levels of melatonin and calcification (Kunz et al., 1999). Degree of calcification has also been correlated to daytime tiredness and sleep disturbance (Kunz et al., 1998). There is one remarkable study published by the *British Medical Journal* more than 20 years ago that indicates a correlation between pineal calcification in humans and a poor sense of direction (Bayliss et al., 1985). This report is intriguing when compared with studies on homing pigeons, whose pineal gland is paramount to survival, indicated by a brain weight of 10% (compared with 1% for humans). When homing pigeons have extensive calcification, they too lose their sense of direction.

Perhaps, researchers should begin to study the correlation between pineal calcification and senility.

Unlike other structures of the central nervous system (CNS), the pineal gland lacks a blood–brain barrier, permitting direct reception of exogenous substances and endogenous hormones or neurotransmitters via the peripheral circulation. In addition, the pineal gland's major hormone, melatonin, is highly lipophilic, which means that it easily passes out of the pineal via cell membranes, including the epithelial cells in the blood vessels, the lymph vessels, the serous cavities, and the cavities of the heart. Consequently, melatonin is found not only in the blood but also in an assortment of fluids, including the saliva, cerebral spinal fluid (CSF), male seminal fluid, amniotic fluid, and the fluid in the anterior chamber of the eye (Reiter, 1991b, 1993a). The lack of a blood–brain barrier and the lipophilic quality of melatonin places the pineal gland in the optimal position for its responsibilities as the primary endocrine transducer and regulator of hormonal signals (i.e., as the master gland).

NEURAL PATHWAY FROM THE ENVIRONMENT TO THE PINEAL: THE RETINOHYPOTHALAMIC–PINEAL SYSTEM

In 1960, Ariëns Kappers identified postganglionic sympathetic neurons as the main source of pineal innervation (Lewy, 1983). In addition, a neural pathway has been established from the eye to the pineal gland (Figure 10.1). The pathway begins at the ganglion cells of the retina, which have axons that make up the retinohypothalamic tract. Electrical signals from the retinohypothalamic tract reach the suprachiasmatic nucleus (SCN), located in the hypothalamus. The SCN is our biological clock, which will be described in more detail later in this chapter. From the hypothalamus, long descending axons of hypothalamic neurons synapse on autonomic neurons of the intermediolateral cell column in the upper thoracic spinal cord. The signals continue via the paraventricular nuclei to the spinal cord, where preganglionic axons exit the spinal cord to terminate on neurons in the superior cervical ganglia. Postganglionic neurons from the superior cervical ganglia travel back up and terminate in the pineal gland. Unlike many invertebrates whose pineal glands are connected to the roof of the brain, in mammals these postganglionic neurons replace any direct nerve connection to the brain.

In the early 1960s, Richard Wurtman and his mentor Julius Axelrod determined that in periods of darkness, the postganglionic (sympathetic) fibers from the superior cervical ganglia release norepinephrine (the major hormonal input) into the synaptic cleft, activating the retinohypothalamic–pineal system (Wurtman et al., 1963a, 1963b, 1964). The pineal contains both neuroglial cells and pinealocytes. The pinealocytes are the all-important receptor cells within the pineal. Pinealocytes secrete various peptides and neurotransmitters (see next section) in addition to melatonin (the major hormonal output). When norepinephrine stimulates β-adrenergic receptor sites at night, melatonin is synthesized and secreted from the pinealocytes. The melatonin is quickly released into the CSF and venous circulation, probably by passive diffusion (Reiter, 1991b; Reiter et al., 1995).

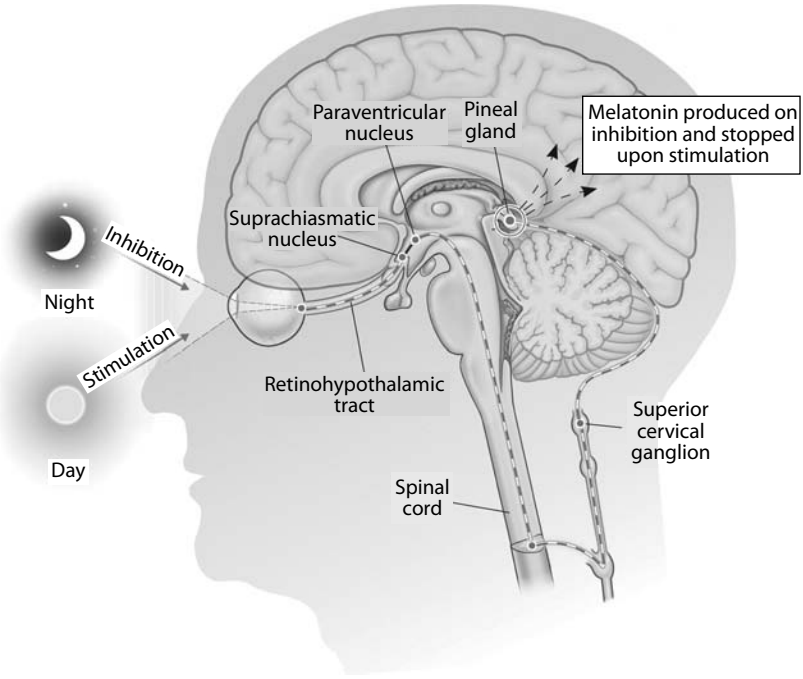

FIGURE 10.1 (See color insert following Page 160.) Neural pathway from the eye to the pineal.

SECRETIONS OF THE PINEAL

Neuropeptides in the Pineal

The pineal contains receptor cites for various neuropeptides, including those for norepinephrine (α- and β-adrenergic), serotonin, dopamine, glutamate, benzodiazepines, γ-aminobutyric acid (GABA), acetylcholine, and nicotine (Ebadi and Govitrapong, 1986). As just mentioned, norepinephrine is the primary pineal neurotransmitter. Recall that in the chapter on the relaxation system (Chapter 4), we learned that melatonin not only fits into its own receptor, but also into the benzodiazepine receptor (Marangos et al., 1981).

A group of researchers from Buenos Aires first showed that there are benzodiazepine receptors in the bovine pineal, and then a few years later they located them in the human pineal (Lowenstein and Cardinali, 1982; Lowenstein et al., 1984). Both benzodiazepines and melatonin reduce anxiety, alleviate depression, and aid insomnia. Melatonin, however, has fewer side effects (Garfinkel et al., 1999; Raghavendra et al., 2000). Recall that diazepan can suppress melatonin-binding sites, an action reversed by exogenous melatonin, and that peripheral benzodiazepine receptors can reverse the antidepressant action of melatonin (Atsmon et al., 1996; Raghavendra et al., 2000). In addition to the pineal, benzodiazepine receptors are present on platelets and monocytes, which implicates melatonin in the modulation of the cardiovascular

TABLE 10.1
Hormones Found in the Pineal Gland

Melatonin
Serotonin
N-acetyl-serotonin (NAS)
Cortisol
Corticotropin-releasing hormone (CRH)
Aldosterone
Insulin
Thyrotropin-releasing hormone (TRH)
Growth hormone (GH)
Gonadotropin-releasing hormone (GnRH)
Follicle-stimulating hormone (FSH)
Luteinizing hormone (LH)
Prolactin
Adrenocorticotropic hormone (ACTH)
Oxytocin
Somatostatin
Antidiuretic hormone
Prostaglandins
Melanocyte-stimulating hormone (MSH)

and immune system—more on melatonin and the immune system will follow (Moingeon et al., 1984; Ruff et al., 1985). Clearly, a portrait emerges of a reciprocal and interactive relationship between these two molecules.

Hormones in the Pineal

The list of hormones found in the pineal is quite extensive (see Table 10.1 for a partial list). The pineal influences the secretion of these hormones, potentially resulting in significant functional and physiological changes. It is possible that some of the hormones are synthesized in the pineal and others arrive there via the circulation, but their presence still appears to have an impact on system function. For the most part, the pineal has an inhibitory impact on hormones and body function (e.g., it can reduce adrenal or gonadal weight), but there are some notable exceptions (e.g., it generally enhances the immune system). The extensive number of hormones found in the pineal, alone, is indicative of the broad influence of the pineal gland (Table 6.1) (Relkin, 1983; Vaughan, 1984).

MELATONIN: THE MAJOR PINEAL HORMONE

Melatonin is the hormone that regulates our circadian, or sleep–wake, cycle. In 1958, melatonin (*N*-acetyl-5-methyoxytryptamine) was first isolated by Aaron Lerner, an American dermatologist (Lerner et al., 1958). Lerner isolated the melatonin, which was known to lighten skin melanocytes of amphibians and fish, from

250,000 bovine pineal glands (Binkley, 1988). Curiously, melatonin also is found in plants, particularly of the rice family, and some researchers claim that it can enter the blood and bind to melatonin receptor cites when ingested (Hattori et al., 1995; Reiter et al., 2001). However, in a personal communication, Richard Wurtman at Massachusetts Institute of Technology (MIT) said, "At present, there is no evidence that any food, eaten in any quantity, significantly elevates plasma melatonin levels." In so many words, conclusive evidence simply has not been established. It is, however, an intriguing line of research, which in my opinion, warrants further study.

Endogenous circadian rhythms of not only melatonin, but also of core body temperature and cortisol, average 24.18 hours in both young and elderly humans (Czeisler et al., 1999). Daytime administration of small doses of melatonin increases fatigue, decreases oral temperature, and impairs vigilance tasks (Arendt et al., 1984, 1985; Dollins et al., 1994). An 80-mg dose of melatonin can raise normal nighttime concentrations by 350 to 10,000 times (Waldhauser et al., 1984).

As any new parent might guess, infants under three months of age secrete very little melatonin. Fortunately, this trend soon changes as humans reach peak concentration levels in the first to third years of life (Brzezinski, 1997). As mentioned, melatonin production progressively declines throughout life, showing considerable depletion with age: 250 pg/ml at ages 1 to 3; 120 pg/ml at ages 8 to 15; and declining gradually to 20 pg/ml by age 50 to 70 (Utiger, 1992).

Melatonin Dosing and Side Effects

The side effects of melatonin, as reported in research studies, are remarkably low and mainly concern headache and fatigue. Because melatonin is not regulated by the U.S. Food and Drug Administration (it is categorized as a supplement because it is naturally found in foods), it is possible that there are detrimental effects that are not generally known. Important research shows that an optimal dose of melatonin for those individuals whose levels are subnormal seems to be 0.3 mg, although it is presently sold in tablets many times greater than is needed for this therapeutic effect (Zhdanova et al., 2001). At the relatively safe dose of 0.3 mg, the areas for physician-guided administration that appear to be the most promising include its use for perimenopausal women, the blind or elderly patient who suffers from insomnia, and possibly for some cancer (e.g., there have been encouraging results from some studies on estrogen-dependent breast cancer) and AIDS patients.

Measuring Melatonin

As stated, melatonin concentrations can be measured from plasma, saliva, the CSF, or urine. Melatonin synthesis occurs in the retina, Harderian gland, lymphocytes, monocytes, bone marrow cells, ovary, and the gut (Arendt, 1988; Reiter et al., 2000). Animal studies show that the increased level of pineal melatonin production during darkness is paralleled by an increased level of melatonin in the blood (Rollag et al., 1978). Although melatonin can be synthesized in areas other than the pineal, it is generally thought that the contribution of melatonin measured in blood plasma is

solely of pineal origin because pinealectomized animals had no detectable plasma melatonin (Cogburn et al., 1987; Foa et al., 1992; Lewy et al., 1980b). However, other research on animals shows that at least some of the plasma melatonin loss from pinealectomy is regained if the animal is retested several weeks later (Osol et al., 1985; Vakkuri et al., 1985). A case study published in the *New England Journal of Medicine* reported that the removal of a cancerous pineal gland from a patient resulted in the disappearance of plasma melatonin, although the diseased gland had been capable of normal melatonin secretion and circadian rhythm (Neuwelt et al., 1983). The researchers concluded that the pineal is the sole source of plasma melatonin in humans. In support of this concept is the knowledge that pineal gland removal in humans is accompanied by chronic and severe insomnia, which can in turn be ameliorated by melatonin administration (Etzioni et al., 1996; Jan et al., 2001; Vorkapic et al., 1987).

While concentrations of urinary and salivary melatonin are not identical to plasma melatonin levels, there is a consistently parallel relationship. For example, levels of a major melatonin urinary metabolite closely correlate to plasma melatonin levels, and saliva concentrations of melatonin maintain a correlation that is approximately 70% lower than those in the blood (Arendt, 1988; Kennaway and Voultsios, 1998; Lynch et al., 1975; Waldhauser et al., 1984). The Kennaway study found that there is a highly significant correlation between the ratio of free plasma to total plasma melatonin and in the saliva melatonin to total plasma melatonin ratio. These results were the first solid confirmation of an association between salivary and circulating melatonin levels.

Melatonin Synthesis

The process of melatonin synthesis (see Figure 10.2) was investigated and resolved in the 1960s, largely by Julius Axelrod, Richard Wurtman, and David Klein (Wurtman, 1963b, 1964). When norepinephrine stimulates the β-adrenergic receptor sites in the pineal, melatonin is not directly secreted from the pinealocytes, but rather it triggers a series of intracellular responses by which the pineal metabolizes the amino acid, tryptophan, into melatonin (Arendt, 1988; Wurtman and Moskowitz, 1977a). Tryptophan is taken up by the pineal from the circulating blood and converted to 5-hydroxytryptophan (5-HTP) by tryptophan 5-hydroxylase, a process that occurs more actively at night. Greater quantities of 5-HTP are stored in the pineal than anywhere else in the CNS. The decarboxylation of 5-HTP by the enzyme, aromatic l-amino acid decarboxylase, results in the production of serotonin, which also is found in large quantities in the pineal. The enzyme serotonin *N*-acetyltransferase (NAT) then *N*-acetylates serotonin to *N*-acetyl-serotonin (NAS). At night, when norepinephrine stimulates the β-adrenergic receptors, it causes the stimulation of the nucleotide cyclic adenosine monophosphate (cAMP), which serves as a second messenger. A cAMP-dependent protein kinase and a transcription of messenger RNA are fundamental to the activation of the NAT enzyme. Finally, the enzyme hydroxyindole-O-methyltransferase (HIOMT) O-methylates NAS, resulting in melatonin (Reiter, 1991a, 1991b, 1993a). More than 40 years ago, two prominent researchers, Julius Axelrod and Herbert Weissbach, at the National Institutes of Health (NIH)

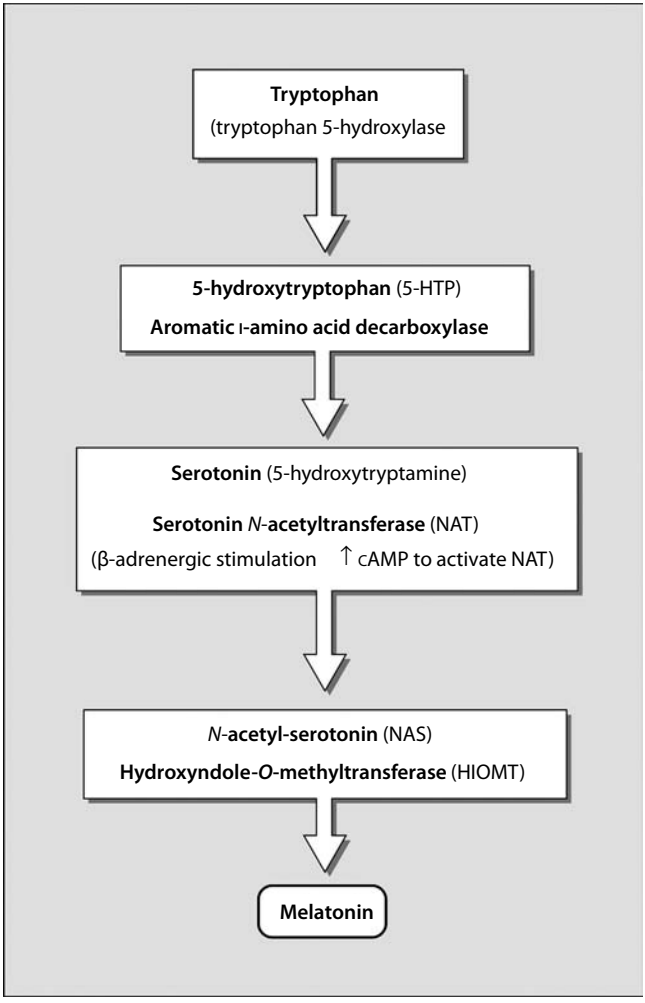

FIGURE 10.2 Synthesis of melatonin.

determined that the two enzymes NAT and HIOMT were essential to the synthesis of melatonin (Axelrod and Weissbach, 1960; Weissbach et al., 1960).

A great deal of research has been performed to determine the importance of the role of each of the precursors of melatonin. For example, because levels of NAT increase 25 to 100 times within a few minutes of darkness, it is presumed that NAT is the rate-limiting enzyme in melatonin synthesis (Maestroni and Conti, 1991a). Results of a study performed on mice showed that autocrine and paracrine actions of 5-HTP in the pineal may be involved in the regulation of the secretion of melatonin (Reiter et al., 1990). Furthermore, levels of both 5-HTP and NAS decline after midnight (Oxenkrug et al., 1990). These fluctuations correspond to the research on melatonin phase shifts and light suppression, which are described in the following section.

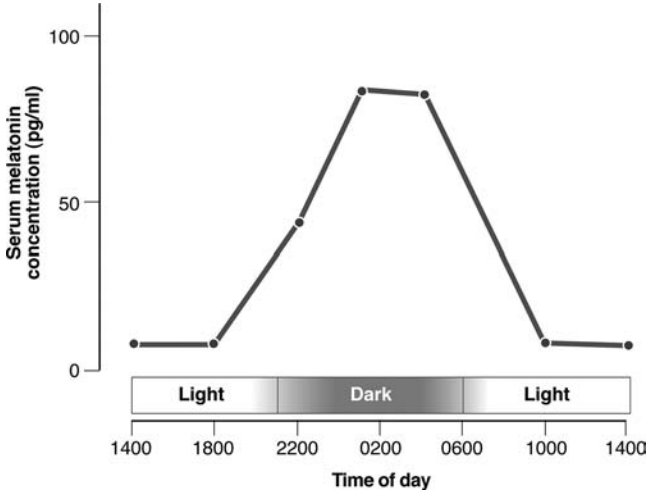

FIGURE 10.3 Variations in melatonin levels.

Melatonin Phase-Response Curve and Suppression by Light

Normally, melatonin follows a reliable bell-shaped pattern of peaking at night and returning to lower levels by morning (see Figure 10.3). This phase-response curve may vary significantly even among healthy individuals (up to 30 ng per 8 h interval), but it maintains a fairly consistent pattern for any particular person, allowing for the gradual and steady changes that correlate to shifts in season (Wurtman and Moskowitz, 1977b). Light does not actually cause the response curve (the SCN does), but rather entrains or alters it.

A "reset" of the phase-response curve or a "phase shift" occurs when an environmental factor (e.g., travel) or an exogenous substance (e.g., β-adrenergic blocking agents or melatonin) changes the time of melatonin secretion. A delayed response or phase shift takes place when the secretion of melatonin shifts to a later time, which could occur from exposure to bright light at night or β-adrenergic blocking agents. An advanced response or phase shift occurs when there is exposure to bright light in the latter part of the night or very early morning hours. This results in a phase shift that causes melatonin to secrete earlier in the night.

Virtually all investigations into the function of melatonin utilized the experimental setup of determining whether a phase shift has occurred. Hundreds of studies that have been performed on plants, insects, and mammals, including humans, confirm the fact that exposure to bright light at night causes a phase delay, and exposure to bright light in the very early morning hours results in a phase advance (Czeisler et al., 1989; Jewett et al., 1991; Lynch et al., 1978). The optimal time of melatonin administration to shift the cycle to an earlier time of day is between eight hours before and four hours after the increase in endogenous plasma melatonin production. The optimal time of melatonin administration to shift the cycle to a later time of day is between 8 and 16 hours after the increase in endogenous plasma melatonin

TABLE 10.2
Illumination Levels Associated with Environmental Situations

Event	Illumination Level (lux)
Noontime, summer solstice, 35° N latitude	113,284
Noontime, winter solstice, 35° N latitude	58,895
Most extreme black storm cloud conditions	7,000–11,000
Twilight begins	8,200
Full moon	0.37 (max)
Typical school classroom (general lighting)	400–700
General office lighting (typing)	500–750

Source: Adapted from Hughes, P.C., et al., *Pineal Res.*, 5, 1–67, 1987.

production (Sack et al., 2000). This information is crucial to the effective clinical administration of melatonin and to achieving experimental results that are not needlessly spurious. In humans, gender does not appear in any way to affect light-induced melatonin suppression (Nathan et al., 2000). Table 10.2 shows the illumination levels associated with commonly encountered environmental situations.

As long ago as the early 1960s, researchers recognized that the enzyme HIOMT (the last catalyst in melatonin production) is suppressed when animals are exposed to continuous light (Wurtman et al., 1964). However, in a landmark experiment in 1980, Alfred Lewy and colleagues discovered, contrary to previous trials, that light does suppress human melatonin levels. The salient variable was that it took an intensity of light higher than ordinary room light to achieve the suppression (Lewy et al., 1980a). By the end of that decade, the dose-dependent relationship between light intensity and the associated degree of melatonin suppression had been established. The suppression levels at intensities of 3,000, 1,000, 500, 350, and 200 lux were 71%, 67%, 44%, 38%, and 16%, respectively (McIntyre et al., 1989a). The different light intensities produced discrete suppression of melatonin within one hour of light exposure at midnight, regardless of the intensity. A light intensity of 1,000 lux is sufficient to suppress melatonin to near daytime levels (McIntyre et al., 1989a). However, light intensity of 200 lux does not produce statistically significant melatonin suppression when compared with control samples (McIntyre et al., 1989b). Interestingly, Charles Czeisler, at Harvard Medicine School, has now shown that the pineal is most susceptible to the influence of light when core body temperature is lowest, that is, around 4 a.m. to 5 a.m. (Boivin and Czeisler, 1998).

Clinical Applications for Melatonin

Insomnia and Jet Lag

Melatonin, perhaps, is best known for its ability to alleviate insomnia and jet lag. An understanding of phase shifts provides a medical framework by which melatonin is used to ameliorate insomnia and to speed the adjustment to a new time zone. Its

use for the elderly with subnormal levels and for blind people with free-running rhythms indicates that there is an enormous improvement in quality of life for many of these individuals. However, the research is mixed on both efficacy and safety for long-term use in individuals with inherently normal levels. While melatonin may be effective in some people to reduce jet lag, there are serious questions about what effects its use might have on the other hormones of the body (Arendt and Marks, 1982; Arendt, 1988).

Nighttime Work, Mental Disorders, Antiaging

Charles Czeisler and colleagues at Harvard performed research that shows precisely what environment factors must be maintained in order to provide a reasonable adjustment to nighttime work (Czeisler et al., 1990). The researchers explain that thousands of U.S. employees are required to work at night, significantly increasing their risk of sleep disorders and possibly adversely affecting cardiovascular disease, gastrointestinal illness, and reproductive dysfunction in women. They found that conditions of intensely bright light (7,000 to 12,000 lux) during the nighttime working hours and complete darkness during the daytime sleeping hours (in spite of exposure to outdoor lighting during a morning commute) causes a complete circadian adaptation to the night work schedule after four days. Concomitant shifts of plasma cortisol levels and urinary excretion rates plus higher alertness and cognitive performance assessments indicated that the subjects adapted significantly better than did controls.

Abnormal levels of melatonin also have been associated with some mental disorders, particularly depression. Its use as a therapeutic agent has not been well established for mental illness, but the use of light therapy has been shown to relieve depression, particularly with seasonally related depression (see Chapter 5).

Data on melatonin's role as an antiaging substance is controversial, but intriguing. Researchers have hypothesized that the pineal is the gland that defines aging—as it involutes and melatonin production decreases, the signs of aging increase (Cardarelli, 1990; Nair et al., 1986; Rozencwaig et al., 1987). Other researchers speculate that as we age, our melatonin levels decrease, and, therefore, the body's ability to protect itself against oxidative damage, and thus cancer, is diminished (Reiter, 1993a). Although it has not been substantiated in humans, chronic evening administration of melatonin to rodents has been shown to lengthen life. Nineteen-month-old mice that were administered melatonin in drinking water had a mean survival time of 931 days compared with 752 for the controls, approximately a 20% longer life span (Maestroni et al., 1988a). There appeared to be quality-of-life factors present as well, with the experimental mice retaining greater weight, better quality of fur, and superior all-around vigor.

Whether or not scientists are ever able to establish a correlation between the pineal and the aging process remains to be seen, but research has already shown that there is a significant correlation between aging and peak levels of plasma melatonin (Nair et al., 1986). In the early 1990s, Richard Wurtman and his colleagues at MIT showed that physiological doses of melatonin (which raise blood levels to those occurring normally at nighttime) promote sleep onset. Ten years later, they showed that the reason many people over 50 have insomnia is because their nocturnal melatonin

secretion is below normal. Administration of a physiological dose of melatonin largely cures their insomnia (Zhdanova et al., 2001).

Melatonin Receptors

There are melatonin receptors not only in the brain, but also in various tissues throughout the body. The neural receptors found in the SCN are involved in circadian rhythms. The nonneural, membrane-signaling receptors are largely involved in reproductive regulation, including seasonal breeding. The receptors in the peripheral tissues are as yet a mystery and may be involved in a variety of interactions, including the regulation of body temperature and functions relating to the vascular system and the heart.

Membrane-Signaling Pathway

Recent work has determined that melatonin function is dependent upon high-affinity G protein-coupled seven-transmembrane receptors, called ML1 and ML2. These membrane receptors, or binding sites, have been cloned in humans and are called Mel_{1a} and Mel_{1b} (Reppert et al., 1995; Slaugenhaupt et al., 1995). Mel_{1a} receptors are far more numerous than Mel_{1b} receptors. Mel_{1b} receptors are predominantly found in the retina and are possibly involved in melatonin phase-shifting functions (Carlberg, 2000). Mel_{1a} is found predominantly in the SCN and the pars tuberalis (Carlberg, 2000; Stankov and Reiter, 1990). The receptors are also expressed in the pars distalis (also located in the anterior portion of the pituitary), but only during the fetal and perinatal stages of life, and these may be instrumental in the light-induced development of the gonadotropic axis (Hazlerigg, 2001). Mel_{1a} receptors are possibly the melatonin receptors involved in limiting the action of the SCN, our biological clocks, and binding sites appear to be different for daily circadian cycles than for longer photoperiodic melatonin variations (Schuster et al., 2001).

Nuclear-Signaling Pathway

There is also a nuclear-signaling pathway for melatonin, but it does not appear to be as sensitive as the membrane-signaling pathways. Nuclear receptors in humans include RZR/RORα and RZRβ (Wiesenberg et al., 1995). The RZR/RORα receptors are found both in the brain and the peripheral nervous system (Wiesenberg et al., 1995). There is evidence that these are the receptors predominantly involved in immune modulation. However, Mel_{1a} receptors also have been found on lymphocytes, so obviously membrane receptors are involved in the peripheral system as well (Carlberg, 2000). When melatonin appears in concentrations higher than that provided by membrane or nuclear binding, it has a free radical scavenging function. We will review this and other immune-related topics in the chapter section entitled "Melatonin and the Immune and Stress Systems."

Our Wake–Sleep Switch

In 1998, two studies were published attesting to the existence of novel neuropeptide proteins found in the hypothalamus. One group of researchers called the

proteins hypocretins (HCRT-1 and HCRT-2) and determined that they were excitatory CNS neurotransmitters (de Lecea et al., 1998). The other group called them orexin (OR-R1 and OR-R2) and reported that the proteins were important to the control of feeding and to energy homeostasis (Sakurai et al., 1998). Hypocretin and orexin are two names for an identical molecule; therefore, we have chosen to use the name orexin for the rest of our discussion. A few years later, some of the same researchers determined that these neuropeptides were located in the pineal gland and that they had the ability to limit norepinephrine stimulation (Mikkelsen et al., 2001). This was big news because norepinephrine is the neurotransmitter, you will recall, that stimulates melatonin synthesis. A group at Harvard determined that there is actually an on–off switch that controls our movement between sleep and wakefulness states (Saper et al., 2001). In short, two opposing sets of neurons create a mechanism akin to a flip-flop switch in which there is great internal resistance to the switch being flipped. It is infrequent but rapid, and it is triggered by orexin. It moves us from being asleep to being awake and vice versa. While, as we are about to learn, the SCN is the location of the on–off switch, orexin actually flips the switch.

Clockworks: The Suprachiasmatic Nucleus (SCN)

The SCN is our biological clock and it, not light, ultimately is the location of the on-off switch for melatonin synthesis (Stetson and Watson-Whitmyre, 1976; Weaver, 1998). However, light both entrains and suppresses the levels of melatonin via the SCN. The SCN is located in the hypothalamus and receives environmental input via the retinohypothalamic tract. A measurement of melatonin is the most effective way to track a change in the circadian rhythm of the SCN. The SCN is fundamental to each of three major components of the circadian system: entrainment pathways, pacemakers, and output pathways to effector systems (Moore, 1995a). It modulates our neuroendocrine systems according to the current light pattern by regulating the secretion of melatonin and other hormones of the pineal. Clearly, the biological clock is indispensable to the basic functioning of the human body. But how is light information conveyed from the environment to this tiny SCN nucleus? What do the clock parts look like? And what resets the clock when the days start getting longer in the spring and shorter in the fall and winter?

We know that light somehow travels to the SCN via retinal projections in the retinohypothalamic tract that arise from discrete retinal ganglion cells (Moore 1995a, 1995b). The portion of retinohypothalamic tract that carries the transduced light impulse to the SCN also ends at the anterior hypothalamus (Leak and Moore, 1997). This is significant because lesions to the anterior hypothalamus result in impaired immune function. As we will see in the chapter section entitled "Melatonin and the Immune and Stress Systems," the SCN and melatonin production are closely related to immune performance.

The SCN is a paired structure with two subdivisions: a ventral core, which is located above the optic chiasm and receives transduced photic input, and a dorsal shell, which surrounds the core and receives input from nonvisual sources. Research has shown that the core and shell differ in their functioning in several respects

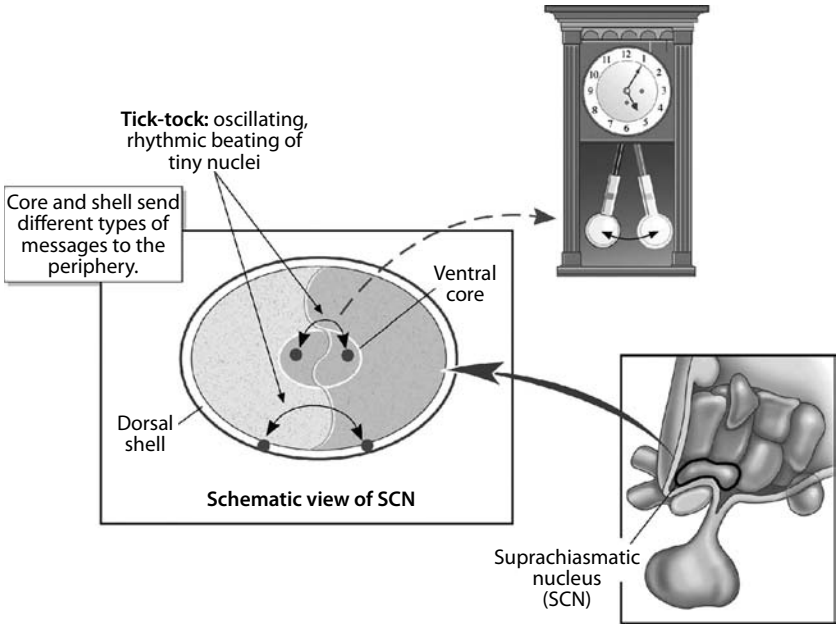

FIGURE 10.4 (See color insert following Page 160.) Oscillating patterns within the SCN.

(Leak and Moore, 2001). Efferent fibers project from both the core and the shell to similar areas on the other side of the SCN, and messages that travel via efferent projections to the periphery vary, depending on whether they originated from the core or the shell (Leak et al., 1999; Leak and Moore, 2001). Similarly, afferent neuronal messages going to the SCN contain functionally discrete messages that differ, depending upon whether they are being sent to the core or the shell. It may be that the projections from the SCN to the posterior hypothalamus mediate the arousal function of the circadian timing system (Abrahamson et al., 2001).

Local connections as well as afferent and efferent patterns offer insights into the pacemaker functions of the SCN. Circadian rhythm is determined by light via neural inputs and other information that flows through and out of the SCN. The rhythmic beating of these tiny nuclei is the timepiece of our lives. The physiological setup gives rise to strong speculation that the rhythm is the result of individual SCN neurons that are coupled (either between the core and shell or between the nuclei on each side, or both) to produce the circadian message (Leak et al., 1999). In fact, there is evidence to support the theory that the SCN is functionally organized into two left- and right-side oscillatory components that cycle in antiphase (see Figure 10.4), with efferent projections to brain regions outside of the SCN that maintain the rhythm (de la Iglesia et al., 2000).

Keep in mind a portrait of a timekeeper whose task it is to harmonize not only our daily cadence, but our lifetime rhythms as well. Then, mentally step back and try to hold the image of this internal timekeeper in harmonic resonance with the physical

Earth as well as with seen and unseen energy. We will speak more about this notion at the end of the chapter.

Clock Components

Single-Cell Oscillators

What are the clock components? Recall the fascinating experiment reviewed in Chapter 1 in which nuclei from the SCN placed in a petri dish continued an electrical firing that maintained a 24-hour circadian rhythm (Hastings, 1998; Welsh et al., 1995). The neurons in the petri dishes did not synchronize to one another, however, which meant that they fired off independently, without any oscillating pattern (Welsh et al., 1995). The SCN is composed of many of these autonomous single-cell oscillators, which when coordinated or synchronized generate a circadian output that affects our body rhythms, as we know them (Reppert and Weaver, 2001).

In this section, we will look at some of the factors that produce synchronization among the autonomous circadian oscillators and how the synchronization influences the body rhythms (see Ishida et al., 1999; Jin et al., 1999; Miller, 1998, for a review). Interesting research shows that circadian oscillators reside in peripheral tissues as well as in the SCN of the pineal, but the SCN also controls the rhythm of the peripheral oscillators (Balsalobre et al., 2000; Reppert, 2000; Reppert and Weaver, 2001). As a result of this synchronization, the body maintains circadian rhythms for not only the sleep–wake cycle but for temperature, blood pressure, immune-cell count, and hormones that impact entire body systems, such as cortisol (stress) and prolactin (immune and reproduction).

Gene-Driven Feedback Loops

How do the opposing oscillations within the clock, for instance, for day and night rhythms, stay in sync? The entrainment of the SCN is triggered by a complex process (involving genes and proteins encoded to regulate numerous physiological processes) and then calibrated and reset by contact with light (Morris et al., 1998; Vitaterna et al., 2001). Circadian oscillator genes have transcriptional and translational autoregulated feedback loops with both negative and positive elements (Allada et al., 2001; King and Takahashi, 2000; Shearman et al., 2000). Various components of the negative feedback loop were first and more easily identified, but recently progress has been made in identifying the components of positive feedback loops, which are the core elements to circadian rhythmicity.

To understand the functions of a gene, researchers find genetic mutations of the wild-type or normal genes (which also provide an opportunity to clone the gene). They then insert or breed this mutation into test subjects (e.g., mice, fruit flies). How the mutation changes normal performance (e.g., causes phase advances, phase delays, or arrhythmic patterns) provides information regarding its inherent functioning. The research on clock genes began with two proteins from fruit flies (drosophila) and one from a bread mold (neurospora). The genes from the fruit flies are period (per) and timeless (tim), and the clock gene discovered from the bread mold is called frequency (frq) (Konopka and Benzer, 1971; Sehgal et al., 1991). The two fruit-fly

genes were eventually located in the mouse (Ishida et al., 1991; Sangoram et al., 1998; Zylka et al., 1998). Two proteins involved in restarting the SCN clock genes, Clock and BMAL1, also have been located in both the fruit fly and mouse (Antoch et al., 1997; Darlington et al., 1998; King et al., 1997). The clock gene is an activator of the circadian system.

Joseph Takahashi and colleagues at Northwestern University were the first to identify the circadian clock gene in humans, which is expressed particularly in the SCN and cerebellum (Steeves et al., 1999). It appears that the clock gene in humans (as in mice) is required to maintain a rhythmicity in individual SCN neurons, but that a separate (but still unknown) mechanism within the SCN is synchronizing all of these neurons (Herzog et al., 1998). Think about it: your biological clock just keeps going … tick, tick, tick. These genes and proteins may well be the power source to the incessant, rhythmic ticking.

Ocular Phototransduction: Research on Individuals Who Are Blind

Photoreceptors receive the information to reset and adjust our biological clocks via the entrainment of light. We digress a moment before a discussion of photoreceptors to examine research performed on blind people, which gives important insight into ocular phototransduction. The majority of individuals who are blind have either an unusual circadian rhythm or a free-running rhythm (approximately 50% of those examined), but they show no impairment in the synthesis of melatonin. Free-running rhythms are characterized by a consistent delay in the circadian rhythm of about 60 to 70 minutes a day. Therefore, these people spend about half a month with their melatonin level telling them to sleep during the day and the other half of the month in a normal sleep–wake cycle (Lewy and Newsome, 1983; Sack et al., 1992).

In 1995, Charles Czeisler and several of his colleagues at Harvard performed some very interesting research on 11 blind subjects who had no conscious perception of light (Czeisler et al., 1995). They used the classic experiment of exposing the subject and controls to bright light at night to assess whether the normally higher nighttime melatonin levels would decrease. In 3 of the 11 blind subjects exposed to light, the melatonin levels decreased at essentially the same percentage as it did for the sighted controls. Curiously, it was only these three subjects who had reported no prior sleeping difficulties, while the remaining eight subjects reported a history of insomnia. These results strongly suggest that there is some photic function retained in the subjects whose melatonin is suppressed by light, despite the presence of damage that has eliminated the pupillary reflex and any perception of light. The researchers reasoned that the photoreceptive system that mediates melatonin expression must be distinctly different from the photoreceptive system that governs light perception "either quantitatively (i.e., in requiring only a few conventional receptors) or qualitatively (i.e., in using a novel phototransductive system with a distinct subgroup of retinal ganglion cells)."

Studies on the ocular photoreceptive system in blind people appropriately led to the therapeutic use of melatonin to entrain their circadian rhythms. Research now shows that melatonin, given at a dose of 10 mg per day, can appropriately phase-advance the circadian cycle for blind people, alleviating the burden of insomnia

(Sack et al., 2000). It also appears that the dose of melatonin can be reduced to 5 mg once the individual is entrained to a nighttime sleep cycle. Research to determine whether the dose could be further lowered is warranted in light of the work by Zhdanova et al. (2001), who demonstrated that a dose of 0.3 mg was optimal in those individuals whose levels are subnormal. Furthermore, researchers encourage a comprehensive evaluation of the circadian system before bilateral enucleation (i.e., removal of eyes damaged from disease or injury) is performed (Czeisler et al., 1995).

How Is the Clock Set? Capturing and Sending Light to the SCN

As we have indicated, light has something to do with how our biological clock adjusts itself, that is, how it makes the necessary corrections as days lengthen or shorten with seasonal changes. So, naturally, scientists want to locate the photoreceptors that pass this information from the environment to the SCN. The obvious place to look would be the light-sensitive rods and cones in the retina that provide us with our visual information. However, research on people who are blind gives us cause to question the role of rods and cones as primary phototransducers. Corroborating this supposition is a study that found that cone degeneration in aged mice did not render them incapable of circadian phase shifts and that their responses to light were similar to that of controls (Provencio et al., 1994). Following this study, two experiments established that mutant mice, lacking both rods and cones, still exhibited melatonin suppression when exposed to light (Freedman et al., 1999; Lucas et al., 1999). This finding conclusively demonstrates that something other than rods and cones are conveying the light information; in other words, they are not the sought-after photoreceptors. Research on humans is similar and shows that there is a unique short wavelength-sensitive photopigment involved in light-induced melatonin suppression, providing the first direct evidence of a nonrod, noncone photoreceptive system in humans (Thapan et al., 2001). So, if not rods and cones, what might these photoreceptors be?

One possibility is cryptochrome, the vitamin B-based, light-absorbing protein pigment in the eye and SCN, which is sensitive to blue light (Ivanchenko et al., 2001). It is found both in the retinal ganglion and the inner retina (Sancar, 2000). Cryptochrome was discovered in plants and identified as the protein that allows plants to bend toward light. Other possible photoreceptors are the nonrod, noncone vitamin A-based opsin photopigments, such as melanopsin (Provencio et al., 1998). The retinal distribution of melanopsin cells bears a striking resemblance to the retinal cells known to connect to the SCN in rodents. The inner retina seems to be the only mammalian site at which melanopsin is expressed, suggesting a role in nonvisual photoreceptive tasks (Provencio et al., 2000). So, in the end, melanopsin and cryptochrome are viable, but unconfirmed, photoreceptor candidates of the mammalian clock.

There are those working on finding the receptors who are convinced that multiple photoreceptors will be identified, which is a feasible conclusion given the complex interactions of the clock components (Lucas et al., 2001). It also is known that nonmammalian vertebrates possess multiple photoreceptors (Foster and Soni, 1998). There are, however, others who have done work showing that a single photopigment

may be responsible for photo entrainment, suggesting that it may involve a novel opsin (Brainard et al., 2001). Scientists know that the photoreceptors for melatonin synthesis have a spectral sensitivity (i.e., the range most sensitive to stimulating melatonin release) between 400 and 650 nm. This helps to limit the choices but, unfortunately, a definitive mammalian photoreceptor has not yet been established.

MELATONIN AND THE IMMUNE AND STRESS SYSTEMS

As discussed in the chapter on the relaxation system (Chapter 4), melatonin is an important immune modulator of both the innate and acquired immune systems (Jankovic et al., 1970; Maestroni et al., 1989). However, melatonin may most effectively support the immune system by reducing the effects of stress (Maestroni and Conti, 1991a). Immune system suppression caused by corticosterone is reversed by melatonin, and its stress-ameliorating qualities appear to occur via melatonin's immune-enhancing capability (Khan et al., 1990; Maestroni et al., 1986; Maestroni et al., 1987a). The benzodiazepine receptors present on platelets and monocytes may be the avenue through which melatonin modulates the immune system (Moingeon et al., 1984; Ruff et al., 1985). Evidence also exists that melatonin is involved in an integrative systemic response designed to increase immune resiliency during the winter months (Nelson and Drazen, 2000). Because immune suppression is a major consequence of chronic stress, it is possible that melatonin's stabilizing properties promote equilibrium and ease the body back from stress to homeostasis by invigorating the immune system. Further research needs to be performed in order to understand this relationship more fully.

Melatonin's Humoral Immune Responses

Melatonin is involved in both humoral and cell-mediated immune responses, and pinealectomy or other means of blocking melatonin are correlated with distinct immune depression (Maestroni and Conti, 1991a). Furthermore, melatonin produces antistress and immune-enhancing effects in rodents in a circadian-dependent manner, i.e., the effects are dependent upon evening administration (Maestroni and Conti, 1989). Researchers tested the immune-enhancing effects of melatonin in mice by giving them exogenous melatonin and then exposing them to an immunosuppressant—sheep red blood cells (SRBC). They found that melatonin administered in the evening enhances the antibody response in a dose-dependent manner, beginning at the low dose of 10 μg/kg of body weight, and results in reversal of the humoral suppression (Maestroni et al., 1986). The work of untangling the mechanisms of action for these functions is ongoing. However, it is known that melatonin, at least in part, stimulates humoral immune responses by increasing the survival rate of B-lymphocyte precursor cells found in the bone marrow (Yu et al., 2000).

Melatonin's Cell-Mediated Immune Responses

Melatonin stimulates cell-mediated immune responses by inhibiting apoptosis of T lymphocytes in the thymus and by enhancing T lymphocyte cytokine and opioid

release (Maestroni, 1993; 1999; Yu et al., 2000). In other words, it allows more T lymphocytes to mature and to function more effectively. In addition, melatonin increases the proliferation of cells, such as monocytes, natural killer (NK) cells, and pre-B lymphocytes, during red blood cell formation (Maestroni and Conti, 1996; Maestroni, 1999, 2001b). Activation of the melatonin receptors results in an enhanced release of T helper cell cytokines, including γ-interferon, IL-1, IL-2, and others (Guerrero et al., 2000; Maestroni and Conti, 1996; Maestroni, 1999, 2001b). Monocytes at certain states of maturation actually express melatonin receptors (Maestroni, 2001a). Furthermore, melatonin is capable of enhancing immunological memory to a primary specific T-cell-dependent antigen during immunization (Maestroni et al., 1988b; 1989). All of these findings point to the fact that melatonin plays a significant role in cell-mediated immune responses.

Melatonin's Nonreceptor Immune Actions: Free Radical Scavenger

Research on the immune system has established that melatonin also has nonreceptor immune actions, particularly its ability to be a powerful free radical scavenger (Poeggeler et al., 1993; Tan et al., 1993). As mentioned, melatonin is highly lipophilic, allowing it to easily enter any cell in the body and permitting it to be an effective free radical scavenger (Reiter et al., 1996, 2000). When presented to the hydroxyl radical, the most toxic of the oxygen-based radicals, melatonin has been shown to be a more effective antioxidant than the better-known glutathione or vitamin E (Reiter et al., 1995). Other work being done by Reiter's team purports to have demonstrated that melatonin also can scavenge hydrogen peroxide (Tan et al., 2000). Melatonin is capable of interacting with many of the inflammatory cytokines involved in immune responses and, consequently, reduces the potential damage of some of the powerful chemicals used in chemotherapy that destroy healthy tissue (Reiter, 1993a; Reiter et al., 1996, 2000). Tests on rats using a carcinogen, safrole, showed that melatonin protects against DNA-associated damage (Tan et al., 1993). Furthermore, melatonin significantly augments the immune response to IL-2 in advanced cancer patients (Lissoni et al., 1992, 1994).

Melatonin is found in higher levels in human estrogen receptor-positive breast cancer cells than in the blood (Reiter et al., 2000). Pretreatment of human breast cancer cells with melatonin prior to administration of the chemotherapeutic agent tamoxifen renders the tamoxifen a hundred times more powerful an inhibitor of breast cancer cell growth (Wilson et al., 1992). Melatonin and tamoxifen are both free radical scavengers that, when used together, are more able to prevent the membrane rigidity that occurs from free radical attack than either alone (Garcia et al., 1998). The obvious next step would be to test these findings on human breast cancer patients. Our search turned up studies from only one lab—Paolo Lissoni and his group in Milan, Italy. The results of Lissoni's phase II trials indicate that in about 28% of metastatic cancer patients, concomitant use of melatonin and tamoxifen (or other appropriate chemotherapy) resulted in some positive therapeutic response, whether or not the primary tumor was breast cancer (Lissoni et al., 1995, 1996). Similar enhancement of therapeutic response of melatonin in combination with chemotherapeutic agents has been confirmed in studies published more recently

(Cerea et al., 2003; Lissoni et al., 2003). Lissoni's research also showed that the combination of melatonin and chemotherapy significantly reduces side effects of chemotherapy, including malaise and weakness (Lissoni et al., 1997).

While research in this area appears to be progressing at a snail's pace, the results of epidemiological studies actually warrant further investigation into the correlation between melatonin and breast cancer. Disturbing findings from two separate labs show a correlation between increased rates of breast cancer in women who work night shifts. While the increased risk is moderate in the beginning, the more years that their nighttime melatonin levels are disturbed by night work, the greater the risk women have of developing breast cancer. One study reported that a daily average of 5.7 hours of night work over 10 years doubled a woman's chance of developing breast cancer (Davis et al., 2001b). In another study, 30 years of some night shift work placed the women at a 36% higher risk of developing breast cancer (Schernhammer et al., 2001). The beguiling aspect of the study is that the greater number of years of night work, the higher is the rate of cancer. Can low levels of melatonin (for a whole host of reasons, including stress) over many years influence a person's health? There is now some research to support this speculation.

Opioid Peptides, Melatonin, and Immunity

Interactions between melatonin and the immune system are mediated by endogenous opioid peptides (secreted either from the immune cells themselves or from the neuroendocrine system) and require a primed immune cell to be activated (Lissoni et al., 1994; Maestroni et al., 1987a, 1987b; Maestroni and Conti, 1989, 1991a). The fact that an opioid antagonist (naltrexone) completely abolishes melatonin's immune-enhancing role and that melatonin is completely ineffective when used for *in vitro* experiments confirms the crucial role of opioids in the proper functioning of melatonin (Lissoni et al., 1986; Maestroni et al., 1988a). Activated, circulating T lymphocytes and T helper cells are stimulated by melatonin, likely in a paracrine or autocrine manner, and then release endogenous opioids. This process results in immune-enhancing and stress-reducing responses (Maestroni and Conti, 1991a). In humans, melatonin is elevated during the night, and β-endorphin secretion is low; the opposite holds true during the day. Intriguingly, the thymus (the site of T-lymphocyte maturation) is one of the main targets of melatonin. The presence of both melatonin and opioid receptors in the thymus strongly suggests a role for melatonin in immune recovery following elevated corticosteroid levels, such as occurs with stress or disease (Maestroni and Conti, 1991b, 1991c).

Melatonin and Hematopoiesis

Hematopoiesis is the production of the formed blood elements, which occurs primarily via the bone marrow stromal cells and, secondarily, in the liver. The blood cells include erythrocytes, platelets, polymorphonuclear neutrophil leukocytes, and B lymphocytes. Like the immune system, hematopoiesis is influenced by both neural and endocrine factors. The multifaceted regulation of hematopoiesis involves a variety of circulating

and membrane-based cytokines, growth factors, and antigens that are presented to B and T cells. Recently, work has been done to identify new entities, such as neuropeptides or neurotransmitters, involved in hematopoiesis. Melatonin has been identified as one of these new factors that performs a crucial function in the hematopoietic process. It appears that melatonin has roles both in acute immune conditions as well as in general immune homeostasis or maintenance via the hematopoietic system.

It is already known that bone marrow contains high concentrations of melatonin as well as both the NAT and HIOMT enzymes needed for its synthesis (Conti et al., 2000). Levels of bone marrow melatonin in pinealectomized animals remain high, which indicates that melatonin most likely is synthesized in the bone marrow itself or at least is concentrated there (Conti et al., 2000; Tan et al., 1999). Amazingly, levels of melatonin in bone marrow are three orders of magnitude greater than those measured in the blood at night—even for pinealectomized animals (Maestroni, 2000; Reiter et al., 2000).

Fascinating studies by Georges Maestroni in Switzerland indicate that bone marrow from mice not only has high levels of melatonin, but also contains a substantial amount of catecholamines—with both factors being involved in hematopoiesis (Maestroni et al., 1997, 1998; Maestroni, 2000). Melatonin's role as a regulatory hormone in the hematopoietic process, like the catecholamines, is predominantly related to immune function. Maestroni and colleagues determined that the activation of melatonin receptors causes an increase in the secretion of T helper cytokines, such as γ-interferon, IL-2, various opioid cytokines, and possibly several others. The opioids induced by melatonin receptor activation subsequently bind to κ-opioid receptors that are present on stromal bone marrow macrophages (Maestroni, 1999). It is these melatonin-induced opioids that actually are capable of influencing the hematopoietic process.

This newly identified immune–hematopoietic network receives messages from the environment via the brain, conveyed, at least in part, by catecholamines and melatonin. Maestroni points out that we now have two (i.e., the catecholamines and melatonin) intriguing and unsuspected factors that are capable of transducing environmental information into the process of blood and immune cell formation. Maestroni explains, "This subtle environmental influence of the blood-forming system might be even more fundamental than that exerted by the cytokine network" (Maestroni, 2000). Catecholamines transduce aspects of the rest–activity rhythm, and melatonin conveys circadian information. Maestroni appropriately wonders if there could, therefore, be a neural regulation of the hematopoietic process that might influence a disease, such as leukemia, acute infection, or stress (Maestroni, 2000). In other words, this is clearly an avenue by which our general level of well-being or heightened state of stress is conveyed to our blood-forming mechanisms, and thus to our immune system. This is but one more major example of both whole systems integration and an environmentally based feedback loop between the endocrine, the immune, and now, the hematopoietic system.

Melatonin and Prolactin

The influence of the pineal on the immune system is complex and varied. For example, the pineal helps regulate the secretion of prolactin from the anterior pituitary

(Lissoni et al., 1990). In humans, prolactin is dependent on both light and melatonin for its synthesis. Like melatonin, prolactin is a modulator of the immune system. It stimulates lymphocytes to secrete cytokines, is secreted by lymphocytes, and inhibits natural killer (NK) cell activity (Bernton et al., 1991; Hiestand et al., 1986; Matera et al., 1990; Reichlin, 1993). New research indicates that prolactin actually is produced within the thymus (as mentioned, a major target site for melatonin) and has paracrine and autocrine actions, which serve to regulate thymic action (Savino et al., 1998).

Summary: Melatonin and the Immune System

Just as melatonin boasts discrete immune-enhancing characteristics, certain immune products (e.g., γ-interferon, colony-stimulating factors, and IL-2), in turn, are capable of modulating the synthesis of melatonin in the pineal (Maestroni, 1993). Here again we have one of those remarkable instances of systems interacting in a bidirectional manner, reminiscent of the systems integration paradigms reviewed in Chapter 2 (Maestroni, 1999). What can be culled from the various studies cited in this section? Similar to the picture that emerged with the systems integration paradigms, we see that melatonin has a variety of major endocrine actions. However, it also has autocrine or paracrine actions that enable interactive and integrative mechanisms to occur in a cumulative manner, which can result in outcomes just as significant as the more forcefully acting hormones and neurotransmitters. Melatonin potentially could allow the body to remember not only chemical information, but it could also help to retain a memory of the environmental factors contributing to or just simply present at the time of illness or stress. All of these issues provide more evidence that the pineal is our master gland.

MELATONIN AND THE REPRODUCTIVE SYSTEM

Although it is known that melatonin is involved in the reproductive patterns of seasonal breeders, such as animals and birds (the darker times of year increase melatonin production and decrease reproductive hormones), its significance in human reproduction has remained controversial. In animals, melatonin limits the pituitary release of GnRH and regulates LH, FSH, and prolactin (Reiter, 1980). Historically, evidence supporting a relationship between melatonin and the reproductive hormones in humans was based on findings of reproductive disorders associated with diseases (e.g., tumors) of the pineal gland. For example, in 1898 Heubner described a boy with a pineal tumor who exhibited precocious puberty (the thinking being that melatonin was not available to suppress the sexual development). Then, in 1954, when Kitay showed that destructive tumors were associated with precocious puberty and that hyperactive tumors were associated with delayed puberty, much research energy was invested in trying to determine a functional relationship between melatonin and the sex hormones (reviewed in Lewy, 1983, and Tamarkin et al., 1985). Because there are melatonin receptors in both the brain and the reproductive organs and because there are reproductive hormone receptors in the pineal gland, it is very tempting to speculate that there must be a causal relationship (Luboshitzky and Lavie, 1999). However, whether or not a correlation exists in humans remains ambiguous.

Animal Studies

In 1963, Richard Wurtman and coworkers were the first to show that exogenous melatonin negatively impacts mammalian reproductive functions (Wurtman et al., 1963a). Russel Reiter and his colleagues in Texas have been instrumental in determining the various effects of melatonin on the reproductive system (Reiter and Johnson, 1974a, 1974b; Reiter, 1980). Reiter worked with hamsters to assess correlations between the size of the reproductive organs and exposure to light, dark, and/or melatonin. One significant finding was that the constant administration of melatonin caused a "functional pinealectomy" in both the male and female hamsters (Reiter et al., 1981).

However, there were seemingly conflicting results from his studies. The discovery in 1976 that antigonadotropic effects are influenced by the time of day in which exogenous melatonin is administered provided the first piece to unraveling the puzzle of why the research had yielded conflicting findings (Tamarkin et al., 1976). If melatonin is administered in the afternoon or evening, it combines with the endogenous melatonin and results in the dramatic gonadal degeneration seen in the earlier studies. However, morning administration of melatonin does not exhibit these effects. Reiter put these findings together with his knowledge that various hormones are capable of inhibiting their own actions (recall the role that cortisol plays in the stress response), desensitizing or down-regulating their own effects. He deduced that morning administration falls on already saturated melatonin receptors and creates a state of chronic down-regulation, which therefore prevents antigonadotropic effects (Reiter et al., 1981). Such information about the effects of melatonin on animals opened the way to a better understanding of its impact on humans.

Human Studies

In humans, as already mentioned, absolute concentrations of plasma melatonin peak somewhere between the ages of two and five years and then proceed to decline throughout life (Wurtman, 2000). At the turn of the last century, Marburg posed the theory that the pineal regulates the onset of puberty, and researchers have been trying to prove him right (or wrong) ever since. By the 1990s, researchers began to realize that the decrease in melatonin levels was not so much linked to the child's age as to the child's level of sexual maturation. Russel Reiter and Franz Halberg, for example, both determined that the Tanner stages 1 to 5 of sexual maturation (which is a method to classify pubertal development) are correlated to significant decreases in nocturnal melatonin (Reiter, 1998; Salti et al., 2000; Tanner and Whitehouse, 1976). However, these studies still do not establish a causal relationship. Furthermore, other research shows that prepubertal children, who have a higher melatonin secretion rate, may simply metabolize melatonin faster than adults (Carvallo and Ritschel, 1996). Clearly, there is a correlation between a decrease in melatonin and the onset of puberty, but why this is so still remains an enigma.

Although it has not been established that melatonin regulates gonadotropic hormones in men, a correlation between melatonin and these hormones has frequently been reported, particularly because of abnormalities in hormone levels. Low GnRH

levels, for instance, are correlated to increased melatonin, while elevated gonadotropin levels are correlated to low melatonin (Luboshitzky et al., 1996). But, once again, a cause-and-effect relationship remains questionable because long-term administration of melatonin does not alter the secretions of the major reproductive hormones (e.g., LH, testosterone, and FSH), although evening administration of melatonin to normal males does result in a next-day reduction of LH (Luboshitzky et al., 1999, 2000). In spite of melatonin's apparent antigonadotropic properties, a functional relationship has not yet been definitively established.

Research on the correlation between women's menstrual cycles and melatonin levels suggests that melatonin is not a factor in the cyclical menstrual phases (Berga and Yen, 1990; Brzezinski et al., 1988). However, elevated melatonin levels have been observed in amenorrheic women and decreased levels with premenstrual depression (Berga et al., 1988; Brzezinski et al., 1987, 1988; Parry et al., 1990). As stated, levels of melatonin decrease with age, and Russel Reiter and others have established that there are significant decreases in nocturnal melatonin during menopause (Reiter, 1998). Researchers in Finland determined that urinary melatonin excretion declined by 41% in women 40 to 44 years of age and that there was then a second significant decline of 35% in women between the age groups of 50 to 55 and 55 to 59 (Vakkuri et al., 1996). These decreases occurred in inverse relationship to FSH, whose levels are known to increase with age. The fact that the largest decline in melatonin occurs before the onset of menopause is intriguing, yet once again, it does not establish a causal relationship. Nonetheless, the correlation is pronounced, with research showing that healthy menopausal women who were given melatonin for up to 6 months exhibited an increase in thyroid hormone levels. In addition, a decrease in the pituitary hormones LH and FSH (both increase with age) was observed for younger menopausal women and those with low levels of melatonin before treatment initiation (Bellipanni et al., 2001).

Recall that, in the sections on the SCN, we proposed that its rhythmic beating is not only the timepiece of our daily cycles, but also of the totality of our lives, cradle to grave. The physiological and scientific correlations between melatonin and its impact on our reproductive development and denouement are examples of the role that the SCN plays in configuring the larger rhythmic patterns of life. The SCN and melatonin are integral to lifelong personal patterns, potentially in a harmonic resonance with the environment around us.

CHRONOBIOLOGY

Chronobiology involves the science of our biological clock (i.e., the SCN) as it is expressed in our personal physiological rhythm (e.g., am I a morning or an evening person?). However, chronobiology also concerns the science of how our biological clocks are disrupted by or determine the daily rhythms of a particular illness and even the time of optimal medication administration. Franz Halberg, who some called the father of chronobiology, initiated the study of body rhythms in the late 1950s and continues to provide valuable research to the field (Halberg, 1983; Halberg et al., 2001). Halberg ascertained literally dozens of circadian patterns present in humans and other species, including thyroid function in Peking ducks; rhythms of susceptibility to an insecticide (pyrethrum) in cockroaches and houseflies; and the

peak times of the day that symptoms of asthma, schizophrenia, and narcolepsy are expressed in humans (Astier and Bayle, 1970; Halberg et al., 1968; Passouant et al., 1969; Reinberg et al., 1970; Reindl et al., 1969; Sullivan et al., 1970).

In the intervening years, we have learned much about body rhythms and how they relate to particular diseases. These findings interface with our knowledge of the pineal and circadian hormonal secretions. For instance, the morning surge in sympathetic activity (e.g., increased epinephrine and norepinephrine secretion, higher blood pressure and heart rate levels) and increase in cortisol levels correlate to cardiovascular disease, including ischemia, myocardial infarction, stroke, and sudden death (Muller et al., 1987, 1989; Panza et al., 1991; Pepine, 1991; Quyyumi, 1990). The fact is that humans tend to have a heart attack in the morning—generally between about 6 a.m. and noon—when the sympathetic system is fully active and our stress hormone system is at its peak.

Similarly, the progression of disease and the intensity of side effects for patients with colorectal cancer are enormously influenced by the time of day that chemotherapeutic drugs are administered and their correlation to concurrent radiation therapy (Bressolle et al., 1999; Hrushesky, 1985, 2001; Peters et al., 1987; Thrall et al., 2000). Regrettably, these factors have been brought to the attention of few physicians in the United States. Research stemming from a laboratory in Villejuif, France, has actually shown that lack of a distinct circadian rest–activity rhythm in cancer patients is a novel independent prognostic factor for survival (Levi, 2000; Mormont et al., 2000). The researchers encourage chronotherapeutic adjustments as part of these patients' overall cancer treatment (i.e., protocols designed to adjust their circadian rhythms more in line with usual patterns and with normal levels of melatonin expression).

From a broader perspective, chronobiology is expressed in the patterns of both human and animal nervous, stress, immune, and reproductive systems. We have discrete daily, yearly, and lifetime biochemical patterns and rhythms. In the following section, we will begin to consider how the articulation of our internal hormonal energy is reflected in and reflective of energetic variations that surround us.

ELECTROMAGNETIC ENERGY AND THE PINEAL: A LINK TO EASTERN ENERGY CONCEPTS

Light can be described as the visible portion of the electromagnetic spectrum (see Figure 10.5). We have already explained how light can modify our internal clocks, causing phase advances or delays. Is it possible that other portions of the electromagnetic spectrum can also entrain our biological clocks? An increasingly large body of research seems to support this hypothesis (see Wilson et al., 1989, for a review of earlier studies). Russel Reiter and his colleagues, for example, have performed numerous experiments showing that the nonvisible portion of the electromagnetic spectrum decreases melatonin levels, just as visible light does. Reiter has shown that nighttime exposure of animals and humans to pulsed static and very low-frequency magnetic fields reduces melatonin production and plasma levels in a manner very akin to nighttime exposure to light, although it is not known whether the mechanism of action is the same (Reiter, 1992, 1993a, 1993b, 1994; Reiter and Richardson, 1992).

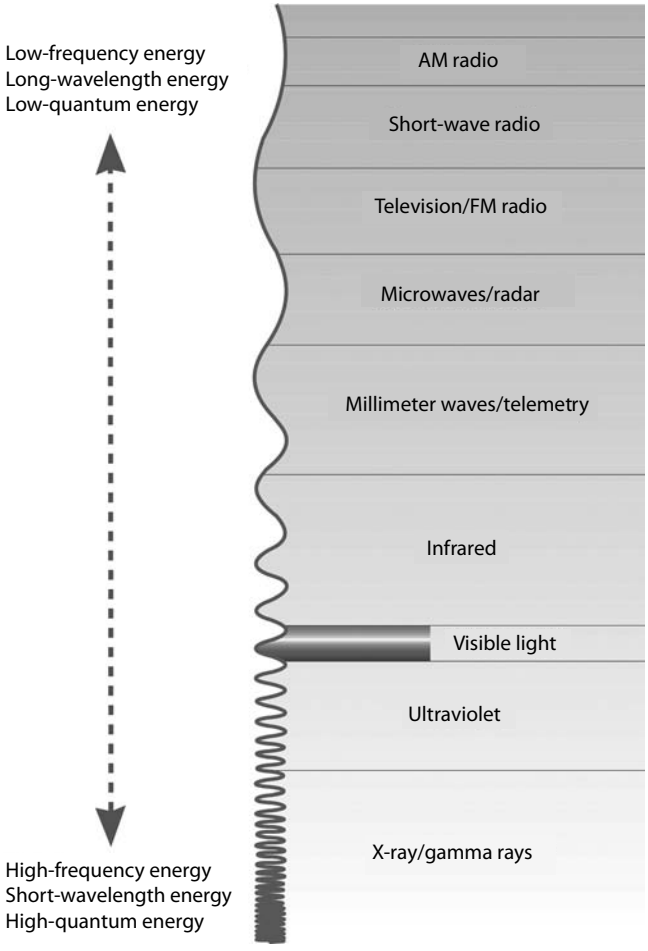

FIGURE 10.5 Electromagnetic spectrum.

Reiter's research is significant because of the ongoing, and often heated, debate as to whether these low-frequency magnetic fields are detrimental to our health. Studies on humans show that nighttime residential exposure to 60 Hz lowers urinary melatonin levels, particularly in winter and especially in women taking various medications, including calcium-channel blockers and beta blockers as well as psychotropic medications (Davis et al., 2001a). A study performed at the Lawrence Berkeley National Laboratory and then replicated by the U.S. Environmental Protection Agency established that 60 Hz reduced the ability of both melatonin and of tamoxifen to effectively inhibit human breast cancer cells *in vitro* (Blackman et al., 2001; Harland and Liburdy, 1997). Although I have yet to see comparable *in vivo* experiments, I find this research disconcerting, particularly when juxtaposed with the previously mentioned research on women who work night shifts and have

increased rates of breast cancer (Davis et al., 2001b; Schernhammer et al., 2001). While the researchers from the night shift studies speculate that the cause may be increased release of estrogen induced by decreased melatonin, there is also the possibility that the increased incidence of breast cancer is simply related to the role that melatonin plays as an effective free radical scavenger (Reiter, 1994). Furthermore, it is plausible that similar amounts of melatonin are synthesized, but that tissue that is exposed to larger amounts of free radicals from the electromagnetic exposure may be using the circulating melatonin at augmented rates (Reiter, 1998).

Duration of exposure to electromagnetic fields may be a key variable. While it is known that electromagnetic exposure in the 50- to 60-Hz range can suppress melatonin levels, there may be a set, but unknown, length of time before the suppression occurs (Brendel et al., 2000; Rosen et al., 1998). Most of the experiments (that we have found) showing a correlation between exposure to electromagnetic fields and reduced melatonin levels indicate an effect only when they are carried out for weeks and not days (Graham et al., 2000; Grota et al., 1994; Selmaoui and Touitou, 1999). However, contrary to this trend, researchers at the NIH exposed pinealocytes from rodents to low-frequency electromagnetic fields and found an average melatonin suppression of 46% after only 12 hours (Rosen et al., 1998).

In the mid-1990s, Ewa Lindstrom and her colleagues at Umea University in Sweden did a series of experiments on magnetic fields and lymphocytes. In one experiment, she found that cells (called *Jurkat* cells) from a leukemia cell line, subjected to low-frequency magnetic fields, responded in a manner similar to what would occur if the cells had been exposed to antibodies (Lindstrom et al., 1993, 1995a, 1995b). Lindstrom continues to perform research in support of these findings (Lindstrom et al., 2001). She suggests that her original findings may buttress the speculative, but provocative, findings of Liboff and colleagues, who are also doing research on electromagnetic fields and cell membranes.

Liboff claims to have shown that certain resonance frequencies, applied by pulsed magnetic fields, exist for several biologically important ions, including calcium (which is required for proper nerve function, among other things). Liboff calls this phenomenon *ion cyclotron resonance*. The resonance frequency is effective only if the magnetic field is within the Earth's amplitude range (Liboff and McLeod, 1988; Liboff, 1997; Smith et al., 1987). The pulsed magnetic field induces the ion to revolve in a circular path, at right angles to the Earth's magnetic field, as if it were being accelerated in a cyclotron. This research is profoundly controversial because it indicates that electromagnetic energy can cause changes in the membrane gradient. The notion that a calcium ion could pass through a cell's membrane without the interaction of some ligand goes against all that is understood about ion channels. However, it is current knowledge that all known receptors interact with their endogenous ligands through mechanisms that include electromagnetic properties. Ion cyclotron resonance may enhance the interactions between ligands and receptors, including the movement of important ions across cell membranes. We found one researcher who purports to have disproved both Lindstrom and Liboff's findings (Coulton and Barker, 1993). Liboff's research may not be well known and, therefore, few scientists would be trying to replicate it or to determine why Coulton was unable to replicate it.

CONCLUDING THOUGHTS

Let us quickly review the information presented in this chapter. The pineal is the central component to an amazing tract of electromagnetic information, which is dependent on light impingement. Special phototransducing receptors convert light information to electrical signals, which then travel through our biological clock or circadian pacemaker (i.e., the SCN) to set and adjust our inner rhythms. The electrical signals continue their journey, checking in with the hypothalamus, in case there is any input there, traveling down the brainstem, and finally traversing to the pineal. The power of the pineal is in its ability to then interpret and decipher the already decoded environmental input and disseminate it, via a neuroendocrine response, to all of the body systems. As we have reviewed, the pineal affects endocrine, autonomic, hypothalamic, and immune responses. The pineal is our all-purpose, comprehensive regulatory gland. It is primarily inhibitory, but plays the crucial role of facilitating the translation of environmental messages (i.e., energy) into neuroendocrine signals that can be dispersed throughout the body. Ergo, scientifically, I would call the pineal our master gland.

It is my contention that our inner rhythms, which are influenced by environmental light, electricity, and magnetism, are a reflection of, or complement to, the sun-center geophysical signatures of our physical universe. The pineal gland senses magnetic alterations in the environment. The oscillating neurons of the SCN entrain the endocrine and nervous systems according to the cues received by the external environment. This occurs daily, but it also occurs in longer pacemaker rhythms, called *ultradian cycles*, such as puberty or menopause for women. Consequently, there is circadian and ultradian rhythmicity to each of our internal body systems. Ultimately, this interaction allows for something like a harmonic resonance between our internal rhythm (both circadian and ultradian) and the subtle energies, which are also called *spiritual energy* or referred to as *Qi* in the Chinese system of medicine. This harmonic resonance is perpetually present, but it is more accessible to our personal experience when we entrain our body and mind to a subtler energy frequency. It is why music can be so calming to our souls—it restores the endocrine symphony when we are distressed or stressed. The musical harmonics are entrained by the SCN and modulated by the pineal.

The pineal is the cornerstone of the biochemical interface with our environment and with the subtle energy that both supports and transcends our sense perceptions and sustains our body as much as any nourishment we consume (see Chapter 8 for a discussion of subtle energy). While the pineal is the energy transducer that sends hormonal and electrical messages throughout the body, the chakras, as described in Eastern religious and medical systems, are the energy transducers for subtle energy. Chakras, speculatively, are energetic portals that permit a subtler, but profoundly sustaining, energy to enter the body. Chakras, speculatively, open and connect into the ANS, interacting richly with the endocrine system. We will cover this topic in some detail in the final chapter of the book (Chapter 11).

However, for now I would like to deliver the caveat that the seventh chakra, which is located at the crown of the head, is in physiological terms associated with the pineal and the CNS. The seventh chakra would theoretically connect, via the CNS, to the

autonomic nervous system and then to interact richly with the endocrine system. This construct allows for a systemic coherence of our internal and external environments. Hold these thoughts and we will revisit this topic again in the last chapter of the book.

Our understanding of time is based on scientific constructs that bundle up traversing energy in a linear fashion, yet mystics through the ages have made statements to the effect that "all things are one." If we have the courage to alter our belief systems a bit, we can begin to see that all things are part of a tapestry—the body, the mind, the spirit. So perhaps the pineal, as Descartes declared, is indeed the "seat of the soul," because it may well be the interface between our body and our soul—that is, the corridor by which we can experience our spirituality.

Next, we will take a look at the healing modalities that fall into the NIH Category 5 (as described in Chapter 5), which encompasses energy therapies. We will describe how energy-medicine modalities can help us live healthier lives.

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11 Soul Medicine
Crossing the Border

WE ARE ENERGY

In the course of writing this book, the authors discussed the fact that, from a very young age, we both remember asking the question: "Who is God?" We really wanted to know; however, we found the answers to be wholly unsatisfying. We came from different types of Western religious traditions, but in both cases, the information did not satisfy our analytical minds. We wanted to know what God is. What is that energy that ends at death; what is that energy that allows for spontaneous healing; and what is that energy that is referred to as our "higher self"? When the Eastern and Western mystics claim to be "one with all beings," or "one with God," or "one with the universe," what is happening in their bodies and minds? Is there a physiology of spirituality?

Chapter 2 provided an overview of psychoneuroimmunology (PNI) and the interactions of body systems previously thought to be pristinely separate, demonstrating that the field of medicine can no longer refute the inextricable integration of the mind and the body. In Chapter 4, compelling indications of a relaxation system and distinct features of its hormonal cascade were proposed. Now we must ask whether there is enough medical evidence to begin to speculate about the physiological events that occur during experiences that transcend, yet inform, the five senses. These experiences, which traditionally have been relegated to mystics and spirituality, are currently finding their way into medical research and are typically referred to as *subtle energy medicine*.

Subtle energy is the final component to the paradigm of integral physiology—a system of medicine that incorporates not only the body and the mind/emotions, but that also addresses the impact of subtle energy on an individual's overall health. In this chapter, we begin by introducing a theoretical construct of subtle energy, and then we present some compelling research that evaluates physiological responses to experiences that traditionally have been called spiritual or transcendent, but are increasingly referred to as subtle energy. We have chosen a set of thinkers to explain the subtle-energy component of integral physiology, but we firmly believe that four or five other well-chosen individuals would have allowed us to arrive at the same understanding. We encourage the reader to engage intuitively, not just intellectually, while reading this chapter.

THE SCIENCE OF SUBTLE ENERGIES: A THEORY

In his General Theory of Relativity, Albert Einstein gave us the now famous theorem: $E = mc^2$, or energy (E) equals mass (m) times a constant (c), which Einstein designated as the speed of light, squared (c^2). Einstein asserted that the speed of light

TABLE 11.1
Energy Continuum

Slower vibration (matter is more dense) → Faster vibration (matter is less dense)

is an absolute constant that unites time and space in a continuum and, therefore, that time, space, and matter can be compressed or expanded. Einstein demonstrated that time cannot be separated from matter and that all matter is energy.

Energy and mass (i.e., matter) are thought to be different forms of the same basic substance from which all existence is constructed. They are different parts of a spectrum of vibrating molecules. Just as we know that light and electromagnetic energy have a frequency spectrum, similarly all matter has a frequency of oscillation that varies depending upon the density of the matter. The more dense the matter, the slower is the vibration, and theoretically, the more subtle the matter, the higher or faster is the frequency of oscillation (Table 11.1). As energy becomes subtler and the frequency of oscillation increases significantly, the five common senses are no longer able to cognitively experience the "matter." However, this does not mean that such energy does not affect the physical body. In fact, it is our contention that this form of energy informs, but transcends, the five common senses.

Out of necessity, Einstein also developed a theory of antigravity. In order for the predictions of his relativity theory to be accurate and to match what astronomers thought the universe looked like, there had to be antigravity. Einstein called this the "cosmological term." In the 1920s, when it was discovered that the universe was expanding, Einstein called his antigravity theory "my greatest blunder." Yet, scientists have recently shown that there is antigravity. By measuring the changing brightness of supernovas and their distances from Earth, scientists have determined that the forces of antigravity now have exceeded the gravitational forces, causing the expansion of the universe to occur ever more quickly (Lemonick, 2001).

Physicists have generally concurred that matter cannot be moved at a velocity beyond the speed of light. The newly illustrated existence of antigravity reverses this doctrine in principles of physics too complex to include here (see Tiller et al., 2001). Scientist call antigravity, "dark matter" because it is so poorly understood and largely remains a mystery. However, it is known that Einstein's relativity theory accommodates the existence of antigravity and that antigravity is equivalent to nonphysical matter.

The discovery of antigravity dovetails with, and perhaps someday will confirm, the work done by Dr. William Tiller of the Department of Material Science and Engineering at Stanford University, who has postulated a theory of nonphysical matter or subtle energy. His theories are shared here only insofar as they help to convey the subtle energy component of integral physiology. Tiller's writing incorporates evidence of subtle energy, via various principles of physics, to an extent that is beyond the scope of this book. However, if you are inclined to read further in this area, you might want to acquire his text, *Science and Human Transformation* (Tiller, 1997).

Long ago, Tiller postulated that there are various subtle energies arising from magnetic, monopole substance, having an indiscernible form and traveling at a

TABLE 11.2
Properties of Subtle Energy, Physical Energy, and Deltrons

Subtle energy:
Magnetic energy traveling at a velocity greater than the speed of light ($v > c$)

Physical energy:
Electrical energy traveling at a velocity slower than the speed of light ($v < c$)

Deltrons:
Particles capable of interacting between physical and subtle energies ($v = c$)

velocity greater than the speed of light. Furthermore, he determined that subtle energies are part of a continuum of energy. In an analogy of numbers or temperatures that lie above or below zero, subtle energies would be the nonphysical matter that lies below zero. Tiller describes subtle energies as different from those arising from the four accepted fundamental forces (forces commonly known to any physicist) and lacking the features that are accessible to the five common senses. Because subtle energy exists beyond the speed of light, it therefore exists outside of time as we experience it. (Einstein's $E = mc^2$ is used to deduce this.) Our physical world is in the arena of electrical energy, which travels at a velocity slower than or equal to the speed of light (see Table 11.2). Therefore, according to some scientists, matter can be thought of as condensed light.

Tiller asserts that the dividing line between physical and subtle energy is v (velocity) = c (constant), or the point at which velocity reaches the speed of light (Einstein's constant). It would be a hypothetical "zero" point in our analogy of numbers on a thermometer. Tiller explains that "because of the light barrier at v = c, the two systems are designed to stay isolated from each other" (Tiller, 1997). He postulates that any communication between the physical and subtle energies occur via special particles "from a higher dimensional domain than space time," which he has named deltrons (see Figure 11.1). Deltrons can interact with particles whose velocity

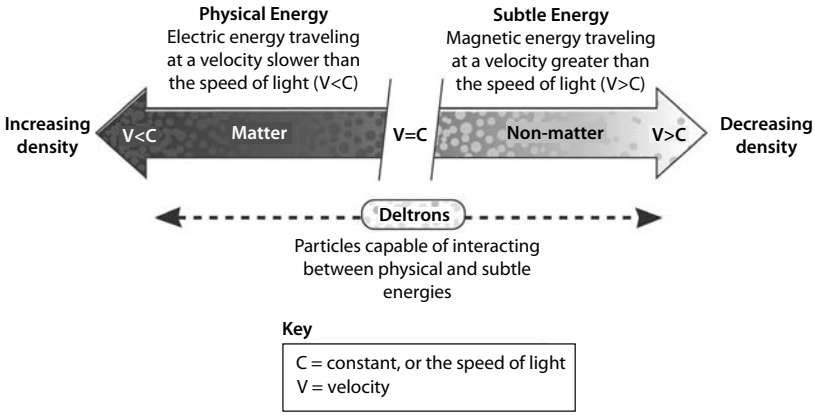

FIGURE 11.1 Deltrons.

is greater or less than the speed of light ($v > c$ or $v < c$), permitting communication between the physical and the subtle types of substance. It is possible for the "light barrier" to be broken, causing what many people would call a spiritual experience. In other words, it is what occurs when humans experience the realm of subtle energy.

Humans are made up of both relatively dense matter as well as subtle matter. We have an innate ability to tap into subtle energy, which historically has been referred to as a "transcendent experience," "intuition," "our higher self," "God," or just "spirituality." Understanding the concept of subtle energy allows us to step well beyond a mechanistic view of physically repairing the body and allows responsible exploration of new modalities for curing disease. Energy fields literally influence cellular growth. Subtle energy is known to assist healing (e.g., see the studies on prayer or therapeutic touch that we reviewed). When the physical body cannot be healed, spiritual or subtle energy also can assist the individual to reach a state of peace, both emotionally and intellectually. There is a synergistic interplay between our subtle and mundane (i.e., physical) energies, which can work to promote optimum health and expand the types of awareness that can be available to us.

Tiller believes that by focusing our "intentionality" (which, for example, occurs during meditation, deep relaxation, or other transcendent states of awareness), we can encounter the field of subtle energy. It is my feeling that we can create a receptive or hostile atmosphere for subtle energy, depending upon the health of our bodies and the soundness of our minds. Self-judgment, for example, can completely close off the vibrational resonance at which we can experience subtle energy. Emotional soundness supports "returning to" and living in the everyday world after an experience of subtle energy. If we can hold the duality of our physical life and our subtle energy experiences, without needing to dismiss or fear them, we potentially can develop both a keener understanding of life as well as obtain our personal optimum health.

THE INTERFACE OF HUMAN PHYSIOLOGY AND SUBTLE ENERGIES

According to Eastern Indian tradition, the body has seven major chakras or energy centers that are conduits for subtle energies. The word *chakra* actually comes from a Sanskrit word meaning *wheel*. Chakras are the openings or pathways by which spiritual or subtle energy is taken into the body and translated into a form of energy that the body can use, literally use, at the cellular level. Just as the pineal gland is the energy transducer for our bodily experience, the chakras are the energy transducers for subtle energies. They convert the subtle energies to a resonance that the body can use, which means that the subtle energy band is transduced into hormones and neurotransmitters. Each chakra is correlated to actual physiological structures, such as endocrine glands and major nerve areas, resulting in a complex network of energy that courses through the body. This is the energy that is referred to in Chinese medicine as *Qi* and is loosely translated as "vital energy" or "life force." Chakras, speculatively, open and connect into the autonomic nervous system (ANS), interacting richly with the endocrine system.

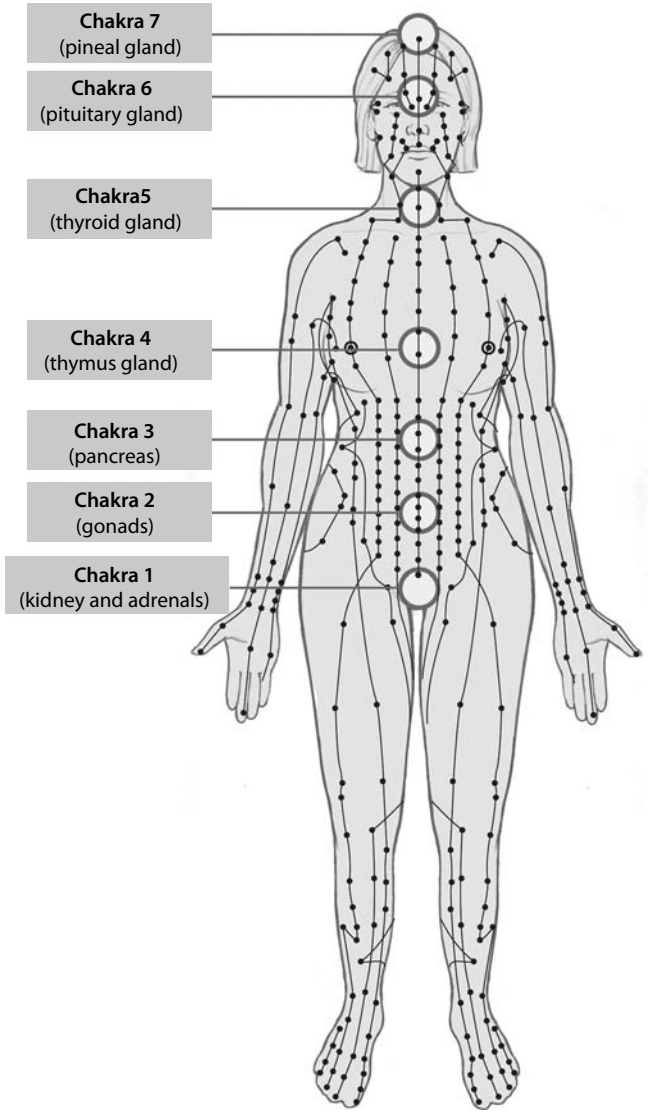

FIGURE 11.2 Chakras and acupuncture meridians.

Although different belief systems have slight variations, the seven chakras generally are conceptualized as follows (see Figure 11.2):

1. The first chakra, also called the root chakra, is located near the coccyx or sacral plexus. It is associated with the kidneys and the adrenal glands.
2. The second chakra is located just below the umbilicus at the pelvic plexus. It is associated with the reproductive system.

3. The third chakra is located in the upper part of the abdomen at the solar plexus. It is associated with the pancreas and the digestive system.
4. The fourth chakra is located in the middle of the sternum, near the heart. It is also called the heart chakra. It is associated with the thymus and the circulatory system.
5. The fifth chakra is located in the throat just below the Adam's apple. It is associated with the thyroid and the respiratory system.
6. The sixth chakra is located above the bridge of the nose. As discussed in the chapter on the pineal gland, it is also called the third eye. It is associated with the pituitary and the ANS.
7. The seventh chakra is located at the crown of the head. It is associated with the pineal and the central nervous system (CNS).

The "principal meridians" are pathways within the body along which Qi flows. They intersect both with the chakras and with acupuncture points. Qi is subtle energy, the invisible but wholesome energy that flows through the meridians, nourishing both the body and the mind.

Speculatively, in Tiller's terms, Qi is the deltron interface, an energy interchange between $v > c$ and $v < c$. It is nonmatter; indeed, it is subtle energy interacting with matter. According to the Chinese system of medicine, any blockage in the flow of Qi will result in dysfunction, physical or emotional, to the area of the body that is associated with the part of the body that is blocked.

According to Chinese medicine, there are actually various types of Qi. For example, *wei Qi* is a coarse energy that circulates on the outside of the body and is protective during the awakened state. It is the energetic equivalent of the immune system. It is part of the body's inner clock and circulation of energy. If an emotional or physical trauma occurs, the wei Qi surrounds the corresponding organ and reverberates in that area while we sleep. It is my feeling that any trauma is stored in the fascia (connective tissues) and in the limbic system during those sleeping hours. The limbic system encodes the various memories, including repressed memories. Through modalities, such as those described in Chapters 5 and 6, the repressed memories can be released from the fascia as well as from the limbic system. They can be released through bodywork, but the optimal method is through work both on the body and the mind.

Another type of Qi is called *yuan Qi*, which is said to represent the energy we brought with us into this life, including ancestral energy and the energy of the soul. In systems that possess a belief in reincarnation, it represents the essence of who we were, are, and that which we will bring into our next life. Long Qi is derived from the food we eat and the air we breathe, that is, from our environmental surroundings. We also take in this type of Qi while we sleep and during sexual orgasm. For certain people, their only interaction with subtle energy will occur from elements taken from the environment, such as dreams. In other words, even without a conscious effort, humans are nurtured by subtle energy. Yuan Qi is housed in deeper meridians, called the extraordinary or curious meridians. When yuan Qi flows through the principal meridians, it is an indication that the chakras have opened to allow subtle energy to permeate the body.

As one takes the requisite step of clearing repressed or known emotional issues through work on the body and the mind, a shift occurs by which the principal meridians

become infused with yuan Qi, a type of subtle energy. This event causes the chakras to open, allowing yet more yuan Qi to enter the body and to increase our conscious awareness of experiencing subtle energy, which is manifested as increased mental clarity, heightened creativity, or, perhaps, emotional calmness. It is my contention that the greater the development of personal serenity or equanimity, the greater is the infusion of subtle energy from the curious meridians into the principal meridians. Curiously, there is also a striking correlation between the increased amount of energy attributed to a chakra (as represented in drawings by the number of lotus petals assigned to it, moving from the root or lowest chakra to the crown or highest chakra) and the energetic output of the hormone for the gland designated to that chakra.

IS THERE A PHYSIOLOGY OF SPIRITUALITY?

There is no question in my mind that we can teach ourselves to perceive subtle energy. It is my experience (and apparently that of Tiller as well) that the heart chakra is the site at which humans most easily open to subtle energy, and human feelings of love and compassion are most similar to the vibration of subtle energy. But the spectrum of emotions that we call "love" can include a wide variety of emotions, including less wholesome aspects that are predominantly involved with cravings. These are not vibrations that are conducive to connecting with subtle energy.

> For those who are curious or so inclined, a simple exercise may offer you the opportunity to experience subtle energy. Start by bringing your attention to the heart chakra and letting yourself experience sensations of openness, as if your heart is breathing (as in the HeartMath technique; see the modalities section of Chapter 5). Next, let yourself experience deep feelings of appreciation, almost like love but deep appreciation, such as appreciation for the beauty of the magnolia or the trout lily in springtime. Let your heart "breathe" this sense of appreciation. It is possible that you will have an experience of subtle energy of which you are consciously aware.

The Buddha, Jesus, Mohammad, Abraham, Confucius, and other spiritual leaders through the ages have left us with stories about the knowledge they gained during prayer or meditation. These stories, theoretically, are insights gained during their personal encounters with subtle energy and have become the cornerstones of their respective religions. The stories often incorporate a benevolent or loving "God," reflecting the nature of the subtle energy that they had experienced. Stories are used to attempt to express experiences that are not particularly conducive to being verbalized. Analogously, think how difficult it can be to convey the contents of a dream. Their stories are the anthropomorphic expression of the experience of subtle energy via the heart chakra.

RESEARCH SUPPORTING A PHYSIOLOGY OF SPIRITUALITY

In the chapter on relaxation (Chapter 4), biochemical windows that may facilitate experiences of deep relaxation were identified based on current research. Similarly, there are medical studies that begin to identify discrete biochemical and physiological

changes that occur when an individual experiences subtle energy, that is when an individual has an experience that transcends, yet informs, the five senses.

Brain Scans of Spiritual Experiences

Two physicians, friends, and research partners, Dr. Andrew Newberg and Dr. Eugene D'Aquili, performed intriguing research in which they captured brain images of individuals in the midst of transcendent spiritual experiences. Their subjects were long-time Tibetan meditators and Franciscan nuns. Before the experiment, the subjects reported having broadly similar experiences during meditation or prayer. These included the impression of being on a deep, inner journey; a feeling of unity with God or with all beings; a sense of the self as limitless or of no self; and experiences of space and time as limitless. Such mystical experiences of the dissolution of the self are common to religions worldwide.

Newberg and D'Aquili's subjects were asked to meditate or pray until they felt that they were at a moment of peak experience. At that point, their instructions were to tug on a string to alert the researchers to begin injecting a small amount of radioactive material via an intravenous line. The line traveled into the subject's room, where it was hooked up to a vein in the subject's arm. Moments later, the meditator was given a brain scan with a camera that detects radioactive emissions. The radioactive isotope, or tracer, emits a single photon of light, which can be photographed by a SPECT (single photon emission computed tomography) camera and converted into a three-dimensional image of the brain. This type of isotope follows the path of the blood to various areas of the brain. The technique provides an image of blood flow patterns and, thus, a picture of how the brain is functioning; it does not provide a picture of brain structures. This research created the first pictures of what the brain looks like during a spiritual experience (D'Aquili and Newberg, 1999; Newberg et al., 2001).

Simplifying the researchers' findings, it is apparent that two key events occur during a spiritual experience. First, the imaging showed that the prefrontal cortex, which they dub the attention association area (AAA), has increased activity. Among various other activities, the AAA is the part of the brain that processes emotions and allows us to be goal-oriented, to form intentions, and to concentrate. Zen meditators show pronounced electrical activity in this region during meditation, as measured by electroencephalogram (EEG). So, what this tells us, which Eastern meditators have known for centuries, is that the mind must be concentrated, focused, and quiet to allow a spiritual experience to occur.

Second, the imaging showed quiescence in an area of the brain (corresponding to posterior superior parietal lobe) that orients a person as a three-dimensional being in physical space and, thus, is typically extremely active. The researchers call this area the orientation association area (OAA). It integrates visual, auditory, and somaesthetic (i.e., body position and touch) information. It is actually the left side of this area that has the least activity during meditation. The left portion of the OAA gives us the sense of ourselves as a limited, physically separate entity: I am here; you are there. It is the job of the OAA "to sort out the 'you' from the infinite 'not you' that makes up the rest of the universe" (Newberg et al., 2001). Neural input to this area is

limited or blocked during a deep spiritual experience. The OAA no longer receives the neural information that distinguishes self from other and, according to Newburg, "would have no choice but to perceive that the self as endless and intimately interwoven with everyone and everything" (Newberg et al., 2001). This reflects the descriptions of Christian mystics, Buddhist meditators, and others who describe experiences of feeling one with an absolute reality and a connectedness to all.

The researchers found a strong inverse association between increased activity in the AAA and decreased activity in the OAA. In other words, the more the meditator is able to concentrate, the greater is the neural blockage to the OAA, and, consequently, the stronger is the experience of unity or no self. Newberg and D'Aquili refer to this as a "unitary continuum" that "links the most profound experiences of the mystics with the smaller transcendent moments most of us experience" (Newberg et al., 2001). Their language is reminiscent of Tiller's description of subtle energy being part of a continuum.

In addition, the researchers identified areas of the brain concerned with language and visual associations that are important to spiritual experiences. An area of the brain that they call the verbal conceptual association area is positioned at the bottom of the parietal lobe at a junction with the temporal and occipital lobes—an area of highly integrated verbal function that permits the conceptualization and expression of religious experience. The visual association area, which is located toward the bottom of the temporal lobe, but receives information from the occipital lobes, facilitates spontaneous visions. It is the area of most highly integrated visual function. Because the visual association area has exhaustive interconnections with the limbic system, meditation can correlate to experiences of emotion and memory (D'Aquili and Newburg, 1999).

Newberg and D'Aquili deduce that our biology compels us to seek an answer to the unanswerable question of what happens when we die. They write that the spiritual urge is a "biologically driven need to make sense of things through the cognitive analysis of reality," which they call the "cognitive imperative." Although mystics and others who have profound spiritual experiences have historically been ridiculed as being a little addled, if not suffering from a mental illness, Newberg and D'Aquili point to research showing that these individuals actually are psychologically more stable than others. Other researchers have found a correlation to well-being, greater purpose, and optimism among individuals having paranormal experiences (Kennedy et al., 1994; Kennedy and Kanthamani, 1995). The SPECT scans of transcendent spiritual experiences confirm that these individuals are coherently describing what they have experienced. Furthermore, the researchers claimed to have established that mystical experiences are "biologically observable" and thus "scientifically real." Newberg (D'Aquili died before the book was written) courageously pushes the issue and asks the question: "Are these unitary experiences a result of neurological function—which would reduce mystical experience to a flurry of neural blips and flashes—or are they genuine experiences that the brain is able to perceive?"

Brain Scans of Emotional Experiences

Another neuroscientist, Dr. Antonio Damasio, has performed some research that is much like Newberg's, except that he uses positron emission tomography (PET)

instead of SPECT and emotions instead of spiritual experiences. Damasio found that the induction or recall of experiences of sadness, happiness, anger, or fear engaged the somatosensory cortices and the upper brainstem nuclei that are involved in the regulation of these internal states. Furthermore, each emotion had a discrete neural mapping pattern. For instance, sadness consistently constructs a pattern or map that reveals activation of the ventromedial prefrontal cortex, hypothalamus, and brainstem. This research strongly supports the idea that the subjective process of feeling emotions is partly grounded (neurotransmitters and hormones would also influence such events) in dynamic neural maps (Damasio, 1999, 2000). Damasio asserts that rational thinking must go hand-in-hand with feelings and emotions (i.e., the somatic marker hypothesis) and the insula plays a key role in this pattern. In the next section, we will see that the insula is central to the experience of empathy. If Damasio's research is widely accepted as an objective mapping of a specific emotion, then is there not a persuasive and logical reason to accept Newberg's work as a reliable mapping of a spiritual experience?

Neuroplasticity and the Biology of Meditation

In addition to Newberg and D'Aquili's work, there is ongoing research out of the laboratory of Richard J. Davidson, in Wisconsin, that continues to provide insight into the processes that occur during meditation and, in particular, how meditation impacts the plasticity of the brain. Brain plasticity or neuroplasticity concerns the ability of the brain to reorganize and change based on new material that an individual learns, memorizes, or experiences. In Chapter 4, we discussed Jon Kabat-Zinn and the fact that he took a Buddhist mindfulness-based meditation practice (i.e., a keen moment-to-moment awareness, developed by observing thoughts and bodily sensations) and secularized it, providing meditation training for medical patients. In Buddhist meditation, the practitioner first learns to concentrate the mind, then mindfulness-based practice, and finally a "pure compassion" meditation (a meditation that focuses on loving kindness toward all people, not just on one's own family and friends). Davidson and colleagues have shown that meditation induces beneficial long-term changes, or neuroplasticity, in regard to attention, emotion, and empathy. Thus, it is now known that we can train our minds to have more compassion and to acquire helpful, positive qualities via mediation, just as we can train ourselves to learn any other skill.

As demonstrated on EEG profiles, long-term (15 to 40 years), Buddhist meditators had a higher rate of fast (gamma waves: 25 to 42 Hz) versus slow (alpha waves: 8 to 12 Hz) oscillations at baseline than controls who had undergone a one-week meditation training course (Lutz et al., 2004). This finding alone indicates that the baseline, resting state of the brains of mediators are altered by long-term practice. Further, the experienced meditators not only demonstrated longer periods (seconds versus a half second or less for controls) of emitting significantly higher amplitude gamma waves, but also a greater magnitude of change from slower rhythms to gamma during and after compassion meditation, compared with controls (Davidson, 2005; Lutz et al., 2004).

In addition, in the same study, the adept meditators showed "greater synchrony of the gamma signals between distant regions of the cortex" (Davidson, 2005; Lutz

et al., 2004). As we learned in Chapter 3, synaptic plasticity stimulates synchronous oscillatory activity in the subiculum—in that case, during theta (4 to 7 Hz), not gamma, oscillations. Similarly, regular meditation induces neural synchronicity that trains the mind in a distinct mode of operation that, over time, influences the spectral distribution of a baseline EEG; in other words, synaptic plasticity again stimulates synchronous oscillatory activity, which informs behavior. The investigators suggest that their data indicate that "massive distributed neural assemblies are synchronized with a high temporal precision in the fast frequencies during this [meditative] state," which may reflect the moment-to-moment awareness, postulated by Buddhist and other meditation practitioners, and may indicate a discrete quality of consciousness (Lutz et al., 2004).

According to Davidson, the gamma frequency is "a sign of activation in the brain," which not only occurs during pure compassion meditation, but also is briefly increased during periods when perception is clarified, such as the moment of transition when a picture first appears to be a vase and then a face (Davidson, 2005). Furthermore, gamma frequencies take place during times that require neural synchrony, including attention, working-memory, learning, or conscious perception (Lutz et al., 2004). Davidson and colleagues discovered that during compassion meditation, brain activity of experienced meditators was primarily in the gamma range (Davidson, 2005; Lutz et al., 2004). This finding is striking as gamma waves produce much faster rhythms (25 to 42 Hz) than the theta waves (4 to 7 Hz) found for other types of meditation. Although the study focused on a meditation of empathy or compassion, these adept practitioners also would have spent years learning to concentrate the mind and focus their attention as well as in practicing the mindfulness-based technique of moment-by-moment awareness, which is purported to develop a balanced mind, thus increasing emotional control. The concentration and mindfulness techniques tend to exhibit an oscillatory activity that is slower; as more meditation is practiced, including compassionate/empathetic techniques, higher amplitude gamma oscillations and increased phase synchronicity is seen, especially at electrodes placed in the medial frontoparietal area.

The brain areas involved in an empathetic response include the limbic region and anterior cingulated cortex, but, perhaps most strongly, in the insular cortex, which plays a key role in mapping physical responses to emotion, such as heart rate. With mediation training, a human being can learn to have the same response to an event as if it actually had happened to oneself. Using functional magnetic resonance imaging (*f*MRI), a heightened response to emotional sounds (positive: a laughing baby; negative: a distressed person) versus a neutral vocalization (restaurant noise) was observed in both controls and experts, during meditation versus during rest (Lutz et al., 2008a). However, the adept meditators showed a larger response than the novices to emotional sounds, particularly to negative vocalizations. For the adept meditators, there was a right-sided bias activation response in the limbic system (which includes the insula) and in areas associated with mental processes that involve concern for others, compared with the novices, who had virtually no single-side activation preference to the sounds during meditation. This finding is very interesting because (as discussed in Chapter 1), left prefrontal cortex activation indicates optimistic thought patterns. So, while the adept meditators were generating compassion, the side of the

cortex associated with pessimistic thought patterns was activated. The investigators demonstration that cultivating compassion/empathy enhances the response in corresponding brain areas, particularly the insula, also correlated to greater cortical thickness in regularly practicing meditators than controls. Higher amplitude activation in the insular and anterior cingulate cortices correlated to reports of perceived intensity of the meditative state; in other words, we know when we feel compassion. But, if meditation is known to balance the mind, why did the expert meditators have stronger responses than novices?

Another study out of Davidson's lab may answer this question. Using a concentration meditation practice (typically focusing on the breath, but this study also used a dot on a screen) and *f*MRI scans, the investigators found that adept meditators with an average of 19,000 hours of practice had more activation in areas of the brain related to concentration than novices did (not a surprise). However, curiously, long-term meditators with an average of 44,000 hours of practice had *less* activation than the meditators who had an average of 19,000 hours of practice (Brefczynski-Lewis et al., 2007). Brain regions used to generate and sustain meditation as well as an evaluation of distracting sounds, used to assess distractibility, were assessed by *f*MRI brain scans. The very long-term meditators had less brain activation in regions related to emotion and more activation in areas known to be correlated to both attention and inhibition as well as in regions related to monitoring, including the anterior insula. Concentration meditation initially requires a lot of effort to focus the mind, with distracting thoughts constantly arising. As the practice continues over years, the meditator becomes more easily able to enter "a state of decreased mental effort but alert focus" (Brefczynski-Lewis et al., 2007).

So, it appears that very long-term meditators are able to enter a state of deep concentration with little effort, thus, it makes sense that they would have a relatively small response in brain regions corresponding to attention, which once again suggests that plasticity in this regard likely results from long-term practice. The investigators stated that the longest practicing meditators use fewer mental resources "without any compromise in performance," and reasoned that the effect might stem from "fewer cognitive processes competing for resources" (Brefczynski-Lewis et al., 2007). The practical application, speculatively, is that the increased efficiency in processing mental content allows long-term meditators to selectively inhibit cognitive processes and to respond to external events with a balanced mind. In another study, adept meditators, indeed, showed less amygdala (the fear center) activation than novices during concentration meditation (Lutz et al., 2008b). Thus, concentration meditation is a trainable skill that can significantly decrease emotionally reactive behavior by increasing the individual's ability to focus (Lutz et al., 2008b). Theoretically, this skill would permit the individual to have equanimity in the face of life's stresses, which becomes more meaningful in light of studies showing that activity originating in the insular cortex and amygdala is "strongly predictive of a discharge of sympathetic activity in the heart—that we can measure in very precise ways" (Davidson, 2005). Individuals with a higher change in MRI activation in the prefrontal and insula cortices induced by an aversive emotion (i.e., the anxiety of anticipating being shocked) also had a larger, nearly simultaneous magnitude of

cardiac contractility (Dalton et al., 2005). Meditation not only can make us more focused and aware, it can impact our physical health as well. Thus, while Newberg and D'Aquili explain how humans are hard wired for spiritual experiences, Davidson and colleagues demonstrate very practical applications.

N,N-Dimethyltryptamine (DMT) Revisited

DMT, as mentioned in Chapter 4 on the relaxation system, is an endogenous molecule with hallucinogenic properties (Strassman, 2001). Recall Rick Strassman's research describing how the monoamine oxidases (MAOs) enzymes quickly break down DMT and prevent its hallucinogenic effects. Strassman injected DMT into volunteers (to bypass the MAOs), which resulted in their having classic stress responses and almost no meaningful spiritual insights. Although Strassman remained convinced that DMT was "the spiritual molecule," he saw that it had no therapeutic value.

Strassman reasoned that the pineal gland is the endogenous source of DMT. It does seem plausible that there could be a synergistic relationship in which melatonin reaches a threshold that triggers the synthesis of DMT. It has already been established that melatonin is secreted during meditation. Could it be that DMT is released during deeper states of meditation, such as those described by Newberg's Tibetan meditators and Christian nuns? Could it also be that DMT is the molecule that is released when an individual's concentration (and increased blood flow to AAA) intensifies enough to switch off the area of the brain that orients us to space and time (i.e., the OAA)? Yes, I think so. Endogenous DMT, seemingly, is the first hormone identified as belonging to the subtle energy system.

In Chapter 4 on the relaxation system, we talked about β-carbolines, which are synthesized in the pineal. They increase melatonin production and inhibit MAOs from breaking down DMT (recall that β-carbolines keep ayahuasca, the South American drink, psychoactive after ingestion). The β-carbolines probably also contribute to keeping our bodies from hallucinogenic-type experiences. Speculatively, β-carbolines also may be the chemical, and ultimately the energetic, gatekeepers to the barrier between the matter and nonmatter realms of which Tiller writes.

INTEGRAL PHYSIOLOGY: INTEGRATION OF THE BODY, MIND/EMOTIONS, AND SPIRIT

In developing the theory of integral physiology, we have often utilized the image of the Rosetta Stone. Deciphering the Rosetta Stone of ancient Egypt unlocked enormous knowledge. Each part of the stone revealed a portion of the information crucial to deciphering the whole. Analogously, integral physiology incorporates the "language" of physiology, of the mind and emotions, and of subtle energy—the various sides to our stone. Interactions between the body and the mind/emotions are now a well-established fact of medical research. Integral physiology takes the bold step beyond the so-called body–mind connection to recognize the importance of experiences traditionally called intuitive or spiritual and to begin to verify their impact on both the body and the mind/emotions. In fact, there is now evidence that our bodies

not only are hard wired, but also are chemically designed, to permit interactions with subtle energy.

The manner in which the human body functions is more complicated and extensive than scientists have previously identified. Deciphering the Rosetta Stone of integral physiology may require shattering beliefs as we have held them, only to bring us back to the essence of those beliefs that we held most dear. Perhaps, in this book, you have come to understand that, reduced to a common denominator, everything and everyone arises from energy of one sort or another. Subtle energy can explain and be incorporated into any belief system—from scientific to religious. Ultimately, it is a language of the heart embedded in the stories that spiritual leaders, mystics, philosophers, scholars, physicians, and others have left us.

My silence, like an expanding sphere, spreads everywhere.… My silence spreads like a wildfire of bliss. The dark thickets of sorrow and the tall oaks of pride are all burning up. My silence, like the ether, passes through everything, carrying the songs of earth.

Swami Yogananda

Small is the number of them that see with their own eyes and feel with their own hearts.

Albert Einstein

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