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An Introduction to Scientific Integrative Medicine

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The value of a man is not measured by the truth he possesses, but rather by his sincere effort to discover truth . . . even though this search be fraught with constant and unremitting erring.

G. E. Lessing, 1729–1781

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Preface

This book tells a life story, but it isn't a biography. It paints a family portrait, but not of a human family. Instead, this book depicts the world's most famous hormone, adrenaline, and its chemical family, the catecholamines (pronounced cat-a-COLA-means, or, if you are British, cat-a-coal-AY-means). They are part of you. They have kept you alive and are keeping you alive now as you read this, just as they sustained your ancestors from the beginning of mammalian time. Through them I hope to teach you a bit about the "wisdom of the body," as the great American physiologist, Walter B. Cannon, titled his classic book about seventy-five years ago.

I use the term *life story* quite deliberately here. Adrenaline exemplifies a type of chemical called *biogenic*. The word *biogenic* has a double meaning. Biochemists use it to signify that living things make these chemicals. Another meaning—and a main message of this book—is that higher organisms depend crucially on these chemicals for life, because catecholamines enable regulation of the body's "inner world" by the brain.

The year 2001 marked the centennial of adrenaline's discovery. Adrenaline was first purified, its structure was deduced, and attempts to measure it began in the early twentieth century. Indeed, adrenaline was the first hormone ever to be identified and produced in a laboratory. During the decades that followed, adrenaline acquired a unique mystique and folklore, which, for reasons that were largely technical, outpaced its science. Injected as a drug, adrenaline potently produces obvious effects. The skin turns pale, the heart pounds, the blood pressure rises, and the individual feels energized. Because of this potency, however, the plasma of healthy humans at rest contains remarkably low levels of adrenaline—a few millionths of a millionth of a gram per milliliter—measurable only during the past thirty years or so, since the introduction of sufficiently sensitive, specific assay methods. Inferences from the indirect physiological evidence of the early

twentieth century led to speculative notions, then to legends, and then to pulp myths.

The technical problem of actually measuring levels of adrenaline directly in the bloodstream, rather than indirectly via adrenaline's effects, had consequences beyond obtaining scientific understanding about this particular hormone. The coinage of science is discovery, and novelty makes for easy sales. After the measurement of adrenaline levels posed a seemingly insurmountable challenge, biomedical researchers turned to other, newly discovered compounds in a succession extending until the present—insulin, adrenocortical steroids, serotonin, vasopressin, the renin-angiotensin-aldosterone system, hypothalamic releasing factors, prostaglandins, kinins, neurotrophic factors, atriopeptins, endothelins, nitric oxide, leptin, orexins, aquaporins, and an imposing, expanding array of cytokines.

In doing so, researchers followed a long tradition of studying such compounds one at a time. Dwelling on the workings of single systems, using single effector chemicals, is always easier and cheaper than focusing on interactions among multiple systems that use different effector chemicals. The emphasis on single systems in medical science comes from the belief that one best acquires knowledge by dissecting a problem into its component parts; reassembling the parts presumably would solve the problem. This approach is called *reductionism*. The technical difficulty in measuring adrenaline levels, coupled with the reductionist tradition in medical science, retarded development of integrative approaches that have only recently begun to attract bioscientists.

Scientific integrative medicine is not a discipline, a group of disorders, or a method of treatment but an approach, a way of thinking. Scientific integrative medicine uses *systems* concepts to explain disease processes and develop strategies to treat, prevent, or palliate them. It emphasizes disorders of the multiple interacting systems that regulate the body's inner world. Scientific integrative medicine asks researchers and clinicians to consider more than one system at a time, as assessed by measuring levels of more than one chemical effector at a time. One of those chemical effectors—but a very important one—is adrenaline.

For more than a century, from the discovery of adrenaline as the active principle of the adrenal gland, to the identification of norepinephrine, adrenaline's chemical father, as the neurotransmitter of the sympathetic nervous system, to the elucidation of the role of dopamine, adrenaline's chem-

ical grandfather, as a neurotransmitter in the brain, research based on the adrenaline family has proven remarkably consistently fruitful and led to many Nobel Prizes. I believe that the evolution of scientific integrative medicine will depend on even more refined understanding of adrenaline's family and its interactions with other families of chemical effectors in the systems that the brain uses to regulate the inner world of the body.

Everyone Knows about Adrenaline—Why a Book about It?

Everyone knows legends about adrenaline. Few know the facts. For a century researchers and laypeople alike have viewed adrenaline as the "fight or flight" hormone, important in primitive emergencies but not in everyday life. In fact, adrenaline and its family are essential not only in emergencies but also for the continual, rapid adjustments required to tolerate even mundane stresses, such as simply standing up or walking out into the chilly outdoors. In fact, changes in activities of internal body systems, mediated by members of the adrenaline family, accompany virtually every motivated behavior and every experienced emotion. Moreover, externally observable effects of the same chemicals serve highly important roles in instinctive communication, a fact recognized since antiquity, as you will learn.

Writers in psychology and psychosomatic medicine have taught that the faster pace of human cultural than of physical evolution has led to inappropriate expression of built-in, instinctive, primordial, unconscious, involuntary behaviors—that is, behaviors mediated by the "automatic" nervous system—and that this inappropriate expression causes or contributes to chronic diseases. People therefore have come to think of chronic stress and distress, by way of high adrenaline levels, as causes or contributors to the development of medical problems such as high blood pressure and coronary artery disease. In fact, researchers still don't know for sure about the correctness of this belief.

People think that, during exercise, an adrenaline "surge" increases the force and rate of the heartbeat and raises the blood pressure. Instead, these changes depend mainly on release of norepinephrine from nerves in the heart and blood vessel walls. As you will learn, this seemingly trivial misidentification probably cost a Nobel Prize for one of the most prominent physiologists of the twentieth century—the venerable Walter B. Cannon.

People think there is "good stress" and "bad stress" and that "too much"

stress harms health. For this sort of notion, the issue is not truth but value. As you will learn, the notion of "good stress" and "bad stress" has little value as a scientific idea because of circular definitions and untestability.

The popular notion, that adrenaline plays a key role in the responses to and experience of distress, probably *is* correct. In the setting of an independent disease, such as coronary artery disease, adrenaline release can even kill; however, most researchers who study mechanisms by which stressors exert their effects have focused on a different system, the system involving steroids produced in the outer layer of the adrenal gland. Adrenaline, produced in the core of the adrenal gland, has been relatively ignored.

Adrenaline is important scientifically, as demonstrated by numerous Nobel Prizes for discoveries based on it and the other members of its chemical family. It is important medically because of its many contributions to manifestations of disease, as a basis for monitoring responses of the body to treatments, and in establishing a prognosis. It is important culturally because of its ubiquity in politics, sports, and entertainment. In this book you will read about why a former Attorney General with Parkinson disease has a tendency to faint; why young astronauts in excellent physical shape can not stand up when re-exposed to earth's gravity, why professional football players can collapse and die of heat shock during summer training camp, and why baseball players spit so much. Adrenaline is important legally because of worker's compensation claims for alleged job stress–induced, adrenaline-mediated heart attacks, the medical risk of standing trial, alleged effects of toxic exposures—even the meaning and significance of the "plaintive wail" of Nicole Brown Simpson's pet Akita in the timing of her murder. Adrenaline is important philosophically because it operates at exactly the border between the mind and body, the voluntary and involuntary, the creature and the human. Adrenaline is important aesthetically because artists and playwrights have always relied on its effects to depict emotional states that are communicated instinctively and that words cannot hide. It is even important religiously for correct understanding of biblical narrative about Jacob's "faint," Miriam's "leprosy," the only biblical example of trial by ordeal, and the nose as the organ of rage.

Is This Book for You?

I wrote this book to supplement academic coursework in several fields—psychology, philosophy, biblical studies, physiology, biochemistry, the history

of medicine, psychiatry, endocrinology, cardiology, and complementary and alternative medicine. You might be a college student seeking a bachelor of arts degree, a graduate student in natural sciences, a medical student, a practicing physician, or an academician. Taking into account the obviously diverse abilities to digest the medical scientific information, I have included a large glossary. The figures and figure legends provide a kind of parallel text simpler than the main text. The book teaches by analogy, example, and anecdote, with the intention of drawing you, by sheer fascination, into the world that populates you.

I wrote this book also for patients and their families, caretakers, and support groups seeking a source of information about dysautonomias. Dysautonomias are conditions in which altered function of the "automatic nervous system" adversely affects health. Dysautonomias are ubiquitous in modern society, ranging from occasional annoying sensations in otherwise healthy people to progressive, debilitating, fatal diseases. They occur in all age groups. Some are established diseases, with changes in body tissues that a pathologist can see. Some are functional disorders, with chemical or biological changes that a clinical investigator can measure. Some are mysterious and controversial because of a lack of accepted objective tests and treatments. All involve multiple body functions, multiple internal effector systems, and multiple disciplines in medicine. These features render dysautonomias an ideal entrée to scientific integrative medicine, which I believe will be at the forefront of medical thought and practice in the postgenome era.

I dedicate this book to my family—particularly my partner in life, Minka—for their support and understanding in allowing me the time to write this book; to my colleagues and friends at the National Institutes of Health (NIH) for their devotion to our research mission and to me; and to the many patients who have put their trust in me and provided sparkles of insight about adrenaline and the body's automatic systems in regulation and dysregulation of the inner world. Patients serve as a unique scientific resource. They report what is wrong; we have to make sense of what they teach. They tell us the truth; we have to avoid dismissiveness as a defense of our own ignorance. They seek our help; we have to commiserate with their unintended, unwanted metamorphosis from independent, private, integrated personhood to dependent, exposed, disintegrated patienthood.

I thank Mr. Herbert Abramowitz and Dr. Melvin Plotinsky for reading the book in its entirety and conveying their points of view and their always

constructive suggestions for improvement. Finally, I thank my mentor and colleague, Dr. Irwin J. Kopin, an example of intellectual rigor, productivity, perspective, and integrity, an inspiration throughout my career at the NIH. Irv, you paid a high compliment to me as a scientist when you told me, "You ask good questions."

Adrenaline and the Inner World

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1 The Inner World

Inside you is an inner world, full of comings and goings and the beautiful paradox of seeming constancy despite continuous change. We are born, we develop and mature, we reproduce, we live out our lives, we get old, we get sick, and we die, yet for most of our existence we believe in our essential sameness day to day.

On average, human beings live longer than any other animals have ever lived. For most of this amazing longevity, we rarely notice the internal workings that constitute the political affairs of the inner world. Cells of the body "turn over"—you literally replace yourself over time—yet things inside seem to stay in a steady state so well, for so long. Body temperature, blood levels of key fuels, concentrations of red blood cells in the bloodstream, amounts of electrolytes, the rate of the heartbeat, blood flows to organs, and many more "variables" normally don't vary much. Even mood and personality remain about the same, characterizing us to others and to ourselves. When levels of these variables do change and you feel sick, you don't feel "like yourself."

These steady states do not happen by chance. In higher organisms, they depend on complex coordination by the brain. This chapter introduces a way of thinking about how the brain regulates the inner world, to maintain apparent constancy despite continual change. In a single word, the brain does so via *systems*. Just as the brain receives information from sense organs about and determines our interactions with the outside world, the brain also receives information from internal sensors and acts on that information to regulate the inner world. For most of our lives we can cling to our belief in sameness only because the brain tracks many monitored variables, by way of internal sensory information, and acts on this information to maintain levels of monitored variables at controlled, steady values by modulating numerous effectors that work simultaneously, in parallel.

A remarkable array of effectors, working largely unconsciously and auto-

matically, maintain the stability of the inner world. For these effectors to work often depends on a small family of messenger chemicals, the catecholamines (pronounced cat-a-COLA-means). The most famous member of this chemical family is adrenaline. It is so famous that in this book I refer to the catecholamines as the adrenaline family. Keep in mind, though, that, as in actual families that achieve fame, the one that gives the family its name is not necessarily the one the family relies on to run the business. A major theme of this book is that the brain uses many effectors. You will have to learn about several to begin to acquire the knowledge necessary for thinking of diseases by using a systems approach.

"Systems biology" has gained cachet recently in academic medicine. Systems biology has been defined variously as an analytic approach to relationships of elements in a biological system to understand emergent properties of that system; the exploration of cell functions at the molecular level; the analysis of networks and interactions among genes, proteins, and other cellular chemicals; or the mathematical modeling of cellular control mechanisms to explain the functions of living things.

Scientific integrative medicine builds on systems biology, but it is also distinct in several ways. (1) Scientific integrative medicine recognizes that in higher organisms, including us humans, the brain dominates regulation of the inner world. The brain regulates the many internal monitored variables of the body in parallel—analogous to a computer's multitasking. (2) The brain has plasticity, which enables modifications in the step-by-step instructions for cellular, tissue, organ, and systemic processes—the algorithms of life. According to the concept of allostasis, about which you will learn later in this chapter, set points and other elements of these algorithms vary, depending on recollections, sensations, and anticipations by the brain. (3) Scientific integrative medicine is *medical;* its overall mission is to understand and rationally treat disorders and diseases. The systems that maintain the stability of the inner world eventually degenerate. Their efficiencies decline, and as they decline the likelihood of deleterious, self-reinforcing positive feedback loops increases, threatening organismic stability and survival. Clinicians rarely cure; they manage. They exploit negative feedback loops and attempt to forestall or counter positive feedback loops. (4) The medications and treatments clinicians prescribe interact with their patients' internal systems. Multiple, simultaneous degenerations, combined with multiple effects of multiple drugs and remedies and myriad interactions between the degenerations and the treatments, constitute the bulk of modern medical prac-

tice. The scientific integrative medicine approach provides a framework for understanding highly complex and dynamic challenges to our integrity as organisms.

A specific example may help make the point here. As we age, the efficiency of heart muscle function declines—in some sooner than in others, depending on hereditary predispositions and life exposures. As intrinsic heart muscle function declines, the brain senses the decreased pumping ability and directs a compensatory increase in nervous system outflow to the heart. This augments the delivery of norepinephrine (adrenaline's chemical father in the catecholamine family) to its receptors on heart muscle cells, keeping the cells' contractility and the heart's ejection of blood within normal limits. Bombardment of heart muscle cells by norepinephrine, however, decreases the threshold for the development of abnormal heart rhythms (arrhythmias). When an arrhythmia occurs, the heart instantaneously pumps less blood. The brain immediately directs a further increase in norepinephrine release from nerves in the heart, but this augments further the automaticity of the cells. When segments of heart muscle begin to contract autonomously, rather than synchronously, the heart ceases to function as a pump, and the patient suddenly, often unexpectedly, dies. A goal of scientific integrative medicine is to devise means to detect early or even prevent such a catastrophic positive feedback loop. Even after symptoms of heart failure develop, judicious treatment with drugs that modulate norepinephrine's effects could enhance survival.

Integrative medicine has also gained popularity recently. The word *integrative* has been used synonymously with *holistic*, *mind-body*, *complementary*, or *alternative*. The *scientific* integrative medicine approach, however, actually fits quite well with conventional, mainstream clinical medicine. Effective clinicians apply such an approach all the time. Observations over years and gleanings from course work and discussions with colleagues lead to inductions about disorders and predictions about what might help patients. Each patient is like an experiment, with the number of experimental subjects—the legendary *n* of statistics—being 1. The scientific integrative medicine approach provides a more formal framework, including controls and randomized placebo treatments, calculations of statistical parameters such as significance, power, sensitivity, specificity, and negative and positive predictive values, assessments of multiple, quantitative dependent measures, searching databases, cybernetic computer models, and so forth. The essence of the approach, however, the formulation of ideas and testing of predic-