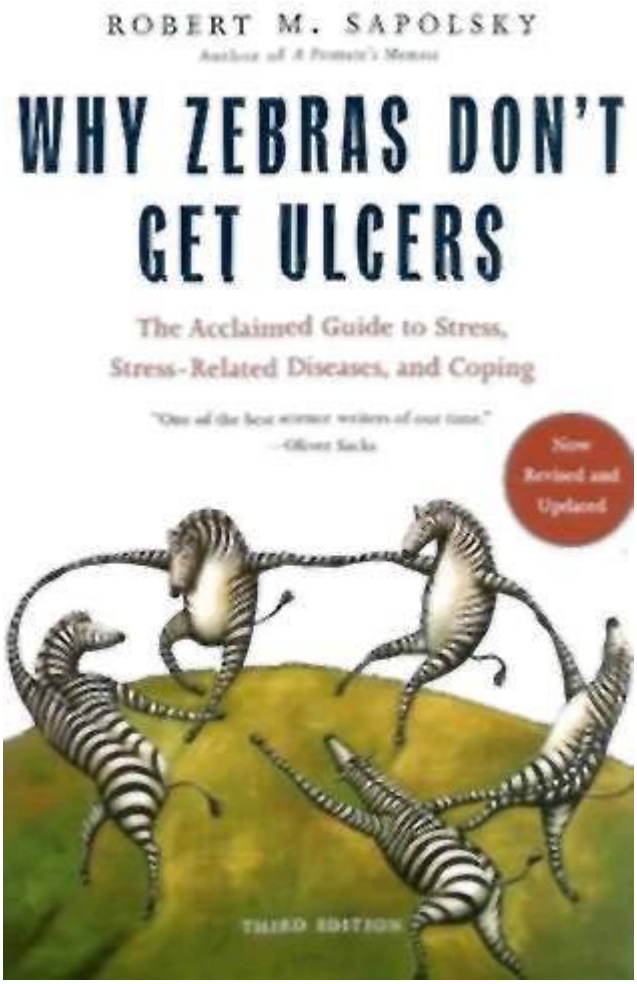

WHY ZEBRAS DON'T GET ULCERS

Third Edition

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For Lisa, my best friend, who has made my life complete

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PREFACE

Perhaps you're reading this while browsing in a bookstore. If so, glance over at the guy down the aisle when he's not looking, the one pretending to be engrossed in the Stephen Hawking book. Take a good look at him. He's probably not missing fingers from leprosy, or covered with smallpox scars, or shivering with malaria. Instead, he probably appears perfectly healthy, which is to say he has the same diseases that most of us have—cholesterol levels that are high for an ape, hearing that has become far less acute than in a hunter-gatherer of his age, a tendency to dampen his tension with Valium. We in our Western society now tend to get different diseases than we used to. But what's more important, we tend to get different kinds of diseases now, with very different causes and consequences. A millennium ago, a young hunter-gatherer inadvertently would eat a reedbuck riddled with anthrax and the consequences are clear—she's dead a few days later. Now, a young lawyer unthinkingly decides that red meat, fried foods, and a couple of beers per dinner constitute a desirable diet, and the consequences are anything but clear—a half-century later, maybe he's crippled with cardiovascular disease, or maybe he's taking bike trips with his grandkids. Which outcome occurs depends on some obvious nuts-and-bolts factors, like what his liver does with cholesterol, what levels of certain enzymes are in his fat cells, whether he has any congenital weaknesses in the walls of his blood vessels. But the outcome will also depend heavily on such surprising factors as his personality, the amount of emotional stress he experiences over the years, whether he has someone's shoulder to cry on when those stressors occur.

There has been a revolution in medicine concerning how we think about the diseases that now afflict us. It involves recognizing the

interactions between the body and the mind, the ways in which emotions and personality can have a tremendous impact on the functioning and health of virtually every cell in the body. It is about the role of stress in making some of us more vulnerable to disease, the ways in which some of us cope with stressors, and the critical notion that you cannot really understand a disease in vacuo, but rather only in the context of the person suffering from that disease.

This is the subject of my book. I begin by trying to clarify the meaning of the nebulous concept of stress and to teach, with a minimum of pain, how various hormones and parts of the brain are mobilized in response to stress. I then focus on the links between stress and increased risk for certain types of disease, going, chapter by chapter, through the effects of stress on the circulatory system, on energy storage, on growth, reproduction, the immune system, and so on. Next I describe how the aging process may be influenced by the amount of stress experienced over a lifetime. I then examine the link between stress and the most common and arguably most crippling of psychiatric disorders, major depression. As part of updating the material for this third edition, I have added two new chapters: one on the interactions between stress and sleep, and one on what stress has to do with addiction. In addition, of the chapters that appeared in the previous edition, I rewrote about a third to half of the material.

Some of the news in this book is grim—sustained or repeated stress can disrupt our bodies in seemingly endless ways. Yet most of us are not incapacitated by stress-related disease. Instead, we cope, both physiologically and psychologically, and some of us are spectacularly successful at it. For the reader who has held on until the end, the final chapter reviews what is known about stress management and how some of its principles can be applied to our everyday lives. There is much to be optimistic about.

I believe that everyone can benefit from some of these ideas and can be excited by the science on which they are based. Science provides us with some of the most elegant, stimulating puzzles that life has to offer. It throws some of the most provocative ideas into our arenas of moral debate. Occasionally, it improves our lives. I love science, and it pains me to think that so many are terrified of the subject or feel that choosing science means that you cannot also choose compassion, or the arts, or be awed by nature. Science is not meant to cure us of mystery, but to reinvent and reinvigorate it.

Thus I think that any science book for nonscientists should attempt to convey that excitement, to make the subject interesting and accessible even to those who would normally not be caught dead near the

subject. That has been a particular goal of mine in this book. Often, it has meant simplifying complex ideas, and as a counterbalance to this, I include copious references at the end of the book, often with annotations concerning controversies and subtleties about material presented in the main text. These references are an excellent entree for those readers who want something more detailed on the subject.

Many sections of this book contain material about which I am far from expert, and over the course of the writing, a large number of savants have been called for advice, clarification, and verification of facts. I thank them all for their generosity with their time and expertise: Nancy Adler, John Angier, Robert Axelrod, Alan Baldrich, Marcia Barinaga, Alan Basbaum, Andrew Baum, Justo Bautisto, Tom Belva, Anat Biegon, Vic Boff (whose brand of vitamins graces the cupboards of my parents' home), Carlos Camargo, Matt Cartmill, M. Linette Casey, Richard Chapman, Cynthia Clinkingbeard, Felix Conte, George Daniels, Regio DeSilva, Irven DeVore, Klaus Dinkel, James Doherty, John Dolph, Leroi DuBeck, Richard Estes, Michael Fanselow, David Feldman, Caleb Tuck Finch, Paul Fitzgerald, Gerry Friedland, Meyer Friedman, Rose Frisch, Roger Gosden, Bob Grossfield, Kenneth Haw-ley, Ray Hintz, Allan Hobson, Robert Kessler, Bruce Knauft, Mary Jeanne Kreek, Stephen Laberge, Emmit Lam, Jim Latcher, Richard Lazarus, Helen Leroy, Jon Levine, Seymour Levine, John Liebeskind, Ted Macolvena, Jodi Maxmin, Michael Miller, Peter Milner, Gary Moberg, Anne Moyer, Terry Muilenburg, Ronald Myers, Carol Otis, Daniel Pearl, Ciran Phibbs, Jenny Pierce, Ted Pincus, Virginia Price, Gerald Reaven, Sam Ridgeway, Carolyn Ristau, Jeffrey Ritterman, Paul Rosch, Ron Rosenfeld, Aryeh Routtenberg, Paul Saenger, Saul Schanburg, Kurt Schmidt-Nielson, Carol Shively, J. David Singer, Bart Sparagon, David Speigel, Ed Spielman, Dennis Styne, Steve Suomi, Jerry Tally, Carl Thoresen, Peter Tyak, David Wake, Michelle Warren, Jay Weiss, Owen Wolkowitz, Carol Worthman, and Richard Wurtman.

I am particularly grateful to the handful of people—friends, collaborators, colleagues, and ex-teachers—who took time out of their immensely busy schedules to read chapters. I shudder to think of the errors and distortions that would have remained had they not tactfully told me I didn't know what I was writing about. I thank them all sincerely: Robert Ader of the University of Rochester; Stephen Bezruchka of the University of Washington; Marvin Brown of the University of California, San Diego; Laurence Frank at the University of California, Berkeley; Craig Heller of Stanford University; Jay Kaplan of Bowman Gray Medical School; Ichiro Kawachi of Harvard University; George Knob of the Scripps Clinic; Charles Nemeroff of Emory University;

Seymour Reichlin of Tufts/New England Medical Center; Robert Rose of the MacArthur Foundation; Tim Meier of Stanford University; Wylie Vale of the Salk Institute; Jay Weiss of Emory University; and Redford Williams of Duke University

A number of people were instrumental in getting this book off the ground and into its final shape. Much of the material in these pages was developed in continuing medical education lectures. These were presented under the auspices of the Institute for Cortext Research and Development, and its director, Will Gordon, who gave me much freedom and support in exploring this material. Bruce Goldman of the Portable Stanford series first planted the idea for this book in my head, and Kirk Jensen recruited me for W H. Freeman and Company; both helped in the initial shaping of the book. Finally, my secretaries, Patsy Gardner and Lisa Pereira, have been of tremendous help in all the logistical aspects of pulling this book together. I thank you all, and look forward to working with you in the future.

I received tremendous help with organizing and editing the first edition of the book, and for that I thank Audrey Herbst, Tina Hastings, Amy Johnson, Meredyth Rawlins, and, above all, my editor, Jonathan Cobb, who was a wonderful teacher and friend in this process. Help in the second edition came from John Michel, Amy Trask, Georgia Lee Hadler, Victoria Tomaselli, Bill O'Neal, Kathy Bendo, Paul Rohloff, Jennifer MacMillan, and Sheridan Sellers. Liz Meryman, who selects the art for *Natural History* magazine, helping to merge the cultures of art and science in that beautiful publication, graciously consented to read the manuscript and gave splendid advice on appropriate artwork. In addition, I thank Alice Fernandes-Brown, who was responsible for making my idea for the cover such a pleasing reality. In this new edition help came from Rita Quintas, Denise Cronin, Janice O'Quinn, Jessica Firger, and Richard Rhorer at Henry Holt.

This book has been, for the most part, a pleasure to write and I think it reflects one of the things in my life for which I am most grateful—that I take so much joy in the science that is both my vocation and avocation. I thank the mentors who taught me to do science and, even more so, taught me to enjoy science: the late Howard Klar, Howard Eichenbaum, Mel Konner, Lewis Krey, Bruce McEwen, Paul Plotsky, and Wylie Vale.

A band of research assistants have been indispensable to the writing of this book. Steve Bait, Roger Chan, Mick Markham, Kelley Parker, Michelle Pearl, Serena Spudich, and Paul Stasi have wandered the basements of archival libraries, called strangers all over the world with questions, distilled arcane articles into coherency. In the line of

duty, they have sought out drawings of opera castrati, the daily menu at Japanese-American internment camps, the causes of voodoo death, and the history of firing squads. All of their research was done with spectacular competence, speed, and humor. I am fairly certain this book could not have been completed without their help and am absolutely certain its writing would have been much less enjoyable. And finally, I thank my agent, Katinka Matson, and my editor, Robin Dennis, who have been just terrific to work with. I look forward to many more years of collaborations ahead.

Parts of the book describe work carried out in my own laboratory, and these studies have been made possible by funding from the National Institutes of Health, the National Institute of Mental Health, the National Science Foundation, the Sloan Foundation, the Klingen-stein Fund, the Alzheimer's Association, and the Adler Foundation. The African fieldwork described herein has been made possible by the long-standing generosity of the Harry Frank Guggenheim Foundation. Finally, I heartily thank the MacArthur Foundation for supporting all aspects of my work.

Finally, as will be obvious, this book cites the work of a tremendous number of scientists. Contemporary lab science is typically carried out by large teams of people. Throughout the book, I refer to the work of "Jane Doe" or "John Smith" for the sake of brevity—it is almost always the case that such work was carried out by Doe or Smith along with a band of junior colleagues.

There is a tradition among stress physiologists who dedicate their books to their spouses or significant others, an unwritten rule that you are supposed to incorporate something cutesy about stress in the dedication. So, to Madge, who attenuates my stressors; for Arturo, the source of my eustress; for my wife who, over the course of the last umpteen years, has put up with my stress-induced hypertension, ulcerative colitis, loss of libido, and displaced aggression. I will forgo that style in the actual dedication of this book to my wife, as I have something simpler to say.

1

WHY DON'T ZEBRAS GET ULCERS?

It's two o'clock in the morning and you're lying in bed. You have something immensely important and challenging to

that next day—a critical meeting, a presentation, an exam. You have to get a decent night's rest, but you're

still wide awake. You try different strategies for relaxing— take deep, slow breaths, try to imagine restful mountain scenery—but instead you keep thinking that unless you fall asleep in the next minute, your career is finished. Thus you lie there, more tense by the second.

If you do this on a regular basis, somewhere around two-thirty, when you're really getting clammy, an entirely new, disruptive chain of thought will no doubt intrude. Suddenly, amid all your other worries, you begin to contemplate that nonspecific pain you've been having in your side, that sense of exhaustion lately, that frequent headache. The realization hits you—I'm sick, fatally sick! Oh, why didn't I recognize the symptoms, why did I have to deny it, why didn't I go to the doctor?

When it's two-thirty on those mornings, I always have a brain tumor. These are very useful for that sort of terror, because you can attribute every conceivable nonspecific symptom to a brain tumor and justify your panic. Perhaps you do, too; or maybe you lie there thinking that you have cancer, or an ulcer, or that you've just had a stroke.

Even though I don't know you, I feel confident in predicting that you don't lie there thinking, "I just know it; I have leprosy." True? You are exceedingly unlikely to obsess about getting a serious case of dysentery if it starts pouring. And few of us lie there feeling convinced that our bodies are teeming with intestinal parasites or liver flukes.

Influenza pandemic, 1918.

Of course not. Our nights are not filled with worries about scarlet fever, malaria, or bubonic plague. Cholera doesn't run rampant through our communities; river blindness, black water fever, and elephantiasis are third world exotica. Few female readers will die in childbirth, and even fewer of those reading this page are likely to be malnourished.

Thanks to revolutionary advances in medicine and public health, our patterns of disease have changed, and we are no longer kept awake at night worrying about infectious diseases (except, of course, AIDS or tuberculosis) or the diseases of poor nutrition or hygiene. As a measure of this, consider the leading causes of death in the United States in 1900: pneumonia, tuberculosis, and influenza (and, if you were young, female, and inclined toward risk taking, childbirth). When is the last time you heard of scads of people dying of the flu? Yet the flu, in 1918 alone, killed many times more people than throughout the course of that most barbaric of conflicts, World War I.

Our current patterns of disease would be unrecognizable to our great-grandparents or, for that matter, to most mammals. Put succinctly, we get different diseases and are likely to die in different ways

from most of our ancestors (or from most humans currently living in the less privileged areas of this planet). Our nights are filled with

worries about a different class of diseases; we are now living well enough and long enough to slowly fall apart.

The diseases that plague us now are ones of slow accumulation of damage—heart disease, cancer, cerebrovascular disorders. While none of these diseases is particularly pleasant, they certainly mark a big improvement over succumbing at age twenty after a week of sepsis or dengue fever. Along with this relatively recent shift in the patterns of disease have come changes in the way we perceive the disease process. We have come to recognize the vastly complex intertwining of our biology and our emotions, the endless ways in which our personalities, feelings, and thoughts both reflect and influence the events in our bodies. One of the most interesting manifestations of this recognition is understanding that extreme emotional disturbances can adversely affect us. Put in the parlance with which we have grown familiar, *stress can make us sick,* and a critical shift in medicine has been the recognition that many of the damaging diseases of slow accumulation can be either caused or made far worse by stress.

In some respects this is nothing new. Centuries ago, sensitive clinicians intuitively recognized the role of individual differences in vulnerability to disease. Two individuals could get the same disease, yet the courses of their illness could be quite different and in vague, subjective ways might reflect the personal characteristics of the individuals. Or a clinician might have sensed that certain types of people were more likely to contract certain types of disease. But since the twentieth century, the addition of rigorous science to these vague clinical perceptions has made stress physiology—the study of how the body responds to stressful events—a real discipline. As a result, there is now an extraordinary amount of physiological, biochemical, and molecular information available as to how all sorts of intangibles in our lives can affect very real bodily events. These intangibles can include emotional turmoil, psychological characteristics, our position in society, and how our society treats people of that position. And they can influence medical issues such as whether cholesterol gums up our blood vessels or is safely cleared from the circulation, whether our fat cells stop listening to insulin and plunge us into diabetes, whether neurons in our brain will survive five minutes without oxygen during a cardiac arrest.

This book is a primer about stress, stress-related disease, and the mechanisms of coping with stress. How is it that our bodies can adapt to some stressful emergencies, while other ones make us sick? Why are some of us especially vulnerable to stress-related diseases, and what does that have to do with our personalities? How can purely psychological turmoil make us sick? What mighl stress have to do with our

vulnerability to depression, the speed at which we age, or how well our memories work? What do our patterns of stress-related diseases have to do with where we stand on the rungs of society's ladder? Finally, how can we increase the effectiveness with which we cope with the stressful world that surrounds us?

SOME INITIAL CONCEPTS

Perhaps the best way to begin is by making a mental list of the sorts of things we find stressful. No doubt you would immediately come up with some obvious examples—traffic, deadlines, family relationships, money worries. But what if I said, "You're thinking like a speciocentric human. Think like a zebra for a second." Suddenly, new items might appear at the top of your list—serious physical injury, predators, starvation. The need for that prompting illustrates something critical— you and I are more likely to get an ulcer than a zebra is. For animals like zebras, the most upsetting things in life are *acute physical* crises. You are that zebra, a lion has just leapt out and ripped your stomach open, you've managed to get away, and now you have to spend the next hour evading the lion as it continues to stalk you. Or, perhaps just as stressfully, you are that lion, half-starved, and you had better be able to sprint across the savanna at top speed and grab something to eat or you won't survive. These are extremely stressful events, and they demand immediate physiological adaptations if you are going to live. Your body's responses are brilliantly adapted for handling this sort of emergency.

An organism can also be plagued by *chronic physical* challenges. The locusts have eaten your crops, and for the next six months, you have to wander a dozen miles a day to get enough food. Drought, famine, parasites, that sort of unpleasantness—not the sort of experience we have often, but central events in the lives of non-westernized humans and most other mammals. The body's stress-responses are reasonably good at handling these sustained disasters.

Critical to this book is a third category of ways to get upset—*psychological and social* disruptions. Regardless of how poorly we are getting along with a family member or how incensed we are about losing a parking spot, we rarely settle that sort of thing with a fistfight. Likewise, it is a rare event when we have to stalk and personally wrestle down our dinner. Essentially, we humans live well enough and long

enough, and are smart enough, to generate all sorts of stressful events

Robert Longo, Untitled Work on Paper, 1981. (Two yuppies contesting the last double latte at a restaurant?)

purely in our heads. How many hippos worry about whether Social Security is going to last as long as they will, or what they are going to say on a first date? Viewed from the perspective of the evolution of the animal kingdom, sustained psychological stress is a recent invention, mostly limited to humans and other social primates. We can experience wildly strong emotions (provoking our bodies into an accompanying uproar) linked to mere thoughts.* Two people can sit facing each other, doing nothing more physically strenuous than moving little pieces of wood now and then, yet this can be an emotionally taxing event: chess grand masters, during their tournaments, can place metabolic demands on their bodies that begin to approach those of athletes during the peak of a competitive event.+ Or a person can do nothing more exciting than sign a piece of paper: if she has just signed the order to fire a hated rival after months of plotting and maneuvering, her physiological responses might be shockingly similar to those of a

* The neurologist Antonio Damasio recounts a wonderful study done on the conductor Herbert von Karajan, showing that the maestro's heart would race just as wildly when he was listening to a piece of music as when he was conducting it.

+ Perhaps journalists are aware of this fact; consider this description of the Kasparov-Karpov chess tournament of 1990: "Kasparov kept pressing for a murderous attack. Toward the end, Karpov had to oppose threats of violence with more of the same and the game became a melee."

savanna baboon who has just lunged and slashed the face of a competitor. And if someone spends months on end twisting his innards in anxiety, anger, and tension over some emotional problem, this might very well lead to illness.

This is the critical point of this book: if you are that zebra running for your life, or that lion sprinting for your meal, your body's physiological response mechanisms are superbly adapted for dealing with such short-term physical emergencies. For the vast majority of beasts on this planet, stress is about a short-term crisis, after which it's either over with or you're over with. When we sit around and worry about stressful things, we turn on the same physiological responses—but they are potentially a disaster when provoked chronically. A large body of evidence suggests that stress-related disease emerges, predominantly, out of the fact that we so often activate a physiological system that has evolved for responding to acute physical emergencies, but we turn it on for months on end, worrying about mortgages, relationships, and promotions.

This difference between the ways that we get stressed and the ways a zebra does lets us begin to wrestle with some definitions. To start, I must call forth a concept that you were tortured with in ninth-grade biology and hopefully have not had to think about since—*homeostasis.* Ah, that dimly remembered concept, the idea that the body has an ideal level of oxygen that it needs, an ideal degree of acidity, an ideal temperature, and so on. All these different variables are maintained in homeostatic balance, the state in which all sorts of physiological measures are being kept at the optimal level. The brain, it has been noted, has evolved to seek homeostasis.

This allows us to generate some simple initial working definitions that would suffice for a zebra or a lion. A *stressor* is anything in the outside world that knocks you out of homeostatic balance, and the *stress-response* is what your body does to reestablish homeostasis.

But when we consider ourselves and our human propensity to worry ourselves sick, we have to expand on the notion of stressors merely being things that knock you out of homeostatic balance. A stressor can also be the *anticipation* of that happening. Sometimes we are smart enough to see things coming and, based only on anticipation, can turn on a stress-response as robust as if the event had actually occurred. Some aspects of anticipatory stress are not unique to humans—whether you are a human surrounded by a bunch of thugs in a deserted subway station or a zebra face to face with a lion, your heart is probably racing, even though nothing physically damaging

has occurred (yet). But unlike less cognitively sophisticated species, we can turn on the stress-response by thinking about potential stressors that may throw us out of homeostatic balance far in the future. For example, think of the African farmer watching a swarm of locusts descend on his crops. He has eaten an adequate breakfast and is not suffering the homeostatic imbalance of starving, but that farmer will still be undergoing a stress-response. Zebras and lions may see trouble coming in the next minute and mobilize a stress-response in anticipation, but they can't get stressed about events far in the future.

And sometimes we humans can be stressed by things that simply make no sense to zebras or lions. It is not a general mammalian trait to become anxious about mortgages or the Internal Revenue Service, about public speaking or fears of what you will say in a job interview, about the inevitability of death. Our human experience is replete with psychological stressors, a far cry from the physical world of hunger, injury, blood loss, or temperature extremes. When we activate the stress-response out of fear of something that turns out to be real, we congratulate ourselves that this cognitive skill allows us to mobilize our defenses early. And these anticipatory defenses can be quite protective, in that a lot of what the stress-response is about is preparative. But when we get into a physiological uproar and activate the stress-response for no reason at all, or over something we cannot do anything about, we call it things like "anxiety," "neurosis," "paranoia," or "needless hostility."

Thus, the stress-response can be mobilized not only in response to physical or psychological insults, but also in expectation of them. It is this generality of the stress-response that is the most surprising—a physiological system activated not only by all sorts of physical disasters but by just thinking about them as well. This generality was first appreciated about sixty-five years ago by one of the godfathers of stress physiology, Hans Selye. To be only a bit facetious, stress physiology exists as a discipline because this man was both a very insightful scientist and lame at handling lab rats.

In the 1930s, Selye was just beginning his work in endocrinology, the study of hormonal communication in the body. Naturally, as a young, unheard-of assistant professor, he was fishing around for something with which to start his research career. A biochemist down the hall had just isolated some sort of extract from the ovary, and colleagues were wondering what this ovarian extract did to the body. So Selye obtained some of the stuff from the biochemist and set about studying its effects. He attempted to inject his rats daily, but

apparently not with a great display of dexterity. Selye would try to inject the rats, miss them, drop them, spend half the morning chasing the rats around the room or vice versa, flailing with a broom to get them out from behind the sink, and so on. At the end of a number of months of this, Selye examined the rats and discovered something extraordinary: the rats had peptic ulcers, greatly enlarged adrenal glands (the source of two important stress hormones), and shrunken immune tissues. He was delighted; he had discovered the effects of the mysterious ovarian extract.

Being a good scientist, he ran a control group: rats injected daily with saline alone, instead of the ovarian extract. And, thus, every day they too were injected, dropped, chased, and chased back. At the end, lo and behold, the control rats had the same peptic ulcers, enlarged adrenal glands, and atrophy of tissues of the immune system.

Now, your average budding scientist at this point might throw up his or her hands and furtively apply to business school. But Selye, instead, reasoned through what he had observed. The physiological changes couldn't be due to the ovarian extract after all, since the same changes occurred in both the control and the experimental groups. What did the two groups of rats have in common? Selye reasoned that it was his less-than-trauma-free injections. Perhaps, he thought, these changes in the rats' bodies were some sort of nonspecific responses of the body to generic unpleasantness. To test this idea, he put some rats on the roof of the research building in the winter, others down in the boiler room. Still others were exposed to forced exercise, or to surgical procedures. In all cases, he found increased incidences of peptic ulcers, adrenal enlargement, and atrophy of immune tissues.

We know now exactly what Selye was observing. He had just discovered the tip of the iceberg of stress-related disease. Legend (mostly promulgated by Selye himself) has it that Selye was the person who, searching for a way to describe the nonspecificity of the unpleasantness to which the rats were responding, borrowed a term from physics and proclaimed that the rats were undergoing "stress." In fact, by the 1920s the term had already been introduced to medicine in roughly the sense that we understand it today by a physiologist named Walter Cannon. What Selye did was to formalize the concept with two ideas:

■ The body has a surprisingly similar set of responses (which he called the general adaptation syndrome, but which we now call the stress-response) to a broad array of stressors.

■ If stressors go on for too long, they can make you sick

HOMEOSTASIS PLUS: THE MORE STRESS-APPROPRIATE CONCEPT OF ALLOSTASIS

The homeostasis concept has been modified in recent years in work originated by Peter Sterling and Joseph Eyer of the University of Pennsylvania and extended by Bruce McEwen of Rockefeller University* They have produced a new framework that I steadfastly tried to ignore at first and have now succumbed to, because it brilliantly modernizes the homeostasis concept in a way that works even better in making sense of stress (although not all folks in my business have embraced it, using "old wine in a new bottle" imagery).

The original conception of homeostasis was grounded in two ideas. First, there is a single optimal level, number, amount for any given measure in the body. But that can't be true—after all, the ideal blood pressure when you're sleeping is likely to be different than when you're ski jumping. What's ideal under basal conditions is different than during stress, something central to allostatic thinking. (The field uses this Zen-ish sound bite about how allostasis is about "constancy through change." I'm not completely sure I understand what that means, but it always elicits meaningful and reinforcing nods when I toss it out in a lecture.)

The second idea in homeostasis is that you reach that ideal set point through some local regulatory mechanism, whereas allostasis recognizes that any given set point can be regulated in a zillion different ways, each with its own consequences. Thus, suppose there's a water shortage in California. Homeostatic solution: mandate smaller toilet tanks.+ Allostatic solutions: smaller toilet tanks, convince people to conserve water, buy rice from Southeast Asia instead of doing water-intensive farming in a semi-arid state. Or suppose there's a water shortage in your body. Homeostatic solution: kidneys are the ones that figure this out, tighten things up there, produce less urine for water conservation. Allostatic solutions: brain figures this out, tells the kidneys to do their thing, sends signals to withdraw water from parts of your body where it easily evaporates (skin, mouth, nose), makes you feel thirsty Homeostasis is about tinkering with this valve or that gizmo. Allostasis is about the brain coordinating body-wide changes, often including changes in behavior.

* McEwen and his work are going to pop up frequently in this book, as he is the giant of this field (as well as a wonderful man and, a long time ago, my thesis advisor).

+ Physiologists actually spend a lot of time thinking about the inner workings of toilet

bowls

A final feature of allostatic thinking dovetails beautifully with thinking about stressed humans. The body doesn't pull off all this regulatory complexity only to correct some set point that has gone awry It can also make allostatic changes in *anticipation* of a set point that is likely to go awry. And thus we hark back to the critical point of a few pages back—we don't get stressed being chased by predators. We activate the stress-response in anticipation of challenges, and typically those challenges are the purely psychological and social tumult that would make no sense to a zebra. We'll be returning repeatedly to what allostasis has to say about stress-related disease.

WHAT YOUR BODY DOES TO ADAPT TO AN ACUTE STRESSOR

Within this expanded framework, a stressor can be defined as anything that throws your body out of allostatic balance and the stress-response is your body's attempt to restore allostasis. The secretion of certain hormones, the inhibition of others, the activation of particular parts of the nervous system, and so on. And regardless of the stressor— injured, starving, too hot, too cold, or psychologically stressed—you turn on the same stress-response.

It is this generality that is puzzling. If you are trained in physiology, it makes no sense at first glance. In physiology, one is typically taught that *specific* challenges to the body trigger *specific* responses and adaptations. Warming a body causes sweating and dilation of blood vessels in the skin. Chilling a body causes just the opposite—constriction of those vessels and shivering. Being too hot seems to be a very specific and different physiological challenge from being too cold, and it would seem logical that the body's responses to these two very different states should be extremely different. Instead, what kind of crazy bodily system is this that is turned on whether you are too hot or too cold, whether you are the zebra, the lion, or a terrified adolescent going to a high school dance? Why should your body have such a generalized and stereotypical stress-response, regardless of the predicament you find yourself in?

When you think about it, it actually makes sense, given the adaptations brought about by the stress-response. If you're some bacterium stressed by food shortage, you go into a suspended, dormant state. But if you're a starving lion, you're going to have to run after someone. If you're some plant stressed by someone intent on eating you, you stick poisonous chemicals in your leaves But if you're a zebra being chased

by that lion, you have to run for it. For us vertebrates, the core of the stress-response is built around the fact that your muscles are going to work like crazy. And thus the muscles need energy, right now, in the most readily utilizable form, rather than stored away somewhere in your fat cells for some building project next spring. One of the hallmarks of the stress-response is the rapid mobilization of energy from storage sites and the inhibition of further storage. Glucose and the simplest forms of proteins and fats come pouring out of your fat cells, liver, and muscles, all to stoke whichever muscles are struggling to save your neck.

If your body has mobilized all that glucose, it also needs to deliver it to the critical muscles as rapidly as possible. Heart rate, blood pressure, and breathing rate increase, all to transport nutrients and oxygen at greater rates.

Equally logical is another feature of the stress-response. During an emergency, it makes sense that your body halts long-term, expensive building projects. If there is a tornado bearing down on the house, this isn't the day to repaint the garage. Hold off on the long-term projects until you know there is a long term. Thus, during stress, digestion is inhibited—there isn't enough time to derive the energetic benefits of the slow process of digestion, so why waste energy on it? You have better things to do than digest breakfast when you are trying to avoid being someone's lunch. The same thing goes for growth and reproduction, both expensive, optimistic things to be doing with your body (especially if you are female). If the lion's on your tail, two steps behind you, worry about ovulating or growing antlers or making sperm some other time. During stress, growth and tissue repair is curtailed, sexual drive decreases in both sexes; females are less likely to ovulate or to carry pregnancies to term, while males begin to have trouble with erections and secrete less testosterone.

Along with these changes, immunity is also inhibited. The immune system, which defends against infections and illness, is ideal for spotting the tumor cell that will kill you in a year, or making enough antibodies to protect you in a few weeks, but is it really needed this instant? The logic here appears to be the same—look for tumors some other time; expend the energy more wisely now. (As we will see in chapter 8, there are some major problems with this idea that the immune system is suppressed during stress in order to save energy. But that idea will suffice for the moment.)

Another feature of the stress-response becomes apparent during times of extreme physical pain. With sufficiently sustained stress, our

perception of pain can become blunted It's the middle of a battle;

soldiers are storming a stronghold with wild abandon. A soldier is shot, grievously injured, and the man doesn't even notice it. He'll see blood on his clothes and worry that one of his buddies near him has been wounded, or he'll wonder why his innards feel numb. As the battle fades, someone will point with amazement at his injury—didn't it hurt like hell? It didn't. Such stress-induced analgesia is highly adaptive and well documented. If you are that zebra and your

innards are dragging in the dust, you still have to escape. Now would not be a particularly clever time to go into shock from extreme pain.

Finally, during stress, shifts occur in cognitive and sensory skills. Suddenly certain aspects of memory improve, which is always helpful if you're trying to figure out how to get out of an emergency (Has this happened before? Is there a good hiding place?). Moreover, your senses become sharper. Think about watching a terrifying movie on television, on the edge of your seat at the tensest part. The slightest noise—a creaking door—and you nearly jump out of your skin. Better memory, sharper detection of sensations—all quite adaptive and helpful.

Collectively, the stress-response is ideally adapted for that zebra or lion. Energy is mobilized and delivered to the tissues that need them; long-term building and repair projects are deferred until the disaster has passed. Pain is blunted, cognition sharpened. Walter Cannon, the physiologist who, at the beginning of the century, paved the way for much of Selye's work and is generally considered the other godfather of the field, concentrated on the adaptive aspect of the stress-response in dealing with emergencies such as these. He formulated the well-known "fight-or-flight" syndrome to describe the stress-response, and he viewed it in a very positive light. His books, with titles such as *The Wisdom of the Body*, were suffused with a pleasing optimism about the ability of the body to weather all sorts of stressors.

Yet stressful events can sometimes make us sick. Why?

Selye, with his ulcerated rats, wrestled with this puzzle and came up with an answer that was sufficiently wrong that it is generally thought to have cost him a Nobel Prize for all his other work. He developed a three-part view of how the stress-response worked. In the initial (alarm) stage a stressor is noted; metaphorical alarms go off in your head, telling you that you are hemorrhaging, too cold, low on blood sugar, or whatever. The second stage (adaptation, or resistance) comes with the successful mobilization of the stress-response system and the reattainment of allostatic balance.

It is with prolonged stress that one enters the third stage, which Selye termed "exhaustion," where stress related diseases emerge. Selye believed that one becomes sick at that point because stores of the

hormones secreted during the stress-response are depleted. Like an army that runs out of ammunition, suddenly we have no defenses left against the threatening stressor.

It is very rare, however, as we will see, that any of the crucial hormones are actually depleted during even the most sustained of stressors. The army does not run out of bullets. Instead, the body spends so much on the defense budget that it neglects education and health care and social services (okay, so I may have a hidden agenda here). It is not so much that the stress-response runs out, but rather, with sufficient activation, that *the stress-response can become more damaging than the stressor itself,* especially when the stress is purely psychological. This is a critical concept, because it underlies the emergence of much stress-related disease.

That the stress-response itself can become harmful makes a certain sense when you examine the things that occur in reaction to stress. They are generally shortsighted, inefficient, and penny-wise and dollar-foolish, but they are the sorts of costly things your body has to do to respond effectively in an emergency. And if you experience every day as an emergency, you will pay the price.

If you constantly mobilize energy at the cost of energy storage, you will never store any surplus energy. You will fatigue more rapidly, and your risk of developing a form of diabetes will even increase. The consequences of chronically activating your cardiovascular system are similarly damaging: if your blood pressure rises to 180/100 when you are sprinting away from a lion, you are being adaptive, but if it is 180/ 100 every time you see the mess in your teenager's bedroom, you could be heading for a cardiovascular disaster. If you constantly turn off long-term building projects, nothing is ever repaired. For paradoxical reasons that will be explained in later chapters, you become more at risk for peptic ulcers. In kids, growth can be inhibited to the point of a rare but recognized pediatric endocrine disorder—stress dwarfism— and in adults, repair and remodeling of bone and other tissues can be disrupted. If you are constantly under stress, a variety of reproductive disorders may ensue. In females, menstrual cycles can become irregu-lar or cease entirely; in males, sperm count and testosterone levels may decline. In both sexes, interest in sexual behavior decreases.

But that is only the start of your problems in response to chronic or repealed stressors. If you suppress immune function too long and too much,you are now more likely to fall victim to a number of infectious diseases, and be less capable of combating them once you have them.

Finally, the same systems of the brain that function more cleverly

during stress can also be damaged by one class of hormones secreted

during stress. As will be discussed, this may have something to do with how rapidly our brains lose cells during aging, and how much memory loss occurs with old age.

All of this is pretty grim. In the face of repeated stressors, we may be able to precariously reattain allostasis, but it doesn't come cheap, and the efforts to reestablish that balance will eventually wear us down. Here's a way to think about it: the "two elephants on a seesaw" model of stress-related disease. Put two little kids on a seesaw, and they can pretty readily balance themselves on it. This is allostatic balance when nothing stressful is going on, with the children representing the low levels of the various stress hormones that will be presented in coming chapters. In contrast, the torrents of those same stress hormones released by a stressor can be thought of as two massive elephants on the seesaw. With great effort, they can balance themselves as well. But if you constantly try to balance a seesaw with two elephants instead of two little kids, all sorts of problems will emerge:

■ First, the enormous potential energies of the two elephants are consumed balancing the seesaw, instead of being able to do something more useful, like mowing the lawn or paying the bills. This is equivalent to diverting energy from various long-term building projects in order to solve short-term stressful emergencies.

■ By using two elephants to do the job, damage will occur just because of how large, lumbering, and unsubtle elephants are. They squash the flowers in the process of entering the playground, they strew leftovers and garbage all over the place from the frequent snacks they must eat while balancing the seesaw, they wear out the seesaw faster, and so on. This is equivalent to a pattern of stress-related disease that will run through many of the subsequent chapters: it is hard to fix one major problem in the body without knocking something else out of balance (the very essence of allostasis spreading across systems throughout the body). Thus, you may be able to solve one bit of imbalance brought on during stress by using your elephants (your massive levels of various stress hormones), but such great quantities of those hormones can make a mess of something else in the process. And a long history of doing this produces wear and tear throughout the body, termed *allostatic load.*

■ *A* final, subtle problem: when two elephants are balanced on a seesaw, it's tough for them to get off. Either one hops off and the other comes crashing to the ground, or there's the extremely delicate task of coordinating their delicate, lithe leaps at the same time. This is

a metaphor for another theme that will run through subsequent chapters—sometimes stress-related disease can arise from turning off the stress-response too slowly, or turning off the different components of the stress-response at different speeds. When the secretion rate of one of the hormones of the stress-response returns to normal yet another of the hormones is still being secreted like mad, it can be the equivalent of one elephant suddenly being left alone on the seesaw, crashing to earth.*

The preceding pages should allow you to begin to appreciate the two punch lines of this book:

The first is that if you plan to get stressed like a normal mammal, dealing with an acute physical challenge, and you cannot appropriately *turn on* the stress-response, you're in big trouble. To see this, all you have to do is examine someone who cannot activate the stress-response. As will be explained in the coming chapters, two critical classes of hormones are secreted during stress. In one disorder, Addison's disease, you are unable to secrete one class of these hormones. In another, called Shy-Drager syndrome, it is the secretion of the second class of hormones that is impaired. People with Addison's disease or Shy-Drager syndrome are not more at risk for cancer or diabetes or any other such disorders of slow accumulation of damage. However, people with untreated Addison's disease, when faced with a major stressor such as a car accident or an infectious illness, fall into an "Addisonian" crisis, where their blood pressure drops, they cannot maintain circulation, they go into shock. In Shy-Drager syndrome, it is hard enough simply to stand up, let alone go sprinting after a zebra for dinner—mere standing causes a severe drop in blood pressure, involuntary twitching and rippling of muscles, dizziness, all sorts of unpleasantness. These two diseases teach something important, namely, that you need the stress-response during physical challenges. Addison's and Shy-Drager represent catastrophic failures of turning on the stress-response. In coming chapters, I will discuss some disorders that involve subtler undersecretion of stress hormones. These include chronic fatigue syndrome, fibromyalgia, rheumatoid arthritis, a subtype of depression, critically ill patients, and possibly individuals with post-traumatic stress disorder.

* If you find this analogy silly, imagine what it is like to have a bunch of scientists locked up together at a stress conference working with it. I was at a meeting where this analogy first emerged, and in no time there were factions pushing analogies about ele-

phants on pogo sticks, elephants on monkey bars and merry-go-rounds, sumo

wrestlers on seesaws, and so on.

That first punch line is obviously critical, especially for the zebra who occasionally has to run for its life. But the second punch line is far more relevant to us, sitting frustrated in traffic jams, worrying about expenses, mulling over tense interactions with colleagues. If you *repeatedly turn on* the stress-response, or if you *cannot turn off* the stress-

response at the end of a stressful event, the stress-response can eventually become damaging. A large percentage of what we think of when we talk about stress-related diseases are disorders of excessive stress-responses.

A few important qualifications are necessary concerning that last statement, which is one of the central ideas of this book. On a superficial level, the message it imparts might seem to be that stressors make you sick or, as emphasized in the last few pages, that chronic or repeated stressors make you sick. It is actually more accurate to say that chronic or repeated stressors can *potentially* make you sick or can increase your *risk* of being sick. Stressors, even if massive, repetitive, or chronic in nature, do not automatically lead to illness. And the theme of the last section of this book is to make sense of why some people develop stress-related diseases more readily than others, despite the same stressor.

An additional point should be emphasized. To state that "chronic or repeated stressors can increase your risk of being sick" is actually incorrect, but in a subtle way that will initially seem like semantic nit-picking. It is never really the case that stress makes you sick, or even increases your risk of being sick. Stress increases your risk of getting *diseases* that make you sick, or if you have such a disease, stress increases the risk of your defenses being overwhelmed by the disease. This distinction is important in a few ways. First, by putting more steps between a stressor and getting sick, there are more explanations for individual differences— why only some people wind up actually getting sick. Moreover, by clarifying the progression between stressors and illness, it becomes easier to design ways to intervene in the process. Finally, it begins to explain why the stress concept often seems so suspect or slippery to many medical practitioners—clinical medicine is traditionally quite good at being able to make statements like "You feel sick because you have disease X," but is usually quite bad at being able to explain why you got disease X in the first place. Thus, medical practitioners often say, in effect, "You feel sick because you have disease X, not because of some nonsense having to do with stress; however, this ignores the stressors' role in bringing about or worsening the disease in the first place.

With this framework in mind, we can now begin the task of under-standing the individual steps in this system. Chapter 2 introduces the

hormones and brain systems involved in the stress-response: which ones are activated during stress, which ones are inhibited? This leads the way to chapters 3 through 10, which examine the individual systems of your body that are affected. How do those hormones enhance cardiovascular tone during stress, and how does chronic stress cause heart disease (chapter 3)? How do those hormones and neural systems mobilize energy during stress, and how does too much stress cause energetic diseases (chapter 4)? And so on. Chapter 11 examines the interactions between stress and sleep, focusing on the vicious circle of how stress can disrupt sleep and how sleep deprivation is a stressor. Chapter 12 examines the role of stress in the aging process and the disturbing recent findings that sustained exposure to certain of the hormones secreted during stress may actually accelerate the aging of the brain. As will be seen, these processes are often more complicated and subtle than they may seem from the simple picture presented in this chapter.

Chapter 13 ushers in a topic obviously of central importance to understanding our own propensity toward stress-related disease: why is psychological stress stressful? This serves as a prelude to the remaining chapters. Chapter 14 reviews major depression, a horrible psychiatric malady that afflicts vast numbers of us and is often closely related to psychological stress. Chapter 15 discusses what personality differences have to do with individual differences in patterns of stress-related disease. This is the world of anxiety disorders and Type A-ness, plus some surprises about unexpected links between personality and the stress-response. Chapter 16 considers a puzzling issue that lurks throughout reading this book—sometimes stress feels *good*, good enough that we'll pay good money to be stressed by a scary movie or roller-coaster ride. Thus, the chapter considers when stress is a good thing, and the interactions between the sense of pleasure that can be triggered by some stressors and the process of addiction.

Chapter 17 focuses above the level of the individual, looking at what your place in society, and the type of society in which you live, has to do with patterns of stress-related disease. If you plan to go no further, here's one of the punch lines of that chapter: if you want to increase your chances of avoiding stress-related diseases, make sure you don't inadvertently allow yourself to be born poor.

In many ways, the ground to be covered up to the final chapter is all bad news, as we are regaled with the evidence about new and unlikely parts of our bodies and minds that are made miserable by stress. The final chapter is meant to give some hope. Given the same external stressors, certain bodies and certain psyc hes deal with stress

better than others. What are those folks doing right, and what can the rest of us learn from them? We'll look at the main principles of stress management and some surprising and exciting realms in which they have been applied with stunning success. While the intervening chapters document our numerous vulnerabilities to stress-related disease, the final chapter shows that we have an enormous potential to protect ourselves from many of them. Most certainly, all is not lost.

2

GLANDS, GOOSEFLESH, AND HORMONES

In order to begin the process of learning how stress can

make us sick, there is something about the workings of

the brain that we have to appreciate. It is perhaps best

illustrated in the following rather technical paragraph

from an early investigator in the field:

As she melted small and wonderful in his arms, she became infinitely desirable to him, all his blood-vessels seemed to scald with intense yet tender desire, for her, for her softness, for the penetrating beauty of her in his arms, passing into his blood. And softly with that marvelous swoon-like caress of his hand in pure soft desire, softly he stroked the silky slope of her loins, down, down between her soft, warm buttocks, coming nearer and nearer to the very quick of her. And she felt him like a flame of desire, yet tender, and she felt herself melting in the flame. She let herself go. She felt his penis risen against her with silent amazing force and assertion, and she let herself go to him. She yielded with a quiver that was like death, she went all open to him.

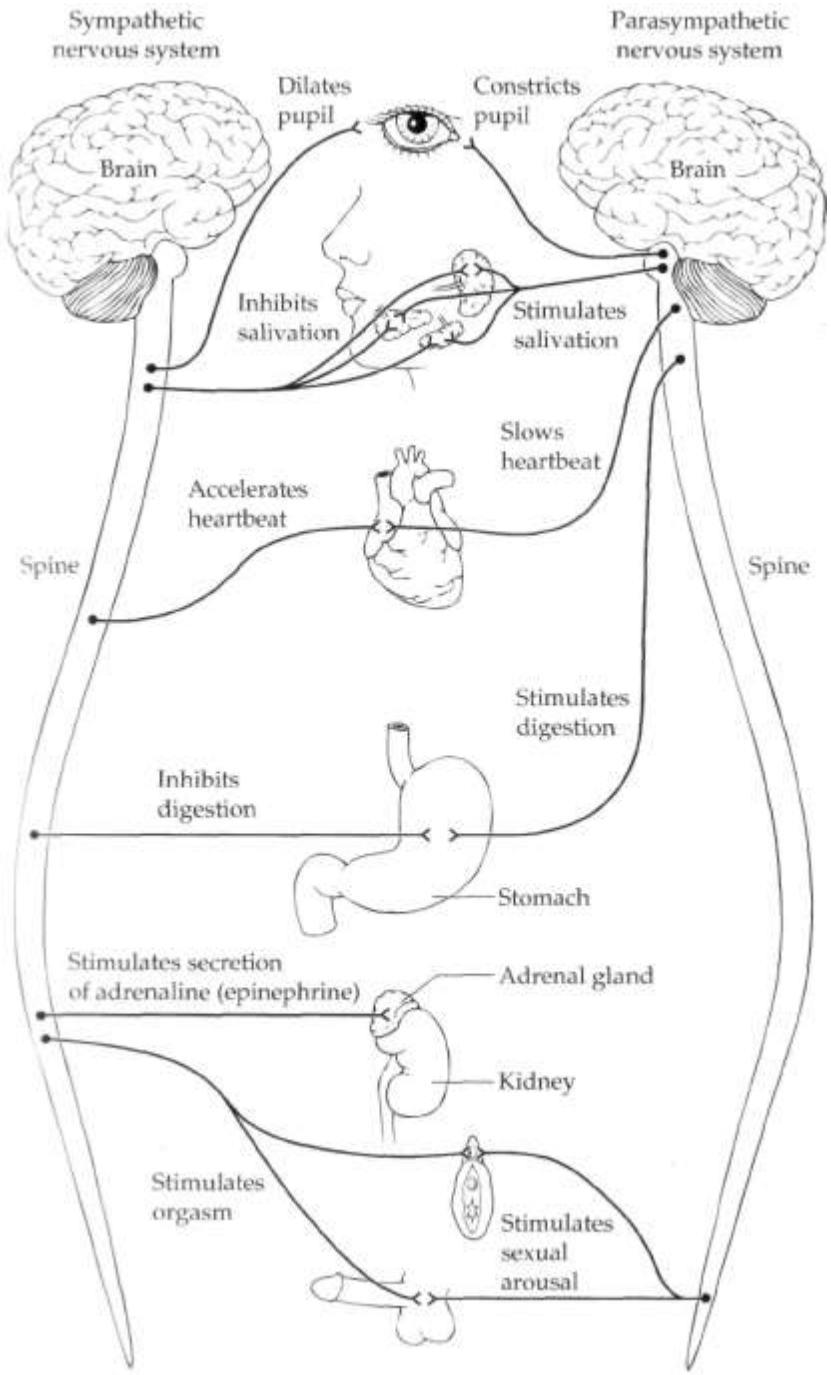
Now think about this. If D. H. Lawrence is to your taste, there may be some interesting changes occurring in your body. You haven't just run up a flight of stairs, but maybe your heart is beating faster. The temperature has not changed in the room, but you may have just activated a sweat gland or two. And even though certain rather sensitive parts ofyour body are not being overtly stimulated by touch, you are suddenly very aware of them.

You sit in your chair not moving a muscle, and simply think a thought, a thought having to do with feeling angry or sad or euphoric or lustful, and suddenly your pancreas secretes some hormone. Your *pancreas?* How did you manage to do that with your pancreas? You don't even know where your pancreas is. Your liver is making an enzyme that wasn't there before, your spleen is text-messaging something to your thymus gland, blood flow in little capillaries in your ankles has just changed. All from thinking a thought.

We all understand intellectually that the brain can regulate functions throughout the rest of the body, but it is still surprising to be reminded of how far-reaching those effects can be. The purpose of this chapter is to learn a bit about the lines of communication between the brain and elsewhere, in order to see which sites are activated and which are quieted when you are sitting in your chair and feeling severely stressed. This is a prerequisite for seeing how the stress -response can save your neck during a sprint across the savanna, but make you sick during months of worry.

STRESS AND THE AUTONOMIC NERVOUS SYSTEM

The principal way in which your brain can tell the rest of the body what to do is to send messages through the nerves that branch from your brain down your spine and out to the periphery of your body. One dimension of this communication system is pretty straightforward and familiar. The voluntary nervous system is a conscious one. You decide to move a muscle and it happens. This part of the nervous system allows you to shake hands or fill out your tax forms or do a polka. It is another branch of the nervous system that projects to organs besides skeletal muscle, and this part controls the other interesting things your body does—blushing, getting gooseflesh, having an orgasm. In general, we have less control over what our brain says to our sweat glands, for example, than to our thigh muscles. (The workings of this automatic nervous system are not entirely out of our control, however; biofeedback, for example, consists of learning to alter this automatic function consciously. Potty training is another example of us gaining mastery. On a more mundane level, we are doing the same thing when we repress a loud burp during a wedding ceremony.) The set of nerve projections to places like sweat glands carry messages that are relatively involuntary and automatic. It is thus



(*Outline of some of the effects of the sympathetic and parasympathetic nervous systems on various organs and glands.*

termed the *autonomic nervous system,* and it has everything to do with your response to stress. One half of this system is activated in response to stress, one half is suppressed.

The half of the autonomic nervous system that is turned on is called the *sympathetic nervous system** Originating in the brain, sympathetic projections exit your spine and branch out to nearly every organ, every blood vessel, and every sweat gland in your body. They even project to the scads of tiny little muscles attached to hairs on your body. If you are truly terrified by something and activate those projections, your hair stands on end; gooseflesh results when the parts of your body are activated where those muscles exist but lack hairs attached to them.

The sympathetic nervous system kicks into action during emergencies, or what you think are emergencies. It helps mediate vigilance, arousal, activation, mobilization. To generations of first-year medical students, it is described through the obligatory lame joke about the sympathetic nervous system mediating the four F's of behavior—flight, fight, fright, and sex. It is the archetypal system that is turned on at times when life gets exciting or alarming, such as during stress. The nerve endings of this system release adrenaline. When someone jumps out from behind a door and startles you, it's your sympathetic nervous system releasing adrenaline that causes your stomach to clutch. Sympathetic nerve endings also release the closely related substance noradrenaline. (*Adrenaline* and *noradrenaline*

are actually British designations; the American terms, which will be used from now on, are *epinephrine* and *norepinephrine.)* Epinephrine is secreted as a result of the actions of the sympathetic nerve endings in your adrenal glands (located just above your kidneys); norepinephrine is secreted by all the other sympathetic nerve endings throughout the body. These are the chemical messengers that kick various organs into gear, within seconds.

The other half of the autonomic nervous system plays an opposing role. This parasympathetic component mediates calm, vegetative activities—everything but the four F's. If you are a growing kid and you have gone to sleep, your parasympathetic system is activated. It

* Where did this name come from? According to the eminent stress physiologist Seymour Levine, this goes back to Galen, who believed that the brain was responsible for rational thought and the peripheral viscera for emotions. Seeing this collection of neural pathways linking the two suggested that it allowed your brain to sympathize with your viscera. Or maybe for your viscera to sympathize with your brain. As we'll see shortly, the other half of the autonomic nervous system is called the parasympathetic nervous system. Para, meaning "alongside," refers to the not very exciting fact that the parasympathetic neural projections sit alongside those of the sympathetic

"Oh, that's Edward and his fight-or-flight mechanism."

promotes growth, energy storage, and other optimistic processes. Have a huge meal, sit there bloated and happily drowsy, and the parasympathetic is going like gangbusters. Sprint for your life across the savanna, gasping and trying to control the panic, and you've turned the parasympathetic component down. Thus, the autonomic system works in opposition: sympathetic and parasympathetic projec-tions from the brain course their way out to a particular organ where, when activated, they bring about opposite results. The sympathetic system speeds up the heart; the parasympathetic system slows it down. The sympathetic system diverts blood flow to your muscles; the parasympathetic does the opposite. It's no surprise that it would be a disaster if both branches were very active at the same time, kind of like putting your foot on the gas and brake simultaneously. Lots of safety features exist to make sure that does not happen. For example, the parts of the brain that activate one of the two branches typically inhibit the other,

YOUR BRAIN:

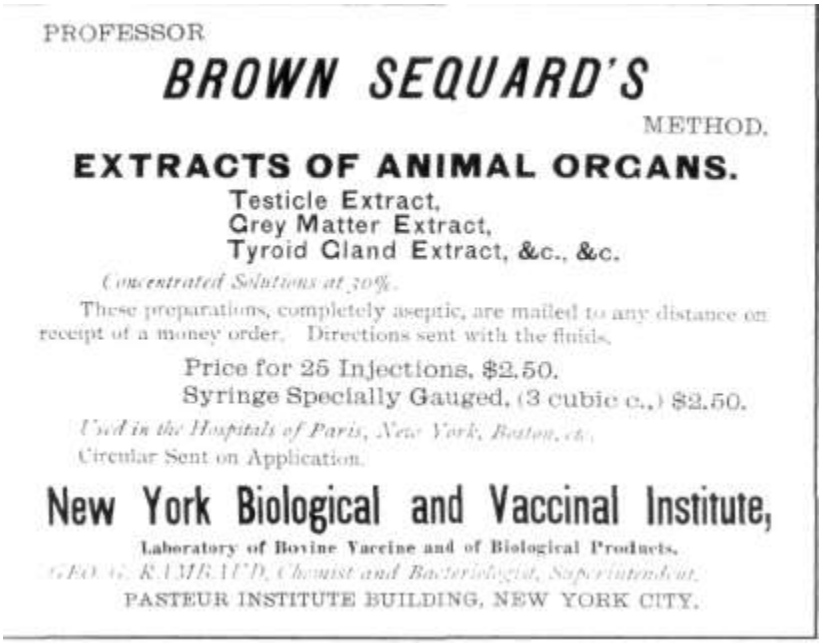
THE REAL MASTER GLAND

The neural route represented by the sympathetic system is a first means by which the brain can mobilize waves of activity in response to a stressor. There is another way as well—through the secretion of hormones. If a neuron (a cell of the nervous system) secretes a chemical messenger that travels a thousandth of an inch and causes the next cell in line (typically, another neuron) to do something different, that messenger is called a neurotransmitter. Thus, when the sympathetic nerve endings in your heart secrete norepinephrine, which causes heart muscle to work differently, norepinephrine is playing a neurotransmitter role. If a neuron (or any cell) secretes a messenger that, instead, percolates into the bloodstream and affects events far and wide, that messenger is a hormone. All sorts of glands secrete hormones; the secretion of some of them is turned on during stress, and the secretion of others is turned off.

What does the brain have to do with all of these glands secreting hormones? People used to think, "Nothing." The assumption was that the peripheral glands of the body—your pancreas, your adrenal, your ovaries, your testes, and so on—in some mysterious way "knew" what they were doing, had "minds of their own." They would "decide" when to secrete their messengers, without directions from any other organ. This erroneous idea gave rise to a rather silly fad during the early part of the twentieth century. Scientists noted that men's sexual drive declined with age, and assumed that this occurs because the testicles of aging men secrete less male sex hormone, testosterone. (Actually, no one knew about the hormone testosterone at the time; they just referred to mysterious "male factors" in the testes. And in fact, testosterone levels do not plummet with age. Instead, the decline is moderate and highly variable from one male to the next, and even a decline in testosterone to perhaps 10 percent of normal levels does not have much of an effect on sexual behavior.) Making another leap, they then ascribed aging to diminishing sexual drive, to lower levels of male factors. (One may then wonder why females, without testes, manage to grow old, but the female half of the population didn't figure much in these ideas back then.) How, then, to reverse aging? Give the aging males some testicular extracts.

Soon, aged, monied gentlemen were checking into impeccable Swiss sanitariums and getting injected daily in their rears with testicu-lar extracts from dogs, from roosters, from monkeys. You could even

go out to the stockyards of the sanitarium and pick out the goat of



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your choice—just like picking lobsters in a restaurant (and more than one gentleman arrived for his appointment with his own prized animal in tow). This soon led to an offshoot of such "rejuvenation therapy," namely, "organotherapy"—the grafting of little bits of testes themselves. Thus was born the "monkey gland" craze, the term *gland* being used because journalists were forbidden to print the racy word *testes.* Captains of industry, heads of state, at least one pope—all signed up. And in the aftermath of the carnage of World War I, there was such a shortage of young men and such a surfeit of marriages of younger women to older men, that therapy of this sort seemed pretty important.

Naturally, the problem was that it didn't work. There wasn't any testosterone in the testicular extracts—patients would be injected with a water-based extract, and testosterone does not go into solution in water. And the smidgens of organs that were transplanted would die almost immediately, with the scar tissue being mistaken for a healthy graft. And even if they didn't die, they still wouldn't work—if aging testes are secreting less testosterone, it is not because the testes are fail-nig, hul because another organ (stay tuned) is no longer telling them to do so. Put in .1 brand-new sel of testes and they should fail also, for

lack ol .1 stimulatory signal. Uui nol a problem, Nearly everyone

reported wondrous results anyway. If you're paying a fortune for painful daily injections of extracts of some beast's testicles, there's a certain incentive to decide you feel like a young bull. One big placebo effect.

With time, scientists figured out that the testes and other peripheral hormone-secreting glands were not autonomous, but were under the control of something else. Attention turned to the pituitary gland, sitting just underneath the brain. It was known that when the pituitary was damaged or diseased, hormone secretion throughout the body became disordered. In the early part of the century, careful experiments showed that a peripheral gland releases its hormone only if the pituitary first releases a hormone that kicks that gland into action. The pituitary contains a whole array of hormones that run the show throughout the rest of the body; it is the pituitary that actually knows the game plan and regulates what all the other glands do. This realization gave rise to the memorable cliche that the pituitary is the master gland of the body.

This understanding was disseminated far and wide, mostly in the *Reader's Digest,* which ran the "I Am Joe's" series of articles ("I Am Joe's Pancreas," "I Am Joe's Shinbone," "I Am Joe's Ovaries," and so on). By the third paragraph of "I Am Joe's Pituitary," out comes that master gland business. By the 1950s, however, scientists were already learning that the pituitary wasn't the master gland after all.

The simplest evidence was that if you removed the pituitary from a body and put it in a small bowl filled with pituitary nutrients, the gland would act abnormally. Various hormones that it would normally secrete were no longer secreted. Sure, you might say, remove any organ and throw it in some nutrient soup and it isn't going to be good for much of anything. But, interestingly, while this "explanted" pituitary stopped secreting certain hormones, it secreted others at immensely high rates. It wasn't just that the pituitary was traumatized and had shut down. It was acting erratically because, it turned out, the pituitary didn't really have the whole hormonal game plan. It would normally be following orders from the brain, and there was no brain on hand in that small bowl to give directions.

The evidence for this was relatively easy to obtain. Destroy the part of the brain right near the pituitary and the pituitary stops secreting some hormones and secretes too much of others. This tells you that the brain controls certain pituitary hormones by stimulating their release and controls others by inhibiting them. The problem was to figure out how the brain did this. By all logic, you would look for nerves to pro-

ject from the brain to the pituitary (like the nerve projections to the heart and elsewhere), and for the brain to release neurotransmitters that called the shots. But no one could find these projections. In 1944, the physiologist Geoffrey Harris proposed that the brain was also a hormonal gland, that it released hormones that traveled to the pituitary and directed the pituitary's actions. In principle, this was not a crazy idea; a quarter-century before, one of the godfathers of the field, Ernst Scharrer, had shown that some other hormones, thought to originate from a peripheral gland, were actually made in the brain. Nevertheless, lots of scientists thought Harris's idea was bonkers. You can get hormones from peripheral glands like ovaries, testes, pancreas— but your *brain* oozing hormones? Preposterous! This seemed not only scientifically implausible but somehow also an unseemly and indecorous thing for your brain to be doing, as opposed to writing sonnets.

Two scientists, Roger Guillemin and Andrew Schally, began looking for these brain hormones. This was a stupendously difficult task. The brain communicates with the pituitary by a minuscule circulatory system, only slightly larger than the period at the end of this sentence. You couldn't search for these hypothetical brain "releasing hormones" and "inhibiting hormones" in the general circulation of blood; if the hormones existed, by the time they reached the voluminous general circulation, they would be diluted beyond detection. Instead, you would have to search in the tiny bits of tissue at the base of the brain containing those blood vessels going from the brain to the pituitary.

Not a trivial task, but these two scientists were up to it. They were highly motivated by the abstract intellectual puzzle of these hormones, by their potential clinical applications, by the acclaim waiting at the end of this scientific rainbow. Plus, the two of them loathed each other, which invigorated the quest. Initially, in the late 1950s, Guillemin and Schally collaborated in the search for these brain hormones. Perhaps one tired evening over the test tube rack, one of them dissed the other in some way—the actual events have sunk into historical obscurity; in any case a notorious animosity resulted, one enshrined in the annals of science at least on a par with the Greeks versus the Tro-jans, maybe even with Coke versus Pepsi. Guillemin and Schally went their separate ways, each intent on being the first to isolate the puta-tive brain hormones.

How do you isolate a hormone that may not exist or that, even if it does, occurs in tiny amounts in a minuscule circulation system to which you can't gain access? Roth Guillemin and Schally hit on the same strategy. They Started collecting animal brains from slaughterhouses. Cut

out the part at the base of the brain, near the pituitary. Throw a bunch of those in a blender, pour the resulting brain mash into a giant test tube filled with chemicals that purify the mash, collect the droplets that come out the other end. Then inject those droplets into a rat and see if the rat's pituitary changes its pattern of hormone release. If it does, maybe those brain droplets contain one of those imagined releasing or inhibiting hormones. Try to purify what's in the droplets, figure out its chemical structure, make an artificial version of it, and see if that regulates pituitary function. Pretty straightforward in theory. But it took them years.

One factor in this Augean task was the scale. There was at best a minuscule amount of these hormones in any one brain, so the scientists wound up dealing with thousands of brains at a time. The great slaughterhouse war was on. Truckloads of pig or sheep brains were collected; chemists poured cauldrons of brain into monumental chemical-separation columns, while others pondered the thimblefuls of liquid that dribbled out the bottom, purifying it further in the next column and the next.... But it wasn't just mindless assembly-line work. New types of chemistry had to be invented, completely novel ways of testing the effects in the living body of hormones that might or might not actually exist. An enormously difficult scientific problem, made worse by the fact that lots of influential people in the field believed these hormones were fictions and that these two guys were wasting a lot of time and money.

Guillemin and Schally pioneered a whole new corporate approach to doing science. One of our cliches is the lone scientist, sitting there at two in the morning, trying to figure out the meaning of a result. Here there were whole teams of chemists, biochemists, physiologists, and so on, coordinated into isolating these putative hormones. And it worked. A "mere" fourteen years into the venture, the chemical structure of the first releasing hormone was published.* Two years after

* "So," asks the breathless sports fan, "who won the race—Guillemin or Schally?" The answer depends on how you define "getting there first." The first hormone isolated was one that indirectly regulates the release of thyroid hormone (that is, it controls the way in which the pituitary regulates the thyroid). Schally and crew were the first to submit a paper for publication saying, in effect, "There really does exist a hormone in the brain that regulates thyroid hormone release, and its chemical structure is X." In a photo finish, Guillemin's team submitted a paper reaching the identical conclusion five weeks later. But as a complication, a number of months before, Guillemin and friends had been the first to publish a paper saying, in effect, "If you synthesize a chemical with structure X, it regulates thyroid hormone release and does so in a way similar to the way hypothalamic brain mash does; we don't know yet if whatever it is in the (continued)

that, in 1971, Schally got there with the sequence for the next hypothalamic hormone, and Guillemin published two months later. Guillemin took the next round in 1972, beating Schally to the next hormone by a solid three years. Everyone was delighted, the by-then-deceased Geoffrey Harris was proved correct, and Guillemin and Schally got the Nobel Prize in 1976. One of them, urbane and knowing what would sound right, proclaimed that he was motivated only by science and the impulse to help mankind; he noted how stimulating and productive his interactions with his co -winner had been. The other, less polished but more honest, said the competition was all that drove him for decades and described his relationship with his co-winner as "many years of vicious attacks and bitter retaliation."

So hooray for Guillemin and Schally; the brain turned out to be the master gland. It is now recognized that the base of the brain, the hypothalamus, contains a huge array of those releasing and inhibiting hormones, which instruct the pituitary, which in turn regulates the secretions of the peripheral glands. In some cases, the brain triggers the release of pituitary hormone X through the action of a single releasing hormone. Sometimes it halts the release of pituitary hormone Y by releasing a single inhibiting hormone. In some cases, a pituitary hormone is controlled by the coordination of both a releasing and an inhibiting hormone from the brain—dual control. To make matters worse, in some cases (for example, the miserably confusing system that I study) there is a whole array of hypothalamic hormones that collectively regulate the pituitary, some as releasers, others as inhibitors.

(continued) hypothalamus also has structure X, but we wouldn't be one bit surprised if it did." So Guillemin was the first to say, "This structure works like the real thing," and Schally was the first to say, "This structure is the real thing." As I have discovered firsthand many decades afterward, the battle-scarred veterans of the Guillemin-Schally prizefight years are still willing to get worked up as to which counts as the knockout.

One might wonder why something obvious wasn't done a few years into this insane competition, like the National Institutes of Health sitting the two down and saying, "Instead of us giving you all of this extra taxpayers' money to work separately, why don't you two work together?" Surprisingly, this wouldn't necessarily be all that great for scientific progress. The competition served an important purpose. Independent replication of results is essential in science. Years into a chase, a scientist triumphs and publishes the structure of a new hormone or brain chemical. Two weeks later the other guy comes forward. He has *every* incentive on earth to prove that the first guy was wrong. Instead, he is forced to say, "I hate that son of a bitch, but I have to admit he's right. We get the identical structure." That is how you know that your evidence is really solid, from independent confirmation by a hostile competitor. When everyone works together, things usually do go faster, but everyone winds up sharing the same assumptions, leaving them vulnerable to small, unexamined mistakes that can grow into big ones.

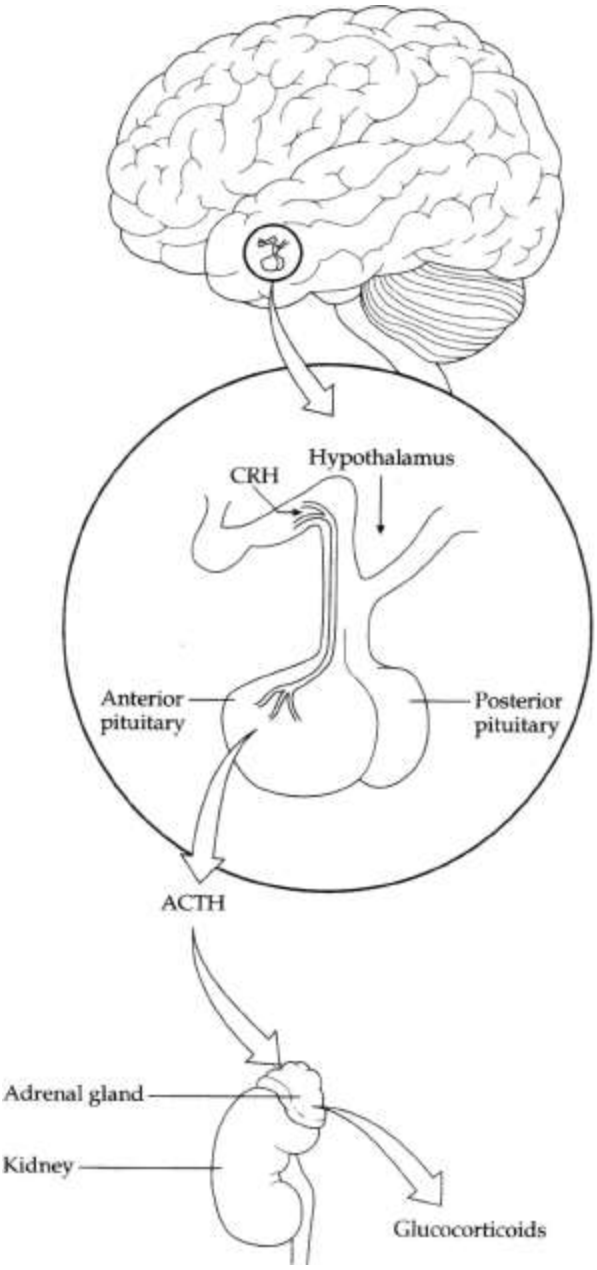
HORMONES OF THE STRESS-RESPONSE

As the master gland, the brain can experience or think of something stressful and activate components of the stress-response hormonally. Some of the hypothalamus-pituitary-peripheral gland links are activated during stress, some inhibited.

Two hormones vital to the stress-response, as already noted, are epinephrine and norepinephrine, released by the sympathetic nervous system. Another important class of hormones in the response to stress are called *glucocorticoids.* By the end of this book you will be astonishingly informed about glucocorticoid trivia, since I am in love with these hormones. Glucocorticoids are steroid hormones. *(Steroid* is used to describe the general chemical structure of five classes of hormones: androgens—the famed "anabolic" steroids like testosterone that get you thrown out of the Olympics—estrogens, progestins, mineralocor-ticoids, and glucocorticoids.) Secreted by the adrenal gland, they often act, as we will see, in ways similar to epinephrine. Epinephrine acts within seconds; glucocorticoids back this activity up over the course of minutes or hours.

Because the adrenal gland is basically witless, glucocorticoid release must ultimately be under the control of the hormones of the brain. When something stressful happens or you think a stressful thought, the hypothalamus secretes an array of releasing hormones into the hypothalamic-pituitary circulatory system that gets the ball rolling. The principal such releaser is called CRH (corticotropin releasing hormone), while a variety of more minor players synergize with CRH.* Within fifteen seconds or so, CRH triggers the pituitary to release the hormone ACTH (also known as *corticotropin).* After ACTH is released into the bloodstream, it reaches the adrenal gland and, within a few minutes, triggers glucocorticoid release. Together, glucocorticoids and the secretions of the sympathetic nervous system (epinephrine and norepinephrine) account for a large percentage of what

* For the three people on earth who are reading this book, read the prior edition, *and* remember anything from it, you may be wondering why the hormone previously known as CRF (corticotropin releasing factor) has been transformed into CRH. By the rules of endocrinology, a putative hormone is referred to as a "factor" until its chemical structure is confirmed, at which point it graduates into being a "hormone." CRF achieved that status in the mid-1980s, and my continued use of "CRF" as recently as the 1998 edition was merely a nostalgic and pathetic attempt on my part to hold on to those reckless days of my youth before CRF was tamed. After much painful psychological work, I have come to terms with this and will use "CRH" throughout.



Outline of the control of glucocorticoid secretion. A stressor is sensed or anticipated in the brain, triggering the release of CRH (and related hormones) by the hypothalamus. These hormones enter the private circulatory system linking the hypothalamus and the anterior pituitary, causing the release of ACTH by the anterior pituitary. ACTH enters the general circulation and triggers the release of glucocorticoids by the adrenal gland.

happens in your body during stress. These are the workhorses of the stress-response.

In addition, in times of stress your pancreas is stimulated to release a hormone called *gluc*agon. *Gluc*ocorticoids, *gluc*agon, and the sympathetic nervous system raise circulating levels of the sugar *gluc*ose. As we will see, these hormones are essential for mobilizing energy during stress. Other hormones are activated as well. The pituitary secretes prolactin, which, among other effects, plays a role in suppressing reproduction during stress. Both the pituitary and the brain also secrete a class of endogenous morphine-like substances called *endorphins* and *enkephalins,* which help blunt pain perception, among other things. Finally, the pituitary also secretes vasopressin, also known as *antidiuretic hormone,* which plays a role in the cardiovascular stress-response.

Just as some glands are activated in response to stress, various hormonal systems are inhibited during stress. The secretion of various reproductive hormones such as estrogen, progesterone, and testosterone is inhibited. Hormones related to growth (such as growth hormone) are also inhibited, as is the secretion of insulin, a pancreatic hormone that normally tells your body to store energy for later use.

(Are you overwhelmed and intimidated by these terms, wondering if you should have bought some Deepak Chopra self-help book instead? Please, don't even dream of memorizing these names of hormones. The important ones are going to appear so regularly in the coming pages that you will soon be comfortably and accurately slipping them into everyday conversation and birthday cards to favorite cousins. Trust me.)

A FEW COMPLICATIONS

This, then, is an outline of our current understanding of the neural and hormonal messengers that carry the brain's news that something awful is happening. Cannon was the first to recognize the role of epinephrine, norepinephrine, and the sympathetic nervous system. As noted in the previous chapter, he coined the phrase "fight-or-flight" response, which is a way of conceptualizing the stress-response as preparing the body for that sudden burst of energy demands. Selye pioneered the glucocorticoid component of the story. Since then the roles of the other hormones and neural systems have been recognized. In the dozen years since this book first came out, various new minor

hormonal players have been added to the picture, and, undoubtedly, more are yet to be discovered. Collectively, these shifts in secretion and activation form the primary stress-response.

Naturally there are complications. As will be reiterated throughout the following chapters, the stress-response is about preparing the body for a major expenditure of energy—the canonical (or, perhaps, Can-nonical) "fight-or-flight" response. Recent work by the psychologist Shelley Taylor of UCLA has forced people to rethink this. She suggests that the fight-or-flight response is what dealing with stress is about in males, and that it has been overemphasized as a phenomenon because of the long-standing bias among (mostly male) scientists to study males rather than females.

Taylor argues convincingly that the physiology of the stress-response can be quite different in females, built around the fact that in most species, females are typically less aggressive than males, and that having dependent young often precludes the option of flight. Showing that she can match the good old boys at coming up with a snappy sound bite, Taylor suggests that rather than the female stress-response being about fight-or-flight, it's about "tend and befriend"—taking care of her young and seeking social affiliation. As will be seen in the final chapter of the book, there are some striking gender differences in stress management styles that support Taylor's view, many of them built around the propensity toward social affiliation.

Taylor also emphasizes a hormonal mechanism that helps contribute to the "tend and befriend" stress-response. While the sympathetic nervous system, glucocorticoids, and the other hormones just reviewed are about preparing the body for major physical demands, the hormone *oxytocin* seems more related to the tend and befriend themes. The pituitary hormone plays a role in causing the female of various mammalian species to imprint on her child after birth, to stimulate milk production, and to stimulate maternal behavior. Moreover, oxytocin may be critical for a female to form a monogamous pair bond with a male (in the relatively few mammalian species that are monogamous).* And the fact that oxytocin is secreted during stress in females supports the idea that responding to stress may not just consist of preparing for a mad dash across the savanna, but may also involve feeling a pull toward sociality.

A few critics of Taylor's influential work have pointed out that sometimes the stress-response in females can be about fight-or-flight,

* A list of species that probably should not include humans, by a number of biological criteria. But that's another book.

rather than affiliation. For example, females are certainly capable of being wildly aggressive (often in the context of protecting their young), and often sprint for their lives or for a meal (among lions, for example, females do most of the hunting). Moreover, sometimes the stress-response in males can be about affiliation rather than fight-or-flight. This can take the form of creating affiliative coalitions with other males or, in those rare monogamous species (in which males typically do a fair amount of the child care), some of the same tending and befriending behaviors as seen among females. Nevertheless, amid these criticisms, there is a widespread acceptance of the idea that the body does not

respond to stress merely by preparing for aggression or escape, and that there are important gender differences in the physiology and psychology of stress.

Some more complications arise. Even when considering the classic stress-response built around fight-or-flight, not all of its features work quite the same way in different species. For example, while stress causes a prompt decline in the secretion of growth hormone in rats, it causes a transient increase in growth hormone secretion in humans (this puzzle and its implication for humans are discussed in the chapter on growth).

Another complication concerns the time course in actions of epinephrine and glucocorticoids. A few paragraphs back, I noted that the former works within seconds, while the latter backs up epinephrine's activity over the course of minutes to hours. That's great—in the face of an invading army, sometimes the defensive response can take the form of handing out guns from an armory (epinephrine working in seconds), and a defense can also take the form of beginning construction of new tanks (glucocorticoids working over hours). But within the framework of lions chasing zebras, how many sprints across the grasslands actually go on for hours? What good are glucocorticoids if some of their actions occur long after your typical dawn-on-the-savanna stressor is over with? Some glucocorticoid actions do help mediate the stress-response. Others help mediate the *recovery* from the stress-response. As will be described in chapter 8, this probably has important implications for a number of autoimmune diseases. And some glucocorticoid actions *prepare* you for the next stressor. As will be discussed in chapter 13, this is critical for understanding the ease with which anticipatory psychological states can trigger glucocorticoid secretion.

Another complication concerns consistency of the stress-response when it is activated. Central to Selye's conceptualization was the belief that whether you are too hot or too cold, or are that zebra or that lion

(or simply stressed by the repetitiveness of that phrase), you activate the same pattern of secretion of glucocorticoids, epinephrine, growth hormone, estrogen, and so forth for each of those stressors. This is mostly true, and this intertwining of the various branches of the stress-response into a package deal starts at the brain, where the same pathway can both stimulate CRH release from the hypothalamus and activate the sympathetic nervous system. Moreover, epinephrine and glucocorticoids, both secreted by the adrenal, can potentiate each other's release.

However, it turns out that not all stressors produce the exact same stress-response. The sympathetic nervous system and glucocorticoids play a role in the response to virtually all stressors. But the speed and magnitudes of the sympathetic and glucocorticoid branches can vary depending on the stressor, and not all of the other endocrine components of the stress-response are activated for all stressors. The orchestration and patterning of hormone release tend to vary at least somewhat from stressor to stressor, with there being a particular hormonal "signature" for a particular stressor.

One example concerns the relative magnitude of the glucocorticoid versus the sympathetic stress-responses. James Henry, who has done pioneering work on the ability of social stressors such as subordinance to cause heart disease in rodents, has found that the sympathetic nervous system is particularly activated in a socially subordinate rodent that is vigilant and trying to cope with a challenge. In contrast, it is the glucocorticoid system that is relatively more activated in a subordinate rodent that has given up on coping. Studies of humans have shown what may be a human analogue of that dichotomy. Sympathetic arousal is a relative marker of anxiety and vigilance, while heavy secretion of glucocorticoids is more a marker of depression. Furthermore, all stressors do not cause secretion of both epinephrine and norepinephrine, nor of norepinephrine from all branches of the sympathetic system.

In some cases, the stress signature sneaks in through the back door. Two stressors can produce identical profiles of stress hormone release into the bloodstream. So where's the signature that differentiates them? Tissues in various parts of the body may be altered in their *sensitivity* to a stress hormone in the case of one stressor, but not the other.

Finally, as will be the topic of chapter 13, two identical stressors can cause very different stress signatures, depending on the psychological context of the stressors. Thus, every stressor does not generate exactly the same stress-response. This is hardly surprising. Despite the dimensions common to various stressors, it is still a very different

physiological challenge to be too hot or too cold, to be extremely anxious or deeply depressed. Despite this, the hormonal changes outlined in this chapter, which occur pretty reliably in the face of impressively different stressors, still constitute the superstructure of the neural and endocrine stress-response. We are now in a position to see how these responses collectively save our skins during acute emergencies but can make us sick in the long run.

3