MELTDOWN

and the Neuroscience of Stress

Arnold Eggers

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This book is dedicated to my children, Serena and Christian.

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I would like to thank my devoted friend Barbara Brewka, who functioned as my chief critic, test-subject, and editor in writing this book.

CHAPTER ONE

HOW THIS BOOK CAME TO BE AND WHAT IT IS ABOUT

This is a book about stress, how it causes a cluster of life-threatening diseases, and what you can do to save yourself. Stress is not always associated with neuroscience but, in fact, understanding what happens in the brain is the key to understanding stress. It all begins and ends in the brain. The focus will be on diseases that actually destroy the brain, although the entire body is ravaged.

STRESS is the physiological response to the perception of overwhelming threats or demands. Notice that this definition starts off psychological, how you react mentally to something that is happening or might happen to you, and ends up physiological, what that perception does to your body. The competitive demands people face in contemporary society can be just as destructive as physical danger. Stress is like starting to slide down the maw of a carnivorous plant where the slope keeps getting steeper and steeper.

STRESS-INDUCED BRAIN DESTRUCTION is the gradual or step-wise irreversible loss of brain tissue with concomitant loss of function caused by stroke and Alzheimer's disease. The process begins with headaches, high blood pressure and obesity. The end point is not necessarily death of the entire body but rather the moment at which the soul decides, in horror, to flee. Remnants of brain tissue linger on.

The plan of this book is to explain to you how stress causes destruction of the brain, stroke and Alzheimer's disease being the words used to describe the final stages of ruin, but the catastrophic process starts much earlier. We will also cover several related diseases that do not, per se, destroy the brain but are intimately related to stress, for example schizophrenia and autoimmune diseases such as hypothyroidism. Dear reader, I trust that you sincerely want to understand this process and will, therefore, introduce some scientific ideas which might be new to you. They will be presented

as metaphors and a qualitative understanding will be enough for you to get a basic understanding of what is going on.

How I became interested in stress is a roundabout story. As a first-year medical student at Columbia University College of Physicians and Surgeons, I was in a state of decline until the first lecture of neuroanatomy, which was in the spring semester, when Malcolm Carpenter, the professor, told us that "the mind is in the brain". Wow! What a revelation. Who would have guessed? That sentence changed my life. I decided I wanted to become a neurologist. Because my father died of cancer while I was a third year medical student, I was inspired to go into cancer immunology with a focus on brain tumors. After training at the National Institutes of Health and a period at Columbia as a faculty member, I took up joint appointments at SUNY Downstate Medical School and Kings County Hospital, which are across the street from each other in Brooklyn, New York. Then one day the Food and Drug Administration arrived on a surprise site visit at my lab; I had managed to acquire what is called a BNDD#, which is usually only given to drug companies who conduct basic and translational research, but my work involved synthesizing new compounds and using them to treat cancer patients. I was doing as an individual what drug companies do on a larger scale and, therefore, needed a BNDD#. That visit was the end of my research career because the FDA imposed an impossible plethora of new regulatory demands. I was nearly fifty years old and had to reinvent myself. Find my sea legs again. Besides my frustration there was an undertow of another emotion which I didn't want to fully admit to myself: I had been given permission to slow down, to be less driven and somehow that was a relief.

The first thing that happened was that friends arranged for me to testify in Congress at a House Government Oversight and Reform Committee session concerning the Food and Drug Administration and how it interfered with the development of new cancer treatments. At that time the committee was headed by Rep. Dan Burton. My testimony went unnoticed by the world except by Dr. Sam Adams, the kindly veterinarian who headed the Downstate animal care department, who saw me on C-span. Sitting next to me and also giving grumpy testimony was a retired congressman from Iowa, Berkeley Bedell. Shortly after the meeting, he contacted me and told me he was setting up a National Foundation of Alternative Medicine to look at alternative and complementary treatments for cancer which were being blocked by the Food and Drug Administration in the United States but which were available in other countries. Would I come onboard? I said yes, but refused to be paid,

saying that all I wanted was a nice dinner every day which had to include good wine. A deal was struck and I became one of the two medical doctors who went on Foundation trips. I did several trips, most of them to Germany. The German government was, and is, much more open to unconventional ways of thinking about cancer treatment than is the case here.

One of the clinics we visited was in Kassel, in central Germany; it had been founded by Mr. Werner Wicker, who had a chain of such clinics and the two of them we visited both seemed to be thriving. The clinic was infused with an extraordinary air of peace and healing. In the lobby was a twiggy white tree which functioned as an antenna to gather in healing energy from the cosmos. Patients were treated with an Ayurveda regimen of diet and massage plus the "usual" relaxation treatments. In almost all of the cancer clinics we visited relaxation therapy was the platform upon which other therapies were laid. All the clinics agreed that the best one was the "continuous shower": the patient, dressed only in a skimpy bathing suit, lies on a table in an otherwise empty room and a horizontal pipe with a row of nozzles releasing spritzes of warm water passes back and forth over them from head to toe. This goes on for maybe a half hour. Apparently they are so totally drained emotionally by this treatment that they sometimes sleep for hours immediately afterwards.

Even though the clinic focused on cancer, they had a few patients with other diagnoses. One of the doctors showed me the medical record of a middle-aged man with a recent diagnosis of high blood pressure. After a couple weeks of Ayurveda and relaxation therapy, his high blood pressure had gone away. The doctor said he had many such patients but, that, alas, after they went back to their jobs and the stress associated with them, the high blood pressure would inevitably come back within a few months. It was an absolutely novel and astonishing concept for me that you could cure, even if only temporarily, what I had been taught to think of as a relentlessly progressive disease. And what was all this stuff about stress? I couldn't wrap my mind around it. Cognitive dissonance abounded. I had to figure it out—what was the relationship between stress and high blood pressure? Trying to understand the effects of stress in general was to become my second career. I was also going back to my first passion, which was straight clinical neurology.

Now, when I "attended" on the ward service at Kings County Hospital, which I did five or six months a year, I not only paid attention to teaching the residents and medical students and taking care of the patients, but also

listened to the questions that were always playing in the back of my mind: Why did so many of our patients have headaches or recent stressful events in their lives? What is the relationship between migraines and high blood pressure? Why does blood pressure rise dramatically at the time of a stroke? In the afternoons, I would go into the wonderful medical library at Downstate and research the literature. The Downstate library, at the time of its founding, incorporated the holdings of the Academy of Medicine of Brooklyn and, as a result, had holdings going back to the beginning of the twentieth century, which was when the medical literature as we know it more or less began. I have always loved sitting in libraries, surrounded by shelves of books. I also began submitting articles to a journal called *Medical Hypotheses*. Over the years I submitted seventeen articles to this journal which set forth my evolving theories about stress. I worked with all three editors of the journal. The first editor and founder of the journal was David Horrobin, who belongs to the lineage of eccentric or slightly eccentric English geniuses. An extraordinarily handsome man, he was married at one time to an Arabian princess; at another time he founded a company to manufacture evening primrose oil, which is a rich source of omega-3 fatty acids. He was one of the founding professors at the School of Medicine at the University of Nairobi in Kenya. Geography was a fortuitous blessing. His interest in phospholipid chemistry combined with the nearby excavations of early hominid skeletons led to the writing of his masterpiece *The Madness of Adam and Eve: How Schizophrenia Shaped Humanity*. The second editor was Bruce Charlton, who was variously a member of the faculty at the University of Newcastle, UK, and a visiting Professor of Theoretical medicine at the University of Buckingham. Think of it: *professor of theoretical medicine*. Everyone knows about theoretical physics and maybe about theoretical chemistry. But theoretical medicine? Apart from *Medical Hypotheses* and invited guest editorials, which requires having connections to get invited, there is no place for medical researchers to publish novel ideas. It is an English publication and the English seem to be on to something. The third and current editor, Mehar Manku, is a phospholipid guy and the editor whom I dealt the most with. Sometimes he and his reviewers would give me what I thought was a hard time--they were strict gatekeepers—but in retrospect I realize it was all a kind of tough love. There were papers I never got published, even if I put them aside for a year, reworked them, and tried to sneak them in as something new. The journal welcomed new ideas, however eccentric, but the ideas had to be supported by facts. Some of the reviewers were also extraordinarily helpful in assisting me to organize masses of jumbled ideas. Eventually a German publishing house contacted me: they had read

an article of mine entitled "A gedanken experiment to find a neuroanatomical model for post-traumatic stress disorder", liked it very much, read some of my other articles, and asked me to write a monograph for them summarizing my thinking. I soon realized that, from a practical point of view, I would need to quote large passages from the articles themselves instead of trying to paraphrase everything. They told me to contact Elsevier to ask about copyrights and, to my delight and eternal gratitude, Tanya Wheatley, the publisher, under Elsevier, of *Medical Hypotheses*, asked "Why don't we republish all your articles in a special virtual online edition?", which they did with an accompanying introductory essay by myself and an editorial by Basant Puri, who is an associate editor of the journal and professor of medicine at the Imperial College, London. The edition was entitled "How Stress Changes the Brain and Causes a Cluster of Uniquely Human Diseases".

So that is the background of how I came to write this book: it was inspired by the Elsevier publication but so many new ideas have been added and the genre is so different that it is basically something completely new. The focus will be on destruction of the brain, rather than, say, myocardial infarction, because standing by, helplessly watching the crucifixion of patients undergoing brain destruction has been at the center of my career. The role of stress in this process is summed up by the Elsevier title: stress changes the brain in a way that leads to the emergence of a cluster of uniquely human diseases. Which diseases are we talking about? Migraines; hypertension; obesity, which is the cause of both high cholesterol and type-2 diabetes (the common type of diabetes); stroke; schizophrenia; autoimmune diseases such as hypothyroidism; atherosclerosis and Alzheimer's disease. There are three things these diseases all have in common. First, they tend to occur together, coming on over time in the same patient. When I would present stroke patients to my attendings as a resident, it seemed like every patient had both hypertension and type-2 diabetes. Plus they might have a history of heart disease and hypothyroidism, and there might be some schizophrenia or early Alzheimer's disease in there too. If you scratched the surface, you found out they had headaches. But I knew many older people, age-matched controls to the stroke patients, who had not a single one of these diagnoses and were more or less perfectly healthy. It seemed like some people went down a bad road and collected several related diagnoses, whereas other people had none. The diseases came as a "package deal". The second thing to know about these diseases is that none of them can be satisfactorily modeled in animals, i.e. they are uniquely human. When I was a medical student I remember Dr. H. Houston Merritt, the head of the Neurological Institute at Columbia,

telling us that the way to do research is to start with an animal model--this was what the National Institutes of Health wanted and would fund--then you could draw inferences from the model and apply them to patients in what is now called "translational research". I now think that Dr. Merritt, who was the greatest neurologist I have ever known, was wrong. How can you tell if an animal has a headache of schizophrenia? *Do* animals get headaches or schizophrenia? The animal models of high blood pressure and obesity depend on mutant strains of rodents and bear little resemblance to the human diseases. Animal models of atherosclerosis are woefully inadequate and animal models of Alzheimer's disease contrived. The third characteristic of our group of diseases is that the genetic revolution has, for the most part, passed them by. Genome-wide screening has failed to find common genes which are of major causal importance. To be sure, every disease is polygenetic in the sense that genes modify and, as a collective whole, determine the biological substrate of our lives, but the diseases we are talking about are not genetic like cystic fibrosis, Huntington's disease, or hemophilia, where having the disease depends on having a specific gene and the disease marches through families from generation to generation according to the pattern of inheritance of the gene. None of the diseases we are going to discuss is defined by the presence or absence of a specific gene.

Longevity is a relevant concept in this context. In 1870 patients began to be enrolled in a very interesting study, the Danish twin study. 2872 Danish twins, some of whom were identical and some fraternal, were enrolled between 1870 and 1900 and then followed until the times of their deaths. The causes of death were not part of the study, only the age at death. The lifespans or longevity of the study subjects was compared to that of people of the same age in the general population. The people in the study did not die from the big three killers for our species, which are war, plague and famine. Modern medicine was starting to creep in but they did not have access to all the treatments we do. What the study showed was that identical twins were more likely to die at the same or similar age than fraternal twins, while fraternal twins were no more likely to die at the same or similar age than two people chosen at random from the general population. This is surprising if you believe that genes have a lot to do with longevity—people say you have to be born with the right genes if you want to live to a ripe old age—because fraternal twins share half their genes and, if genes have a big impact on longevity, they should have had closer lifespans than two unrelated people in the general population. But they didn't. A statistical analysis of the results led to the conclusion that genetics accounted for only about a quarter of the variability of longevity,

26% for men and 23% for women. All the rest of it is "environmental", but what does that mean? Some of it might be exposure to carcinogens or getting run over by buses, but I would suggest that most of it is stress. Stress and how we handle it is a major determinant of how long we live. I am specifically talking about a relationship between stress and the diseases listed above, which is the topic of this book.

Recap: The diseases of stress tend to occur as a cluster, so that one either gets many of them or few-to-none; none of them can be adequately modeled in animals because they are uniquely human; and none of them depend on the presence or absence of a particular gene—they are not genetic in the narrow sense of the word but, like all complex biological happenings, they are molded by many genes. Longevity studies show that most of longevity is not genetic but environmental, possibly relating to stress: anyhow, that is our starting hypothesis.

Now we are going to see what happens to someone who starts to go down the bad road. The place to start is with migraine because having uncontrolled headaches is a key which many people inadvertently turn in the door that opens onto the bad road. Our species was born under an evil star and most of us, in modern society, are destined to walk at least partway down the bad road.

CHAPTER TWO

HOW MIGRAINE WORKS

At any given point in time approximately 15% of the population is suffering from migraine headaches, women having a higher incidence than men. The lifetime incidence approaches 100% in women, being somewhat lower in men. The word "migraine" is a medieval French word which is derived from the Latin word "hemicranium" by dropping the "he", changing the "c" to a "g", and fiddling with the end of the word. "Hemicranium" means "half of the head" in Latin and, as patients with migraines know, a typical headache is one-sided, occurring on different sides of the head in different attacks. There are other kinds of headache, too, bilateral headaches, whole-head headaches, headaches around the eye that wake you up in the middle of the night, tension headaches, and so on, all of which are members of the overall migraine family of headaches. Often patients get more than one kind of headaches and the headaches tend to get worse over time, often progressing to a condition of chronic daily headaches. Migraine pain is peculiarly unpleasant—migraine patients who try to draw or paint what it is like will sometimes depict a large eagle or vulture sitting on the top of their head trying to pry open their skull. The pain responds poorly to narcotics.

Where does the pain originate? This question was answered in classical experiments published by Harold Wolff in 1940. He was the chief of neurology at New York Hospital-Cornell Medical School in Manhattan. In those days—this is now hard to believe—brain surgery was often done under local anesthesia. The famous epileptologist Wilder Penfield, an American who worked at the Montreal Neurological Institute, stuck electrodes into the brains of epilepsy patients undergoing surgery and reported what happened: he would apply pulses of alternating current to the surface of the brain and a patient's arm might move involuntarily, or they might feel a strong fearful emotion; patients were awake and could describe their subjective experiences. Sometimes he triggered an epileptic seizure, which was what he was looking for because he was trying to find a scar to remove to cure the patient's epilepsy. Wolff did not open the "dura", which is the thick membrane between the brain and skull. He

applied a DC rather than AC stimulus to the dura and found he was able to reproduce all the main syndromes in the migraine family of headaches. If he stimulated the dura next to the middle meningeal artery, one of the main arteries supplying the dura, the patient reported a unilateral throbbing headache, which is, of course, the most typical kind of migraine headache. If he applied his stimulus next to one of the large veins draining the dura, the patient would report a unilateral "tension" (i.e. non-throbbing) headache. Stimulation of an area called the "anterior fossa" caused headache around the eye ("cluster headache") and stimulation of the "posterior fossa" caused pain in the lower back of the head going down into the neck ("cervicalgia"). It is now generally accepted that migraine headaches are caused by inflammation of the dura. Wolff's electrical pulses reproduced the effect of inflammation. Inflammation is caused by a local accumulation of white blood cells which "extravasate" or leave the blood vessels; they release small chemicals called "cytokines" which cause the classic signs of inflammation, which are pain, swelling, redness, and heat. Inflammation is usually caused by trauma, infection, or an allergic reaction—think about banging your thumb, having an abscess, or getting bitten by a mosquito. The pain of migraine inflammation is what we call "referred pain" as opposed to direct damage to a nerve. Migraine headache pain being "referred" to the surface of the head is similar to appendicitis pain being felt around the umbilicus or heart attack pain being felt going down the left arm. In each case, the brain makes a curious mistake in figuring out exactly where the problem is and "refers" the problem to the wrong place. Referred pain is often poorly localized.

Then what causes the inflammation? This question was answered definitively in an article published by Morris Maizels et al. in the *Journal of the American Medical Association* in 1996. The investigators placed patients suffering with an acute headache in an uncomfortable position: lying face-up on a table with their head projecting beyond the edge of the table and bent downwards. A dilute solution of a local anesthetic (4% lidocaine, to be exact) was then dripped into the patient's nose so it could trickle down into the upper nasal passages, which were then below the level of the table. The headache was relieved in a few minutes in a majority of cases. The way it worked was that the local anesthetic diffused through the nasal mucosa and paralyzed nerves in what is called the "sphenopalatine ganglion" at the base of the skull. As most medical students recall with horror, this little base-of-skull region has probably the most complicated anatomy of any place in the body outside the brain. To put it in technical terms, paralyzing nerves of the "autonomic nervous system" terminated the inflammation in the dura and relieved the pain.

Nerves which leave the brain and spinal cord and travel out into the rest of the body are called "peripheral nerves"; most of them do one of two things: either they bring in sensory information from the periphery, such as where your fingers are in space or whether or not your foot is getting burned, or else they cause contraction of voluntary (also called "skeletal") muscles, which is the basis of all volitional movement, such as moving your hand or walking. A small subset of peripheral nerves belongs to the autonomic nervous system, which is involved with housekeeping functions, such as regulating blood pressure, pulse, digestion, and metabolism. Autonomic nerves can also trigger inflammation and this is what happens in the dura in migraine. It is an aberrant event and not a normal physiological function. The inflammation causes pain which the brain then mistakenly refers to some part of the surface of the head, depending on where the inflammation is localized in the dura. Some pain specialists will put nerve blocks in the sphenopalatine ganglion, which can relieve migraines for months at a time. The original journal article received little publicity at the time because lidocaine is an old non-patentable medication and, therefore, there was no possibility for a pharmaceutical company to make a profit from it or motive to advertise it.

There are also a lot of non-headache symptoms in migraine. The condition is named after the headache but the headache is just one symptom among equals and the non-headache symptoms can occur without a headache: we call this "acephalgic migraine". The most common non-headache symptoms which accompany headaches are "photophobia" and "phonophobia" which doesn't mean you are afraid of light or sound but that a normal intensity of light or sound becomes unpleasant. Thresholds for sensory perception can be lowered. There is a memorable passage in Ian McEwen's novel *Atonement* in which the matriarch of the family, who seems to spend all her time lying in bed with a migraine, is described as being able to hear everything that happens in the entire large house, so acute is her hearing. The most common non-headache symptom which occurs without a headache is, in my experience, "vertigo", which is a spinning sensation that can throw you off balance. Visual migraine symptoms are legion: flashing lights, colored spots, and zigzag lines are the most common. The zigzag lines are usually part of a "fortification figure", in which bright opalescent or rainbowy zigzags form a partial circle reminiscent of a bird's eye view of the zigzag walls of a medieval castle or fort. Outright formed visual hallucinations occur. I remember a woman in clinic who, after she got to know me, confided that she saw her grandfather's ghost during her headaches. She believed the ghost was real and that it came to visit her only during her headaches. I remember a young woman hospitalized with

an acute migraine who told us that the sunlight streaming in around the edges of the window shade was bright green in color, as were the white sheets on her bed, and there was a large rat sitting in the crack under the bathroom door. Patients can go blind in one eye, part of one eye, or both eyes. Nausea, vomiting, and diarrhea are common. I have known migraineurs who suffered unpredictably from day-long bouts of diarrhea unassociated with headache. Weakness and/or numbness on one side of the body is common. Perhaps the most bizarre migraine story I can remember is that of a West Indian man who was a retired carpenter. His son had borrowed one of his carpentry tools earlier in the day without permission and this led to the patient having a rage attack. A few hours later when he was trying to change his clothes, he found he couldn't remember how to put his legs into his pants—he wasn't paralyzed, he just couldn't make it happen. Neurologists refer to this as a "dressing apraxia" and it localizes to what we call the "right parietal lobe" of the brain. Then he had a brief sudden excruciating headache, what we call a "thunderclap headache", followed by going totally blind. Within a half hour he was back to normal. Of course, we rounded up the usual suspects and ruled out a stroke or epileptic seizure, but it was apparent from the history that this was a "complicated migraine", that is, a migraine with headache plus non-headache symptoms, which, in this case, was clearly related to acute stress. Another very interesting non-headache migraine symptom is what we call "transient global amnesia", an episode lasting from hours to days in which a patient is unable to lay down new memories and has variable loss of memory for past events. Patients live in a perpetual present, not knowing where they are. I have never had a headache, but I do get visual fortification figures and once had an episode of transient global amnesia. I was on vacation in Japan, having just come off a stressful period at work and having recently been mugged in the subway in Manhattan. I remember coming back to my room in a hotel in a village in the Japanese Alps. I saw my suitcase but didn't recognize the room or the hotel. I had a map of the village in my hand which I had apparently used to get back to the hotel (there was a festival going on) but I didn't remember that either. I somehow managed to keep up with my travel group but they told me afterwards that I had been a bit odd and I eventually discovered that I had taken curiously lopsided and out-of-focus photographs of things I didn't recognize. I went in and out of this twilight state for three or four days.

How can migraine do all these strange things? The answer is that it is an electrical disease of the brain, the *other* electrical disease of the brain, epilepsy being the one everyone thinks of first when brain electricity is

mentioned. We are now going to have a lesson on how the brain works. Be brave, it is simple

The cells in the brain are called "neurons", which have a round or polygonal cell body which is usually quite plump and is called the "soma" (see Fig. 2-1). On one side of the soma are a cluster of little branched arms or legs, which are called "dendrites", and on the opposite side is a branching tube-like extension cord which can run long distances, sometimes from the front of the brain to the back. The extension cord is called an "axon" and each branch of the axon makes contact with one of the dendrites of a target neuron, which can be compared to an electrical outlet. The trick is that the axonal extension cord doesn't quite plug into the dendritic socket: there is a little gap between them called a "synapse" and the arrival of an electrical signal going down the axon causes the axon to release a chemical called a "neurotransmitter" which has to diffuse across the gap and give a chemical signal to the dendrite. The chemical signal can be positive (what we call "depolarizing") or negative (what we call "hyperpolarizing"). It's like an election with yes votes or no votes. In general, many axons terminate on the dendrites of a given neuron and all the votes have to be tallied up. If the yes votes win, then a new electrical signal is launched to go down that neuron's axon and all its branches, where it will eventually participate in a new votes at new target neurons to decide whether or not those neurons will continue to propagate the chain of signals. Notice that electrical signals alternate with chemical signals: when the electrical signal going down the axon reaches its target dendrite, it causes release of the neurotransmitter, which registers the yes or no vote about sending off a new electrical signal. The synapse is microscopic, whereas axons are the long-distance telephone wires running all over the brain and may be inches in length. A given neuron always votes either yes or no when its neurotransmitter arrives at its destination: it is either an "excitatory" neuron or an "inhibitory" neuron. There is another category of neuron, which are very interesting: the pacemaker neurons. They are like pacemaker cells in the heart. The brain is chockablock full of them. If you take a pacemaker neuron out of the brain and put it into a tissue culture dish, it spontaneously generates a rhythmic stream of electrical signals that go down its axon. It doesn't have to wait for the results of an election to decide whether or not it is going to fire. When electrical signals going down pacemaker axons arrive at their destination, they don't submit a conventional yes or no vote at the synapse. They release chemicals which do something different, which is to "modulate" the dendrite so as to make either the yes votes or the no votes coming from conventional neurons count more than they would otherwise, which is a kind of vote

fraud. Technically, it's called an "excitatory" or an "inhibitory" effect. They can also do something even more astonishing: they can function as "growth factors", which are chemicals that stimulate cell division of certain neurons in certain parts of the brain.

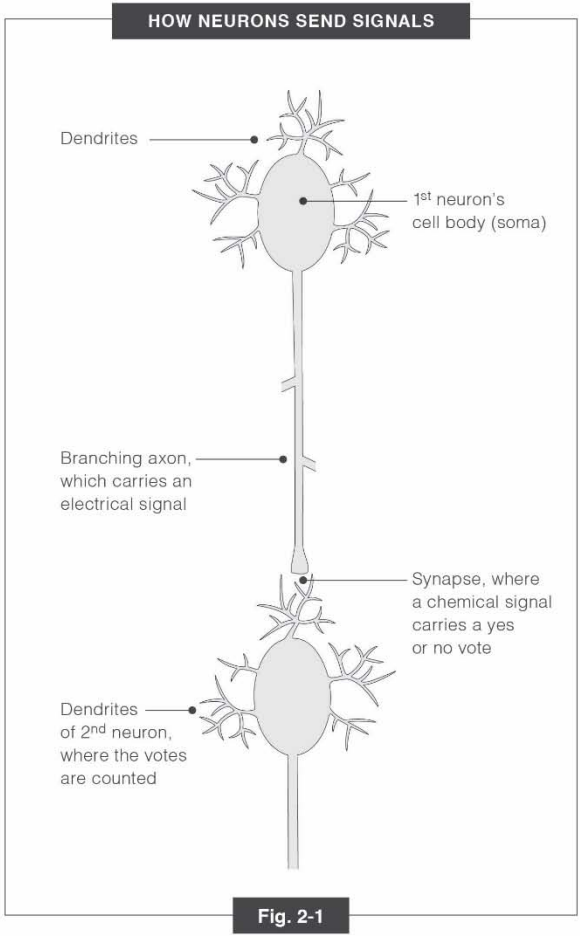
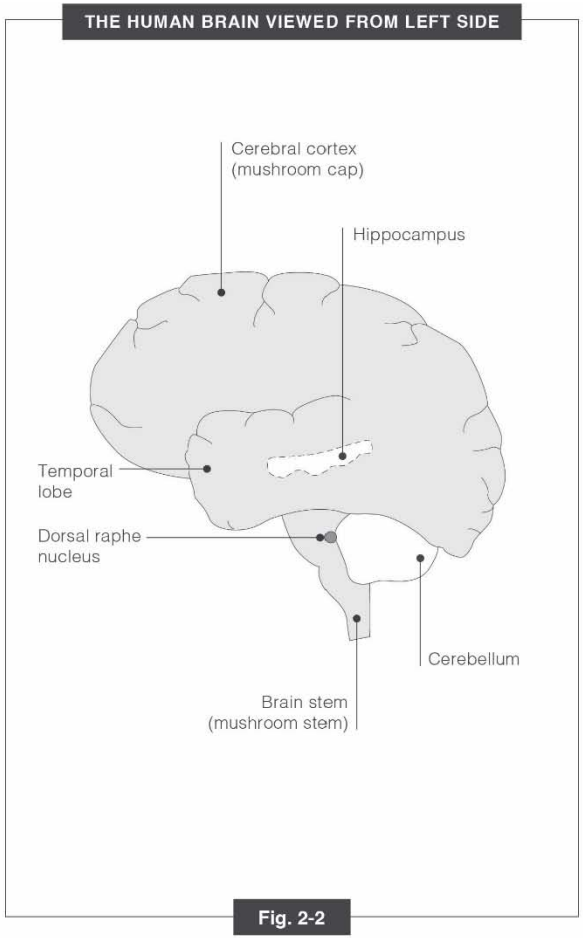


Fig. 2-1

Let us now explore the key role of pacemaker cells in migraine. In 1995 a group of German investigators published a historic paper in the journal *Nature Medicine*; the lead author was C. Weiller. They used PET (positron-emission) scanning to image the brains of patients with acute migraine headaches. This technique images areas of the brain which are

most active metabolically; continuing the analogy used above, it shows which areas of the brain where either: (1) conventional neurons are holding the most elections and sending new electrical signals down their axons, or (2) busy pacemaker neurons are launching repetitive signals without the need for vote tallies. What the German group found was that a specific area of the brain is consistently very "hot" or metabolically active during migraines, with neurons firing at a persistent extremely high rate, similar to that associated with epilepsy, although it is not epilepsy This area is the "dorsal raphe nucleus" (DRN), which is now considered to be the "brainstem generator" of migraines. The brain is shaped something like a mushroom (or the cloud formed by an atom bomb explosion). See Fig. 2-2. The cap of the mushroom is the "cerebral cortex", where "higher" brain functions such as sensory perception, volitional movement, thinking, memory and consciousness reside. The cerebral cortex is arranged in zones, each of which has a distinctive pattern of layered sheets of neurons (it's like a layer cake); many of the zones can be associated with specific functions, like vision, movement, language, memory. The stem of the mushroom is called the "brain stem"; in this part of the brain neurons are organized in clusters of cells called "nuclei" rather than in layered sheets. Some of the nuclei are "relay nuclei" for sensory information coming in from the periphery, some are relay nuclei for motor commands going out to the periphery, and some do other things such as organize eye movements or supervise housekeeping functions. The DRN is half way up the brain stem, in the "midbrain". It a nucleus or cluster of neurons which are pacemaker neurons; when their axons arrive at their destinations, they don't give a simple yes or no vote: they modulate or bias the vote tallies being held in that neuron in either a yes (excitatory) or no (inhibitory) direction. The chemical released by DRN neurons is "serotonin". This is the same chemical which is so important in depression. The DRN is also remarkable for the fact that its axons go almost everywhere in the brain and even down into the spinal cord, which means it is perfectly situated to organize complicated brain-wide events like migraine. It is not understood in detail how this happens but the basic picture is clear: the DRN, suddenly decides to fire manically and takes over the brain. One of the things it can do is to cause inflammation of the dura, which causes the headache. But it can do so much more, causing all the non-headache symptoms and even the bizarre vignettes described above. As mentioned earlier, the headache is only one symptom among equals and the non-headache symptoms can occur without the headache, which is an acephalgic migraine.



Why does the DRN fire aberrantly? Occasional situational headaches are just that: they relate to situations, specifically to stressful situations. This is only common sense. My favorite case in literature concerns the governor's wife in Bertolt Brecht's play *The Caucasian Chalk Circle*, who has a migraine headache every time she is exposed to the lower classes. Let us return to our earlier definition of stress, which is "the physiological response to the perception of overwhelming threats or demands". The key point is the sense of almost losing control. It is surprisingly difficult in the medical literature to find documentation of the relationship between acute stress and headaches, although recent clinical studies have finally put this

on a firm basis. The explanation of this paradox is that migraines, over time, tend to evolve from a pattern of occasional clearly situation-related events to one of frequent, eventually more-or-less daily, headaches which arise spontaneously without acute stressors. The "chronic daily headaches" pattern, as it is called--and it doesn't have to be literally every day--of patients with late or established migraine, as opposed to patients with early situational migraine, obscures the role of stress. The transition point between "acute situational migraine", where the DRN goes manic only in response to specific events in which the individual has the sense of losing control, and established or "chronic or daily headache" migraine, where the DRN goes manic ad lib, is when a person starts to go down the bad road and puts themself at risk of developing a whole series of other diseases. How this comes about is the topic of most of the rest of this book.

Recap: Migraine is an electrical disease of the brain. The way information is passed along in the brain can be compared to holding votes at synapses. Pacemaker nuclei commit vote fraud at synapses. The dorsal raphe nucleus (DRN), which is a pacemaker nucleus located in the mid-brain, fires aberrantly and organizes a complex array of both headache and non-headache migraine symptoms. The headache is caused by inflammation in the dura which gets referred to the surface of the head.

So far we have looked only at the part of the migraine iceberg which is above water. In the next chapter we will look at the part that is under water. It's the under-water part of an iceberg that sank the Titanic.

CHAPTER THREE

SYSTEMIC PLATELET ACTIVATION

As I studied the medical literature, I discovered that there is a hidden disease which has never been recognized—bits and pieces of it appear here and there--but it has never been pulled together as a single entity. I have named this disease "systemic platelet activation" (the last thing the world needs is yet another medical term, so I kept it simple). It is a major so-called cardiovascular risk factor for heart attacks and strokes and an important piece of the puzzle in trying to conceptualize several other diseases as well. This chapter is very important and contains some new scientific ideas; you only have to understand them qualitatively in order to keep up with our story. You could skip to the recap at the end of the chapter if you want but I recommend ploughing through. The bravest cohort will read the chapter twice. It's all downhill after this chapter.

Platelets are one of the three kinds of blood cells: red blood cells carry oxygen, white blood cells fight infection and cause inflammation, and platelets participate in "thrombosis" or "coagulation", both of which are considered more correct medical terms than "clotting". Platelets are the smallest of the three types of blood cell. They break off as little chunks from mother cells in the bone marrow called "megakaryocytes", like the way icebergs break off a glacier touching the ocean, and then they circulate in the blood, waiting to be called into action. Unlike proper cells, they have no nucleus—they broke off as icebergs—and therefore no DNA, which would be required to sustain metabolism; their lifespan is only eight to nine days. In order for platelets to do their thing, you have to press an ON button, which means a chemical in the blood has to bind to a specific receptor on the surface of the platelet. There are several of these chemicals, but the one that interests us here is "epinephrine" (also called "adrenalin"), which can be released by the adrenal medulla. The adrenals ("ad"-meaning on top of, and "renal" meaning kidney) are paired endocrine glands which sit like little hats on top of the kidneys, one on each side. See Fig. 3-1. The outer shell of the adrenal secretes cortisol and some other hormones and the inner core, or adrenal medulla, secretes epinephrine in response to stimulation by the autonomic nervous system, the

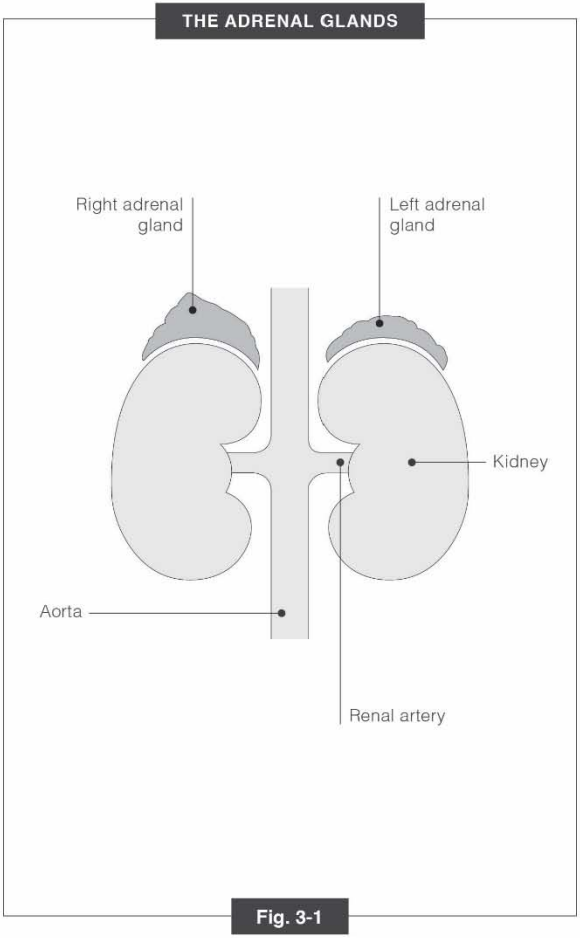


Fig. 3-1

part of the nervous system that handles housekeeping functions. Stress is the signal that causes the adrenal gland to secrete epinephrine, which activates all the platelets in the blood because it goes everywhere, hence the term "systemic platelet activation", which we will refer to as SPA. The stress can be either physiological, for example, part of a response to infection or major blood loss, or it can be psychological. Historically, the first discovery of SPA was reported by Federigo Sicuteri et al, published in the *International Archives of Allergy* in 1961. Sicuteri appeared to be on a fishing expedition, searching for disease correlations of abnormally high or low levels of chemicals called "monoamines", which include serotonin—

yes, the same chemical the DRN releases at synapses. What he found was that most but not all migraineurs during an attack have elevated urine levels of serotonin breakdown products ("metabolites"), which at that time were easier to measure than serotonin itself in the blood. He became interested in a possible relationship between serotonin, which is a "vasoconstrictor" (a chemical that constricts or narrows blood vessels) and "vasospasm" (which occurs when blood vessels are so narrowed that blood can hardly get through them), which was part of an old and now discarded theory about what happens in migraine. One of the largest pools of serotonin in the body is in "granules" stored in platelets. Platelets store several kinds of chemicals, including serotonin, in these granules, which are like little Ziploc® bags which are unzipped and their contents released into the blood on cue when platelets are activated by pressing an ON button. See Fig. 3-2. The high level of serotonin breakdown products in the urine of many migraine patients is a marker for activated platelets releasing serotonin. When people realized that there was a poor correlation between serotonin release and migraine symptoms, they lost interest in the topic. But it is a major physiological event. Platelet granules contain important biologically active chemicals. By studying blood levels of these chemicals, much has been learned about SPA. For example, 66% of platelets—that's 2/3 of them—dump a package of chemicals into the blood in a typical migraine, although, interestingly the platelet count doesn't fall because the bone marrow quickly releases new platelets to take their place. Activated platelets "aggregate" or clump together and are probably cleared from the circulation by the spleen or liver, being unable to function a second time. It has also been found that migraineurs undergo "platelet degranulation" (dumping the Ziploc® bags), which is the marker for SPA, in between headaches and that SPA may be just as intense between headaches as during headaches. This means SPA is often an asymptomatic event. Perhaps the most practical test for quantifying SPA is to measure blood levels of one of the chemicals released by the Ziploc® bags called "beta-thromboglobulin".

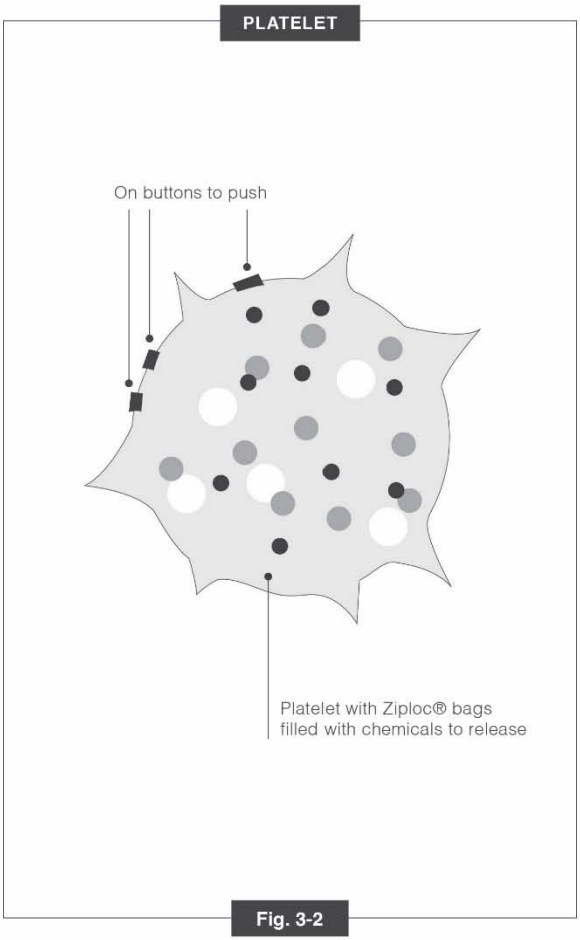


Fig. 3-2

Vasoconstrictors released by platelets

"Vasoconstrictors" are chemicals that cause the circular ring of muscle cells in the walls of blood vessels to contract, thereby narrowing the blood vessel. The two vasoconstrictors discharged by activated platelets are serotonin and "thromboxane A_2"; both are very powerful. While it might be a good thing to constrict "arterioles" (or small arteries) when platelets are called to the site of a hemorrhage, it does not sound like a good idea to constrict all the arterioles in the body for no reason at all and potentially

on a long-term basis. It can raise blood pressure, for starters, as we will see in the next chapter.

Initiation of the coagulation cascade independently of tissue injury

The formation of a thrombus (clot) requires two things: activation of platelets and activation of the coagulation cascade, which is a whole series of proteins that have to be triggered in a specific sequence. When one protein is activated, it activates the next one in turn. Whenever you find something like this is in biochemistry, you know that this is a pathway of critical biological importance and the reason for so many steps is to permit tight control of the process. The coagulation cascade is shaped like a Y with two separate pathways, the two arms, which then come together in some common final steps which constitute the stem of the Y. Medical students usually hate having to memorize all the individual steps, which include the various proteins involved in the various kinds of hemophilia. For example, Factor VIII deficiency is the cause of the hemophilia which famously afflicted members of the intermarried European royal families in the years before WWI. The hemophilia proteins are, so to say, in the left arm of the Y. When local tissue injury or trauma occurs, the right arm of the Y is activated or turned on by "tissue factor", which is a protein which is usually hidden in subcutaneous tissue and does not come into contact with the coagulation proteins in the blood unless there is trauma and disruption of normal tissue structure. But platelets have to be turned on as well, which is done by "collagen", another common protein in subcutaneous tissue. The whole coagulation cascade plays out on the surface of activated platelets, the platelets both speeding up the process and protecting it from natural anti-coagulant proteins normally circulating in the blood. It is the left arm of the Y which initiates thrombosis when blood is placed in a sterile glass test tube, which is what happens in laboratory tests of coagulation. It turns out that glass, because it is a negatively charged surface, can activate both platelets and Factor XII, the starting point of the left arm of the Y. The left arm of the Y is more than just a way to measure coagulation in the laboratory: it is of great physiological importance. The other name for Factor XII is Hageman Factor, which is named after Mr. John Hageman, a railroad worker whose blood was discovered not to coagulate in a glass tube, even though he had no bleeding problem. (It is like a New Yorker cartoon I saw as a child which was entitled "The day the bar of soap sank at Procter and Gamble" and depicted worried men in business suits walking around a rectangular indoor swimming pool with a

little gurgly vortex in the center—Ivory soap was supposed to be so pure it floated.) A very important experiment was reported by Peter Walsh et al. in the *British Journal of Haematology* in 1972. Walsh found that platelets from a normal person which are activated by a chemical called ADP and mixed with "plasma" also taken from a normal person would coagulate in a plastic (non-glass) test tube. Plasma is blood that has been spun so fast in a centrifuge that all the blood cells, including the platelets in this case, go down to the bottom of the tube and you can pour off the cell-free liquid which contains all the coagulation proteins. You have separated platelets and coagulation proteins, which enables you to mix together platelets and coagulation proteins from different people. Walsh's result was surprising because plastic does not activate the coagulation cascade the way glass does and it was unclear how coagulation got going: remember that you need to activate both platelets and one of the two arms of the Y cascade. Then he repeated the experiment using platelets or plasma from a patient who, like Mr. John Hageman, had a congenital deficiency in Factor XII. What he found after a series of experiments was that the platelets from a Factor XII deficient subject, which were inherently normal, didn't work unless they were pre-incubated with normal plasma containing Factor XII. What this meant was that platelets, any platelets, bind inactive Factor XII and, when the platelets are activated, they in turn activate the bound Factor XII, thereby initiating coagulation. This initiation pathway can be called the "activated platelet initiation pathway". Now we have a direct pathway going from release of epinephrine by the adrenal medulla to activation of platelets by epinephrine to initiation of a thrombotic process which occurs diffusely in the entire vascular tree. Better watch out! This is a "pro-coagulant state", also known as a "hypercoagulable state", which means you are already halfway to having blockage of an artery or vein by a focal thrombosis. It is also worth noting that there is a reciprocal relationship between platelet activation and the coagulation cascade because the product of the next to last step of coagulation, the protein "thrombin", has its own special ON button on platelets to push. The two processes are interconnected and reciprocally activate each other.

The oxidative burst of free radicals

What is a free radical? As many people will remember from high school chemistry, an atom consists of a nucleus surrounded by a cloud of electrons. The nucleus, in turn, is made up of protons and neutrons. Atoms join together into larger chemical structures called molecules, which are held together by chemical bonds between the atoms. According to

chemical theory, a molecule is most stable if all the electrons are "paired"; that means they are supposed to come in two's when you draw a diagram of the chemical structure of the molecule according to chemists' rules. A free radical is a molecule that has an unpaired electron, which may or may not spell trouble. This leads us to the larger issue of the central role that unpaired electrons play in biology. It all starts with chlorophyll in plants. Chlorophyll molecules in a plant are able to trap some of the energy in sunlight--they literally catch photons--and use this energy to lift electrons out of water molecules and transfer them to a receptor molecule destined to carry energy from sunlight. The sun's energy is changed into chemical energy in the receptor molecules and oxygen molecules are formed from the remnants of the water molecules. Let's take this slow. What is energy? When I was freshman in Columbia College, I placed into an advanced Physics course taught by Professor Melvin Schwartz, who later went on to win a Nobel Prize. I got an A in the course because I was very good at calculus and could substitute skill with handling equations for understanding of underlying realities. In the case of energy, I am still baffled by the concept. I don't think anyone has ever understood what potential energy is. The concept is a mathematical construct invented by Isaac Newton. Tycho Brahe, who was Danish, accurately plotted the motions of the planets in the sky. Johannes Kepler, who was German, then interpreted Brahe's data to show that the orbits of the planets around the sun were elliptical and not circular as previously thought. Newton then invented calculus (simultaneously and independently of the German mathematician Gottfried Wilhelm Leibniz) plus he discovered his laws of motion and the law of gravity. He explained mathematically why planets travel in elliptical orbits, which was the proof of his theory. So energy, a key component of Newton's theory, is valid in a utilitarian sense, it's just inscrutable. Energy comes in different forms: kinetic energy, potential energy, gravitational energy, electromagnetic energy, chemical energy, heat energy, etc., all of which can be converted back and forth. Einstein predicted that mass can be converted into energy, which is what happens in an atom bomb explosion.

So what is chemical energy, i.e. the energy stored in a chemical bond? This can be explained only by quantum mechanics—the proof of quantum mechanics is that it explains the chemical bonds between atoms in a molecules. In formal terms, a chemical bond leads to a decrease in electrostatic potential energy between two atomic nuclei, which can come closer together because of the increased density of the electron cloud between them. Anyhow, it is a special form of energy which explains why molecules hold together and don't come apart into individual atoms.

To review, chlorophyll is able to use energy from the sun to remove electrons from water and insert them into recipient molecules, where the sun's radiated electromagnetic energy is now stored as chemical energy. Oxygen is created as a byproduct of this chemical reaction.

What happens now is quite extraordinary. Molecules which are carrying the extra electron with the sun's energy now move to a specialized part of the cell called the "mitochondrion" (plural "mitochondria"). The sun's energy can also be stored in sugar molecules and then moved to special carrier molecules during the breakdown ("metabolism") of sugar. The carrier molecules take the energy to the mitochondria. The mitochondrion is a "cell organelle", a specialized structure within the cell; in remote evolutionary times, the mitochondrion was thought to be a separate bacteria-like organism which moved into plant and animal cells to form a symbiotic relationship, like a fungus and an algae forming a lichen or like oak trees and truffles helping each other out. Mitochondria have some DNA of their own, but need help from the cell to supply them with nutrients and to help them divide, which they do when the cell itself divides. Mitochondria are the energy plant of the cell. They take the unpaired electron and pass it along a chain of large molecules in mitochondria called "protein complexes"; at the end of the "electron transport chain", the chemical energy from the sun is transferred to a molecule called adenosine triphosphate (ATP) and the electron itself is returned to oxygen we breathe in. The oxygen goes back to water. There was no oxygen in the earth's atmosphere before chlorophyll molecules in plants and blue-green algae started taking electrons off of water molecules. ATP is the money of the cell. It is used to drive all chemical reactions of the cell and make life happen. For example, the way "enzymes", the proteins that carry out important chemical reactions in the cell, work is that ATP attaches a phosphate group (one of the three phosphate groups in ATP) to the protein, which then folds into a new shape where it can carry out its function. When the phosphate group is removed, the protein goes back into the inactive shape.

Another important concept is that some molecules with unpaired electrons (i.e. free radicals) are reactive and some are not. Oxygen, for example, is not very reactive. It rusts iron, which is a very slow process indeed, and only moves fast if the entire reaction is heated up, in which case you have a fire. You strike a match on the match box so that friction can start combustion of the matchstick. Other free radicals don't need to be heated up; at body temperature they initiate unwanted and destructive chemical reactions, often attacking large molecules like lipids (fats), proteins and

nucleic acids (genetic material like DNA). They particularly like to zoom in on the double bonds found in some lipids. A very common dangerous free radical is the "superoxide anion", which is an oxygen molecule which has acquired an extra election; it is somehow very reactive, more reactive than oxygen, damaging to large molecules and disruptive of cell function.

When you push the ON button on platelets and activate them, they release a burst of superoxide anions (hence the term "oxidative burst"). This is the same thing that white blood cells do when fighting bacterial invaders. It is like a barrage of machine gun fire. The superoxide anion can undergo some rapid chemical transformations, one of which leads to the formation of hydrogen peroxide, which can diffuse across cell walls and cause damage inside cells. The oxidative burst of platelets, while as intense as that produced by white blood cells, is of shorter duration. White blood cells are the main defense force against bacteria but platelets get called up as a reserve force. Both types of blood cells shoot the same superoxide anion bullets at invading bacteria. It is easy to see that if systemic platelet activation were to occur when there is no bacterial threat, as is indeed what happens in migraine, then there might be a problem with having bullets go all over the place. The body has protective mechanisms against free radicals, the dangerous kind of unpaired electrons; they include specific enzymes like "superoxide dismutase", and free radical buffers like ascorbic acid (vitamin C) and coenzyme Q. The enzymes neutralize the free radicals by specific chemical reactions and the buffers, which are small molecules, bind to them to form a new compound that has a less reactive unpaired electron. However, these defenses are easily overwhelmed and then you get what is called "oxidative stress". If the situation is truly out of control, you get what I call "free radical storm", which, as we will see in later chapters, is a major cause of both atherosclerosis and Alzheimer's disease.

Both parts of the adrenal gland, the inner core or "medulla", which produces and releases epinephrine, and the outer shell, which produces and releases "cortisol", participate in the physiologic response to stress. Historically, much of the literature about the physiology of stress focused on the role of cortisol release, which is under the control of "adrenocortical stimulating hormone", which is a hormone produced by the "pituitary gland" at the base of the brain. Acute stress was understood to be a sudden a drop in blood pressure ("shock") caused by either massive hemorrhage or bacterial infection of the blood ("septicemia"); the drop in blood pressure threatens the blood supply to vital organs like the brain and heart. Hans Selye, a Hungarian-Canadian endocrinologist, understood that

the response to stress could be both psychologically-induced and chronic, leading to long-term upregulation of cortisol secretion. However, cortisol is not part of our story. We are focusing instead on stimulation of the adrenal medulla by the autonomic nervous system in response to stress, which causes release of epinephrine and SPA. All the effects of SPA make sense in the setting of shock: the vasospasm raises blood pressure to protect vital organs, the pro-coagulant state helps staunch bleeding if blood loss is the problem, and the superoxide anion bullets help kill bacteria if septicemia is the problem. Walter Cannon, who was the head of the Department of Physiology at Harvard Medical School in the first part of the last century, popularized the idea of "fight or flight". An animal that experiences the stress of a major life threat has to choose between fighting and fleeing, both of which responses involve stimulation of the adrenal gland and the release of epinephrine. Our definition of stress includes the competitive demands of contemporary society and we have worked out in more detail the physiological effects of releasing a large quantity of epinephrine into the blood.

Recap: Migraines often trigger release of epinephrine (or adrenaline) from the adrenal medulla, the inner part of the adrenal glands, the small endocrine glands sitting on top of the kidneys; this, in turn, causes activation of platelets, the blood cells responsible for thrombosis or coagulation (blood clotting). Blood-wide or systemic platelet activation (SPA) is dangerous because it does three bad things: it causes vasospasm (constriction of small arteries), which contributes to high blood pressure; it produces a pro-coagulant state, which means you are teetering on the brink of thrombosing off arteries and veins; and it causes oxidative stress, which is the presence of dangerous free radicals, which are small molecules which normally function as bullets to shoot at bacteria, but which, if produced inappropriately in high concentration in the blood, can cause widespread damage to large molecules. Measuring oxidative stress tells you how many dangerous free radicals there are and, if the number is large, you are in a state called "free radical storm. An important idea is the distinction between normal physiologic unpaired electrons carrying energy from the sun, resulting finally in the minting of ATP "money" in mitochondria, and dangerous free radicals, the superoxide anion bullets. SPA can occur in people who are not experiencing a headache.

CHAPTER FOUR

HOW HYPERTENSION WORKS

High blood pressure or hypertension, which we will refer to by the standard medical abbreviation of HTN, is the central disease of modern society. The incidence rises in adulthood to something well over fifty percent. But HTN is not normal; it's a disease, a perturbation of normal physiology, and the most common reason people continue down the bad road.

The way arterial blood pressure works is as follows. The aorta is the giant artery which receives blood from the heart and distributes it via a branching tree to all parts of the body. The entire arterial tree can be thought of as an elastic balloon which stretches to receive the large volume or "bolus" of fluid ejected into it with each beat of the heart; the aortic valve of the heart immediately closes to prevent backflow and, depending on the size of the bolus and the stiffness of the balloon, you get a temporary maximum pressure in the balloon, which is the "systolic blood pressure", the upper number. The very smallest arterioles, less than 500 mμ in diameter, are the valves which determine where the blood goes. The arterioles can be stimulated by the autonomic nervous system. It is like when Egyptian farmers distributing irrigation water from the Nile decide whether to water the corn today or the cucumbers—they open and close valves in the irrigation system. The autonomic nervous system decides whether to let blood into muscles, which is a good thing when you are exercising, or the digestive track, which is a good thing when you are eating. The collective tension or resistance to flow in the arterioles determines how fast the bolus of fluid injected into the arterial tree can run off into capillaries. The lowest pressure reached in the arterial balloon is the "diastolic blood pressure", the lower number. Normal blood pressure is traditionally taken as 120/80, although the range of normal is broad and a person's blood pressure has a normal diurnal rhythm, being lowest before and around the time of awakening and highest late morning into the middle of the day.

There is an important relationship between HTN and migraines. Many years ago I noticed that I couldn't adequately control migraine headaches

in hypertensive patients unless I first controlled the HTN; I might get some kind of response to migraine prophylaxis, that is, to a medicine you take every day even if you don't have a headache in order to make the whole condition go away, but the response was never complete. After delving into the literature I found an illuminating article published in 1913 in the *Archives of Internal Medicine* by Theodore Janeway, who was a Professor of Medicine at Columbia University College of Physicians and Surgeons. The special reserve section of the Downstate library had a fragile copy of it. Janeway described the symptomatology and natural history of HTN, which was then a relatively new disease. It was basically untreatable, the only treatment being some spa and relaxation techniques, but they didn't have the continuous shower described in Chapter 1. Janeway described the three end-organ targets of HTN, which are the heart, which suffers congestive heart failure; the kidney, which goes bad and causes uremia; and the brain, which suffers strokes. He then said the main symptoms of HTN were headaches and vertigo! Sometimes HTN is said to be a "silent killer". In my experience asymptomatic HTN occurs in about half of cases; in the rest of the cases, patients get migraine symptoms, the most common being headaches and vertigo, just as Janeway said. Janeway also said that in most patients the migraine symptoms began years or decades before the HTN. John Gardner, a physician at the Mayo Clinic, confirmed the relationship between migraine symptoms and HTN in an article published in the *American Journal of Medicine* in 1940 (there was still no effective treatment for HTN at that time). He compared 100 patients in the outpatient clinic with HTN, defined as a systolic blood pressure of 160 or greater, to 100 non-hypertensive age-matched controls. 15% of the non-hypertensive patients had either concurrent migraines or a history of migraines compared to 79% of hypertensive patients. This represents a fivefold higher incidence, which means there is a pathophysiological relationship.

HTN is not a necessary part of aging, although it is so common in our society that it seems like it might be. In a famous study published in the journal *Hypertension* in 1988 (Mario Timio was the lead author) 144 Italian nuns living in an Italian convent were followed for twenty years. They were compared to 138 women from the same village who were matched for age but not cloistered. The authors said the nuns, who belonged to a Benedictine order, lived in a "stress-free monastic environment characterized by silence, meditation, and isolation from society". After twenty years, the nuns had an average blood pressure of 128/82 and the laywomen a blood pressure of 165/92. In 1945 James Graham published a study in *Lancet* of British soldiers in an armored

brigade involved in combat in the Western Desert campaign in North Africa in World War Two. They had served in active field operations for a period of one to five years, the average being two to three. The average blood pressure of the 695 men was 154/90; 26.9% had a diastolic (bottom number) of 100 or higher and 38% had a systolic (top number) of 160 or higher. When 33 of the hypertensive soldiers were re-examined after two months of rest from active combat conditions, blood pressure had returned to normal in 28. Separation from combat was their version of getting the continuous shower described in Chapter 1. Sidney Cobb et al. studied HTN, peptic ulcer, and diabetes in air traffic controllers (*Journal of the American Medical Society*, 1973). After adjusting for age, the incidence of HTN in 4,325 air traffic controllers was four times that of 8,435 second class airmen. Norman Hollenberg et al. published a study of Kuna Indians in the journal *Hypertension* in 1997. The Kuna were the indigenous inhabitants of Panama before the Spanish arrived. Hollenberg compared the blood pressure of Kuna still living a traditional life style on the San Blas Islands off the coast of Panama with that of Kuna who moved to Panama City and lived a more modern competitive life-style. Taking 140/85 as his cutoffs in the upper and lower numbers for diagnosing HTN, he could not find a single case of diastolic HTN among 142 island-dwelling Kuna and only two cases of mild systolic HTN. Among 84 city-dwelling Kuna, the overall incidence of HTN was 10.7%, rising to 45.1% in those over age 60. Figures were intermediate for 90 Kuna living in "a more traditional" Kuna community on the outskirts of Panama City. The common denominator of all these studies is that they document a relationship between HTN and stress. The stress can be either immediate physical danger (the case of the British soldiers), constant performance anxiety (the case of the air traffic controllers) or general daily competitive life-style stress (the cases of the non-cloistered Italian villagers and the Kuna who moved from the San Blas islands to Panama City). The underlying cause of HTN is stress, as is the case with migraine.

The first thing that happens when a person develops HTN is that the brain stem set point for blood pressure is raised. I remember that Lewis P. Rowland, the chairman of neurology at the Neurological Institute at Columbia when I was a neurology resident there, used to say that no one knew the cause of HTN but, who knows, it might be a neurological disease. He also used to say that internal medicine was that part of neurology which dealt with the rest of the body. Today I think Dr. Rowland was correct in both of these whimsical statements (that was his style) and most of internal medicine, including HTN is, in fact, a brain disease. The body measures blood pressure in the "carotid body receptor",

which is located in the neck in the carotid artery, which is one of the main arteries carrying blood to the brain, and then relays this information to a network of neurons in the brain-stem which are interested in this kind of thing. Ordinarily blood pressure, apart from its normal daily rhythm, is maintained within a fairly narrow range. Having said that, everyone has lots of small labile (rapidly changing) swings in blood pressure every day. Systolic blood pressure goes up during exercise while diastolic blood pressure falls, so that mean blood pressure stays about the same. Anger tends to raise blood pressure, sometimes dramatically. One of the main ways the body maintains its set point for blood pressure is through a specialized part of the kidney called the "juxtaglomerular apparatus". The juxtaglomerular apparatus monitors local arterial blood pressure as well as the salt content of blood. If either one is too low, it secretes a hormone called renin which signals the adrenal gland to secrete aldosterone, a hormone which causes the kidney to retain sodium—retaining sodium increases blood volume and, therefore, raises blood pressure by putting more liquid into the vascular balloon. Renin also tightens the valves in the irrigation system by causing contraction of muscle cells in the arteriolar cell wall; this increases resistance (or "total peripheral resistance") to run-off of fluid in the arterial balloon and, like sodium retention, raises blood pressure. This may seem a little complicated, but it is all very logical: if a person has a sudden critical drop in blood pressure (or "shock"), which is usually caused by sudden blood loss or a bacterial infection in the blood ("gram negative sepsis"), then it makes sense to maintain blood pressure in order to protect vital organs like the brain and heart. The autonomic nervous system also stimulates the juxtaglomerular apparatus. This makes sense, too, in situations of shock because the brain stem learns from the carotid body, the blood pressure receptor in the neck, that blood pressure has fallen and it sends a signal to the juxtaglomerular apparatus to reinforce the local signals it is getting about blood pressure and salt concentration.

At this point, it is worthwhile to pause and notice the similarity between the clinical course of migraines and HTN. Both begin as sporadic events and then move on to a chronic phase. When a doctor diagnoses HTN, he usually wants to see at least two readings above 140/90. These are often sporadic readings and blood pressure is not yet continually elevated. Migraines usually start as sporadic events and then occur daily. How the fluctuating phase of these two diseases moves into a chronic phase is a topic we will discuss in the next chapter. It is also worth noting that sudden labile rises in blood pressure are potentially very dangerous, because this is when strokes occur; this will also be discussed later.

When the brain stem resets the set point for blood pressure in response to stress, three things happen: (1) the heart pumps harder and sometimes faster as well, (2) the juxtaglomerular apparatus is continuously stimulated or upregulated, and (3) SPA (systemic platelet activation) is activated on a continuous basis—platelets have the ON button permanently pushed on. To take number (1) first, the autonomic nervous system stimulates increased strength of cardiac contraction, which increases the volume of each bolus or injection of blood released into the arterial balloon. This raises systolic blood pressure, the upper number, which, by itself has always been regarded as not so serious an event. The serious clinical event is a rise in diastolic blood pressure (the lower number), which requires a rise in total peripheral resistance, which means the arteriolar valves controlling blood flow into the capillary beds, must tighten. This comes about in the following way: renin released by the juxtaglomerular apparatus chronically tightens the valves, an effect which is potentiated by vasoconstrictors released by platelets in SPA, which we remember were serotonin and thromboxane A_2. The three vasoconstrictors or valve tighteners work together to turn the screws. There is a serious problem here. Activated platelets are shooting superoxide anion bullets all over the body. If that weren't bad enough, it turns out renin is doing the same thing. Renin causes "endothelial cells", the cells which line blood vessels, to also generate superoxide anions, in fact through the same enzyme white blood cells and platelets use.

Over time, the small capillaries in untreated or unsuccessfully treated HTN undergo "remodeling". What this means is that, either due to the stimulus of elevated blood pressure or due to a direct effect of renin, the muscle cells in the blood vessel rearrange themselves—they move into a tighter circle so that the arteriole is now permanently anatomically narrowed. At this point, renin levels fall—the kidney calms down—but total peripheral resistance remains elevated, not because the muscle cells are contracting all the time but because the holes are smaller. These changes occur everywhere in the body, including the brain. It is a pickle for doctors trying to treat HTN. If you treat it too aggressively, then there is not enough blood getting through narrowed arterioles into capillary beds in the brain. In fact, you can get a specific pattern of widespread strokes in the brain, which is technically called "leucoaraiosis". I have seen more than one case of a patient with long-standing hypertension whose blood pressure was treated too aggressively and they suffered a sudden fall-off of intellectual function due to this effect.

Recap: HTN occurs when the brain raises the set point for blood pressure in response to stress. The heart pumps harder. SPA is activated and the platelet-derived vasoconstrictors serotonin and thromboxane A_2 go to work. The kidney releases renin, which also causes vasoconstriction. Superoxide anion bullets are shot everywhere because of SPA and because of stimulation of endothelial cells by renin. In addition, there is a constant danger of stroke because, as we will see, strokes occur when there is a wobble in the set point for blood pressure.

CHAPTER FIVE

WHEN THE BRAIN CHANGES

This chapter presents the last of the main scientific ideas that will carry us through the rest of the book.

The theoretical mechanism by which acute stress damages the brain and triggers the diseases of chronic stress is based on the concept of a "negative feedback loop", which is the mechanism by which the body maintains equilibria. This model is very pared down, so pared down that it must by necessity be omitting some relevant aspects. The brain functions in terms of networks, but if you diagram a network and every brain region or nucleus in the network is connected by reciprocal arrows to every other, then intellectual paralysis sets in. Paring down makes visible the underlying schema. These ideas are presented as theoretical, but, as one of the reviewers noted when I submitted what was actually the second of the two articles I wrote about this topic to *Medical Hypotheses*, "There is nothing in the scientific literature to disprove Dr. Eggers' ideas". Is there a nuance of skepticism there? According to Karl Popper, the great philosopher of scientific method, all scientific ideas are really hypotheses waiting to be disproven. The longer they go without being disproven, the more likely they are to be true.

The negative feedback loop is a central concept in medicine because it is the mechanism by which the body maintains metabolic equilibria, whether of glucose, blood pressure, thyroid hormone, energy stores, etc. (see Fig. 5-1). You already know all about the negative feedback loop because it is how the thermostat in your house works: when the temperature falls below a certain set point, then the furnace comes on to raise the heat up to the set point. If the temperature is too high, the furnace stays off and the thermostat waits for the house to cool down. There are two parties in a negative feedback relationship, which is usually diagrammed as a loop. The first one, call him Mr. A, stimulates the second one, call him Mr. B, who in turn inhibits the first one. It is a "feedback loop" because they give each other alternate signals and "negative" because the second signal is negative or inhibitory. The regulation of thyroid hormone is a perfect example.

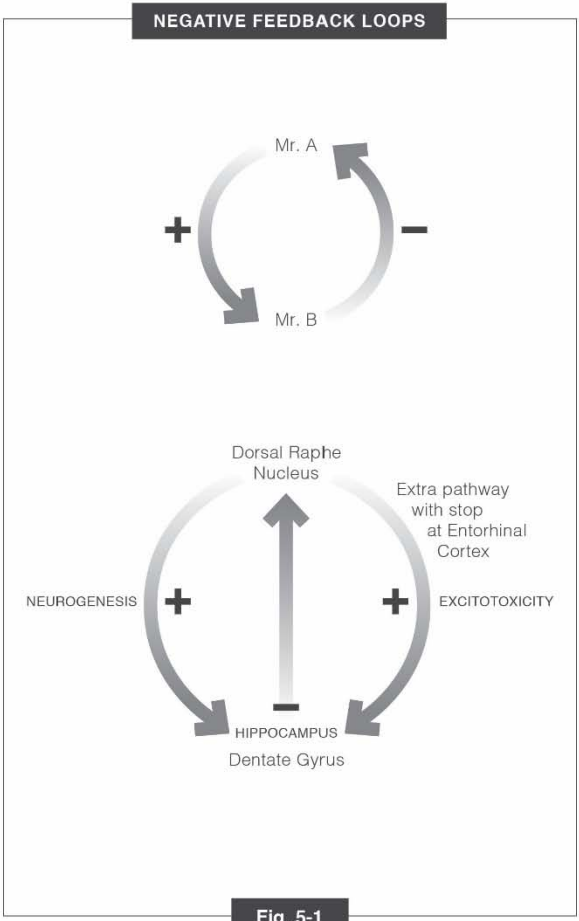


Fig. 5-1

The pituitary gland (Mr. A) produces thyroid stimulating hormone, which triggers the thyroid gland (Mr. B) to release thyroid hormone, which is like heat production by your furnace. Thyroid hormone then *inhibits* pituitary production of thyroid stimulating hormone. If thyroid hormone levels fall too low, there is less of it to inhibit the pituitary, which puts out more thyroid stimulating hormone, which raises thyroid hormone production back to normal. If thyroid hormone levels rise too high, there is more of it to inhibit the pituitary, which puts out less thyroid stimulating hormone, which lowers thyroid hormone production back to normal. The body has a

set point for the level of thyroid hormone just as your house does for temperature.

In the brain, Mr. A is our old friend the serotonergic dorsal raphe nucleus (DRN) and Mr. B is the "hippocampus", a part of the brain we have not met before but was already included in Fig. 2-2. We are also going to add a second pathway going from the DRN to the hippocampus and put an extra stop on one of the pathways, which is the "entorhinal cortex", another new part of the brain, all of which we will explain below (see Fig. 5-1). The word hippocampus is derived from the Greek for "sea horse", those charming little beasties of the deep. When cut in cross-section, the hippocampus resembles a seahorse. The hippocampus is a bilateral sausage-shaped structure situated deep in the cerebral cortex (the mushroom cap) toward the back of the brain. It is famous for being the part of the brain most associated with memory, but it also does other things such as processing visual information. The 2014 Nobel Prize in physiology or medicine was given to scientists who discovered visual "place cells" in the hippocampus. The great neuroanatomist Walle Nauta described in one of his books the strong reciprocal anatomical connections between the DRN and the hippocampus but had no ideas about the physiological meaning of this relationship. The hippocampus also has a unique property in contrast to all other parts of the brain: neurons in the dentate gyrus portion of the hippocampus can divide, that is undergo cell replication. For decades, the brain was thought to be "post-mitotic" or incapable of having cells that divide, which made sense because all the knowledge and innate talents of a given person must have something to do with hard wiring of a fixed set of neurons. You can't have neurons dividing higgledy-piggledy all over the place like blood cells in the bone marrow. But it is now well established that some of the neurons in the dentate gyrus part of the hippocampus can in fact divide. This turns out to be the mechanism of how anti-depressants work. The main two categories of anti-depressants, the tricyclics and selective serotonin reuptake inhibitors (SSRI's), both work by making more serotonin available to neurons in the dentate gyrus. The serotonin acts like a "growth factor" which is a chemical that stimulates neuronal cell division, an effect it has only on neurons in the dentate gyrus. It is also possible that newborn neurons in the dentate can migrate locally to repopulate nearby regions of the hippocampus. The reason anti-depressants take several weeks to work is that this is how long it take neurogenesis (cell division of neurons in the dentate gyrus) to occur.

Another property of the hippocampus is that it is the part of the brain which is most susceptible to what is called "excitotoxic cell death". This plays a big role in the pathogenesis of certain types of epilepsy. What excitotoxic cell death means is that when a neuron gets too many yes votes on its dendrites, to use our previous analogy, the effect is toxic for the cell. (In technical terms, what happens is that too much calcium enters the cell and kills it.) So neurons in the hippocampus have two unusual properties compared to neurons elsewhere in the brain: they easily undergo cell death and, if they haven't all been killed, they can make a comeback through cell division. It's an interesting ying-yang.

Let's go back to the diagram. The basic idea is that there is normally a negative feedback loop between the DRN and the hippocampus which serves as a control mechanism for the rate of neurogenesis in the hippocampus. The direct serotonergic connection stimulates cell division there, which is like the way your furnace puts out heat when the thermostat is triggered or your thyroid gland puts out thyroid hormone when triggered by thyroid stimulating hormone. In this case, the set point controls the rate of neurogenesis in the hippocampus rather than the temperature of your house or the level of thyroid hormone in your body. But the DRN can also fire in an aberrant manic way in response to stress—we saw how this happens in migraine, where it can be imaged on PET scans—which leads to the delivery of a toxic neuronal signal to the hippocampus via the indirect or extra-stop route. The extra stop is the entorhinal cortex, which is the entry zone for most information passed to the hippocampus. The theoretical reason for this route, which is supported by neuroanatomy, is that the DRN signal has to be converted from a pacemaker-type signal, which, as you remember, can't directly cast a yes or no vote (they only do vote fraud), into a signal from the entorhinal cortex, which can. The entorhinal cortex can cast too many yes votes, which is toxic. The DRN overstimulates the entorhinal cortex, which then delivers a knockout blow to the hippocampus. This means the hippocampus, as Mr. B, is no longer able to give a negative feedback signal to the DRN, Mr. A, who is now disinhibited and free to engage in mischief. A possibility of recovery, which certainly occurs to a variable degree in depression, migraine, and HTN, ensues when the toxic signals abate and surviving neurons divide under the influence of normal serotonin stimulation.

The mischief wrought by the disinhibited DRN explains the diseases of chronic stress which will be addressed in later chapters of this book. Going down the bad road generally begins with isolated stress-induced migraine episodes, which, as explained in chapters 2 and 3, may be acephalgic (no

headache) or even completely subclinical, consisting only of SPA. If the migraines involve headaches, the headaches become chronic or daily. Other diseases then appear, HTN often being the first. Eventually the poor individual, who now has HTN, diabetes, hypothyroidism and maybe severe mental illness or a history of heart attack, goes to the emergency room with a life-threatening stroke. Meanwhile, the lucky person who has not gone down the bad road is completely well and stays at home.

There are three ways the disinhibited DRN causes disease. The first is systemic platelet activation (SPA), which was discussed in Chapter 3; the second is the damaging effect of a continual barrage of serotonergic signaling to the frontal lobe of the cerebral cortex, which is different from the extra-stop pathway described above and is key to understanding schizophrenia; and the third is elevation of set points, which occurs in HTN and obesity. Atherosclerosis and Alzheimer's disease are both caused secondarily by HTN, obesity, and SPA, which are all vascular risk factors

Recap: The DRN and hippocampus form a negative feedback loop. If a stress-induced barrage from the DRN knocks out the hippocampus, then a disinhibited DRN is free to orchestrate the diseases of chronic stress. It does this by raising the set points for blood pressure and adipose mass, by stimulating SPA, and by unremitting excessive stimulation of the frontal lobe. A disinhibited DRN is like an irascible elderly professor at a medical school.

CHAPTER SIX

HOW STROKE WORKS

Stroke is a disease of wobbles and white clots.

We will take a long periphrastic digression before coming back to explain that sentence. Stroke is often a catastrophic illness, coming on with terrible suddenness, as the word itself suggests. I vividly recall going in to make rounds one Saturday morning at Kings County Hospital several years ago and the residents presented to me the case of a young man who the night before had suddenly stopped talking in the middle of a conversation with his wife—he became "aphasic" as we say—as well as completely weak on the right side of his body. It is hard to fully grasp what it means to lose all language. There are two parts of language: understanding what other people are saying and expressing your own thoughts. People who recover from a stroke involving only the latter, the "expressive" part of language, usually say that they knew what they wanted to say but couldn't put it into words. Somehow thoughts must dwell in a place prior to being put into words. For people who speak more than one language, it must be the place where thoughts reside before the unconscious decision is made about which system of words to put them into. This young man had also lost the ability to understand anything said to him; he was awake, he sometimes moved his non-paralyzed side in seemingly purposeful ways, but he had a glazed look. I had to explain to his wife that he had had a stroke of his "left hemisphere"; the whole top left half of the mushroom cap, which controls language and movement of the right side of the body, had "infarcted" or died due to blockage of blood flow. This stroke was very dangerous because of the likelihood of brain swelling. Several hours later, after I had seen other patients and written my notes, I passed his wife sitting on the floor of one of the airport-like glass-walled corridors that interconnect the buildings at Kings County Hospital. She was rocking back and forth, sobbing uncontrollably like King Lear when he carries in the dead body of his daughter. Her husband died the next day from brain swelling.

Neurologists have so much intellectual fun puzzling out the localization of strokes that it is easy to lose touch with the human element. What happens in the most typical stroke is that you get suddenly or rapidly weak on one side of your body owing to the blockage of an artery in the brain. Often there are other symptoms as well, for example, language problems, trouble swallowing, or double vision. In some strokes there is no weakness at all, maybe just clumsy hand movements and unsteady gait, or blindness or vertigo (spinning sensation). It all depends on where the damage occurs in the cap or stem of the mushroom. We already know one other disease which can cause all different kinds of symptoms, many of which overlap with the symptoms of stroke, and that is migraine. Epilepsy, which doesn't always have to cause rhythmic jerking movements and can present in subtle ways, and multiple sclerosis are other diseases which can cause a rapid onset of symptoms. We neurologists love to ponder all this, knowing that the MRI (magnetic resonance image) will probably have the answer. The solution to the crossword puzzle is published the next day.

But why do strokes occur? Here we will exclude from discussion hemorrhagic strokes (bleeding into the brain) and strokes due to "thrombi" (clots) traveling to the brain from a heart suffering from an irregular heartbeat called "atrial fibrillation", which is a very different disease which we will talk about later. One of the striking things about most stroke patients is that they come in with very high blood pressure, particularly the lower number, the diastolic, which is typically way above 80 (normal blood pressure being 120/80) or even the usual treatment goal for someone with HTN, which is 90 (goal of 140/90), something higher than they usually run, often 105, 110 or more. What I like to call "very strokish". The high blood pressure usually lasts for only a couple days and then goes back down to the patient's baseline. Sometimes there is no pre-existing diagnosis of HTN and the blood pressure goes entirely back to normal. Sometimes the elevated blood pressure persists for several days, even a week or more and the patient goes into "hypertensive crisis", when the out-of-control blood pressure may send them to the intensive care unit for continuous intravenous drip of medications to lower it. Something similar can happen with migraine headaches, which can become unbearable for a period of a week or more and, like hypertensive crisis, be resistant to any treatment you use. In both cases, out-of-control blood pressure or out-of-control headaches, the condition eventually abates, although it is not obvious that treatment has any effect. Stroke patients also often get migraine headaches at the time of onset of the stroke. Sometimes a severe headache precedes the stroke by hours, even a day or more, in which case it is called a "sentinel headache". Both a rise in blood pressure and a

migraine at the onset of a stroke, hmm? The clever reader who, like my daughter, can always figure out where a novel or mystery story is headed, will already be one step ahead of the rest of us and know what is coming next: on their lips we see formed the words "systemic platelet activation"! The headache and rise in blood pressure are markers for what is really happening, which is that SPA, which as we learned before, often occurs in association with migraine headaches and can produce a pro-coagulant state, has intensified so much that the pro-coagulant state has now become coagulant or clinically manifest—it has gone over the top, so to say, and caused a stroke, either by blocking a blood vessel in the brain or causing a thrombus to form someplace else, maybe on the surface of an "atheroma" (or plaque, we will discuss this later on) and travel to the brain to block an artery, which is called an "embolism". The DRN fires manically, the adrenal medulla releases epinephrine, and there is sustained blood-wide activation of platelets. These catastrophic events are accompanied by a headache and a labile rise or "wobble" in the set-point for blood pressure. Headaches in general can be associated with small rises in blood pressure but large rises in association with a headache are more typical of an acute stroke. Sometimes the whole process is "acephalgic" which, as we learned before, means the headache part of the clinical picture is missing.

Why are some clots white and some red? (Somehow we still talk about the color of clots, because these terms were invented by pathologists before the hematologists told us we had to call the clinical thing a "thrombus" and not a "clot".) White clots consist only of clumped platelets and red clots have layers of red blood cells mixed in, which makes them red, or brown if it's a scab on the surface of the skin. We mentioned before that activated platelets stick to each other or "aggregate" (this is why they can't be reused after activation). When there's local tissue injury, aggregated platelets get enmeshed with "fibrin", the protein which is the end-product of the coagulation cascade, and the fibrin traps red blood cells. The whole gemish then contracts and gets hard. It the case of the arterial blockage associated with a stroke, the clot lacks much of a red cell component. Why this happens probably relates to the rapidity of thrombus formation; as we will see later, red thrombi which are found within the vascular tree unaccompanied with tissue injury form slowly and are associated with other diseases, namely, irregular heartbeat (atrial fibrillation) and deep vein thrombosis in the legs.

The greatest and most informative study of stroke prevention in the literature was organized by J. P. Mohr, a stroke neurologist at Columbia, and published in the *New England Journal of Medicine* in 2001. It was

called the WARS study (Warfarin vs. Aspirin in the prevention of Recurrent Stroke) and forever changed the way we look at stroke. I was taught as a neurology resident that the best way to prevent a recurrent or second stroke in a patient who has suffered a first stroke is to put them on an anti-coagulant or "blood thinner", which at that time meant the drug warfarin (tradename Coumadin). Doctors distinguish between anti-platelet drugs, like aspirin, and anti-coagulants, like warfarin or the newer wave of drugs like Pradaxa, Xarelto, and Eliquis. Thrombus formation, as we know, involves activation of both platelets and the coagulation cascade—the two cannot be separated physiologically—so distinguishing between them conceptually is a subtle kind of thinking. However, empirically, in clinical trials there is often a big difference. The WARS study randomized patients between getting either aspirin or warfarin and, confounding the expectations of all neurologists, including the doctors who set up and ran the study, aspirin turned out to be just as effective as warfarin—the anti-coagulant was no better than the anti-platelet drug. There was a follow-up study done later by other investigators who pushed the dose of warfarin to the max, the point where bleeding complications set in, and, again, aspirin was just as effective as warfarin. In retrospect, one can wonder why this should have been so surprising. Stroke, within the limits of how we are using the term here (i.e. not including cases of atrial fibrillation of the heart), is a disease of white clots, which means platelet aggregation. We remember that the next-to-last protein in the coagulation cascade is thrombin, which has its own ON button on platelets, which is different from that of epinephrine. Aspirin doesn't block a specific ON button per se; rather, it interferes with the synthesis of one of the chemicals released in platelet granules, specifically thromboxane A_2, which we remember from the chapter on HTN narrows or constricts small blood vessel and contributes to elevated diastolic blood pressure. Thromboxane A_2 also pushes yet another ON button on platelets. The effects of the two categories of drugs, "anti-platelet drugs" and "anti-coagulant drugs", on platelets seem to be about equal; it's a matter of which ON button is blocked. A priori, maybe one of the ON buttons would be the most important, but that doesn't seem to be the case.

Recap: Strokes are caused by severe episodes of SPA associated with an uptick or wobble in the set point for blood pressure. The SPA causes a "white" or platelet-predominant thrombus, which blocks an artery in the brain. Headaches often occur at the onset of a stroke.

CHAPTER SEVEN

HOW OBESITY WORKS

I hope no one will feel shamed by reading this chapter. I don't think I have all the answers but I will share with you what I know. When I was a medical student, the section on high cholesterol and atherosclerosis in Cecil and Loeb's textbook of medicine, one of the two standard internal medicine textbooks, was hidden away in the chapter on obesity. This baffled me at the time but now it makes perfect sense. An important concept in internal medicine is the "metabolic syndrome", which consists of either type-2 diabetes or the first stage thereof, which is called "insulin resistance", plus some blood lipid abnormalities such as high "triglycerides" (these are ordinary fat molecules, like the kind stored in fat cells but being carried around in the blood), elevated levels of "bad" cholesterol and/or decreased levels of "good" cholesterol (we will explain this later) and HTN. This statistical association between type-2 diabetes and HTN is why all the stroke patients I presented on rounds as a resident seemed to have both conditions. The word "diabetes" is derived from a Greek word meaning "syphon". People with high blood sugar drink excessive amounts of water because their kidneys can't hold onto all the sugar and the sugar takes a lot of water with it when it is excreted into the urine, hence the syphon-like effect of drinking and urinating excessive amounts of water. The less common form of diabetes, Type-1, which most typically begins in childhood, is an autoimmune disease in which the body makes an allergic or immunological attack against the cells in the pancreas that produce insulin. This illness usually begins abruptly. Type-2 diabetes, the more common form, which we will henceforth simply call "diabetes", usually occurs in middle-aged or older people and has a gradual onset, beginning with an "insulin-resistance" stage and then progressing to frank diabetes. The likelihood of abnormal cholesterol levels and/or diabetes increases the more obese a person is and one could argue that obesity should be defined by the presence of either abnormal cholesterol levels or diabetes rather than by some arbitrary body mass index. Of course, what counts is not lean body mass (muscles, bones, etc.) but the total volume of fat stored in fat cells, which is called "adipose mass". Storing fat is a defense mechanism against famine. Camels store fat in their humps and fat-tailed

sheep around their hind quarters; in our species, men tend to store fat in the abdomen and women around the hips. The high cholesterol and diabetes associated with excessively large adipose mass are "vascular risk factors" for both atherosclerosis and Alzheimer's disease and, as we will see later, are both associated with free radical storm, that is, superoxide anion bullets zooming all over the place. Like temperature and blood pressure, adipose mass is tightly regulated in people, as it is in all other species. An animal with fat stores that are too small is at increased risk of starvation and one with fat stores that are too large is at risk of being so heavy it can't walk around. Again like temperature and blood pressure, there is a set point regulating adipose mass. In the case of blood pressure, pressure receptors in the carotid artery in the neck, as we saw, measure blood pressure and then report back to a network of cells in the brain stem. The main measure of adipose mass is a hormone called "leptin", which is a molecule secreted by fat cells. The level of leptin in the blood increases with increases in either the number or size of fat cells is but it is not quite a directly proportional or linear relationship. This information is conveyed to the "arcuate nucleus", which is a cluster of cells in the hypothalamus, which is up near the top of the stem of the mushroom. The word "leptin" means "thin". Congenital absence of leptin is the cause of extreme obesity in either the "ob/ob mouse model" of obesity or the rare human being born with this genetic defect. Leptin keeps you thin and, if you don't have it, you go the other way. D. Schoeller et al. published an early study of leptin levels in the *Journal of Clinical Investigation* in 1997. The test subjects were four healthy young males. Leptin levels, like those of many hormones, were shown to have a diurnal rhythm, being highest around midnight. Leptin did not rise following individual meals, which makes it perplexing to understand why it is sometimes called a "satiety hormone", a term which would seem to imply that levels should rise after meals to make you feel full. Leptin is a measure of adipose mass reporting back to the arcuate nucleus to help it maintain a physiological set point. In the same way that the body goes into action to protect the set points for temperature and blood pressure, so it also responds defensively to alterations of adipose mass by trying to restore things back to where they were. A physiologist would say the body is trying to maintain an equilibrium, which is defined by the set point. This is a key concept and there is compelling human data for protection of the set point for adipose mass against changes in either direction, which we will now discuss. In a famous study by Rudolph Leibel and Jules Hirsch published in the journal *Metabolism* in 1984, the caloric requirements of "reduced-obese" subjects was compared to that of age-matched controls who had never been obese.

The study was performed on patients admitted long-term to a research unit at Rockefeller University Hospital in New York City and included approximately equal numbers of males and females. The hospitalized obese subjects successfully lost weight, going from an average weight of 152.5 kg to 100.2 kg; a "kilogram" or "kg" is 2.2 pounds, which means they went down from about 300 pounds to 200 pounds. Their caloric requirements for maintaining the baseline and reduced weights were 1432 kcal/m^2/d and 1021 kcal/m^2/d respectively; numbers for caloric intake have to be adjusted for body size, which is why the results don't come out as absolute numbers of calories. It's an approximately proportionately small drop in calories—29%-- for losing 34% of your weight. By contrast, the never-obese subjects who weighed an average of 62.6 kg (about 125 pounds) could eat 1341 kcal/m^2/d of food without gaining weight. Look closely—they weighed 75 pounds less than the reduced-obese subjects but were able to eat 320 kcal/m^2/d (31%) more per day without gaining weight! The authors ascribed these startling results to differences in "metabolic efficiency", which is a dubious concept. It was a puzzlement. The opposite kind of study, asking normal weight subjects to gain weight by deliberate overeating, was done by Ethan Sims et al. (*Transactions of the Association of American Physicians*, 1968). Nineteen volunteers at the Vermont State Prison overate four meals a day of standardized frozen dinners until they weighed an average of 21% more than at baseline. To maintain the new weight, the men had to increase their food intake from an average of 1800 kcal/m^2/d to 2700 kcal/m^2/d. This means they had to eat 50% more to keep on 21% more weight. Again, the results are counter-intuitive.

In both of these studies there is a problem with the arithmetic of energy. Why do obese people who have starved themselves to a normal weight have to keep starving themselves to keep the weight off and normal weight people who have over-eaten to the point of obesity have to keep over-eating to keep the weight on? In the first case, where did the extra calories that the non-obese (normal weight) controls ate go? In the second case, where did the extra calories the over-eating test subjects ate go? The simplest idea how about the set point for adipose mass is maintained is thermodynamic: body weight depends on a balance between food consumption and exercise, gluttony and sloth if you like. We remember from before that the chemical energy in food, which originally came from the sun and got converted in mitochondria into dollar bills called ATP can either be spent driving chemical reactions in the body, which includes making muscles contract—when muscles contract, this is a chemical reaction paid for by ATP; the chemical energy is converted into the kinetic

energy of movement—or else the energy gets stored in fat. If you don't spend all your income, it goes into the camel's hump. Right away we can make two refinements to the gluttony and sloth hypothesis. First, the lung and the heart use a significant amount of muscular energy in making the lung bellows blow and the heart pump. Second, many chemical reactions involved in basic metabolism are a little bit inefficient and some chemical energy is lost inadvertently as heat energy. This is why there is "thermogenesis" (heat production) associated with digesting a meal. The place where the most chemical energy is lost as heat is in muscular contraction, which is why people overheat with exercise and why shivering, which consists of involuntary muscle contractions, is a defense mechanism against cold. But none of this solves the energy arithmetic problem. The laws of thermodynamics cannot be violated, so what is happening? The conceptual breakthrough came when doctors started doing PET scans (those are the scans which detected high-energy firing of pacemaker cells in the DRN during a migraine attack) on cancer patients, the idea being that cancer cells are more energetic than normal cells and any metastatic cancer cells or cancer cells remaining after a series of chemotherapy or radiation treatments will be bright on PET scans, they found that patients often had inexplicable bright spots in the neck and this was particularly true in the winter. Doctors finally figured out what was going on: contrary to received wisdom, normal adult people, like new-born babies and hibernating animals, can have "brown fat" (Aaron Cypess et al. *New England Journal of Medicine*, 2009). In brown fat, what happens at the end of the electron transport chain in mitochondria is different from normal. Instead of the electrons removed from water in chloroplasts being given back to oxygen molecules to make water again accompanied by transfer of chemical energy to ATP, the process is "uncoupled". Water is made but the chemical energy is converted to heat energy instead of being given to ATP. This is a good thing if you are cold, like newborn babies or hibernating animals. There is some debate as to the extent to which "uncoupling of oxidative phosphorylation" (the scientific name for throwing away chemical energy as heat) plays a role in the normal regulation of adipose mass, but it is certainly an intellectual solution to the arithmetic problem of making the calories add up. One has only to assume that there is a normal baseline of brown fat metabolism which can be regulated up or down. Uncoupling of oxidative phosphorylation is controlled by both thyroid hormone and stimulation of fat cells by the autonomic nervous system. What does thyroid hormone do? It is supposed to have some role in "regulating metabolism" (the vague concept we were taught in medical school) and it stimulates thermogenesis in brown fat.

The main symptoms of hypo- or hyper- thyroidism are increased or decreased sensitivity to cold, respectively. Patients presenting with hyperthyroidism may be febrile. I vividly recall consulting on a patient in the medical intensive care unit at Kings County Hospital some years ago who was suffering from a condition called "Wernicke's encephalopathy". This disease is caused by thiamine deficiency and presents with confusion, double vision and trouble with balance; it causes irreversible brain damage unless treated rapidly. What had happened to the patient was that he had new-onset aggressive hyperthyroidism. He was using up so many unpaired electrons in mitochondria in his brown fat and throwing away the chemical energy associated with them as heat that his body's basic glucose metabolism couldn't keep up. Glucose is where plants put a lot of the energy that they get from the sun, but breaking down glucose and transferring the unpaired electrons to mitochondria uses up vitamins such as thiamine and the patient had developed an acute thiamine deficiency syndrome. Drug companies have tested drugs to stimulate brown fat and, therefore, weight reduction in clinical trials, but the results are proprietary secrets. Either the drugs didn't work or they had unacceptable side-effects.

We saw that HTN is caused by the brain stem raising the set point for blood pressure in response to stress. Ditto for obesity but substitute the phrase "adipose mass" for "blood pressure": obesity is caused by the brain stem raising the set point for adipose mass in response to stress. If HTN and obesity are both part of the metabolic syndrome, then it makes sense they are both caused by the same thing, which is stress. Think about it. This is an important idea. The two set points are statistically linked and often, but not always, rise in fairly close temporal conjunction.

What about diets? The most logical drug treatment for obesity would be to give people leptin, that is, to try to fool the hypothalamus into thinking that adipose mass is too high and then the hypothalamus would decrease appetite levels, increase the urge to exercise, and increase brown fat thermogenesis in an attempt to bring adipose mass down to where the set point says it should be. In the first such study, carried out by the pharmaceutical company Amgen and published in *The Journal of the American Medical Association* (*JAMA*) in 1999, normal-weight controls but not obese subjects started to lose weight within four weeks. In an extension of the study to twenty-four weeks for obese subjects only, the highest dose of leptin led to an average weight loss of only seventeen pounds. Many subsequent studies, done by a number of different drug companies with a number of different dosing tricks, all failed to produce a great enough weight loss to induce the companies involved to take their

products to market. What this means is that the hypothalamus doesn't do much to protect the set point of obese people on the high side. It "doesn't care" very much if the person becomes still more obese. Technically this is referred to as "leptin resistance" and it is a tragic reality.

What about low-carbohydrate diets? In a study published in the *New England Journal of Medicine* in 2003, seventy-nine subjects weighing 286 pounds on average were randomized to six months of either low-fat or low-carb diets. 40% of the subjects dropped out, but of those who persevered, the low-fat-diet subjects lost an average of 4.2 pounds and the low-carb-diet patients an average of 13.2 pounds. So low-carb was better than low-fat but still not very exciting: down from 286 pounds to 273 pounds. Patients who lost weight did have improvement in triglyceride levels and insulin resistance. The best long-term diet study is the 10-year follow-up of the Diabetes Prevention study, which was published in *Lancet* in 2009. This was a complicated study, but the take-home message was that, while dieting led to an average weight loss of fifteen pounds in the first year, by ten years the gain was lost and treated subjects and untreated controls weighed the same. I have personally known a couple of strong-willed people who lost significant weight on a low-carbohydrate diet and maintained the weight loss long term without having to fight continuous hunger pangs. I suspect they reset their set points back to normal, which implies healing of a broken negative feedback loop. There is always a possibility for healing, at least early on in the disease. This holds for both HTN and obesity. The one treatment for obesity that works is the gastric bypass variety of bariatric (weight-loss) surgery. Why these procedures produce significant long-term weight loss associated with concomitant improvement in lipids and diabetes seems to depend on disconnection of the "distal" (or lower) stomach from exposure to food. The distal stomach produces a hormone called "ghrelin" that gives the hypothalamus a hunger signal that it hasn't seen food for a while and it's time to eat. It might seem logical that a disconnected distal stomach would signal the hypothalamus continuously for food, but what happens is the opposite: the distal stomach gives up and stops making ghrelin. The loss of normal hunger-signaling somehow confuses the hypothalamus about how to interpret the data that it is collecting for set point management: leptin levels start falling relative to the set point for an obese person but the stomach says it's eating non-stop. Finally the hypothalamus gives up, too, and stops trying to defend an obesity set point.

Recap: As is the case with temperature and blood pressure, the body protects a set point for adipose mass, which is a critical parameter for

survival from an evolutionary point of view. Leptin, a hormone produced by fat cells, is the normal physiological measure of adipose mass. Obesity ensues when the set point for adipose mass is raised due to stress. The simple thermodynamic idea that obesity is caused by a mismatch between food consumption and exercise is probably an oversimplification because it ignores the role of heat production (energy loss) in brown fat. Heat production in brown fat probably fine tunes maintenance of the set point for adipose mass. The only successful treatment for obesity is bariatric surgery.

CHAPTER EIGHT

HOW SCHIZOPHRENIA WORKS

I always enjoy spending time with people with severe mental illness. I loved going with the residents to the R Building at Kings County Hospital to do neurology consults on psychiatry patients. There is a fascinating overlap with many interconnections between the two fields. Schizophrenia goes deep. In his book *The Madness of Adam and Eve: How Schizophrenia Shaped Humanity*, David Horrobin postulated that the key evolutionary mutations that produced our species, *homo sapiens sapiens* and its salient characteristics, also produced schizophrenia. One of the salient characteristic features he discusses is that we are, as a species, psychopathic killers. The word "psychopathic" means lacking a conscience, being unable to empathize with the shared humanity of your opponents. The earliest literature that emerges out of prehistory, works such as the *Iliad* and the *Mahabharata*, are stories of unremitting warfare. The two other homo sapiens subspecies, *homo sapiens neanderthalensis* and *homo sapiens denisova*, both which are known to have passed on genes to modern humans, the former mostly to Europeans and the latter mostly to Melanesians and Australian aborigines, disappeared as distinct entities. One can infer that either the three subspecies fused peacefully —boys and girls falling in love and getting married—or that our subspecies tracked down all surviving members of the other two, slaughtering the men and raping and enslaving the women. Which version sounds more likely? One can picture some of the last Neanderthals hiding in the cave on the rock of Gibraltar which contains so many of their artifacts. When overpopulation caused social collapse and cannibalism on Easter Island, some of the survivors hid in caves in cliffs on the side of the island.

Mental illness is also closely related to creativity and high achievement—there's the rub. In a famous study by Jon Karlsson on the inheritance of schizophrenia in Iceland, published as a supplement in *Acta Psychiatrica Scandinavia* in 1974, data was presented on the relationship between high achievement and schizophrenia. At that time, Iceland had a population of only 200,000 people; they had genealogical histories that included almost everyone on the island as well as excellent mental health records going

back into the nineteenth century. Karlsson studied several thousand people in a single large family or kindred, using the book *Who's Who in Iceland* to identify high-achievers or "giftedness" and medical records to identify schizophrenics. One branch of the large family had a rate of giftedness of 6.0% and an incidence of schizophrenia of 2.6% whereas another branch had a rate of giftedness of only 2.1%, but also a lower incidence of schizophrenia of only 0.5%. The overall rate of giftedness in the kindred was 4.0% and the overall incidence of schizophrenia 1.6%, the latter being a typical figure for various populations around the world. Karlsson also found that the schizophrenics in his study had a 13% rate of giftedness in first degree relatives and 18% in second degree relatives. These data show there is a high correlation between high achievement and family history of schizophrenia; it means the same genes are involved. My favorite composer, Richard Strauss, was composing one of his masterpiece, the opera *Elektra*, at the same time his mother was hospitalized in a sanitarium with one of her "nervous breakdowns"; her exact diagnosis is unknown, maybe recurrent unipolar depression, maybe bipolar disorder, but the relationship between mental illness of a first- or second- degree relative and creativity is clear.

"Schizophrenia" is a word invented by the psychiatrist Paul Bleuler, who thought that there was a splitting (hence "schizo-") of different aspects of higher intellectual function. I have never quite grasped what that means and prefer the original term used by Emil Kraepelin in 1893, which was "dementia praecox", i.e. "precocious" or early-onset dementia. He thought it was a degenerative or metabolic disease which probably involved the entire body. He distinguished it from "manic depression" (what we now call bipolar disorder). In some ways, bipolar disorder is schizophrenia-lite. The dominance of strict Freudian thinking in psychiatry was curbed in 1980 when the American Psychiatric Association approved the third Diagnostic and Statistical Manual (DSM). When I was a medical student, we had a lecture about homosexuality in pre-adolescent children. I don't think that this happens anymore. If you look in a modern textbook of psychiatry, you will find the story of Sigmund Freud reduced to a quarter page inset, including a little photograph. This doesn't mean there aren't still many people benefitting from old-fashioned lying-on-a-couch psychoanalysis. It means the field changed and what changed it was the DSM, which shifted the focus of psychiatry from theorizing to making rigorous clinical diagnoses, which could then underpin scientific research and clinical trials. Making a diagnosis of schizophrenia involves navigating a Chinese restaurant menu of criteria. There is no gestalt of symptoms that holds the whole thing together because, as we will see,

Kraepelin was right about schizophrenia being a degenerative disease of the brain which also involves the rest of the body. The most characteristic clinical feature of schizophrenia is being "psychotic", which means having hallucinations, which are usually auditory—hearing voices—and/or having delusions. There is a little grey zone around where exactly you draw the line between normal and abnormal with both of these symptoms. Certain features of the auditory hallucinations are, however, "very schizy", such hearing two voices holding a conversation or having an outside entity insert thoughts into your brain. Other features of schizophrenia include breakdown of social functioning in personal relationships and on the job, sometimes a predominance of "negative" symptoms (the withdrawn teenager who hides in his room listening to the voices), motor stereotypies (abnormal repetitive or sustained movements), a characteristic kind of abnormal speech (what we, as neurologists, recognize as a "fluent aphasia with preserved comprehension"), wearing inappropriate clothing, etc. There are certain people walking down the street who you know from how they look and act that they have to be either schizophrenic or under the influence of a drug. One complication in making the formal clinical diagnosis is that many patients, during acute relapses, can look more depressed than schizophrenic. This has led to a large number of patients being put into an in-between category of "schizoaffective disorder", which is a disease somewhere between schizophrenia and bipolar disorder, although closer to the former. It all appears to be a spectrum, with patients at the pure bipolar end having a "better outcome", although the better outcome destroys the lives of so many creative people and wrecks their families.

Schizophrenics have a normal size skull but shrunken brains. This means that the disease doesn't really get under way before age six years, which is when the skull reaches 95% of maximum size. That soft squishy little thing, the human brain, somehow pushes out the skull as it grows. Then, in schizophrenics, the brain reverses gear and begins to shrink. Diagnosis is made typically in early adulthood; the brain continues to shrink slowly for decades and, besides having all the typical psychiatric symptoms, the patient also develops, as Kraepelin emphasized in his name for the disease, "dementia". We will discuss dementia more in a later chapter; what it means is that you can't do "tests of higher intellectual function", simple things like spelling the word "world" backwards or doing the months of the year backwards; it is associated with failure to lay down new memories and failure of "visuospatial" testing, doing things like copying a medium-tricky drawing. In advanced cases, the patient does not know where he is or what the time is, his thought processes being much poorer than those of

a one-year old child who is, after all, busy decoding language, sometimes multiple languages at once, something his parents can't do. Schizophrenics don't develop severe dementia like Alzheimer's patients, but they do dement.

The neuropathology of schizophrenia is unique, unlike that of any other brain disease. They have a decrease in the "neuropil" as well as well as shrunken neurons (nerve cells). Let's take this slowly. The neuropil is the region where interconnections are made between the branching axons and the branching dendrites: it's where the votes are cast. If the neuropil shrinks, it means there are few elections being held and the neurons shrink because not much is happening. Everyone goes fishing. There is an animal model for this: Edward Jones and Tim Pons reported in the journal *Science* in 1998 an experiment on macaque monkeys in which all sensory input to the left arm was surgically severed. The monkeys were then examined pathologically 12 to 20 years later. The authors found that the initial downstream neuron which is located in the spinal cord and is supposed to be getting sensory input but isn't shrinks and the neuropil shrinks as well: there is no information coming in on axons and so the dendrites and neurons atrophy. Everyone puts up a "gone fishing" sign. What is even more dramatic is that the next neuron in the sensory pathway, which is located high up in the stem of the mushroom in a nucleus called the "thalamus" also shrinks and puts up the "gone fishing" sign. So the question is, why do neurons in the brains of schizophrenics, and we are talking primarily about parts of the front of the mushroom cap called the "frontal lobe" and "cingulate gyrus" go fishing?

The problem starts in the hippocampus, the seahorse, which has reciprocal connections with the DRN. And it relates to stress. Stress is the trigger that initiates the schizophrenic process in a vulnerable individual, vulnerability being caused by multiple genetic risk factors, there being no specific "schizophrenia gene". This is the same story as with HTN and every other disease being discussed in this book. The Italian nuns who were shielded from stress by living a cloistered life did not develop HTN; their friends and relatives who lived in the community mostly did, depending on life circumstances and their genetic risk for that specific disease. The most extensive schizophrenia stress-as-trigger literature involves West Indian immigrants to England. In a recent review of this topic published in the *Pan American Journal of Public Health* in 2005 by Frederick Hickling, the author reports that the incidence of new-diagnosis schizophrenia in Jamaica and other West Indian countries is about the same as that in England or the United States. The diagnosis of schizophrenia is usually

clear-cut, if you don't parse it too finely—I remember an old Jewish psychiatrist at Kings County Hospital who, if you asked him the diagnosis of so-and-so, would say "He's crazy!" which usually made sense. Madness is recognized world-wide. The incidence of new-diagnosis schizophrenia in both first-generation (the people who moved) and second generation (their children) schizophrenia is as much as ten times higher in West Indian immigrants to England than in native-born English people. The only explanation for this that anyone has been able to come up with is that the stresses of poverty and cultural dislocation trigger the disease in genetically vulnerable individuals. There is somehow a reluctance in the recent American literature to acknowledge the role of stress in triggering schizophrenia; however, if you go to the website of the National Health System in England (NHS.uk), you will find a list of the triggers of schizophrenia, which includes "the end of a relationship", "losing your job or home", "bereavement", "divorce" and "physical, sexual, or emotional abuse". (Another reference for those who are interested is the "East London first episode psychosis study" published in the *Archives of General Psychiatry* in 2008.) It is true, however, that sometimes schizophrenia comes on, as the French say, "like a lightning bolt out of a clear sky". The study we are leading up to was performed at Columbia University and published in *Neuron* in 2013 (the lead author was Scott Schobel). These authors used a special kind of magnetic resonance imaging (MRI) to show that there was excessive electrical activity in the hippocampus in young people with early but not yet fully diagnostic symptoms of schizophrenia, so-called "clinical high-risk patients". MRI used in this way is similar to the PET scan described previously to measure firing of the DRN in migraine but has much higher resolution. The excessive electrical activity got even worse in patients who progressed to a clinical diagnosis of schizophrenia. The pathology in this part of the brain in schizophrenia is different from the typical pathology described previously, which was shrinkage of neurons and neuropil; in the hippocampus, there is outright death of neurons. The authors had an animal model of excitotoxicity in the hippocampus which reproduced the MRI and pathological findings seen in schizophrenia, that is, excessive electrical activity followed by death of neurons. Animals could be protected by pretreating them with a drug that blocked the excitotoxicity pathway going from the entorhinal cortex to the hippocampus on the bottom right side of the lower drawing in Fig. 5-1. You already know what is coming next: if you damage the hippocampus, the DRN (the serotonergic nucleus half-way up the brain-stem) will be disinhibited because of loss of

the negative feedback loop. And this is precisely what happens in schizophrenia: a disinhibited DRN overfires and causes the clinical disease

At this point it is necessary to talk about "phospholipids". Be brave. Phospholipids are the major class of molecules making up the cell wall. The cell wall is the membrane or bag that holds a cell together; it keeps everything inside the cell from leaking out indiscriminately and keeps out everything that isn't supposed to be there. Transport across the cell membrane in either direction is tightly regulated with a specific transport mechanism for every specific molecule. The body invests a lot of energy in making the cell wall work. Phospholipids are shaped like tuning forks; there is a layer of tuning forks on both the inside and outside of the cell membrane with the two sets of prongs pointing towards the inside of the cell membrane; that is, the two sets of prongs point toward each other. This is the basic structure of a cell membrane. The body then proceeds to nibble on both side of the cell membrane. It is like the children in Hansel and Gretel who start eating the witch's house, which is made largely of cookies. The two main categories of phospholipids are the "omega-3's" and the "omega-6's". They are both "essential" nutrients because the body cannot synthesize them from precursors and they must be supplied by your diet. Phospholipids arise in the food chain in chlorophyll-containing organisms. In the sea, this means blue-green algae and, on land, it means plants. Little creatures in the sea, like shrimp, eat the blue-green algae, and they, in turn, get eaten by other larger organisms and so on up the marine food chain. On land, herbivores eat plants and get eaten by carnivores. Interestingly enough, omega-3's are found in close proximity to chlorophyll and are somehow essential in making photosynthesis work. When you eat phospholipids, they get inserted into cell membranes as prongs of the tuning forks. Then the body proceeds to nibble on them, using an enzyme called "phospholipase A_2" to break off the cookies. When the nibbling occurs on the outside of the witch's house (the cell membrane), the phospholipid that the enzyme removes is then changed by a series of chemical reactions into a variety of small molecules called "prostaglandins", which regulate inflammation. We recall that inflammation is tissue swelling, redness, heat, and pain caused by trauma, infection, or immunological reaction. Cookies are taken from the inside of the wall of the witch's house only in response to electrical signaling at a synapse, and the signaling that interests us here is serotonin. When serotonin modulates the votes being cast at a synapse, it does so by causing release inside the neuron of a phospholipid, either an omega-3 or an omega-6 phospholipid. It is not understood in detail how this works, but the phospholipid is what carries out the vote fraud.

A lot of important ideas are coming together here. Omega-3's and omega-6's are not stored as energy sources in adipose tissue—that's the job of "unsaturated" lipids—and, in fact, play their crucial biological role by being inserted into cell membranes and then being removed by the enzyme phospholipase A_2. On the outside of the cell, they are converted into prostaglandins that regulate inflammation, and on the inside of the cell, they are released in response to serotonin signaling and mediate vote fraud. (There are other types of electrical signaling that can activate phospholipase A_2, but this is not part of our story.)

An extraordinary feature of schizophrenia is that there is a body-wide deficiency of phospholipids, which means that Kraepelin's idea that it is a metabolic disease is correct. It has been known for a long time that schizophrenics don't feel certain kinds of pain. I was recently astonished by a schizophrenic patient who told me she didn't mind having blood drawn from her arm vein because it didn't hurt. Pain in response to tissue injury, e.g. getting poked with a sharp needle, is part of inflammation and inflammation is mediated by prostaglandins, which come from phospholipids removed from the outside of a cell membrane. The pain insensitivity of schizophrenics can be tested clinically by a "histamine scratch test", in which various concentrations of histamine, a molecule that causes white blood cells to release prostaglandins, are applied to the skin and the presence or absence of a "flare" (red inflammatory skin reaction) is documented. Basant Puri, one of the editors of Medical Hypotheses, recently confirmed the older literature and standardized the test, which has high sensitivity and specificity for schizophrenia. It is one of those clinical tests that could be used but isn't. Measurements of red blood cell membrane phospholipids in schizophrenics show a deficiency relative to normal controls; this is another potential diagnostic test for the disease.

The basic pathological process in schizophrenia is that there is so much overdrive of serotonin electrical activity in the brain that phospholipids, being linked to serotonin firing, get depleted in the brain. Neurons try to recycle serotonin being released on the inside wall of cell membranes at synapses, but the process is imperfect and eventually the brain runs out of omega-3's and omega-6's. It then draws them in from the periphery, i.e. the rest of the body, which then starts to run out of them, too. Because omega-3's are present in much smaller quantities than omega-6's, they go first. When neurons start to run out of phospholipids, then they can't function properly and electrical signaling starts to falter. In the end, they put up the "gone fishing" sign, neuronal cell bodies and neuropil (the connections between axons and dendrites where the votes are cast) shrink,

and the brain atrophies. All the symptoms of schizophrenia then ensue, although it is not understood in very much detail where the various symptoms localize in the brain. The newer class of drugs used to treat schizophrenia, the so-called "atypical anti-psychotics", which includes Risperdal, Zyprexa, Abilify, etc., as opposed to older drugs like Thorazine and Haldol, can actually slow down the basic pathological process just described. In a landmark study led by JA Lieberman at Columbia and published in the *Archives of General Psychiatry* in 2005, patients with newly-diagnosed schizophrenia were treated with either Zypexa, an atypical anti-psychotic or Haldol, an older drug, in a randomized double-blinded study. After a year, it was found that patients treated with Zyprexa were protected from the usual progressive brain atrophy, as measured by MRI whereas patients treated with Haldol were not. In technical terms, the difference between the two drugs is that only the Zyprexa blocks serotonin signaling and, therefore, phospholipid depletion. (Both drugs blocked something called "dopamine signaling", but that is not part of our story.)

David Horrobin initiated treatment of schizophrenia with phospholipids and soon discovered that what patients need is omega-3's and not omega-6's, perhaps because they run out first, as noted above. These clinical trials are ongoing. Basant Puri et al, reported a very informative detailed study of a single patient conducted at the Hammersmith Hospital and Imperial College of Medicine in London (*International Journal of Clinical Practice*, 2000). A 31-year-old man with the diagnosis of schizophrenia was treated for six months with omega-3 supplementation (a phospholipid called "EPA") but no anti-psychotics, that is, none of the usual drugs. By two months his clinical scores improved dramatically, auditory hallucinations (hearing the voices) disappearing and delusions improving, although some "thought disorder" persisted. The low phospholipid content of his red blood cell membranes normalized and, most dramatically, the progressive brain atrophy, which had been documented on serial MRI's for twelve months before starting omega-3 treatment, also reversed completely. This last finding meant that the neuropil, the region of interconnections between axons and dendrites, had recovered and taken down its "gone fishing" signs. In a double-blinded placebo-controlled study performed by G. Paul Amminger et al. at a hospital in Vienna, Austria, and published in the *Archives of General Psychiatry* in 2010, patients with early symptoms of schizophrenia who did not yet meet the formal Chinese menu criteria for a full diagnosis (so called "ultra-high risk" patients) were treated with either omega-3 supplementation or placebo ("sugar pill") for twelve weeks and then monitored for additional 40 weeks. After twelve months, 11 out of 40 patients getting the sugar pill

transitioned to a formal diagnosis of schizophrenia, compared to only 2 out of 41 patients getting omera-3. One can only wonder at what the outcome might have been had the omega-3 patients received treatment for the full 52 weeks instead of only the first 12 weeks.

To review these treatment studies: both the newer anti-psychotic drugs, which inhibit manic serotonin over-firing, and omega-3 supplementation, which corrects the omega-3 deficiency caused by manic serotonin over-firing, have been shown to result not only in clinical improvement but also in reversal or slowing of cortical atrophy. The "gone fishing" signs come down and the brain goes back to work.

There are some other interesting aspects to schizophrenia we have not yet discussed. Patients at the time of diagnosis (or "first episode" as psychiatrists say) are already developing insulin resistance, which is the first stage of obesity as manifested in the metabolic syndrome. Obesity in schizophrenia is worsened by some of the medications used to treat it, but it is already present at the time of diagnosis. Schizophrenic patients also have elevation of a phospholipid-related enzyme in the blood that can be interpreted as a marker for SPA. There is no literature about the incidence of migraines in schizophrenia and schizophrenia usually starts at a younger age than HTN. When they start their journey down the bad road, schizophrenics already seem to have co-diagnoses of early obesity and possibly SPA. The pattern described in earlier chapters of migraines coming first, then HTN, then other diseases is an oversimplification. Every journey down the bad road is different. But staying at home is always the same.

Recap: Schizophrenia begins when stress triggers excitotoxic damage to the hippocampus. The negative feedback loop with the DRN is broken and a disinhibited DRN overstimulates wide areas of the brain. Because of the linkage of serotonin signaling to phospholipids, phospholipids (omega-3's and omega-6's) get depleted, both in the brain, which causes failure of electrical signaling, brain atrophy, and psychiatric symptoms, and in the periphery, where lack of prostaglandins leads to insensitivity to pain. The class of newer anti-psychotics which block serotonin signaling can slow down brain atrophy. Omega-3 supplementation, which makes sense because omega-3's are depleted before omega-6's, is another clinically-proven treatment that reverses brain atrophy.

CHAPTER NINE

HOW ATHEROSCLEROSIS WORKS

The word "atherosclerosis" comes from "athero" (gruel or porridge) plus "sclerosis" (hardening or scarring). When someone undergoes a demise owing to this diagnosis, the pathologist doing the autopsy will find lots of abnormal little balls or spheres called "atheromas" in the vascular tree, all occurring just beyond branch points of arteries. One of them will have caused blockage of a critical artery or, in the case, of the brain, an atheroma may have bled and led to a "hypertensive intracranial hemorrhage". When the pathologist looks through his microscope, he will find the characteristic abnormalities: there is an accumulation of soft watery porridge-like material filling up most of the little balls and narrowing blood flow at that point. The porridge consists of white blood cells that have taken up cholesterol; many of the white blood cells are in the process of dying or have died, which is what causes the soft consistency. There is also proliferation of "smooth muscle cells", the kind of muscle cells inside of blood vessel walls that contract in order to narrow blood vessels and regulate blood flow. In advanced cases, there is scarring, which is the "sclerosis" component. In "myocardial infarctions" (heart attacks), the acute event is thought to be rupture of the fragile "plaque", ("plaque" being the fragile interior lining of the atheroma) into the artery with instantaneous formation of an occlusive white clot. In the brain, atheromas look a little different in that there is less porridge; in a stroke, the plaque does not rupture but rather there is formation of an occlusive white clot within the artery at the site of the atheroma. The localization of atheromas to sites just beyond branch points relates to turbulence, which occurs in flowing streams of blood where they divide just as they do in flowing streams of water. Endothelial cells, the cells lining blood vessels, have pressure receptors and, at one time, there were dueling theories that turbulence caused either increased or decreased pressure. The problem wasn't solved until scientists grew the endothelial cells in flow chambers and carefully measured pressure. The answer was that turbulence causes less pressure in a plane parallel to the surface of the endothelial cells (not the plane pushing in on them) and this is what causes "activation" of the endothelial cells. Another ON button is pushed, this time on endothelial

cells instead of on platelets, and the formation of the porridge begins, as will be described in more detail below.

Having discussed the pathology or microscopic appearance of atheromas, let us turn to "cardiovascular risk factors", which are risk factors for developing atheromas; the big four are high cholesterol, HTN, diabetes, and smoking. Even one of them, for example chain smoking by itself, may suffice to cause fatal atherosclerosis. Historically a lot of attention was paid to cholesterol because the porridge consists largely of cholesterol. It is now realized that eating cholesterol does not cause atherosclerosis any more than eating sugar causes diabetes or eating salt causes HTN. "Meta-analysis", that is, combining the statistical weight of several individual studies, has shown that there is no convincing data that eating cholesterol is bad for your health. The same is true for eating "saturated fats", the kind found in animal fat and fatty meat. Saturated fat is the main fat in adipose tissue, the insurance policy against starvation. The Government's old "low-fat" food pyramid encouraged everyone to go on a high carbohydrate diet, which was eventually challenged by the rise of low-carbohydrate/high-fat diets. As we saw before, neither type of diet is very effective for losing weight; they also fail to lower cholesterol.

The thing that cardiovascular risk factors have in common, their lowest common denominator if you will, is that they all cause massive oxidative stress, i.e. "free radical storm", which is having molecules with reactive unpaired electrons zooming all over the place, destroying large molecules like proteins, lipids, and DNA. The good kind of unpaired electrons are the ones involved in carrying energy from the sun through all the stages of herbivore and carnivore life and ending up being restored to oxygen molecules in mitochondria when ATP money is minted. The bad ones are the reactive ones, the bullets, formed, for example, by platelets in SPA and released everywhere in the blood in toxic quantities. In a classic paper published in the journal *Circulation* in 2001 by Thomas Heitzer et al., the magnitude of the free radical storm was measured. The article is a little bit complicated but worth looking at in detail. The authors tested the "vasodilatory response of the brachial (or forearm) artery", using a technique called "venous occlusion plethysmography". I know "plethysmography" sounds like name of a dinosaur (maybe in its adjectival form it could be used to describe an après-ski mood or a beautiful spring day); let's take it slowly since it's an example of how important scientific information can be discovered with a simple, low-budget clinical technique. In plethysmography a blood pressure cuff is placed on the arm above the elbow, the same place your doctor places it when they are taking

your blood pressure. The pressure in the cuff is then raised intermittently to a level that blocks venous return from the forearm but does not block arterial blood going in through the brachial artery. The forearm swells during the period of venous occlusion, the blood going into muscles. The "plethysmograph" is a device that measures how much the forearm swells, which, of course, depends on how much blood goes into the muscles. You can infuse chemicals through a small catheter placed in the brachial artery and study the behavior or physiology of endothelial cells, the cells lining blood vessels. Endothelial cells release chemicals that constrict or dilate arteries and, therefore, influence how much blood goes in and how much the forearm swells when the cuff is inflated to block venous return. Heitzer et al studied 281 patients who had undergone coronary artery angiography because of cardiac symptoms and had documented narrowing or occlusions of coronary arteries due to the presence of atheromas. Patients' brachial arteries were infused with the chemical "acetylcholine" that would ordinarily cause dilation of the arteries and increase swelling of forearm muscle mass during venous occlusion. Test results showed that patients who went on to have a subsequent clinical "event" in a follow-up period averaging four years, an "event" being most frequently a myocardial infarction or cardiac symptoms that led to the need to perform a balloon "angioplasty", which is a treatment to mechanically widen a coronary artery, were much less responsive to the effects of this chemical than those who subsequently remained free of events. The poor vasodilatory response of patients who went on to have subsequent events could be reversed by infusion of vitamin C, which is an anti-oxidant, a small molecule that binds to and neutralizes free radicals, which means that free radicals were blocking the vasodilatory effect of acetylcholine. The patients without events were not normal; they were also going down the bad road—on average their cholesterol was elevated and many of them smoked or had HTN or diabetes. We do not know how much vitamin C might have been required to bring the vasodilatory response of the relatively healthier group of patients, the patients without events, up to the level of people who had not gone down the bad road. The amount of vitamin C required to produce the effect reported in the study was already extraordinarily high, 24 mg per minute. This works out to 3.5 grams a day, but taking 3.5 grams a day as a health supplement will not produce the same effect because only arterial or venous infusion of vitamin C will maintain the necessary steady-state blood levels and such a dose is already getting into the danger zone for vitamin C supplementation with oral tablets, which can produce very high peak levels after ingestion and toxic side effects such as premature cataracts and possible carcinogenicity. Linus Pauling was the great guru of

vitamin C. Pauling was a great scientific literary stylist and in an elegant paper published in *The Proceedings of the National Academy of Sciences* in 1970 he points out that our species is of one of only a few species, the list also including guinea pigs and certain fruit-eating bats and Passeriform birds, that are unable to synthesize vitamin C. Deficiency of vitamin C causes scurvy, which can be prevented by the consumption of a relatively small amount of vitamin C, only 10mg daily (remember that a mg (milligram) is $1/1000^{th}$ of a gram). Pauling argues that, in order to be in line with the vitamin C consumption of other large primates such as the gorilla we should consume 2 to 5 grams of vitamin C daily. He has no data to back up his arguments, and other people have argued that the high blood levels of uric acid found in our species indicate that, from an evolutionary point of view, uric acid levels have risen to replace vitamin C in its role as a key anti-oxidant. In any case, the magnitude of the free radical storm in is why taking anti-oxidants is futile; the doses which a person can take by mouth are much too small to maintain effective steady state blood levels without risking toxic side-effects.

Let us return to cardiovascular risk factors and, in particular, to cholesterol. Cholesterol has several normal functions in the body. It is a component of the cell wall, where it helps regulate the fluidity of the wall, and it is the starting chemical for the synthesis of the steroid hormones of the adrenal cortex and of sex hormones in both males and females. Being a fat, it is not soluble in water but has to carried around in the blood bound to proteins called either low-density lipoproteins (LDLs) or high-density lipoproteins (HDLs). These proteins deliver cholesterol, which is synthesized in the liver, to various tissues in the body. LDLs are not pathological per se, but if the LDL protein is damaged by a superoxide anion or other reactive free radical, then it can be taken up by what is called a "scavenger receptor" on white blood cells. This is how formation of the porridge starts: white blood cells in an area of an arterial cell wall just beyond a branch point, where turbulence has pushed the ON buttons on a zone of endothelial cells, start to take in damaged LDLs and store the cholesterol bound to them. HDLs (the "good type of lipoprotein) have some ability to remove cholesterol being stored by white blood cells and carry it back to the liver for disposal.

Prevention of atherosclerosis has focused on lowering cholesterol levels. Eating cholesterol is not bad for you because the more you eat, the less your liver synthesizes, and vice versa. LDL levels are a function of adipose mass and what is dangerous is to have a high LDL blood level because LDLs damaged by free radicals are taken up by scavenger

receptors on white blood cells in an atheroma and form the porridge. Obesity is the underlying cause of high cholesterol and, therefore, high LDL. Current medical treatment is very effective at lowering LDL. Unfortunately, there is no effective treatment for free radical storm, which is the other part of the equation. The cause of the free radical storm in patients with cardiovascular risk factors is somewhat unclear. Allowing for the fact that few people in the civilized world smoke anymore and the fact that both high cholesterol and diabetes are side effects of obesity, then the risk factors collapse into the metabolic syndrome, which, as we remember from Chapter 7, is the statistical conjunction of HTN with obesity. Most of the stroke patients I saw as a resident had both HTN and diabetes. More research needs to be done on the mechanisms of oxidative stress in the metabolic syndrome. There are recognized biochemical mechanisms by which either very high glucose or very high cholesterol by itself can generate free radicals, but most patients do not have glucose or cholesterol riding at stratospheric levels. This leaves superoxide anions produced by endothelial cells in HTN patients with high renin levels and SPA as the culprits. Only a minority of hypertensive patients have high renin and, in the end, SPA may be the big player. The key piece of missing information is the incidence of SPA in diabetics with normal blood pressure.

Recap: Atherosclerosis, a disease that particularly affects the heart and brain, is characterized by the formation of atheromas, which are spherules containing a porridge-like substance formed by the uptake of LDL proteins that have been damaged by free radicals. High cholesterol and free radical storm are the two key players in this process. The narrowed arteries within the atheromas thrombose and block blood flow, causing a myocardial infarction or stroke. The major cause of free radical storm is probably SPA. The incidence of SPA in diabetics without HTN is unknown.

CHAPTER TEN

HOW ALZHEIMER'S DISEASE WORKS

Some people say the final stage of life is being an elderly pensioner. They are wrong. The final stage of life is lying in a persistent vegetative stage for several years. Then someone comes with a pillow to suffocate you.

What is dementia? It is a loss of "higher intellectual functions" and can be tested clinically in various ways. First of all, mental retardation and a "delirium" or temporary metabolic or drug-induced impairment of intellectual functions must be excluded: dementia is a gradual or step-wise decline from a level of normal functioning. When I was making rounds with the residents and in a rush, which was usually the case, I started by testing orientation. If patients were not "oriented times three", i.e. to person, place, and time, they probably had a severe dementia, again assuming they once had a normal baseline and did not have a reversible temporary condition. Everyone can be assumed to know their own name, so the questions that I asked were: "What is the name of this hospital, the month and the year". If a patient knew that much, I could test for a milder degree of dementia if I wanted to with the following three questions or requests: spell the word "world" backwards, name the months of the year backwards, and tell me how many quarters there are in $2.75. When I was a first year neurology resident, we would ask patients "Is it true that helicopters devour their young?" and we would drink the orange juice off the breakfast trays of demented patients to see if they reacted. Inability to give a good history of the present illness is usually the first clue to a diagnosis of dementia. More formal tests, like Mini-Mental status exam or MOCA (Montreal Cognitive Assessment), give you a number which can be followed over time. Dementia specialists refer patients for extensive testing which can last a couple hours, which might seem excessively long but such tests can reveal very characteristic features of Alzheimer's disease, for example, "visuospatial" defects: a patient might report that they see the bottom part of a glass moving but not the top part. Evaluation for depression can also be very informative.

Alzheimer's disease (AD) begins in so many ways and the clinical course in every case is different. The paradigmatic symptom of having to ask the same question over and over again because of a failure of short-term memory is usually not the first symptom, as I have learned from personal experience. I once had a friend who wrote theology books and the first symptom of his illness was a precipitous fall-off in the quality of his books. All of these people stand before me, hovering like ghosts, as I write. I had a relative who lost a great deal of money in bogus fortune-telling and other scams, particularly an inheritance scam. This was combined with hoarding behavior. I had another relative who began having word-finding problems that progressed to the point where she couldn't get out more than a few halting stuttering words when she tried to say something, but her comprehension seemed to be intact. I had a friend who developed a certain impreciseness in his thinking, having previously had a razor sharp mind--it's hard to ask your friends or relatives to spell the word "world" backwards or do the months of the year backwards, that's the doctor's job—and then an unsteady shuffling gait appeared, what neurologists call a "frontal lobe gait". A colleague and scientific collaborator who was mostly alone in the world except for one close friend suddenly decompensated when the friend died; she probably had pretty advanced Alzheimer's disease which was symptomatically camouflaged by her continuous high level of intellectual functioning and then, when her friend died, everything fell apart. Patients who self-refer with a chief complaint of "trouble with my memory" usually do not have AD but rather "pseudo-dementia", which is intellectual impairment caused by depression; this can sometimes be surprisingly severe and can include visuospatial problems. Alzheimer patients typically do not complain about their symptoms, except maybe about how they keep losing everything, but even this symptom relates more to the specific items they've lost that to the pattern of losing things. They don't self-refer but get dragged in by the family to see the doctor. Then they sit passively, seemingly disinterested, while the doctor discusses their case with the family. The diagnosis is usually tragically obvious to a neurologist, but we do a pretend work-up by ordering a computerized tomography (CT) scan of the brain or MRI of the brain and blood tests for vitamin B12 level, thyroid function, and syphilis exposure. Only in cases with atypical features, such as onset before age 65 in a non-diabetic, are we likely to change the original diagnostic impression. Finding a sort of treatable cause for dementia is, of course, very gratifying for a neurologist. I recently saw an interesting case at Kings County Hospital: a man in his late fifties was brought to the emergency room on a Sunday morning by his family because, according to

them, he had become "paranoid" and falsely accused them of hiding his clothes. But the real issue was that he had recently lost his job as a school bus driver when the company changed his route and he had been unable to learn the new route, delivering children to their homes as much as two hours late. I was the weekend attending as well as the ward attending and admitted him with a diagnosis of "encephalitis". Then I went through a differential diagnosis of dementia with the residents, which included the observation that dementia due to vitamin B12 deficiency is usually accompanied by both paranoia and signs of spinal cord impairment ("myelopathy") and that I had been looking ever since residency for a case without myelopathy and that neurologists still talked about whether or not this could happen. Our patient had no myelopathy. So I stood there dithering, blah blah blah. To my great surprise, the patient turned out to have an extraordinarily low B12 level and made at least a modest improvement after treatment. You never know how a given case will play out.

A very small percentage of AD cases, 5% or less, are due to a single gene mutation. In **1906 Alois** Alzheimer, who was a friend and colleague of Emil Kraepelin, the man who first described dementia praecox (schizophrenia), published a clinical and pathological study of a woman in her mid-fifties who died from dementia. It was Kraepelin who introduced the term "Alzheimer's disease". A few years ago Alzheimer's original pathology slides for that case were discovered and a technique called "polymerase chain reaction" was used to study her DNA and show that she suffered from a mutation of a protein called "presenilin", which is now known to be the most common cause of the genetic cases. The vast majority of patients do not have a single mutation of a single gene. As with the other diseases being discussed in this book, there are polygenetic risk factors, many genes that mold individual susceptibility and the course of the disease. The main risk factors turn out to be the same as those for stroke and atherosclerosis: HTN, diabetes, high LDL, and smoking. A particularly elegant paper documenting the crucial role of vascular risk factors was published by the Columbia group led by Richard Mayeux in *Neurology* in 2004; they enrolled 1,138 initially non-demented subjects who lived in upper Manhattan near the medical school and documented any "baseline diagnoses" which might be risk factors. They followed the subjects for ten years, at which time 22% met criteria for the development of possible or probable AD. The risk factors clustered (we already know how HTN and diabetes are statistically associated or "clustered" in the metabolic syndrome) and patients with three or more of the baseline diagnoses of diabetes, HTN, heart disease, and smoking had 3.4 times the

risk of developing of developing AD as those who lacked these diagnoses. Hmm. I remember when I was very young—this was the early days of television—seeing a movie in which people dressed in animal skins were fleeing down the slope of a mountainside, pursued by dinosaurs. Then they got caught up in a lava flow. I particularly remember how a beautiful young woman slipped gracefully into the molten lava. I have never been able to track down the movie, but it probably had something to do with being stressed-out.

In a paper published in 2006 in the *Journal of Alzheimer's Disease*, Heiko Braak, a neuropathologist at the J. W. Goethe University in Frankfurt, Germany, reviewed the staging system that he had developed for the progression of both AD and Parkinson's disease (PD) through the cerebral cortex, the cap of the mushroom, which turns out to be the same for the two diseases. In both diseases, the pathology involves specific neurons and not little regions of diseased brain. A dying neuron can be located next to a healthy neuron. The neurons that die are "projection neurons", those with axons like long-distance telephone wires that connect far flung parts of the brain. Sending electrical signals down long-distance cables requires a lot more ATP money than sending signals down short cables. The long-distance cables have a kind of electrical insulation called "myelin", which reduces the ATP cost, but it is still very expensive. The development of the insulation, which is called "myelination", advances gradually throughout childhood and into early adulthood in a predetermined pattern which may account, at least in part, for sequential changes in intellectual function with age, for example, the appearance of reading around age six or seven. Myelination starts first in certain parts of the brain, for example the "motor strip" that is responsible for initiating voluntary movements, and completes its job finally in a region called the "transentorhinal cortex". This is next door to the entorhinal cortex, which was the entry zone for signals coming into the hippocampus from the DRN via the indirect route in Fig. 5-1. Projection neurons arising from regions which myelinate last are the least-well myelinated or, according to Braak, in some cases, even unmyelinated. AD and PD work their way anatomically through the cerebral cortex in a reverse pattern to myelination, with the transentorhinal cortex going first and the motor cortex and other early-myelinating regions seldom if ever involved. AD and PD have different "intracellular markers" and different risk factors. "Intracellular markers" are characteristic changes inside affected neurons that a neuropathologist sees when he stains the cells at autopsy: this helps him make his diagnosis. AD neurons have "neurofibrillary tangles" and PD neurons have "Lewy bodies". AD brains also have characteristic deposits of a protein called

"beta-amyloid" (Aβ) around the outside of affected neurons The major risk factors for AD are, as mentioned earlier, the usual cardiovascular risk factors; the major risk factor for PD is age. So they are clearly different diseases but they share a propensity for attacking projection neurons, particularly the ones that are the least well-myelinated and, therefore, have the highest ATP costs, the highest Con Ed bill, so to say. Braak suggests that poor myelination is perilous for projection neurons because of oxidative stress. This makes a great deal of sense because mitochondria are not perfect and some of the electrons carrying energy from the sun leak out and go rogue, turning into superoxide anion bullets. The neurons that have the greatest problem with these internally-generated, dangerous free radicals are the long projection neurons. They are also at increased risk for any oxidative stress coming from outside the cell, which would produce an additive effect.

In an important article published in 2001 in the *Journal of Neuropathology and Experimental Neurology* by George Perry's group (Akihiko Nunomura was the lead author), the scientists studied markers of oxidative stress in the brains of Alzheimer's patients who had come to autopsy. They stained the neurons for markers of recent damage due to oxidative stress, which they could see under the microscope. Surprisingly, the patients with the longest duration of disease and the greatest overall loss of neurons had the fewest signs of recent damage by oxidative stress. Emphasis on the word "recent". They also had the highest levels of neurofibrillary tangles, the intracellular marker for AD, within surviving projection neurons. To be precise, neurons with high levels of neurofibrillary tangles had 40-56% percent less recent oxidative damage. This data leads to the crucial idea that neurofibrillary tangles play a protective role against oxidative stress, i.e. that oxidative stress causes neurons to form neurofibrillary tangles in self-defense; of course, this only buys time and the neurons die in the end. Neurofibrillary tangles slow down but cannot stop the disease. Braak used the presence of neurofibrillary tangles as his marker for how AD marches through the brain.

So how do we put this all together? As we learned in the chapter on atherosclerosis, the lowest common denominator of the vascular risk factors is that they all cause free radical storm. The vitamin C infusion study measured the awesome intensity of the storm. Superoxide anion bullets are converted into other chemicals, for example hydrogen peroxide, which cross the cell membrane and synergize with free radicals produced internally. This is why long projection neurons with high ATP costs are

the first to die and why AD moves in reverse direction to myelination of the brain, the neurons myelinated last being the least well myelinated. Some patients with vascular risk factors have their first stroke before they start to dement and some start to dement before the first stroke. In general, they have what the pathologists call "dual pathology", which means that they have both strokes of all different shapes and sizes plus Alzheimer changes to account for their dementia. In many cases, the clinical effects of "vascular dementia", which is dementia caused by strokes, cannot be parsed out from the effects of Alzheimer's disease. The strongest MRI machines, which have seven tesla strength magnets, can demonstrate microscopic strokes in the "grey matter", the layer cake that forms the surface of the cerebral cortex. Sometimes a stroke in a "strategic hit" area, for example the left hippocampus, causes sudden-onset or worsening of dementia. Losing half your cerebral cortex in a stroke is also obviously very bad. But most patients simply dwindle away with a discrete step down from time to time. Another discouraging aspect of the situation is that the Aβ or beta-amyloid protein mentioned earlier, which is leaked by neurons dying from oxidative stress, has the chemical property of being able itself to cause free radical damage. It is like the song title from the musical "Phantom of the Opera": Past the point of no return. The local creation of free radical damage and oxidative stress also explains how the rare genetic form of Alzheimer's disease works: these patients, because of the presence of a specific abnormal gene, leak Aβ, which then causes local free radical storm independent of the presence or absence of vascular risk factors.

So the story of stress has come full circle: it began with a change in the brain, excitotoxic damage to the hippocampus, which left the DRN free to raise set points for blood pressure and adipose mass and otherwise orchestrate the diseases of chronic stress. It ends with the dual pathology of stroke and Alzheimer's disease. The bad road leads to a place no one wants to go.

Recap: Dementia is the gradual loss of higher intellectual functioning. Alzheimer's disease selectively hits long projection neurons, which have the highest baseline ATP costs as well as the highest baseline leakage of electrons from mitochondria, which leads to the highest baseline levels of oxidative stress within these neurons. Free radical storm caused by vascular risk factors synergizes with baseline internal oxidative stress to kill the most vulnerable neurons. Neurofibrillary tangles are a defense mechanism against oxidative stress.

CHAPTER ELEVEN

HOW PARKINSON'S DISEASE WORKS

There is a third common pathology associated with dementia and that is Parkinson's disease (PD). At autopsy, the pathologist sees Lewy bodies instead of neurofibrillary tangles inside of surviving neurons, which leads him to make a diagnosis of PD rather than AD. Some patients have both kinds of intracellular markers as well as strokes, which is triple rather than dual pathology. PD is much more likely than Alzheimer's to start in the brain stem (the stem of the mushroom) and, in fact, Braak begins his staging of PD in the brain stem. Very early symptoms can include constipation, loss of smell and unusual kinds of sleep disturbances. Then the characteristic "resting tremor" appears. A "tremor" is a more-or-less rhythmic involuntary movement; in this case, it is an oscillation of the hands when they are at rest, usually one side being affected before the other. Interestingly, rare cases of resting tremor have been reported in which the patient had Alzheimer intracellular markers and not Parkinson markers at autopsy. However, AD is inconstant in its penetration of the brain stem, whereas PD characteristically involves the brain stem before the cerebral cortex, which is why the diagnosis is usually made at the tremor stage before dementia sets in. There is a very effective medicine for the tremor stage of PD, which is L-dopa (or Sinemet, the usual brand name). I have seen two patients with advanced untreated Parkinsonian tremors, one an old man fished out of a nursing home somewhere in south Brooklyn and the other a woman flown up from the Caribbean (Kings County Hospital functions as a tertiary care referral center for the Caribbean). In both cases, the resting "tremor" was so bad that it was more like a flinging movement than a tremor, and, in both cases, the patients were restored to normal within a half hour of taking one tablet of L-dopa; only some subtle abnormalities on neurological exam persisted. Unfortunately, as the disease progresses, eating up more and more projection neurons as it goes, we run out of treatments.

The clinical picture of PD when it is diagnosed usually includes, in addition to the resting tremor, stiffness and slowness of movement plus a characteristic stooped unsteady "shuffling gait" ("shuffling" means scuffing

the ground with your heels), lacking arm swing, all of which is attributed to dysfunction of the "basal ganglia". These are large paired nuclei at the top of the brain stem which are sort of hidden by the overhanging edges of the mushroom cap. When you decide to make a voluntary movement, the movement starts in the "motor strip" in the cerebral cortex. Then two feedback loops are immediately brought into play, each one lasting only milliseconds. One involves the basal ganglia and the other the "cerebellum", which is a large nucleus at the base of the brain stem. The basal ganglia loop involves the selection of one or more templates on which to structure the planned movement; it is as if the motor strip doesn't have to start from scratch in putting together the planned movement but can build on some pre-programmed sets of sequential coordinated muscle contractions. The cerebellar loop fine tunes precision of movement, for example, making the baseball go exactly where you want it to. In advancing PD, the motor templates start to appear on their own—it is like zoo animals escaping from their cages. These movements are described by the rather vague word "dystonia" and are made worse by L-dopa. I have seen a patient with end-stage Parkinsonian dementia who was incapable of communication but had constant vocalizations (sounds with no meaning) and wild synchronous movements bringing both arms and legs together in the mid-line (gestures with no intent). The more typical end-stage picture is for stiffness to swallow up the escaped templates and the patient lies rigid as a board, mute and staring into space with glazed eyes.

What is the cause of this terrible decline and how is it different from AD? PD has nothing to do with cardiovascular risk factors and its incidence increases linearly with age, being constant over decades in communities where such data exist. Denham Harman hypothesized in a famous paper in the *Journal of the American Geriatric Society* published in 1972 that the mitochondria are a "biologic clock" that determines the relative longevity of different species. This theory was later amended by other scientists to focus on cells that do not divide, specifically neurons. Mitochondria are, as we recall from chapter 3, prehistoric unicellular organisms that took up residence inside of cells and began minting ATP money. They have a small amount of DNA of their own but they have weak protective mechanisms against oxidative stress. Mitochondria constantly leak some of the electrons carrying the sun's energy and the leaked electrons turn into superoxide anion bullets that damage mitochondrial DNA and mitochondrial structural proteins and lipids. Over time the mitochondria slowly degrade and the minting of ATP money falters. Hung-Hai Ku et al., in a study published in *Mechanisms of Aging and Development* in 1993, compared mitochondrial electron leakage and anti-oxidant defenses in the

pigeon and the rat, two animals of similar size and metabolic rate. The life span of the pigeon is 35 years and that of the rat 4.5 years. Brain mitochondria in the rat leaked more unpaired electrons, generating 71% more superoxide anions and three times as much hydrogen peroxide as did those in the pigeon; leaked electrons turn first into superoxide anions and then much of this goes on to form hydrogen peroxide, so the difference was huge. Anti-oxidant defenses in the pigeon brain were about 20% higher than in the rat brain. In summary, rats have vastly more electron leakage and slightly weaker anti-oxidant defenses, which correlates with their shorter lifespan. Even though we don't have a databank of pigeon and rat autopsies, these data show a correlation between oxidative stress in the brain and lifespan in these two species and support the idea that an age-related disease such as PD could be caused by gradual failure of cellular energy production in the brain; the long projection neurons, which have the highest energy needs and the most active mitochondria, die first because their mitochondria leak the most electrons. There are two animal models of Parkinson's disease; they both utilize mitochondrial poisons which are taken up by cells in the basal ganglia and reproduce the classic tremor stage of the disease, including early Lewy bodies. Lewy bodies, like neurofibrillary tangles in AD, may reflect a protective mechanism against the disease. In a tragic case, a young man unknowingly ingested one of these poisons, which was formed as an accidental by-product of an inept illicit synthesis of meperidine, which is an addictive drug something like heroin. He developed tremor-stage symptoms overnight and never recovered.

Recap: PD is not related to stress, but it is important to understand it, both because of its inherent compelling interest and because it exemplifies a second vulnerability of metabolically active long projection neurons, which have a high baseline level of intracellular oxidative stress: in AD, additional oxidative stress enters from outside the cell; in PD, mitochondria fall victim over time to the oxidative stress they themselves produce and the minting of ATP fails.

PD would seem to put an outside limit on the possible human lifespan. Old age itself is the sickness.

CHAPTER TWELVE

HOW AUTOIMMUNE DISEASES WORK

Those of us who were living in Manhattan on September 11, 2001, will, of course, never forget the day. We still find it emotionally important to share stories about what happened. The only person I knew personally who was in the World Trade Center at the time of the attacks worked for a consulting company and was visiting an office in the North Tower (Tower One), which was the first tower to be struck but the second to go down. He was on a floor below the impact level (people above the impact level were trapped) and immediately decided to ignore the advice being put on the loudspeaker system, which was to stay put. He headed down a stairwell and made it safely to the ground before the tower collapsed. He said the major impediment to his escape had been all the firefighters going up the stairwell. Cell phone service was overwhelmed and non-functional and he had no way to communicate with his wife, who was convinced he had died. But he made it home safe that night. Then a month or so later he developed "polymyalgia rheumatica", (also called "giant cell arteritis"), which is an autoimmune disease. It is usually a self-limited disease and, after a course of steroids, he made a full recovery.

The literature on autoimmune disease is replete with stories about stress. The older literature focused on case series and the more recent literature on statistical analyses. Some articles talk about psychodynamics, some about migraines and some about stressful life events. The lowest common denominator is stress. The literature about "hyperthyroidism", which is also called Grave's disease, is especially rich in psychological analyses. When we were in medical school, we had a lecture about the psychodynamic underpinnings of autoimmune disease. Like most of my classmates, I was very skeptical and laughing behind the psychiatrist's back, especially when he told us that all these patients had a dominating mother and that he couldn't explain why they developed different autoimmune diseases if the psychopathology was always the same. This was already the dawn of the genetic era and psychoanalysis seemed passé. Now that I have been tempered by life, I can appreciate the value of the psychiatrist's insights. Theodore Lidz published an informative article in 1949 in *Psychosomatic*

Medicine entitled "Emotional factors in the etiology of hyperthyroidism", in which he discussed what was at that time the older literature on Grave's disease and presented data on 15 new cases that he had seen personally at Johns Hopkins University. He said that the literature indicated that "prolonged and depressing emotional reactions" were more frequent harbingers of autoimmune disease than were "short-lived upsets", the latter being what my friend had experienced at the World trade Center. In his own series, 14 out of 15 patients had experienced "events that terminated or threatened to terminate an essential relationship…immediately prior to the onset of the hyperthyroidism"; his patients all had "persistence of extremely immature dependent needs". Is anyone ever grown up? As I get older and keep looking at my own age cohort, the more and more skeptical I become of the concept of "being grown up", but I do think there is a spectrum of immaturity and some people cope with life setbacks better than others. That is what this literature is about. There are a number of recent articles in the multiple sclerosis field that document the non-random occurrence of major life upsets prior to onset of or relapse in this autoimmune disease, which affects the brain and spinal cord. Charalampos Mitsonis et al. published an article in *European Psychiatry* in 2008 that described a prospective study which followed twenty six women with multiple sclerosis for an average of 56 weeks. Women who experienced three or more "stressful life events" in a four-week period had a fivefold increase in relapse rate, which was highly significant statistically. The stressful life events related to "marital/love relationships", difficulties with job or finances, divorce, death in the family, violations of the law, injuries and illness, etc. The onset of schizophrenia, which is, of course, not an autoimmune disease is, we remember, also triggered by major life setbacks. The lists of setbacks for multiple sclerosis and schizophrenia are essentially identical.

At this point, we need to explore in more detail what an "autoimmune disease" is. There is a special class of white blood cells called "lymphocytes" that carry out "immunological reactions", which include allergic reactions to various chemicals, for example bee stings and penicillin, and also defend against invading pathogens such as bacteria and viruses. The immune system is constructed imperfectly and sometimes immunological reactions can be directed at normal organs and tissues in the body, which is what an "auto" (against self)-immune" disease is. It is the immune system gone haywire. Sometimes the lymphocytes assault the autoimmune target directly and sometimes they produce "antibodies" and other chemicals to carry out the attack. Antibodies are a special kind of protein that bind to small molecules or that recognize and bind to specific

small regions of large molecules. Surprisingly, all normal people harbor lymphocytes which can attack normal tissues; why this should be the case is not entirely clear, but it seems to relate to how the immunological system develops embryologically. Normally these undesirable autoimmune lymphocytes are held in check by a special category of lymphocytes called "regulatory lymphocytes", which were discovered by a Japanese scientist named Shimon Sakaguchi. If you selectively destroy the regulatory lymphocytes in a mouse, autoimmune diseases spontaneously pop up in a seemingly random fashion, autoimmune diseases against the thyroid gland being the most common in mice as they are in humans. This is the answer to question of why a patient's psychiatric diagnosis does not predict or correlate with any specific autoimmune disease: there is no specificity because once you open Pandora's box, they all come spilling out, the most common ones being the ones with the most lymphocytes-in-waiting for that disease. The best literature for clarifying the role of stress is that of "systemic lupus erythematosus", "SLE" or "lupus" for short, which is a disease that occurs predominantly in young women and causes a panoply of symptoms, often including arthritis and kidney damage. The lupus literature focuses not on stress per se but on migraine headaches, which we have come to understand are a symptom of stress. Migraines are sometimes said to be the most common neurological symptom of lupus but they are not caused by lupus—the arrow points the other way. Having active migraines is statistically associated with the severity of lupus and migraines cluster before relapse. Lymphocytes, like many cells, use internal signaling pathways to regulate their function. We remember that omega-3 and omega-6 phospholipids are intracellular signals released inside of dendrites when neurotransmitters such as serotonin bind to receptors on the dendrite. Surprisingly enough, and this may come as a shocker, lymphocytes often use superoxide anion bullets in small puffs as internal signals. From a broader biological perspective, this is not surprising because the body is very parsimonious in how it uses and reuses the same biological molecules and pathways in different situations. Superoxide anions perform a useful job both when fired in a barrage at invading bacteria and when produced inside of lymphocytes in a whiff for regulatory purposes. The problem is that migraine headaches, which are probably not part of the evolutionary scheme of things, cause SPA and high levels of extracellular oxidative stress which can cross the cell membrane and cause intracellular oxidative stress—this is just like the case of AD. What seems to happen is that SPA subverts normal lymphocyte signaling and temporarily inhibits the normal functioning of regulatory lymphocytes. Pandora's box is opened and autoimmune

diseases appear. Having one autoimmune disease is a risk factor for having more; in some patients autoimmunity almost seems to be a tragic lifestyle decision. It all comes back to uncontrolled migraine. Autoimmune diseases can also be associated statistically with frequent infections; the immunological response to infections probably also leads to local oxidative stress in lymph nodes, which may lead to loss of regulatory lymphocyte function at that level, but this is not part of our story.

Recap: Everyone normally harbors lymphocytes that can cause autoimmunity, but they are held in check by a subcategory of lymphocytes called regulatory lymphocytes. Autoimmune diseases are linked to stress. Stress-induced SPA causes oxidative stress, which penetrates the regulatory lymphocytes, subverts the normal role of low level superoxide anions used as a signaling pathway in these lymphocytes, and permits the emergence of autoimmune diseases, of which autoimmune thyroid disease is the most common.

CHAPTER THIRTEEN

HOW DEEP VEIN THROMBOSIS AND THROMBOSIS ASSOCIATED WITH ATRIAL FIBRILLATION WORK

The other kind of clot besides a white clot is a red clot. Red clots are the topic of this chapter. When a pathologist looks at a red clot through his microscope, he sees that it has stripes or layers which are referred as "lines of Zahn". There are red stripes alternating with white stripes: each white stripe represents a wave of platelet activation and deposition of the aggregated or clumped platelets (we remember that platelets clump when the ON button is pushed); the red stripes represent the more gradual deposition of red blood cells, which get trapped in a microscopic film of coagulation proteins that forms on top of each layer of platelets. The red clot builds up over time, like a super accelerated geological process, with the key event being intermittent waves of SPA. On the arterial side of the vascular tree, blood is flowing too rapidly and the blood pressure is too high to allow this process to occur: aggregating platelets would immediately get swept away by high-pressure pulsations of the blood and a layered clot could never form. But there are two places where the process can occur; one is in the quiet backwaters of the venous side of the circulation and the other is in the first chamber of the left side of the heart, which is called the "left atrium", in the setting of an abnormal heart rhythm called "atrial fibrillation". Atrial fibrillation is actually quite a common diagnosis in older people and seems to be caused by HTN. The left side of the heart receives blood from the lung and stores it temporarily in the left atrium before pumping it into the "left ventricle", the second and more muscular chamber that is the main heart pump; the left ventricle pumps blood into the aorta, the main artery coming out of the heart. When the atrium "fibrillates", the muscles in its walls contract in an uncoordinated fashion, like a bag of squiggly worms, and the chamber never develops high pressure. It is as if it were on the low-pressure venous side of the circulation and not on the arterial side, which is what permits the formation of red clots. Red clots need an area of "stasis" or low pressure to form, so they won't get washed away. When large red clots form in large

veins, which happens most frequently in the legs, they can occlude the vein, which is a "deep vein thrombosis". This leads to swelling of the leg, which is unpleasant; the really bad thing is that the thrombus can suddenly break loose and travel to the lungs, which is a "pulmonary embolism". Showers of small pulmonary emboli can blockade and shut down more and more zones of the lung, eventually leading to shortness of breath because the patient cannot take in oxygen, and a large embolism can cause reflex sudden death. In the case of the heart, loosened thrombi travel out into the arterial tree, occluding random arteries, which is particularly devastating in the case of the brain, where they cause "embolic strokes".

So that was simple. No surprises.

Recap: Red clots are large clots which build up over time in areas of stasis in the vascular tree, such as on the venous side of the circulation or in the left atrium of the heart when there is low pressure because the heart is contracting in an uncoordinated fashion due to an abnormal heart rhythm called "atrial fibrillation". Red clots can break loose on the venous side of the circulation and travel to the lung, causing a pulmonary embolism, or the arterial side, causing an embolic stroke.

CHAPTER FOURTEEN

SUMMARY CHAPTER: WHAT DOES THE "MELTDOWN" IN THE TITLE REFER TO?

Please study Fig. 14-1. Pay special attention to "brain meltdown" at the bottom left; it is the sum of stroke plus AD. Also notice the arrow going from HTN to SPA. This diagram sums up the pathology of stress. What you can do to protect yourself is coming up in later chapters.

What is the key effect of stress that causes *dis-ease,* i.e. long-term loss of ease or well-being? It is the extra pathway with the stop in the entorhinal cortex on the right side of Fig. 5-1. Let us go back to that diagram. There is a negative feedback loop between the DRN and the hippocampus, which functions like the thermostat in your house. The purpose of the loop is not to control the temperature of your house but the rate of cell division of neurons in the hippocampus. The DRN stimulates cell division in the hippocampus and when there are too many neurons, the hippocampus puts the brakes on the DRN, in the same way that high temperature causes your thermostat to temporarily turn off the furnace. The DRN has the property of sometimes firing excessively in response to stress ("burst firing"), which can be imaged as a hot spot on PET scans during migraine headaches. The burst of excessive firing can be projected to the hippocampus via the indirect pathway through the entorhinal cortex and cause "excitotoxic" death of neurons there; the neurons die because they undergo too much electrical stimulation. Hippocampal neurons have the property of being especially susceptible to excitotoxic death but, at the same time, being capable of neurogenesis, or undergoing cell division and giving birth to new neurons; this creates a ying-yang situation, a place of high drama where the battle of stress is played out. The tragedy is that the DRN fires excessively, that the indirect pathway exists to transmit the firing, and that hippocampal neurons are so vulnerable to it. It is the tragic flaw in our species. Why this should be is a mystery, darker than any mystery. It opens the door to the bad road. Primates evolved from rodents and much experimental work on stress is done in rodents, primarily mice

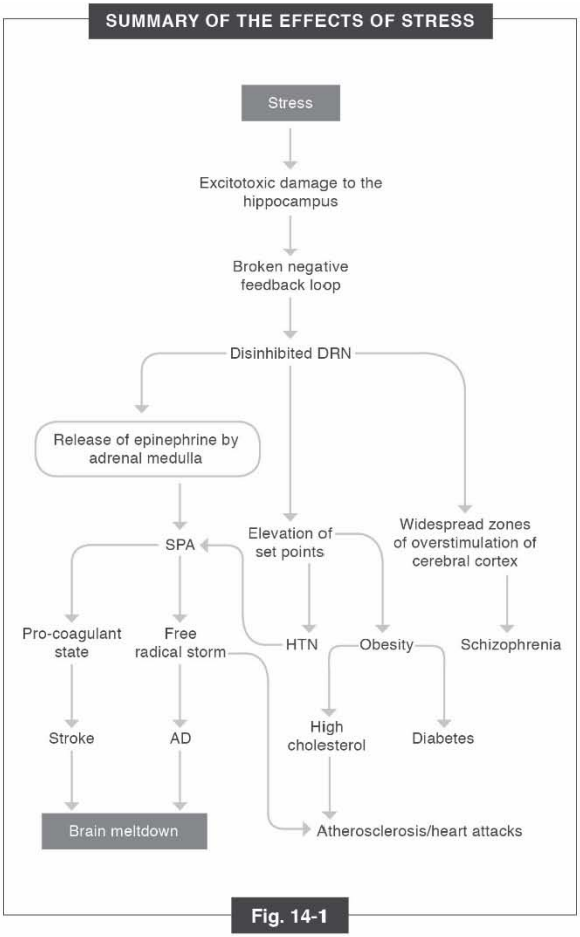


Fig. 14-1

and rats, but animals in the other higher species, dogs, cats, parrots, elephants and so many more, also clearly suffer long-term damage from stress. In all cases, there is hope for at least a measure of recovery if the excitotoxic cannonades abate and there are surviving hippocampal neurons to begin neurogenesis anew. A broken negative feedback loop is the basis of the long-term effects of stress; without signals from the hippocampus to rein it in, the DRN is free to organize the diseases of chronic stress.

The other key idea in this book is systemic platelet activation (SPA). In response to stress, whether acute or chronic, the autonomic nervous system

stimulates the adrenal medulla to release epinephrine, which pushes ON buttons on platelets and causes them to do three things that make sense physiologically in short term situations of shock (dangerous low pressure caused by massive hemorrhage or bacterial infection of the blood) but are damaging if the buttons are locked in the ON position: (1) they release vasoconstrictors, which are chemicals that tighten small arterioles and raise blood pressure; 2) they activate the coagulation cascade, which is good for acute shock caused by hemorrhage, but bad if it produces a chronic pro-coagulant state, which means you are always teetering on the brink of occluding a major artery or vein; and (3) they release superoxide anion bullets, which make good weapons against bacteria, but are bad if they produce free radical storm, which is severe oxidative stress.

As depicted in Fig. 14-1, the disinhibited DRN has three mechanisms for causing disease: (1) SPA; (2) the elevation of set points; and (3) overstimulation of large zones of the cerebral cortex, which is the unique case of schizophrenia. Notice the arrow going from HTN to SPA: the pathophysiology of HTN includes SPA.

Two general neuroscience ideas that you have been taught relate to information transmission in the brain, which is done via electrical signaling, and the roles of the good and bad kinds of unpaired electrons.

Electrical signaling in the brain can be compared to holding elections. Neurons send electrical signals down long cell processes or wires called "axons", which sometimes travel to distant parts of the brain. Just before arriving at their destinations, the axons, when stimulated by an electrical signal, release a chemical or "neurotransmitter", thus converting the electrical signal into a chemical signal, which then diffuses across a microscopic gap called a "synapse" and binds to special receptors on "dendrites", which form the receiving zone of the next neuron. The yes votes from all the excitatory axons and the negative votes from all the inhibitory neurons are tallied to determine whether or not the next neuron will send a signal in its turn or remain silent. "Pacemaker" neurons are a special and very important category of neurons that continuously send out signals without having to be stimulated and that do not vote either yes or no at a synapse, but rather shift the vote count in a yes or no direction, which is like vote fraud. The DRN is one of many pacemaker nuclei: its neurons send out axons which commit vote fraud by releasing the neurotransmitter serotonin at synapses, thereby modulating and controlling the function of various regions of the brain. By committing widespread vote fraud, it can seemingly take over the brain.

An important distinction can be drawn between two kinds of "free radicals", which are "unpaired electrons". The good kind carry energy from the sun from its entrapment by chlorophyll in plants, up the food chain to ingestion by carnivores, then to delivery to mitochondria, which are specialized structures within cells that convert the sun's energy into ATP money, which is used to drive all the chemical reactions of a cell. The potentially bad kind of unpaired electron, of which the superoxide anion is the major example, is very energetic chemically and causes structural damage to cells. Superoxide anions are produced in large bursts of gunfire to fight bacterial invasion but can also be used in small puffs as signals within cells to regulate cell function. Inappropriate large-scale superoxide anion production, which occurs when platelet buttons are locked in the ON position, leads to free radical storm.

Every journey down the bad road is unique. Often but not always it begins with migraine headaches, which are followed by HTN or obesity. Migraine syndromes are driven or organized by intense burst firing of the DRN; migraine is an electrical disease that can seemingly take over the brain. Headache symptoms are caused by sterile inflammation of the dura, which is a thick membrane enclosing the brain. The pain is referred to the surface of the head. The non-headache symptoms of migraine are caused by the DRN committing vote fraud in various regions of the brain.

HTN and obesity are caused by elevation of the set points for these two key physiological parameters when a person is in a state of chronic stress because of damage to the hippocampus and disinhibition of the DRN. A physiological set point is another example of a negative feedback loop. The set points for blood pressure and body weight are "protected" in the same way the temperature setting in your house is. The simultaneous occurrence of HTN and obesity is called the "metabolic syndrome"; severe obesity causes diabetes and/or high cholesterol.

The elevation of blood pressure in HTN depends on stimulation by the autonomic system of the heart, the adrenal medulla, and the juxtaglomerular apparatus of the kidney; the latter causes release of "renin", which is another vasoconstrictor and also causes production of superoxide anions. High blood-pressure cuff readings are markers for what is really happening, i.e. there is a pro-coagulant state and free radical storm.

Strokes are caused when there is sudden transient worsening of SPA, i.e. increased epinephrine release by the adrenal medulla, which is flagged by a transient or labile rise in blood pressure and, often, a migraine headache.

The pro-coagulant state is pushed over the brink into a coagulant state with the formation of a white clot, which can block a blood vessel in situ in the brain or travel to the brain from its site of formation elsewhere, which is an "embolic stroke".

Atherosclerosis is caused by free radical damage to low density lipoproteins (LDLs), which are the proteins that carry cholesterol around in the blood. Damaged LDLs accumulate in atheromas, which are abnormal spherules filled with a soft porridge-like substance that form just beyond branch points of arteries in certain key organs of the body, such as the heart and brain; atheroma formation ultimately leads to blockage of arteries in these organs. The two driving forces behind atherosclerosis are free radical storm and hypercholesterolemia.

Alzheimer's disease (AD) and Parkinson's disease (PD) are both degenerative diseases of the brain that selectively target long projection neurons, the neurons that send out long-distance axons, which are like long-distance telephone wires. These neurons are vulnerable because they have very high energy demands to manage long-distance transmission, which causes their mitochondria to work overtime minting ATP money. Mitochondria, unfortunately, leak some of the unpaired electrons carrying the sun's energy (the good kind); the leaked electrons go rogue and turn into superoxide anions (the bad kind). This means that these neurons have baseline oxidative stress. In the case of AD, free radical storm caused by vascular risk factors crosses the cell membrane to the inside of neurons and begins to kill them, the ones with baseline oxidative stress going first. In essence, both stroke and AD are caused by SPA. The combination of stroke and AD is the common mechanism of brain destruction or meltdown. In the case of PD, the problem is old age itself; as the years go by, the effects of baseline oxidative stress from electrons leaked by mitochondria build up and kill the mitochondria. Cellular energy production fails.

Schizophrenia is a disease with a unique pathology: neurons in large areas of the cerebral cortex are shrunken and the "neuropil", the web of axonal-dendritic connections between neurons, is atrophied. What happens in schizophrenia is as follows: stressful life situations trigger excitotoxic damage to the hippocampus, which frees the DRN to strike the cerebral cortex with an aberrant, pervasive barrage of electrical signals that leads to depletion of omega-3 and omega-6 phospholipids, which are chemicals involved in the processing of neurotransmitter signals by dendrites. The phospholipids, especially the omega-3's, get depleted and the neurons are

no longer able to process *any* signals, whether from the DRN or elsewhere. The neurons and neuropil become non-functional and atrophy (they put up "gone fishing" signs). Drugs that block serotonergic receptors on neurons (the ON buttons where the serotonin binds) and omega-3 dietary supplementation are treatments that can slow down or reverse the disease.

Autoimmune diseases appear when oxidative stress caused by SPA subverts the role of regulatory lymphocytes in reining in auto-reactive lymphocytes.

Red clots induced by SPA form in areas of stasis in the vascular tree. If the clots form in the legs, they can break free and cause pulmonary emboli; if they form in the heart in a patient with atrial fibrillation, they can cause embolic strokes.

What does the "meltdown" in the title refer to? It refers to emotional meltdown in stress. It refers to the appearance of a brain ravaged by stroke and AD. And it refers to a necessary reset in medical thinking. The old ways of conceptualizing internal medicine must melt away so that a new pattern of thinking can emerge. There is a schema underlying and unifying internal medicine. But there must be a meltdown of old ideas before new ideas can rise up to take their place. It is time to recognize the pitiless centrality of stress: did we not know beforehand that this was the case?

CHAPTER FIFTEEN

OUTRAGEOUS PROPOSAL FOR HOW TO PREVENT SYSTEMIC PLATELET ACTIVATION

There was a funny article published in 1932 in *Surgery, Gynecology and Obstetrics* (volume 54, pages 294-298) by George W. Crile entitled "Denervation of the adrenal glands for neurocirculatory asthenia". Diagnostic terminology was different then from what it is now, which is what I meant by the word "funny". Crile says neurocirculatory asthenia is a civilian equivalent of "soldier's heart", a disorder described by Jacob Mendes Da Costa in American Civil War soldiers. It is not unlike the contemporary diagnosis of post-traumatic stress disorder given to psychologically disabled military veterans or to the lingering symptoms reported by many British soldiers who experienced chlorine gas attacks in World War 1 but were not permanently injured by the gas per se. Besides a component of depression, all these patients suffered from symptoms identical to those caused by an epinephrine-releasing tumor of the adrenal gland called a "pheochromocytoma". These symptoms include palpitations (irregular, fast or pounding pulse), "nervousness" (i.e. anxiety), sweating, pallor, weakness, dizziness, tremors and shortness of breath. A related entity is "Takotsubo cardiomyopathy" or "broken heart syndrome", in which there is such an outpouring of epinephrine from the adrenal medulla in response to a stressful life event that the high level of epinephrine itself becomes toxic to heart muscle. It is common in stroke patients to see a mild rise in a chemical called "troponin", a marker of cardiac muscle damage, which is caused by the rise of epinephrine associated with a burst of SPA at the time of a stroke. Crile said that he was able to weed out as potential surgical candidates patients suffering from psychosis, psychoneurosis or hysteria and identify patients whose "sympathetic system (was) under...uncontrollable stimulation". 18 out of the 21 cases of "neurocirculatory asthenia" that formed the basis of his report and on whom he performed bilateral adrenal gland denervation "remained well to date". There is pause for thought here. The point that belongs to our story is that Dr. Crile's surgical technique for denervation of the adrenal gland appears, on the face of it, to be successful. I am not a surgeon and cannot

evaluate surgeon-speak, but he gives what appears to me to be a detailed, thoughtful, anatomically-based description of the operation, which he performed as a staged procedure, one side at a time.

The outrageous proposal for prevention of SPA is, of course, bilateral surgical denervation of the adrenal glands. There are no drugs that can selectively block the epinephrine ON button on platelets; for theoretical reasons, any such drug (or the new modality of "antisense RNA" therapy) faces the daunting challenge of being so selective that it would not also block closely related or identical epinephrine receptors (ON buttons) that are distributed widely in the brain, which could cause a plethora of unforeseeable side effects. Besides operative morbidity and mortality, which was already very low for Crile, and potential limitation of rigorous aerobic exercise, the main downside of the operation would be permanent inability to mount a proper physiological defense against shock whether caused by blood loss or septicemia. The adrenal cortex, which releases cortisol, would still work because cortisol release is controlled by a hormone produced by the pituitary gland at the base of the brain, but the adrenal medulla would not. Both the adrenal cortex and the adrenal medulla participate in the response to shock. The seriousness of this problem is difficult to quantify and would have to be weighed against the long-term benefits of the operation. There is something very elegant about the specificity and finality of a surgical procedure. It is a one-time expense. Please re-examine Fig. 14-1. Erasing the arrow leading between the disinhibited DRN and epinephrine release by the adrenal medulla would secondarily erase all downstream parts of the diagram below that point, which consists of stroke, AD, and atherosclerosis as well as some diseases omitted from the diagram for lack of space, namely, autoimmune diseases, deep vein thrombosis/pulmonary embolism and embolism caused by atrial fibrillation of the heart. No more brain meltdown! Timing of the operation would have to be worked-out for different people taking their various journeys down the bad road.

About the time that Dr. Crile was doing his work, a number of surgeons, particularly Dr. Max Minor Peet at the University of Michigan, were starting to denervate the kidneys in hypertensive patients in an attempt to block stimulation of the kidneys by the autonomic nervous system, which, we remember, causes release of renin, a vasoconstrictor that raises blood pressure and also causes endothelial cells to produce superoxide anion bullets (*JAMA*, 1940, volume 115, pp. 1875-1885). Dr. Peet and the other surgeons did not pay attention to the fact that, in most cases, they were also denervating the adrenal glands, their understanding of how

hypertension works being incomplete. Basically, they were knocking out the "solar plexus". The solar plexus is located in the center of the upper abdomen just below the rib cage and punching someone there, as happens in old cartoons, the movies, and real life, causes them to buckle over in pain. Bilateral surgical denervation of the kidneys and, inadvertently, the adrenals as well, was the first effective treatment for hypertension. Its usefulness was limited by serious side-effects, particularly something called "orthostatic hypotension", which means that you faint when you stand up. There is a recently-developed technique for placing a catheter in the renal artery to denervate a kidney: the catheter emits radiofrequency waves that zap autonomic nerve fibers running in the wall of the artery, much like the way a microwave oven heats or overheats food. Potentially this technique could be used to supplement adrenal gland denervation in the minority of hypertensive patients with high renin whose renin does not return to normal with anti-hypertensive medications. The goal is to make unwanted superoxide anion bullets go away and prevent free radical storm.

Recap: SPA, which is probably the major player in carrying out the mischief of chronic stress, could theoretically be blocked by bilateral surgical denervation of the adrenal glandsIn some patients, the procedure might need to be supplemented by bilateral radiofrequency denervation of the kidneys.

CHAPTER SIXTEEN

REWARD FOR READERS WHO HAVE GOTTEN THIS FAR: HOW CONSCIOUSNESS WORKS

Dear reader, if you have gotten this far, it means you enjoy exploring new ideas and deserve a lollipop.

In the latter part of his life, Francis Crick, of Watson and Crick fame, these two gentlemen being the co-discoverers of the double helix structure of DNA, worked at the Salk Institute in La Jolla California. He became interested in consciousness, among other things. In particular, he focused on what he called the "binding problem". How is it that consciousness, which is perceived from the inside as a single thing, can arise out of the firing of the hundred billion neurons in the human brain? (As an aside, there are two to three hundred billion stars in the Milky Way, which is our galaxy.) Vote tallies are happening at individual synapses all the time and, somehow, the results of some or all of these vote tallies, each of which is an isolated event in time and space, are "bound" together into the single entity of consciousness. How can such a thing happen?

First of all, it is generally agreed that consciousness arises in the cerebral cortex, the cap of the mushroom, and not in the brain stem. This is supported by both clinical observations and experiments in animals. Another important point is that the cerebral cortex, with its layer-cake structure, loves to generate sine waves. Those of us who studied trigonometry in high school remember that the sine wave is a very basic construct in both mathematics and physics and leads into fascinating concepts such as the sine, cosine, and tangent. Hans Berger, who was a German psychiatrist, discovered in 1924 that if you put electrodes on the surface of the scalp, you could record rhythmical electrical activity coming from the brain. He was not actually the first person to detect electricity in the brain, but his invention of the "electroencephalogram" or "EEG" made possible the routine study of brain waves in both the normal physiologic state and in disease. Much of the electrical activity is just a lot of little

squiggles, but some of it is clearly rhythmical, sine waves in fact. Anything that can be detected on the surface of the brain is the result of the coordinated or synchronized firing of a great many neurons. Mathematicians who model brain activity tell us that this results, in part, from the fact that many neurons in the layers of the cerebral cortex are wired to form loops between excitatory and inhibitory neurons: the excitatory neuron stimulates a nearby inhibitory neuron, which projects back to the excitatory neuron in a way that limits when and how often it can fire. If there is coordinated firing between many nearby neurons and you put an electrode into the fluid space between neurons to measure the electromagnetic "local field potential" (oh dear, another inscrutable kind of energy, and the worst possible kind, a new example of potential energy), you find that the local field potential follows a sine wave pattern. If neurons are coordinated over large regions of the surface of the brain, you generate sine waves that are strong enough that you can pick them up with an electroencephalogram on the scalp. Sine waves are central to understanding epilepsy. I like to refer to migraine as the "other" electrical disease of the brain. The disease it is "other to" is epilepsy. In epilepsy, the brain spontaneously produces a massively coordinated sine wave discharge that blots out normal cortical function, suspends consciousness, and produces its own characteristic clinical accompaniments, such as falling to the ground, foaming at the mouth, and convulsively shaking both arms and legs, followed by a period of unresponsiveness. Wilder Penfield made some important discoveries relevant to the binding problem of consciousness. He was the epilepsy neurosurgeon mentioned in Chapter 2 who performed operations under local anesthesia, which left his patients awake and able to talk. In his influential book *Epilepsy and the Functional Anatomy of the Human Brain*, which he published with his colleague Herbert Jasper in 1954, he reported that stimulating around the temporal lobe (the side regions of the mushroom cap) in his epilepsy patients with a 40-60 Hz stimulus—this was an alternating current stimulus at the rate of 40-60 sine waves per second—could sometimes elicit conscious perceptions, such as hearing music, voices talking, or a cluster of emotions centering around fear. This means that driving a local group of neurons to fire synchronously within a certain frequency range *caused consciousness*! 20 Hz was too slow and 100 was too fast. These are relatively high frequencies, although some neurons can go up to at least 250 Hz. Frequencies in the 40-80 Hz range are called gamma frequencies, although different authorities set different limits for the gamma range. The full import of Penfield's discovery was not appreciated at the time. Heribert Reitboeck was a scientist with sequential business and academic careers.

Austrian by birth, he worked for a number of years at the Westinghouse Research Laboratories in the United States and then took a position at the University of Marburg in Germany. While at Westinghouse, he worked out a technique for doing simultaneous recordings from multiple electrodes implanted in the brain of an experimental animal. In a paper published in *Biological Cybernetics* in 1988, he studied the responses of individual neurons in two different regions of the cat brain that were both involved in interpreting visual stimuli. Stimuli could be varied according to their position in the visual field, orientation, speed of movement, etc. He was able to find clusters of neurons in separate but nearby regions of the visual cortex that fired in "phase synchrony" in the gamma frequency range in response to the same visual stimulus. The two populations of neurons were reacting to different aspects of the stimulus; for example, one might be interested in its orientation in space and the other in its rate of movement. "Phase synchrony" means the tops of the sine waves in the two local field potentials are lined up, which, in turn, meant the neurons were firing at the same rate and at the exact same moments in time (see Fig. 16-1). Consciousness is, therefore, an emergent property of phase-locked sine wave discharges produced by clusters of neurons in the gamma frequency range. An equivalent and equally valid way to state this is to say that consciousness is an emergent property of populations of neurons firing synchronously at the same gamma frequency. With my love of trigonometry and my familiarity with electroencephalograms, I prefer the first wording, but they are equivalent. It follows that the fluid, ever-changing totality of consciousness arises from the participation of shifting subsets of the vast array of cortical neurons phase-locked in simultaneous discharges in the gamma frequency range. How the brain manages to pull off this feat is not known.

Another thing you might have been fretting about is how memory works. It turns out we know less about memory than we do about consciousness. The main thing we do know about memory is that depends on the integrity of the hippocampus and its projections into other regions of the brain. As soon as it was discovered that cells in the dentate gyrus in the hippocampus can divide, the idea sprang up that the purpose of neurogenesis might be to provide a mechanism to arrange memories in time; this is a different kind of binding problem from consciousness, the issue here being to lock together all the memories that happened close together in time. A new neuron every day could bind together that day's memories in new functional circuits in the brain that are linked to that neuron. The idea is so appealing that it seems like it has to be correct (which perhaps means it is wrong). I also find the idea attractive because it

provides a raison d'être for the existence of a negative feedback loop between the DRN and the hippocampus. The feedback loop supplies an ordered stately march of new neurons with which to measure and record personal time.

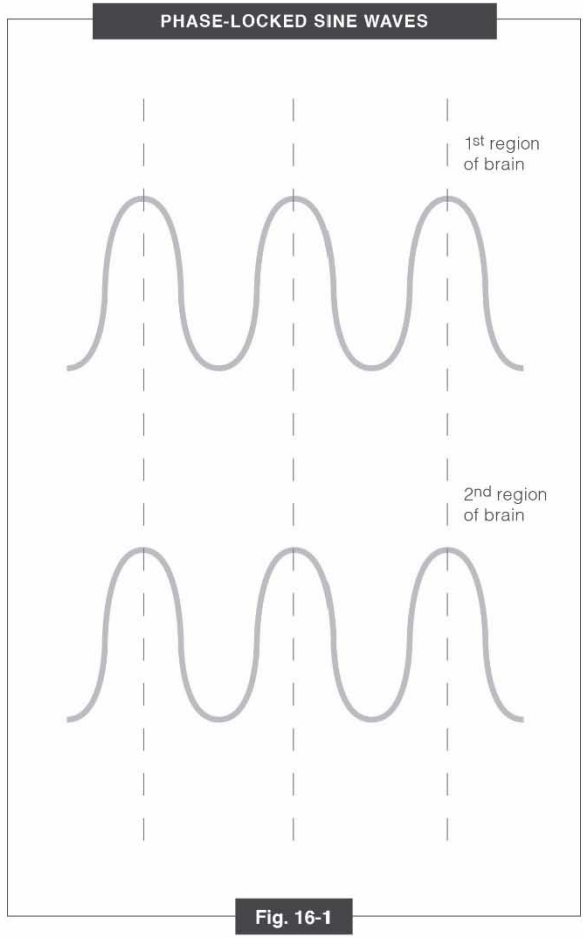


Fig. 16-1

CHAPTER SEVENTEEN

PRACTICAL ADVICE ABOUT MANAGING MIGRAINE

In the beginning was depression.

I have withheld this important fact from you until now. Depression is even more primordial than migraines. It belongs to an older generation of gods. Before talking about the milder form of depression that so often underlies migraine, let us review the full-blown syndrome of classic unipolar depression. The three cardinal symptoms are feelings of sadness, "anhedonia" (inability to enjoy normally pleasurable activities) and lack of energy, although psychiatrists sometimes debate whether lack of energy is a "core feature" or just a common feature. The most dangerous symptom is sadness because this is the one that leads to suicide; the word "sadness" does not do justice to the concept and no one who has not experienced it can really understand it, but it is apparently a feeling of despair that is so intense as to be unbearable. Suicidal sadness occurs as part of schizophrenia and as part of bipolar disorder, but it also stands by itself in unipolar disorder. In 2006, an extraordinary article was published in the journal *Neuron*, Helen Mayberg being the lead author. Mayberg's group had previously reported that a specific small region of the cerebral cortex called "Brodmann area 25" (also called "subgenual cingulate, Cg25") lit up on PET scans in depressed patients. The PET scan, we remember, lights up in very active or over active areas of the brain. As the article reported, her group implanted permanent electrodes in the Cg25 of depressed patients; what this meant was that they, in effect, did the same thing that Penfield did during his neurosurgery: they gave patients sine wave pulses, but they left the wires or "electrodes" in permanently; patients were left with little wires sticking out of their skulls attached to a box. Instead of stimulating in the gamma frequency, 40-80 Hz, which supports consciousness, they used a much higher frequency, 130 Hz, which drove local neurons at a frequency that prevented them from participating in consciousness, thereby blocking the perception of sadness. Patients felt instantaneous improvement of symptoms which they

described as "disappearance of the void", "sudden calmness or lightness" and "connectedness". This is the second emotion that has been localized: Penfield localized fear to the anterior or mesial temporal lobe and Mayberg localized sadness to Cg25. Driving a population of local neurons at a gamma frequency can create the emotion and driving them at an incorrect frequency can prevent the emotion from occurring. No other emotions have been localized in the brain. Some but not all of Dr. Mayberg's patients had improvement of their other depressive symptoms: the anhedonia and the lack of energy. However, when the electrode was turned off, the sadness returned and so this does not seem to be a practical treatment for the vast population of depressed people in the world.

To get back to migraine, there are two categories of patients: those who are getting situational migraine, which are headaches occurring in response to something awful happening to them that day, and "chronic daily headaches", which is the second stage of migraine when headaches occur frequently independently of the presence or absence of acute stressors. Neurologists ordinarily do a complete neurological examination on new migraine patients, paying particular attention to the opthalmoscopic examination of the eyes for signs of increased pressure around the brain, and then order a CT scan or MRI of the brain and maybe some blood tests to rule out certain rare inflammatory causes of headaches. But in the vast majority of cases, a migraine is just a migraine. What fateful words! The door is opening onto the bad road. Treating situational migraines is usually straight-forward and involves prescribing anti-inflammatory drugs such as ibuprofen or naproxen, which block the sterile inflammation in the dura causing the pain. Treatment of chronic migraine is more complicated. Most patients turn out to have an underlying relatively mild depression or else previously-undiagnosed hypertension. I empirically worked out three screening questions to ask migraine patients: Do you ever wake up in the middle of the night and find that you can't get back to sleep? How is your memory? Do you ever find that tears well up in your eyes for no reason? The questions should be asked in that order. I remember a couple years ago when a male resident presented to me in clinic the case of a young man in his mid-twenties with disabling chronic migraines. I asked if the patient was depressed, and the resident assured me that no way was he depressed. Had he asked the three questions? No. We went together to see the patient and I asked the three questions; the patient broke down, sobbing in front of us. Real men do cry. The underlying life problems in migraine patients are the same as those that trigger schizophrenia and cause autoimmune disease. It is the hand of playing cards of a hundred different genes a person is dealt at birth that determines what if anything

medical happens to them at difficult times in life. Women at menopause, perhaps partly because of hormonal changes and partly because of psychological issues, are very vulnerable to the onset of migraines; menopause can be the full explanation in these patients. One must also be sensitive to the age threshold of forty in women who have not had children. In the case of HTN, somewhere up to fifty percent of patients get migraine symptoms, usually headaches and/or vertigo, when their blood pressure goes up. They are the lucky ones because they can, within limits, monitor their own blood pressure. Hypertensives patients who get no symptoms are the ones in whom HTN can be a silent killer. We see patients, often young African-Americans in their twenties, who arrive in the emergency room with major kidney damage and an acute confusional state caused by HTN-induced brain swelling.

There are three categories of drugs used for migraine prevention or prophylaxis in patients with chronic headache; these are medicines that the patient takes every day irrespective of whether or not they have a headache that day. All these medicines may take a few weeks to build up their effect, although sometimes they work in a day or two. They are all medicines that are also used for something else but happen to work in migraine, too: the three categories are anti-depressants, anti-hypertensives, and anti-epileptics. If a patient has high blood pressure, no medicine will work very well unless the blood pressure is first brought under control. A patient who is depressed should logically be treated with an anti-depressant, and all the various categories of anti-depressants seem to work equally well, although an individual patient may respond better to one medicine than another. Patients who are not hypertensive and give negative answers to "the three questions" are candidates for anti-epileptic drugs. In my heart of hearts, I think that these patients are depressed and haven't been forthcoming in the history that they were willing to provide. This is always the patient's prerogative—why should they share secret loss with a stranger no matter how kindly the stranger might seem?

It is time now for a brief technical interlude: the anti-epileptic drugs used for migraine prevention, such as valproate, zonisamide, ethosuximide, and (by inference) topiramate, all block a specific "pacemaker current" in the DRN, called the "low voltage-gated T-type calcium channel". These terms may be meaningful to some readers, which is why I give them. The point is that these drugs all slow down manic burst firing of the DRN, which is what drives migraine attacks. Anti-depressants permit healing and repopulation of the hippocampus by causing extra serotonin release via the direct or left-side pathway in Fig. 5-1. How anti-hypertensives work in

migraine prevention is a complete mystery; all categories of anti-hypertensives, including thiazide diuretics, are effective. Any drug used for migraine prevention is a double-edged sword: it usually helps patients but it may, in a minority of patients, make the headaches worse. The explanation for the paradoxical effect is unknown; presumably the drugs act on more than one location in the brain and, while the effect in the desired location usually predominates, sometimes an effect at another undesired location takes over. The drugs with the fewest overall side-effects at the doses used are the anti-depressants and they can be very effective in non-hypertensive patients, even in patients who deny symptoms of depression. The old standby drug for migraine prophylaxis when I was a resident was the anti-depressant amitriptyline and it is still the old standby drug. When used for migraine prevention, it is prescribed at much lower doses than for major depressive disorder, and side-effects are usually mild. Almost all patients with migraine can be managed successfully if treatment is started early: the patients who are really daunting to manage are patients with one or more psychiatric diagnoses who have been on a shifting array of psychiatric medications for years and have had migraine symptoms for an equally long period of time. It turns out that many of the medications other than anti-depressants prescribed by psychiatrists can also be used to prevent migraines and they also cause or worsen migraines in a subset of patients. There was an older neurology attending at the Neurological Institute at Columbia when I was a resident who prescribed a drug called "haloperidol" for migraine prevention. It was very effective, but no one today would ever think of using it for migraine because it belongs to the main category of drugs used for schizophrenia called "phenothiazines" and has too many serious long-term side-effects to be used for migraine. It is often impossible to sort out what is happening in patients with long-term coincident psychiatric disease and migraine, particularly if there is no clear-cut record of when the migraines began and what their temporal relationship is to various medications. Are they getting headaches because the depressive component of their illness is undertreated or overtreated? Everything I have said about managing migraine headaches applies equally to patients with acephalgic migraine (migraine syndromes without headache), which are usually patients with recurrent or chronic low-grade vertigo. The bottom line is that patients with situational migraine can manage their disease with anti-inflammatory drugs but patients with chronic daily headaches need to realize that a certain door is opening.

CHAPTER EIGHTEEN

PRACTICAL ADVICE ABOUT MANAGING HYPERTENSION

In the first chapter, I mentioned Dr. H. Houston Merritt, who was the emeritus head of the Neurological Institute at Columbia when I trained there and my all-time favorite neurologist. I got to know him a little bit as a resident and then as a junior attending, but he was already starting to slow down intellectually. He demented in a kindly and gracious way and retained a great deal of humor and insight. Before he became too impaired, he still met with residents and medical students. I remember a case presented to him by the residents. It concerned a woman sitting in a wheelchair who had previously been in good health but suddenly became paralyzed from the waist down, with preservation of bladder and bowel function. Dr. Merritt had no questions to ask her and spent almost the whole time talking to her about North Carolina—they had both been born in North Carolina and grew up there. Then he asked one of the residents for a reflex hammer, but he was unable to elicit any reflexes and soon gave up trying to examine her. After the woman was wheeled out of the conference room, he said that she had had a conversion reaction, i.e. she had a hysterical or psychiatrically based paralysis, because strokes don't affect the spinal cord. This was before the era of MRI, but, looking back, I have no doubt that Dr. Merritt was correct in his diagnosis and his rule that strokes, except in obvious situations with something else going on, don't effect the spinal cord has served me well. On another occasion, he was meeting with medical students, who complained to him that rich patients could afford private physicians while poor patients were consigned to the ward service. Dr. Merritt smiled his bemused smile and then pointed out that poor patients got excellent care on the ward service at academic places like Columbia while rich people went to society doctors and got poor care. I saw society-doctor medicine in action when I was an intern at New York Hospital in Manhattan. The point I am leading up to is that I remember seeing Dr. Merritt standing one day at the corner of West 168th St. and Fort Washington Ave., just across the street from the Neurological Institute. A cold winter wind was blowing in from the Hudson River and

he was about to be swept away. I was paralyzed by the fascination of watching what was happening, and then another attending rushed up and saved him. The reason that Dr. Merritt was almost blown away by the wind because of a gait impairment and the reason that he developed dementia were the same: he did not take his anti-hypertensive medications. He suffered a series of small strokes from which he recovered one by one, but he also suffered from the kind of vascular dementia mentioned in Chapter 4 called "leucoaraiosis", which is caused by remodeling of small arterioles in HTN. So Dr. Merritt, my all-time favorite neurologist, did not take medications and was, in fact, a poster boy for non-compliance. Let this be a lesson to us all.

How do American doctors treat HTN today, knowledge of the continuous shower not having made it across the Atlantic Ocean? First, salt restriction is not a logical part of treating HTN. If salt retention were the cause of HTN, then all patients could be cured by giving them "diuretics", which are drugs that flush salt out of the body through the kidneys. The strongest diuretic in common use is furosemide or Lasix, which is often given to patients with severe congestive heart failure. When too much Lasix is given to a patient with HTN, their blood volume contracts and they faint when they stand up, having achieved only a modest reduction in blood pressure. I make these remarks about the futility of salt restriction in the hope of preserving for patients the joie de vivre of eating good food and with no intention whatsoever of undermining any doctor-patient relationships. There are four main categories of anti-hypertensives: "beta-blockers", "ACE inhibitors", "calcium channel blockers", and "thiazide diuretics". Beta blockers keep the autonomic nervous system from stimulating the juxtaglomerular apparatus in the kidney, which, we remember, causes release of the vasoconstrictor renin by the kidneys. ACE inhibitors block the function of renin. Calcium channel blockers inhibit contraction of smooth muscle cells in small arterioles, i.e. they stop the vasoconstriction. Thiazide diuretics flush salt out of the body but it is known that the diuresis is weak and temporary, lasting only a few months, whereas the anti-hypertensive effect is permanent. All four categories of drugs were developed according to the logic of affecting the peripheral mechanisms of HTN, which they all accomplish with varying degrees of success, but all the drugs also have effects on the brain stem set point for blood pressure that are not understood. They somehow move the set point back towards normal. The problem with taking these medications is that they all cause, to varying degrees, at least two unpleasant side effects, namely, fatigue or loss of energy plus dizziness. The loss of energy varies in severity; it is like what patients with depression suffer and can be very

disabling. It occurs most famously with beta-blockers but can be caused by any anti-hypertensive. The dizziness seems to be a little different from vertigo or spinning. A West Indian woman at Kings County Hospital once described it to me as having a little motor whirring inside her head and I have found that this description sometimes resonates with other patients. The dizziness tends to occur in the morning, soon after taking the anti-hypertensives, which suggests that it is caused, not necessarily by excessively low blood pressure but by inhibiting the rise of blood pressure which would otherwise occur at this time of day in keeping with the diurnal pattern of blood pressure, which can be exaggerated in hypertensive patients. So patients have a choice: live with some side effects or go on to get stroke and Alzheimer's disease. Of course, doctors can't be this blunt with patients; authors have no such inhibitions. There was an iconic old Jack Benny comedy routine in which a masked gunman stuck a gun between Jack Benny's shoulder blades and said "Your money or your life." Jack Benny raised his arms in the air and had a quizzical smile on his face, but said nothing. The gunman repeated, "Your money or your life." Jack Benny replied irritably, "I'm thinking!" Everyone with a diagnosis of HTN needs to purchase a home blood pressure monitor, available at any pharmacy, which is a simple cuff to wrap around the arm, plus a box with a button to press to take the reading. Patients should help their doctors monitor blood pressure. This is particularly true for patients after a stroke, patients who get no symptoms when their blood pressure goes up and patients with wildly-fluctuating blood pressure.

One of the purposes of this book is to point the way forward. More research needs to be done to define the precise chemical composition of free radical storm, i.e. severe oxidative stress. The hypothesis in this book, which I believe is supported by the preponderance of available evidence, is that free radical storm consists of superoxide anions engendered by SPA, with a smaller component in patients with early HTN and high renin being attributable to the effect of renin on endothelial cells. It would be of great theoretical interest to know the incidence of SPA in diabetics without coincident HTN. The intensity of free radical storm can be quantified by measuring levels of a chemical called "isoprostanes" in urine, which seems to be reliable, but it may not be the cheapest test and it requires a urine collection, not just a spot test on a urine sample. As mentioned in Chapter 3, blood β-thromboglobulin levels are probably a reliable measure of SPA. Monitoring both oxidative stress and SPA ought to be a routine part of internal medicine. I hope that a brave surgeon somewhere will start denervating the adrenal glands.

The critical thing for anyone with migraine or HTN to do is to take ownership of the diagnosis. Controlling these diseases early can halt the trip down the bad road, which, as we know, ends in meltdown of the brain. The key issue is managing stress. Is this even possible? I once had a friend who was a voice teacher specializing in opera. A key issue for her students was managing the "passaggio", which is the transition between the lower vocal register and the upper register and occurs around the E above middle C. She said that she could give her students imagery but, in the end, every student had to figure out his or her own way of handling the passaggio. The solution was waiting within but it had to be discovered. Managing stress is something like that. When I was in college, Kenneth Clark, the British art historian, had a TV program, subsequently turned into a book, called *Civilisation*. He pointed out that the French philosophes or philosophers of the eighteenth century, men such as Voltaire and Rousseau, were always depicted smiling the "smile of wisdom". Some of these men had rather gloomy ideas, yet they were apparently happy or wanted to be depicted as happy. I really do think there is a place of peace on the far side of stress, but everyone has to make his or her unique discovery of how to get there. This doesn't mean there are no guideposts. Martin Heidegger, in his book *Being and Time*, which is one of the foundational books of existentialism, says we spend most of our time enmeshed in the distracting details of daily life; we must learn to be grounded and authentic. Other writers have taught about following your passion, mindfulness, and meditation. So many people today are caught up in today's competitive society and internalize the expectations of society rather that looking for how to develop their own true talents, which is how to find happiness. These talents may not lead to heroic achievement but rather to a rich web of personal relationships. Trying to thwart destiny by living an inauthentic life leads to stress. I can only wish my readers a safe passaggio.

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