Meltdown and the Neuroscience of Stress

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By

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

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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 or 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.

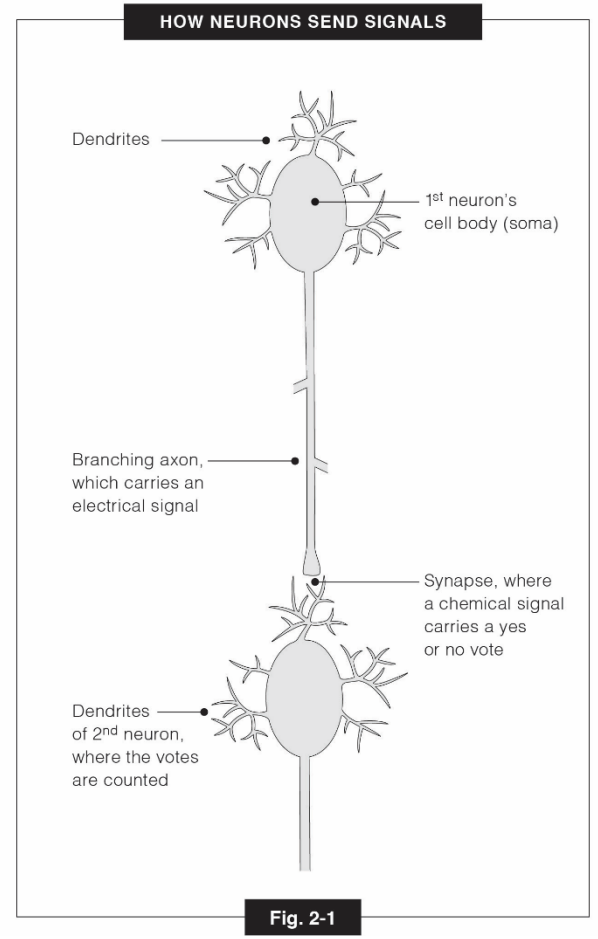
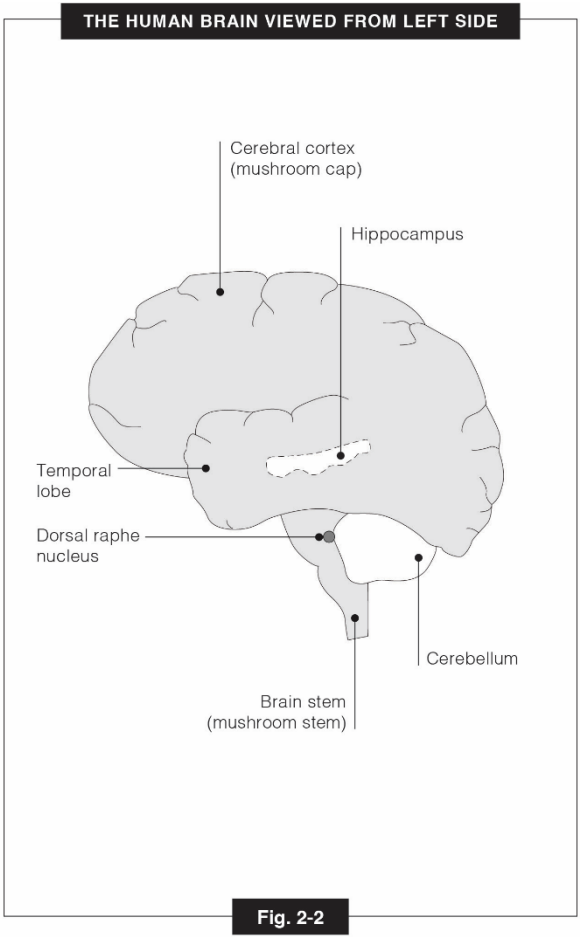


Fig. 2-1

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 themselves 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 "adrenaline"), 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

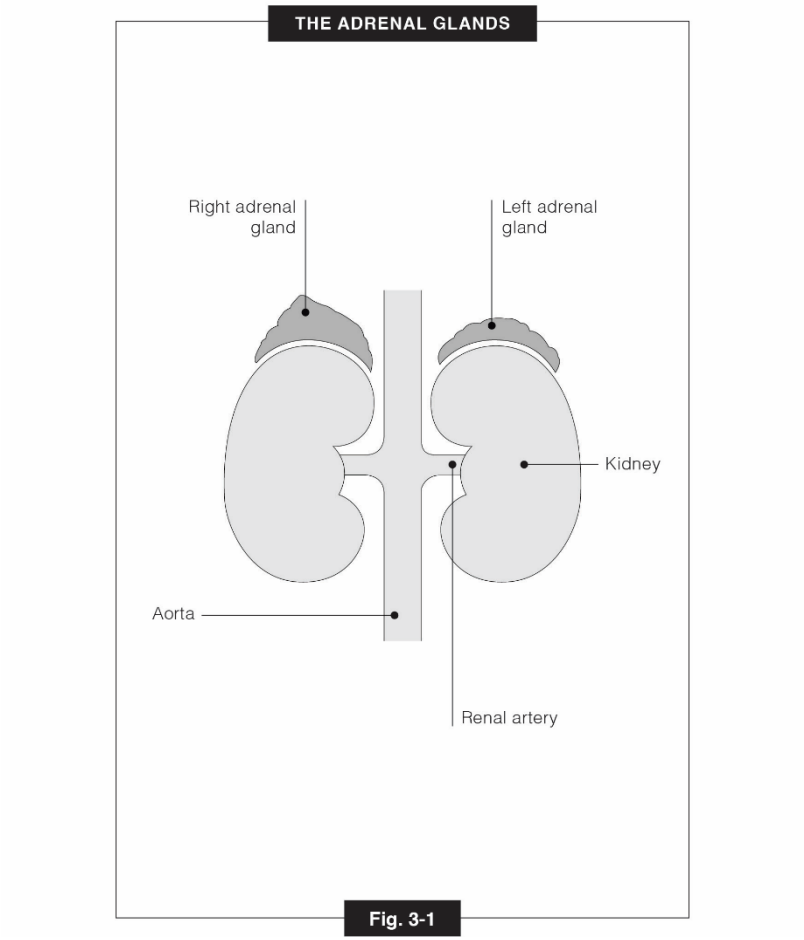


Fig. 3-1

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—