

Stress, hormones and disease

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Abstract

My postdoctoral training under Dr. Gerard Smith began me on a lifetime of investigation on the role of stress, hormones, and disease. The first set of experiments asked what hormone, if any, best reflected the range of aroused behaviors. We found that catecholamines performed substantially better than glucocorticoids did, despite the belief that glucocorticoids were sensitive indices of stress. But we also learned that hormones themselves were nowhere near as good in monitoring stress than motor behaviors were. In a second set of experiments, we tried to understand how stress affected medical disease. We learned that stress can produce disease in a healthy organism but has its most profound effects when disease already exists. Finally, in the early 1990s, I shifted my focus on stress and disease to a broader problem in behavioral medicine, namely, medically unexplained fatigue and pain. Among the studies we have done investigating these disorders, we looked specifically at veterans of the first Gulf War—many of whom developed problems with severe fatigue. A critical question in the literature asked if unexplained fatigue was simply a physical component of concurrent posttraumatic stress disorder (PTSD). In a large epidemiological study, we found that PTSD tracked stressor intensity in a stepwise fashion, while fatiguing illness increased with stressor intensity only on the milder side of the intensity spectrum. This result indicated that the two ailments are both stress sensitive but dissimilar.

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I was always interested in the psychosomatic hypothesis—that certain environmental stimuli were perceived by the organism as stressful and that this started a chain of neurological events ending in organic disease. I do not remember the details, but while I was a medical student at the University of Pennsylvania in the mid-1960s, someone referred me to Dr. Gerard Smith, who was then an Assistant Professor of Physiology. Gerry encouraged me and recommended that I figure out a way to do a postdoctoral fellowship in his laboratory. He explained to me that he was about to leave Penn to move to the Bourne Lab, where he would begin working in close association with his former collaborator and friend Dr. Paul McHugh. He arranged for me to meet Paul. At that time, Paul was 100% a neurologist and had not begun his shift to full time psychiatry. Because of my interests in stress, Paul advised me to train in neurology because the brain was the mediator of environmental stress. With that advice, I applied to and was

accepted at the Neurology Residency Program at the Albert Einstein College of Medicine in the Bronx. Early on, the Program Director, Dr. Labe Scheinberg, agreed to allow me to spend part of my residency working as a fellow at the Bourne Lab under Gerry's mentorship.

Gerry had always had an interest in stress and in ways of quantifying it physiologically. Prior to coming to Penn, he and Paul had worked at Walter Reed Army Institute of Research, where a famous psychoendocrinologist, Dr. John Mason, had published a number of papers in which he stated that cortisol was a sensitive index of stress [10]. But there were only limited data available supporting that conclusion, namely, that 17-hydroxy glucocorticoids (we could not measure cortisol at that time) were higher during the week than over the weekend and were substantially higher than basal weekly values when the monkeys had to work to avoid shock.

For my fellowship, Gerry proposed our implanting of electrodes into the lateral hypothalamus of monkeys also prepared with chronic indwelling catheters. The idea was to produce the defense reaction—a state of physiological arousal beginning with alerting and ending with excitement. We

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used the defense reaction as a way of increasing arousal in a stepwise fashion: If plasma hormones were a sensitive index of stress, one would expect to find a monotonic increase in their levels as the animal went from quiet, to aroused, and on to excited behavior. We did not find this result [17]. Despite clear behavioral arousal, glucocorticoid levels did not change from controls and only increased when the monkeys manifested excited behavior. Interestingly, glucose levels did a better job of tracking stress than glucocorticoids—an effect that we showed was mediated via the adrenal gland [16,17].

That initial experiment got me started on a lifetime of experimentation aimed at (a) finding a peripheral substance that was a sensitive index of arousal, the body's behavioral manifestation of stress, and (b) exploring the medical consequences of stress. Shortly thereafter, thanks to Gerry and Paul, I spent my required army time doing a second post-doctoral fellowship in the Division of Neuropsychiatry at the Walter Reed Army Institute of Research. The first experiment I did there was an outgrowth of the brain stimulation work. The research question was to see if plasma cortisol tracked arousal produced by making an animal work to avoid shock. Again, I found large increases in cortisol concurrent with the animal's showing excited behavior during the first shock avoidance session. However, if I sampled late in that initial session, dissociations were often seen—the animal was still excited, but cortisol could have fallen back to control levels. And when I looked at the animal's 10th session, when it was performing the avoidance task flawlessly, it was still aroused, but cortisol levels had fallen to levels even lower than those at baseline before the first shock was delivered [14]. Subsequent work made it clear that a habituation process had begun at the time of the first shock [15] and that this habituation process made it impossible to use glucocorticoids as an index of stress in any but the most acute conditions. Having found that glucose tracked aroused behavior better than the glucocorticoids in the brain stimulation experiment, I assessed glucose and plasma renin, which, like glucose, was released with sympathetic activation [13]. Both substances showed a stepwise increase as the animals' behavior went from quiet, to aroused, and then on to excited. Of the two substances, renin tracked arousal best on an individual animal basis.

I did the last experiments in this series some years after I had left Walter Reed to join the Department of Neurosciences at the New Jersey Medical School. First, I asked if appetitively induced arousal would also produce increases in plasma cortisol [18]. To answer this question, I trained monkeys to associate a light with food delivery 30 min later. As expected, monkeys showed behavioral arousal during this conditional stimulus, but cortisol levels were lower than in control conditions when signal did not reliably predict food delivery. The results of this experiment suggested that cortisol could not be used to track arousal produced by positive events.

The final set of experiments used chronically catheterized rats exposed to different intensities of foot shock [19]. Again,

the research question was to see if hormones tracked arousal and if they did, just how well. By the time I did this experiment, it was possible to extend the work to include the catecholamines—an idea fostered by the glucose and renin results. Again, I found that corticosterone was, at best, a poor index of stressor intensity. The pattern of adrenocortical activation was the same whether the rat received a 0.25-mA burst of foot shock or substantially higher shock intensities. In contrast, both plasma norepinephrine and epinephrine were sensitive respondents to stressor intensity, increasing monotonically along with foot shock intensity. However as Fig. 1 indicates, variability for each of these respondents also increased greatly with shock intensity. This limits the usefulness of these indices to the milder end of the stress spectrum.

Finally, I wondered just how well the catecholamines tracked arousal for any individual animal. This is a critical question for any visceral stress respondent. For a useful stress respondent, one would want a measure that increased reliably with different intensities of stress from subject to subject. If that condition were met and if there were also reliable group differences, one would have a laboratory test that “quantified stress”. Again, I used the chronically catheterized rat, but here, I sampled blood every few days at one of several foot shock intensities. While corticosterone showed its usual insensitivity to stressor severity, both epinephrine and norepinephrine tracked stress sensitively, showing stepwise increases in each hormone for most individual rats with stepwise increases in foot shock intensity. But again, there were problems that limited the potential usefulness of these hormones as visceral indices of stress. First, the reliability of these visceral indices dropped off rapidly after the immediate postshock blood sample. And second, although the catecholamine patterns of individual rats did, in fact, show a sensitive relation to stressor intensity, the absolute levels of each hormone overlapped across a broad range of stressor inten-

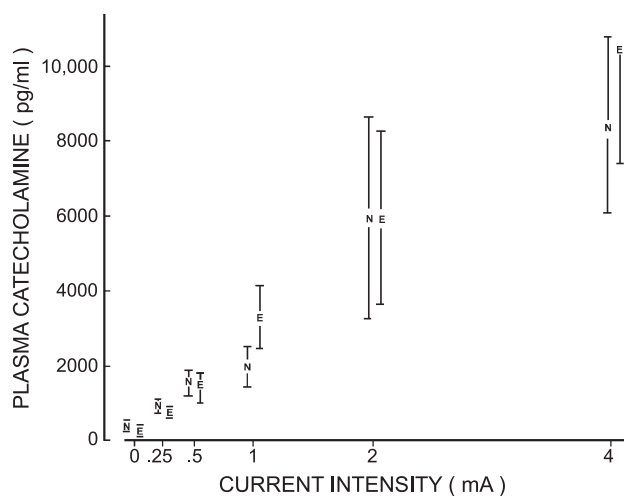


Fig. 1. Average ($\pm$ S.E.M.) of immediate postshock values of plasma norepinephrine (N) and epinephrine (E) at each of the foot shock intensities used [19]. Note that as shock intensity increases, so do N and E, as well as the magnitude of the variability about each mean [19].

sities. Hence, for example, hormone levels in one rat might overlap with those in a second rat receiving a dose of foot shock either 25% or 400% of that given to the first rat. In contrast, behavioral measures, namely, the number of squares that the rat crossed during the period of foot shock, were as sensitive a measure of arousal as the hormonal measure. Because one can assess behavior directly and immediately, I concluded that future efforts to find sensitive respondents of stressor intensity should concentrate on assessing somatic motor behavior rather than visceral measures.

Concurrent with this line of research, I had begun a series of experiments in which I investigated the relation between stress and serious medical disease. That research was stimulated by the famous “executive ulcer” experiment of Brady et al. [1]. Brady et al. [1] had monkeys working to avoid shock for alternating 6-h shifts; surprisingly, some of the monkeys got sick and, when examined, were found to have duodenal ulcer disease. I sought to replicate this outcome by applying the psychological principles known to reliably produce gastric erosions in rats [23], while repeatedly using noninvasive techniques to examine the gastroduodenal mucosa of the test animals. I found that I could reliably produce lesions, but that very often, the lesions healed despite the continuation or increase of stressfulness [12]. Hence, even for stress-induced disease, habituation occurred. This result led me to hypothesize that stress produced disease only in vulnerable animals. Had I known that a bacterium—*Helicobacter pylori*—played an important role in the pathogenesis of peptic ulcer disease; infecting the stomachs of my test animals would have been my next step. Unfortunately, the link between *H. pylori* infection and gut disease was not made until years after I had finished these experiments.

Hence, I turned to the cardiomyopathic hamster (CMH). This is an animal that is born with a normal heart but with a predisposition for heart disease. In the second month of the hamster’s life, its heart begins to develop tiny infarcts due to coronary microvascular spasm. By the third or fourth month of its life, this process winds down, but the heart disease is sufficient that over the next few months, the animal starts to develop congestive heart failure (CHF). This heart disease shortens the life of this animal by about 50% when compared with healthy hamsters. As CHF gets worse, the heart dilates and actually hypertrophies. Fig. 2 shows the development of CHF in CMH hamsters living quietly in their cages (labeled “C”). Note that cardiac weight increases monotonically and significantly as the hamster ages. But the addition of stress (labeled “S”) produces a multiplicative shift in the rate at which heart failure develops, such that a 6-month-old-stressed CMH has the same degree of failure as a 10-month-old-unstressed hamster has. Moreover, the older 10-month CMH, which is starting to show overt signs of heart failure in the form of impaired grooming, gets substantially worse and some even succumbed to their illness.

Although this experiment did not reveal an effect of stress in the young animal during the lesion-forming period of its

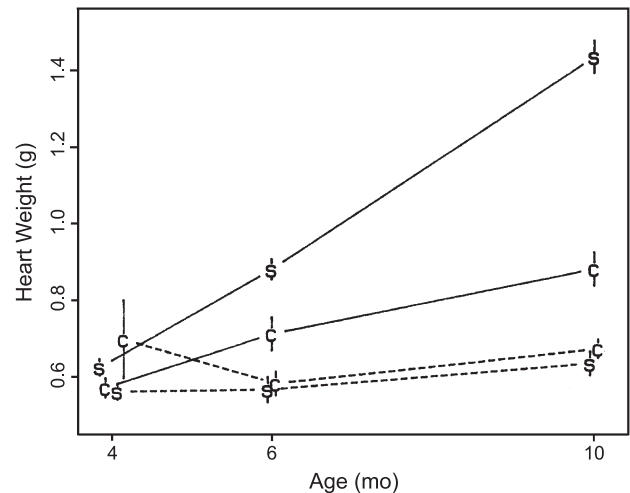


Fig. 2. Cardiac weights in CMH (solid lines) and healthy hamsters (dashed lines) [22]. The letter “S” denotes the hearts of those animals sacrificed 2 days after the completion of five daily stress sessions, while “C” denotes those of nonstressed controls.

life, we reasoned that stress may have influenced the vaso-spastic process responsible for the cardiac pathology in CMH. To test this hypothesis, we used an in vitro method to study cardiac mechanics in isolated hearts of 2.5- and 6.5-month CMH following exposure to stress [4]. Stress produced ventricular dysfunction in the older but not in the younger CMH. However baseline coronary vascular resistance was higher in the younger than in the older CMH; moreover, the microvasculature of the stressed, younger animal was more reactive than in the nonstressed, age-matched controls. These data suggested that stress enhances vasoconstriction that is consistent with coronary spasm, but only in the 2.5-month CMH. We concluded that stress triggered different pathophysiological mechanisms in younger versus older CMH. In another experiment [2], we determined that the effect of stress was weaker than the underlying vasospastic process in 1.5-month CMH but that stress could and did accelerate this process in 2.5-month CMH. Thus, these hamsters had a period of organ vulnerability in which stressor intensity interacted with microvascular vulnerability to alter the consequences of stress. Finally, we manipulated stressor intensity across the breadth of the animal’s lifespan—as it transitioned from a well-appearing animal with microvascular spasm to an ill-appearing animal with CHF [3]. We found the same sort of multiplicative relation between stressor intensity and organ vulnerability for cardiac mechanics. For the older CMH with signs of overt CHF, stressors of any intensity exacerbated ventricular dysfunction, while only the most intense stressors had such an effect with the 6.5-month CMH, which appeared to be in good health. However, stress had no effect at all in exacerbating the vasospastic process in 2.5-month CMH, probably because the underlying pathological process was so substantial to start with.

At the time we had started these experiments in the late 1980s, my own research focus changed dramatically. A few

years before this time, I had written a book aimed at telling young people interested in the medical profession what it was like being a doctor [11]. The idea of the book was to provide potential medical students information that was not in the standard curriculum—how to tell a patient they had a lethal disease and how to deal with patients that fell between the cracks of the medical profession. At around the same time, I was given the opportunity to take care of patients with medical complaints that had no obvious medical cause, i.e., patients that fell between the cracks of classical medicine. Hence, in late 1989, I started seeing patients with medically unexplained fatigue, and I began a set of studies designed to try to understand the illness process(es) of patients with medically unexplained severe fatigue.

A set of initial studies led to a successful grant proposal establishing a Chronic Fatigue Syndrome (CFS) Cooperative Research Center at UMDNJ in 1991. Gerry's early mentoring was critical in allowing me to think broadly about medically unexplained fatigue and to take a behavioral medicine approach to trying to understand its pathophysiology. The program I built mixed internal medicine with health psychology and was multidisciplinary in the fullest sense of the word.

As we were studying patients with medically unexplained fatigue, veterans from the Persian Gulf conflict started coming forward with complaints that also turned out to have no obvious medical explanation. We immediately hypothesized that some of these veterans had CFS and that something about serving in the Gulf had produced a mini epidemic of this disorder. Our work on civilians with medically unexplained fatigue allowed us to successfully apply for a VA-based center paralleling the UMDNJ-based center. Funding from the VA center supported an epidemiological study on veterans coming for health care and showed that over 14% of these veterans had what appeared to be the same sort of severe medically unexplained fatigue known as CFS in civilians [7]. However, the rate in Gulf veterans was substantially higher than any published for civilians.

One of the frequent questions in dealing with medically unexplained illness regards whether it is a variant of a psychiatric illness. Specifically for veterans, the question arose as to whether their medically unexplained fatigue was a somatic manifestation of posttraumatic stress disorder (PTSD). PTSD was a diagnosis that came out of the Vietnam War, and it was applied to veterans with disturbing dreams, hyperarousal, and substantial psychiatric morbidity. The idea of PTSD was that it was a stress-related psychiatric disorder, whose rates would track stressor intensity: The rates were known to be lowest in nondeployed veterans, higher in noncombat Vietnam veterans, and highest in combat veterans [8]. An excellent epidemiological study on veterans with PTSD showed that many of them also had medically unexplained symptoms [5]. This led to the following research question: Is it necessary that veterans with severe medically unexplained fatigue also have PTSD?

To answer this question, I initiated a collaboration with Dr. Han Kang, the VA's head epidemiologist. Dr. Kang had questionnaire responses from many thousands of veterans, some of whom were deployed to the Gulf, others outside of the Gulf, and yet, others not deployed at all but instead were living at home serving in the Reserves. Because we had combat exposure data from these veterans, I reasoned that we could do a natural experiment based on the amount of stress that individual veterans had experienced. Fig. 3 shows the results [6]. We sorted the veteran data as follows: those who had not been deployed (i.e., least amount of stress exposure; Number 1 on the horizontal axis of Fig. 3), those who had been deployed to areas outside of the Gulf (Number 2 on the horizontal axis), those who had been deployed to the Gulf but had not seen action (Number 3 on the axis), and those who had one, two, or three of any of the following experiences: involved in active combat, saw dead bodies, or had to don chemical protective suits because of alarms warning of possible nerve gas attack (Numbers 4 through 6 on the axis, respectively).

The logic of this natural experiment was to determine if the rates of each disorder paralleled one another across the broad range of stress. That was not the result we found. Rates of PTSD-like illness—based on questionnaire and not corroborated by direct psychiatric interview—tracked stressor intensity sensitively as stressor intensity increased, monotonic increases in rates of PTSD. In fact, rates increased significantly at every step except going from Step 2 to 3. However, rates of CFS-like illness—based on self-report and not corroborated by physician evaluation—increased significantly only going from Step 1, to 2 and, finally, to Step 3. Despite that veterans in Steps 4–6 had seen

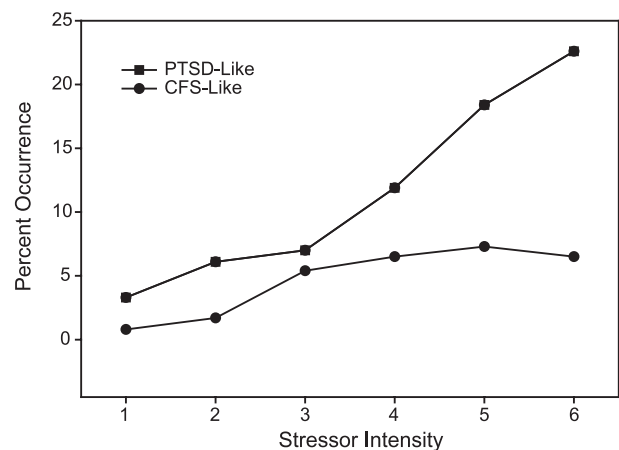


Fig. 3. Rates of PTSD- and CFS-like illnesses based on self-report of veterans who saw duty from 1990 to 1991 [6]. The data have been ordered based on the stressfulness of the veteran's experience: 1 = not deployed from home station; 2 = deployed outside of the Gulf (i.e., either to a base within or outside of the United States); 3 = deployed to the Gulf but saw no combat; 4 = having one of the following exposures: active combat; saw dead bodies; had to don chemical protective suits in response to alarms signaling a possible nerve gas attack; 5 = had exposure to two of the stressors listed in Number 4; 6 = had exposure to all three of the stressors listed in Number 4.

substantial amounts of combat stress, rates of CFS-like illness were no higher than in the group of veterans deployed to the Gulf and not exposed to other stressors. These results led us to conclude that both PTSD and CFS were stress-related illnesses, but that stress reactivity was very different in the two disorders. While PTSD tracked stressor intensity sensitively, CFS seemed to have more of an “all or nothing” relation with stress: When veterans were stressed simply by being deployed outside of the United States, the rates increased but did not track stress sensitively. It was as if CFS was like cortisol, while PTSD was like epinephrine. While most of my work has now moved away from questions related to stressor intensity to issues of stress reactivity [20,21], a critical research question is to determine if stress also plays a role in the pathogenesis of CFS in civilians. We have shown that patients with CFS have increased numbers of abnormalities in brain magnetic resonance imaging studies [9] and that cardiac stroke volume is low in some patients [20]. Thus, it is important to try to understand the trigger for CFS in this nonveteran population. However, without thousands of CFS patients to poll, the answer to that question will have to wait.

In conclusion, my postdoctoral with Gerry Smith started me on a lifetime of research. I have viewed myself as quite lucky over the years. I can design an experiment that can produce data that open new vistas of understanding about stress and disease, but it does this with a variable interval type of reinforcement schedule, namely, long periods of hard work with no reinforcement or even punishment (i.e., a grant proposal that does not get funded despite months of preparation). In contrast, my clinical practice brought me in contact with people who often thanked me profusely after one office visit. My patients brought me short-term reinforcement while my research often, but not always, brought me long-term reinforcement. Working with Gerry taught me how to make medicine fun for a lifetime.

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