



Briefing on the Brain-Body Connection

Subcommittee on Labor-DHHS, Education and Related Agencies
Committee on Appropriations
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Mr. Chairman and Members of the Subcommittee:

I am Steven E. Hyman, Director of the National Institute of Mental Health. It is my pleasure to appear before you to discuss research that today is beginning to elucidate some of the specific neurobiological mechanisms that play a role in conditions that were long considered to be subjective, the exclusive province of the mind. I also will comment on how this new information promises to broaden our understanding of health and illness and the approaches we take to treating illness.

The French philosopher, Rene Descartes, who crystallized the very bad idea that mind and body are radically distinct, has been dead for 347 years. His ideas have been universally rejected by serious modern thinkers, yet one would too rarely gain that impression in the offices of modern physicians. Would that this were just a dry academic matter; unfortunately it impacts many Americans in search of care. Although often destructive and disabling, conditions which manifest themselves largely with symptoms of pain, anxiety, or sadness are often construed as somehow less real than other conditions that happen to leave visible lesions (or at least produce visible blood test abnormalities. Disorders of thought and emotion, which have terrible impacts on individuals, families, and national productivity, are often made light of and ignorantly stigmatized. The marginalization of the subjective and behavioral contributes to the widespread undertreatment of pain, and the failure to recognize or treat anxiety disorders and depression.

In this testimony, I would like to focus, then, on three aforementioned conditions: pain, anxiety disorders, and depression, all of which represent major public health problems. In each of these conditions suffering often goes unrecognized or uncredited, and in each, cognitive and behavioral treatments may be critical complements to and, occasionally, alternatives to pharmacotherapies.

Understanding Pain

More than just another form of "touch" sensation, pain demands our attention. When serious, it may stop us in our tracks, and it carries intense negative emotions. Pain is a great teacher, altering our behavior in the service of survival: to put it simply, a child does not put a hand in the fire twice. Pain is a protector: an injured person is forcibly reminded to protect an injury until it heals. But there is also a terrible price to pay for possessing such an effective survival system. When pain becomes chronic it may disrupt and even destroy lives. Worse yet, chronic pain often persists long after the source of tissue damage is gone, and thus conveys no benefit at all, but only suffering. The most common cause of serious chronic pain, whether caused by injury, cancer, or a herniated disc, is damage to the nervous system itself, leading to persistent false alarms to the brain. Pain that is caused by an injury to the nervous system itself is called neuropathic pain. Basic and clinical neuroscience have, over the last decade, made remarkable advances in understanding pain, but as anyone with chronic neuropathic pain knows all too well, much remains to be discovered.

Why is pain such an insistent form of sensation? Why does it keep coming into the foreground of thoughts and feelings, when the sufferer would rather tune it out and return to work? Incoming pain messages from skin, muscle, bone, or internal organs are relayed to higher centers in the brain via two largely segregated pathways beginning in the spinal cord. The smaller of these pathways is more recent in evolution, and therefore sometimes is called the neospinothalamic tract. It relays information about the precise localization and nature of the pain to those brain regions that analyze bodily sensations. It permits us to point to an area of our bodies in the doctor's office and to describe the sensations, for example, as pricking or burning.

The older and larger tract conveying pain information is called the paleospinothalamic tract. It does not relay specific sensory information at all, but rather communicates with brain regions that produce arousal, that increase the heart rate and blood pressure, and most importantly, that process emotion. Via this tract, pain messages are hardwired into emotional centers that ensure that pain has an intense, aversive quality. The nervous system must be set up this way if pain is to protect even the stoics among us from damaging themselves, but this emotional hard wiring means that chronic pain brings with it chronic suffering.

Many individuals with chronic pain become depressed, not because they are weak, but because of the direct relentless stimulation of brain regions that produce negative emotion. Depression in chronic pain often responds to antidepressant treatments, even when the pain itself cannot be fully relieved, but depression in the chronic pain patient too often goes untreated, due to a misplaced sense that it is somehow appropriate that the pain sufferer be depressed. Depression and pain lead to a vicious cycle, however; pain can cause depression, and depression turns up the gain on pain, making the pain less tolerable and moving it front and center in the sufferer's life.

I have been speaking of the relentless quality of chronic pain, but one of the most remarkable observations about acute pain, is that it can be suppressed, at least transiently, depending upon the context in which it occurs. The great anesthesiologist, Beecher, noted with surprise, as he examined men with serious shrapnel wounds at Anzio beach, that many of them refused morphine, something that he almost never saw in Boston, when he tended to patients with the far less serious wounds produced by controlled surgery. How could such a phenomenon be explained? Under conditions that produce extreme stress or fear, higher emotional centers in the brain can activate a descending system that suppresses incoming pain signals. This descending analgesic system utilizes the body's own endogenous opiate-like neurotransmitters, the endorphins. The threshold for activation of descending analgesia by stress is high; otherwise pain would lose its survival value, but the nervous system appears to be organized such that in circumstances which produce the greatest stress or fear, for example, pursuit by a predator, or mortal combat, circumstances in which the survival value of running or fighting far outweighs the risk of using already damaged limbs, pain can be completely suppressed.

Opiate drugs are analgesic because they mimic the body's endorphins. Unlike stress, however, opiate drugs are extremely reliable in their ability to suppress pain (they work even when one is not fleeing for one's life. Unfortunately, opiate drugs act not only on pain pathways, but elsewhere in the brain and peripheral organs with the result that unwanted side effects markedly limit their use.

Of particular interest in the context of today's hearing, there has been research as to whether acupuncture and also the much misunderstood placebo response might act via descending analgesic pathways (but this research has been hard to perform for many reasons, including the fact that acupuncture, while effective for some people in some circumstances, is not as potent or reliable as pharmacologic analgesics). You can see now, parenthetically, that placebos do not separate malingerers from those with real pain (indeed a "placebo" injection might work very well, if only for a very limited time, on someone suffering severe pain and stress, by serving as a trigger for descending analgesic

pathways).

What can we take away from this discussion? First we need research not only on pharmacologic alternatives to opiates, and an understanding of how to deliver and use opiates better, but also on better nonpharmacologic strategies to deal with chronic pain (perhaps there are ways of tapping into the descending pain suppression systems within us that are more robust than the approaches we now have, which include transcutaneous electrical nerve stimulation, or its acronym TENS, and acupuncture). Second, when patients with chronic pain become depressed, it is important not to write it off as expectable, but to treat it vigorously. Third, for many there can be a vicious cyclic of depression and disability if people disengage from their normal work and family lives. People with chronic pain should be encouraged to work and to retain responsibility at home at the level their pain and underlying medical conditions allow. I should add that I have not discussed in this testimony the issue of the all too common phenomenon of undertreatment of acute pain. This is a separate but important issue that has been addressed in many other forums.

The Circuitry of Fear

If chronic neuropathic pain represents the perversion of neural systems that under normal circumstances are engaged in protecting us from harm, anxiety disorders such as panic disorder and post-traumatic stress disorder represent the perversion of another survival circuit, that which underlies fear.

Emotion has been dismissed by some philosophers as little more than a base avatar of our animal origins. How wrong they were. Modern behavioral neuroscience has illuminated that fact that our higher cognitive functions, as wonderful as they are, could not, by themselves, help us to eat, drink, reproduce, or respond to danger: emotions are necessary partners which appraise the survival significance of all information that we take in through our senses. It is our emotional circuits that decide whether what we perceive is a danger to be escaped, or alternatively something positive to be approached. Individuals with damage to certain emotional circuits are unable to make appropriate choices in life, to plan, or to exhibit normal motivation. Despite normal intelligence and cognitive function, their lives fall apart. Emotion is not represented by a single system in the brain; rather different emotions are processed by different specific circuits in the brain. Thanks to the work of several NIMH funded investigators, the circuitry underlying fear is particularly well understood.

When thinking about an emotion like fear, we often think only of our subjective emotional experience, but much of the survival value of fear depends on the unconscious physiologic outcomes of emotional processing. When our senses provide information about something that might be dangerous, they pass the information on to brain regions involved in higher cognitive processing. These cognitive circuits will tell us, for example, that what is in our path is a diamond back rattle snake about 3 feet long, coiled and ready to strike. We will also perceive the context (the precise circumstances under which the snake was encountered). More rapidly than this precise cognitive processing can occur, however, our sensory systems pass information to a structure in the temporal lobes of the brain called the amygdala where the emotional appraisal will occur. Although occurring in different parts of the nervous system, this organization is analogous to pain, in which there is also separate and parallel processing streams that carry the cognitive, sensory-discriminative aspects of pain and the emotional-aversive aspects of pain. Subjectively, in the case of both pain and fear, we experience the cognitive and emotional aspects as seamless. Interestingly in both cases, people with lesions of one pathway or another may experience a dissociation of the cognitive and emotional aspects of pain or fear.

The amygdala appraises the incoming information and, if it is indeed a rattlesnake, ascertains it to represent danger. The amygdala then orchestrates a series of rapid physiologic responses effected by several other parts of the brain, including the hypothalamus. It activates the "fight or flight response" which shunts blood flow from the digestive system to the muscles and increases the pumping of the heart. It causes the release of stress hormones that will increase the availability of glucose (needed fuel) and which will suppress the immune system (if you have to fight or flee, this is no time to have a swollen knee). It activates the descending pain suppression system, about which we have already spoken. It also produces species-specific escape behaviors. Deer and many other animals exhibit the behavior of freezing in response to danger, presumably because the vision of many predators is more sensitive to motion than to form. Of course when deer freeze in the headlights of an oncoming car, this is not a survival response (but this may serve as a reminder that the evolution of deer occurred earlier than the invention of the automobile). In addition to all of these physiological and behavioral responses, humans also experience the subjective feeling of fear. There is much evidence that this subjective feeling does not cause the other responses, but occurs in parallel with them.

One additional and very important result of emotional processing, whether it is associated with fear or pain, is that it produces deeply etched emotional memories. For example, the next time you are hiking and come to a place similar to where you had previously encountered a rattlesnake or some other danger, perhaps before you even realize it, your heart will be pounding, and your attention has turned from focusing on the wildflowers to scanning vigilance. You are experiencing anxiety. Of course, such anxiety is exactly what serves survival. However, when there are false alarms, such as the intense dread of a spontaneous panic attack, these survival circuits get hijacked and become a source of debilitating trouble. Thus, when out of the blue, you suffer the entire physiologic and subjective experience of extreme fear (a panic attack) whatever you happen to be experiencing at that moment becomes associated with that dread. Neutral places (shops, bridges, classrooms) become associated with the fear, and upon returning to those places, the fear may come flooding back (it may even trigger another panic attack). Since panic attacks recur both spontaneously and may be triggered by environmental cues, much of the world gets painted with aversive emotional memories, and individuals suffering with panic disorder may retreat to their homes, a condition called agoraphobia, which actually causes more disability than the original panic attacks.

These survival circuits meant to ensure that danger is remembered indelibly and thence avoided can also become usurped by the experience of overwhelming trauma, especially if it is repeated. For those who have experienced combat or who have suffered abuse, torture, or atrocities, emotional memory is no longer adaptive, but rather a source of suffering and disability. Any reminder of the circumstances of the trauma may bring flooding back the entire experience, complete with the physiologic responses.

For the most vulnerable individuals who have suffered severe trauma, treatment of post-traumatic stress disorder is still far from adequate. After all, treatment would somehow have to erase or suppress what has been overlearned by a system, the job of which is never to forget. In the treatment of panic disorder with agoraphobia we do better. With medications we can usually abolish the panic attacks, and with cognitive-behavioral psychotherapy we can begin to override, if not erase, the emotional memories that have painted the entire outside world as dangerous. One classic treatment is systematic desensitization, which involves developing a hierarchy of anxiety-provoking situations, learning relaxation techniques, then associating these situations with relaxation, beginning at the bottom, or least anxiety-provoking, part of the hierarchy. When the feared situation is encountered, but no panic attack occurs (e.g., because of the medicine or because the desensitization was successful), the learned response is eventually extinguished (it stops recurring). With the complementary effects of medication and psychotherapy, we can now produce marked improvement in the majority of patients who suffer panic disorder.

Even though it can be so effective, psychotherapy is much misunderstood in our society. This derives, in part, from the devaluation of treatments that engage the mind, and in part, no doubt, from the checkered history of psychotherapy itself. Untested claims have been made in the past (and to some extent continue to be made) for a wide variety of psychotherapies, and some practitioners have rather illogically argued that their style of psychotherapy is effective for a wide range of life problems and mental illnesses, as if we were to prescribe penicillin for any physical ailment rather than for specifically sensitive bacterial infections. Modern psychotherapies have been designed for specific symptoms and age groups, and are subjected to rigorous empirical tests, quite analogous to those for medications.

Psychotherapy works (and this would come as a great surprise to our deceased whipping boy, Rene Descartes) because, like medication, it works on the brain.

Understanding Mental Illness

There is perhaps no phenomenon that better illustrates the disastrous implications of separating mind and body than the way our society has treated even severe mental illness. While attitudes toward mental illness are palpably improving, fear and stigma remain major obstacles to appropriate recognition and treatment, and, in turn, the continued productivity of individuals suffering from one of these brain diseases. The most common serious mental illness in the United States is depression. Major depression (a clinical condition that warrants and benefits

significantly from medical treatment) affects approximately 10 million Americans in a given year; for 2 million severely depressed patients, appropriate specialty treatment is an urgent medical necessity. Yet because of inappropriate shame, many individuals with depression do not ask for help. At the same time, there is a well documented failure to recognize depression in primary care settings. The *Journal of the American Medical Association* early this year published a thorough review of research concerned with the undertreatment of depression. Data suggest that in the general population, only one in ten people who meet diagnostic criteria for depression receive adequate treatment. The likelihood of getting needed treatment is better (but not much better) among people who are actively seeking health care. One study that looked at patients who were particularly heavy users of primary health care services, half of these patients were determined, by a psychiatrist, to be depressed and in need of treatment; only 55 percent of these patients had received any antidepressant medication in the prior year, however, and only 10 percent received an adequate dose and duration of medication. In another study that looked at a blend of treatment settings (HMOs, fee-for-service, and solo practices) and medical specialties, only 41 percent of patients received an adequate dose of antidepressant medication. In pediatric primary care settings, the rate of recognition of mental and developmental disorders may be as low as 20 percent.

The popular press has pointed out repeatedly that people's willingness to seek treatment for depression has been influenced dramatically over the past decade by the introduction of new selective serotonin reuptake inhibitors, or SSRI antidepressants; we know that some of this medication use appears to be by individuals with real, but milder, depressive symptoms who have less shame about self-identification and therapy. It also has been hypothesized that the wide use of potentially antidepressant herbal treatments such as St. John's Wort will further extend treatment; however, prior to completion of adequate clinical trials (particularly a multi-site study that NIMH is sponsoring in collaboration with the NIH Office of Alternative Medicine) we must temper our optimism and, indeed, exercise caution, in encouraging such treatments. And we should be aware that much of the popularity of St. John's Wort reflects continuing stigma attached to a depression diagnosis in a medical setting and even the use of SSRIs.

There is perhaps no more compelling reminder of our failure as a society to diagnose and treat depression than our failure to prevent suicide. The "purest" picture of the role of depression in suicide is seen in the subgroup of the population with the highest rates of suicide: older white men, 40 percent of whom saw a primary care provider in the week that they died, and 70 percent in the month of their suicide. Rigorous psychological autopsy studies reveal that these men typically are experiencing a first onset, unipolar depression of moderate severity that is not complicated by the comorbid, or co-existing substance abuse or psychotic illness likely to be seen in younger suicides. In other words, these suicide victims are suffering the most successfully treated form of clinical depression (but, tragically, their illness rarely is recognized and treatment never is initiated).

Depression is a disease of the brain that generally does not respond to attempts to work, think, or even pray oneself out of. Indeed, the disease insidiously strips individuals of the belief that they can get better or even deserve to get better, and it produces a counterproductive withdrawal from those who are in a position to help. Nonetheless it is highly treatable in more than 80 percent of cases with pharmacotherapy, often in combination with specific short-term psychotherapies such as cognitive behavior therapy.

Summary

Mr. Chairman, modern medical and neurobiological science today enables us to inter, finally and decisively, the worst idea of Rene Descartes. Research has demonstrated that the conditions and disorders we are discussing here (pain, anxiety, and depression) are real medical disorders of one particular organ of the body, the brain. The next urgent challenge is to succeed in communicating to the public and to front-line health care providers what we know through research: That disorders that affect and express themselves through our mental lives are no less real, no less painful, and no less worthy of our attention, expertise, and treatment than diseases that affect the heart or any other organ.

Moreover, as I have cited research to show, treatments that clearly act through the mind (psychotherapies, for example, and behavioral therapies) can have a positive, and literally discernible, effect on the workings of the brain. Learning how words, thoughts, and insights can change the physical workings of the brain, with what therapeutic effects and what side effects, is one of the great challenges before us. But learn we will, by means of research that must be every bit as rigorous as is research that we conduct to demonstrate that a given medication will eliminate a bacterial infection.

Until we succeed in these tasks (public education, and encouragement of the necessary integration of research-based knowledge into clinical practice) Descartes' ghost will continue to sow confusion and fear and shame in the paths of people who are coping, often so valiantly, with mental illnesses and other brain disorders. There is no shame in mental illness; the shame lies only in the fear, the misunderstanding, the ignorance, and that shame must end.

Thank you. I will be pleased to answer any questions.

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