The Harvard Mahoney Neuroscience Institute Letter
ON THE BRAIN
Vol. 2, Special Issue

DEPRESSION

"Tell your friends: depression is not a moral weakness, nor mental sloth, but a true brain disease that can be successfully treated."

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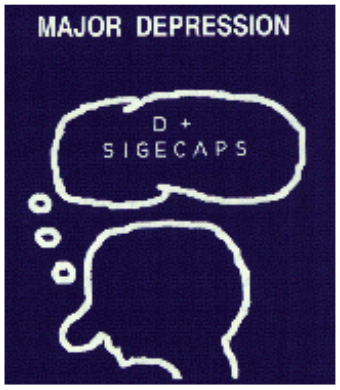
DR. CASSEM: Have you felt blue or down in the dumps today? Could you have a disease of the brain? Now, likely not. What is depression? What does it take for a psychiatrist to diagnose the brain disease known as major depression? It is not one symptom, but five of the total nine symptoms.

Any five of the nine and we're in trouble: Mood depressed; sleep disturbed; interest and enjoyment blunted; guilt feelings and self-reproach, energy gone, replaced by exhaustion. Concentration shot, indecisiveness present; appetite and weight are down (sometimes they are up, more often down). Psychomotor agitation (can't sit still) or retardation (just sit and vegetate); and suicidal thoughts.



*Cassem's mnemonic: mood **D**epressed + **S**leep disturbed; **I**nterest, enjoyment blunted' **G**uilt, self-reproach; **C**oncentration shot; **A**ppetite doun (or up); **P**sychomotor agitation, retardation; **S**uicidal thoughts.*

The diagnostician wants to know: Either depressed mood or blunted, shattered interest, out on strike and a total aggregate of five of the nine? If you have five of the nine mostly all day, every day for more than two weeks, you have got it, the big "D."

I am saying to you that depression is not a moral weakness or mental laziness, as you often still hear. It is a disease of the brain. About this disease, as about everything, there is good news and bad news. Of course, you always want the bad news first.

The bad news is that this disease is common, One of every ten people will sometime have either a major or minor episode of this disorder. It is serious. Fifteen percent of people with this disorder die by their own hand.

In Alzheimer's disease, you have a bunch of abnormal cells that, in essence, commit suicide. In this disease, the whole person commits suicide. It is chronic; it tends to recur. Almost two-thirds of all people who have a depressive episodes will go on after one bout to have four or more episodes in their lifetime.

Finally, it is getting worse, this disease, with every generation. In every birth cohort in the United States, beginning with 1905, it shows.

The good news about depression is that there is a better solution for it than the Tobin Bridge or a .357 magnum bullet. The good news about depression is that our treatments work. Drugs and ECT (electroconvulsive therapy) with psychotherapy work so well that 70 to 90 percent of people with a depressive episode, if treated properly, will get well.

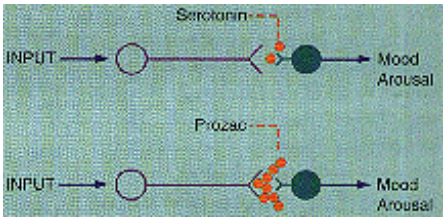
In Alzheimer's disease we don't have a treatment to reverse it. With drug addiction, we don't have a record that we can be proud of. With this disease, we are already proud of what can be accomplished. So, tell your friends: depression is not a moral weakness, nor mental sloth, but a true brain disease that can be successfully treated.

Now, to Dr. Coyle. Joe, when a person gets this constellation of symptoms, what is going on in his brain and why do our drugs work so well?

DR. COYLE: Of particular importance, research is bridging the gap--the previously contentious gap--between life experiences and brain mechanisms. Ned emphasized that major depressive disorder is an eminently treatable condition in the majority of cases. A chemically diverse group of drugs, including monoamine oxidase inhibitors, tricyclic antidepressants and the recently introduced Prozac, will induce a remission in most cases in four to eight weeks.

The efficacy of these drugs obviously provides a way into the brain for identifying their sites of action. It must be appreciated that the site of therapeutic action of the drug does not necessarily correspond to the primary defect in the disorder. For example, the action of aspirin in arthritis is not at the pathologic consequences. Nevertheless, both aspirin and antidepressants place researchers on the pathway that can be followed forward and backward to the causes of the disorder. Twenty years of research have provided compelling evidence that antidepressants act by enhancing the function of two neurotransmitters in the brain, norepinephrine and serotonin.

Let me focus primarily on serotonin--a substance made by a small group of neurons in the middle of the most primitive part of the brain.



Antidepressants inhibit re-uptake of the neurotransmitter serotonin, enhancing its action.

The influence of serotonin is pervasive in the brain, because these neurons emit axons, fine projections that enervate neurons throughout the entire nervous system. This anatomy is certainly consistent with the variable symptoms of depression, which affects thinking and sleeping in the cortex, memory in the hippocampus, appetite in the mid-brain, and hormonal functions in the hypothalamus.

Most tricyclic antidepressants and Prozac act by preventing re-uptake of serotonin into the nerve terminals that released it. The major mechanism for inactivating serotonin in the brain is this re-uptake process. Inhibiting the process markedly enhances the action of serotonin at the specific contacts that these neurons make with adjacent neurons.

Recently, the gene encoding for this uptake mechanism has been characterized and identified. This knowledge should provide us with better ways of understanding the action of serotonin in the brain, as well as designing more effective drugs.

The fact that serotonin's function in the brain may be reduced or impaired in major depression is supported by clinical studies on the spinal fluid that bathes the brain and on brain tissue of individuals who died with depression, particularly after suicide. The studies indicate a decrease in serotonin release in depression, a problem that can be

corrected with antidepressant treatment.

Dr. Cassem alluded to a relationship between life events, in particular, stress, in major depression. In fact, over half the patients with severe depression exhibit striking abnormalities in the function of their pituitary-adrenal axis. The pituitary gland is the master gland of the body, connected and directed by the brain, that controls hormonal function throughout the body.

In depressed patients, there is a marked increase in the release of the hormone that causes secretion of the stress hormone, corticosterone. Furthermore, this release from the pituitary is markedly disregulated. When severely depressed patients are treated with antidepressants, this normal mechanism of control is restored.

The loss of pituitary control indicates that the primary defect in depression is in the brain. Recent studies have revealed that the brain neurotransmitter that regulated the pituitary-stress axis is overactive. This neurotransmitter is called corticotrophin-releasing factory, or CRF. There is a markedly increased release of CRF from brain neurons driving the pituitary, as well as an increase in CRF throughout its ramifications within the brain. Finally, we now know that the neurotransmitter systems, norepinephrine and, especially, serotonin play a very important role in regulating the function of these CRF neurons.

Clinical studies have provided compelling evidence that the risk for severe depression runs in families and is transmitted by genetic mechanisms. Several centers, including Harvard, are attempting to find the sites on human chromosomes linked to this heritable vulnerability to depression. This has been successful with Huntington 's disease, Alzheimer's disease and amyotrophic lateral sclerosis.

However, the search is quite complicated in the case of depression for two reasons. First, major depression is so common that several gene mutations are likely to account for the vulnerability to this disorder. Secondly, unlike the degenerative disorders, in which we can see clear structural changes in the brain, the episodic course, the variable age of onset of depression and the fact that depression can occur as a normal consequence of losses in our life make it much more difficult to track in families.

Nevertheless, we feel that these studies will be productive. As we increasingly identify genes that are associated or encode for proteins and transmitter substances related to the stress axis, we may have a way of getting at a genetic level to the caused of depression.

In summary, neuroscience research, coupled with informed clinical observations, is closing in on the underlying mechanisms responsible for the most serious, common and potentially fatal psychiatric disorder, severe depression.

Ned, neuroscientists burrow in and look at a more cellular and molecular understanding of these conditions. Still, we appreciate that depression and allied psychiatric disorders can be fully understood only by taking into account life experience, which shapes symptoms and affects the course of the disorder. So, if you have someone with depression and you treat them and they get better, is there any way of preventing a recurrence of this condition?

DR. CASE: Well, I like prayer. But seriously, first of all, we know that constellation of symptoms. When you have a little group of them all day every day for two weeks, then seek treatment immediately. That would be the second one. While on treatment, don't stop the treatment until not only is the depression gone, but you feel completely back to your old self.

The vegetative symptoms, those SIGECAPS, may be gone in four to eight weeks.. You are not better; you need to feel like your old self in your job function and in your interpersonal function. That may take six months to two years. You should not stop. We don't know low long to keep up the drugs unless you have had more than three episodes in less than three years. Now, state of the art says, for that person, the antidepressants should be maintained at the therapeutic level, like two hundred milligrams of amicrimine, for at least five years and accompanied by monthly psychotherapy. That is the recommendations as of now.

Now, Joe, to again put you on the spot. In the secrets of the brain, think of a person twenty-five years old who has

a family history. So, perhaps vulnerability, but a straight A student. Then something outside the person totally, the death of a parent or failing their Ph.D. exam and within a month and a half, they have a profound SIGECAPS depression. What I want to know is, how do you get from the outside into the brain? It's not only that; it's as though the arrow went right into the brain and that gene that was vulnerable, right into the gene and got all this going. How does that happen?

DR. COYLE: Well, if I knew the complete answer I'd be on my way to Stockholm. Let me respond to it in two ways. In studies with experimental animals, we are learning a lot about what we would have previously considered symbolic issues--such as the symbolic nature of the value nature of a mother or loved one and what that loss may mean. We do know from studies on experimental animals that separation can affect both the neuronal circuits that are involved in stress, as well as the neuronal circuits that are involved in pleasure that Steve alluded to in his talk on addiction.

I think our clinical experience tells us what happens with a severe loss. There is a normal response, which is called grief. If one loses a parent or a loved one, a loss like that excludes a diagnosis of depression unless the symptoms persevere.

The point is, after a severe loss, you can get problems with concentration, depressed mood, problems with appetite, anhedonia, et cetera--the complete syndrome. That responds normally. The question is: What is going on for those individuals who are presumably genetically predisposed--where they go from a response to this loss that doesn't remit and proceeds into a persistent episode of major depression?

In addition, I think what is of further interest is those individuals who do not suffer apparent losses but develop autonomous episodes of depression. There may be other factors that go on there. We are now seeing, for example, that changes in season, length of day, can affect the vulnerability to depressive episodes in what is known as Seasonal Affective Disorder.

Following up the question I asked you before, I think a major concern among patients, especially those who may have had more than one episode of depression, do you become addicted to antidepressants? Is that something to be concerned about?

DR. CASSEM: That's an excellent question; many people are afraid of that. Although I'm fond of oversimplification, as by now you can tell, I would have to say that by and large all antidepressant drugs fall into the class of broccoli; no junkie will give you much on the street for these agents. The take-home point of that is a very serious one.

Now, the person to come off the Prozac decreases the drug and they begin to feel bad again. It is not likely they are addicted to the Prozac. It is much more likely that the disease is coming back again and it has not been wiped out. So, that is a practical question of some consequence.

DR. COYLE: I think we need to take questions from the press.

MR. RAEBURN: Dr. Cassem, given the stigma that has historically been associated with mental illness, how can you be sure that your generation data that you showed isn't really an artifact of greater openness say, to acknowledge and to diagnose depression.

DR. CASSEM: Well, people actually had a chance to look at that carefully; there have been some exceedingly careful studies that are ongoing. You can compare--for instance Switzerland has now about forty years of diagnostic date--and can look at how much the carefulness of diagnosis is affecting that. That does not appear to be a major factor. You see these curves throughout the world. It's remarkable.

MR. RAEBURN: Do you have any idea why that would be taking place?

DR. CASSEM: A lot of speculation is there. No one knows, but the two leading culprits are, one, the breakdown of the family and the way in which the family holds the person's behavior and nurtures them through episodes. Number two is the widespread increased use of drugs. So that those two factors, among others, are thought to be the most likely suspects in that striking rate of change in depression.

MS. TOUFEXIS: I was curious about needing the five out of nine signs in order for a formal diagnosis. If someone has four out of the nine, does this mean they don't have a brain disease?

DR. CASSEM: There is actually a clinical judgment to be made there. It depends on how disabled you are in your function. How much distress? That would lower my threshold to start you on drugs, but of renewed interest over the past five years has been a minor form of this disease. What if you only have two? What if you have a disease known as dysthymia in which, for a minimum of two years, a couple of these symptoms have dogged your existence? At least a couple of the studies have shown that if you put those people on medication, it actually can be quite helpful. So, not only is the major form--the five out of nine and you feel you've got it--important; I think it is very important to take seriously the lesser forms as well.

MS. TOUFEXIS: Would you be inclined to take them seriously?

DR. CASSEM: I often would. Those are individual clinical decisions. My threshold is low to issue drugs to patients for this disorder because it's terrible; it is so disabling.

MR. RAEBURN: I've always been a little bit skeptical that 10 percent of people suffer from depression. I guess I am skeptical because it doesn't seem that way to me. I don't know if that means the people I socialize with may have it and I don't know it, or I've got some other disorder and can't tell what's going on around me. I wondered what you think about that and, also, is that 10 percent weighted with people who are in extreme poverty or other kinds of extreme situations where it is more common than it might be in some other groups?

DR. CASSEM: I said it includes the minor forms, too. So, when you look at the Epidemiologic Catchment data--which are the best data we have a careful randomized sampling of the population--for hard-wired depression it is around 4-1/2 (sometimes people say uppermost 6) percent for major. Then dysthymia, you might get 2-1/2 or 3 percent there, then assorted other, but more minor, conditions. So, to get to the 10 percent, I have to add in the minor forms as well.

DR. COYLE: The other thing to remember is that depression is an episodic disorder. What they are talking about is lifetime prevalence. An average episode of depression lasts nine months. So, someone in their lifetime may have seventy years doing just fine, but for nine months they have an episode of depression. That means they have been affected.

The importance of it, again, is that untreated, it not only is disabling but potentially fatal. I think you are right, most of your friends are not depressed--now. *

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