Are We Becoming A Nation of Depressives?

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By many estimates depression has become the scourge of Western Man. Already the fourth leading cause of disability in the workforce, it is projected to reach Number Two by the year 2020 (after respiratory infections). Psychiatrists have taken the position that this apparent increase in depression is just a mirage. We'll argue that this much depression has always been present in the population. The party line is that it is simply better diagnosis and the decreased stigma associated with our treatments that are responsible for the climbing numbers of depressed people. Some of us remain unconvinced.

Research indicates that in any given year over seventeen million Americans experience major depression. Fifteen percent of our population (twenty percent if you are an American woman) are diagnosed with depression at some point in their lifetimes. The treatment of depression has become an enormous industry in this country. Sales of antidepressant medications are at over 13 billion dollars per year and have tripled in the U.S. in just a decade. In many parts of the country people wait for several months or longer for a fifteen- minute appointment with their psychiatrist so that they can continue to receive their antidepressant pills. Family practitioners are dispensing even more of these medications than the psychiatrists. Yet the consistent message to the treaters of depression is that only a small portion of the people who are suffering from depression are receiving treatment for it. Countless others are suffering and it is our responsibility to bring treatment- almost always in the form of expensive new medications- to the untreated.

This view of depression raises questions in the minds of many observers. Why should this disorder be on the rise despite the treatment efforts of several generations of psychiatrists and the combined resources of multi-billion dollar pharmaceutical companies? Is there something new about depression itself or does this represent a problem inherent in modern western society? How did humans manage to get through life before Prozac was introduced? Fortunately, some preliminary answers to these questions are beginning to emerge. Startling discoveries from basic research in neuroscience have forced us to begin thinking about the problem of depression in new and different ways. Before looking at these new findings, however, a review of how we got to our present state of affairs may be worthwhile.

Part of the helping profession's difficulty in dealing with depression is that we have never really understood what would cause one person to be depressed while a neighbor in similar circumstances remains symptom free. A number of explanatory theories have had their day: anger turned inward results in depression; depression is a reaction to real or

imagined loss; depression represents the gap between our real view of ourselves and our unconscious, idealized version of how our lives should be; depression is a genetically inherited disorder; depression is a result of "chemical imbalances" in neurotransmitter systems that can only be understood by trained psychiatrists. Since each of these models undoubtedly have some truth in them, any new model of depression will have to explain why each of these diverse viewpoints has led to the relief of suffering in at least some individuals.

Clouding our view of depression even further is the fact that bona fide depression can arise from variety of "physical" causes. Pancreatic cancer, heart attacks, strokes, thyroid problems, side effects of a host of non-psychiatric medications, even changes in exercise routines have all been clearly linked to the onset of depression in some individuals.

Modern psychiatry has dealt with this uncertainty about the root cause of depression largely by ignoring it. The sequence of *Diagnostic and Statistical Manuals* released by the American Psychiatric Association have been, by design, heavy on description and devoid of explanatory theories. The most recent manual requires that at least five of nine key symptoms be present for at least two weeks for major depression to be diagnosed: depressed mood, decreased interest in activities, significant weight loss or gain, disturbed sleep patterns, being physically agitated or slowed down, fatigue, feelings of worthlessness or excessive guilt, decreased ability to concentrate or make decisions, and recurrent thoughts of death or suicide. The manual does make the provision that if these symptoms are "clearly due to a medical condition" the diagnosis of major depression is not given. Otherwise, if you've experienced five of these nine symptoms for at least two weeks you qualify as a depressed person.

The APA's treatment recommendations do acknowledge that some depressions of lesser severity may be treated successfully with *either* medication or psychotherapy but, in practice, if you receive a diagnosis of major depression in an American psychiatrist's office a prescription for an antidepressant medication is almost certain to follow. Today this translates into a prescription for Prozac or one of its chemical cousins (the serotonin specific reuptake inhibitors or "SSRI" medications like Paxil, Zoloft, Celexa,Lexapro, Luvox, and the like). This new generation of antidepressants has been so much safer and easier to use that it is now rare for psychiatrists to prescribe any of the older, "tricyclic" antidepressants that were the mainstay of treatment until the late 1980's. Millions of Americans take these new medications each day, usually showing some benefit from the treatment. Yet a number of problems make this very common equation of *five- of- nine depressive symptoms = treatment with a newer antidepressant* rather problematic.

First of all, there is no research to suggest that these newer - and dramatically more expensive- medications are more effective in reducing depressive symptoms than the older ones. In fact, just the opposite seems to be the case. In severe depressions the "tricyclics" prove to be a bit more effective than the new drugs. It is the decreased frequency of side effects that have fueled the upsurge in use of the new medications. But that very tolerability has led to their being prescribed for a host of new maladies: mild depression, phobias, obsessions, post- traumatic stress symptoms, anxiety disorders of

any kind, eating disorders, excessive shopping, hair pulling, skin picking, religious scrupulosity, sexual disorders, gambling, aggression, environmental sensitivities, and slow eating. It is difficult to imagine a single human problem that American psychiatrists have not reported as being successfully treated with SSRI's.

This wide-ranging effectiveness raises important questions about whether these drugs could possibly have a specific beneficial action in each of these disorders or whether some other overriding but unrecognized action is at work. The most plausible idea encountered so far is that these medications induce some sort of fundamental shift in the relationships between areas of the brain involved with thought and those involved with emotion. Perhaps SSRI's decrease the emotional response to mental events so that chronic worries, obsessions, sad thoughts, and the like do not result in emotional responses of the usual magnitude. This effect has been likened to turning the brightness knob on your television all the way up. Everything is brighter but there isn't much contrast. Days can feel pretty much the same regardless of their events. Some experience this as a welcome relief from mental anguish; others have described it as "soul robbing".

Compounding matters further is the fact that all sorts of therapies have proven beneficial in reducing depressive symptoms. Psychotherapy looks as good or better at relieving depression, especially at one year follow up, as antidepressant drugs. Exercise is a powerful and well recognized antidepressant. St. John's Wort and other herbal preparations are widely used as antidepressants in some parts of the world. Artificially lengthening the short days of winter with phototherapy lights has dramatic antidepressant effects for some individuals. Some have found that even exposing the back of the knees to such lights can treat depression. Depriving a person of an entire night's sleep is an old but effective antidepressant therapy. While this is just a partial list of effective alternatives to antidepressant medication, it is unlikely that you would hear mention of any of them in a psychiatrist's office these days.

In reality, the newer antidepressant drugs are such a mainstay of treatment for depression that alternatives are rarely considered. The fact that these drugs offer only a 20- 30 % improvement over treatment with placebos (sugar pills) isn't a common topic of discussion in the office. Nor are patients routinely told that even if they do respond well to antidepressants they might have a great deal of difficulty discontinuing them, even several years down the road.

In some patients stopping SSRI's may result in a variety of symptoms including depression, insomnia, nightmares, anxiety, headache, nausea and even neurological effects such as restlessness and tingling sensations. The Internet abounds with personal tales of people who have been on antidepressants for years and can't get off them no matter what they do. Some also find that they have to increase their dosage over time or add a second antidepressant to maintain the same degree of benefit - "Prozac poop out" as it is known in the trade. By diagnostic criteria used in the third *Diagnostic and Statistical Manual* this need for increasing doses (tolerance) and the emergence of significant adverse effects when the medication is stopped (withdrawal) were sufficient to qualify a compound as an addictive drug. Definitions change. We now speak of

"antidepressant discontinuation effects" rather than "withdrawal" and the suggestion that these drugs may be addictive is not particularly welcome in psychiatric circles.

So a brief and simplistic assessment of the modern psychiatrist's position on depression would be that we really don't know what causes depression. We don't know why it should be increasing in our population. We don't know why it responds to so many types of treatment. We don't know how our medications work but we're happy that they do.

It is very difficult to understand depression and its treatment without consideration of economic factors. Psychiatrists can make an excellent living doing nothing else but prescribing SSRI's to people who endorse having five or more depressive symptoms. If, like a great many prominent American psychiatrists of today, you also receive money directly from the pharmaceutical companies for speaking engagements, research, or "consultation" you can do a whole lot better than making a comfortable living. Imagine the effects if the medical-legal climate dictated that every depressed person had to be offered twice-weekly psychotherapy as an alternative to medication. The financial effects would be catastrophic for all of the major players in the depression industry. The interests of the psychiatric profession, the pharmaceutical companies, and Health Maintenance Organizations are so intertwined that it is hard to begin to get an objective view of the questions surrounding depression.

It should come as no surprise that the clearest current look at the issue of depression comes from the hard science researchers. In the late 1990's several striking findings began to emerge from their laboratories.

Perhaps the most unexpected and important finding was that the brain continues to make new brain cells in some key areas all the way through the life span. This ran contrary to the commonly accepted belief that the number of our brain cells was fixed by early adulthood and that a gradual decline in these cells was about the best that could be hoped for. We now know that stem cells- the cells capable of transforming themselves into any other kind of cell- operate in the nervous system. And it is looking like the activities of these multipotential cells may be involved in depressive illness.

Two main areas that continue to produce new neurons in the brain have emerged. The olfactory bulb (which is involved with our sense of smell) and the hippocampus. The hippocampus has been the focus of much of the latest depression research. It is a part of the limbic system, an ancient area of the brain that is involved in the generation of emotions in humans and other mammals. Specifically, the hippocampus appears to be primarily involved in the formation of memories. How memory actually works remains quite mysterious. The idea that we can recall specific events from our past as a result of instantaneous electrochemical communications between living nerve cells seems almost far- fetched if one really thinks about it. The idea that forming new nerve cells would be involved does make some intuitive sense. The evolving data suggesting that we add new brain cells in the hippocampus every day raises the intriguing possibility that nerve cells that we make today are somehow connected to the memories that we make *of* today. Perhaps the common experience of having odors trigger powerful, specific memories is

related to the fact that each of these brain areas has nerve cells and brain connections that were formed at the same time.

Scientists have also been surprised to discover a connection between the size of the hippocampus and depressive illness. One study suggests that the hippocampus may shrink by an average of 19% in depression. Other research has found that SSRI antidepressants and shock treatment, among other factors, restore the hippocampus to more normal volume. This increase in size of the hippocampus is now considered to be a possible mechanism by which these treatments promote recovery from depressive illness. This puzzling idea would have seemed beyond the realm of possibility even a decade ago. Modern psychiatry is in the very early stages of trying to make sense of these findings. How it will impact the treatment of depression in psychiatric practice is anybody's guess.

Psychiatrists have known for decades that there is a powerful connection between depression and memory. Anyone who has been around a lot of depressed people has become aware of an interesting phenomenon: memories change when one is depressed. Ask a person who is suffering from severe depression about their childhood and a depressing picture may emerge. They had no friends, they had no particular talents, their parents were mean, and nothing good ever happened to them. Ask the same question when they have recovered to a more normal mood and very different, more optimistic stories are recounted.

In some severe depressions a syndrome called *pseudodementia* is encountered. Basically, the memory functions become so impaired that it can be difficult to determine whether the person is actually suffering from Alzheimer's disease or some other dementing illness rather than major depression. A number of sophisticated neuropsychological tests have been developed to help make this determination. So the connection between depression and memory is a robust one. But psychiatry has not really considered the possibility that the memory problems could be anything but a simple result of the depressive process. The idea that *causation* could somehow be involved is new to us.

Depression involves a good deal more than sad feelings or even memory problems. When we are exposed to any incoming stimuli a predictable sequence of events occurs. The brain processes this raw sensory data through a primary and then a secondary association cortex. Once the information is in usable form it is sent directly down to the limbic system. The brain asks "What is out there? What is new? What have I seen like this before?" This involves comparing the new data with existing memories and stored symbols. Once evaluated, we then must decide what to do about it; the appropriate emotions, impulses, and responses are then generated. The most striking feature of many people who suffer from severe memory disorders is that they cannot activate themselves in response to the changes in their world. They may seem listless and incapable of motivation or they respond in ways that don't fit their surroundings.

As the link between depression and changes in the hippocampus has become clearer a search for factors that increase or decrease the growth of these critical cells has ensued.

Even more interesting than the emerging list of positive and negative growth factors has been the new picture of brain functioning that has developed within just a matter of a few years. This new model of the brain may ultimately shed some light on the age-old question of what depression really is.

For the past couple of decades psychiatrists have been very concerned with events occurring at the synapse - the area where two nerve cells meet and communicate via the release of neurotransmitters. Antidepressants have been presumed to work by affecting the messages transmitted across these synapses. The introduction of SSRIs is believed to inhibit the reabsorbtion of serotonin by the cell that released it, extending its time at the synapses and therefore communication with the receiving cells. Or so the theory goes. But why the increase in serotonin should have an antidepressant effect has remained a mystery. The fact that an antidepressant medication used in Europe (Tianeptine) has exactly the *opposite* effect at the synapse, i.e. *increases* serotonin reuptake, but works equally well, has called into question our assumptions about how SSRI's actually exert their effects.

The new neuroscience has shifted attention from synapses to genes. Messages carried across synapses by neurotransmitters represent just one type of communication that neurons receive. They also receive direct hormonal signals through circulating chemicals like steroids and sex hormones. Even gases such as nitrous oxide are used by neurons to communicate with each other. The ultimate effect of these communications is eventually mediated by turning individual genes on and off.

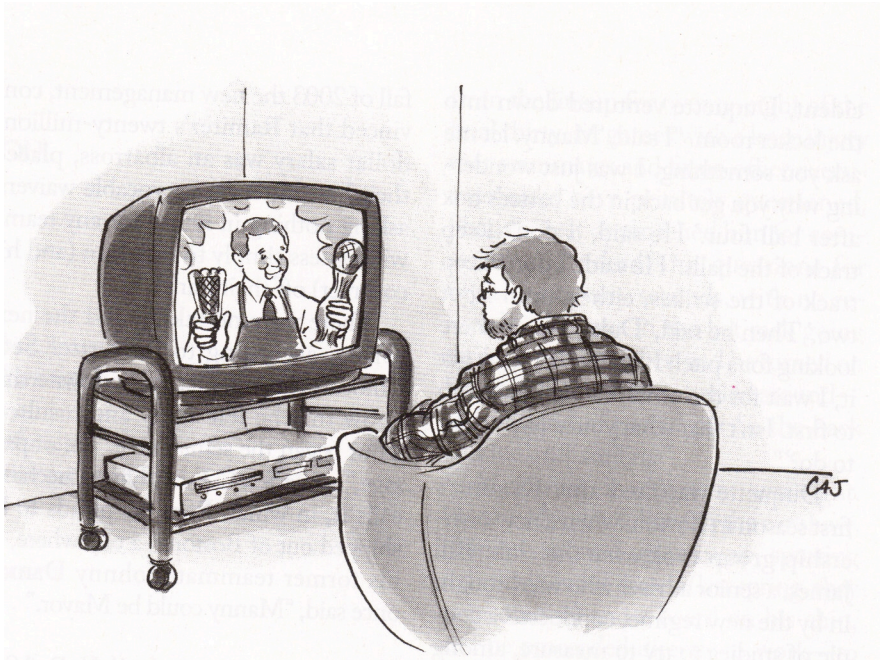
Several surprising findings have come out of the mapping of the human genome. The actual number of our genes- approximately 35,000- is startlingly low compared to earlier estimates, until one considers the possible variations in arrangement. And the search for factors responsible for influencing genes that are responsible for developing new neurons in the hippocampus- and for fending off depression- has turned up some candidates that psychiatrists may have intuitively expected.

Shock treatment, antidepressant medications, and physical exercise appear to have this effect. And an enriched, stimulating environment promotes new neuronal growth in these key areas involving memory. This might translate into having a decent, safe place to live, some meaningful work, and loving relationships with other humans but there is much room for individual variation.

Novelty- experience that is new or unexpected- is another logical factor that has been shown to positively affect the growth of hippocampal neurons. Why would we spend a lot of our resources supporting the areas of the brain involved with making new memories if we weren't having any new experiences to remember? An intriguing outgrowth of this research is the possibility that *sameness* might ultimately prove to be the worst stressor of all for the human brain.

Mundane jobs, boring routines, and the absence of real struggles for survival may all contribute to depression's increasing place in our society.

We cannot discount the possibility that the activities which seem to add diversity to our modern existence don't provide the sorts of stimulation that healthy brains thrive on. Perhaps the novelty of images dancing on electronic screens is enough to capture our attention but is insufficient to cause brain changes that depend on real life experiences.



"It's 4 A.M.—maybe you'd sleep better if you bought some crap!"

The role of sleep in the generation of new neurons is an interesting story in itself. Research has suggested that in rats a gene called zif-268 is involved in the ongoing reorganization of the memory portion of our nervous system. This gene becomes activated during Rapid Eye Movement sleep -the sleep in which we dream. Activation only takes place, however, if the rat has been exposed to sufficiently powerful stimulation (e.g. mazes, toys, exploration, etc.) during the waking hours before sleep. The implication may be that we sleep differently- and do different work reconstructing our brains- if our days are filled with new and interesting experiences. Disturbed sleep or a stimulus-poor life might result in a decrease in new neurons.

Circulating hormones are known to affect the hippocampus. Premenstrual mood changes, depression following pregnancy, and depression around menopause may all be mediated by changes in estrogen levels. One researcher suggests that the hippocampus "almost pulsates" in response to estrogens. Testosterone has been implicated in the migration and hook up of undifferentiated neurons throughout the brain. Sex hormones, and sexual activity, are likely to be recognized as major factors in the emerging model of depression. And the glucocorticoid hormones- released by the adrenal glands in response to stress-

may have the most far- reaching implications in terms of why we become depressed.

Scientists have determined that we humans share about 97 percent of our genes with chimpanzees- but that 3 percent difference is very important. Some of the difference is obvious in how our big human frontal lobes are constructed and wired. This enlargement of our frontal lobes is responsible for our ability to manipulate *symbols* to a far greater extent than all other mammals. We are unparalleled in our ability to construct a different reality in our minds, one that can be entirely separate from the objective external reality that all animals must interact with. The biggest problem with this talent is that we can also attach *emotions* to these private internal events.

When it comes to the sorts of emotions that we attach to our incessant thoughts, we are more similar to the chimpanzees than we care to admit. Our big symbol producing frontal lobes are basically hooked up to limbic -or emotional systems- that are not too evolved from other primates. As a result we are hard-wired to deal with the same issues and emotional responses as the other social primates. Who is superior in the troop to whom? Who will be an acceptable and willing mate? Take away these two basic issues: mating, and dominance to other humans in the social group and there would be nothing to put on television. We wouldn't know what to think about anymore. Some have suggested that there wouldn't be as much depression in humans either.

When we humans worry, what is it about? Our place in the hierarchy? What other humans thinks of us? How the boss will react if we don't land a deal or make our productivity goals? Are our neighbors superior to us because of their expensive possesions ? Do the latest objects of our sexual desires have any inclination to copulate with us? How do we compare today to what we were like when we were at our best? Each of these sorts of mental events can trigger the release of glucocorticoids- the molecular carriers of the stress reaction, which directly impact the genes. No interaction with a synapse is necessary; they result in the inhibition of factors that would lead to continued neural growth in the hippocampus and, perhaps, keep depression at bay. But to what end?

An interesting current theory of depression is that it develops as a way to limit our strivings for dominance in the social hierarchy. Humans aren't generally comfortable with the idea that they are built to compete for status within the social troop, just like the apes, chimps, people that drive slowly in the left lane, and other lower primates. One need look no further than the modern equivalent of the Rorschach test, the American freeway, to see these competitive strivings in action.

People buy expensive cars aimed at making themselves look successful and important- in fact to establish a particular identity. Cut in front of another human's automobile and rage reactions akin to a gorilla tearing up shrubbery may result. Drivers compete furiously to get to their destination before their competitors, even though the time saved driving like a Nascar driver may only amount to a minute or less compared to traveling at a more moderate speed. Is there really something important that will be done with the extra minute? Or is this about competition?

If we examine our emotional reactions to the person who is trying to get down the highway faster than us, we may have to admit that some deep-seated and irrational feelings seem to be at work. These same competitive feelings lie behind our culture's preoccupation with accumulating other visible trappings of success. The latest fashions, the biggest homes, the fanciest restaurants all give expression to our desire to set ourselves apart from humans of lesser status. The "silverback male" in our culture has become the man with the most zeroes on his net-worth statement.

Further proof of our strivings for status is our society's preoccupation with sexuality. Beautiful young people are used to sell all types of products. Entire industries are devoted to helping people convince themselves that they are sexually attractive to other people. The fact that actual copulation with the fantasized partners almost never results does not deter us from our preoccupation; our brains simply compel us to attach importance to our sexual status within our groupings.

While these competitive tendencies and sexual preoccupations have a great deal of significance for our species when we are in our reproductive years, they may ultimately be a burden as we get older. Continue to live life as though it were a contest and the brain will be constantly exposed to the stress hormones that result from that world view. If enough stress hormones circulate for a long enough period of time depression becomes increasingly likely.

If there is one thing that we can absolutely count on, it is that our current ideas about how human brains work will seem hopelessly primitive a hundred years from now. We will certainly know more about the causes of depression. Already we are finding out that some of the ways that we use to try to feel good for a while may cause us to be more depressed in the long run.

Drink too much alcohol and the hippocampus suffers. Depression can result. Opiates? More tablets of Percocet were dispensed than any prescription drug in America in 2000. There may be a lot of severe pain being treated these days, but one suspects that a little mood elevation is going on as well. Unlike SSRI's, which typically take two to eight weeks to relieve depression, opiate medications like Percocet provide the sort of immediate increase in good feelings that people really want from their antidepressant pills. Unfortunately, opiates have already been shown to decrease the birth of new neurons in the hippocampus. While providing good feelings today they may carry the cost of increased depression tomorrow. Research finding this to be true of cocaine and methamphetamines is probably just around the corner.

Of course we'll find out that the whole theory of the hippocampus in depression is too simplistic. Maybe it's not just the fact that the hippocampus isn't growing its new nerve cells in depression, it's where that energy goes instead. The amygdala is looking like the next candidate for the root cause of depression. A tiny almond shaped organ that encapsulates the hippocampus, the amygdala is involved with producing negative emotions like fear and hostility. It is also involved in "reward pathways". It's activity

appears to increase in depression (and addictions) just as the hippocampus declines. A good example may be the stereotype of the powerful businessman who becomes increasingly argumentative and suspicious after retirement. This might ultimately reflect a shift to using more amygdala as demands on the hippocampus are reduced.

We may never achieve our goal of truly understanding the brain - mind problem. Our idea that one specific area of the brain is involved in one particular action or emotion is hopelessly outdated. Everything seems to happen as a simultaneous network of activities in different brain areas, but our scientific approaches demand that we study one variable at a time. For now the best way to think about depression may be that it is analogous to a warning light glowing on the dashboard of our car: it tells us that there is something amiss under the hood but not what the problem is or what should be done about it.

Like a good mechanic, the modern psychiatrist's job is to figure out what is really wrong with the engine. We should wonder whether someone is depressed because of an unstimulating environment, a lack of satisfying relationships, boring routines, or insufficient physical exercise. The depression might reflect an excessive preoccupation with one's self-importance or could be the result of a toxic substance. In some instances a diet poor in the Omega III fatty acids found in fish oil could be causing depression. In others the symptoms may be signaling that it is time to reassess one's values and make some basic life changes. Our antidepressant medications are pretty good but it's a bit unreasonable to think that they would address *all* of these problems.

Any enlightened model of Major Depression will have to take these new research findings about nerve cell growth into account. It will have to contain sufficient power to explain why so many diverse treatments may be equally effective in reducing depressive symptoms. The fact that depression is usually self-limited and will eventually go away without treatment must also be considered. The amazing impact of beliefs and expectations that is seen in the placebo response must have a physical correlate but we still know little about the mechanism. The fact that the incidence of depression in our population is increasing suggests that depression is related to sociological variables that are also poorly understood. The new model cannot come soon enough.

As we become more sophisticated in our understanding of depression the psychiatric profession will be challenged to help our society grow in new directions. We may eventually be able to provide information about how to raise our children in a manner that makes them more resistant to depression. More stimulating environments, enhanced curiosity, better relationships with caregivers, and more exercise will undoubtedly help our kids to build brains that are less depression prone. The influence of circulating maternal hormones (reflecting the mother's emotional state) on the fetus' brain development is becoming another exciting area of research.

Learning more about the fuels and activities that keep brains healthy should trigger changes in how humans lead their lives. For depressed adults, future prescriptions might include travel, activities aimed at increasing exposure to novel experiences, and new challenges for the memory apparatus. Therapies aimed at improved relationships or at

decreasing our eternal preoccupation with striving for status may become as respected as medications - especially if neuroscience provides the means to document that they evoke similar changes in brain functioning.

For now, psychiatrists will continue to prescribe antidepressant medications with little regard for the factors that may have led to the depressive illness. In the future, however, our task will be to develop multidimensional treatments that are specifically tailored to the needs of the individual. Specialized environments may be developed to carry out the assessments and varied therapies that a more complex understanding of depression will require. Perhaps, ultimately, psychiatrists will be concerned with helping people to live more *memorable* lives.