# 3 The Brain Amine Theory of Depression

Bacterial pneumonia and TB used to be major killers until we discovered they were caused by the presence of bacteria which could be eradicated by antibiotics. But not all illnesses have a single cause of this sort and therefore cannot be so successfully controlled or eliminated. The current major causes of death are diseases such as cancer, heart disease, stroke and Alzheimer's, which simply do not have any single basis of origin. They are multidetermined, with genetic, environmental, dietary, lifestyle and psychological causes all coming into play. Depression is one of these potentially multifactorial illnesses.

Among the causes of depression we do know about, research has shown that imbalances in certain brain chemicals play a critical role. In fact, *regardless of the overt triggering factors, the underlying chemical mechanism of depression is almost always a shift in the brain chemistry.* This understanding makes depression a treatable illness, though it is best treated in a way that addresses all the contributing factors involved in its development.

## HISTORY OF DEPRESSION

Though this understanding of the chemistry of the problem is relatively recent, depression has been with us as long as recorded history. It has afflicted individuals of every rank in society, from King Saul and Alexander the Great to the humblest in their services. Through the ages this darkness of the mood has been variously viewed as caused by evil spirits, disobedience to God, moral failings, divine possession, black bile, anger and grief. Whatever the presumed causes, there were no answers and no predictable methods of cure. The depressed were misunderstood and stigmatized, treated with amulets, spells and bloodletting. The best, kindest treatment available consisted of suggestions to "feel better," entertainment with "amusing stories and diversion," and mild reprimanding of the sufferers' "groundless sorrow."

More recently, medical and psychiatric science have gone through numerous cycles in their attitudes toward depression. Ironically, in the nineteenth century depression was thought to be caused by imbalances in the body's chemistry and little attention was paid to the idea that psychological factors might be involved.

About the turn of the present century, Freud and Jung suggested that depression should be considered a psychological disease, caused by the activity of a demanding, exacting and punishing conscience. That attitude, for better or worse, dominated professional thought for much of this century and still exists in some circles.

The message? If you are depressed, be glad you live now rather than in the past. For only recently have we begun to unravel the provable, physiological causes of mood changes and thus to have predictable, physical treatment.

Such understanding began during the 1940's and 1950's when scientists who were researching a drug called reserpine for use as a tranquilizer and as a means to control high blood pressure noticed that it produced depression in some patients. Shortly thereafter, another group of scientists noted that some of the antihistamine drugs that are used in the treatment of allergies produced a lifting of depression in certain individuals. About the same time, an Australian doctor reported that lithium affected the mood of patients who took it.

Each of these discoveries implied that there is a strong relationship between our mood and our body's chemistry. Researchers began to watch more closely for any other hints that drugs could influence or change the moods of depressive patients or even create depression.

The point was this: if depression is purely psychological, as Jung and Freud suggested, then why are medications able to have such a marked effect on mood? The pendulum began to swing back: medical science again acknowledged the importance of chemical factors in the creation of depression. We now know that brain chemicals mediate virtually all feelings of love, hate, sadness, pleasure and anxiety in response to our experiences.

The present trend in medical science emphasizes the biochemical and genetic origins of depression. Psychological factors are now seen by many experts as catalysts that trigger a change in chemistry. Al-

most all psychiatrists now treat their patients both biochemically and psychologically. Research also makes it clear that in depressive illness, given the choice of treatment of only medication or only psychotherapy, medication alone far surpasses psychotherapy in effectiveness. However, I want to stress that both, together, work best.

There are now many different kinds of antidepressant drugs on the market and new ones with slightly different effects are discovered each year. One reason for this continuing search for new drugs is that not all antidepressants work equally well for all the people who suffer from depression. Indeed, this fact seems to support the theory that depression has many causes. Different types of depression respond to different kinds of medicine. Some antidepressants, such as Elavil, Ludiomil and Sinequan, act as sedatives for agitated, anxious and insomniac depressives. Others such as Aventyl, Parnate and Nardil work as stimulants for patients who are lethargic, immobilized and apathetic.

The very diversity of the disease makes it difficult to know ahead of time which medication will eliminate which depression. So far, physicians have simply used their best judgment in each case, drawing upon their own experience and the available medical literature to know what kind of depressed person usually responds well to which pill.

This trial and error approach puts us in something of a predicament, however, since most antidepressants have to be taken for two to six weeks before their full effects are experienced. You can imagine the additional suffering involved if the first or second drug chosen by the doctor proves not to be the best one. When these delays take place, the depressed person (who feels utterly hopeless and incurable in

any case) may lose what little willingness he may have had to seek treatment in the first place, sometimes with terrible results.

My friend Joan was visiting from Florida. She was terribly worried about a dear friend, a gifted artist, who recently had withdrawn from his friends, stopped doing all the things he enjoyed, and starting drinking heavily. I suggested she tell him to seek professional help.

In a later visit, she again mentioned her friend. He had gone to a psychiatrist who had placed him on antidepressant medication. When he did not respond, a different medicine was tried, and then another—all without response. Then they tried shock treatment, which apparently also did not work. Because he was becoming progressively more desperate, Joan told him about the nutritional treatment. Though he was interested, because of his inertia he kept postponing a visit to Los Angeles to investigate.

A few months later Joan phoned me to say her friend had died of an overdose of drugs. To add to the tragedy, a ticket to Los Angeles for the following week was found on his desk.

A great deal of research is being devoted to discovering specific ways to predict what patient will respond best to what medicine. As yet, no one single type of cure works for all depressions, but all depressed people can be cured of any single episode of depression, or of chronic depression, by the appropriate treatment. Some sufferers may respond well to the first medication they try. Even more respond positively to the multinutrient health-promoting approach described in this book—an approach that covers many bases and is virtually free from negative side effects.

## BRAIN AMINE THEORY

As it became more clear that depression was alleviated by the use of various medications, researchers began looking for the reasons why these responses took place. They began to measure all kinds of substances in the blood, the brain, the spinal fluid and the urine, to find out what chemical changes occurred during depression, and what changes came about as a result of treatment. They discovered that depressed people often have alterations of several chemicals in their blood, spinal fluid and urine. Such alterations are now called "chemical markers" for depression. In other research, abnormal sleep brain wave patterns have been shown to accompany depression. Many of these chemical and brain wave tests are still primarily performed at the research level, although a few are available for clinical use.

## NEUROTRANSMITTERS

While research into depression progressed, other neurological and psychiatric scientists were discovering a group of substances in the brain known as the neurotransmitters. So far, about forty of them have been identified, and it is here that most professionals feel the greatest promise lies for understanding and treating neuropsychiatric disorders.

Neurotransmitters are chemicals that are released at nerve endings in the brain where one nerve cell is close to another. They allow messages to pass from one cell to the next and are essential for communication between cells. The releasing cell that passes along an effect is called the presynaptic neuron and the cell that receives the message is called the postsynaptic neuron. Their connection is called a syn-

apse. After release, the neurotransmitter attaches to a location on the receiving cell called a receptor, that can link only with it and with no other neurotransmitter. It's much like calling someone on the telephone. You need two phones (two cells) and a signal connection between them, and each phone rings only on receiving the activation of its given number.

The function of the relayed message is dependent upon the location of the nerve cell and the particular neurotransmitter it releases. One neurotransmitter, for instance, helps to pass what are called excitatory impulses through the nervous system, while another transmits "inhibitory" impulses. This is a little like putting your foot on the accelerator or the brake pedal of your car. Some neurotransmitters stimulate positive or "rewarding" thoughts and behavior, while others produce negative or "punishing" responses.

The quantity of available neurotransmitters is important, but so also is the "sensitivity" of the receptor cells. An altered or impaired sensitivity is another marker of depression. Using the previous analogy, if you press your car brakes and such pressure is not received on the brake drum, your car will not stop.

When certain sites in the brain contain too much or too little of these chemicals, or when the receptors are not sensitive and connecting with the chemical, serious problems can result. Parkinson's disease, for example, is caused by an imbalance of the neurotransmitter dopamine in specific areas of the brain. It is a neurological disorder that usually comes on in older age and makes deliberate movements difficult. People with the illness walk with a slow shuffle, holding their arms stiffly at their sides with little free movement, and have mask-like faces devoid of spontaneous expression. They also usually have a tremor. Depression, forgetfulness and other "psychological" symptoms may go along with the disease. Happily, in

the case of Parkinson's the discovery of which neurotransmitter was deficient led to the development of a treatment which replaces the missing substance, providing dramatic relief. Because of such successes, researchers are always looking for neurotransmitters in order to determine how they might relate to neuropsychiatric disorders.

Probably the most popularly known neurotransmitter is endorphin, which is associated with the relief of pain and can also produce a euphoria-like state. We have all read about the apparent increase of endorphin in the brains of those who jog regularly and for a sufficient length of time. The endorphins are considered to be the cause of the "high" that runners commonly experience.

Endorphin reacts or binds to certain "receptor sites" in the brain (as do all neurotransmitters). Interestingly, it reacts with the same receptor sites as do potent external medication pain killers such as Demerol, morphine and heroin. One reason people may feel little or no pain under severe trauma, like the loss of a limb, is because the body releases a flood of endorphin to block temporarily what would otherwise be excruciating pain.

According to one theory the heroin or morphine addict may have a brain deficiency of the naturally occurring endorphins, which could then lead him to crave outside endorphin-like substances. This provocative concept needs further exploration.

In addition to the general maintenance of all brain activity, the neurotransmitters regulate your mood and control your sleep, appetite, aggression, memory, alertness and many other functions. Their deficiency also creates depression, and there is now no question that many depressed people contain below average amounts of certain neurotransmitters in the mood centers of their brains. Their nerve signals are not

relayed from one cell to the next at a fast enough rate to maintain a normal level of mood and behavior. Researchers have found that higher levels of neurotransmitters actually increased the amplitude of the message sent to the next cell. They have also learned that once depression is treated and cured, the neurotransmitters actually return to normal.

## SEROTONIN AND NOREPINEPHRINE

Serotonin and norepinephrine are the most significant neurotransmitters that are depleted in the brains of those who are depressed. Norepinephrine is present in excess in the brains of those experiencing mania, which is, in many ways, the opposite or obverse of depression.

When researchers began to investigate how the different antidepressants work, they discovered that these medications tend to bring about the same end result—increases of serotonin and norepinephrine in the brain. This in turn produces a marked improvement in the mood and outlook of previously depressed people.

Since norepinephrine and serotonin belong to a chemical group called the amines, the theory of depression that emerged from all this very persuasive research became known as the *brain amine (or monoamine) theory of depression.* Ninety percent of these amines are located in an area deep in the brain known as the limbic system. This system controls emotions, pain perception, sleep, and involuntary functions such as digestion, elimination and so on.

Because the amines are so important, the normally functioning brain has a mechanism for conserving them. This process is called *reuptake.* After the reaction takes place, the nerve cell takes back about 85

percent of the amines it has released and conserves them for later use. The other 15 percent is broken down by an enzyme called MAO (monoamine oxidase) and usually leaves the body in the urine. Thus, in the normal brain only 15 percent of the amine concentration regularly needs to be newly manufactured in order to keep the nerve cell communication mechanism going.

What can happen to foul this astonishing chemical process?

1. There may not be enough amines in the first place because of inadequate "raw materials" or precursors, chiefly amino acids, and their necessary cofactors, enzymes, vitamins and minerals.
2. There may be a genetically determined excessive need for the substances required to form the brain amines.
3. The reuptake mechanism may not be functioning properly.
4. There may be too much MAO so there is excessive destruction of the amines. This tendency toward excess MAO may be inherited. Also, as we age we have increased MAO, a factor leading to higher risk for depression in the elderly.
5. The receptor cells may not be properly sensitive or receptive to a normal level of the amines.

The common purpose of all biochemical treatments for depression is to increase the amount of these neurotransmitters at the synapse. Some drugs, such as the tricyclics, block the reuptake mechanism, allowing more amine to accumulate in the synapse. Others, such as the MAO inhibitors, block the MAO enzyme and slow the breakdown. Other drugs increase the sensitivity of the receptor cells, and still newer medicines act by mechanisms we've yet to understand.

The precursor nutrients (amino acids, enzymes, vitamins and minerals) appear to be the safest, most effective way of increasing the brain amine levels. They simultaneously increase both norepinephrine and serotonin, while the more traditional antidepressant drugs generally increase only one or the other of these brain amines and may not work if both amines are depleted.

To put things bluntly, the research and results indicate we are almost to the point where ignoring such chemical factors in a person with major depression might constitute negligence, if not malpractice.

## GENETIC CAUSES OF DEPRESSION

A 1981 report from Yale University begins with the words: "Inherited variations in the activity of enzymes involved in neurotransmitter metabolism are thought to affect individual differences in neurophysiology, behavior, and susceptibility to disease" (Pintar et al., J. Neuroscience). The tendency toward depression is one of those traits related to neurotransmitter metabolism that can definitely be inherited. This is one reason why family history may be important in determining diagnosis. Those depressions that begin before the age of thirty, and are severe or recurrent, are most likely to be strongly influenced genetically.

Though the exact mechanism by which depression is transferred from parent to child is not yet fully understood, we are already pretty certain that the trait can be transferred on many different genes. When only a few of these predisposing genes are inherited, they'll result in milder forms of depression; when many of the genes are inherited, severe depression can occur. This multiple gene action explains

why mood disorders do not follow as set, or predictable a pattern as do some other inherited traits.

Also, we are ultimately products of the interaction between our genetic influences and our environment. What goes on in our lives can exaggerate or diminish our genetic tendencies. If our genes predispose us toward fat accumulation, sadly, we must eat less and exercise more than the lucky ones with lean producing genes. If we have inherited a tendency toward insufficient neurotransmitters, a little stress and a little alcohol may plunge us into despair, whereas our friend can drink every day, lead a fast-paced, stressful life and feel okay—for a while anyway.

If you are depressed, there is a 20 to 25 percent chance that what is called a "first degree relative"—your parents, children or siblings—is also depressed. If you are not depressed, the chances of a first degree relative of yours being depressed is only 7 percent.

When one parent is depressed, the lifetime risk for the children to be affected is 17 percent. When both parents are depressed, the risk to their children of developing depression at any time in their life is 55 to 75 percent. You can see that genetic counseling can be extremely important for depressed parents.

Some professionals attempt to explain these familial patterns by arguing that we merely copy or imitate the depressed moods of family members. Yet, studies have been done on depressed persons who have had little or no contact with their families. The findings? The percentage of hereditability is basically the same, even when the patients have never known any of their biological relatives. For instance, when identical, same-egg twins are raised in entirely different environments, there is a 67 percent chance of both being depressed, if one is depressed.

There is also evidence to suggest that genetic fac-

tors may operate in vulnerability to suicide: the suicide rate in the relatives of depressed patients is more than ten times that of control groups. A striking example of this kind of genetic loading was presented very early in my career. In medical school, the psychiatry professor who taught us about depression candidly told us the horrible story of losing both parents in his childhood when they committed suicide together in their carbon monoxide-filled garage. Thereafter he spent his life trying to understand depression. In the end, perhaps he understood the agony too well, for a few years after I completed medical school I heard he had chosen to take his own life with an overdose of sleeping pills. Later I learned that his son, too, was suffering from depression.

## GENETIC ASSOCIATION WITH OTHER DISORDERS

Studies show a higher incidence of depression in families with alcoholism, drug abuse, eating disorders, anxiety disorder, agoraphobia and hyperactive children, leading us to believe that the genetic influences sometimes overlap in these conditions. Treatment for depression can often improve or eliminate these genetically associated conditions.

It's no surprise to find a connection between depression and eating disorders, because our appetite and mood control centers are in the same area of the brain and both are influenced by the same neurotransmitters.

As yet, orthodox psychiatry has not developed any treatment intervention that can work preventively to reduce such genetic risks. But those who are so disposed would be wise to be careful about diet, nutrient

supplementation and stress reduction programs as means of decreasing or negating these tendencies.

We can't control our genetic inheritance. So what do we do with all this tremendously valuable information? We use it. Positively. Optimistically. And for all it's worth.