CHAPTER 8

SCHIZOPHRENIA
A Mind Divided

I felt a Cleaving in my Mind—
As if my Brain had split—
I tried to match it—Seam by Seam—
But could not make them fit.
The thought behind, I strove to join
Unto the thought before—
But Sequence raveled out of Sound
Like Balls—upon a Floor.
—Emily Dickinson
"Poem 937"

Scott's mom and dad, Sue and Phil, were puzzled and frightened. Scott, a nice-looking kid despite his rather scraggly blond hair and baggy, ill-fitting clothing, was no longer taking care of his appearance. He showered infrequently and seemed to have stopped brushing his teeth. Even his younger sister, Laura, was beginning to say he was outside the normal range for cool teenage scruffiness. He was also spending lots of time alone in his room and seemed to have lost interest in hanging out with his friends. Was he on drugs? Was he depressed? What could be wrong?

If I tell them what is happening, they will probably think I am losing my mind and make me see a psychiatrist, Scott thought to himself. God, it's scary. Maybe I should *tell them.*

Everyone is making fun of me all the time. Mom and dad wouldn't believe it if I told them how bad it really is.

You can't imagine what it is like. My whole life has changed. It is like I woke up and found myself living in hell. Almost everyone around me is like a demon who is tormenting me. I get to school in the morning, and everyone is staring at me. A bunch of kids will be standing in the hall. I can tell that they are talking about me. I hear them saying my name, while they're standing around laughing and making jokes. I can just tell. Really, they say "See, Scott just walked in the door. He looks like he has been jerking off all night long. He's Scott the jerk-off jerk." Then they laugh like it's the funniest thing in the world. Those lines "Scott the jerk-off jerk" keep running through my head. I hear it all the time. It's like the kids at school are talking to me even when they are not around. Sometimes they say other nasty things too, like, "Scott, you are an asshole" or "Scott, just get lost."

Kevin and Clyde, my two best friends, haven't done anything to stick up for me. In fact, they have turned against me. It would be OK if they just decided not to be my friends and left me alone. But they want to torment me too . . . I don't know why. I never did anything to them. We used to have such a good time, getting together to fix up our car, listening to music, and stuff like that. Now they are sending electrical signals from the car battery. It shouldn't be that strong, from a 12–volt battery, but they can actually give me electrical shocks on my skin. I don't know how they transmit the current through the air, even through walls. But they do. Sometimes they even hit my nipples. I don't try to see them any more. If I told anyone that this was happening, they probably wouldn't believe it. It really burns and hurts. Sometimes I hear them talking to me too, saying the same kind of shitty things that the other kids at school are saying.

I have to keep this secret. Otherwise people may even lock me up. I may just have to run away somewhere to escape.

There isn't any point in studying any more. I can't keep anything straight in my head. It is really weird. I start to have a thought, and then things just don't connect right. It is like my brain is babelized. I try to do an assignment, and at first a million thoughts occur to me. Then they get all jumbled up and my mind goes blank. A terrible empty blank. Like standing on the edge of a cavern and being about to fall into it.

I'm so confused. I am so scared. *I can't describe this to anyone. I have to deal with this alone. I used to be one of the guys. But now I'm an outcast. Why is this happening? What did I do? I've completely lost control over who I am, what I do, what I think. God, I've got to do something to stop what is happening to me, but I don't even know what it is. Could it really be that I* am *losing my mind, like one of those people in* One Flew Over the Cuckoo's Nest? *If I am, then I should just kill myself. I don't want to keep living if it is going to be this bad the rest of my life.*

Sue and Phil just couldn't figure it out. Scott had been such a joy most of his life, and now he had become withdrawn and even a little hostile at times. No kids are perfect, but both Scott and Laura were fun and a great source of pride—good students, lots of interests, and many friends. What a change now. Scott was sullen, apathetic, and even dirty and smelly.

Scott, now seventeen, had been an adorable little boy. Sue was tiny,

only four foot eleven and under 100 pounds, and so Scott's birth was a little hard on her. The labor lasted almost 24 hours, and they nearly did a C-section. But finally they managed to deliver an 8 pound 1 ounce baby boy by using forceps. Scott's head looked like a banana during the first week or so, but its shape gradually became normal, and he was otherwise a very alert and bright-eyed little guy. Sue and Phil would look at him in his crib and wonder at the tiny miracle they had produced together. They had no worries that he might have problems—just the opposite, in fact. He sucked vigorously, cried loudly, held his head up strongly, and kicked his arms and legs actively. He did almost everything earlier than the little boy next door, who was born just a week later. He crawled at six months and toddled at nine. He seemed a little behind in speech, saying only a few words until around 18 months, but then he started talking to them in complete sentences. It was as if he had wanted to take it all in and do it right, rather than sounding like a baby.

Phil was thrilled to have a son, and he played all sorts of games with him. As Scott grew older, he became accomplished at both physical and intellectual games. He learned to swim when he was only two, to play checkers when he was three, and chess when he was five. He was the star pitcher and leading batter on every baseball team that he joined, right on through high school. He also picked up tennis fairly well and learned to play a solid game against his father and his friends. He was remarkably ambidextrous, which was an asset in both baseball and tennis. People could never be sure whether they would have to deal with a right-hander or a lefty.

Although Phil and Sue were pleased with Scott's athletic achievements, they most enjoyed his playful and loving nature. He was a little blue-eyed towhead who looked like Dennis the Menace, but behaved like Anthony Angel . . . most of the time anyway. When he was only one-and-a-half, they developed a tuck-in ritual that they kept up for many years. Sue would say, "love you," as she turned to leave the room, and Scott would call back, "no, love you first." Soon, "love you first" became a family expression that Phil, Sue, Scott, and (eventually) Laura all used, as a way of expressing how much they cared for one another.

Scott was their golden boy. They watched him grow from an adorable toddler to a rambunctious preschooler to an alternately grave or giggly grade-schooler. They watched his body move from chubby to muscular as he matured from childhood to adolescence. He was a handsome and appealing kid at each stage. They watched his mind expand and grow from wondering where butterflies go in winter to wondering how airplanes fly. He never got less than a B in any course in school and was always in the upper quarter of his class. They expected big things from him. He could become a lawyer, an engineer, a veterinarian, a pilot, a leader in business—anything he wanted.

It all started to fall apart the summer before his senior year at North High. He had just broken up with his girlfriend. She was his first serious girlfriend, and for the previous year they had seemed to be madly in love with one another. Phil and Sue never knew exactly what went wrong with the relationship, and Scott didn't seem to want to discuss it, even though he was usually pretty open with them. They wrote it off to "disappointed love" and "teenage growing pains" when he started to spend more time in his room alone—at first listening to music, but later just staring silently at the wall, sometimes for three or four hours. They were more surprised when he also stopped hanging out with his buddies Kevin and Clyde. Those three kids had been inseparable since junior high—riding bikes, playing catch, hanging out at the mall, ordering pizza late at night, and eternally dismantling and reassembling a 1982 Pontiac Firebird that resided in Clyde's garage. When they finally asked Scott about Kevin and Clyde, he gave them a funny look and said, "I told them that I didn't want to hang out with them any more. It's because they don't like me any more. They aren't really my friends after all." That seemed very strange to Phil and Sue.

Scott seemed to be having a personality change—going from a friendly outgoing kid who was a self-starter to a lethargic lump. He had a summer job as a checker at the supermarket. He had had to work his way up to the checker job by loading groceries in cars for the previous year, and he was pleased with the extra pay and responsibility. But he actually quit the job in mid-July and didn't even tell Phil and Sue about it for a week or two. The only explanation that he gave was that "the customers made fun of the way that I looked and talked." Now Scott did look a little funny to his graying parents, but lots of other kids had the same funny look, and Phil and Sue believed that the way a kid acts is more important than how he wears his hair or jeans. Scott, their athlete, was wearing his blond hair in long golden ringlets and donning baggy, torn trousers every day. They worried more when he stopped washing that golden hair and when it became greasy and even bad smelling. He seemed to have lost all interest in his appearance. He slept late in the morning, and spent his time aimlessly. In fact, he seemed to have withdrawn into a different world. When school started in the fall, he had difficulty getting up and was reluctant to attend classes.

At first Phil and Sue thought it was just adolescent moodiness. Then they wondered about drugs. Normally respectful of his privacy, they decided to check his room when he was away. No signs of drugs. Not much of anything that gave them any clues—a few car magazines, a few rock magazines, and a few copies of *Playboy*. They didn't know what to do or what to think. They decided to watch carefully and to give Scott his space and time, at least for a little while.

Then one night Scott disappeared. He left for the evening around 8 p.m., mumbling something about going out for a walk to "think things over." He had a kind of preoccupied and wild expression on his face. They didn't ask him where he was going, because they just assumed that he would walk for an hour or so and return home. He had done that many times before. When 10 p.m. arrived, they started to worry. By midnight they were frightened. Scott had always been good about telling them what he was doing, and it was unlike him to disappear like this. At 1 a.m. they decided to call the police for help. However, the police could do nothing—kids stayed out late all the time without telling their parents . . . law enforcement officers can't be surrogate parents. Then around 1:30 they got another call. Scott had been found. A driver had seen him on a bridge and then seen him jump over the side. His body was found on the railroad tracks below. He had been taken by ambulance to Mercy Hospital, still alive but probably seriously injured.

Saving Scott's life and setting his two shattered legs were the first priority. As he awakened from the anesthetic and began to talk to Phil, Sue, and Laura, the rest of story came out. They listened in horror as he explained that Kevin and Clyde were devil worshipers who had been transformed into demons, as had all the rest of the kids at school. They were mocking him all the time, telling him that he was worthless, calling him names, tormenting him by sending electrical shocks to his body. Sometimes he could even smell sulphur when he was around Kevin and Clyde. That night they had told him exactly how to "get lost." He should go to the Winston Street Bridge and jump off. He was just following their orders. He was powerless to resist the control they were exercising over him.

What had happened to Scott? This was the sort of thing that happened in movies, not to real people. It couldn't be true. Scott was a good kid, a normal kid, a promising kid. This was just delirium, due to the pain of the broken legs, the confusion caused by anesthesia. It couldn't be *mental* illness.

But Scott's account of inner torment turned out to be only too true.

The psychiatrist who cared for him during the six weeks that he lay in traction on the orthopedic ward gently explained Scott's illness to them. After the doctor confirmed from them that there was no history of drug abuse and no strong evidence for a mood disorder, he concluded that Scott must be suffering from schizophrenia. Scott had described an abundance of the painful inner experiences that plague people who develop schizophrenia—all the symptoms that doctors consider "psychotic," such as hearing voices when no one is around or feeling that others are tormenting them, controlling them, or sending them signals and messages through indirect methods. He also had the telltale signs of a change in personality, inability to think clearly, and social withdrawal.

Scott's "broken brain," the psychiatrist explained regretfully, would be tougher to heal than his broken legs. The broken brain of a person with schizophrenia cannot be put in traction and casts. Fortunately, medications can help a great deal, especially with psychotic symptoms. New ones had been developed recently that would be especially helpful. The doctor assured them that Scott's delusions and hallucinations would probably diminish markedly within a few weeks after medications were begun and that they might disappear altogether. Phil and Sue were very relieved. But . . . the doctor also explained that schizophrenia is a complex brain disease that affects many aspects of its victim's life and personality. It might be hard to get the "old Scott" back completely—the sunny cheerful kid who approached life like a tennis ball on its upward bounce. Schizophrenia could sometimes drain away emotions and drive, and medications were less successful in transfusing these mental traits back in again. But love, attention, and support from everyone in the family would certainly help.

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The next few years turned out to be rocky and rough for the whole family. As predicted, Scott's psychotic symptoms vanished for nearly six months. Scott was able to return to school, reluctantly, after Christmas. He had enough credits so that he could even graduate on schedule with his class. Kevin and Clyde were great, once they realized that Scott's strange behavior had been due to a mental illness. They stopped by the hospital often, and by the house after he returned home, and they tried hard to keep him on track in every possible way—getting him to class, taking him out on weekends, working on the car together. Scott tried hard too. But something had changed. He just wasn't very motivated. His

mind wandered. He didn't concentrate very well. He graduated, but everyone agreed that he should put off college for another year while he continued to get his life back together. Then the voices and the demons came back again right after graduation, even though he was still on medication. The dose was increased, but he began to be restless and fearful. The doctor decided that, since he had made a serious suicide attempt while psychotic, he should go into a psychiatric hospital for a few weeks until the psychosis diminished.

For the first time, Phil, Sue, and Laura saw a "schizophrenia treatment unit." There, in a group, were approximately thirty people ranging from teens to early thirties—all of them with symptoms similar to Scott's. It was chilling. Would this be Scott's future? Would he, now 18, become like that 28–year-old man, sitting in front of a TV, chain-smoking, and rocking back and forth? Their first reaction was to want to run away, to take Scott somewhere else, to refuse to hospitalize him at all. Scott had the same feeling. Although Scott had come to the hospital because he was pacing and restless and mentally tormented, he felt he couldn't really be like all these other people who were pacing and worried. The doctor explained that these were all people like him, people with families, people who were suffering. He suggested to Sue and Phil that they might, in fact, like to join an organization that was composed of patients with mental illnesses and their families, the National Alliance for the Mentally Ill (NAMI), which had a local chapter that met monthly. They might even be surprised at who they would meet there. They would find a lot of families not very different from their own, fighting the same battle against fear and grief. It turned out to be a great suggestion. NAMI was an invaluable resource for information, advice, consolation, and even hope during the ensuing years.

Scott was able to leave the hospital within ten days, with his psychotic symptoms much improved. But over the next two to three years he had occasional relapses and had to return to the hospital. Phil and Sue discovered that their insurance had placed a "cap" on treatment for mental illness—only 60 days were covered for an entire life! Hardly enough. A social worker assigned to Scott by the hospital explained that Medicaid would cover him if he applied for permanent disability. But that would be like admitting defeat. Scott was going to get better, not be disabled for life. However, as they watched Scott's college fund disappear and Laura's diminish, they finally capitulated. It took nearly a year to process all the paperwork. Still worse, if Scott were to recover enough to work more than half time, he would have to lose his Medicaid coverage. What a disincentive! There ought to be a way to provide good medical care for people

with schizophrenia without penalizing them for trying to return to a productive life.

After five years or so, fortunately, the relapses stopped occurring. Scott stabilized and even improved. Eventually he was able to get a half-time job and to take an occasional class at the local community college. He was a clerk at a local garden center, and he actually enjoyed the contact with customers. The family learned to live with his illness, which remained below the surface, still robbing him of drive and energy and impairing his ability to read other people exactly right. He was still a little suspicious and untrusting. The golden boy never returned to his old sunny self. But he was still their Scott, still sweet, lovable, and loving in his own way. Phil and Sue, who had been haunted by worries about how Scott would survive if anything would happen to them, felt their fears eased a bit.

* * *

Schizophrenia is probably the cruelest and most devastating of the various mental illnesses. An estimated 1% of the population has schizophrenia, which claims its victims at a youthful age and prevents their full participation in society. Schizophrenia also creates an enormous economic burden, costing society billions of dollars annually.

Primarily a disease of young people, it typically strikes during the late teens and early twenties. It is a disease that has many different faces. Some sufferers, like Scott, appear to be perfectly "normal" kids before becoming ill, catching family and friends by surprise as they begin to experience symptoms. Some have subtle indicators that can be identified retrospectively, especially in comparison with brothers and sisters who do not become ill. As children, they may have been less well coordinated, shyer, more anxious, or slower learners. Scott had none of these indicators, although he did have two others that research studies suggest are "predisposing factors." First, his mother had a prolonged labor, and his delivery was difficult. Second, perhaps as a consequence of a subtle head injury incurred at the time of birth, he was ambidextrous—neither strongly right nor left-handed.

Such "early signs" can be misleading when they are a product of hindsight. It is easy to look back and see a higher rate of "clues" after a son or daughter has already become ill. During the past decade, however, clever scientists have looked for such early indicators using what is called a "prospective design." That is, they obtain information that was somehow recorded about the child *before* the illness of schizophrenia had become manifest.

One approach, applied by Elaine Walker and Rich Lewine at Emory University, was to obtain home movies from families who belonged to NAMI and who had at least one child suffering from schizophrenia. All the children in the movie were rated by trained professionals using standardized methods to assess how well they were coordinated or how well they interacted with brothers, sisters, and other children. The raters did not know which of the children would later become mentally ill. Analyzing these "blind ratings," Walker and Lewine found that the children who eventually developed schizophrenia tended to be more awkward both physically and socially.

Another approach, used by Robin Murray and his team in England, was to examine the records from a national health study conducted in England shortly after the Second World War. All the children born during a single week in 1947 were identified and had all aspects of their health measured at regular intervals. This forward-looking and innovative national study has told us a great deal about many illnesses, including schizophrenia. As of the last few years, 37 of these children have developed schizophrenia. Murray and his group were able to look back at health and school records and determine how those who eventually became ill differed as children from those who did not. They have found some interesting things that are what psychiatrists call premorbid indicators—small signs that may be early markers of a predisposition to become ill and that are present before the full illness emerges. Among them is an increased rate of mixed-handedness, or ambidextrousness. Yet another prospective study, conducted by Michael Davidson in Israel, used health records collected by the military. Israel has a policy of universal military service for both men and women, so Davidson was able to examine later development of schizophrenia in a representative group of young people tested during their late teens prior to onset of illness. Problems in relating socially with others were found to exist in those who later became ill. These prospective studies are among the strong evidence that has been accumulating to suggest that schizophrenia is due to an abnormality in brain/mind development that may begin well before the person develops obvious symptoms.

What Is Schizophrenia?

Unfortunately, "schizo" has become a slang term, often used in a derogatory way. Schizophrenia was given its name by a Swiss psychiatrist, Eugen Bleuler, early in the twentieth century. Bleuler wanted to choose a name that would describe the most important features of this illness, which had

previously been called dementia praecox by Emil Kraepelin, the German psychiatrist who originally identified it as a discrete mental illness. Kraepelin named the illness dementia praecox because that name means "an illness that affects the ability to think clearly and is persistent and chronic" (dementia) and "an illness that occurs primarily in young people" (praecox).

His colleague in Switzerland, Eugen Bleuler, initially took exception to some aspects of Kraepelin's definition. Like Kraepelin, Bleuler worked in a large psychiatric hospital, the Burgholzli, and saw many patients over long periods of time. Bleuler believed that some patients showed substantial improvement after their initial onset of illness. Therefore, the use of the term "dementia" was misleading, since it suggested that the patients would steadily worsen over time, as typically happens in neurodegenerative disorders. Further, he noted that some patients developed their illness at a later age—in their twenties, thirties, or (rarely) forties. Therefore he suggested that the name "dementia praecox" be replaced with one that was more descriptively accurate. He proposed the name "schizophrenia." This name literally means "splitting" or "fragmenting" of the mind and is derived from classical Greek (schizo = split, fragmented; phren = mind). Bleuler chose this name because he believed that the essential feature of schizophrenia was an inability to think clearly and to link together "associative threads" during the process of thought and speech. His new name gradually replaced Kraepelin's "dementia praecox."

Schizophrenia is an illness that can be difficult to explain or define because patients have so many different kinds of symptoms. Perhaps the most striking thing about schizophrenia is its sweepingly broad injury to a large array of cognitive and emotional systems in the human brain. The signs and symptoms of schizophrenia are diverse; they include disorders of perception (i.e., hallucinations), inferential thinking (delusions), goal-directed behavior (avolition), and emotional expression (affective blunting), to mention only a few. No single one of its many signs and symptoms can be considered to be pathognomonic or defining. Each is present in some patients, but none is present in all. In this respect, schizophrenia differs from most other mental illnesses, which typically affect a single mind/brain system, such as Alzheimer's disease (memory) or manic-depressive illness (mood).

Because the signs and symptoms of schizophrenia are so complex and diverse, an effort has been made to simplify thinking about the illness by subdividing them into natural categories. The most widely accepted subdivision is into "positive" and "negative" symptoms. This terminology is a

bit confusing because there is nothing that is positive or good about the positive symptoms—they are unpleasant experiences such as hallucinations. This terminology derives from a nineteenth-century British neurologist, John Hughlings-Jackson. As often happens in science and medicine, Jackson's theories were shaped by new ideas from an unrelated field—in this case, Darwin's theory of evolution. He thought of the human brain as like an onion. It contained more primitive levels at its inner core, with "higher" governing levels encasing and enclosing this inner core. The "higher" levels were added on during the process of evolution. He thought the positive symptoms of psychosis were a "release phenomenon." Thoughts from a lower level of evolution would break through out of the inner core because some higher governing brain region had lost control, and so the person would have hallucinations or delusions. Negative symptoms, on the other hand, were due to a simple loss of function, presumably due to neuronal loss. They were expressed by apathy or disinterest.

My research program has been studying the symptoms of schizophrenia and the best ways to define it for more than twenty years. One of our more useful contributions was the reintroduction of Jackson's ideas in a modern form. We dropped the Darwinian baggage, which was unproved, and redefined positive and negative symptoms in a simple descriptive way. We also emphasized the importance of negative symptoms and their underlying relationship with cognitive and emotional impairments.

This modern reconceptualization defines positive symptoms as an exaggeration of normal functions (the presence of something that should be absent), and negative symptoms as a loss of normal functions (the absence of something that should be present). We classified the array of signs and symptoms as positive or negative according to the kinds of mental functions involved, revealing that the two groups together include nearly all the mental functions that human beings possess. A summary of the symptoms and their corresponding mental functions appears in Table 8–1.

Positive symptoms are typically those that call attention to the illness. People usually are recognized as being mentally ill because their positive symptoms are clear indicators that they suffer from a serious problem that impairs their sense of reality. Scott's positive symptoms are what led to his suicide attempt, for example, and they shocked and frightened his parents when Scott initially described them.

Negative symptoms are often the first signs of the illness to appear. For example, Scott became withdrawn and lost interest in things that he previously enjoyed. Positive symptoms tend to respond to treatment more rapidly and readily than negative symptoms. Even when positive symptoms have been reduced, however, it is usually clear that the person is still "not well." The negative symptoms often persist and lead to impairment in many important aspects of life—the ability to work, to return to school, to have close friends, to enjoy hobbies and sports, to have a girlfriend or boyfriend, or to feel close to family members. The negative symptoms can sometimes be mistaken for laziness or bad manners, but they in fact reflect a loss of the ability to start things and follow through on them and a loss of the capacity to experience joy and pleasure in the normal activities of daily living. People with schizophrenia often notice this loss of pleasure and drive, and they find it as troubling as the positive symptoms. In some ways, negative symptoms are even worse because they seem to rob patients of their personality and identity.

TABLE 8–1
The Symptoms of Schizophrenia

SYMPTOMS	MENTAL FUNCTIONS
Positive	
Hallucinations	Perception
Delusions	Inferential thinking
Disorganized speech	Organization of language and ideas
Disorganized behavior	Monitoring and planning of behavior
Inappropriate emotions	Emotional appraisal and response
Negative	
Alogia	Fluency of language and thoughts
Affective blunting	Expression of emotions and feelings
Anhedonia	Ability to experience pleasure
Avolition	Ability to start things and follow through
Attentional impairment	Ability to focus attention

What Causes Schizophrenia?

When a young person develops a mental illness, the knee-jerk response is often: "what did the parents do wrong?" Schizophrenia is not a disease that parents cause. Nor is it a disease that parents can prevent or arrest, much to the despair of people like Phil and Sue. Despite parental love and care, the disease strikes, injures, and leaves its suffering victims and their families in pained submission. Schizophrenia is a brain/mind disease. In

most cases several causes have conspired to injure the developing brain and mind, but bad parenting is not one of them.

Genetic Influences

Studies showing that genetic factors may contribute to the development of schizophrenia provided the earliest evidence that schizophrenia has a biological basis. As described in chapter 5, our methods for studying genes and their contribution to disease has grown steadily more sophisticated. The earliest genetic work on schizophrenia was based on the simple observation that mental illnesses sometimes run in families—an observation that suggests a role for genes but does not prove this, since familial aggregation could be due to learned behavior and role modeling. In the case of schizophrenia, the actual pattern of familial transmission does suggest a role for genes. If one parent has schizophrenia, there is about a 10% chance that one of the children will develop schizophrenia. If both parents have schizophrenia, then this risk increases substantially to about 40 or 50%. Likewise, chances for developing schizophrenia if one brother or sister has the illness are about 10%, and these increase to about 20% if one parent and one brother or sister is ill with schizophrenia. So there is a modest risk if one family member has the illness, and the risk increases substantially if two or more family members are ill.

During the past fifty years, more sophisticated methods have been used to translate these observations into a more precise study of genetic influences. Comparing the rates of illness in identical and nonidentical twins provides a more direct test of the influences of genes. The higher the concordance rates in identical twins as compared to nonidentical twins, the greater the probability that an illness is genetic, since identical twins share almost exactly the same genes, while nonidentical twins share approximately 50%. The term "concordance rate" refers to both twins having the same illness. More than ten twin studies of schizophrenia have now been done, involving hundreds of twin pairs. They have consistently demonstrated higher concordance rates in identical (monozygotic) twins than in nonidentical (dizygotic) twins—around 40% as compared to 10%. The 10% rate seen in nonidentical twins is similar to that for brothers and sisters. The summary of this comparison is sometimes referred to as the monozygotic:dizygotic ratio, or MZ:DZ ratio, which is a rough index of the degree to which an illness is under genetic influence. For schizophrenia the MZ:DZ ratio is approximately 4:1—clear evidence that genes must play a role.

Doubters who wish to argue that schizophrenia is due to bad parenting or a poor family environment might still point out, however, that twins grow up in the same home, and that identical twins tend to be encouraged to behave in similar ways. Therefore, two gifted scientists, Seymour Kety and Leonard Heston, independently pioneered a new and more powerful approach to isolating the role of genes in schizophrenia. They separated the role of family environment and the role of genes by studying adopted children who grew up without knowing anything about their birth (biological) parents. Both groups of adoptees were reared in families that were considered to be "normal" or "healthy." Kety and Heston compared the rates of schizophrenia in adopted children who had a birth mother with schizophrenia to adopted children who had a birth mother with no evidence of mental illness. Both studies found essentially the same thing. The rate of schizophrenia in adopted children reared apart from their birth mothers was about the same as for children who had a schizophrenic parent and grew up in the same home. It was around 10%. On the other hand, the rate in the children of healthy birth mothers was similar to the population rate, or about one percent.

Although these studies of the rates of schizophrenia in families, twins, and adopted children are often cited as proof that schizophrenia is "a genetic disease," close inspection of this evidence indicates that the story is not really that simple. If identical twins have almost identical genes, and if schizophrenia is a disease caused solely by genetic influences, then the concordance rate in identical twins should come close to 100%. The actual rate of around 40% is nowhere near that high. The various genetic and family studies suggest that genes must indeed play a role, but genes alone do not cause schizophrenia. Other factors, described later, probably need to be added to a genetic predisposition for schizophrenia to develop. This is good news, since it is more difficult to make changes in genes than it is in other predisposing factors in order to achieve the long-term goal of preventing schizophrenia in predisposed children.

As described in chapter 5, scientists are working strenuously to apply the tools of molecular genetics and molecular biology to identifying the genes that may be involved in the development of schizophrenia and other major mental illnesses. The early success in finding a single gene that caused Huntington's disease raised the hope that single genes might be found for illnesses like schizophrenia, but this has not turned out to be the case. Most experts now think that schizophrenia is clearly multifactorial, involving multiple genes, and possibly even different genes in different individuals, as well as many nongenetic or environmental influences. The fact that multiple genes are probably involved is the main reason

why the various reports that "the schizophrenia gene has been found on chromosome 5" (or 11 or 22 or elsewhere) have not been consistently repeated. Any single gene can probably only explain a small fraction of the causation of schizophrenia. Although this makes the search for the genetic influences more difficult on a scientific level, it is again good news on the human level. If multiple genes are required and have to co-occur, the chances of developing schizophrenia are reduced, and genetically predisposed children cannot be considered to be "doomed from the womb."

Since an emphasis on genetic influences can lead to undue pessimism, especially in families where at least one member has schizophrenia, another potentially optimistic note should be struck. That is about the relationship between creativity or originality and schizophrenia. The relationship between mood disorders and creativity has been frequently publicized during the past twenty years. When I initiated the objective scientific study of creativity and mental illness some thirty years ago, I expected to find a relationship to schizophrenia. My early studies, begun in the early 1970s, were inspired by anecdotal observations of familial relationships between genius and schizophrenia. James Joyce, one of my favorite writers, had a daughter, Lucia, who suffered from life-long schizophrenia, was treated by Jung, and died in a mental hospital in England. Bertrand Russell, a cultural icon of the twentieth century, had an uncle, a son, and a granddaughter who suffered from schizophrenia. Albert Einstein also had a son with schizophrenia. Further, Leonard Heston (at that time one of my colleagues at Iowa) had observed that a substantial number of the adopted children of schizophrenic mothers pursued creative interests or hobbies, suggesting that there might be a genetic association between schizophrenia and tendencies to be creative or think in original ways.

These observations are coupled with another interesting fact. Although people with schizophrenia often do not marry and do not themselves have children, the disease appears to have persisted down through the centuries and at an equal rate throughout the world. What could explain this? The answer might be that "schizophrenia genes" may also confer some evolutionary benefit that leads them to persist. Having them may transmit some abilities that are useful to human beings, either on an individual or a group basis. Physicians are familiar with other models of this for nonmental illness. Sickle-cell anemia, for example, persists in Africa because it protects against the development of malaria.

Recent films and other events have brought the relationship between genius and schizophrenia back to the forefront. The film *Shine*, although

unfortunately implying that the young artist's illness might have been caused by an overpunitive and aloof father, portrayed the artistic triumph of a musical genius who had a schizophrenia-like illness. In 1994 many of us who have worked with people suffering from schizophrenia rejoiced to learn that the gifted economist John Forbes Nash had won the Nobel prize for his work on game theory. Not only had Nash made major contributions to this and many other branches of mathematics, but he also had been seriously ill with schizophrenia during his thirties and forties, eventually improving markedly and functioning again at a very high level, supported by his loving wife, Alicia. An interesting anecdote in the prologue to a recent biography of Nash highlights the possible relationship between genius and schizophrenia. Hospitalized in a psychiatric facility in 1959, Nash was asked by one of his friends how he, such a rational and logical man, could believe that he was getting messages from aliens in outer space. Nash looked at his friend and replied, "The ideas I had about supernatural beings came to me the same way that my mathematical ideas did. So I took them seriously."

People with schizophrenia indeed perceive the world in unusual and original ways. The ability to do this may lead to erroneous insights that we consider psychotic. On the other hand, this ability may also lead to highly original ideas or observations that turn out to be true. Einstein, the father of a son with schizophrenia and himself a highly eccentric man, is an obvious example. Isaac Newton, who identified the laws of mechanics that laid the foundation for the industrial revolution, was also a solitary and eccentric man who experienced a psychotic episode in his forties. Perhaps giftedness in mathematical, scientific, and abstract creativity is particularly related to schizophrenia. In any case, people who seem to have carried "the schizophrenic tendency" provided the two major scientific contributions of modern physics. We owe the laws of gravity and mechanics and the theory of relativity to the two original and beautiful minds of Newton and Einstein.

Neurodevelopmental Factors: Are People with Schizophrenia Doomed from the Womb?

How do the various genetic and nongenetic influences actually add up and eventually cause a person to develop schizophrenia? Most clinical neuroscientists now suspect that schizophrenia is a "neurodevelopmental disorder." Something—and probably several different things—has gone wrong in the orderly process of brain development that begins at the time of conception and continues on into young adult life.

Many other neurodevelopmental disorders are well recognized in pediatrics and general medicine. Some of these are due to brain abnormalities that begin during pregnancy, causing their victims to be "doomed from the womb." Down's syndrome, or trisomy 21, is a genetically caused disease that is due to an abnormality in chromosome 21. The genetic mutation leads to a classic syndrome of mild to moderate mental retardation, typical physical traits such as "mongoloid" or oriental-appearing facial features, a sweet and loving personality, and a tendency to show intellectual decline in the thirties and forties. Trisomy 21 occurs with increasing frequency in the children of older mothers, presumably because the genes in the mother's ova become less efficient during cell division with increasing age. (Women have a lifetime supply of eggs in their ovaries; this supply does not increase or get replenished over time.) Older mothers now often obtain genetic testing early in pregnancy to determine whether their developing baby has this genetic abnormality.

At the other end of the continuum is a neurodevelopmental disorder that is completely nongenetic, fetal alcohol syndrome (FAS). FAS occurs when children developing in the uterus are exposed to massive amounts of alcohol because the mother drinks too much during pregnancy. Children with FAS have a low birth weight, small heads, small brains, learning disabilities or mild mental retardation, and behavioral hyperactivity. They have characteristic facial features such as wide-set eyes, flattened noses, or a lack of the characteristic dent in the upper lip. Our work at Iowa studying children with FAS, led by Victor Swayze, indicates that they also have marked and easily visualized abnormalities in their brains that reflect failure of the normal formation of connections in brain regions that occur across the midline (e.g., agenesis of the corpus callosum; see chapters 4 and 6 for more details). Scientists have not yet determined exactly how or when alcohol causes this damage to brain development. Alcohol consumed by a pregnant mother does pass directly to her developing baby and enters into brain tissue, since alcohol is soluble in fats and brain tissue is very rich in fat. Most evidence seems to suggest, however, that an occasional glass of wine is not likely to do much damage, and that the mischief is caused primarily by intermittent binges when very large amounts of alcohol are consumed.

Both of these neurodevelopmental disorders begin before birth. Trisomy 21 lays out the wrong genetic program for brain development, while FAS introduces a toxic substance that interferes with the orderly progression of the genetic plan for connecting brain regions. In either case the damage is done irreversibly before the child is even born, and the diagnosis is usually obvious in the delivery room or during the first few days of life.

Schizophrenia, however, is a different type of neurodevelopmental disorder, and it is unlikely the people with schizophrenia are doomed from the womb due to either genetic or nongenetic factors. Most people who have it were either completely normal or relatively normal at the time of birth. They do not show their first signs of illness until much later. Some people who eventually develop schizophrenia have mild premorbid indicators, but many are as normal as Scott was before he became ill. As described in chapter 4, we know that brain development is an ongoing process that does not end until sometime in the mid-twenties. Unlike Trisomy 21 or FAS, the factors that negatively affect brain development in schizophrenia, probably occur at multiple times. Any one factor could cause the illness if severe enough, but probably in most cases they need to add up. The most critical abnormality must be one that occurs during the late stages of brain development, when the brain does its final "growing up" during the late teens and early twenties. This is a critical time for young people, since they must learn to fly out of the parental nest and live on their own, choose an occupation, and find friends and partners with whom they can share their lives and perhaps ultimately marry.

The scientific evidence suggesting that schizophrenia is a neurodevelopmental disorder affecting multiple stages of brain development is substantial and steadily increasing. This evidence indicates that many different kinds of influences may be involved, and that they may be both genetic and environmental. Genetic factors were just reviewed. Scientists have also documented the importance of several environmental factors. For example, people with schizophrenia are more likely to have been born in the wintertime, a season during which mother and child are more often exposed to a variety of viral illnesses. Higher rates of schizophrenia have been observed among people who have been born during influenza epidemics, also suggesting that viruses may be a factor. Viruses, of which poliovirus or the human immunodeficiency virus (HIV) are notorious examples, are famous for their ability to damage tissue in the nervous system and also for their ability to invade the cells and produce changes in the genetic material. Studies of regions in Europe exposed to severe famine during the Second World War have also shown that malnutrition during pregnancy can contribute to the development of schizophrenia. Like Scott, people who develop schizophrenia are more likely than average to have a history of birth injury or perinatal complications. These may cause a hidden brain injury that sets the stage for the later development of schizophrenia.

Perhaps the strongest evidence supporting neurodevelopmental abnormalities comes from neuroimaging studies. Our research group, as well as

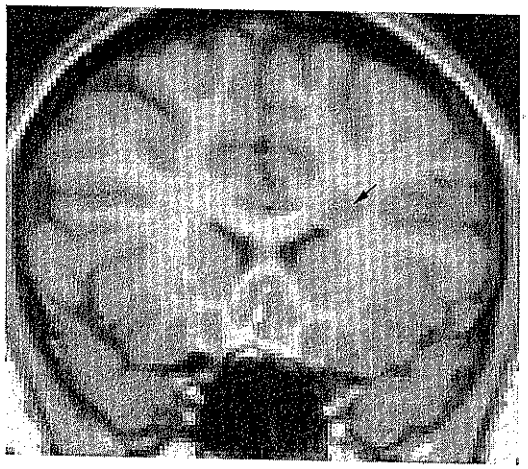

Figure 8–1: MR Scan Showing Ectopic Gray Matter in a Person with Schizophrenia

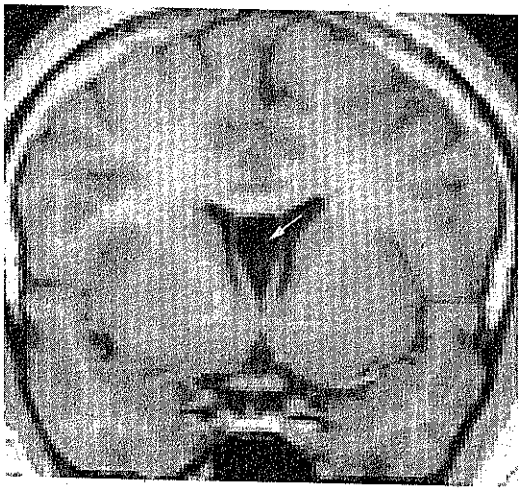

Figure 8–2: MR Scan Showing Enlargement of the Cavum Septi Pellucidi in a Person with Schizophrenia

several others, has been especially interested in using MR to examine the brains of patients with schizophrenia for telltale signs that something went wrong during the process of brain growth. One such abnormality is "ectopic gray matter," or tiny islands of neuronal cells that did not make it to their proper destination when they began the arduous task of neuronal migration to the cortex during the second trimester of pregnancy (see chapter 4). Although this clue is not seen very often, ectopic gray matter is nevertheless more common in people with schizophrenia than in healthy normal individuals. Figure 8–1 shows the brain from a person with schizophrenia who has ectopic gray matter (found in about 5% of males with schizophrenia). Another more common neurodevelopmental abnormality is found in about 20% of males with schizophrenia. Most of us are born with a small gap between the two hemispheres of our brain, known as the cavum septi pellucidi. As our brains mature during early childhood, this gap closes. However, it has failed to close in approximately 20% of men who have schizophrenia, suggesting that something went wrong in brain growth during early childhood or later. The brain of a person with schizophrenia, showing this abnormality, appears in Figure 8–2.

Imaging studies of large numbers of people with schizophrenia studied shortly after onset of symptoms also suggest that some abnormality in brain development has occurred prior to onset. Clinical scientists refer to these as "first-episode studies." MR is used to visualize the living brain in

young people who typically are in their late teens or early twenties and who have become ill only recently. Such studies can be very informative, since they let us examine possible causes early in the game, before treatments with medication or the effects of chronic illness may have caused changes. Five or six studies of first-episode patients have now been done by centers throughout the world, ranging from Australia and the Orient to England and Europe to the United States and Canada.

Quite consistently, these studies have shown that first-episode patients have the same types of brain abnormalities that are seen in people who have been more chronically ill. These include enlargement of the ventricles, enlargement of the sulci on the surface of the brain, a general decrease in overall size, and specific decreases in size in crucial brain regions such as the prefrontal cortex or the hippocampus. In addition, the cortex is thinner, although the total number of cells is not decreased, suggesting that the change is due to a loss of the projections from the cell bodies of nerves that permit them to make connections (i.e., dendrites and spines). Such substantial structural brain abnormalities (e.g., overall smaller brain size, increased ventricular size) have probably been present for at least a few years and preceded the development of the illness. The most likely interpretation is that they are additional indicators of a previous problem in brain growth and development that led eventually to the symptoms of schizophrenia.

This inference has been given even more solid support by recent studies of childhood onset schizophrenia conducted by Judy Rapoport's team at the National Institute of Mental Health (NIMH). They have now studied brain growth in large numbers of healthy children and adolescents and compared them to children and young adults who have recently developed schizophrenia. Both groups are being studied repeatedly over time using anatomic brain measurements obtained with MR. This very interesting work has focused on the crucial teenage years, when young people are maturing mentally and socially. Their brains are making the key connections that permit them to grow up and become mature and functional adults. We know from basic neuroscience that this process involves overgrowth of connections, which subsequently need to be pruned back. The NIMH group has shown that during the teenage years (between 13 and 18), brain growth and change occurs in both healthy control subjects and those with schizophrenia, but that the developmental curves are quite different. The progression of brain development in the childhood-onset schizophrenia patients involves a decline in total brain volume, and an increase in the volume of gray matter. These studies add

further evidence that the brain changes in schizophrenia may occur at multiple points in time, ranging from early fetal development to late adolescence or young adulthood.

Why does this matter?

Pinpointing the crucial time window for the development of an illness is an important step in figuring out how to prevent it. Determining whether people with schizophrenia are "doomed from the womb" is not limited to asking whether the disease is genetic or not. It also means asking about nongenetic factors such as birth injuries or viral infections. If the key brain injury occurs during fetal development, we have few opportunities to arrest the progression of the illness. If, on the other hand (as is probably the case), maturational brain changes during the teenage years are important, then eventually we may be able to identify what they are and arrest them very early. Most treatment programs currently being developed for Alzheimer's disease and other neurodegenerative disorders are based on this kind of strategy—to identify the neurobiological processes that produce the illness and then to influence or arrest their occurrence or progression. Many of us have similar hopes that we can do the same for schizophrenia.

Schizophrenia as a Disorder of Misconnections in the Brain

So far we have seen how schizophrenia is caused by a mixture of genetic influences and nongenetic influences such as head or birth injuries, viral infections, exposure to toxins and drugs of abuse, hormonal changes, and other factors. These influence the development of the brain during the prolonged period of brain maturation that occurs in human beings and that is probably not completed until the early twenties. But exactly what effect do these neurodevelopmental aberrations have? If we were to go hunting for the locus of schizophrenia in the brain/mind, where would we look? To answer this question, we must think about "functional genomics," or how the influence of specific genes is translated to abnormalities in the functions of the brain and mind.

We would look for the locus of schizophrenia almost everywhere. But it will be hard to find it in any single place.

Some mental illnesses, such as Alzheimer's disease, have characteristic changes in specific cells and cell layers. Other mental illnesses, such as Huntington's disease, affect a single brain region. For schizophrenia, however, a diligent search by many talented neuroscientists has not identified any such specific regional abnormalities or nerve cell lesions. Some skeptics of neurobiological explanations for schizophrenia have suggested that the illness cannot therefore be considered a brain disease. A much more

likely explanation, however, is that schizophrenia is a disease that affects the brain in ways that are different from Alzheimer's or Huntington's disease. It does not damage specific cells or even specific regions. Instead it damages the way regions are connected to one another, so that a breakdown in signal transfer occurs, and the messages sent back and forth between various brain regions are garbled or confused. In the language of neuroscience, schizophrenia is a disease that affects distributed neural circuits rather than single cells or single regions. Such disorders are sometimes referred to as misconnection syndromes.

When I talk to patients with schizophrenia, I often begin by asking them what kinds of problems are troubling them the most. They tend to come up with answers like this:

My thinking is confused.

My ideas don't seem to connect quite right.

I have trouble filtering out unimportant information.

I feel bombarded by stimuli.

In short, most people with schizophrenia have a subjective sense that their ability to think and feel has somehow become disorganized, disconnected, or misconnected. The tools of neuroimaging, already briefly described in chapter 6, have allowed us to study how the brains of people with schizophrenia function differently from healthy individuals when they are performing similar mental tasks. These studies have shown us that the subjective experience of "misconnection" or "disorganization" reflects an underlying problem in the ability of distributed brain regions to send messages back and forth efficiently and accurately.

Although computers are not a perfect metaphor for the brain, using them as a model can be somewhat helpful. The typical computer system has to continually link up information from multiple sources, such as a variety of software programs, stored data, and peripheral devices such as printers and scanners. We have all seen how computers can get tied up in knots and crash if we ask them to do too many things at once, or if incompatibilities occur between various software programs or between software and hardware. Performance can become sluggish and inefficient if the information transfer rate becomes too slow or if files become too large to handle. The underlying brain abnormalities in schizophrenia are somewhat analogous: they occur because of problems with integrating multiple components. Therefore, we are not likely to succeed in localizing schizophrenia in any single brain region, although we do observe that some regions are abnormal if measured anatomically or functionally using MR or PET.

Some specific abnormalities in subregions of the brain have been

found relatively consistently. Measures of structural size using MR have demonstrated decreases in the frontal lobes, temporal lobes, or hippocampus. More recently our group has suggested that the thalamus and the regions of the cerebellum also have specific size decreases. These subregions are scattered all over the brain, and they are quite numerous. The only way to make good sense of these findings is to conclude that schizophrenia is not "in" any single one of them, but instead occurs because of problems in all of them, caused by the connections or relationships between them. Like a malfunctioning computer, the various nodes in brain networks send information back and forth in a way that causes file corruption, garbled information, or crashes. For a few people with schizophrenia, the neurodevelopmental abnormality producing the misconnections may be due to abnormal wiring on a large scale—e.g., connections between neurons at the level of axons. This is evident in those rare cases of ectopic gray matter. Most of the time, however, the abnormality is at a finer level, involving the sending and receiving of messages by synapses or spines on dendrites.

Although we cannot see the lesions of schizophrenia at postmortem as we can for Alzheimer's disease, we can see the abnormalities in connections between functional circuits using in vivo imaging techniques such as PET. These studies show that people with schizophrenia have trouble transporting signals and information back and forth around their brains in the same way and at the same speed as normal people performing the same task.

In our own PET center, we have now studied healthy volunteers and people with schizophrenia while they perform many different tasks. These have included remembering past experiences, learning and later remembering word lists or stories, responding emotionally to pleasant or unpleasant visual images, sniffing nasty or pleasing odors, focusing attention on specific areas of a video screen, listening to sounds and identifying which ear is receiving them, tapping fingers in a particular rhythm, or judging how long a particular time interval is. That is obviously a long list of very different kinds of mental tasks. They were chosen to examine the diverse kinds of mental problems that people with schizophrenia have, such as focusing attention, encoding and using memories efficiently, or responding emotionally and experiencing pleasure.

Rather remarkably, people with schizophrenia have abnormal patterns of blood flow in all of these tasks, but some regions are abnormal in almost every kind of task. These consistently abnormal regions include the thalamus and the cerebellum. We now suspect that the cerebellum

may be malfunctioning as a "metronome" or timekeeper, causing signaling to lose its synchrony and coordination. The thalamus, which functions as a filter or gatekeeper that helps determine how much information should be let in or out of the brain, may be failing to screen information out, so that the system becomes overwhelmed with so much data that the person's thinking becomes confused or sluggish. The net effect is incoordination or miscommunication between key processing centers needed for a given task that are distributed throughout the brain. Figure 8–3 (A-C) illustrates these abnormalities in distributed brain circuits in schizophrenia. These studies from our research center, as well as many from other centers, suggest that schizophrenia is not a disease of any specific brain region, but rather a disease of functional connectivity between distributed regions. For this reason, we need to see the lesion or injury using different techniques from those used for illnesses such as Alzheimer's disease or Huntington's disease. At the level of genetic influences, we must now work to understand how genes regulate the ongoing process of establishing and maintaining connections throughout widely distributed regions of the brain, including all components (e.g., synapses, spines, cells, and key nodes such as the thalamus.)

The Neurochemistry of Schizophrenia

The circuits that link brain regions together use chemical messengers that permit the cells on either end to communicate with one another. Disturbances in the chemical activity of the brain create another "invisible lesion" that cannot be seen with the naked eye or under a microscope. Evidence from several sources indicates that chemical imbalances in schizophrenia are "real," contribute to the development of symptoms, and can be corrected through medications that affect brain chemistry.

Dopamine was the first neurotransmitter to be discovered as a contributor to the symptoms of schizophrenia. Several lines of evidence have suggested that dopamine is important in this illness. First, schizophrenia-like symptoms can be produced through stimulant drugs such as amphetamine, which produce their exhilarating effects by causing large amounts of dopamine to be released. In fact, chronic amphetamine abuse may produce a permanent change in the brain and be yet another nongenetic factor contributing to the development of schizophrenia in predisposed individuals.

A second piece of evidence is provided by our knowledge of how antipsychotic drugs work. Almost all the drugs that successfully reduce symptoms of schizophrenia decrease the activity of the dopamine system

in the brain by blocking dopamine receptors, the little patches on nerve cell membranes that are designed in order to receive chemical messages. Nearly all antipsychotics, ranging from older ones such as chlorpromazine to newer ones such as risperidone or olanzapine, lock into these receptors and shut out dopamine molecules that may be trying to transmit messages. As dopamine tone is reduced, the psychotic symptoms are also quieted down. These observations led to the formulation of the "dopamine hypothesis of schizophrenia" by Arvid Carlsson, a distinguished Swedish neuropharmacologist and Nobel laureate, in the 1960s. Direct support for this hypothesis was provided by several different studies of postmortem brain tissue independently conducted by two eminent psychiatrist/pharmacologists, Solomon Snyder and Phillip Seeman. These studies showed a direct relationship between the ability of drugs to block dopamine (type 2) receptors and their antipsychotic potency. Studies also showed an increase in dopamine receptors in limbic brain regions such as the nucleus accumbens in patients with schizophrenia.

The dopamine hypothesis was universally accepted as explaining the chemical imbalance in schizophrenia for nearly thirty years. Simply stated, it suggested that the symptoms of schizophrenia were due primarily to hyperactivity in the dopamine system. In the past decade, however, the plot has thickened, as our knowledge about neurotransmitter systems has increased further and as new antipsychotic and antischizophrenic drugs have been developed. The dopamine hypothesis has not been supplanted, but it has had to deal with the arrival of at least two new younger siblings, serotonin and glutamate. More recent hypotheses suggest a key role for both serotonin and glutamate in the development of the symptoms of schizophrenia, based on multiple recent studies of the neurochemistry and neuropharmacology of the illness. Clinician scientists now think that schizophrenia occurs as a consequence of a much more complex chemical imbalance that includes multiple neurotransmitter systems that interact with and modulate one another. Dopamine is almost certainly a crucial component, but other neurotransmitters also play a role.

What Treatments Are Available?

The development of new medications for schizophrenia is one example of the remarkable progress that has occurred in the treatment of mental illness over the past fifty years. Although we all wish that mental illnesses such as schizophrenia could be cured completely, and we are as yet unable to achieve this, we should pause and take stock of how far we have actually come.

Fifty years ago a person diagnosed as having schizophrenia was faced with three or four options, all of them relatively unpleasant. One was the irreversible surgical treatment, prefrontal leucotomy, developed by the Portuguese neurologist Egas Moniz. Insulin coma and electroconvulsive therapy were other alternatives. These three treatments were palliative measures that worked in some patients. The majority of people with schizophrenia remained chronically ill and required lifetime care because they experienced so much confusion, lack of drive, or psychotic agitation that they were not able to care for themselves independently and meet the demands of ordinary daily living. Literally every other hospital bed was occupied by someone suffering from schizophrenia—50% of the people in hospitals throughout the world.

New Medications and False Hopes

In this context, a new medication, chlorpromazine (with the trade name Thorazine), burst on the scene in the early 1950s. The first experiments were conducted in Paris in 1952 by two French psychiatrists, Jean Delay and Pierre Deniker. They tried the new drug in psychiatric patients with many different diagnoses, including mania, schizophrenia, and depression. They observed that, in addition to calming or tranquilizing, it also markedly reduced the terrifying hallucinations and troubling delusions that were causing patients to be agitated, fearful, and restless. Their observations were quickly confirmed in many other countries, including the United States, and a new era in the care of schizophrenia was launched. The number of inpatient beds needed for psychiatric patients dropped steadily, institutions were closed, and more and more patients began to receive their care in community settings where they could lead more normal lives. Soon other new antipsychotics, many of them with fewer side effects, were added to the armamentarium, such as haldoperidol, which was developed by Paul Janssen in Belgium.

Psychiatrists began to approach the care of first-episode patients with new hope. Many believed that if the first episode of psychosis could be treated aggressively and further relapses prevented with the new medications, schizophrenia could potentially be cured altogether. Gradually, however, these hopes were dashed, and schizophrenia continued to be viewed as a devastating and grim diagnosis. The antipsychotic medications, it turned out, were simply that: they were effective for reducing psychotic symptoms, such as delusions and hallucinations, but they were much less helpful with negative symptoms. Although no longer psychotic, patients continued to suffer from a reduction in the ability to

think fluidly, to experience joy or pleasure, or to start tasks and finish them.

People would be admitted to the hospital in the midst of an agitated psychotic episode, improve markedly with antipsychotic treatment, and be discharged with plans to return to work or school. Despite their best efforts, and despite encouragement from family and friends, they often were unable to do the things that used to come easily to them. They would simply lose interest in classes, wander away from a job in the middle of the day, or fall into a pattern of staying in bed or spending all their time watching TV. It became increasingly clear that the negative symptoms were due to a reduction in the ability to function cognitively and emotionally. The antipsychotics did not seem to cure the "schizo-phrenia," the fragmentation of mind and emotion, that was described by Bleuler and used to name this often incapacitating illness. After an era of hope launched in the 1960s with the introduction of antipsychotics, the treatment of schizophrenia failed to improve further. Yes, patients were better, but they were far from well.

The Next Generation of Medications

Things have improved again recently, however, raising hopes that increasing progress will be made in the care of schizophrenia. A "new generation" of antipsychotic medications has been developed, with the hope that they will be truly "antischizophrenic." These are the so-called atypical antipsychotics.

Clozapine was the first of the new atypical medications. Although it had been used to a modest degree in Europe, it was largely abandoned after it was noted to produce a dangerous reduction in the number of white blood cells, a condition known as agranulocytosis. Two American psychiatrists, John Kane and Herbert Meltzer, decided to explore its utility in a group of people with schizophrenia who had remained severely and chronically ill. They were "treatment refractory." That is, they had not responded to any of the antipsychotics that had been tried. In this desperate situation, it seemed worthwhile to try a somewhat risky medication, using weekly checks of white blood count to determine whether agranulocytosis was developing. Gratifyingly, Clozapine worked! Many patients who had been chronically ill improved markedly.

Clozapine is an interesting medication for several reasons. First, unlike every antipsychotic developed up to that point, it did not work intensively on the dopamine system to block the dopamine type 2 receptor, which had been the primary target for drug development. Further, it

seemed to work not just for positive psychotic symptoms but also for the negative symptoms of schizophrenia. People with the illness gradually began to regain their interest in life, their ability to enjoy things, and the capacity to think in a clearer, more logical way. Finally, clozapine had minimal extrapyramidal side effects.

In addition to being less effective for improving cognition or reducing negative symptoms, the older antipsychotic medications produced a variety of unpleasant side effects, many of which are related to their blockade of the dopamine system. Extrapyramidal side effects, sometimes called EPS for short, include a rigidity of muscles, a frozen blank expression on the face, a tremor, and a tendency to walk with a shuffling gait. Another unpleasant side effect produced by older neuroleptics is akathisia. This is an intense subjective sense of anxiousness, which causes the person to want to pace and move around restlessly. Some people on traditional antipsychotics also feel depressed. Because these side effects are so unpleasant, many people with schizophrenia do not want to take traditional antipsychotic medications. For them, the treatment is almost worse than the disease itself. Some would prefer to have psychotic symptoms if they have to pay the price of having EPS in order to get rid of them.

The new atypical medications have been a godsend in this regard. Paul Janssen, who had previously developed haloperidol, has devoted much of his life to finding better treatments for schizophrenia, and he synthesized and tested yet another new medication, risperidone, which worked on other neurotransmitters besides dopamine and was the first of the new atypical medications that could be used without the difficult blood-monitoring required for clozapine. Other new atypicals subsequently followed Janssen's lead. These include olanzapine (Zyprexa), quetiapine (Seroquel), and ziprasidone (Zeldox). These drugs have now become "first-line treatments." That is, they are normally the first choice for treating people in their first episode of illness, and they are largely supplanting the older antipsychotic medications for most people who have schizophrenia. The traits that define "atypical" include relatively less D2 blockade, reduced extrapyramidal side effects, ability to improve both psychotic and negative symptoms, and an ability to improve mental alertness. The atypicals are also less likely to produce tardive dyskinesia, a potentially irreversible movement disorder that occurs in 20–30% of patients treated with traditional neuroleptics. This movement disorder is a relatively disfiguring tendency to grimace, twitch, and pace.

The newer atypicals do have their own problems with side effects, however. One of the most troubling is that some of them cause excessive

weight gain, partly as a consequence of increased appetite, but partly as a direct effect of the medication. A related side effect is an increased tendency to develop diabetes mellitus. Another problem is an effect on one component of the endocrine system (prolactin, which stimulates breast development).

Cognitive and Psychosocial Rehabilitative Treatment

When the diagnosis of schizophrenia was considered to carry a grim prognosis, few people worried about introducing psychotherapy, psychosocial rehabilitation, or cognitive retraining. Because people with schizophrenia who have been treated with the new atypicals are more alert and interested, both patients and families now hope that the addition of various psychotherapeutic interventions to the newer medications can substantially improve outcome. Programs that emphasize this aspect of treatment may soon become a mainstay, as novel approaches are developed. These treatment programs will probably have two components.

First, people with schizophrenia may need help with learning how to organize the activities of everyday life, which psychiatrists call psychosocial rehabilitation. This illness strikes its blow at a critical period in development, the teenage and young adult years. This is the time when people are just becoming emancipated from the home. Therefore, young adults with schizophrenia may need to learn to pass through the natural maturational processes of learning how to set up an independent home, look for a job, or plan a routine normal day. People with schizophrenia are sometimes shy or fearful of being around others, and so they may need help in figuring out how to join group activities and make friends. Partial hospitalization, group programs, and outpatient therapies may all be helpful.

Cognitive relearning is a second approach. Treatment programs implementing this strategy are in their infancy. Their essence is to focus on the fundamental cognitive abnormalities that characterize schizophrenia. They are designed to help patients learn to focus attention more precisely, to solve problems more efficiently or more rapidly, to monitor ideas and speech more effectively, and to improve both motor and mental coordination. These programs are founded on the concept of neuroplasticity, described in chapter 4: "neurons that fire together wire together." The hope is that if people with schizophrenia can go through extensive retraining similar to that used to rehabilitate stroke patients or train children with specific hearing or learning disabilities, they will gradually rewire their brains so that new connections are formed, and they can then learn to think and function more clearly and effectively.

CHAPTER 9

MOOD DISORDERS
Riding the Emotional Roller Coaster

> For aught we know to the contrary, 103 degrees or 104 degrees Fahrenheit might be a much more favorable temperature for truth to germinate and sprout in, than the more ordinary blood heat of 97 or 98 degrees.
>
> —William James
>
> *Varieties of Religious Experience*

Marcia was puzzled. Hal was really acting strange. He was doing things that were completely out of character for him.

Marcia and Hal were getting ready to celebrate their fifteenth wedding anniversary. It had been a great fifteen years. True, Marcia had given birth to two kids and no longer weighed 105 with a 22–inch waist, but she still was a pretty good-looking 112. Hal was the one who should be able to use the pregnancy excuse! On Marcia's cooking he had ballooned from 140 to 175 and acquired a loveable paunch.

Their fortunes had ballooned as well. Hal was a developer in Santa Fe, and he had a real knack for it. Although the market had leveled a bit during the late 1980s and early 1990s, things had been booming for the last five years. Hal himself had really done well, even during the "soft" times. Hal knew what he was doing and cared about doing it exactly right. People respected his meticulousness. Hal could anticipate better than most, and he worried about all the right details. He could look at 120 acres of land, and where other people saw a wasteland, he could envision roads that took interesting turns to well-sited houses looking at the Jemez or Sangre de Cristo mountains. He wasn't one of those shoddy developers. He also worried about the community and the environment. People trusted him. They knew he was honest, that he wouldn't compromise quality or standards to make an extra buck or two. In the wild whirlwind of Santa Fe real estate, a guy like Hal was a community treasure. Lots of locals were selling out to the Almighty Dollar, and carpetbaggers were also coming in from both coasts . . . quite literally to capitalize on what could be done in the still unspoiled Southwest. These days Hollywood