This need not mean that we should never use medications merely to relieve symptoms. It does mean that this approach goes against the Hippocratic view of medicine, and we should take it only in the short term, reluctantly, and for immediate relief of symptoms. In psychiatric populations, where diseases are poorly understood (as in children and the elderly), and there is rampant symptomatic polypharmacy. And many psychiatrists consider this state of affairs to be acceptable. Osler's rule would give us pause.

SUMMARY

To paraphrase the great German psychiatrist, Karl Jaspers (who in my view is a much greater thinker for psychiatry than either Sigmund Freud or Emil Kraepelin), most of our mistakes and disagreements stem from our beliefs and concepts rather than from science or research. Readers who have picked up this book to better diagnose or treat mood disorders will not gain much benefit unless they first think about their conceptual assumptions about psychiatric treatment. In the past, we avoided medications too much: Psychoanalysis was seen as the solution. Now, I believe that we use medications too much: We practice a symptom-oriented psychopharmacology that belongs in the nineteenth century. We need to be clear about what we need to do: We should prescribe medications primarily for diseases, not for symptoms, and not even for all diseases; we should avoid prescribing them by habit, only doing so when proof of benefit exists and far outweighs risks. With this basic philosophy, we can then turn to studies and research and data, leading to a scientific Hippocratic psychopharmacology. Otherwise, in my view, the science and the data will be twisted by doctors and patients to their own whims, producing that eclectic mishmash that is contemporary psychiatry.

6 Genes and Environment

Essential Concepts

- There are roughly equal genetic and environmental causes for mood disorders.
- The genetic part consists of polygenic susceptibility to illness rather than Mendelian inheritance.
- The environmental part consists of specific life events, which mainly serve to trigger individual episodes.

I will discuss the etiology of mood disorders in two major categories: genetics and environment.

GENETICS

Numerous years of research have failed to find a single gene or a few genes that "cause" mood disorders (or psychotic disorders). This is likely the case because most psychiatric conditions are not analogous to classic Mendelian illnesses. In Mendelian genetics, qualitative changes occur with often a single-gene change. Thus, if a gene is dominant, it produces a certain trait. If a gene is recessive, it produces a certain trait in the homozygous mode (two recessive genes occurring together), meaning one-fourth of the time. These occurrences are predictable. This type of genetics accounts for many inherited diseases in which the environment plays little to no role. However, many common chronic medical illnesses do not follow this pattern of inheritance. For instance, we know that hypertension and diabetes mellitus (type II) have heritable aspects, yet they are neither autosomal dominant nor recessive in their frequency patterns. Similarly, normal physical features, such as height or weight or intelligence, are inherited, but not in an autosomal manner. Instead, with such chronic illness or such physical features, what seems to be inherited is a tendency to have more or less susceptibility to those conditions or features. These kinds of genetic effects are quantitative rather than qualitative. A single gene has relatively little effect, and it appears

that numerous genes with small effects need to add up to produce the illness or trait. Such genetic features seem to apply to most psychiatric conditions.

Thus genetic studies of psychiatric illnesses often tend to be quantitative studies, based on statistical analyses, rather than qualitative chromosomal analyses or gene loci mapping. While the latter kind of qualitative genetics research is conducted frequently, it has been spectacularly unsuccessful to date. On the other hand, quantitative genetics methods have been more than modestly useful in advancing our knowledge of the genetic basis of psychiatric disorders.

TIP

The genetic basis of most psychiatric illnesses involves multiple small gene effects rather than few large gene effects. The environment is also an important part of the etiology of psychiatric illnesses.

Behavior Genetics

The field of behavior genetics, then, is largely a field of quantitative genetic research. If the father of qualitative genetics was Mendel, the father of quantitative genetics was Francis Galton. Galton was a first cousin of Charles Darwin and was heavily influenced by his famous relative. Galton was intrigued by how intelligence and success in intellectual activities (e.g., science, academics, and law) seemed to run in families. He devised various mathematical methods to assess this inheritance. These methods were later refined by others and are now in common use.

Perhaps the most popular method in quantitative genetics is the twin study. Monozygotic twins share all their genes; dizygotic twins share half. Otherwise, such twin pairs are similar environmentally. They are the same age, inhabited the same uterus, and usually are raised in the same family. Thus such twin pairs are ideal "natural experiments" in which one might be able to tease out the effects of genes and environment. If a condition is completely genetic, then all monozygotic twins should share the same illness, and half of dizygotic twins should do so. If less than 100% of monozygotic twins share the same illness, then the condition is not completely genetic, and the remaining influence must be environmental. With complex mathematical models, geneticists can look at the actual prevalence

of a certain illness in twin pairs and then determine the ***heritability*** of that illness, meaning the amount of the variance for that illness attributable to genetics alone. Further, using the same mathematical models, geneticists can assess the remaining environmental component and determine if it is *shared* (such as a common family environment or a common larger culture) or *specific* to one twin but not the other ("the slings and arrows of outrageous fortune").

Numerous twin studies have been conducted during major depression. In a recent meta-analysis of five such twin studies, the mean heritability of this condition appears to be 37% (range 31% to 42%). Further, it is very clear that there is a negligible effect of the shared environment on the remaining variance of the illness (63%, range 58% to 67%). Rather, the environmental component seems to be almost all specific environmental effects not shared by a twin pair. I will discuss these environmental issues further in a moment.

TIP

The genetic susceptibility to major depression explains 37% of the risk of the illness. The larger portion of risk is due to specific environmental effects, but not, apparently, to shared environmental effects, such as the family environment.

What does it mean, in practical terms, when we note that the genetic basis of depression is quantitative rather than qualitative and that the heritability approaches 37%? First, we must conclude that there is a large environmental component to the etiology of mood disorders—even larger than the genetic component. One cannot write off mood disorders as simply inherited. Second, the genetic basis of these disorders consists of a susceptibility that may or may not lead to illness based on other factors (mostly environmental). (These conclusions were foreshadowed long ago by Adolf Meyer, who deemphasized the heritability of psychiatric illnesses and focused on the adjustment and prevention of their psychosocial circumstances.) Thus the stress-diathesis model of illness seems applicable (Fig. 6.1). One way to understand how the etiology of mood disorders is influenced by treatment is to think of biological treatments (such as medications) as targeting the genetic diathesis and to think of psychotherapeutic treatments (or other psychosocial effects) as targeting the recurrent environmental stressors.

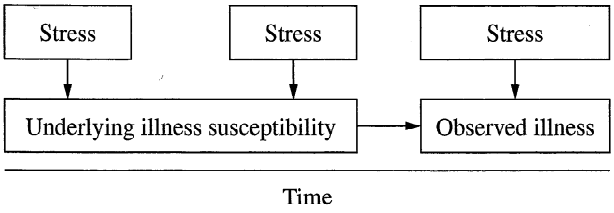

FIG. 6.1. Stress-diathesis model of psychiatric illness.

TIP

Simplistically, medications may be targeting the genetic diathesis; psychotherapies may be targeting the environmental stressors.

Family Studies

Another type of genetic study is a family study, in which individuals from families where one person (the *proband*) is identified as having a psychiatric illness are interviewed for psychiatric illnesses. First-degree relatives (i.e., parents, siblings, and children) share 50% of the proband's genes. With each degree of separation, the shared genes fall by one-half. If random inheritance of multiple small genes is assumed, then the risk of mood disorders similarly would fall by the same factors. A recent meta-analysis identified five family studies in which the odds of major depression occurring in first-degree relatives of depressed probands averaged 2.8% (meaning an almost threefold increased risk compared with the general population).

TIP

First-degree relatives of individuals with depression have a threefold increased risk of developing major depression compared with the general population.

Based on these studies, we are near the point where meaningful genetic counseling can be offered to individuals with psychiatric illness or their relatives so as to at least allow them to make informed choices when shown the chances of

TABLE 6.1. Percentage of Genetic Risk in Families of Patients with Mood Disorders

Patient's Diagnosis	*Familial Risk of BP*	*Familial Risk of UP*
BP	7%	13%
UP	2%	14%

BP = bipolar disorder; UP = unipolar depression; familial risk relates to first-degree relatives. Risk rates are rounded to the nearest whole integer.

developing such illnesses in themselves or their offspring. Based on a recent review of this literature in which a weighted average of risk was based on analyses of various published rigorous genetic studies, the following risks can be described for first-degree relatives (Table 6.1):

- If a patient has any bipolar spectrum illness (type I, type II, or schizoaffective), first-degree relatives have a 20% lifetime risk of any mood disorder.
- If a patient has bipolar disorder, first-degree relatives have a 6.7% risk of developing bipolar disorder over a lifetime and a 12.5% risk of developing unipolar depression.
- If a patient has unipolar depression, first-degree relatives have a 1.9% risk of developing bipolar disorder over a lifetime and a 14.2% risk of developing unipolar depression.

Stated in terms of ranges of risk ratios compared with control groups from the general population, first-degree relatives of patients with bipolar disorder have an eight- to tenfold risk of developing bipolar disorder and a two- to threefold risk of developing unipolar depression. First-degree relatives of patients with unipolar depression have a one-and-one-half- to twofold risk of developing bipolar disorder and a three- to fourfold risk of developing unipolar depression (Table 6.2).

These risk estimates are based on the assumption of unilineality, that is, that only one side of a family demonstrates evidence of mood disorders. The genetic component of psychiatric disorders is additive, so it would be relatively accurate to double these risk estimates in the case of bilineality, in which psychiatric illness is present on both sides of a family genome. For similar reasons, we might consider cutting these risk factors in half for second-degree relatives. However, exact figures for risks in greater than first-degree relatives have not been established.

In addition, although these family studies support a higher risk of bipolar disorder in families of patients with unipolar

TABLE 6.2. Genetic Risk in Families of Patients with Mood Disorders: Odds Ratio

Patient's Diagnosis	*Familial Risk of BP*	*Familial Risk of UP*
BP	8–10	2–3
UP	1.5–2	3–4

BP = bipolar disorder; UP = unipolar depression; familial risk relates to first-degree relatives. Risk rates are presented as the odds ratio: 1 means the same rate as the general population, 2 means twice as likely, and so on.

depression than in the general population, twin studies tend to support the relative absence of bipolar relatives in families of patients with unipolar depression compared with families of patients with bipolar disorder. However, this relative difference is not absolute, and there are exceptions. A very important clue to bipolar disorder in depressed patients who might have subtle or difficult-to-recognize manic symptoms is that they frequently have relatives with bipolar disorder. Those depressed patients with family histories of bipolar disorder are much more likely to themselves have some variety of bipolar illness rather than unipolar depression.

TIP

It is unusual to find evidence of bipolar disorder in the family of a person with unipolar depression. If a relative has bipolar disorder, then the patient is much more likely to have a bipolar-related condition.

CLINICAL VIGNETTE

Marcia is a 36-year-old married woman with two children, ages 14 and 12. She calls seeking advice about having a third child because her sister was diagnosed recently with bipolar disorder. In retrospect, Marcia's great aunt, who had been institutionalized with "schizophrenia" in the 1950s, appeared to demonstrate symptoms consistent with mania. Neither of Marcia's children has yet demonstrated any evidence of mood disorder. Marcia's husband and his family have no known risk of mood or psychotic disorders. Based on this history, the consultant informs Marcia that the likelihood of bipolar disorder (type I) is about 7% in first-degree relatives. Further, he informs her that the genetic risk is additive, decreasing by a factor of one-half in each generation. Since an aunt is a second-degree relative, the risk for her children is 3%. This risk is the same for each child and does not increase in later children if earlier ones are asymptomatic. Further, since the age of onset of bipolar disorder is 19 years, one cannot be certain whether or not her adolescent children will yet develop the condition. The consultant advised her to carefully attend to her prenatal and perinatal health if she became pregnant so as to reduce the environmental contributors to the risk of having mood disorders, which are about equal in effect to the genetic components.

ENVIRONMENT

If the heritability of major depression is 37%, then the majority of the factors leading to that illness are environmental. But what kind of environment?

Twin studies tell us that those factors are not shared. This would seem to make shared familial environmental experiences less important. What does this mean? It may mean that previously espoused theories, such as poor mothering or a generally chaotic household in early life, may not be as relevant as many had assumed. It is often difficult to disprove a theory, but the absence of confirmation might at least increase one's level of doubt. Many of these theories to which I allude are psychoanalytic in origin, and it is my sense that the general trend of twin studies fails to confirm many assumptions put forward based on psychoanalytic theories. The shared family environment does not seem to play a major role in the predisposition to major depression. Assuming that a mother is just as inept with one child as another, these twin studies would absolve her of any influence on later development of depressive illness.

But what if a mother treats one child differently than another? Then we are no longer faced with shared family environment but rather unshared environmental influences, the kind of environmental experiences that twin studies suggest are highly influential in predisposition to depression.

Birth order could be a major such influence; the experience of a first child is much different from that of a seventh child. A large psychological literature generally suggests that

firstborn children tend to identify more strongly with their parents and frequently receive more direct parental attention (helpful or not) than laterborns. Firstborns tend to be more conventionally "successful" in terms of career and income, whereas laterborns tend to be more likely to be creative and try new life plans than their parents. Firstborns are politically and socially conservative; laterborns, more liberal. These personality traits are influenced by differing childhood familial experiences partly based on how many children there are in a family and a child's birth order.

It is possible that susceptibility to depression also may be influenced by such circumstances. For instance, a firstborn child might be more likely to become depressed owing to excessive responsibility placed on him or her by the parents or perhaps owing to excessive demands and expectations of worldly success. Or a laterborn child might be more likely to become depressed owing to being generally ignored by busy parents or owing to a feeling of being less cared for than earlier children. Remember that these experiences do not lead automatically to depression; many people have such experiences without becoming depressed. When combined with a genetic susceptibility, though, and probably other environmental factors as well, they can lead to depression.

TIP

Birth order can be an important environmental factor relevant to depression.

I should emphasize that while twin studies are consistent in suggesting a role for birth order in the etiology of depression, they do not prove that there is such a role. However, unlike shared family environment, twin studies are not *inconsistent* with a role for birth order.

What other unshared environmental influences may be relevant? Perhaps the next major type of unshared environmental influences is peer relationships. A child has one group of friends, and his or her sibling, another. Peer relationships are unshared environmental experiences. Some psychologists have concluded from the twin studies summarized earlier that peer relationships are the most important childhood experience in terms of personality development or psychiatric conditions. This perspective may be seen as the other end of the pendulum from the not-too-distant psychoanalytic days in which "bad

mothering" was the cause of all psychiatric ills. While peer experiences are important, it is unlikely that they replace any kind of familial experience in the etiology of mood disorders (or even personality traits). Genetic research supports the idea that not only should one choose one's family carefully, but one also should choose one's friends carefully. Painful experiences with peers can lead to diminished self-esteem, lack of attention to schoolwork, social and academic decline, and alcohol and drug abuse. These kinds of peer-influenced experiences may be expected to increase the risk of depression in genetically susceptible individuals. Conversely, positive peer experiences, which enhance self-esteem and lead to social approbation, likely reduce the chances of developing depression.

TIP

Peer relationships are an important environmental factor relevant to depression. One must choose one's friends carefully.

In my experience, life events beyond one's control are probably the largest component of unshared environmental experiences that predispose to depression. Chance plays a role in human life in many ways. Behavioral geneticist Lyndon Eaves frequently quotes Shakespeare's phrase, "the slings and arrows of outrageous fortune," to explain most of these unshared environmental events. Things simply happen, sometimes suddenly and unpredictably, and frequently, one can neither predict nor control their occurrence.

Certain life events are shared by many people: breakups of romantic relationships, divorce, death of a parent or sibling, weddings, birth of a child, medical illnesses, occupational success, loss of a job, and conflict with a boss or coworker. Most of us will experience at least some of these typical life events. However, the events are unique for each person in terms of both when those events occur in a person's lifetime and how they occur (sometimes with more emotional conflict, other times with less). In persons with a genetic susceptibility and perhaps other earlier environmental susceptibilities, an episode of major depression may ensue. Usually, these kinds of life events are *triggers* of depressive episodes; they are causative, but in a different sense than early childhood experiences or genetic liabilities. These environmental triggers are sufficient but not necessary for major depression; they complete the causative cycle in many persons, but frequently susceptible

individuals will have depressive episodes without any of these specific life events. On the other hand, one might conceive of genetic and early environmental influences (perhaps birth order and peer relationships) as necessary but not sufficient causes in many persons; this kind of susceptibility might lead to major depression, with the final trigger being a sling or arrow of outrageous fortune. The kindling model, which I will discuss in the next chapter, attempts to integrate many of these concepts.

TIP

The "slings and arrows of outrageous fortune" are unpredictable life events that can trigger mood episodes. They are sometimes sufficient but not always necessary for the occurrence of major depression.

What about major traumatic events, such as the loss of a parent in childhood or sexual or severe physical abuse? Many psychoanalytically derived theories place such major traumata at the core of psychiatric abnormalities of various kinds. Are major traumatic events important components of the etiology of mood disorders? To the extent that such traumatic events are unshared environmental experiences, they would not be inconsistent with the current state of the literature in behavior genetics. There are few direct, well-designed empirical studies on this issue. In one study, childhood parental loss was associated with adult psychopathology, such as major depression, but only to a small degree (explaining about 5% of the variance for the observed illness in adults).

It seems logical that such trauma can serve as an important environmental factor, leading to depression in genetically susceptible individuals. It could even be that if such types of trauma are severe enough, they might increase the risk of major depression—even in persons with quite limited genetic susceptibility.

TIP

Severe traumatic experiences, such as physical or sexual abuse, can be an important part of the environmental aspects of mood disorders, but they are not a central or necessary feature of mood disorders.

GENOTYPE-ENVIRONMENT INTERACTION

Although life can "happen" to you, with Shakespeare's slings and arrows landing around you through no fault of your own, you also may bring about certain life events by your own decisions. For instance, if you walk in crime-ridden neighborhoods, the likelihood of a mugging is greater than if you avoid such areas. While this example involves a conscious decision, it exemplifies the kind of interaction that occurs on a much larger and complex scale biologically, referred to by the concept of *genotype-environment interaction*. In a recent, large, child-development twin study in which children were followed throughout childhood and into adolescence, a group of psychiatric researchers interested in environmental influences on children were surprised to find that genetics proved strikingly important. Children seemed to bring about certain environmental experiences based on their inborn temperaments. These temperaments elicited different interactions from their parents, resulting in different forms of development throughout childhood. This type of genotype-environment interaction also may contribute to the unshared environmental influences that differ among siblings raised in the same household.