INTRODUCTION

Perhaps more than any other domain, the search for etiologic factors in psychiatry has been characterized by an enduring “nature versus nurture” debate, with researchers in medicine, psychology, and public health traditionally emphasizing separate causal factors in the generation of mental disorders. More recently, researchers have increasingly embraced a biopsychosocial model based on a growing body evidence that psychiatric disorders are determined by an interaction of multiple factors. Genetic epidemiology reflects this comprehensive approach by clarifying how both genetic and environmental components produce the complex phenotypes of various forms of disorders. However, its application to psychiatry is still relatively new and its methods and contributions within this domain are not well understood. The purpose of this presentation is to review issues and methodological concepts basic to the genetic epidemiology of psychiatric disorders, and to present examples of its application to this field.

DEFINITIONS OF PSYCHIATRIC DISORDERS AND PREVALENCE IN THE GENERAL POPULATION

Since the time of Sydenham's admonition to classify diseases with the same care that botanists exhibit in the development of their phytologies (1), nosology based on observable characteristics has been central to clinical medicine. Although progress in the characterization and assessment of psychiatric syndromes has strengthened the reliability and validity of current nosology, phenotypic imprecision has often been considered as the major culprit in inconsistencies observed in psychiatric genetic research. Much of the criticism leveled against early psychiatric genetic investigations, and indeed biologic psychiatric studies in general, has concentrated on the subjectivity of psychiatric diagnosis. The accepted solution to this problem has gradually developed over the past quarter century, reflecting a trend toward explicit “operational” definitions. That is, clinicians increasingly diagnose mental disorders from a clearly defined constellation of symptoms that are experienced for a specified duration of time. The first set of criteria in psychiatry that recognizably conformed to this pattern was developed by Robins and colleagues at Washington University in 1972, and became widely known as the “Feighner criteria” (2). Other sets of operational criteria rapidly followed from other groups, culminating in publication of the recent World Health Organization's The ICD-10 Classification of Mental and Behavioral Disorders (3) and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders: DSM-IV (4).

In summary, operational definitions such as those contained in “official” systems of classifications such as DSM-IV (and more recently ICD-10) provide acceptably high levels of reliability. Patients are, therefore, more likely to be diagnosed in a similar manner by different clinicians due to the use of uniform criteria and standards for diagnosis. However, the introduction of operational definitions for psychiatric research has appeared to do little to overcome a more difficult obstacle, that of biologic validity. For example, when the threshold of diagnostic criteria for major depression is systematically lowered, affected individuals still differ from those without depressive symptoms according to numerous validators, including family history, longitudinal stability, suicide attempts, and psychosocial impairment (5). In this way, operational definitions of psychiatric disorders, although reliable, may not always reflect discrete and homogeneous clinical entities. A related problem is the lack of distinct boundaries between psychiatric disorder catego-
ries. For example, many patients suffer from a condition that is characterized simultaneously by both anxiety and depressive symptoms, yet most nosologic systems would classify these individuals as having two separate (albeit co-occurring) diagnoses. Kendell (6) noted that it is unlikely that the etiologic secrets of major psychiatric disorders will be unlocked without accurate and valid identification of the syndromes themselves. While progress in classification is advancing, the findings and conclusions of all psychiatric investigations must still be qualified against imperfect biologic validity.

With the inherent problems of psychiatric nosology in mind, information about the frequency of psychiatric disorders in the general population may be used to provide an initial frame of reference for investigating patterns of familial aggregation in clinically ascertained samples. Table 1 presents the lifetime prevalence rates from the most recent large-scale epidemiologic study of psychiatric disorders in the United States using contemporary diagnostic criteria (7). These data reflect retrospective estimates of 14 diagnostic categories defined by the Diagnostic and Statistical Manual of Mental Disorders: DSM-III-R (8), and were obtained from community residents aged 15–54 years. The results indicate that almost half of the entire sample met diagnostic criteria for a psychiatric disorder at some point over their lifetime. Furthermore, these prevalence rates of psychiatric disorders also vary by demographic characteristics such as age, ethnicity, and gender. For example, prominent gender differences for depression and alcoholism are presented in table 1, and stratification by these variables is often required in epidemiologic research. The high rates of disorder must also be interpreted within the context of psychiatric disorder severity; even the most common forms of disorder examined by the National Comorbidity Survey (7) are often severe enough to prevent basic functioning in social, occupational, and family domains.

The frequency and severity of psychiatric disorders in the general population offer compelling reasons to pursue etiologic studies that may identify key variables for disorder prevention and intervention. It is important to underscore, however, that data about the respective roles of genes and the environment may be difficult to interpret. The expression of genetic factors is rarely independent of the environment, and the discussion of genetic or environmental forces, in the absence of the other, may be limited in meaning from both the theoretical and clinical standpoints. It is for this reason that research paradigms in genetic epidemiology are particularly useful for not only elucidating the separate roles of nature and nurture, but also the importance of their interaction in determining phenotypic expression.

STUDY PARADIGMS IN GENETIC EPIDEMIOLOGY

With their roots in the methods of population and clinical genetics as well as chronic disease epidemiology, investigations in genetic epidemiology are typically based on one of four research paradigms (a more detailed description of these paradigms can be found in Khoury et al. (9)). The basic strategy of these

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Lifetime prevalence (standard error)</th>
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<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>Anxious disorders</td>
<td></td>
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<tr>
<td>Panic disorder</td>
<td>2.0 (±0.3)</td>
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<tr>
<td>Social phobia</td>
<td>3.5 (±0.4)</td>
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<tr>
<td>Generalized anxiety disorder</td>
<td>11.1 (±0.8)</td>
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<tr>
<td>Any anxiety disorder</td>
<td>3.6 (±0.5)</td>
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<tr>
<td>Affective disorders</td>
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<tr>
<td>Major depressive episode</td>
<td>12.7 (±0.9)</td>
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<tr>
<td>Manic episode</td>
<td>1.6 (±0.3)</td>
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<tr>
<td>Any affective disorder</td>
<td>14.7 (±0.8)</td>
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<tr>
<td>Substance use disorders</td>
<td></td>
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<tr>
<td>Alcohol dependence</td>
<td>20.1 (±1.0)</td>
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<tr>
<td>Drug dependence</td>
<td>9.2 (±0.7)</td>
</tr>
<tr>
<td>Any substance use disorder</td>
<td>35.4 (±1.2)</td>
</tr>
<tr>
<td>Psychosis (nonaffective)</td>
<td>0.6 (±0.1)</td>
</tr>
<tr>
<td>Any psychiatric disorder</td>
<td>48.7 (±0.2)</td>
</tr>
</tbody>
</table>

* From Kessler et al. (7).
Family studies

The observation that some disorders aggregate in families serves as prerequisite evidence suggesting a possible genetic component. The basic family study approach involves identifying individuals with a particular psychiatric disorder (the proband) and then determining the rates of disorder in the proband's relatives. These morbidity statistics can then be compared with the rates of disorder in families of unaffected individuals (controls). The common indicator of familial aggregation is the prevalence ratio, which is defined as the ratio of the prevalence rate of a disorder among the relatives of cases to the prevalence rate of a disorder among the controls (9).

While family studies are an important starting point of genetic epidemiology, data from family studies can be difficult to interpret for several reasons. Like all research in psychiatry it is dependent on the diagnostic classification system, and some disorders may show markedly different patterns of familial transmission depending on minor changes in the diagnostic threshold. However, a problem even more specific to family studies is that important environmental factors are also "familial." Key environmental variables, such as social support, chronic and acute life stress, economic status, community environment, and many others, tend to vary along family lines and are known to have independent effects on mental health. For this reason, family studies may look beyond basic familial aggregation to examine specific patterns of transmission that, while still confounded with environmental factors, more clearly suggest genetic influences. These specific patterns of transmission within families may vary according to whether the genes are dominant or recessive, autosomal or X-linked, or multifactorial (including nongenetic factors (10)).

Although the family-study design has typically been employed to elucidate the degree and mode of transmission of most disorders, there are numerous other purposes for the application of such data. The major advantage of studying diseases within families is that the assumption of homotypy of the underlying factor eliminates the effects of heterogeneity which are present in comparisons between families. Family studies can therefore be employed to examine the validity of diagnostic categories by assessing the specificity of transmission of symptom patterns and disorders, compared with between-family designs (11). Data from family studies may also provide evidence regarding etiologic or phenotypic heterogeneity. Phenotypic heterogeneity is suggested by variable expressivity of symptoms, whereas etiologic heterogeneity is demonstrated by homotypic expression of different etiologic factors between families. Moreover, the family-study method permits assessment of associations between disorders by evaluating specific patterns of co-aggregation of two or more disorders within families. Controlled family studies have been employed to date in investigating the comorbidity of panic disorder and depression (12), alcoholism and depression (13), affective disorders and schizophrenia (14), and numerous other applications.

Twin studies

The concordance rate is the measure of association that has been used in twin studies to compare the presence or absence of a trait or disorder within monozygotic twins (who share the same genotype) with that of dizygotic twins (who share an average of 50 percent of their genes in common). The concordance rate is calculated by dividing the number of twins who have the trait or disorder by the number of twins in which at least one has the trait or disorder within each zygosity group (i.e., monozygotic or dizygotic). Concordance rates can be calculated either using the pairwise method, whereby a twin-pair that is concordant for a disorder is counted as one pair in the numerator and in the denominator, or by using the probandwise method, whereby concordant twins are counted as two pairs both in the numerator and in the denominator (but only when each affected twin was identified from the official register of cases independently (see Gottesman (15)). The ratio of concordance rates of monozygotic to dizygotic twins yields an estimate of the extent to which the trait is attributable to genetic factors.

To support a genetic etiology, the concordance rates for monozygotic twins should be significantly greater than those for dizygotic twins, and consistent with the concept of familial aggregation. The degree of concordance between cotwins of either type can also be used to provide information about the magnitude of genetic or environmental effects. However, the problem of same-environment confounds has also been raised against twin-study paradigms. Although monozygotic twins, whether they are raised together or apart, have been shown to have similar concordance rates for some traits (16), a more enduring criticism is that the intrauterine environment is more similar for monozygotic twins than for dizygotic twins. The possibility of environmental factors that may co-vary with zygosity is, therefore, an important consideration.
Adoption studies

Family and twin studies are genetically informative because they hold the environment "constant" while examining the rates of disorder across different levels of genetic relationship. An alternative approach is to vary the environment while comparing individuals with the same degree of genetic similarity. Adoption studies are part of this latter approach in that the psychiatric similarity between an adoptee and his or her biologic versus adoptive relatives is directly compared. Another similar paradigm compares the biologic relatives of affected adoptees with the biologic relatives of unaffected (or control) adoptees. Perhaps the most powerful approach to studying the joint contribution of genetic and environmental factors is the cross-fostering adoption-study design which compares rates of disorder in adoptees without biologic risk, who are raised by affected adoptive parents, with adoptees at biologic risk, who are raised by nonaffected adoptive parents. However, adoption studies are also characterized by certain characteristics that may bias results. Biologic parents of adopted children are known to have higher rates of psychopathology, alcoholism, or criminality than other parents, and adopted children may themselves be at greater risk for psychiatric disorders (e.g., Bohman (20) and Lipman et al. (21)). Although such criticisms may be valid reasons to carefully interpret the rates of disorder found in these studies, they do not negate the value of adoption studies to clarify genetic and environmental effects (in particular for disorders showing specificity of transmission).

Genetic marker studies

The two basic study designs for identifying the genes involved in disease etiology are association studies and linkage studies. Both study paradigms examine links between genetic markers and a specific disease or trait. Genetic markers are a measurable human trait controlled by a single gene with a known chromosomal location. It must also be polymorphic with at least two alleles having a gene frequency of at least 1 percent. The association study tests for a nonrandom relation between a genetic marker and a disease using a case-control design and analytic method. Association studies generally employ unrelated individuals selected from the general population. The chief impediment to association studies is selection of a control group which is similar to the cases on all relevant factors except disease status. Ethnicity has been a particularly troublesome confounding factor in association studies. The transmission disequilibrium test, a modification of the traditional association study in which the nontransmitted alleles of parents of an affected individual are used as controls, offsets some of the limitations in the selection of control samples for association studies (24).

Linkage studies examine the association between genetic markers and disease genes within families, and are based on the principle that two genes that lie close in proximity on a chromosome are transmitted to offspring together. The specific alleles segregating in one particular family may differ from those in another family; for example, an association between bipolar illness and the ABO (blood type) locus may manifest in some bipolar families as association with the A allele, while others manifest the B allele. Whereas association is a property of alleles, linkage is a prop-

Although the traditional application of the twin design focuses on the estimation of the heritability of a trait, there are several other research questions for which the twin study may be of value. Differences in concordance rates between monozygotic and dizygotic twins may be investigated at the level of symptoms or symptom clusters in order to study the validity of symptom complexes. Varying forms or degrees of expression of a particular disease in monozygotic twins may be an important source of evidence of the validity of the construct or disease entity. For example, McGuffin (17) and Kendler et al. (18) have, respectively, employed the twin-study design to investigate the validity of the diagnostic categories of schizophrenia and depression. In addition, Kendler et al. (19) showed that monozygotic twins were not only more often concordant for depression than dizygotic twins, but that they were concordant for specific depression subtypes, underscoring the heterogeneity of these disorders and need for nosology that reflect these entities.

Estimates of heritability derived from adoption studies may also be used to examine the validity of different phenotypic definitions. For example, the original Danish-American studies by Kety et al. (22) on schizophrenia were particularly influential but were criticized by some because of the breadth of the phenotypic definition (which included vague categories such as "latent" and "uncertain" schizophrenia). A subsequent reassessment of the Danish material by Kendler et al. (23) using DSM-III-R criteria was, therefore, valuable. Although the more stringent criteria yielded far lower rates of schizophrenia or schizotypal personality disorder, this definition provided better separation between the relatives of schizophrenics versus controls. Thus, a narrower and more reliable definition of the disorder led to an increase in the genetic effect, thereby validating its definition.
property of loci thereby involving all alleles at that locus (9, 25).

Linkage is quantified through use of the lod score; the lod score is the ratio of the likelihood of observing co-segregation of a disease and marker under linkage versus no linkage within families (26). The sib-pair method is an alternative strategy for testing linkage. Whereas the lod-score method assumes knowledge of the mode of transmission, the sib-pair method is model-free.

The choice of a method for identifying genes depends upon disease frequency, degree of genetic complexity, and strength of the contribution of genes to the disease. The linkage method is still the most powerful method for identifying genes for rare disorders with clear Mendelian patterns of inheritance. In contrast, association studies may require far smaller sample sizes compared with linkage studies when the population attributable risk is moderate (27).

Advances in neuroscience should enhance our understanding of the pathophysiology of the major psychiatric disorders, and with continued family- and twin-study research should lead to a reduction in heterogeneity and other sources of genetic complexity of the psychiatric disorders. The application of linkage studies and association studies to more homogeneous subtypes of mental disorders with strong underlying genetic basis should prove to be more fruitful than the present state of knowledge would indicate. Recent successes in identifying genes for complex disorders, such as apolipoprotein E (28) and several other loci for Alzheimer's disease, should serve to increase optimism regarding our ultimate ability to identify the genetic factors which contribute to psychiatric disorders.

CHARACTERISTICS OF PSYCHIATRIC DISORDERS THAT IMPEDE GENETIC STUDIES

Family, twin, adoption, and genetic marker studies compose the basic research paradigms of genetic epidemiology. However, the application of these paradigms is complicated by several factors germane to psychiatry itself. As mentioned in the beginning of this presentation, one of the most far-reaching impediments to genetic research is the reliability and validity of diagnostic categories. For example, twin studies of male and female alcoholics have revealed a significantly higher heritability for alcohol dependence than for alcohol abuse (29, 30). While narrow definitions of alcoholism may provide a more valid phenotype for future genetic analyses, other disorders may require broader definitions. For example, the apparently low familiality for some illnesses, such as obsessive-compulsive disorder, may be due to the use of narrow diagnostic criteria that may not detect transmission of obsessive-compulsive disorder "spectrum" within families (31). While the use of stricter criteria may reduce the absolute degree of familial aggregation of a disorder, the relative difference in familial aggregation in relatives of cases compared with controls is likely to remain constant. As the appropriateness of using various thresholds is rarely clear in advance of conducting epidemiologic investigations, research in this domain is necessarily dependent on diagnostic definitions that are in the constant process of refinement.

In addition to the paramount issues of nosology, the transmission of mental illness within families may not follow patterns seen for other diseases. The more common reason is that assortative mating with respect to psychiatric disorders has been well-established (32); that is, individuals with a specific form of disorder may be more likely to have children with persons having the same illness, or having the illness in their families. In addition to assortative mating, cross-mating among individuals with different types of psychiatric problems is also frequently observed. For example, schizophrenic females are more likely than normal women to marry men with substance abuse and behavior problems, alcoholic men more often marry women with depression or anxiety, and these women often have a family history of alcoholism (32). Nonrandom mating leads to an increase in variability of a given trait in the population (33). With respect to psychiatric disorders, nonrandom mating leads to a clustering of families with high density of disorder at one extreme and clustering of unaffected families at the other. The bimodal distribution induced by nonrandom mating would be expected to impede our ability to discriminate the role of genetic factors in familial aggregation.

A third barrier to research in genetic epidemiology is the strong co-occurrence among certain disorders within individuals. Comorbidity between psychiatric disorders appears to be the rule rather than the exception: numerous studies of clinical samples have demonstrated the large proportion of patients who simultaneously meet diagnostic criteria for more than a single disorder (e.g., Babor et al. (34), Chambless et al. (35), and Hasegawa et al. (36)) and multiple diagnoses within individuals appear to be quite frequent in epidemiologic surveys of the general population (7, 37). Comorbidity, therefore, confounds the study of "pure" disorder etiology, but also poses important questions as to the specificity of risk factors and the appropriateness of diagnostic boundaries. Cohort effects comprise another limiting factor as it is often unclear if observed effects are artifacts or true differences. A cohort effect is defined as differences in disease prevalence in a particular group of individuals, generally a
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birth cohort, who progress simultaneously through the risk period for a particular disease (38). For any disease which requires a particular environmental exposure for its development, the disease frequency may differ dramatically according to the variation in the degree of exposure to the particular environmental agent. The dramatic increase in availability of certain drugs, for example, may complicate family studies of alcoholism because of the tendency for individuals to use and/or abuse multiple substances over time. Different generations may manifest the agent as a function of drug availability at the time that substance problems are developing, and, therefore, it is not clear whether individuals having drug abuse problems should be classified as affected or not affected in a family study of alcoholism. Evidence from family and twin studies may ultimately help distinguish whether there is a generalized liability to abuse substances of all classes versus specificity in the use and abuse of a particular class of drugs. However, cohort effects presently pose difficult questions in the application or interpretation of research in this domain. A related issue concerns recall biases associated with age, and for this reason, epidemiologic studies increasingly include late adolescent and young adult cohorts in order to minimize reporting biases of childhood disorders.

A final major impediment concerns the genetic complexity of psychiatric disorders. Despite the dramatic success of molecular genetics in the identification of the genetic basis of Huntington's disease (39), Duchenne's muscular dystrophy (40), cystic fibrosis (41), and breast cancer (42), the application of these methods to psychiatric disorders has been quite disappointing. Furthermore, although recent success in identifying vulnerability genes for complex diseases such as diabetes (43, 44) has generated enthusiasm, replication attempts have thus far been unsuccessful. The reasons for these difficulties reside in the critical differences that exist between the psychiatric disorders and the disorders to which the tools of molecular genetics have been successfully applied. Linkage has been reported for diseases which are rare (i.e., <0.01 percent population prevalence), exhibit Mendelian patterns of inheritance, and can be clearly diagnosed with extremely high specificity and sensitivity (45). In contrast, psychiatric disorders are complex disorders, which are conditions characterized by high population prevalence, a lack of clear distinction between affected and unaffected individuals (often with arbitrary thresholds for case definition), and failure to adhere to Mendelian patterns of transmission. For these reasons, Risch and Botstein (46) concluded that the chief impediment to identifying genes for psychiatric disorders is their underlying genetic complexity. Psychiatric disorders are likely to be attributable to a large number of genes, and the interactions among genes and with environmental factors contribute to phenotypic heterogeneity.

EVIDENCE FOR THE ROLE OF GENETIC FACTORS IN THE ETIOLOGY OF PSYCHIATRIC DISORDERS

Although there are formidable challenges to applying genetic epidemiology to the field of psychiatry, progress continues to be made in each of the four paradigms described previously. We will now present a review of research in the genetic epidemiology of the major classes of psychiatric diagnoses: schizophrenia, affective disorders, anxiety disorders, and substance dependence.

Schizophrenia

Schizophrenia is a form of psychotic disorder characterized by delusions, hallucinations, or disturbances in affect and thought processes. More is known about the genetic basis of schizophrenia than perhaps any other psychiatric condition, with genetically-informative studies stemming from early this century. Concerning familial aggregation of this disorder, Gottesman (15) pooled data from approximately 40 family studies reported between 1920 and 1987 and concluded that there is considerable support for the claim that schizophrenia is familial. The risk of schizophrenia and related disorders to first-degree relatives (siblings, parents, children) was on average 9.3 times greater than the risk of schizophrenia to the general population. However, because early family studies used outdated diagnostic criteria and widely differing methodologies, the conclusions that can be drawn from pooling earlier data are limited. In a more recent review, Kendler and Diehl (47) examined only recent family studies that have included a control group, direct in-person interviews, and blind diagnoses of relatives (see table 2). Based on the average risks to first-degree relatives of proband and control groups across studies, a remarkably similar prevalence risk ratio of 9.4 is observed. The conclusion that schizophrenia is highly familial is augmented by twin and adoption studies support for a genetic etiology. As shown in table 2, McGuffin et al. (48) reviewed six twin studies demonstrating an average probandwise concordance rate of 46 percent for monozygotic twins and 13 percent for dizygotic twins. Similarly, adoption studies demonstrated that the average risk to first-degree relatives for schizophrenia spectrum disorders (broadly defined) was 15.5 percent compared with 3.6 percent for controls (giving a grand mean prevalence...
TABLE 2. Evidence for genetic factors in schizophrenia*

<table>
<thead>
<tr>
<th>Type of Investigation</th>
<th>Standard comparison</th>
<th>No. of studies reviewed</th>
<th>Average prevalence ratio</th>
<th>Ratio range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family</td>
<td>Relatives of probands versus relatives of controls</td>
<td>9</td>
<td>8.9</td>
<td>2.7–18.5</td>
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<tr>
<td>Twin</td>
<td>Monozygotic probandwise concordance versus dizygotic probandwise concordance</td>
<td>12</td>
<td>4.4</td>
<td>2.2–12.0</td>
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<tr>
<td>Adoption</td>
<td>Adoptee-biologic relatives versus adoptee-adoptive relatives</td>
<td>4</td>
<td>4.3</td>
<td>1.9–10.6</td>
</tr>
</tbody>
</table>

Data compiled by Kendler and Diehl (47), and McGuffin et al. (48).

risk ratio of 4.3). Very recent adoption studies continue to support the genetic transmission of schizophrenia and related disorders (e.g., Kendler et al. (23)), and have produced findings of similar magnitude.

With such clear evidence of a large genetic role in schizophrenia, it is not surprising that much research has focused on identifying specific genetic markers for this disorder. Although many association studies of schizophrenia have been performed using diverse polymorphisms, the majority of work in this area has focused on linkage studies. Fueled by initial findings of associations of specific cytogenetic abnormalities with schizophrenia, many recent DNA marker studies have focused on regions of chromosomes 3, 5, 6, 8, 11, 22, and sex chromosomes (for review, see Kendler and Diehl (47), Gurling (49), Mowry et al. (50), and Nurnberger and Byerley (51)). However, very few results have been replicated for either association studies or linkage studies despite many exciting initial findings, and the newer approach of scanning the entire human genome with DNA markers has, to date, produced only equivocal findings (see Tsuang and Faraone (52)).

In summary, while considerable evidence exists that schizophrenia is a genetically transmitted disorder, we are presently far from identifying with confidence which genes are implicated. It is also important to underscore that many of the studies in genetic epidemiology indicate that schizophrenia is strongly dependent on nongenetic factors. For example, as the average concordance rate for monozygotic twins is approximately 50 percent, an individual may have a strong genetic vulnerability to the disease but not manifest the illness. Tienari et al. (53) recently reported that the genetic propensity for schizophrenia was only manifested if the individual lived in a disturbed family environment. Similarly, other investigations have revealed that negative life events increase both the chance of relapse and the severity of symptoms (for a review, see Norman and Malla (54)), that marital status is a powerful predictor of schizophrenia course (Jablensky et al. (55)), and that additional diverse environmental factors may be implicated (Kendler et al. (56)). Taken together, these investigations support a diathesis-stress model of the disorder whereby a genetic vulnerability serves as a key etiologic factor that is dependent, at least in part, on environmental factors for its ultimate expression.

Mood disorders

Mood disorders are comprised of a heterogeneous group of syndromes, of which major depression and bipolar disorder (manic depression) are major subtypes. Depressive episodes involve not only depressed mood or anhedonia, but also a variety of somatic or cognitive symptoms that signify a marked change from previous functioning. Manic episodes involve a period of abnormally elevated, expansive, or irritable mood that is severe enough to cause marked impair-

TABLE 3. Evidence for genetic factors in mood disorders*

<table>
<thead>
<tr>
<th>Type of Investigation</th>
<th>Standard comparison</th>
<th>No. of studies reviewed</th>
<th>Average prevalence ratio</th>
<th>Ratio range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family</td>
<td>Relatives of probands versus relatives of controls</td>
<td>4 (bipolar)</td>
<td>10.6</td>
<td>3.7–17.7</td>
</tr>
<tr>
<td>Twin</td>
<td>Monozygotic probandwise concordance versus dizygotic probandwise concordance</td>
<td>5 (bipolar)</td>
<td>5.3</td>
<td>3.6–13.4</td>
</tr>
<tr>
<td>Adoption</td>
<td>Adoptee-biologic relatives versus adoptee-adoptive relatives</td>
<td>1 (bipolar)</td>
<td>2.6</td>
<td>1.7–4.8</td>
</tr>
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</table>

Data compiled by Maier (14), Merikangas and Kupfer (10), and Taylor et al. (58).

* Data compiled by Kendler and Diehl (47), and McGuffin et al. (48).
ment in essential life domains. Table 3 summarizes evidence for genetic factors in bipolar disorder and unipolar depression as reviewed by previous investigations (10, 57, 58). The overall conclusion from this research is that both major depression and bipolar disorder have important genetic components. Controlled family studies show a fivefold risk to relatives of depressed patients, and greater than a tenfold risk to relatives of bipolar patients. The concordance rate for bipolar monozygotic twins is over five times that of dizygotic twins, and depressed twin concordance shows less dramatic but still notable differences. The prevalence ratios based on the few existing adoption studies also confirm that the magnitude of twin concordance or familialism is not due purely to environmental factors and that genes play a prominent role.

Concerning marker studies, progress has been elusive in identifying the specific genetic mechanisms implicated in mood disorders. Association studies have focused on blood groups, human leukocyte antigens, rapid eye movement sleep, and diverse other markers. More recently, these investigations have also moved to using molecular biology to examine specific DNA markers including tyrosine hydroxylase, dopamine, and monoamine oxidase. Linkage studies have also focused on human leukocyte antigen haplotypes and markers associated notably with chromosomes 4, 11, 15, 18, 21, or the X chromosome. Although work is continuing to focus on both previous and new loci (e.g., Blackwood et al. (59) and Ginns et al. (60)), reviews of association studies and linkage studies conclude a present lack of consistent or replicated findings (Merikangas and Kupfer (10) and Craddock and McGuffin (61)).

Anxiety disorders

The anxiety disorders compose a diverse group of syndromes that share core features of anxiety, fear, or behavioral avoidance, and are of sufficient severity to impair the individual's daily functioning. At present, relatively few studies have examined anxiety disorders from the perspective of genetic epidemiology, and there are virtually no data from certain paradigms (such as adoption studies). However, existing research indicates that most anxiety disorders aggregate in families, and several investigations have offered specific support for genetic etiology (examples of three anxiety disorders are shown in table 4). Perhaps the most consistent support for the role of genetic factors has been found for panic disorder. A review of six controlled family studies using direct interviews provides an average prevalence risk ratio of 9.4 (62), and new investigations continue to report high levels of aggregation (e.g., Battaglia et al. (63)). Although there has been some inconsistency reported by twin studies of panic disorder (see McGuffin et al. (48)), two recent studies applying modern diagnostic criteria demonstrated considerably higher rates for monozygotic, compared with dizygotic, twins (64, 65). Furthermore, current estimates derived from the Virginia Twin Registry show panic disorder to have the highest heritability of all anxiety disorders at 44 percent (66).

Genetic factors are implicated in other anxiety disorders, although comparatively few investigations have been completed. For example, social phobia aggregates in families, and twin studies show a higher concordance for monozygotic twins (see table 4). Other phobias (i.e., specific phobia, agoraphobia) have also been shown to be familial, with the three phobia subtypes having similar prevalence risk ratios and specificity of transmission (for review, see Merikangas and Angst (67) and Woodman and Crowe (68)). More recent data from the Virginia Twin Study report the estimated total heritability for phobias to be 35 percent (66). The application of genetic epidemiology to understanding other anxiety disorders has been limited not only due to a dearth of controlled studies, but also because of uncertainty about the appropriateness of phenotypic descriptions. For example, the few family studies of obsessive-compulsive disor-

<table>
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<th>TABLE 4. Evidence for genetic factors in anxiety disorder*</th>
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<td><strong>Type of investigation</strong></td>
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<td>Family</td>
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<td>Twin</td>
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* Data compiled by Chapman et al. (87), Weissman (62), and Woodman and Crowe (68).
order that have used standardized assessments with narrow operationalized criteria have demonstrated no increased risk to relatives (see Table 4). By contrast, an examination of obsessional symptoms in cotwins of obsessive-compulsive disorder probands revealed an increased risk to monozygotic twins over dizygotic twins. Discrepancies such as these will be clarified as more controlled family, twin, and adoption studies are carried out, and as the validity of narrow versus broad definitions is established.

Concerning marker studies of anxiety disorders, the high heritability rates seen for panic disorder has made it the natural focus of research in this area, and many clinical and neurobiologic challenge studies have served as a guide by implicating the adrenergic system (for a review, see Goddard et al. (69)). However, recent linkage studies have excluded the possibility that panic disorder was due to mutations in adrenergic receptor loci on chromosomes 4, 5, or 10 (70), and other work has similarly excluded linkage with gamma-aminobutyric acid beta 1 (GABA A) receptor genes (71). Recent reports from a genomic survey of panic disorder using 600 markers have not yielded evidence of linkage (51). While the status of current biologic marker studies of panic are still in their infancy, there is reason to be optimistic as the Human Genome Project (and the identification of numerous highly polymorphic markers) will soon lead to major increases in the precision of the human genome map (72).

**Substance use disorders**

Substance use disorders involve the maladaptive and typically regular use of psychoactive substances that affect the central nervous system. Substance abuse causes recurrent problems in social, occupational, psychic, or physical functioning, or is characterized by recurrent substance use in hazardous situations (such as drinking and driving). Substance dependence may include any of these problems, as well as increased tolerance, inability to control use, or withdrawal symptoms. The majority of studies concerning the genetic epidemiology of addictive behaviors has focused on alcoholism rather than drug-related problems, and a shared etiology is suspected by some researchers (e.g., Blum et al. (73)). Table 5 summarizes the family, twin, and adoption studies of alcoholism as recently reviewed by McGue (74) and Merikangas (75). Not only does alcohol abuse and dependency aggregate in families (comprising a sevenfold risk to first-degree relatives), but twin and adoption studies indicate that this aggregation is partly due to genetic factors. At present, the evidence for a genetic predisposition to alcoholism is stronger for men than for women (but generally significant for both). The more recent investigations continue to offer consistent support not only for familial aggregation (e.g., Araujo and Monteiro (76) and Maier et al. (57)), but also clarify previously weak areas of evidence by demonstrating a greater concordance for monozygotic over dizygotic female twins (Kendler et al. (77)). The heritability of alcoholism (narrowly defined) has been estimated at 59 percent by some researchers (66), while the heritability of problem drinking (using broad definitions) has been estimated at 8–44 percent in females and 10–50 percent in males (78). However, the genetic information derived from these twin studies is complex, and recent twin evidence also suggests that the heritability of alcoholism (at least in males) is greater when the individual has a comorbid psychiatric diagnosis (79).

Similar to other domains, the search for specific markers through association and linkage studies in alcoholism has produced equivocal findings. The majority of association studies to date have focused on the dopamine (DRD2) and serotonin (5-HT) receptor genes as well as the aldehyde dehydrogenase (ALDH) locus (for reviews, see Blum et al. (73), McGue (74), Gelernter et al. (80), Goldman (81), and Pato et al. (82)). Although several investigations have replicated significant associations between alcoholism and these markers, the majority of investigations are either preliminary, nonconfirmatory, or have revealed potential

<table>
<thead>
<tr>
<th>Table 5: Evidence for genetic factors in alcohol abuse and/or dependence*</th>
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<tbody>
<tr>
<td><strong>Type of investigation</strong></td>
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<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Family</td>
</tr>
<tr>
<td>Twin</td>
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<td>Adoption</td>
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* Data compiled by McGue (74) and Merikangas (75).
sampling biases that may independently explain observed associations.

While genetic marker studies for alcoholism (and psychiatric disorders in general) are still in their infancy, the results from other paradigms support the conclusion that genetic factors play a moderate role for male, and at least a modest role for female, drinking problems (74). In addition, the role of environmental factors in the etiology of alcoholism has been supported by numerous studies from a genetic epidemiologic perspective. For example, twin studies have indicated that concordance rates for alcohol-related disorders are greater for certain geographic areas, possibly due to socioeconomic factors (83). Adoption-study paradigms have shown not only that a disturbed adoptive family environment interacts with a genetic predisposition for alcoholism to affect the risk for the disorder (84), but that the adoptive family environment can predict alcohol abuse or dependency independent from genetic vulnerability (85). Finally, although the majority of work in this area has focused on alcoholism, research on other substance use disorders is growing at a fast pace. Current work indicates that these disorders are familial (e.g., Skre et al. (86)) and that they have complex etiologies involving both genetic and environmental components (see Cadoret (85)).

SUMMARY AND FUTURE STEPS

Advances in standardized definitions of major psychiatric disorders has dramatically enhanced our ability to reliably characterize behavioral phenotypes for genetic studies. The application of family, twin, adoption, and genetic marker paradigms to this domain has offered new opportunities for understanding the respective roles of genetic and environmental factors for classes of disorders that affect large percentages of the general population. However, previous research has been impeded by several factors, notably a lack of biologic validity of diagnostic categories as well as the genetic complexity of psychiatric disorders. In fact, the discovery of the breast and ovarian cancer susceptibility gene (BRCA1) witnesses the importance of maximizing disease homogeneity among study subjects. The application of genetic study paradigms to guide definitions of the thresholds and boundaries of psychiatric syndromes (and to refine the precision of phenotypic definitions) will hopefully enhance the identification of homogeneous subtypes, and thereby increase the power of linkage studies in elucidating their genetic basis.

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