Are We Overestimating the Genetic Contribution to Schizophrenia?

by E. Fuller Torrey

Abstract

That genetic factors contribute to the etiology of schizophrenia is no longer debated; the nature and magnitude of that contribution, however, are still open for discussion. In this article, concordance rates for twin studies of schizophrenia are reviewed as one means of assessing the magnitude of the genetic contribution. Using only those studies in which representative samples were used and zygoity was determined with reasonable certainty, the pairwise concordance rate for schizophrenia was found to be 28 percent for monozygotic (MZ) and 6 percent for dizygotic (DZ) twins. Review of twin studies of other central nervous system diseases reveals that schizophrenia is most similar to multiple sclerosis (MZ concordance rate 27%). Although genetics remains as the single most clearly defined etiological factor in schizophrenia, the question remains whether we are overestimating the magnitude of the genetic contribution.

The fact that genetics plays a role in the etiology of schizophrenia is acknowledged by all researchers in the field. There is considerable debate, however, regarding both the magnitude of that role and its precise nature; recent interest in linkage analysis and molecular genetics has increased such debate.

Theories regarding the genetics of schizophrenia range from monogenic to polygenic. The genes may be either dominant or recessive, at a single locus or several loci, have variable levels of penetrance, and produce variable levels of disease expressivity. The genes may theoretically code for neurochemical (e.g., dopamine) abnormalities which could produce the symptoms of schizophrenia directly. Or they may control specific events in neurodevelopment, such as the proliferation and migration of neurons, which could produce the symptoms more indirectly. Or the genes may act at a greater distance by controlling factors relating to disease susceptibility, for example, the susceptibility of developing cells to anoxia (Mednick et al. 1971) or the susceptibility of the central nervous system (CNS) to a viral infection (Roos 1985; Torrey 1991); in such cases the genes would make schizophrenia more likely but actual acquisition of the disease would depend on exposure to the specific pathogen (e.g., anoxia, virus). Assessing the genetic contribution to the etiology of schizophrenia is further complicated by the existence of phenotypic copies of the disease in which genes may play no role at all.

The debate regarding the role of genetics in the etiology of schizophrenia is not a new one but has changed in focus. For three decades following World War II, geneticists were the major opponents of psychoanalytic and family interaction theorists, who argued that the etiological roots of schizophrenia resided in an individual's childhood experiences. Geneticists were not merely the leaders of biological psychiatry, they virtually were biological psychiatry. To downgrade the importance of genetics in schizophrenia during those years was to implicitly side with the psychoanalytic and family interaction theories. With the discrediting of psychoanalytic and family interaction

Reprint requests should be sent to Dr. E.F. Torrey, Twin Study Unit, NIMH Neurosciences Center, St. Elizabeths Hospital, 2700 Martin Luther King Avenue, SE, Washington, DC 20032.
theories of schizophrenia in recent years, the focus of the debate has shifted to a closer examination of the role of genetics in relation to other biological theories of schizophrenia's etiology.

The standard methods used to assess genetic contributions to the etiology of diseases are to compare concordance rates in monozygotic (MZ) versus dizygotic (DZ) twins, to study family pedigrees, to study the disease incidence in adoptees, and linkage analysis. Of these approaches, the twin method has a long history and has received the most attention in psychiatry. In 1812 Dr. Benjamin Rush commented on the similarity of the brains of identical twins who had both committed suicide (Price 1978), and in 1859 Dr. J. Moreau described identical twins in France with very similar psychotic symptoms (Galton 1875). Following publication of Sir Francis Galton’s classic 1875 article describing how studies of twins “afford means of distinguishing between . . . the effects of nature and of nurture” (p. 391), those with an interest in the genetics of mental disorders increasingly turned their attention toward twins.

For twin studies of any disease to provide useful information regarding the relative contribution of genetics, two criteria must be fulfilled. First, zygosity must be established with relative certainty. The questionnaire method (e.g., “Were the twins as alike as two peas in a pod?”), photographs, and dermatoglyphics can establish zygosity with a high level of certainty if used carefully, but red cell typing, widely used only since World War II, is a more reliable method. More recently deoxyribonucleic acid (DNA) methods to determine zygosity have become available.

Second, the sample must be sufficiently representative so the results are not biased. Vogel and Motulsky, in their textbook Human Genetics (1986), distinguish four types of twin samples: (1) birth registers in which every twin in a population is ascertained; (2) limited representative sampling in which “all twin individuals are ascertained within a population of affected patients of the disease under investigation” (p. 211), for example, the identification of Canadian twins with multiple sclerosis by surveying all clinics that treat that disease; (3) individual case reports; and (4) accumulated case reports. The last two samples may produce biased results because twins who are MZ and those that are concordant for a disease tend to be selectively recalled and therefore referred more frequently than DZ or discordant pairs. Concordant twins are also known to volunteer more readily in response to advertisements. The following review will therefore be restricted to twin studies that meet criteria for careful ascertainment of zygosity and are based on either case registers or limited representative samples.

In analyzing twin studies of CNS diseases, four other methodological problems must be addressed. First, many of these disorders in addition to schizophrenia are thought to be syndromes rather than specific diseases. For example, epilepsy comprises several etiological subgroups and concordance rates in such a heterogeneous sample may reflect genetic factors operating for only one subgroup. Second, the definition of concordance can be problematic in many disorders. For example, co-twins in autism may have significant lags in language development but no other signs of that disease, co-twins in Parkinson’s disease may have a benign essential tremor, and co-twins in multiple sclerosis may have magnetic resonance imaging (MRI) changes indicative of that disease but no clinical symptoms.

Third, there is a problem of defining limits to the risk period and determining when no additional twin pairs will become concordant. For example, in some diagnostic systems for schizophrenia, age 45 has been established as an upper limit for the onset of the disease, but other diagnostic systems permit a later age of onset. Similar problems exist for epilepsy, multiple sclerosis, and Parkinson’s disease.

Finally, twin studies of most CNS diseases use pairwise rates to express concordance; each twin pair is treated as a separate unit and concordance is calculated as a percentage of the pairs in which both twins are sick, for example, 3 of 10 or 30 percent. Many schizophrenia researchers, geneticists, and epidemiologists have argued that proband-wise concordance rates are preferable. According to Gottesman and Shields (1982), in the proband method “some pairs are counted twice if both members of the pair are affected and if each member was ascertained independently” (p. 72). Thus, by the proband method if (in the example given above) both twins in one of the concordant pairs had been ascertained independently, the probandwise concordance rate would be 4 of 11 or 36 percent. Only probandwise concordance rates can be compared with incidence rates in nontwin populations. However, because only pairwise concordance rates are available for virtually all twin studies of diseases other than schizophrenia and because this article will compare twin studies only with each other and not with nontwin
populations, pairwise concordance rates will be used.

Concordance Rates in Twin Studies of Schizophrenia

The first large research study of twins with schizophrenia was carried out by Lukenberger in Germany in the 1920s (Lukenberger 1928). He collected data on twins from Bavarian mental hospitals and established that twinning did not occur more frequently among individuals who developed schizophrenia than among the general population. His method of collecting his twin sample appears to have been remarkably complete. However, he then excluded all cases of schizophrenia with a favorable outcome, did not ascertain zygosity by methods other than physical similarity, and published concordance rates that are internally inconsistent with some of his own data (Gottesman and Shields 1977). His studies are therefore not useful for shedding light on concordance rates.

Another early schizophrenia twin study was carried out in the 1930s by Rosanoff and his colleagues, who identified twins in “every part of the United States and Canada” (Rosanoff et al. 1934). Although details of his sampling are not provided, it appears that the twins in this series are accumulated case reports and therefore a biased sample. Ascertainment of zygosity was also restricted to physical appearance.

The largest and most controversial twin study of schizophrenia was carried out by Kallmann who claimed to have identified 953 twin pairs with one or both affected among patients in New York State psychiatric hospitals (Kallmann 1953). Unfortunately, he provided virtually no details of sampling, diagnostic criteria, clinical case histories, or zygosity determination other than to say that he relied on physical appearances. Apparently he did not personally examine most twin pairs. Although Kallmann’s study has had its supporters (Shields et al. 1967), it seems likely that his twin pairs were an accumulation of case reports and therefore biased toward concordance and monozigosity. On these grounds, as well as uncertain zygosity, the concordance data cannot be considered accurate.

Essen-Moller’s 1941 Swedish twin study was the first one to meet minimum criteria for adequate sampling and zygosity determination. He identified twin pairs using local parish birth registrations and used consecutive admissions to mental hospitals over 11 years to achieve an unbiased sample. He was also the first researcher of twins to use red blood cell groups to confirm zygosity, to examine most pairs himself, and to publish extensive case histories. He followed up his twins over 30 years to ascertain complete concordance rates. In 1970 he reported these rates as 4 of 8 (50%) for MZ twins and 2 of 27 (7%) for DZ twins (Essen-Moller 1970).

The Slater and Shields twin study was based on twin pairs identified in 10 mental hospitals in London (Slater and Shields 1953). The study appears to include a reasonably complete sample although it was somewhat biased toward more severely ill twin pairs because it was hospital based. Many researchers have asserted that greater severity of illness in an index twin increases the chances that the second twin will become ill (e.g., Gottesman and Shields 1977, 1982). The Slater and Shields series therefore could well be biased toward higher concordance. A more serious criticism is that zygosity was established by physical appearance alone in 60 percent of cases; in the other 40 percent, fingerprint analysis was also used. Gottesman and Shields (1977) reported an MZ concordance rate of 24 of 37 (65%) although in 7 of the 24 concordant cases there were said to be “doubtful features or lack of fully adequate information” (p. 215) for establishing the diagnosis. Slater and Shields reported DZ concordance rate was 10 of 112 (9%) with diagnostic questions raised about 3 of the 10 concordant pairs. Overall, considering the probable sample bias toward concordance, uncertain zygosity in more than half the twin pairs, and diagnostic issues, the inclusion of this series in an analysis of concordance rates may be questionable.

A twin study carried out by Inouye in Japan and published in 1961 cannot be included in an analysis of concordance rates because the sample was merely an accumulation of case reports from different areas (Inouye 1961).

Between 1963 and 1973 the findings from three more Scandinavian twin studies were published and established a new standard in sampling quality. Tienari’s study in Finland (1963), Kringlen’s study in Norway (1967), and Fischer’s study in Denmark (1973) all combined national twin registers with disease registers to give the most complete possible sample of twins with schizophrenia. Most of the twins Fischer and Kringlen studied had passed the risk period for developing schizophrenia (Fischer’s were born between 1870 and 1920 and Kringlen’s between 1901 and 1930); Tienari’s twins were born between 1920 and 1929, but he followed them until all were at least 40 years old (Tienari 1975). Zygosity was carefully established in the three studies, with questionnaires and photographs used for twins who had
died, and case histories were published to clarify questions of diagnosis. The concordance rates reported were as follows: Tienari MZ, 3 of 20 (15%) and DZ, 3 of 42 (7%); Kringle MZ, 14 of 45 (31%) and DZ, 14 of 172 (8%). Fischer MZ, 5 of 21 (24%) and DZ, 4 of 41 (10%).

Another twin study of schizophrenia based on a continuous sample was that by Gottesman and Shields (1972), who identified twins among 45,000 admissions to the Maudsley Hospital in London between 1948 and 1964. Like the Slater and Shields study, it was hospital based, but it included outpatients as well as inpatients and thus was less biased toward severity (and therefore concordance). Unlike the Scandinavian studies by Tienari, Kringle, and Fischer, however, it did not include twins with schizophrenia in whom neither twin had been treated at the hospital. Gottesman and Shields (1982) determined zygosity “by blood-grouping and fingerprinting in most pairs” (p. 111) and they personally interviewed most of them. Diagnoses were made by a six-judge diagnostic panel. Using strict diagnostic criteria for schizophrenia, the concordance rate for MZ twins was 9 of 22 (41%) and for DZ twins, 3 of 33 (9%).

The single American twin study to meet minimal criteria for sampling and zygosity derived from the registry set up in 1959 by the National Academy of Sciences (NAS) and the National Research Council (NRC), covering all American military personnel who served in World War II and the Korean War. As such, the register is exclusively male and includes only individuals accepted for military service. It is therefore biased against individuals with an early onset of schizophrenia, the very individuals who are more likely to have a severe form of the disease and thus more likely to become concordant.

The NAS-NRC twin study is strongly biased in favor of lower concordance rates (Kendler and Robinette 1983). Diagnoses were taken from Veterans Affairs (VA) records and included only those cases who were either treated while in the service or later applied for VA disability pensions. This would appear to bias the register toward including more severe cases and excluding less severe cases, a bias that produces a higher concordance rate. Zygosity was ascertained by blood typing in 5 percent of the twin pairs, fingerprints and questionnaires in 36 percent, and questionnaires only in the remainder. In 19 percent of the twin pairs with schizophrenia, zygosity could not be reliably determined. As of 1981 the veterans in the NAS-NRC register were aged 54 to 64, beyond the age of risk for schizophrenia. At that time the concordance rate for MZ twins was 30 of 164 (18%) and for DZ twins, 9 of 268 (3%).

The most recent twin study of schizophrenia concordance rates was carried out by Onstad et al. (1991), using the Norwegian Twin Register. The twins were born between 1936 and 1960 and did not overlap the Norwegian twin cohort previously studied by Kringle. Zygosity was established by a new questionnaire, which was said to be 95 percent reliable, and blood analyses in doubtful cases. Diagnoses were established by two separate rates using DSM-III-R (American Psychiatric Association 1987) criteria. The researchers reported a concordance rate for MZ twins of 8 of 24 (33%) and for DZ twins, 1 of 28 (4%).

In summary, since the late 1930s there have been eight twin studies of concordance rates for schizophrenia that meet minimal criteria for sampling and zygosity ascertainment. Of these studies, the Scandinavian case register studies are methodologically the strongest while the Slater and Shields study (with a sample bias toward higher concordance) and the NAS-NRC study (with an overall sample bias toward lower concordance) are methodologically the weakest. More recent twin studies such as those in the United States by Pollin and colleagues (Pollin and Stabenau 1968; Belmaker et al. 1974), Torrey and colleagues (Suddath et al. 1990), and in England by Reveley and colleagues (1984) have not attempted to collect uninterrupted samples or ascertain concordance rates.

The pairwise concordance rate for the aggregated eight studies, summarized in Table 1, is 28 percent for MZ and 6 percent for DZ. If the Gottesman-Shields and NAS-NRC samples are not included, the rate is 31 percent for MZ and 8 percent for DZ. This MZ rate is lower than the 50 percent rate quoted in many American textbooks of psychiatry for the following reasons: (1) exclusion of twin studies that did not meet minimal criteria for unbiased sample or zygosity determination (those by Luxenberger, Rosanoff and colleagues, Kallmann, and Inouye); (2) use of pairwise instead of probandwise concordance rates; (3) no use of an age correction factor because most twins in the studies cited had passed through the maximum risk period for the disease; and (4) acceptance of diagnostic criteria for schizophrenia used by the original investigators rather than trying to re-diagnose cases retrospectively or including schizophrenia spectrum disorders as concordant.
Table 1. Twin concordance rates for schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Monozygotic concordance (%)</th>
<th>Dizygotic concordance (%)</th>
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<tbody>
<tr>
<td>Essen-Möller (1970)</td>
<td>4/8 (50)</td>
<td>2/27 (7)</td>
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<tr>
<td>Slater and Shields (1953)</td>
<td>24/37 (65)</td>
<td>10/112 (9)</td>
</tr>
<tr>
<td>Tienari (1963)</td>
<td>3/20 (15)</td>
<td>3/42 (7)</td>
</tr>
<tr>
<td>Kringle (1967)</td>
<td>14/45 (31)</td>
<td>14/172 (8)</td>
</tr>
<tr>
<td>Fischer (1973)</td>
<td>5/21 (24)</td>
<td>4/41 (10)</td>
</tr>
<tr>
<td>Gottesman and Shields (1977)</td>
<td>9/22 (41)</td>
<td>3/33 (9)</td>
</tr>
<tr>
<td>NAS-NRC1 (Kendler and Robine 1983)</td>
<td>30/164 (18)</td>
<td>9/268 (3)</td>
</tr>
<tr>
<td>Onstad et al. (1991)</td>
<td>8/24 (33)</td>
<td>1/28 (4)</td>
</tr>
<tr>
<td>Total, all studies</td>
<td>97/341 (28)</td>
<td>46/723 (6)</td>
</tr>
<tr>
<td>Total, all studies except Slater and Shields and NAS-NRC1</td>
<td>43/140 (31)</td>
<td>27/343 (8)</td>
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1National Academy of Sciences-National Research Council Twin Registry.

Twin Studies of Other CNS Diseases

How does a 28 percent pairwise MZ concordance rate for schizophrenia compare with MZ concordance rates in twin studies of other CNS diseases?

Huntington's Disease. Huntington's disease is an autosomal dominant genetically transmitted disease in which half of all children of an individual who has the disease will be affected. The concordance rate among identical twins should be 100 percent. The disease affects the basal ganglia and cerebral cortex, usually beginning between 35 and 50 years of age and results in choreatic movements of the body and limbs.

Although there has been no twin study of Huntington's disease that meets minimal criteria for adequate sampling and zygosity determination, 19 pairs of twins have been described in the medical literature and the results will be included for comparison with other CNS disorders (Sudarsky et al. 1983). In 14 pairs proven or presumed to be MZ, all 14 were concordant (100%) and had an average intrapair difference in age at onset of less than 1 year. In five other twin pairs proven or presumed to be DZ, one of five (20%) were concordant.

Down's Syndrome. Down's syndrome is a syndrome of mental retardation and congenital abnormalities caused by chromosomal abnormalities. Although no twin study of Down's syndrome has met minimal criteria for adequate sampling or zygosity determination, the syndrome is included for purposes of comparison. Among MZ twins with Down's syndrome in the largest study reported, 18 of 19 (95%) were concordant and among DZ twins, 2 of 127 (2%) were concordant (Smith and Berg 1976). It might be expected that Down's syndrome would have 100 percent concordance in MZ twins but rare cases of MZ twins discordant for this disorder have been clearly documented in the literature (Rogers et al. 1982). In such cases the chromosomal abnormality presumably occurs in one twin but not the other after the initial cleavage of the ovum.

Epilepsy. Epilepsy is a syndrome of clinically different types of seizures and may be divided into multiple etiological subgroups. Epilepsy has been clinically classified into two large groups: cases associated with known brain lesions or metabolic causes and idiopathic cases without such an association. Family studies suggest that genetics is important in the etiology of some types of epilepsy (Sunami 1989). Two studies of epilepsy in twins appear to meet minimum criteria for adequate sampling and zygosity determination. Harvald and Hauge (1965) reported on epilepsy from the twin register in Denmark but made no distinction between cases with known causes and idiopathic cases, thus biasing the results toward discordance. They reported a concordance rate of 10 of 27 (37%) among MZ twins and of 10 of 100 (10%) among DZ twins.

Gedda and Tatarelli (1971), using the twin register of the Mendel Institute in Rome, reported concordance rates for idiopathic epilepsy alone; among MZ twins it was 18 of 19 (95%) and among DZ twins it was 3 of 26 (12%). Combining these two studies results in a concordance rate for MZ twins of 28 of 46 (61%) and for DZ twins 13 of 126 (10%).

High concordance rates are consistent with several other studies of idiopathic epilepsy in twins that do not meet criteria for unbiased sampling (Tsuboi 1980). The most noteworthy of these other studies was conducted by Lennox (1960) in Massachusetts. Between 1934 and 1960 he collected 225 twin pairs in which 1 or both had epilepsy. Because the majority of twins were referred to him by other physicians, his sample presumably was biased toward more difficult-to-
treat cases. He not only separated idiopathic epilepsy, but he further divided his sample by the clinical type of idiopathic epilepsy. On this basis, the concordance rates were as follows: for grand mal epilepsy, MZ 82 percent, DZ 15 percent; for petit mal epilepsy, MZ 75 percent, DZ 0 percent; for psychomotor epilepsy, MZ 39 percent, DZ 5 percent. Lennox concluded that "the high degree of concordance in one-egg twins without brain injury leaves no doubt that heredity is very important in the etiology of epilepsy" (p. 552).

Mental Retardation. Mental retardation is a syndrome of cognitive dysfunction known to accompany many chromosomal and genetic abnormalities and thought to be caused by a wide variety of prenatal and perinatal factors. The incidence of mental retardation among twins is twice that among single births, and it frequently coexists with cerebral palsy, autism, and epilepsy.

Two studies of mental retardation in twins have been done in case registers or limited representative samples. A study based on the Denmark twin register reported concordance rates for MZ twins of 12 of 18 (67%) and for DZ twins 0 of 49 (Harvald and Hauge 1965). The other study was carried out as part of the collaborative perinatal project of the National Institute of Neurological Diseases and Stroke. A sample of 55,043 pregnant women was prospectively followed and their offspring were extensively evaluated until they reached age 7. Among the 508 twin pairs in which zygosity could be clearly established, there were 40 pairs in which at least 1 was mentally retarded (IQ < 70). The concordance rate among MZ twins was 6 of 12 (50%) and among DZ twins, 7 of 28 (25%) (Broman et al. 1987).

Bipolar Disorder. Bipolar disorder is a syndrome of mood disturbance with episodes of mania and/or major depression that are often accompanied by psychotic features. Although it is readily distinguishable in its classic forms, in its less classic forms bipolar disorder blends imperceptibly into schizophrenia and diagnosis may be difficult.

The major twin study of bipolar disorder was carried out by Bertelsen and colleagues (1977) in Denmark, using the national twin registry and central psychiatric register. Diagnostic criteria were relatively broad. Zygosity was established in approximately half the cases with red cell typing and in the other half (in which one twin was deceased) using questionnaires. Smaller twin studies of bipolar disorder using registers or limited representative samples were also carried out by Essen-Moller in Sweden, Slater and Shields in England, Kringlen in Norway, and Torgersen in Norway (Bertelsen et al. 1977; Torgersen 1986). The pairwise concordance rate for these 5 studies is summarized in table 2.

Cerebral Palsy. Cerebral palsy is a disorder of movement and posture with what appears to be a multifactorial etiology. Prenatal, perinatal, and genetic factors have all been proposed to be important. The incidence of cerebral palsy among twins is approximately three times the incidence among single births. Three early studies of twins with cerebral palsy carried out in Edinburgh (Russell 1961), London (Alberman 1964), and Manchester (Griffiths 1967) failed to ascertain zygosity and included large numbers of stillbirths in the samples. More recently Petterson and colleagues (in press), using the Western Australia case register for cerebral palsy, reported data on 46 twin pairs in which 1 or both twins had cerebral palsy. Among the MZ twins, 6 of 15 (40%) were concordant and among the DZ twins, 0 of 21 were concordant. Males predominated among twin pairs with cerebral palsy by a ratio of 2 to 1.

Autism. Autism is a disorder of social relationships and language development that also includes stereotypic or repetitive movements. Its onset is within the first 5 years of life. Recent studies of the fragile X syndrome suggest that genetics plays a significant etiological role in some cases of autism. A twin study of autism carried out by Folstein and Rutter (1977) in England met criteria for a limited representative sample; it attempted to "obtain information on all school age autistic twin pairs in Great Britain" (p. 298) by canvassing psychiatric, pediatric, and educa-

Table 2. Twin concordance rates for bipolar disorder

<table>
<thead>
<tr>
<th>Study</th>
<th>Monozygotic Concordance (%)</th>
<th>Dizygotic Concordance (%)</th>
</tr>
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<tbody>
<tr>
<td>Essen-Moller (1970)</td>
<td>2/8 (25)</td>
<td>0/3 (0)</td>
</tr>
<tr>
<td>Slater and Shields (1953)</td>
<td>4/6 (67)</td>
<td>7/30 (24)</td>
</tr>
<tr>
<td>Kringlen (1967)</td>
<td>2/6 (33)</td>
<td>0/20 (0)</td>
</tr>
<tr>
<td>Bertelsen et al. (1977)</td>
<td>32/55 (58)</td>
<td>9/52 (17)</td>
</tr>
<tr>
<td>Torgersen (1986)</td>
<td>4/4 (100)</td>
<td>0/6 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>44/79 (56)</td>
<td>16/111 (14)</td>
</tr>
</tbody>
</table>
infection. CNS symptoms recurring as much as three decades after the initial
known to be a chronic disorder with one or more muscle groups. It is
sis) or paralytic (flaccid weakness in
volvement) to nonparalytic (CNS
systemic symptoms but no CNS in-
dicates infection) or abortive (minor
signs and symptoms but no paraly-
was not carefully ascertained. The definitive
twin study of poliomyelitis was car-
ried out by Herndon and Jennings
(1951) in North Carolina on all re-
ported cases of the disease between
1940 and 1948. Clinical details were
ascertained by contacting treating
physicians and public health nurses
and by examination of birth records.
Zygosity was confirmed by photo-
graphs, red cell typing, and derma-
toglyphics; the twins were all exam-
ined and extensive family histories
taken. Twins were included in the
data analysis only if they were living
together at the onset of the disease,
thereby suggesting that both had been exposed. In 46 twin pairs stud-
ted, the MZ concordance rate was 5
of 14 (36%) and the DZ concordance
rate was 2 of 31 (6%).

Congenital Anomalies of CNS. Congenital anomalies are a measure of prenatal events that may
be caused by chromosomal (e.g., Down's syndrome), genes (e.g.,
polycystic kidneys), infections (e.g., rubella), drugs (e.g., thalidomide), or
other chemicals (e.g., alcohol). In the
majority of cases, however, the etiol-
ology of the congenital anomaly is un-
known. The incidence of congenital
anomalies among twin births is
higher than among single births; in
fact, it has been said that "in itself
MZ twinning can be considered a
congenital malformation" (Myrian-
thopoulos 1975, p. 6).

There have been two studies of congenital anomalies in limited repre-
sentative samples in which CNS
anomalies were reported separately.
The first was reported by Myriantho-
poulos (1975) as part of the collabo-
rative perinatal project previously
described. Of the MZ twin pairs
with CNS congenital anomalies, one
of four (25%) was discordant for anomalies but not for type of mal-
formation (one had hydrocephaly
and the other had macrocephaly).
The remaining three MZ twin pairs
were discordant for anencephaly,
microcephaly, and "a 1946 recom-
bination of CNS malformations"
p. 22). Of the DZ twin pairs with
CNS anomalies, zero of five were
concordant (discordance was for
anencephaly, microcephaly, hydro-
cephaly, macrocephaly, and encepha-
locele). Myrianthopoulos concluded
that "concordance in twins in general
for CNS malformations is low" (p. 22). The other limited representa-
tive sample was reported by Came-
ron and colleagues (1983) who con-
ducted a prospective investigation of
1,074 consecutive twin pairs born in
Birmingham, England, and another
350 twin pairs born in Ghent, Bel-
gium. From this series, one of two
(50%) of the MZ twin pairs born
with CNS congenital anomalies was
concordant (for hydrocephalus) and
the other was discordant (for anen-
cephaly).

Although the numbers of CNS
congenital anomalies from these two
studies are small, the results are rein-
forced by three other studies of
larger numbers of twins that did not
ascertain zygosity carefully and so
cannot be directly compared. Record
and McKeown (1951) studied 20 twin
pairs with CNS anomalies born in
Birmingham between 1940 and 1947;
Hay and Wehrung (1970) reported
on 88 CNS anomalies among 399,700
twin pairs identified by the National
Cleft Lip and Palate Intelligence
Service; and Stevenson and
colleagues (1966) described 12 CNS
anomalies among 5,022 twin pairs in
a World Health Organization (WHO) multicenter study. For these three studies combined, the concordance rate for presumed MZ twin pairs was 12 of 75 (16%) and for presumed DZ twin pairs was 1 of 45 (2%), confirming the low concordance rate for congenital CNS anomalies reported in the two studies with better methodology. In summarizing their findings, Hay and Wehrung (1970) noted: "The literature on congenital CNS malformation contains many individual case reports of nonconcordant MZ pairs, the conclusion usually being that the genetic contribution to the etiology of these conditions is low" (p. 669). This low concordance rate for congenital anomalies of the brain is surprising in view of the fact that rare cases of hydrocephaly are known to be genetically transmitted (Edwards 1961). Furthermore, it suggests that many brain anomalies are caused by prenatal environmental influences that selectively affect only one member of the identical twin pair.

Multiple Sclerosis. Multiple sclerosis is a demyelinating disease of the brain and spinal cord usually beginning between ages 20 and 40. It occurs more commonly in temperate climates and epidemics have been observed among isolated populations. Studies of immigrants from areas of low prevalence to areas of high prevalence have suggested that the original insult to the brain takes place before the age of 20. Infectious agents are suspected, although recent studies of human leukocyte antigens HLA imply that genetic factors may also be involved in some cases.

Since 1966 there have been seven studies of multiple sclerosis in twins; three of these were based on case registers (Heltberg [1987] in Denmark; and Bobowick and colleagues [1978] using the NAS-NRC Twin Register). Another study included a limited representative sample of Canada’s nationwide clinics, which covers virtually all cases of the disease (Ebers et al. 1986). The results of these studies appear in table 3. The Finnish study included MRI analysis. One of the MZ twins classified as concordant was an asymptomatic individual diagnosed on the basis of MRI findings alone. Preliminary data from other studies suggest that the use of MRI elevates the MZ concordance rate but not the DZ concordance rate in multiple sclerosis.

The other three twin studies of multiple sclerosis were based on twins recruited by advertisements and direct referrals from physicians and should therefore be regarded as accumulated case reports (Mackay and Myrianthopoulos 1966; Williams et al. 1980; Currier and Eldridge 1982; McFarland et al. 1984). Interestingly, the MZ concordance rate from these three studies combined was 22 of 80 (28%), a rate virtually identical to the register studies, whereas the combined DZ concordance rate was 9 of 81 (11%), slightly higher than the register studies.

Parkinson’s Disease. Parkinson’s disease classically consists of tremor at rest, rigidity, and bradykinesia and has a peak onset in the seventh decade of life. Occasional case reports of family clusters were found in the literature as early as a century ago. Until recent years it was assumed that the disease had an important genetic component.

Marttila and colleagues (1988) reported the results of a Parkinson’s disease twin study using the Finnish case register with all twins born before 1958 and alive in 1967. The case register was linked with the Finnish hospital discharge register and the

<table>
<thead>
<tr>
<th>Country and study</th>
<th>Monozygotic concordance (%)</th>
<th>Dizygotic concordance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heltberg (1987)</td>
<td>4/19 (21)</td>
<td>1/31 (3)</td>
</tr>
<tr>
<td>Finland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinnunen et al.</td>
<td>2/11 (18)</td>
<td>0/10 (0)</td>
</tr>
<tr>
<td>(1987, 1988)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAS-NRC†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bobowick et al.</td>
<td>2/5 (40)</td>
<td>0/4 (0)</td>
</tr>
<tr>
<td>(1978)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ebers et al.</td>
<td>9/27 (33)</td>
<td>1/43 (2)</td>
</tr>
<tr>
<td>(1986)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>17/62 (27)</td>
<td>2/88 (2)</td>
</tr>
</tbody>
</table>

†National Academy of Sciences–National Research Council Twin Registry.
sickness insurance register to identify cases of Parkinson's disease. Zygosity was established using the questionnaire method. Among MZ twin pairs, 0 of 18 were concordant for Parkinson's disease and among DZ twin pairs, 1 of 14 (7%) was concordant. The authors concluded that "The prevalence of Parkinson's disease in twins compares with the prevalence in the general population . . . suggests that Parkinson's disease is an acquired disease not caused by a hereditary process" (p. 1217).

Two other twin studies of Parkinson's disease have been carried out, but both used accumulated case reports. Ward and colleagues (1983) in the United States identified 62 twin pairs in which 1 or both had Parkinson's disease "through adult twin registries . . . through notices in medical journals, notices in newsletters of voluntary Parkinson's disease organizations, announcements at neurology meetings, and informal inquiries among professional colleagues" (p. 816). Similarly, Marsden (1987) in England identified 22 twin pairs with Parkinson's disease by placing an advertisement in the newsletter of the Parkinson's Disease Society of the United Kingdom. The results of the Ward and colleagues and Marsden studies strongly support the Marttila and colleagues (1988) finding that concordance for Parkinson's disease among either MZ or DZ twins is very rare. These results have puzzled researchers, who have noted that the concordance rate for Parkinson's disease among twins is lower than the concordance rate for siblings or parents of such patients. Eldridge and Ince (1984) have even speculated that twins may acquire a protective factor from their mother in utero.

Tourette Syndrome and Alzheimer's Disease. A twin study exists for each of these CNS disorders, but in neither case is it based on representative samples. A twin study of Tourette syndrome by Price and colleagues (1985) was based on cases recruited through advertising to members of the Tourette Syndrome Association. The reported concordance rate was 16 of 30 (53%) for MZ twins and 1 of 13 (8%) for DZ twins. When criteria for concordance were broadened to include any tics in the co-twin, the concordance rates increased to 77 percent for MZ twins and 23 percent for DZ twins.

There has also been one twin study of Alzheimer's disease by Nee and colleagues (1987), but the twins were recruited "through contacts with the Alzheimer's Disease and Related Disorders Association, families of patients, Mothers of Twins Clubs, and physicians" (p. 359) and thus were accumulated case reports. The reported concordance rate was 7 of 17 (41%) for MZ twins and 2 of 5 (40%) for DZ twins. A followup of "senescent" twin pairs by Jarvik and colleagues (1980) of twins originally recruited by Kallmann with radio and newspaper advertisements is limited because it uses a biased sample and has diagnostic problems. A preliminary report from the NAS-NRC registry found a 60 percent concordance rate for MZ twins with Alzheimer's disease (Breitner et al. 1990); when this study is completed, it should help clarify the concordance rate for this disease.

Discussion

Although twin studies are only one means to assess genetic aspects of diseases (with adoption studies, pedigree studies, and linkage analysis being other means), twin studies are especially useful because they have been carried out for so many different diseases (see table 4). These studies thus afford an opportunity to roughly compare the genetic contribution to different conditions. It is acknowledged that schizophrenia, like epilepsy, mental retardation, cerebral palsy, and some other conditions discussed earlier, is almost cer-

Table 4. Twin concordance rates for central nervous system disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Monozygotic concordance (%)</th>
<th>Dizygotic concordance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huntington's disease</td>
<td>14/14 (100)</td>
<td>1/5 (20)</td>
</tr>
<tr>
<td>Down's syndrome</td>
<td>18/19 (95)</td>
<td>2/127 (2)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>20/46 (61)</td>
<td>13/126 (10)</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>18/30 (60)</td>
<td>7/77 (10)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>44/79 (56)</td>
<td>16/111 (14)</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>6/15 (40)</td>
<td>0/21 (0)</td>
</tr>
<tr>
<td>Autism</td>
<td>4/11 (36)</td>
<td>0/10 (0)</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>5/14 (38)</td>
<td>2/31 (6)</td>
</tr>
<tr>
<td>Congenital anomalies of the CNS</td>
<td>2/8 (33)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>97/341 (28)</td>
<td>48/723 (6)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>17/62 (27)</td>
<td>2/88 (2)</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>0/18 (0)</td>
<td>1/14 (7)</td>
</tr>
</tbody>
</table>

Note.—CNS = central nervous system.
tarily comprised of a variety of etiological subgroups. Also, given subgroups may theoretically range from exclusively genetic to nongenetic in origin. Despite such heterogeneity, the pairwise concordance rate for schizophrenia when compared with other CNS conditions for which twin data are available is roughly comparable to multiple sclerosis and is slightly lower than congenital anomalies of the CNS, poliomyelitis, or autism. The MZ twin concordance rate for bipolar disorder is exactly twice the rate for schizophrenia (56% vs. 28%).

The question remains as to whether we are overestimating the genetic contribution to schizophrenia. Genetics remains the only clearly defined etiological factor for this disease; this may be because genetics are the most important factor or merely because the other etiological factors have not yet been identified. Our assumptions about the answers to such questions are important because they define both the advice provided to families regarding genetic counseling about schizophrenia as well as research strategies that are used to further explicate this disease.

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The Author

E. Fuller Torrey, M.D., is a Guest Worker, Twin Study Unit, NIMH Neuroscience Center, St. Elizabeths Hospital, Washington, DC.