The Genetics of Anxiety Disorders

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ANXIETY AND RELATED DISORDERS

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ALISON M. MACDONALD, BSc, and ROBIN M. MURRAY, MD

There is considerable evidence that fear is partly genetically transmitted in the animal kingdom, as might be expected for an emotion with evolutionary advantages for survival (Marks, 1987). If, as seems likely, the related experience of anxiety in humans is also partly innate, then one way of conceptualizing anxiety disorders is as occurring in vulnerable individuals on the extreme of a continuum of liability distributed normally throughout the population (Falconer, 1965). Such vulnerabilities are generally conferred by a combination of genetic and environmental factors, partly transmitted within families; it is the task of genetic research to identify patterns of familial transmission, to quantify these effects, and to disentangle the relationships of the multiple contributing factors.

The principle tools of psychiatric genetic epidemiology are family, twin, and adoption studies. These rely on the combination of principles derived from Mendelian and quantitative genetics with reliable assessment of psychopathology in relatives of affected individuals. A full discussion of these methods and their current applications to psychiatric disorders may be found

in Tsuang, Kendler, and Lyons (1991).

To date there have been no adoption studies of anxiety disorders. Most work has been conducted on families, usually with first degree relatives alone but one or two studies have also examined second degree relatives; comparisons have also been made between identical (monozygotic, MZ) and non-identical (dizygotic, DZ) twins. Families and twins have usually been ascertained through an index case, the proband, diagnosed with the disorder of interest, either through his or her attendance at a clinic, through answering advertisements, or less often, by population screening. There are also a number of genetic studies of nonclinical samples of volunteer twins that provide complementary information about symptoms of anxiety and neurotic personality traits in the "normal" population.

ANXIETY NEUROSIS

Early studies of anxiety disorder before the development of operational diagnostic criteria (Feighner et al., 1972; Spitzer, Endicott, & Robins, 1978) examined relatives of index cases diagnosed variously as anxiety neurosis (Brown, 1942; Mclnnes, 1937), neurocirculatory asthenia (Cohen, Badal, Kilpatrick, Reed, & White, 1951), irritable heart or DaCosta's syndrome (Wood, 1941). These studies probably include cases who today would be diagnosed as panic disorder (PD) or generalized anxiety disorder (GAD) in

the United States by DSM-III-R (American Psychiatric Association, 1987), or would fall under one of the subcategories of anxiety neurosis covered in the International Classification of Diseases (World Health Organization, 1978) used elsewhere. However, some cases included in these old studies would not meet modern criteria; for example, an individual would have been diagnosed as having neurocirculatory asthenia by Cohen et al. (1951) for reporting headaches and breathlessness (which would not meet modern criteria for PD) or, on the other hand, for suffering anxiety attacks, palpitations, and a range of somatic symptoms (which probably would). This unknown element makes the older reports hard to compare with recent studies. Nevertheless, as seen in Table 6.1, there is considerable agreement among the studies, with the reported rates of disorder in first degree relatives in the range 15% to 16% compared with 1% to 5% in controls.

The early studies relied on the family history (FH) method; that is, the probands were asked about their relatives and judgments were made about the latters' diagnostic status on the basis of such reports. One family history study, conducted using operational criteria (Noyes et al., 1978), produced findings remarkably similar to the earlier studies. However, the FH method is known to underestimate levels of pathology (Andreasen, Endicott, Spitzer, & Winokur, 1977; Andreasen, Rice, Endicott, Reich, & Coryell, 1986) and the preferred method is the family interview (FI); in this, details of the family are obtained from the proband, then as many relatives as possible are directly

interviewed about their psychiatric history and current symptoms. The single family interview study predating operational criteria found a 49% rate of anxiety neurosis (neurocirculatory asthenia) among 37 adult offspring versus 5.6% in controls (Wheeler, White, Reed, & Cohen, 1948). This study was reported only as an abstract for a conference presentation, and few details are given, but it seems to be related to that of Cohen et al. (1951).

Table 6.1 Family Studies of Anxiety Neurosis

Study	Relative[1]	Family History (FH) or Family Interview (FI)	Proband Diagnosis[2]	Prevalence in Relatives (%)		Total	In Controls
				Males	Females		
Brown (1942)	2°	FH	AN			3	
Pauls et al. (1979)	2°	FH	AN	5	14	10	
McInnes (1937)	1°	FH	AN			15	4-5
Brown (1942)	1°	FH	AN			15	0
Cohen et al. (1951)	1°	FH	AN	12	20	16	0.4
Noyes et	1°	FH	AN	13	24	18	3

al. (1978)							
Moran & Andrews (1985)	1°	FH	AG	7	19	13	
Hopper et al. (1987)	1°	FH	PD	9	15	12	
Wheeler et al. (1948)	1°	FI	AN			49	
Crowe et al. (1983)	1°	FI	AN	22	42	31	
Cloninger et al. (1981)	1°	FI	AN (1)[3]	2	13	8	3
			(2)	9	18	14	7

[1] 1° First degree relative
2° Second degree relative

[2] AN Anxiety neurosis (includes Neurocirculatory asthenia)
PD Panic Disorder
AG Agoraphobia

[3] (1) Definite cases
(2) Combined definite and questionable cases

A more recent interview study by Cloninger, Martin, Clayton, and Guze (1981) reported that 8% of interviewed first degree relatives of 66 anxiety neurotics had a definite anxiety neurosis, using strict criteria (Feighner et al.,

1972), rising to 14% when questionable cases were included, a rate comparable with the earlier family history studies. A further feature of the family studies of anxiety neurosis is that about twice as many female relatives are found to be affected compared with male relatives; thus any attempts to fit genetic models to the data must take these sex differences into account (Table 6.1). It is clear from the studies reviewed, for all their faults, that anxiety neurosis is familial, but that does not make it genetic. Twin studies have been used to try and separate genetic and environmental factors.

Two twin studies of anxiety neurosis preceded the development of operationalized criteria. Slater and Shields (1969) studies a series of twins ascertained through the routine registration procedures of the Maudsley Hospital, London, UK. As with the family studies, they found that the proportion of affected co-twins increased as the criteria for concordance were relaxed (Table 6.2). Torgersen (1978) examined twins from the population-based Norwegian twin registry and his lower concordance rates may well reflect the different ascertainment procedures. It can be seen from Table 6.2 that both the London and Norwegian studies reported higher concordance in MZ than in DZ twins, that is, a genetic effect. Torgersen has subsequently shown that concordance rates for neurosis vary according to the “severity” of the treatment center where the proband was ascertained (Torgersen, 1983a), which is assumed to reflect the severity of the disorder. These differing levels of severity will certainly be negatively related to

prevalence rates; this may partly explain the changing concordance rates, but these probably also reflect differing levels of genetic influence on mild and severe disorders.

Table 6.2. Twin Studies of Anxiety Neurosis

Study	Co-Twin Diagnosis	Zygosity	Number of Pairs (N)	Concordance (%)
Slater & Shields (1969)	Any anxiety disorder	MZ	17	41
		DZ	28	4
	Any diagnosis	MZ	20	47
		DZ	40	18
Torgersen (1978)	Definite & anxiety	MZ	30	31
		DZ	56	9

With the introduction of DSM-III (American Psychiatric Association, 1980), subsequent studies have focused on subcategories of anxiety neurosis; panic disorder (PD), agoraphobia (Ag), simple and social phobias (SP), generalized anxiety disorder (GAD), and obsessive-compulsive disorder (OCD). For simplicity, we discuss the genetic research under the diagnostic headings.

TABLE 6.3 Family Studies of SSM-III Categories of Anxiety disorder: Panic Disorder and Agoraphobia

Study	Relative[1]	Family History (FH) or Family Interview (FI)	Proband Diagnosis[2]	Prevalence in Relatives (%)		Total
				Males	Females	
Moran & Andrews (1985)	1°	FH	AG	7	19	13
Hopper et al. (1987)	1°	FH	PD	9	15	12
Crowe et al. (1983)	1°	FI	PD	17	33	35
Harris et al. (1983)	1°	FI	AG	17	46	32
			PD	18	46	33
Noyes et al. (1986)	1°	FI	AG			AG 11.6
						PD 8.3
			PD			AG 1.9
						PD 17.3

[1] 1° First degree relative,
2° Second degree relative

[2] AN Anxiety neurosis (includes Neurocirculatory asthenia)
PD Panic Disorder
AG Agoraphobia

Panic Disorder (PD) and Agoraphobia (Ag)

Most of the recent family interview studies of the DSM-III categories of PD and Ag have been conducted by a group in Iowa (Crowe, Noyes, Pauls, & Slymen, 1983; Harris, Noyes, Crowe, & Chaudhry, 1983; Noyes et al., 1986) using overlapping samples. The results are summarized in Table 6.3.

The final report (Noyes et al., 1986) compared relatives of 40 Ag patients, 40 PD patients, and 20 non-anxious controls, in an attempt to examine whether the separation of Ag from anxiety states (PD) incorporated in DSM-III, could be justified on familial grounds. The morbidity risks for Ag and PD, respectively, among relatives of PD index cases were 1.9% and 17.3%, while among relatives of Ag index cases the corresponding risks were 11.6% and 8.3%; that is, PD occurs in the relatives of both PD and Ag probands, but Ag is largely confined to the relatives of Ag index cases. These findings led the authors to suggest that Ag is a more severe variant of PD, in effect what Hallam (1978) argued. This view has been adopted in DSM-III-R.

Other studies that have focused on agoraphobia have found higher rates

of the disorder in relatives of index cases than in controls. Solyom, Beck, Solyom, and Hugel (1974) examined histories of 47 phobic patients, 91% of whom were agoraphobic, and found that in 45% of the cases there was a family history of psychiatric disorder with 30% of the mothers having phobias, as opposed to between 19% to 23% of families of nonphobic controls.

Buglass, Clarke, Henderson, Kreitman, and Presley (1977) noted a positive family history of phobic disorder in 7% of parents and 8% of siblings of 30 agoraphobic women, compared with 2% and 3%, respectively, in families of controls. Moran and Andrews (1985) investigated the family histories of 60 probands who were consecutive attenders at an Ag treatment unit and found a 12.5% estimated lifetime risk of Ag among their 232 parents and siblings.

Noyes et al. (1986) also noted increased risks of alcohol disorders in male relatives of Ag cases (30.8%), though 30% of probands also had secondary alcohol or sedative drug use disorders. However, they found no increase in affective disorders in either group of relatives, in spite of 35% of PD probands and 48% of Ag probands themselves having secondary major affective disorder. This latter finding may be in part a result of the application of a diagnostic hierarchy (Leckman, Weissman, Merikangas, Pauls, & Prusoff, 1984).

Others (Pauls, Crowe, & Noyes, 1979; Pauls, Bucher, Crowe, & Noyes, 1980) have argued that the mode of transmission of PD is that of an autosomal dominant gene with incomplete penetrance, based on the distribution of cases in second degree relatives and on a pedigree analysis of 19 families. Subsequently, Crowe et al. (1983) fitted single major locus models and multifactorial polygenic transmission models with sex dependent thresholds (Reich, James, & Morris, 1972) to family data on PD. However, the results were inconclusive and they were unable to exclude either model.

A more recent study of pure PD cases with and without agoraphobia, albeit using family history data (Hopper, Judd, Derrick, & Burrows, 1987; Hopper, Judd, Derrick, Macaskill, & Burrows, 1990) used modelling techniques to explore the familial pattern of PD. This study found evidence for contributions to familiality from both genetic factors and sibship environment (i.e., the family environmental factors shared by brothers and sisters and contributing to their resemblance) as well as a suggestion of negative assortative mating. The latter finding, that individuals with PD may be less likely to marry a similarly affected spouse, reflects the experience of many clinicians.

Torgersen (1983b) re-analyzed data from his twin study (Torgersen, 1978) in terms of DSM-IH criteria. The study included 32 MZ and 53 DZ adult same-sexed twin pairs with a proband with an anxiety disorder. They were

selected from a population-based psychiatric twin register, and directly assessed using a structured psychiatric interview. Thirty-one percent of the MZ co-twins of 13 probands with panic disorder and agoraphobia with panic attacks were concordant for anxiety disorder with panic attacks, while there was zero concordance among the 16 DZ twin pairs. It should be noted that none of the 4 concordant MZ pairs had exactly the same diagnostic subtype, and the co-twin concordance was for a looser diagnosis than DSM-III PD, involving less frequent panic attacks.

The results of the recent twin and family studies have been used to support arguments for Panic Disorder (with or without phobic avoidance, i.e., Ag) as a distinct category, distinct that is from other anxiety disorders and from major affective disorder (e.g., Crowe, 1988) in keeping with Klein and Klein (1988) pharmacologically based dissection of the anxiety neurosis category placing primacy upon the panic symptoms. However, family studies of index cases with major depression, with or without secondary anxiety, have found different and apparently conflicting results which are only just beginning to be resolved. The Yale family studies (Leckman, Weissman, Merikangas, Pauls, & Prusoff, 1983; Leckman, Merikangas, Pauls, Prusoff, & Weissman, 1983; Weissman, Leckman, Merikangas, Gammon, & Prusoff, 1984) found that first degree relatives of individuals with both major depressive and anxiety disorders had higher rates of both diagnoses than did relatives of individuals with major depression only. Other studies show that

this pattern only seems to occur if the index cases have mixed disorders, and not among relatives of probands with depression secondary to anxiety; in such cases relatives had higher rates of anxiety disorders but not of depression (Coryell et al., 1988; Van Valkenburg, Akiskal, Puzantian, & Rosenthal, (1984). A recent family study of probands with primary depression and various secondary anxiety syndromes found that only the relatives of cases with secondary panic attacks had higher rates of anxiety disorders than relatives of patients with depression alone. The excess anxiety disorders were obsessional and phobic disorders and not panic disorder (Coryell, Endicott, & Winokur, 1992), a finding which awaits replication, but may reflect a nonspecific vulnerability to neurotic symptoms in these relatives.

A further re-analysis of the Norwegian twin data appears to confirm the family study findings; Torgersen (1990) found that co-twins of MZ twin index cases with major depression or mixed anxiety depression were significantly more likely to have diagnoses of depression or mixed anxiety depression than might be expected by chance. For index twins with "pure" anxiety, however, co-twins were more likely to have a diagnosis of anxiety disorder, but not of depression or a mixed anxiety depression. This relationship became even more marked when the same data were analyzed in terms of depression with and without panic attacks versus anxiety disorder with panic attacks; though the numbers are very small, depression with and without panic attacks

seemed to be related while cases of “pure” anxiety with panic showed concordance for anxiety with panic only. Although 4 of 18 MZ co-twins are concordant for anxiety with panic attacks, the specificity of diagnosis only extends as far as the fact that they all have panic attacks; an earlier paper indicates that the co-twins have different subcategories of anxiety disorder from the index twins in each case (Torgersen, 1983b).

To conclude, interpretation of the literature on familiality of panic disorder and agoraphobia is complicated by methodological differences among the studies, particularly in the selection of probands and application of diagnostic hierarchies. There is considerable evidence that the two subcategories are familial, and that they are related, with both family and twin studies supporting the notion that agoraphobia is a more severe variant of panic disorder. Earlier suggestions that PD is a form of anxiety disorder transmitted according to a Mendelian autosomal dominant pattern have not been vindicated, and the transmission pattern remains unclear; both autosomal dominant with incomplete penetrance and polygenic models have been postulated. The contribution of familial environment and negative assortative mating to familial prevalence further complicates interpretation of segregation patterns in relatives.

The relationship of PD, Ag, and affective disorders is complex; it appears that in families ascertained through probands with mixed disorders, there

may be a predisposition to both anxiety and affective disorders. For those ascertained through a more "pure" anxiety disorder, and panic disorder in particular, the familial predisposition is more specifically to anxiety disorders, though not perhaps to PD alone but to a broader spectrum of related syndromes of PD, Ag, phobias and OCD.

Generalized Anxiety Disorder (GAD)

Only one study has specifically addressed the familiality of GAD. Noyes, Clarkson, Crowe, Yates, & McChesney, (1987) recruited 20 probands diagnosed GAD, according to DSM-III and DSM-III-R, through newspaper advertisements. The frequency of anxiety disorders in their 123 first degree relatives (of whom two thirds were interviewed) was compared with that in 241 relatives of 20 PD probands, 256 relatives of 40 Ag probands, and 113 relatives of controls who had been involved in an earlier study (Noyes et al., 1986).

Noyes et al. found a higher proportion of relatives of GAD probands with GAD than in the other groups (19.5% versus 3.5-5.4%). However, this must, as the authors recognized, be interpreted with caution; the use of volunteer probands, 14 of whom had additional affective disorder and 37% of whom had axis II personality disorders, as well as the nonblind diagnostic assignment and small number of families studied, preclude specific

conclusions about familiality. The lack of evidence for a relationship of GAD and MDD is consistent with earlier family studies of PD and Ag probands (Noyes et al., 1986). The perceived importance of psychological stressors, and the high rates of personality disturbance in relatives of these GAD probands (35% versus 13.7% in controls) is also of interest. It may be that these findings in part reflect ascertainment biases associated with recruiting by advertising, but they also suggest some personality predisposition to GAD; this is of interest to clinicians in the light of other studies finding a relationship between levels of neurotic symptoms and personality disorders (Tyrer et al., 1990).

Phobic Disorders and Fears

Most family studies of phobic disorders deal with agoraphobia, and these have already been discussed. Fyer et al. (1990) conducted a blind family interview study of 49 first degree relatives of 15 simple phobic (SP) probands (without other anxiety disorder) compared with 119 relatives of 38 well controls. Thirty-one percent of 58 relatives versus 16% of control relatives received a lifetime diagnosis of SP and the risk for other psychiatric disorders did not differ. Only 2 of the 15 relatives had the same type of SP as the proband. However, when the simple phobias were subcategorized into animal and situational (non-animal) there was some evidence for specificity of transmission, animal phobias occurring more frequently in relatives of animal

phobics than in relatives of either situational phobics or controls, and a similar pattern for situational phobias. The study also collected family history data on non-interviewed relatives, and found a significant, albeit lower, difference in rates of SP in relatives of SP probands and controls (10% versus 2%). The authors conclude that DSM-III-R simple phobia is a "highly functional disorder that breeds true and does not transmit an increased risk for other phobia or anxiety disorders."

Fyer et al. (1990) also investigated ratings for 17 irrational fears in their study and found no evidence for familiality, nor any association with increased risk for SP. This is in marked contrast with studies of fears conducted in normal populations (Philips, Fulker, & Rose, 1987; Rose & Ditto, 1983).

A single family history study (Reich & Yates, 1988) nonblindly compared relatives of 17 probands with social phobias (6 of whom also had MDD), 10 controls, and 88 probands with panic disorder. The SP group were recruited from a treatment study, the other two groups through advertising. While the rates for SP in relatives of SP and PD probands were significantly different (6.6% versus 0.4%, respectively) the finding that 2.2% of control relatives had SP was not significantly different from the rate in SP relatives, probably due to the small sample size.

Fyer et al.'s (1990) family interview study of simple phobias found no excess of social phobia in relatives.

Obsessive-Compulsive Disorder (OCD)

OCD is a relatively rare disorder amongst the categories of anxiety disorder, with a prevalence rate traditionally accepted as being in the region of 0.05% (Raudin, 1953). Recent studies suggest that individual symptoms and more loosely defined forms of OCD may be much more common in the general population than hitherto realized (Karno, Golding, Sorenson, & Burnam, 1988; Sanavio, 1988). This difficulty in defining OCD has made interpretation of family and twin studies difficult, and the methodology and existing literature are examined in detail by Macdonald et al. (1991).

Family studies predating operationalized criteria report rates of OCD between 1% and 10% in first degree relatives (Brown, 1942; Luxenberger, 1930; Rosenberg, 1967; Raudin, 1953), but when criteria are broadened to include obsessional traits in relatives, these rates rise to between 3% and 37% (Kringlen, 1965; Lewis, 1936; Lo, 1967). The levels are even higher when "any abnormality" is included. Such variable rates make familiality difficult to interpret when the population rates needed for comparison are just as variable (Carey, Gottesman, & Robins, 1980), but these older studies suggest that there is at least some familial component to the disorder.

The one family study of OCD using a series of RDC diagnosed hospital patients and diagnoses of relatives based on SADS-L interviews, and a control group (McKeon & Murray, 1987), found only one case of OCD among the 149 relatives of 50 probands (0.7%) and one case among the 151 control relatives (0.7%). However, the relatives of OCD cases were found to have higher rates of other neurotic disorders, rates for “any abnormality" were 27% versus 14% in control relatives. These results suggest a familial liability to a broader spectrum of neuroses, rather than to OCD specifically.

Twin studies of OCD have been primarily case reports, and as such are biased towards being MZ and concordant (Rachman & Hodgson, 1980), apart from Carey and Gottesman’s (1981) study of phobic and obsessional twins from the Maudsley Hospital Twin Register. Carey and Gottesman (1981) found that 33% of co-twins in 15 MZ pairs had psychiatric or general practitioner treatment involving obsessional symptoms versus 7% of co-twins in 15 DZ pairs. Obsessional symptoms with or without treatment were noted in 87% of MZ co-twins and 47% of DZ co-twins; in the families of these twins, a history of obsessional traits was reported in between 6% and 27% of first degree relatives (depending on definition) with levels of any psychiatric symptoms up to 48%.

Torgersen (1983b) has also reported 3 MZ and 9 DZ twin pairs, ascertained through the Norwegian population-based twin registry, with a

proband with OCD. None of the co-twins were concordant for OCD, but one MZ and one DZ co-twin had other anxiety disorders and three other co-twins had unspecified non-anxiety diagnosis.

The statistical improbability of identifying a pair of MZ twins concordant for OCD by chance (Marks, Crowe, Drewe, Young, & Dewhurst, 1969) has perpetuated the idea that the finding of even one or two such pairs indicates a strong genetic component to the disorder. However, recent indications that obsessional symptoms are more common than previously thought, as well as the well-known biases that nonsystematic ascertainment of affected twins produce (Rachman & Hodgson, 1980), indicate that as in genetic studies of other types of anxiety disorder more weight should be given to studies of systematically ascertained and assessed probands and their relatives, including twins. Such studies (Macdonald, Murray, & Clifford, 1991; Carey & Gottesman, 1981; McKeon & Murray, 1987; Torgersen, 1983b) indicate that while obsessionality is certainly familial, any genetic predisposition to OCD may be a broader spectrum of neurotic complaints, with little specificity.

The higher rates of obsessional symptoms in the general population and availability of questionnaires for dimensional assessment of obsessionality make this a more fruitful field for behavioral geneticists. Clifford, Murray, and Fulker (1984) fitted genetic models to the scores of 419 pairs of volunteer

twins on the Leyton Obsessional Inventory (LOI) (Snowdon, 1980) and the neuroticism scale of the Eysenck Personality Questionnaire (EPQ) (Eysenck & Eysenck, 1975). Heritability of the trait and symptom scales of the LOI were 47% and 44%, respectively; there seemed to be a genetic factor influencing general neuroticism and contributing to the correlation of the obsessional and N scores, as well as a separate genetic factor contributing to obsessional traits. These findings await replication, but are in accord with clinical studies suggesting a familial predisposition to a broader neurotic spectrum.

SYMPTOMS OF ANXIETY IN NON-CLINICAL POPULATIONS

A series of papers (Jardine, Martin, & Henderson, 1984; Kendler, Heath, Martin, & Eaves, 1986; Kendler, Heath, Martin, & Eaves, 1987; Martin, Jardine, Andrews, & Heath, 1988) have analyzed data collected on 3,798 pairs of adult twins from the Australian National Health and Medical Research Council twin register, on the 14 item anxiety and depression scales of the DSSI (Bedford, Foulds, & Sheffield, 1976) and the neuroticism scale of the EPQ (Eysenck & Eysenck, 1975). These authors have shown that some 33% to 46% of the variance in total anxiety symptom scores seems to be due to additive genetic factors, with most of the remaining variation due to environmental factors specific to the individual. More complex multivariate analyses of individual symptom scores (Kendler et al., 1987) have shown that genes seem to act in a fairly nonspecific way, influencing the overall level of symptoms on the

depression-distress (a mixture of depression/anxiety symptoms), general anxiety, and "insomnia" factors generated from the data, but that apparently there are some minor specific influences of genes on somatic anxiety symptoms. Environmental influences differ across the factors. These results are obtained by fitting various genetic models to the data obtained from twin pairs and testing the fit of these models. Applying rules of parsimony, the model with the smallest number of parameters that provides the best fit to the data is accepted.

Though the specific relevance of these questionnaire assessments of "symptoms" to clinical anxiety and depression is not known, it is interesting that these data coincide with the most recent clinical findings from family studies of depressed and anxious patients (vide supra). That is, there seems to be a mixed anxiety-depression type, with higher levels of familial depression and anxiety symptoms, while if a more "pure" form of anxiety is examined, then relatives have raised rates of anxiety symptoms alone and not of other affective symptoms. This is congruent with the model from Kendler et al. (1987) of an overlapping cluster of symptoms of anxiety and depression which they called "depression-distress" that has nonspecific genetic influences on overall level of symptoms, but with another factor of a more specific type of somatic anxiety that does seem to have some separate heritable influence.

Andrews, Stewart, Allen, and Henderson (1990a) have also reported concordance rates for neurotic disorders in a directly interviewed volunteer twin sample of 446 pairs: 10.2% of MZ pairs were concordant for any lifetime diagnosis of neurotic disorder versus 9.6% of DZ pairs, a nonsignificant difference, and only one DZ female pair and one MZ male pair were concordant for PD/Ag among a total of 34 individual twins receiving these diagnoses. In this twin study, the twins were ascertained through a volunteer sample, not through clinics or by crossmatching population samples with psychiatric registers, and so the twins had not necessarily sought treatment for neurotic disorders. Andrews et al. (1990a) suggest that their findings of no MZ/DZ difference in concordance for neurosis in general or any subtype in particular, the co-occurrence of multiple diagnoses, and the comparable prevalences in this sample with other epidemiological studies may indicate that any underlying genetic vulnerability to neurosis is to trait neuroticism that may itself be sufficiently powerful to lead to severe and chronic symptoms and seeking specialist treatment. This would account for the finding of significant MZ/DZ concordance differences in those twin studies that have ascertained twins through affected probands who had sought treatment (who might be expected to have a higher genetic loading). Such a model would also take account of Torgersen's (1983a) findings of a positive relationship between level of genetic influence and severity of neurotic disorder.

The most recent work on this area addresses the idea of a general neurotic syndrome (Andrews et al., 1990b), an idea popular with some European psychiatrists (Tyrer, 1985), by assessing lifetime prevalence of the various neurotic subcategories in a sample of volunteer twins from the Australian NHMRC register. In all, 27% of the subjects reported symptoms consistent with some diagnosis in their lifetime and the frequencies of co-occurrence of multiple diagnoses was higher than might be expected assuming independent co-occurrence. The twins in this study were not used for a genetic analysis, but new studies from the population-based Virginia twin registry involving direct psychiatric interviews of adult female twins should shed further light on this area (Kendler, Neale, Kessler, Heath, & Eaves, 1992).

MOLECULAR GENETIC AND BIOLOGICAL MARKER STUDIES

In spite of the absence of any convincing pedigree data to suggest that PD could be inherited as a single gene disorder, Crowe, Noyes, Wilson, Elston, and Ward (1987) examined the possibility of linkage between PD and 29 blood type and protein electrophoretic polymorphisms in 198 members (39% affected) of 26 pedigrees. Analysis excluded linkage to 18 of the market loci, but revealed one suggestive of linkage at the alpha-haptoglobin locus on chromosome 16q22 (lod score 2.23). A subsequent study including 10 further pedigrees (Crowe, Noyes, Samuelson, Wesner, & Wilson, 1990) however

excluded linkage at this locus.

Other proposed "biological" markers for PD have been of some interest for geneticists. Wooley (1976) suggested an association between mitral valve prolapse syndrome (MVPS) and PD based on the similarity of clinical pictures and the similar epidemiology, both disorders being familial. As MVPS can be diagnosed echocardiographically, it could have proved to be a useful marker for PD for genetic studies, but further studies (Hickey, Andrews, & Wilken, 1983) have not supported the idea that MVPS accounts for a subgroup of PD. Other authors have been interested in the apparent sensitivity to lactate and carbon dioxide of PD sufferers, as markers of biological aetiology, but these associations have also been shown to be nonspecific and complex as well as causing difficulty on theoretical grounds (Margraf, Ehlers, & Roth, 1986).

DISCUSSION AND CONCLUSIONS

Interest in the role of genetic factors in the aetiology of psychiatric disorders has waxed and waned over the course of the last century. The rapid development of recombinant DNA technology in the last decade has led to success in locating the genes that cause a number of single locus mendelian disorders (such as Fragile X mental retardation syndrome, Cystic fibrosis, myotonic dystrophy). This has resulted not only in an upsurge of interest in the genetics of psychiatric disorders but also new challenges for psychiatric

geneticists. The identification of phenotypes (the observed symptom patterns) of disorders that are transmitted according to the patterns found in single gene disorders has become a priority for those whose aim is to identify the disease alleles and develop biological treatments.

Distinguishing the transmission patterns of disorders caused by just a few major genes against a background of other genetic and environmental effects from those that are polygenic multifactorial disorders is extremely difficult and requires large studies (Reich et al., 1972). Therefore, much recent work has focused on development of methodology, as well as refinement of diagnostic techniques to separate heterogeneous types of disorder. Single gene disorders tend to be rare, and, because anxiety disorders are relatively common (Robins et al., 1984), it is likely that the long observed familiality is due to the combination of multiple genetic and environmental factors, each of small effect; there may be some subtypes or families in which major genes are transmitted.

Although genetic studies of anxiety disorders have increased in sophistication, there has been little integration of the considerable advances in both psychological theory and treatment using behavioral (Marks, 1987) and cognitive (Beck, Emery, & Greenberg, 1985) techniques with behavior genetics methods; the importance of environmental factors in anxiety disorders has been thoroughly demonstrated in these areas and

disentanglement of genetic and environmental factors in aetiology requires reliable and valid assessment of the many putative environmental factors as well as of the diagnostic status of relatives. A recent attempt to combine such approaches (Kendler et al., 1992) led the authors to conclude there would be a "great gain in analytic power ... as genetic-epidemiological models for psychiatric disorders move from treating the environment as an unmeasured latent 'black box' to considering it as an array of specific measurable environmental variables."

This study demonstrated that while parental loss, a much researched early risk factor for affective disorders, contributed only a modest amount (2%) to total variance in liability, it contributed substantially to aggregation within sibships of generalized anxiety disorder, panic disorder, and phobias.

The race to identify single gene mutations is paradoxically invigorating the genetic epidemiological field; the simple quantification of heritability or h^2 can no longer be justified as an adequate goal, there are far more complex and interesting issues to tackle. Twin and family studies, using large samples and varied methodologies can be used to identify phenotypes of anxiety disorder which may be "more genetic" than others and hence to justify and guide linkage work. Such studies can also investigate the influence of assortative mating, family environment and other specific environmental factors in aetiology. The identification of new types of non-Mendelian

inheritance (Flint, 1992) will increase the variety of genetic models available to be tested on family data. We are at the beginning of a period of much more systematic application of genetic methods to anxiety disorders. Hopefully, this will finally bury the destructive "nature v. nurture" quarrels, and bring new understanding of our patients' predicaments.

REFERENCES

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.), Washington, DC: Author.

American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders* (3rd. ed., rev.), Washington, DC: Author.

Andreasen, N. C., Endicott, J., Spitzer, R. L., & Winokur, G. (1977). The family history method using diagnostic criteria: Reliability and validity. *Archives of General Psychiatry, 34,* 1229-1235.

Andreasen, N. C., Rice, J., Endicott, J., Reich, T., & Coryell, W. (1986). The family history approach to diagnosis: How useful is it? *Archives of General Psychiatry, 43,* 421-429.

Andrews, G., Stewart, G., Allen, R., & Henderson, A. S. (1990a). The genetics of six neurotic disorders: A twin study. *Journal of Affective Disorders, 19,* 23-29.

Andrews, G., Stewart G., Morris-Yates, A., Holt, P., & Henderson, S. (1990b). Evidence for a general neurotic syndrome. *British Journal of Psychiatry, 157,* 6-12.

Beck, A. T., Emery, G., & Greenberg, R. L. (1985). *Anxiety disorders and phobias: A cognitive perspective.* (New York: Basic Books).

Bedford, A., Foulds, G. A., & Sheffield, B. F. (1976). A new personal disturbance scale (DSSl-sAD). *British Journal of Social Clinical Psychiatry, 15,* 387-394.

Brown, F. W. (1942). Heredity in the psychoneuroses. *Proceedings of the Royal Society of Medicine, 35,* 785-790.

Buglass, D., Clarke, J., Henderson, A. S., Kreitman, N., & Presley, A. S. (1977). A study of agoraphobic housewives. *Psychological Medicine, 7,* 73-86.

Carey, G., Gottesman, I. I., & Robins, E. (1980). Prevalence rates for the neuroses: Pitfalls in the evaluation of familiality. *Psychological Medicine, 10,* 437-443.

Carey, G., & Gottesman, 1.1. (1981). Twin and family studies of anxiety, phobic, and obsessive disorders. In *Anxiety: New research and changing concepts,* D.F. Klein & J. G. Rabkin, (Eds.), pp. 117-136 (New York: Raven Press).

Clifford, C. A., Murray, R. M., & Fulker, D. W. (1984). Genetic and environmental influences on obsessional traits and symptoms. *Psychological Medicine, 14,* 791-800.

Cloninger, C. R., Martin, R. L., Clayton, P., & Guze, S. B. (1981). A blind follow-up and family study of anxiety neurosis: Preliminary analysis of the St. Louis 500. In *Anxiety: New research and changing concepts,* D. F. Klein & J. G. Rabkin. (Eds.) (New York: Raven Press).

Cohen, M. E., Badal. D. W., Kilpatrick, A., Reed, E. W., & White, P. D. (1951). The high familial prevalence of neurocirculatory asthenia (anxiety neurosis, effort syndrome). *American Journal of Human Genetics, 3,* 126-158.

Coryell, W., Endicott, J., Andreasen, N. C., Keller, M. B., Clayton, P. J., Hirschfeld, R. M. A., Scheftner, W. A., & Winokur, G. (1988). Depression and panic attacks: The significance of overlap as reflected in follow-up and family study data. *American Journal of Psychiatry, 145,* 293-300.

Coryell, W., Endicott, J., & Winokur, G. (1992). Anxiety syndromes as epiphenomena of primary major depression: Outcome and familial psychopathology. *American Journal of Psychiatry, 149,* 100-107.

Crowe, R. R. (1988). Genetic studies of anxiety disorders. In M. T. Tsuang, K. Kendler, & M. Lyons (Eds.), *Genetic issues in psychosocial epidemiology.* New Brunswick, NJ: Rutgers University Press.

Crowe, R. R., Noyes, R., Jr., Pauls, D. L., & Slymen, D. (1983). A family study of panic disorder. *Archives of General Psychiatry, 40,* 1065-1069.

Crowe, R. R., Noyes, R., Jr., Samuelson, S., Wesner, R., & Wilson, R. (1990). Close linkage between panic disorder and alpha-haptoglobin excluded in 10 families. *Archives of General Psychiatry, 47,* 377-380.

Crowe, R. R., Noyes, R., Jr., Wilson, A. F., Elston, R. C., & Ward, L. J. (1987). A linkage study of panic disorder. *Archives of General Psychiatry, 44,* 933-937.

Eysenck, H. J. & Eysenck, S. B. G. (1975) *Manual of the Eysenck Personality Questionnaire.* London: Hodder & Stoughton.

Falconer, D. S. (1965). The inheritance of liability to certain diseases estimated from the incidence among relatives. *Annals of Human Genetics, 29,* 51-76.

Feighner, J. P., Robins, E., Guze, S. B., Woodruff, R. A., Winokur, G., & Munoz, R. (1972). Diagnostic criteria for use in psychiatric research. *Archives of General Psychiatry, 26,* 57-63.

Flint, J. (1992). Implications of genomic imprinting for psychiatric genetics. *Psychological Medicine, 22,* 5-10.

Fyer, A. J., Mannuzza, S., Gallops, M. S., Martin, L. Y., Aaronson, C., Gorman, J. M., Liebowitz, M. R., & Klein, D. F. (1990). Familial transmission of simple fears and phobias. *Archives of General Psychiatry, 40,* 1061-1064.

Hallam, R. S. (1978). Agoraphobia: A critical review of the concept. *British Journal of Psychiatry, 133,* 314-319.

Harris, E. L., Noyes, R., Crowe, R. R. & Chaudhry, D. R. (1983). Family study of agoraphobia. Report of a pilot study. *Archives of General Psychiatry. 40,* 1061-1064.

Hickey, A.. Andrews, G., & Wilken, D. (1983). The independence of mitral valve prolapse and neurosis. *British Heart Journal, 50,* 333-336.

Hopper, J. L., Judd, F. K., Derrick, P. L., & Burrows, G. D. (1987). A family study of panic disorder.

Genetic Epidemiology, 4, 33-41.

Hopper, J. L., Judd, F. K., Derrick, P. L., Macaskill, G. T., & Burrows, G. D. (1990). A family study of panic disorder: A reanalysis using a regressive logistic model that incorporates a sibship environment. *Genetic Epidemiology,* 7, 151-161.

Jardine, R., Martin, N. G., & Henderson, A. S. (1984). Genetic covariation between neuroticism and the symptoms of anxiety and depression. *Genetic Epidemiology, I,* 89-107.

Karno, M., Golding, J. M., Sorenson, S. B., & Burnam, M. A. (1988). The epidemiology of obsessive-compulsive disorder in five U.S. communities. *Archives of General Psychiatry, 45,* 1094-1099.

Kendler, K. S., Heath, A., Martin. N. G., & Eaves, L. J. (1986). Symptoms of anxiety and depression in a volunteer twin population. *Archives of General Psychiatry, 42,* 213-221.

Kendler, K. S., Heath, A., Martin, N. G., & Eaves, L. J. (1987). Symptoms of anxiety and symptoms of depression: Same genes, different environments? *Archives of General Psychiatry, 44,* 451-457.

Kendler, K. S.,'Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992). The genetic epidemiology of phobias in women: The inter-relationship of agoraphobia, social phobia, situational phobia and simple phobia. *Archives of General Psychiatry.*

Klein, D. F., & Klein, H. M. (1988). The status of panic disorder. *Current Opinion in Psychiatry, I,* 177-183.

Kringlen, E. (1965). Obsessional neurotics: A long-term follow-up. *British Journal of Psychiatry, 111,* 709-722.

Leckman, J. F., Merikangas, K. R., Pauls, D. L., Prusoff, B. A., & Weissman, M. M. (1983). Anxiety disorders and depression: Contradictions between family study data and DSM-III conventions. *American Journal of Psychiatry. 140,* 880-882.

Leckman, J. F., Weissman, M. M., Merikangas, K. R., Pauls, D. L., & Prusoff, B. A. (1983). Panic disorder and major depression: Increased risk of depression, alcoholism, panic, and

phobic disorders in families of depressed probands with panic disorder. *Archives of General Psychiatry, 40,* 1055-1060.

Leckman, J. F., Weissman, M. M., Merikangas, K. R., Pauls, D. L., & Prusoff, B. A. (1984). Methodologic differences in major depression and panic disorder studies. *Archives of General Psychiatry, 41,* 722-723.

Lewis, A. (1936). Problems of obsessional illness. *Proceedings of the Royal Society of Medicine, 29,* 325-336.

Lo, W. H. (1967). A follow-up study of obsessional neurotics in Hong Kong Chinese. *British Journal of Psychiatry, 113,* 823-832.

Luxenberger, H. (1930). Hereditat und Familientypus derZwangsneurotiker. V KongreBer.f. Psychotherapie in Baden-Baden 1930. Psychiatr. Erblehre, Munchen-Berlin 1938. In Just, *Hdb. d. Erbbiol. d. Menschen.,* Bd.V,2. Teil 853. Berlin: Springer.

Macdonald, A. M., Murray. R. M., & Clifford, C. A. (1991). The contribution of heredity to obsessive-compulsive neurosis and obsessional personality: A review of family and twin study evidence. In M. T. Tsuang, K. Kendler, M.

Lyons (Eds.), *Genetics issues in psychosocial epidemiology.* New Brunswick, NJ: Rutgers University Press.

Margraf, J., Ehlers, A., & Roth, W. T. (1986). Sodium lactate infusions and panic attacks: A review and critique. *Psychosomatic Medicine, 48,* 25-51.

Marks, I. M. (1987). *Fears, phobias and rituals.* New York, NY: Oxford University Press.

Marks, I. M., Crowe, M., Drewe, E., Young, J., & Dewhurst, W. G. (1969). Obsessive-compulsive disorder in identical twins. *British Journal of Psychiatry, 115,* 991-998.

Martin, N. G., Jardine, R., Andrews, G., & Heath, A. C. (1988). Anxiety disorders and neuroticism: Are there genetic factors specific to panic? *Acta Psychiatrica Scandinavia. 77,* 698-706.

Mclnnes, R. G. (1937). Observations on heredity in neurosis. *Proceedings of the Royal Society of Medicine, 30,* 23-32.

McKeon, P., & Murray, R. (1987). Familial aspects of obsessive-compulsive neurosis. *British Journal of Psychiatry, 151,* 528-534.

Moran, C., & Andrews, G. (1985). The familial occurrence of agoraphobia. *British Journal of Psychiatry, 146,* 262-267.

Noyes, R., Clancy, J., & Garvey, M. J. (1978). Is agoraphobia a variant of panic disorder or a separate illness? *Journal of Anxiety Disorders, 1,* 3-13.

Noyes, R., Jr., Clarkson, C., Crowe, R. R., Yates, W. R., & McChesney, C. M. (1987). A family study of generalized anxiety disorder. *American Journal of Psychiatry, 144,* 1019-1024.

Noyes, R., Jr., Crowe, R. R., Harris, E. L., Hamra, B. J., McChesney, C. M., & Chaudhry, D. R. (1986). Relationship between panic disorder and agoraphobia: A family study. *Archives of General Psychiatry, 43,* 227-232.

Pauls, D. L., Bucher, K. D., Crowe, R. R., & Noyes, R. (1980). A genetic study of panic disorder pedigrees. *American Journal of Human Genetics, 32,* 639-644.

Pauls, D. L., Crowe, R. R., & Noyes, R. (1979). Distribution of ancestral secondary cases in anxiety neurosis (panic disorder). *Journal of Affective Disorders, 1,* 287-290.

Philips, K., Fulker, D. W., & Rose, R. J. (1987). Path analysis of seven fear factors in adult twin and sibling pairs and their parents. *Genetic Epidemiology, 4,* 345-355.

Rachman, S. J., & Hodgson, R. I. (1980). Obsessions and compulsions. New Jersey: Prentice-Hall. pp. 39-42.

Raudin, E. (1953). Ein Beitrag zur Frage der Zwangskrankheit, insbesondere ihrer hereditaren Beziehungen. *Archiv fur Psychiatrie und Zeitschrift Neurologie, 191,* 14-54.

Reich, T., James, J. W., & Morris, C. A. (1972). The use of multiple thresholds in determining the mode of transmission of semi-continuous traits. *Annals of Human Genetics, 36,* 162-

184.

Reich, T., & Yates, W. (1988). Family history of psychiatric disorders in social phobia. *Comprehensive Psychiatry. 29,* 72-75.

Robins, L. N., Helzer, J. E., Weissman, M. M., Orvaschel, H., Gruenberg, E., Burke, J. D., & Register, D. A. (1984). Lifetime prevalences of specific psychiatric disorders in three sites. *Archives of General Psychiatry, 41,* 949-958.

Rose, R. J., & Ditto, W. B. (1983). A developmental genetic analysis of common fears from early adolescence to early adulthood. *Child Development, 54,* 361-368.

Rosenberg, C. M. (1967). Familial aspects of obsessional neurosis. *British Journal of Psychiatry, 113,* 405-413.

Sanavio, E. (1988). Obsessions and Compulsions: The Padua Inventory. *Behaviour Research and Therapy, 26,* 169-177.

Slater, E. & Shields, J. (1969). Genetical aspects of anxiety. *British Journal of Psychiatry, 3,* 62-71.

Snowdon, J. (1980). A comparison of written and postbox forms of the Leyton Obsessional Inventory. *Psychological Medicine, 10,* 165-170.

Solyom, L., Beck, P., Solyom, C., & Hugel, R. (1974). Some etiological factors in phobic neurosis. *Canadian Psychiatric Association Journal, 19,* 69-78.

Spitzer, R. L., Endicott, J., & Robins, E. (1978). Research Diagnostic Criteria (RDC). Rationale and Reliability. *Archives of General Psychiatry, 35,* 773-783.

Torgersen, S. (1983a). Genetics of neurosis. The effects of sampling variation upon the twin concordance ratio. *British Journal of Psychiatry, 142,* 126-132.

Torgersen, S. (1983b). Genetic factors in anxiety disorders. *Archives of General Psychiatry, 40,* 1085-1089.

Torgersen, S. (1990). Comorbidity of major depression and anxiety disorders in twin pair.

American Journal of Psychiatry. 147, 1199-1202.

Torgersen, T. (1978). Contribution of twin studies to psychiatric nosology. In *Twin research: Psychology and Methodology* (pp. 125-130). New York: Alan R. Less.

Tsuang, M. T., Kendler, K. S., & Lyons, M. (Eds.) (1991). *Genetic issues in psychosocial epidemiology.* New Brunswick, NJ: Rutgers University Press.

Tyrer, P. (1985). Neurosis divisible? *Lancet, i,* 685-688.

Tyrer, P., Sewewright, N, Ferguson, B., Murphy, S., Darling, C., Brothwell, J., Kingdon, D., & Johnson, A. L. (1990). The Nottingham Study of Neurotic Disorder: Relationship between personality status and symptoms. *Psychological Medicine, 20,* 423-431.

Van Valkenburg, C., Akiskal, H. S., Puzantian, V., & Rosenthal, T. (1984). Anxious depressions: Clinical, family history, and naturalistic outcome— comparisons with panic and major depressive disorders. *Journal of Affective Disorders, 6,* 67-82.

Weissman, M. M., Leckman, J. F., Merikangas, K. R., Gammon, G. D., & Prusoff, B. A. (1984). Depression and anxiety disorders in parents and children: Results from the Yale Family Study. *Archives of General Psychiatry, 41,* 845-852.

Wheeler, E. O., White, P. D., Reed, E., & Cohen, M. E. (1948). Familial incidence of neurocirculatory asthenia ("anxiety neurosis," "effort syndrome"). *Journal of Clinical Investigation, 27,* 562.

Wood, P. (1941). Aetiology of DaCosta's syndrome. *British Medical Journal, I,* 845-851.

Wooley, C. F. (1976). Where are the diseases of yesteryear? DaCosta's syndrome, soldier's heart, the effort syndrome, neurocirculatory asthenia, and the mitral valve prolapse syndrome. *Circulation, 53.* 749-751.

World Health Organization. (1978). Mental disorders: Glossary and guide to their classification in accordance with the ninth revision of the international classification of diseases. Geneva: WHO.