Comorbidity and Family History of Panic Disorder in a Quebec Population: Differences Between Subjects Who Seek Treatment and Those Recruited for a Drug Study.

by Carol Mayne Jacqueline Lane

A thesis submitted to
the Faculty of Graduate Studies and
Research in partial fulfillment of the
requirements for the degree of
Master of Science.

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To My Family

ABSTRACT

The family history and comorbidity of 97 sequential outpatients with DSM-III panic disorder (with or without agoraphobia) was examined. Patients were diagnosed by a psychiatrist and 71 were additionally diagnosed via structured clinical interview (SCID or A-DIS-R). All subjects resided in the province of Quebec. Subjects consisted of two groups: patients referred for treatment and patients recruited by a newspaper advertisement for a drug study on panic disorder. The age of onset in both groups was inversely related to having a family history of panic disorder, or anxiety disorders, or major affective disorders, or substance abuse disorders. To evaluate the presence of psychopathology in family members a semi-structured family history interview was used throughout. Multigenerational panic disorder was defined as having three or more affected relatives in at least two generations. This familial form of panic disorder was present in 15% of the pedigrees overall. There was a significant difference between the two groups in regard to family history of major affective disorder with the referral group having significantly more probands with a family history of major affective disorder. There was no difference between groups with respect to panic disorder, anxiety disorders, or substance abuse disorders. Age of onset of panic disorder was significantly lower in probands who were referred for treatment than those recruited for the drug study.

Subjects were then recombined with respect to a history of comorbid depression. The presence of a comorbid diagnosis of depression in the proband predicted a multigenerational family history of major affective disorder.

RESUMÉ

L'histoire familiale et la comorbidité ont été étudiées chez 97 patients souffrant d'un trouble panique (avec ou sans agoraphobie) suivies consécutivement en clinique externe. Tous les patients ont été évalués par un psychiatre d'après les critères diag-nostiques de DSM-III. Pour 71 d'entre eux, l'évaluation a été effectuée aussi par l'intermédiaire d'une entrevue clinique structurée. Tous les sujets étaient résidents de la province de Québec. Deux groupes de sujets faisaient partie de l'étude des patients adressés pour traitement des troubles paniques et des patient recrutés par annonce pour une étude sur le traitement des troubles paniques. L'âge de début des troubles pour les deux groupes était en correlation inverse à l'histoire familiale des troubles paniques, des troubles d'anxiété, des troubles affectif majeurs ou des troubles d'abus de substances psycho-actives. La presence de psychopathologie parmis les membres de famille a été des déterminé pour tous les sujets par intermedaire du entrevue clinique semi-structurelle de l'histoire familiale. La définition du trouble panique multigenerationel a été établie par la présence d'au moins trois membres de famille affectés dans au moins deux génération. Cette forme familiale des troubles paniques a été présente dans 15% de pedigrees. Une différence significantive a été trouvée entre des deux groupes par rapport à l'histoire familiale des troubles affectif majeurs: dans le groupe adressé par rapport au groupe recruté, il s'avère que les antécédents familiaux de sujet avait significativement plus de troubles affectifs. Concernant les troubles paniques, les troubles d'anxiété, ou les troubles d'abus de substances psychoactives, aucune différence entre les deux groupes n'a été revelée. L'âge de début des troubles paniques a été significativement plus bas chez les sujets qui ont été adressés par rapport à ceux qui ont recrutés. Par la suite, tous les sujets ont été regroupés en fontion de leur comorbidité de depression. La présence de cette comorbidité chez le sujet était en correlation prédictive face à l'histoire familiale des troubles affectifs majeurs. En conséquence, cette étude suggère que la comorbidité aussi bien que la méthode de récrutement permettent de prévoir l'histoire familiale des troubles affectifs majeurs chez le sujets suffrant des troubles paniques.

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LIST OF ABBREVIATIONS

PD, Panic disorder

MAD, Major affective disorder(s)

SAD, Substance abuse disorder(s)

FH, Family history

AG, Agoraphobia

GAD, Generalized anxiety disorder

MG, Multigenerational

MGFH, Multigenerational family history

PREFACE

In accordance with the guidelines concerning this thesis preparation, the candidate has conformed to all the requirements:

> It must include a (1) general abstract in English and in French , (2) a full introduction which clearly states the rationale and objectives of the study, (4) a literature review and (5) a final overall conclusion.

The data presented here have been published, or are in preparation:

Lane CJ, Bradwejn J, Boulanger JP and Palmour RM. (1993) Family History and Comorbidity of Panic Disorder in a Quebec Population, *American Journal of Psychiatry Conference* (Abstract).

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All of the experiments were designed and carried out by the candidate under the supervision of Dr. Roberta M. Palmour. The data presented in this thesis are original and have not appeared elsewhere.

CHAPTER I: LITERATURE REVIEW

A. DEFINITION OF PD

According to the DSM-III-R, [Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) American Psychiatric Association, Spitzer et al., 1987] "a panic attack is described as a discrete period of intense fear or discomfort that is not expected, (i.e.,that did not occur in immediate proximity to a situation that almost always causes intense anxiety) and that was not triggered by situations in which the person was the focus of others' attention."

Panic attacks are typically accompanied by a number of physical symptoms, including: 1) palpitations, pounding heart, or accelerated heart rate; 2) sweating; 3) trembling or shaking; 4) sensations of shortness of breath or smothering; 5) feeling of choking; 6) chest pain or discomfort; 7) nausea or abdominal distress; and 8) feeling dizzy, lightheaded, or faint. Psychological symptoms include: 1) derealization (feelings of unreality) or depersonalization (being detached from oneself); 2) fear of losing control or going crazy; 3) fear of dying; 4) paraesthesia (numbness or tingling sensations); and 5) chills or hot flashes.

Panic attacks may occur in a variety of anxiety disorders and may be unexpected or situationally bound. To meet the DSM-III-R criteria for PD, a person must either have experienced four attacks within a four week period, or one or more attacks must be followed by a period of at least a month of (a) persistent concern about having additional attacks, (b) worry about the implications of the attack or its consequences (i.e.losing control, having a heart attack or "going crazy"), or (c) a significant change in behavior related to the attacks. The attacks must not be due to drug use or to a medical condition, and further, they may not be accounted for by the coexistence of another mental disorder. PD may occur with or without agoraphobia, which is the fear of being in places or situations from which escape might be difficult or embarrassing or in which help might not be available in the event of a panic attack.

As a diagnosis, PD was introduced with DSM III (1980). The prevalence rate of PD prior to that time is difficult to estimate, as persons with symptoms of PD were typically

grouped together with those having generalized anxiety disorder (GAD), in the category termed anxiety neurosis (DSM II). PD presents a variety of symptoms at various levels of severity.

Mental health services are reportedly used more frequently by individuals with panic attacks who meet criteria for one or more additional DSM-III disorders than those with at least two DSM-III disorders but no panic attacks (Narrow et al., 1993). Further, patients with panic attacks were most likely to seek treatment when comorbid with major depression followed by a comorbid diagnosis of substance abuse and phobias and finally the least likely to seek treatment with no comorbidity (du Fort and Bland, 1993).

B. DEMOGRAPHIC CHARACTERISTICS

1. Incidence and Prevalence

Data from the Epidemiological Catchment Area study suggest that approximately 15% of the population suffers from a DSM III anxiety disorder at some point during their lifetimes (Reiger et al., 1984). As stated earlier, PD has only recently (1980) been considered to be a separate disorder. Early research on the prevalence and incidence of anxiety disorders was restricted due to changing diagnoses in the DSM. Despite this, as early as 1969, the prevalence of agoraphobia was reported in the literature to be 0.5% (Agras et al., 1969). A large-scale epidemiological survey conducted in the United Kingdom (Tarnopolsky et al., 1980) provided comparative data on the prevalence of symptoms of panic. The general question asked was "Have you been getting scared or panicky for no good reason (over the past few weeks)?". Approximately half of the sample had this complaint, and 12-14% reported this symptom more or much more than usual. The same question was asked by Stirton and Brandon (1988) seven years later and a prevalence rate of 26% was found. Since at that time the number of studies regarding the prevalence and incidence of panic attacks as well as PD have been continuously changing (Table 1).

Anxiety has been reported by the National Institute of Mental Health Multisite Epidemiological Catchment Area (ECA) Program to be the most common mental illness (Von Korff et al., 1985). This series of studies, conducted between 1980 and 1983 at five sites in the United States (Von Korff et al., 1985), found the six month prevalence of panic attacks to be 3% at each of the sites, while the lifetime prevalence of PD ranged from 0.6-1%. (Von Korff et al., 1985; Myers et al., 1984). In individuals with no previous psychiatric diagnosis a prevalence rate of 9.3% was found for panic attacks (Norton, 1985). Prevalence rates of PD were reported ranging between 0.4 to 1.2 per 100 persons (Weissman et al., 1986). When agoraphobia is classified as a subtype of PD, the lifetime prevalence for the disorder ranges from 5.4%, in a study by Karno et al. (1987) to 8.1% in the Munich Follow-up Study (Wittchin et al., 1986). The prevalence of PD in a community based sample of 1683 subjects in San Antonio, the crude lifetime prevalence rates were found to be 3.8% for PD, 5.6% for panic attacks and 2.2% for limited symptom attacks (Katerndahl et al., 1993).

In 1992, the National Institute of Mental Health ECA program estimated the use of services by persons with mental and addictive disorders (Narrow et al., 1993). In a one year period in the United States, 22.8 million people aged 18 years and older used ambulatory services for the treatment of mental or addictive disorders. One million of these individuals with PD made a total of 21.2 million visits to ambulatory mental health or addiction treatment centers (Narrow et al.,1993).

2. Age and Gender Issues

In terms of the onset of PD, almost all surveys report a mean age of onset in the 20's (Thyer et al., 1985). DSM III-R reports that "the average age of onset of PD is in the late 20's". ECA studies have indicated that for persons having recurrent severe panic attacks, either with or without a formal diagnosis of PD, the mean age of onset for the first attack is between 15 to 19 years; the onset of full blown PD tends to peak between the ages of 25 and 44, which suggests a prolonged incubation period between the first attack and eventual

development of the disorder (Von Korff et al.,1985). The median age of onset for PD occured at 24 years in an ECA study by Burke et al. (1990). This has been compared with earlier studies where the age of onset was found on average to be 26 years (Crowe et al., 1983) or in the case of a study on recurrent panic attacks, between 20-30 years of age which were triggered by life events (Vollrath et al., 1990; Thyer et al., 1985).

The hazard rates are highest between 25 and 34 years for females and between the ages of 30 and 44 years for males (Burke et al., 1990). Simple panic attacks, severe and recurrent attacks and PD were found to be characterized by similar symptom profiles and age of onset distributions. The onset of PD was earlier in patients with moderate to severe agoraphobia and drug abuse (Starcevic et al., 1992).

Studies on childhood separation anxiety and school phobia have also been reported to correlate with an early age of onset of PD (Raskin et al.,1982). Contrary to previous pronouncements, PD does occur in children and adolescents and its clinical representation in this population is similar to that found in adults (Moreau et al., 1992).

Women are consistently reported to have a higher prevalence of anxiety disorders than men. Early studies have reported that female relatives of probands with PD had twice the risk of having an anxiety disorder than do male relatives (Harris et al., 1983; Crowe et al., 1983). In a U.K. study on anxiety, women were significantly more likely to report getting scared or panicky for no good reason (Stirton and Brandon, 1988). In a study of acute chest pain, subjects were grouped according to a diagnosis of PD and/or a diagnosis of acute cardiac ischemia. Patients with a psychiatric diagnosis were younger and more likely to be female, had higher scores on measures of anxiety and had more autonomic symptoms than those without a psychiatric diagnosis (Chignon, 1993).

Thyer et al. (1985) observed that 76 out of 95 agoraphobics (80%) with panic attacks were women. On the other hand, only 35 out of 52 patients (57%) with PD were women. Sex differences within uncomplicated DSM III PD were much smaller than those found in PD with agoraphobia and were typically not statistically significant in the large ECA survey (Myers et

al., 1984). Further, in PD patients without avoidant behaviour (i.e. agoraphobia) the sex ratio is closer to 1:1 (Thyer et al., 1985).

C. DIFFERENTIAL DIAGNOSIS OF PD

Since the early 1980's, when anxiety disorders were recognized as distinct entities, researchers began studying the possible biological causes of anxiety. Although there are a large number of possible differential diagnoses of PD, some of the most common research areas of interest include brain neurotransmission, receptor function, brain biochemistry, and autonomic system function and metabolism.

A recent catchment area study was undertaken to examine not only the prevalence of PD (2.4 per 1000 subjects) but also to determine risk factors for the illness (Kyle et al., 1990). Results regarding prevalence were similar to earlier studies and interestingly the authors concluded that a history of cardiac symptoms, shortness of breath, depression, a major grief episode, drug abuse or dependance, alcohol abuse or dependence, and seizures were strongly associated with panic attacks.

There has been a long history of cardiovascular symptoms and panic. Many patients are first seen in emergency with the fear that they are having a heart attack. While the population prevalence of PD is 2-5%, the prevalence among cardiology patients is 10-15% (Sheehan et al., 1982). The majority (65-75%) of patients seeking emergency care for acute chest pain are released from the emergency department with diagnoses other than cardiac ischemia (Rouan et al., 1987). Yingling et al. (1993) found that one in three patients seeking treatment in emergency for acute chest pain had symptoms consistent with a psychiatric disorder. In fact, 17.5% of these cases were diagnosed with PD and the prevalence of PD was similar in those with and without acute cardiac ischemia.

High rates of PD are also reported in patients referred for ECG (Chignon et al., 1993). However, the prevalence of PD is similar in patients with and without ECG

abnormalities, indicating that in anxious patients the presence of PD does not rule out organic cardiac disease. The authors (Chignon et al., 1993) hypothesize that the high maximal heart rate and shorter P-R interval of the panic patients may be attributed to hypersensitivity of ß-adrenergic receptors.

A significant number of patients with neuromuscular disease appear to have anxiety disorders. Over 40% of myasthenia gravis patients were diagnosed with PD in a study by Paradis et al. (1993). In an earlier discussion by Barlow (1988), it is argued that this relation may be due to the daily uncertainty of the patients' neuromuscular symptoms or a psychological sense of "loss of control". Others prefer a more more biological explanation, for example, that PD is related to the cholinergic effects of myasthenia gravis (Magni et al., 1988).

In reviewing the clinical aspects of PD, Beck (1988) describes the following factors which might predispose an individual to PD: 1) hereditary predisposition; 2) physical disease leading to persistent chemical abnormalities (hyperthyroidism) or producing continual fears of impending disaster (mitral valve prolapse); 3) developmental traumas leading to specific vulnerabilities; 4) inadequate personal experiences or identifications to provide appropriate coping mechanisms; 5) counter-productive cognitive patterns, such as unrealistic goals, unreasonable value assumptions or imperatives learned from significant others. He then goes on to state that factors which might specifically precipitate an attack include: 1) physical disease toxic substances; 2) severe external stress (i.e. physical or psychological danger); 3) chronic insidious stress (i.e. continuous subtle disapproval from significant others); or 4) specific external stress impinging on specific emotional vulnerability.

While the predisposing and precipitating factors of PD must in general remain hypothetical, the predictors of the course of illness can be examined directly. According to Vollrath et al. (1990), the best predictors of outcome are severity and duration of symptoms, as well as comorbidity with depression. In addition this group found evidence of premorbid

anxiousness and overadaptation in childhood to be strong predictors and possible precursors of PD.

D. FAMILIAL AGGREGATION OF PD

PD, like many other psychiatric d :orders, is thought to aggregate differentially in certain families. Long before PD or even anxiety disorders in general were clinically recognized, diagnoses such as neurocirculatory asthesia, soldier's heart, and irritable heart syndrome were reported to cluster in families.

1. Twin Studies

The hypothesis that genes contribute significantly to inter-individual variance is often tested by evaluating rates of illness in twin pairs. Monozygotic (MZ) twins have identical genetic endowment while dizygotic (DZ) twins are no more similar genetically than other siblings. Twin studies make the assumption that environmental factors are similar between members of a twin pair and therefore a higher disease concordance (both twins being affected) in MZ than in DZ twins is interpreted as evidence for the importance of heredity in the development of the disorder.

Many types of anxiety disorders including fears and phobias (Young et al., 1971; Torgerson, 1979 and Rose et al., 1981), post traumatic stress disorder (True et al., 1993), obsessive compulsive disorder (Inouyeet al., 1965) and anxiety neurosis (Slater et al., 1969) have all been studied using twin paradigms. In general, these studies consistently substantiate the hypothesis that the development of anxiety disorders may be inheritable in nature.

In a Norway study of both MZ and DZ twins, genetic factors did appear to influence the development of other anxiety disorders (Torgersen, 1983 A). These early twin studies reported that anxiety disorders in general were twice as high in same sex MZ twins as

compared to same sex DZ twins, while anxiety disorders with panic attacks were more than 5 times as frequent in MZ than in DZ twins (Table 2).

Other twin studies using a specific diagnosis of PD have also found concordance rates to be different between MZ and DZ twins, with specific figures varying greatly between studies. In a study by Slater and Shields (1969), members of MZ and DZ twin pairs were interviewed to diagnose anxiety neurosis (an ICD 9 diagnosis similar to PD and generalized anxiety disorder). Based on 17 MZ pairs, the MZ concordance rate for so-called "anxiety neurosis" was 41%. This was substantially higher than the DZ rate of 4% based on 28 pairs. This large difference in concordance rates in DZ pairs was surprising, as they were much lower than in siblings with anxiety neurosis. In contrast, Torgersen (1983 B) has reported DZ concordance rates of about 15%. Recently Kendler et al. (1993) found that female co-twins of affected PD probands were at increased risk for PD as compared to the general twin population, but that the magnitude of this increase was modest. MZ co-twins of affected twins had a risk 3 times that of the general twin population and 1.5 to 2-fold higher than that for DZ co-twins. In the view of these authors, the inherited vulnerability to PD is relatively weak, as compared to manic depressive illness and schizophrenia.

2. Family Studies

First degree relatives of patients with PD are at a markedly higher risk of developing the disorder. In early studies the incidence of anxiety in first-degree relatives of anxiety probands was about 15% (Carey et al.,1981), while rates of 9.5% morbidity were found for second-degree relatives of PD probands (Pauls et al., 1980). The risk to relatives of probands for having major attacks, limited symptom attacks or both was 24.7% as opposed to a risk of 2.3% for a relative in the control group (Crowe et al., 1983). An additional study by Crowe et al., (1983) found a morbidity risk of 41% for first-degree relatives of PD probands. In a similar study 32% of the first-degree relatives of patients with agoraphobia and panic and 33% of the relatives of the patients with PD showed a risk of having one or more of the anxiety

disorders (Harris et al., 1983). These percentages were far greater than the risk found in the control group. First-degree relatives of patients with PD or PD with agoraphobia showed risks of 16.3% and 22 .4% respectively.

A study by Rosenbaum et al., (1992), which measured the effect of parental anxiety disorders on the risk for childhood-onset anxiety, concluded that the subgroup of inhibited children at extreme risk for developing childhood anxiety disorders might be associated with inheritance of a genetic susceptibility to anxiety disorders from affected parents.

E. INHERITANCE OF PD

1. Risk to Relatives

In a family study on risk of anxiety disorders, agoraphobia probands, PD probands and controls reported a morbidity risk for all anxiety disorders to be 32% among first degree relatives of agoraphobics, 33% among relatives of patients of PD and 15% among relatives of controls (Harris et al., 1983). This study also found relatives of agoraphobics to be at higher risk for alcohol abuse. The risk of anxiety disorders in first-degree relatives of agoraphobics and PD probands was found to be 25%, while it was 32% in controls. More specifically, in a family study (Noyes et al., 1987) involving PD probands and their families, the morbid risk for definite PD was established to be 17.3% in first degree relatives. This contrasted strikingly to a rate of 1.8% in relatives of normal controls. In addition, this study concluded that PD did not aggregate with other psychiatric disordes in most families.

More recently, estimates of the rates of PD in first degree relatives of PD probands have ranged from 7% to 25% (Robins and Regier, 1991). The risk to relatives has also recently been reviewed in a study by Mendlewicz et al. (1993). They found relatives of PD probands to be at 13-fold increase in risk for developing the disorder, as compared to controls.

2. Segregation Studies.

Definitive evidence for the contribution of major loci to the etiology of PD has not yet been provided. Nonetheless, as early as 1951, Cohen et al. suggested the mode of inheritance of PD to be dominant with incomplete penetrance. This hypothesis was again suggested by Pauls et al. (1980) following an analysis of kindreds using the analytic method of Slater (1966). As he states:

> "despite evidence to support the autosomal dominant mode of inheritance, the high frequency of the disorder in the population and shortcomings of the Slater method of computer analysis, cannot rule out the possibility of other modes of inheritance." (p.159)

A more recent study, using complex segregation analysis of 19 multiplex pedigrees also supported a major locus model (Pauls et al., 1980). This model would be consistent with the fact that PD pedigrees often, but not always exhibit vertical transmission from generation to generation. In studies summarized by Crowe (1983), approximately two-thirds of affected individuals had affected relatives. This interpretation however is highly controversial, with some investigators contending that, if this form of PD exists it constitutes only a modest proportion of the general population who meet criteria for lifetime PD (Kendler et al., 1993). Also, in a recent investigation study, both single major recessive and single major dominant models were found to fit the data for PD families (Vieland et al., 1993).

3. Linkage Studies

Crowe (1987) has stated that "among psychiatric disorders, those with familial transmission consistent with Mendelian inheritance are the ones most likely to show linkage," and he states, "panic disorder is such a disease" (Crowe 1987, p. 935).

Linkage studies of PD have not yet been conclusive, but at least two preliminary positive reports have appeared (Crowe et al., 1987; Knowles et al., 1993). In a linkage study by Crowe et al., in 1987, 29 marker systems were analyzed in 26 kindreds with a history of

PD. Results provided suggestive evidence of linkage at one locus on chromosome 16q22 (alpha-haptoglobulin). The odds in favour of linkage were 186:1 over the null hypothesis. The more recent study (Knowles et al., 1993) identifies an anonymous polymorphic DNA marker on the long arm of chromasome 20 (D20S37).

Despite their findings the Crowe paper states:

> "...the possibility that PD may have more than one origin cannot be excluded. In addition to the single locus, other possibilities include independent loci, polygenic inheritance, and environmental phenocopies." (Crowe, 1987, p. 935)

They further state that:

> "Selecting multiplex families maximizes the chances of finding a single locus if one were present, but it still does not exclude the possibility of genetic heterogeneity." (Crowe et al., 1987, p. 936)

These findings underline the probability that a familial form of PD is present in some but not all families and reinforce the principle that genetic, twin, and family studies must address the whole population of PD kindreds and not those selected on purely a genetic basis.

F. COMORBIDITY AND PD

1. Overview

Studies using the DSM-III-R classification system indicate that the majority of patients affected with an anxiety disorder have at least one additional disorder. For example in a large scale study completed at the Center for Stress and Anxiety (Moras et al., 1992) 50% of patients with a principal diagnosis of anxiety disorder had at least one additional clinically significant anxiety or depressive disorder at the time of assessment.

Various definitions of comorbidity have been proposed. Caron and Rutter (1991) have hypothesized that comorbidity is the simultaneous occurrence of two or more unrelated axis-I conditions, presumably meaning that both disorders must be present concommitantly, even if they do not arise at the same time. Another definition, put forth by Johnson et al., (1990), proposes that comorbidity is defined by the lifetime presence of at least two axis-I disorders, regardless of whether they are concurrent. Reich's definition (1987) relies on the simultaneous occurrence of two axis-I disorders or one axis-I and one axis-II disorder. In the context of comorbity, the "primary disorder" refers to the one which occurs prior to all other disorders, whereas the disorder with the greatest severity and which impairsing normal functioning in society to the greatest extent is accorded "principal status".

The DSM-III-R policy, which suggests that diagnoses should be made based on a given constellation of symptoms, regardless of whether other constellations are present or absent, is based on the idea that comorbidity has no effect on the other diagnoses. However, there can be significant clinical implications, in that a patient with several diagnoses can be expected to have different responses to treatment than those of a patient with a single diagnosis; thus inaccurate conclusions may be drawn when comorbidity is ignored.

Patterns of comorbidity also have important scientific implications: certain combinations of disorders may be relevant to genetic epidemiology, and may also reveal something about the epidemiology of the disorders. According to Caron and Rutter (1991), the observed comorbidity rate in PD probands is more than twice that expected in a randomly selected control group. In fact, the epidemiological data suggests a much higher rate of comorbidity due to the pooling of diagnoses.

The rate of comorbidity in a clinical samples can be explained by two factors. First, there is a statistical bias, also referred to as Berkson's bias (Berkson, 1946), which occurs because a patient suffering from two psychiatric disorders may seek treatment for either one of these disorders. Second, there is a clinical selection bias which results from a change in probability of seeking treatment for a specific disorder due to the presence of a comorbid

disorder, causing the number of individuals exhibiting comorbidity to be disproportionately large. Where comorbidity exists, the existence of another disorder may increase the likelihood of hospitalization specific to each disease. Patients with a lower age of onset are more severely affected with their illness and are more often comorbid. This comorbidity may lead them to seek treatment for one or the other of their illnesses thus increasing their probability of seeking treatment and becoming part of a referred treatment group as opposed to an advertised group (du Fort et al., 1993).

In the preceding section, biases which might artifactually inflate the population rates of comorbidity were discussed. In this section four posible causal explanations for comorbidity are explored.

1. Coincidence: two disorders should co-exist by chance in a certain proportion of subjects. The rate of chance co-occurence should be equal to the product of the rates of the two discrete disorders.

2. Shared risk factors, including but not limited to genetic risk factors: Shared risk factors amongst several disorders may entail an increased probability of comorbidity, since many psychiatric disorders are attributable to multiple factors and many causal factors are not specific to a given diagnosis. Overlap between risk factors may lead to comorbidity, since the risk factors for two diseases may be related even though they are distinct. A pattern of comorbidity may constitute a meaningful syndrome. A meaningful test of this hypothesis may be performed by comparing single-disorder diagnoses to comorbid diagnoses based on significant factors such as family history, course of the disorder, or response to treatment (Kendler et al., 1992).

3. Having one disorder might create an increased risk for the other. Cadoret et al., (1978) demonstrated, based on an adoptee design, that adults diagnosed with substance abuse or antisocial personality were four times more likely to exhibit depressive symptomatology, even though the two disorders have differing genetic origins. Other studies have found fluctuating anxiety and depressive symptoms typical of the course of PD. Axis-I and axis-II comorbidity,

specifically personality disorders and MD as well as panic subtypes (uncomplicated, limited and extensive phobic avoidance) are strong predictors of severity of the illness and the social adjustment a patient may obtain after 3 years. In fact, abnormal personality was the best predictor of social maladjustment in both subjects with PD and controls (Noyes, 1990).

4. Assortative mating: The literature includes many studies where PD has been associated with a variety of other psychiatric disorders, including alcoholism, personality disorders, generalized anxiety disorders, obsessive compulsive disorders, MD and suicide. These studies have recently been reviewed (Merikangas 1983).

2. Comorbidity with other Anxiety Disorders

PD has been difficult to discriminate not only due to changing criteria in anxiety disorders but also due to the significant overlap between symptoms. In any comorbid diagnosis it is important to determine which diagnosis came first. (This is a matter of opinion, and many would argue that it is more important to define the core symptoms). In some research groups, comorbidity is now being studied as a possible clue to distinguishing subtypes or alternative presentations of a disorder. While the DSM-III-R does allow for a universal system of diagnosis, and structured clinical instruments increase validity, the severity of symptoms is seldom reported in the literature. Moreover comorbid diagnoses may not be made because very severe symptoms of the primary disorder may overshadow all other symptoms. For example, patients are often treated for their severe panic attacks and not their agoraphobia. In the case of GAD and PD a number of practicing physicians will not diagnose GAD should PD be present. It appears that many believe GAD like schizophrenia, to be a wastebasket diagnosis in which one places only the cases to which a more precise diagnosis cannot be assigned.

Despite this, a large number of studies have reported comorbidity of other anxiety disorders in relation to PD. First and foremost, PD may occur alone or be comorbid with agoraphobia (PD with agoraphobia). According to the DSM-III-R, in PD with agoraphobia,

the panic attacks may be in full remission while the agoraphobia persists, but a history of PD would preclude a current diagnosis of agoraphobia without history of PD. DiNardo and Barlow (1988) found PD to be most commonly associated with depersonalization and agoraphobia. While simple phobia was the most common comorbid disorder in generalized anxiety disorder (GAD) patients. In a study by Noyes et al. (1990) of PD and GAD, phobias of one kind or another accounted for over 30% of subject comorbidity, while anxiety accounted for 18% of comorbidity. In a twin study 4.3% of twins who met a DSM-III-R diagnosis of GAD were comorbid with PD (Kendler et al., 1992). Weismann et al., (1978) reported in a survey in New Haven, Connecticut that the rate of anxiety disorders in the general population was 4.3% and that a many individuals had both anxiety as well as an additional diagnosis. In 30% of individuals with phobias and 80% of those diagnosed with GAD.

3. Personality Disorders

Rates of diagnostic comorbidity among anxiety and personality disorders range from 27% to 65% (Chambless and Renneberg, 1988; Friedman et al., 1987; Reich et al., 1987). Particular personality characteristics have been a strong predictor for PD. The majority of these studies find fearful anxiety personality disorders (i.e. avoident personality disorder, etc.) to be the most common comorbid personality disorder, although conflicting data do exist (Friedman et al., 1987).

4. Major Depression and Suicide

Sanderson et al. (1990) determined that, of 260 subjects in whom depressive disorder diagnoses had principal status, about two thirds were diagnosed with one or more concurrent Axis-I disorders, with anxiety disorders being the most common of these comorbid conditions. A report in the ECA cited by Johnson et al., (1990) indicated that PD preceded MD in 35.5% of subjects affected with both conditions, whereas MD occurred first in 25% of these cases. In 39.5% of subjects it was reported that both disorders first occurred in the same year.

However, the same data shows that only 2.8% of patients with MD had a first onset of PD within the first year, while 8.1% of those with PD developed a MD within the same period. A principle diagnosis of PD may have more serious implications than one of MD because, should the results of Johnson's study be confirmed, a preceding diagnosis of PD may hold a three times greater risk (than a preceding diagnosis of MD) of developing a secondary diagnosis resulting in comorbidity. This is in agreement withx the data of Wittchens et al., (1986) who found that PD preceedes major depressive disorder in a majority of cases.

In a study on PD and suicide rates, 22.7% of individuals with PD were not affected with any other Axis-I disorder. Of those patients with no other Axis-I disorder (uncomplicated PD), the lifetime rate of suicide attempts was 7%, as opposed to 1% for individuals with no psychiatric disorder. The suicide rate for persons with a comorbid psychiatric comorbid disorder (complicated PD) was 22.8%, while the rate for patients with uncomplicated psychiatric disorder was 5.4% (Johnson et al,, 1990). Suicide risk is increased in PD subjects even in the absence of major depressive disorder. Several authors have suggested that this could be related to comorbidity for Axis-II disorders.

The evidence is thus clear that the risk of suicide for persons affected with PD, be it uncomplicated or comorbid with another condition, is much higher than for individuals with no psychiatric disorder and is similar to that of persons with MD.

5. Alcoholism and PD

A number of studies have noted the high rates of comorbidity among the anxiety and substance abuse disorders. Studies examining rates of alcoholism in anxiety disorder outpatient samples indicate that roughly 15% to 25% show a history of current or past alcohol abuse or dependence (Thyer et al., 1986). If data is examined from alcoholic patient samples, studies indicate that the lifetime prevalence of clinically significant Axis I disorders in alcoholics is 25% to 45% (Bowen et al., 1984; Hesselbrock et al., 1985).

Lifetime prevalence rates of 2-21% (in women alcoholics) were found for PD in inpatient alcohol treatment programs as reviewed by Cowley et al., (1992). Studies on men report rates of 5-8% , which is significantly higher than the 1% that would be expected from the general population, while in anxiety clinics the rates of alcoholism range from 7-28% (Noyes et al., 1986). The risk of alcoholism in patients with PD is four times that of the general population, according to Weissman et al., (1988).

Although many investigators have found an increase in alcoholism in first degree relatives of PD patients (Crowe et al., 1978, 1983; Noyes et al., 1986; Harris et al., 1983), this does not necessarily suggest that families of alcoholic probands have an increased prevalence of panic or agoraphobia. There are two possible causal relationships with may explain the co-occurrence of panic-related anxiety disorders and alcoholism. Alcohol abuse may increase anxiety levels and thereby induce panic attacks in susceptible individuals (Malan et al., 1987), or, some anxious patients may begin abusing alcohol in an attempt to "self-medicate" for panic anxiety and/or avoidance (Cox et al., 1990).

G. GENETICS OF DEPRESSION AND ANXIETY

There are two main schools of thought with regard to the genetics of anxiety and depression. First, there are those who believe depression and anxiety are different presentations of one disorder, which occur along a continuum, incorporating anxious and depressive symptoms. Coupled to this diagnostic hypothesis, there is also a genetic hypothesis which states that depression and anxiety share a common genetic root and that the development of the trait (i.e. depression, anxiety or both) is dependent upon the penetrance of the gene and the background of personality, as well as environmental factors. Second, there are those that believe that panic and depression are diagnostically and genetically distinct and that comorbidity is due not to a common genetic diathesis, but rather to the presence of multiple susceptibility factors in a single individual, whether as a consequence of coincidence, assortative mating or environmental risk. Twin and family studies review the possible genetic contributions to both

anxiety and depression. While many researchers firmly believe in one hypothesis or the other, definitive data are lacking, and some notable investigators have changed their hypothesis in view of newer findings. These studies will now be reviewed in detail.

1. Family Studies of Depression and Anxiety

In a study on anxious depression, Clayton et al., (1991) found a significant relationship between anxiety in depressed probands and the risk for primary unipolar depressive disorder, but not for anxiety disorders or alcoholism. Studies by Noyes (1990) and Cloninger (1981) found relatives of probands with anxiety disorders to have no higher frequency of MD than relatives of controls. In contrast, the Yale group (Weismann, 1984) found that first-degree relatives of probands with MD as a primary diagnosis and anxiety disorders as a secondary diagnosis had a higher frequency of MD as well as anxiety disorders than did relatives of probands with MD only. This was not the case when depression was the secondary diagnosis to anxiety. Leckman et al. (1983) reported that PD in probands increased the risk to adult relatives for both anxiety disorder and MD over the risk for relatives with depression alone. Both Leckman et al. (1983) and Price et al. (1987) suggest that depression and PD share, at least in part, an underlying diasthesis. Kendler (1992) takes this position even further with data from twin studies, suggesting that the predisposing genetic factors are completely shared between anxiety and depressive disorders.

Weissman and associates (1984) found in the Yale Family Study that the clinical features of depressed probands which independently associated with familial risk were early onset MD (age<30 years), anxiety and alcoholism. In data from Weissman et al. (1993), the age of onset for uncomplicated PD and PD with MDD averaged 28 years. Rates of MD were highest in families of probands with onset before age 20. Rates were also higher in groups in which the proband had an onset during the third decade of life.

2. Twin Studies of Depression and Anxiety

The hypothesis that anxiety and depression share a common genetic etiology has also been evaluated through twin studies. Torgersen (1983 A) found that only 3 of 32 MZ and 3 of 53 DZ twins in the total group of PD twins were also diagnosed with an affective disorder. More recently Torgersen (1990) has found that by defining the initial diagnosis clearly, an etiological relationship is found between MD comorbid with anxiety, and MD alone. However no clear relationship exists between these two conditions and uncomplicated anxiety disorders. In his 1990 paper on PD in twins, Torgersen reiterates the notion that no etiological connection exists between between stable anxiety or panic attacks and MD.

This theory is in accordance with the study by Van Valkenburg et al. (1984) that found no relationship between depression and anxiety in probands with panic attacks. The hypothesis that genetics may more strongly influence mixed depression and anxiety disorders than depression alone may explain why individuals with mixed disorders have more severe symptoms and and poorer prognosis (Van Valkenburg et al., 1984).

Weissman et al. (1993) recently revised a previous interpretation (Weissman et al., 1984) that PD and affective disorder commonly cosegregated. She states:

> "Panic disorder and major depression are separate disorders with substantial co-occurance in individuals, and that panic comorbid with major depression is not a single distinct disorder" (Weissman et al., 1993, p. 22)

Although PD does appear with major depression, and multigenerational depression does occur in the families of some comorbid probands, the evidence does not strongly support the theory of co-segregation. A recent review by Mendlewics et al. (1993) found the morbidity risk for affective disorders to be approximatly equal in PD probands and controls, thus differentiating PD from MDD. The above study is in agreement with the Coryell group (1992) which states that a patient that presents with PD and depression may have two separate syndroms, and is in disagreement with Leckman et al., (1983) who suggested that patients

with PD and depression have a common predisposition to this form of illness as found in their families.

Despite the fact that there are many theories on the genetics of PD and depression, few researchers would argue that a single genetic form exists for the entire population of PD patients with comorbid depression, and many agree that PD may be a heterogeneous disorder with multiple genetic forms (Weissman et al., 1993). In light of this fact, there is no data available which offers a definitive view of the familial forms of comorbid PD and in what pattern they are commonly found.

H. RATIONALE

Patients recruited for a drug study on panic disorder may differ from patients who are referred to a clinic. These differences can be demographic, symptomatic, familial or diagnostic. This study does not consider symptomatic differences between the two groups, but this data is available and will be reviewed in the future. This study does compares demographic factors, family histories of psychiatric illness and proband comorbidity.

First, we wanted to review the demographic characteristics of the two groups. We asked the questions:

1. Would the ages of onset be different?
2. Would the two groups be different with respect to socio-economic status?
3. Would there be gender differences?

Secondly, family history patterns were reviewed to determine whether familial clustering of psychiatric illness differed by group. We asked the questions:

1) "Given the relative recency of PD as a diagnosis, is it possible to determine determine an accurate measure of familial PD (i.e. do grandmothers of PD probands have PD or can we

only diagnose a more general anxiety disorder). If there are familial forms of PD present in the sample, what patterns and in how many families is this form of PD representative of?"

2) "Would having a family history of one disorder predispose the family to another?"

3) "Would families aggregate with respect to family history with some families being heavily affected with psychopathology while others are relatively unaffected or would there be a normal distribution among families?"

4) "Do some illnessess travel together in families (i.e. depression and anxiety)?"

5) "When families are affected are they affected with one or many different types of illness?"

Finally, we wanted to evaluate the rates of additional disorders in probands (comorbidity). Many of the anxiety disorders, especially agoraphobia (AG) and generalized anxiety disorder (GAD) are believed to be comorbid in many PD patients. Affective disorders such as depression are also commonly seen in probands with PD.

TABLE 1: EPIDEMIOLOGY OF PD.

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YEAR	AUTHOR	PREVALENCE AND INCIDENCE OF PD
1969	Agras	0.5% agoraphobia
1980	Tarnopolsky	12-14% were scared or panicky more than usual
1984	Myers	0.6/1.0 and 0.9% 6 month prevalence rate 3 sites
1984	Robins	1.4% 1 year prevalence
1985	Reiger	1.5% 6 month 1% symptoms 9% of adults ECA lifetime
1985	Norton	9.3% PD 34.4% panic attacks in normals
1985	Von Korff	1.4% 6 months .08% ECA lifetime
1986	Wittchin	8.1% lifetime PD Germany
1986	Weissman	0.4-1.2 per 100 persons with PD
1987	Karno	5.4% lifetime PD PDWAG and AG
1988	Stirton	26% reported getting scared or panicky
1990	Regier	1.6% prevaler ce ECA study lifetime
1990	Kyle	2.4 per 1000
1990	Eaton	1 % incidence I year
1992	Narrow	1.1 per 22.8 million ambulatory cases in the U.S.
1993	Katerndahl	3.8% lifetime attacks 2.2% lifetime PD

TABLE 2: GENETIC HISTORY OF PD

TABLE 2: GENETICS OF PD

YEAR	AUTHOR	RESULTS
1980	Pauls	PD autosomal dominance
1983	Crowe	15-25% risk to relatives of PD probands
1983	Crowe	Sisters of probands 13 times risk of controls
1983	Torgersen	PD as single locus transmission
1983	Torgersen	PD 5x more frequent in MZ than DZ
1986	Kendler	PD as possible dominant CF. GAD
1986	Noyes	Sisters of PD probands had twice risk for PD.

CHAPTER II: SUBJECTS AND METHODS

A. SUBJECTS

Subjects were a sequential sample of 97 outpatients who met DSM III diagnostic criteria for PD with or without agoraphobia. All subjects were seen at one of two University based teaching hospitals, either as a consequence of clinical referral by a general practitioner or by another hospital department (n=43), or as a consequence of recruitment to a clinical trial (n=54) through newspaper advertisement (Appendix 3).

All referred subjects were included in the study if their primary diagnosis was panic disorder with or without agoraphobia. No other restriction criteria were used. Thus this segment of the population was a sequential clinical sample. By contrast, subjects in the advertisement group were typically screened by telephone to determine the presence of a comorbid diagnosis. Persons who met criteria for a diagnosis of panic disorder, but had a present or recent past history (up to 3 three years) of a major affective disorder or substance abuse disorder were excluded from most clinical trial protocols. Subjects seriously affected with other anxiety disorders were also excluded from participation in most clinical trials. All subjects gave written consent to be involved in the study.

Subjects were clinically diagnosed by a psychiatrist and 71 were additionally diagnosed via structured clinical interview (SCID or A-DIS-R). A trained interviewer then conducted a detailed genetic interview, based on a standard format (Andreasen et al.,1977, 1986; Thompson et al.,1982). A symptom checklist based on DSM III R (Appendix 1) was completed for each family member known personnaly to the respondant This checklist provides information consistent with the Family History Research Diagnostic Criteria (Spitzer et al., 1987). It was typically possible to obtain information on all first-degree relatives (parents, siblings, and children of the proband), most second-degree relatives (aunts, uncles, nephews and nieces) and some third-degree relatives (especially cousins). In a few very large families, information on fourth-degree relatives was obtained. Information about psychiatric hospitalization and/or treatments of relatives was also obtained. Family history diagnoses were

only made if there was record of treatment or hospitalization, or if subject reports met operational criteria for the assignment of a family history diagnosis (Andreasen et al.,1977,1986). To avoid artifactual weighting, statistical analysis was restricted to first and second degree relatives.

Although the focus of the interview was the psychiatric family history, each informant was also questioned about a family history of other medical conditions (i.e. heart disease, diabetes, hypothyroidism, Parkinson's disease). A brief personal medical history, information regarding socio-economic status (years of schooling and father's profession) and demographic data (age of onset, duration of illness) were also obtained.

In order to analyze family history trends, diagnoses were grouped as follows:

1) PD: comprises panic with/without agoraphobia. One subject had a current diagnosis of agoraphobia with a past diagnosis of panic.
2) Anxiety includes PD, generalized anxiety disorder, *nervosité, neurasthenie,* phobias and obsessive compulsive disorder.
3) Major affective disorder: includes bipolar depression, unipolar depression, and dysthymia.
4) Substance abuse disorders: includes alcoholism and drug abuse.
5) All other axis-II disorders as well as schizophrenia, and genetic medical disorders, were recorded in the interview but are not included in statistical analysis.

B. STATISTICAL METHODS

Primary comparisons were made between the clinically referred and recruited subject groups. A secondary level of evaluation concerned distinctions between panic disorder probands with a comorbid diagnosis of affective disorder (n=22) and panic disorder probands without a comorbid diagnosis of major affective disorder (n=75). Comparisons between groups with respect to clinical and demographic variables as well as family history data utilized

analysis of variance (ANOVA). A "p" value of 0.05 was accepted as being statistically significant. With regard to family history "multigenerational" was defined as the presence of three affected individuals divided between at least two generations. This may be satisfied in part third degree relatives, despite the fact that information about third-degree relatives was not included in statistical analysis (see families #40 and #42 Appendix 2). In some families, only one or two first or second degree relatives met diagnostic criteria for panic disorder; these families were deemed to be family history posotive (FH+), but not to have multigenerational PD. If the proband was the only family member with a diagnosis of PD, he or she was deemed family history negative (FH-).

In addition the percentage of family members affected with a given diagnosis was determined to evaluate if there was a similarity between families that were MG and those that have a large number of family members affected, ths is estimated from the following equation.

$$\% \text{ Affected} = \frac{\text{1st and 2nd degree relatives affected}}{\text{total 1st and 2nd degree relatives}}$$

The criteria for having a heavily affected family and having a MG family history are thus defined somewhat differently. The term "heavily affected family" is a measure of the proportion of affected first and second degree relatives in relation to the total number of individuals in the family and is arbitrarily defined as present when "% affected", as defined above, is 20% or greater. Some heavily affected families were not multigenerational. In family #4 (Appendix 2), there are three affected individuals but they cluster in only one generation. The converse is also true.

Both affective disorders and anxiety disorders can occur for the first time in mid life or late life. Accordingly, family data are often reported with an age dependent correction factor . This correction estimates the expected lifetime prevalence which would pertain if all first degree relatives had actually passed through the age of risk (Andreasen et al.,1986). This type of correction was not applied in the present study, but individuals were excluded from analysis

unless they had actually entered the age of risk for psychopathology. For this study, the initial age of risk was set at 18.

CHAPTER III: RESULTS

A. DEMOGRAPHIC CHARACTERISTICS OF THE SUBJECT POPULATION

The demographic characteristics of the subject population are shown in Table 3. There were significant differences between groups with respect to the age of onset of PD in the proband. The referral group had a much lower age of onset than the advertised group ($F_{1,95}$= 6.29, p=0.01). The average age at the time of interview for the referral group was 34 years, while the averageage of the advertised group was 39 years.

The female to male ratio was not significantly different between groups. In fact they were very similar with the ratio for the referred group ratio being 1.33:1 and the advertised being 1.35:1. Both groups had similar degrees of education, with the average for each group being 12.8 and 12.7 years respectively. The duration of illness was also similar (10.3 and 10.5 years, respectively). Over 50% of the probands were married and one third were single. The occupation of the father was most commonly labour related, with over one-half of each group being in this category. Skilled labour accounted for close to a third of the father's professions and professional occupations were the smallest in number. Neither the marital status nor the father's profession differed between groups. There were no differences between groups with regard to size (number of first and second degree relatives) of families.

B. PROBAND PSYCHOPATHOLOGY

All probands met diagnostic criteria for PD according to the DSM-III but many probands also had additional diagnoses. Proband diagnoses are shown in Figure 1. A total of 71 subjects was formally diagnosed with a SCID or A-DIS R. This included all members of the referral group and some of the advertised group.

PD with agoraphobia was found in approximately 70% of each group, and there was no difference between the groups. There was a substantial difference between the proportion of individuals with a comorbid diagnosis of GAD or depression in the two

groups, with the referral group having a more comorbidity than the advertised group for both GAD (30% vs.7% respectively, not significant), and for depression (40% vs.7% respectively F=19.05, p=.0001). Simple and social phobias were three times more common in the referral group than in the advertised group, but this result was not significant.. Additional diagnoses of OCD, dysthymia, alcoholism and school phobia were infrequent. One diagnosis of obsessive compulsive disorder was made. There were no diagnoses of bipolar illness, bulimia, anorexia or schizophrenia in probands. Axis-II diagnoses of the subjects were not completed in this study.

C. FAMILY PSYCHOPATHOLOGY

One of the main purposes of this study was to estimate the rates of PD, anxiety disorders, affective disorder, and substance abuse disorders in first and second degree relatives of probands. This was accomplished using a family history interview and symptom checklists. The pedigrees of 97 probands were analyzed for this purpose. Although many mental and physical diagnoses were recorded during the family history interview, most of these were too infrequent to include in the analysis. The more common patterns of illness were anxiety disorders (including but not limited to PD), major affective disorders, and substance abuse disorders.

1. Family History of PD

There was no significant difference in the overall family histories of PD between groups (Table 4). A positive family history of PD was found in 60% and 54% of referral and advertised groups respectively. Of these, a multigenerational pattern of PD was found in 15% of the pedigrees overall (17% advertised and 14% referred, Figure 2). These families all met the criteria of at least 3 persons affected with PD in at least 2 generations. The groups had similar numbers of probands with no family history (46% of the advertised

and 40% of the referred), and with one or two affected relatives (37% advertised and 46% referred).

In order to compare large and small families, a measure of the relative amount of illness in a given family was defined. This is termed percent affected, and refers to the extent of psychopathology in a family as a function of total first- and second-degree relatives of the proband. A family that has greater than or equal to 20% of familiy members affected with PD is deemed heavily affected. Advertised and referral groups were similar with respect to percent of family members affected with PD. Having a multigenerational family history of PD was significantly correlated with the proportion of affected family members ($F = 87.7$, $p=.0001$), therefore given either way of measuring the amount of family history of psychopathology in a pedigree the results are the same.

A history of PD in first-degree relatives was not significantly different in referred and recruited probands. The referral group had 17 families (40%) with at least one first degree family member affected with PD (Table 5), as compared to the advertised group having 18 families (33%) with at least one affected relative (Table 5). Second degree relatives were less frequently affected, with only 11 families in the referred group (26%) having one or more second degree family members affected with PD, compared to 7 families (13%) in the advertised group. This difference however was not significant .

2. Family History of Anxiety Disorders

There was no significant difference in the overall family history of anxiety disorders between groups (Table 4). A positive family history of anxiety disorders was found in 60% and 44% of referred and advertised probands respectively. A multigenerational pattern of anxiety disorders was found in 37% of the pedigrees overall (39% advertised and 35% referred, Figure 2). These families all met the criteria of at least 3 persons affected with an anxiety disorder in at least 2 generations. No family history of anxiety was found in 46% of

the advertised and 40% of the referred, and the less stringent "1-2 relatives affected" criterion was met by 15% of the advertised and 25% of the referred group.

Advertised and referred groups did not differ significantly with respect to proportion of family members affected with anxiety disorders. Having a multigenerational family history of anxiety disorders was significantly correlated with percent of affected family members ($F1,95=99.03$, $p=.0001$).

The frequency of anxiety disorders in first degree relatives was not significantly different for probands in the two groups. The referral group had 21 families (49%) with a history of at least one first degree family member affected with an anxiety disorder (Table 5) as compared to 28 families affected (52%) from the advertised group. Second degree relatives were less frequently affected: 13 families in the referred group (30%) and 14 families in the advertised group (26%) had one or more second degree family members affected with an anxiety disorder.

3. Family History of Major Affective Disorder

Major affective disorders included unipolar and bipolar depression, and dysthymia. There was a significant difference in the overall family histories of MAD between groups ($F1,95=6.9$, $p=.01$ Table 4) A positive family history of MAD was found in 24 families (56%) of referred probands but only 20 families (37%) of advertised families. The referred group had five times the number of multigenerational family histories of MAD than did the advertised group (4% of the advertised and 21% of the referred group, as shown in Figure 3). The number of families with no history of MAD was higher for the advertised group than for the referral group. In the referral group, 44% had no family history of MAD as compared to 63% in the advertised group.

Advertised and referral groups were not similar with respect to percent of family members affected with MAD; in the referral group, a higher proportion of family members were affected ($F1,95=10.19$. $p=.002$). Again, having a multigenerational family history of

MAD was significantly correlated with having a heavily affected family history ($F_{1,95}=87.7$, $p=.0001$).

The referral group had 17 families (37%) with a history of at least one first-degree family member affected with MAD (Table 5) as compared to the advertised group (16 families affected or 30%) This difference was not significant . Second degree relatives were less frequently affected. Fourteen families in the referred group (36%) had one or more second degree family member affected with MAD compared to 8 families (15%) in the advertised group. The referral group had significantly more second degree relatives affected with a MAD than did the advertised group ($F_{1,95}=8.71$, $p=.004$). It should be noted that there was a significant relationship between having a comorbid diagnosis of depression and being a proband of the referral group ($F_{1,95}=14.5$, $p=.0002$), as 82% of the depressed probands were in the referral group. Despite this fact there was still a trend ($p=.07$) for referred patients have a stronger family history of MAD than the advertised group, even when comorbid depressed subjects were excluded from the analysis.

4. Family History of Substance Abuse Disorder

For the purposes of this study, substance abuse disorder included alcoholism and drug abuse disorder. There was no significant difference in the overall family history of SAD between groups (Table 4). A positive family history of SAD was found in 28 families (52%) of the referral group and 23 families (53%) of the advertised group. A multigenerational pattern of SAD was found in 20 families or 21% of the pedigrees overall (11 families or 20% of the advertised group, and 9 families or 21% from the referred group, Figure 3). Both groups had similar numbers of probands with no family history of SAD (26 families or 48% of the advertised and 20 families or 47% of the referred), and family histories with 1-2 relatives affected only, but not multigenerational for SAD (17 families or 32% of the advertised group, and 14 families or 33% of the referred group).

Advertised and referral groups were also similar with respect to percent of family members affected with SAD and did not differ significantly. Having a multigenerational family history of SAD was significantly correlated with having a heavily affected family history (F=84.15, p=.0001).

The groups did not differ significantly with regard to number of families with a history of SAD in first-degree relatives (referral group 33%, advertised group 35%, Table 5), or second-degree relatives (referred group 40% , advertised group 33%).

D. AGE OF ONSET OF PD AND FAMILY HISTORY

Age of onset was inversely correlated with a family history of PD (F1,95=4.78, p=.01, Table 6) or anxiety disorders (F1,95=4.13, p=.02) or SAD (F1,97=3.04, p=.05), but was not related to a family history of MAD. For each case, the age of onset decreased as the family history increased.

E. FAMILY HISTORY OF MORE THAN ONE PSYCHOPATHOLOGY

A family history of PD was not correlated with having a family history of MAD or SAD.

F. CHARACTERISTICS OF PROBANDS WITH AND WITHOUT DEPRESSION

Twenty two (22) probands had a comorbid diagnosis of depression, while 75 did not. There were no significant demographic differences between the two groups (Table 7, Table 8).

G. FAMILY HISTORY AS A FUNCTION OF COMORBID DEPRESSION

A comorbid diagnosis of depression in the proband was significantly associated with having a MGFH of MAD (F1,95=7.45, P=.008) . As shown in Table 8, the proportion of

families with a MGFH of MAD is more than six times higher in the comorbid group than the non-comorbid group (Figure 5). Comorbid probands had significantly more heavily affected family histories than non-comorbid probands ($F1,95=4.02$, $p=.05$) and significantly more second degree relatives affected with a MAD ($F1,95=9.83$, $p=.002$). In fact, there were twice as many second degree relatives affected with a MAD in the comorbid group than in the non-comorbid group (36% and 19%. Although higher proportions of first degree relatives were found in the comorbid group (41% compared to 32% in the non-comorbid group), this difference was not significant. Family history of MAD was strongly correlated with the proportion of family members affected with MAD ($F1,95=87.7$, $p=.0001$). There were no significant differences between groups with respect to a family history of anxiety disorders, PD or SAD (Figure 4).

TABLE 3: DEMOGRAPHIC CHARACTERISTICS OF PROBANDS. This table illustrates the demographic characteristics of the two groups (referred and advertised). There was a significant difference between groups with regard to age of onset of PD in the proband and the age of the proband at the time of the interview (p</= .05).

Table 3: DEMOGRAPHIC CHARACTERISTICS OF PROBANDS				
Method of recruitment	**advertisment**	**clinical referal**	**F**	**p**
Total number of probands	54	43		
1. Age of PD onset (yrs.)	28.87+/-10.7	23.95+/-7.95	6.29	**0.014***
2. Age at Interview (yrs.)	39.33+/-10.25	34.16+/-9.32	6.6	**0.012***
3. Female to male ratio	1.33:1	1.35:1	0.03	0.874
4. Years of education	12.65+/-2.59	12.84+/-3.27	0.1	0.751
5. Years duration of illness	10.46+/-10.21	10.26+/-8.6	0.01	0.916
6. Marital status:	1.81+/-.65	1.74+/-.62	0.3	0.588
Married	56%	56%		
Single	31%	35%		
Divorced/Separated	13%	9%		
7. Father's profession:•	2.35+/-.76	2.62+/-.58	3.35	0.069
Labourer	51%	67%		
Professional	19%	5%		
Skilled labourer	30%	28%		
df=1,95 except • where df=1,89				

TABLE 4: FAMILY HISTORY DIFFERENCES BETWEEN GROUPS. This table illustrates the difference in family histories between the two groups (advertised and referred). There was a significant difference between the two groups with regard to family history of major affective disorders especially multigenerational histories of major affective disorders.

Table 4: Family History Differences Between Groups: Number and Percent of Families Affected

Family History	Total n=97	Advertised n=54	Referred n=43	p
Panic Disorder				
Negative FH of PD	42 (43%)	25 (46%)	17 (40%)	
Positive FH PD	57 (55%)	29 (54%)	26 (60%)	0.78
MG FH of PD	15 (15%)	9 (17%)	6 (14%)	
1-2 relatives affected	42 (40%)	20 (37%)	20 (46%)	
Anxiety Disorders				
Negative FH of anxiety	42 (43%)	25 (46%)	17 (40%)	
Positive FH of anx	55 (57%)	29 (44%)	26 (50%)	0.88
MG FH of anxiety	36 (37%)	21 (39%)	15 (35%)	
1-2 relatives affected	19 (20%)	8 (15%)	11 (25%)	
Major Affective Disorders				
Negative FH of MAD	53 (55%)	34 (63%)	19 (44%)	
Positive FH of MAD	44 (55%)	17 (39%)	27 (54%)	.01*
MG FH of MAD	11 (11%)	2 (4%)	9 (21%)	
1-2 relatives affected	33 (34%)	15 (35%)	18 (33%)	
Substance Abuse Disorder				
Negative FH of SAD	46 (47%)	26 (48%)	20 (47%)	
Positive FH of SAD	51(53%)	28 (52%)	23 (53%)	0.89
MG FH of SAD	20 (21%)	11 (20%)	9 (21%)	
1-2 relatives affectd	31(32%)	17 (32%)	14 (32%)	

* Significant at 95%

TABLE 5: FAMILY PSYCHOPATHOLOGY. This table illustrates the percent of families affected with a given psychopathology (PD, anxiety disorders, MAD and SAD) in referred, advertised comorbid and non-comorbid groups. Percentages for both first and second degree relatives are given.

TABLE 5: FAMILY PSYCHOPATHOLOGY				
RELATIVES' DIAGNOSIS	PD	ANXIETY	MAD	SAD
1st degree relatives				
referral group N=221	40%	49%	37%	33%
advertised groupN=309	33%	52%	30%	35%
2nd degree relatives				
referral group N=424	26%	30%	36%	40%
advertised group N=491	13%	26%	15%	33%
1st degree relatives				
comorbid depression group N=143	32%	41%	41%	36%
no depression group N=387	37%	53%	32%	33%
2nd degree relatives				
comorbid depression group N=221	5%	18%	36%	32%
no depression N=694	21%	29%	19%	37%

TABLE 6: AGE OF ONSET AS A FUNCTION OF FAMILY HISTORY.

TABLE 6: AGE OF ONSET AS A FUNCTION OF FAMILY HISTORY

	BY RECRUITMENT		BY DEPRESSION	
FAMILY HISTORY	REFERRAL	ADVERTISED	COMO DEP	NO DEP
PANIC DISORDER				
MULTIGENERATIONAL	19.30	23.90	22.20	19.00
FH+ BUT NOT MG	22.50	27.80	25.10	25.60
FH-	27.30	31.60	29.40	31.00
ANXIETY DISORDERS				
MULTIGENERATIONAL	21.30	25.60	24.00	22.40
FH+ BUT NOT MG	22.50	28.80	24.80	26.00
FH-	27.30	31.60	29.40	31.00
MAD				
MULTIGENERATIONAL	23.80	26.50	23.00	25.00
FH+ BUT NOT MG	24.00	28.60	26.40	27.20
FH-	24.00	29.10	26.70	30.10
SAD				
MULTIGENERATIONAL	21.80	23.00	22.60	22.00
FH+ BUT NOT MG	25.80	26.70	26.00	27.50
FH-	23.70	32.70	28.30	30.40

TABLE 7: DEMOGRAPHIC CHARACTERISTICS OF SUBJECTS WITH LIFETIME COMORBID DEPRESSION.

TABLE 7: DEMOGRAPHIC CHARACTERISTICS OF SUBJECTS WITH LIFETIME OR CURRENT COMORBID DEPRESSION				
	DEPRESSED	NON-DEPRESSED	F	p
Total number of probands	22	75		
1. Age of PD onset (yrs.)	27.69+/-9.26	26.41+/-10.06	0.29	0.59
3. Female to male ratio	1.27:1	1.36:1	0.57	0.45
4. Years of education	12.91+/-3.1	12.68+/-2.85	0.11	0.75
5. Years duration of illness	8.77+/-8.08	10.84+/-9.86	0.81	0.37
6. Marital status:	1.59+/-.59	1.84+/-.64	2.68	0.11
Married	50%	57%		
Single	45%	30%		
Divorced/Separated	5%	13%		
7. Father's profession:•	2.57+/-.6	2.45+/-.72	0.5	0.48
Labourer	59%	53%		
Professional	5%	12%		
Skilled labourer	32%	27%		
df=1,95 except• where df=1,89				

TABLE 8: FAMILY HISTORY DIFFERENCES BETWEEN SUBJECTS WITH AND WITHOUT COMORBID DEPRESSION: % AFFECTED.

This table illustrates the significant increase in multigenerational family histories of major affective disorder in probands with a comorbid diagnosis.

Table 8: Family History Differences Between Subjects With and Without Comorbid Depression: % Affected

Family History	Total n=97	comorbid n=22	Non-como n=75	p
Panic Disorder				
Negative FH of PD	42 (43%)	11 (50%)	31 (41%)	
Positive FH PD	55 (57%)	11 (50%)	44 (58%)	
MG FH of PD	15 (15%)	2 (10%)	13 (17%)	
1-2 relatives affected	40 (42%)	9 (40%)	31(41%)	
Anxiety Disorders				
Negative FH of anxiety	42 (43%)	11 (50%)	31(41%)	
Positive FH of anx	55 (57%)	11 (50%)	44 (59%)	
MG FH of anxiety	36 (37%)	5 (23%)	31 (41%)	
1-2 relatives affected	19 (20%)	6 (27%)	13 (18%)	
Major Affective Disorders				
Negative FH of MAD	53 (55%)	9 (41%)	44 (59%)	
Positive FH of MAD	44 (45%)	13 (59%)	31 (41%)	0.01
MG FH of MAD	11 (11%)	7 (32%)	4 (5%)	
1-2 relatives affected	33 (34%)	6 (27%)	27 (36%)	
Substance Abuse Disorder				
Negative FH of SAD	46 (47%)	11 (50%)	35 (47%)	
Positive FH of SAD	51 (53%)	11 (50%)	40 (53%)	
MG FH of SAD	20 (21%)	5 (23%)	15 (20%)	
1-2 relatives affected	31 (32%)	6 (27%)	25 (33%)	

* Significant at 95%

Figure 1: Diagnoses in probands: differences between advertised and referred probands

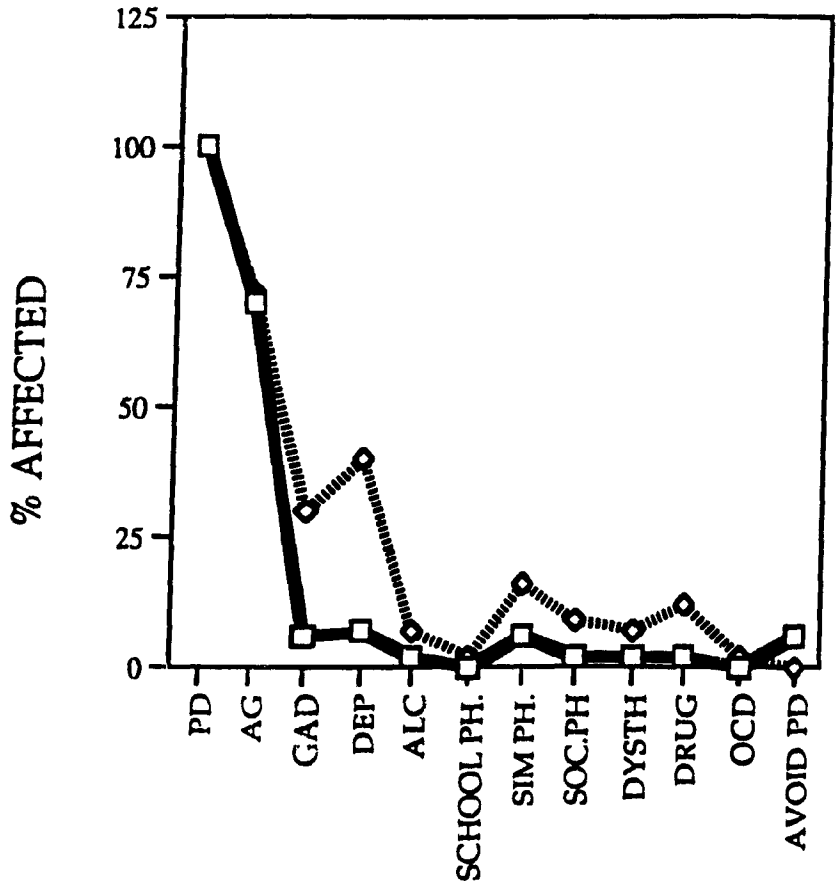
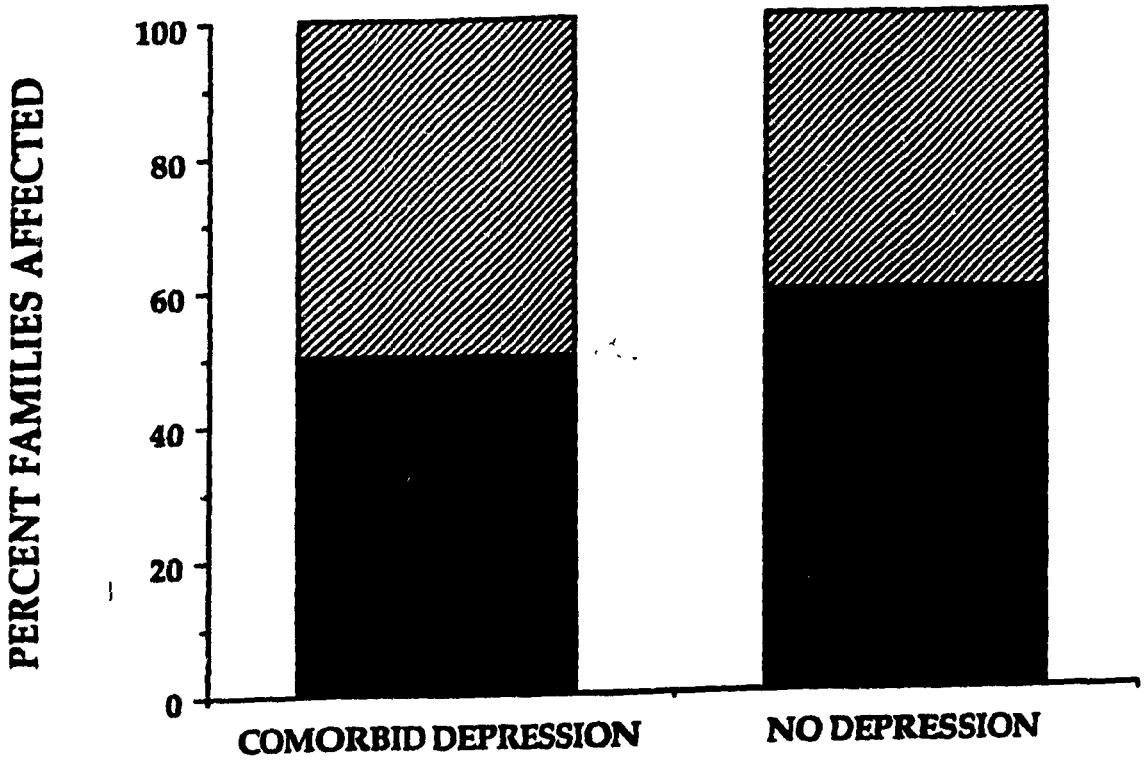

125
100
75
50
25
0
% AFFECTED
PD
AG
GAD
DEP
ALC
SCHOOL PH.
SIM PH.
SOC.PH
DYSTH
DRUG
OCD
AVOID PD
PROBAND DIAGNOSIS
ADVERTISED
REFERRED

Figure 2: Familial patterns of PD and anxiety disorders: differences between advertised and referred probands.

FAMILIAL PATTERNS OF PD



FAMILIAL PATTERNS OF ANXIETY

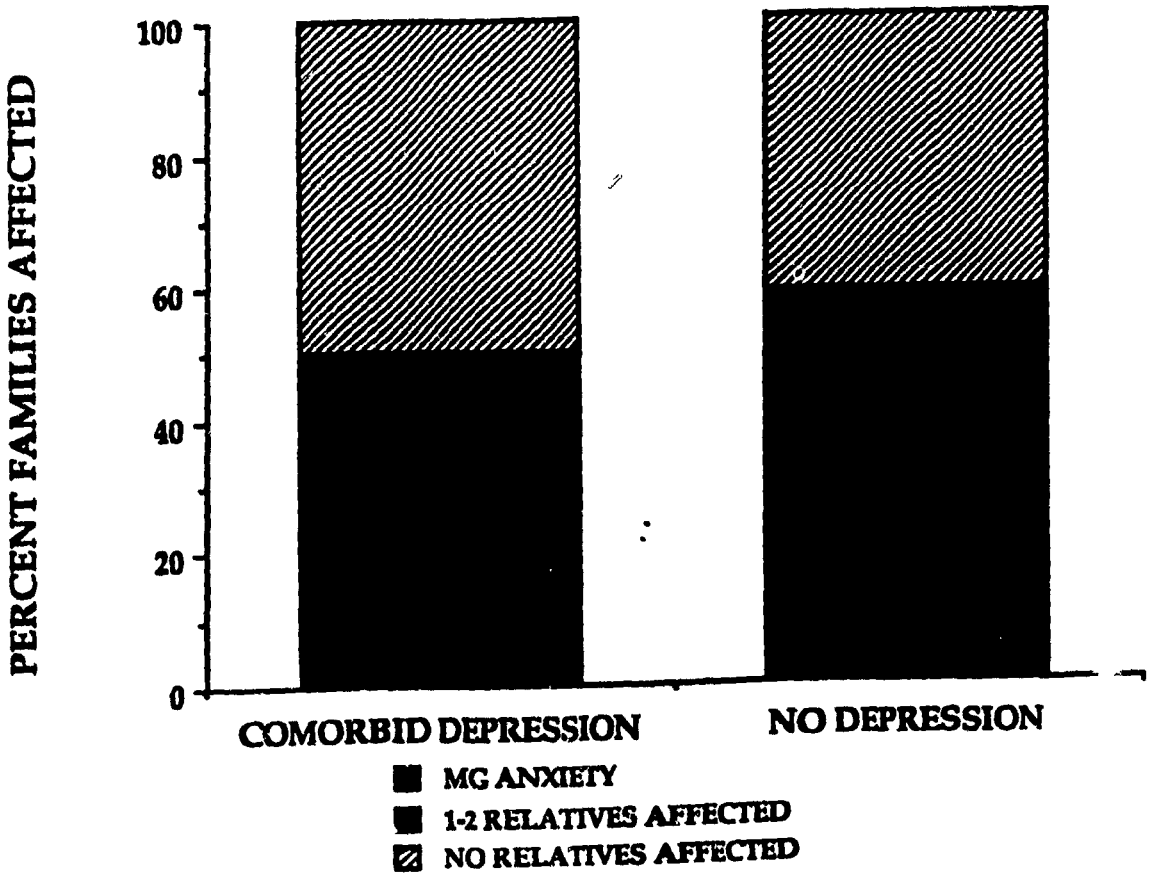
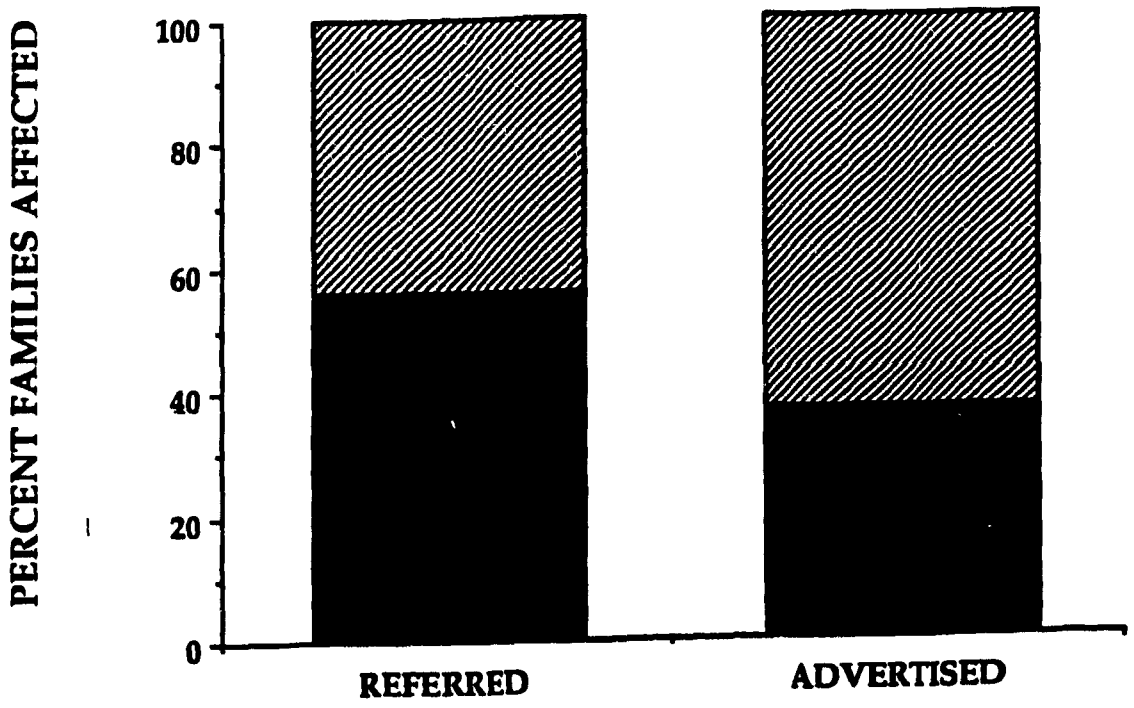


Figure 3: Familial patterns of MAD and SAD: differences between advertised and referred probands

FAMILIAL PATTERNS OF MAD



FAMILIAL PATTERNS OF SAD

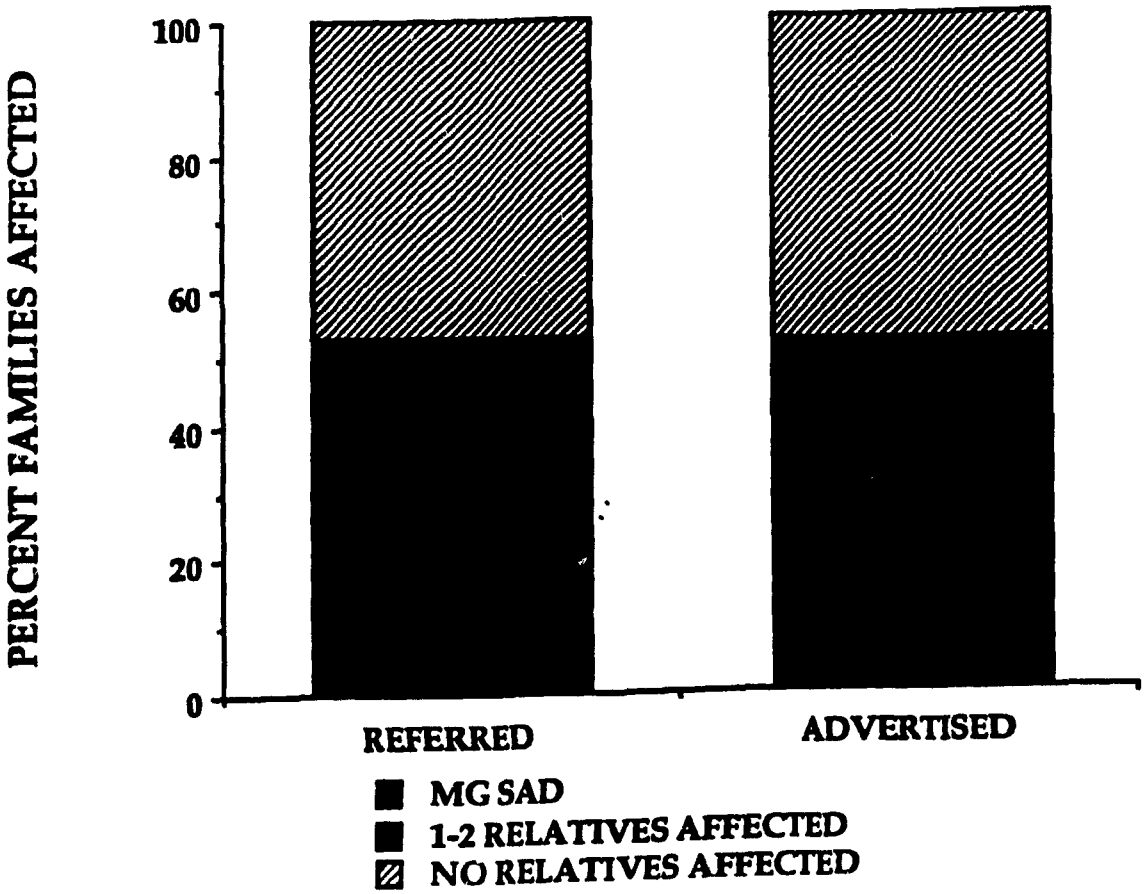
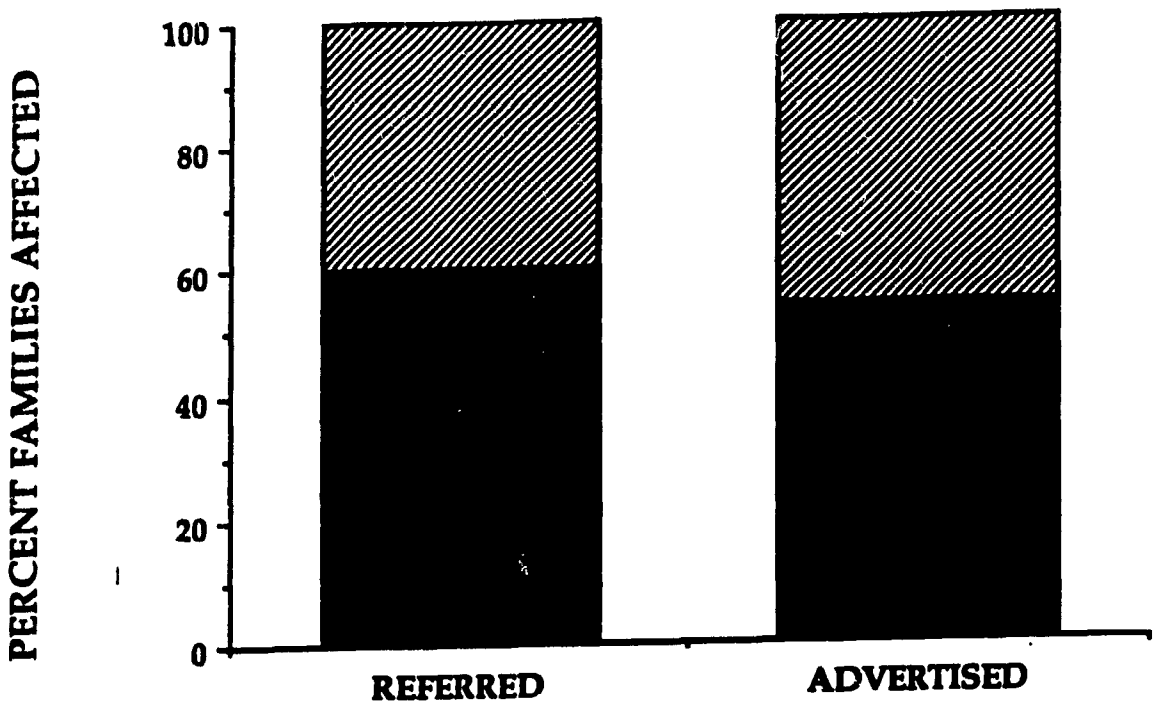


Figure 4: Familial patterns of PD and anxiety disorders: differences between comorbid and non-comorbid depressed groups.

FAMILIAL PATTERNS OF PANIC DISORDER



FAMILIAL PATTERNS OF ANXIETY DISORDERS

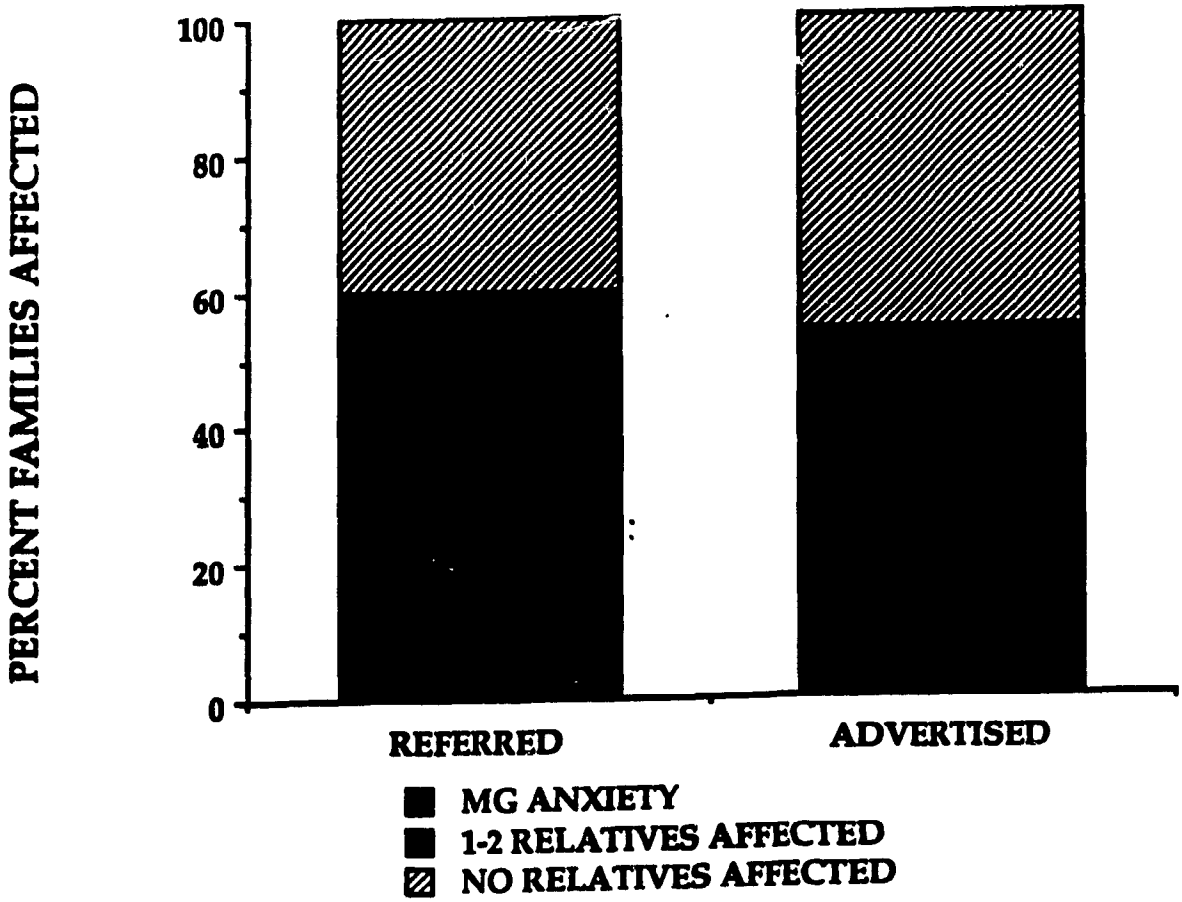
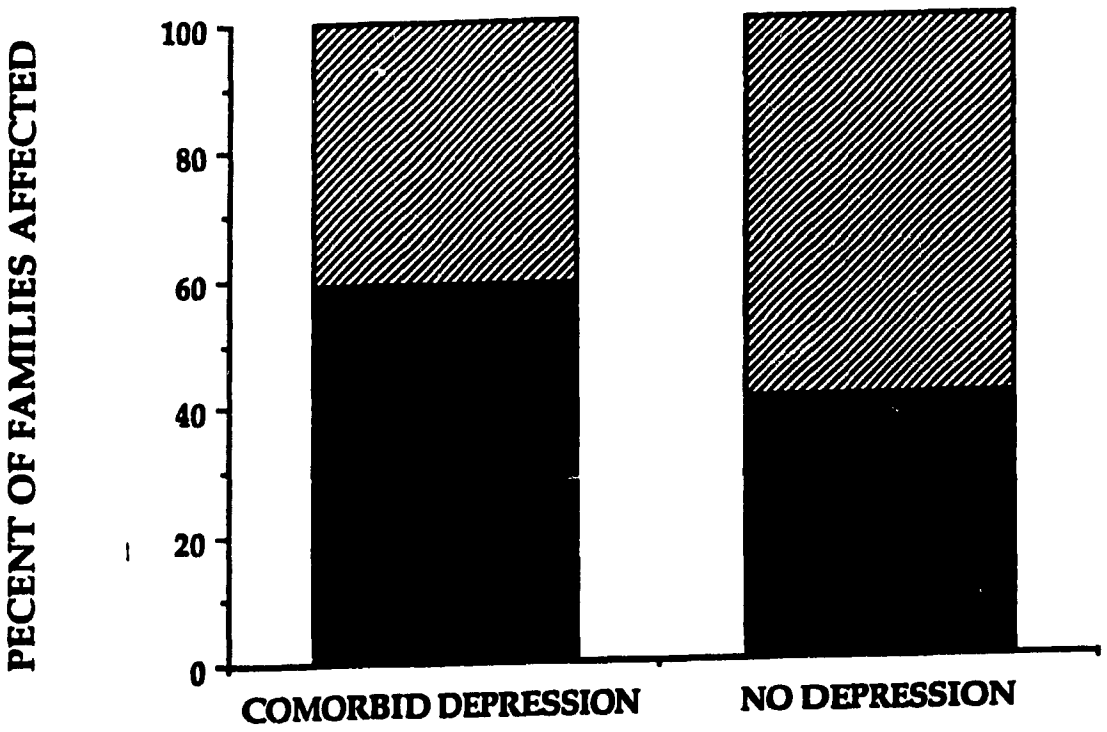
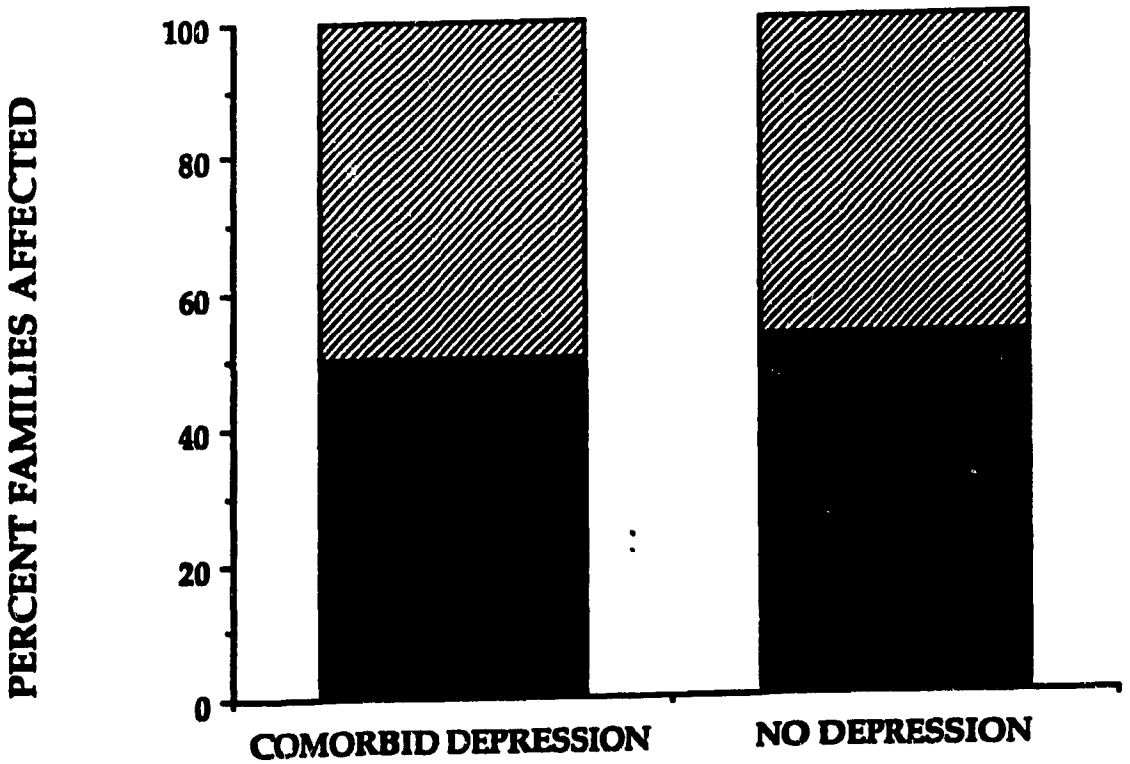


Figure 5: Familial patterns of MAD and SAD: differences between comorbid and non-comorbid depressed groups.

FAMILIAL PATTERNS OF MAJOR AFFECTIVE DISORDER



FAMILIAL PATTERNS OF SUBSTANCE ABUSE DISORDER



CHAPTER IV: DISCUSSION AND CLAIMS OF ORIGINALITY.

A. SUMMARY

Two sequential outpatient samples (referred vs. advertised) meeting DSM III criteria for PD were contrasted. There were no demographic differences between the two groups. Probands in the referral group had significantly younger ages of onset and had more comorbidity of depression and anxiety disorders than the advertised group. This difference in comorbid diagnosis is biased to an unknown extent, as probands with current comorbidity are excluded from some therapeutic studies.

One focus of the study was to define patterns of familial aggregation of PD. Overall 15% of families had MGPD, and 37% were MG for anxiety disorders (broadly defined). 43% of families had no FH of panic or anxiety. The remainder had one to two relatives affected. These patterns did not differ between recruited and referred groups. 21% of families had a MG pattern of SAD but this also did not differ between groups. Twelve percent of families had a MGFH of MAD, and this was reported significanty more frequently by referred (9 of 43) than recruited (2 of 54) probands. In 7 of 11 cases of MG MAD, the proband was comorbid. In only one of these kindreds was there also MGPD. Also, a significantly higher proportion of relatives of referred probands were affected with some form of MAD. Depressive comorbidity in probands was significantly predicted an MGFH of MAD, but not PD, anxiety disorders or SAD.

B. COMPARISONS TO THE LITERATURE

The demographic characteristics of the subject population as a whole are similar to those reported by other investigators. In the present study, the average age of onset was 26 years. In data collected from the ECA studies the age of onset of PD was found on average to be 23 and 24 years for men and women, respectively (Burke et al., 1990). In an ECA study covering three sites the reported peak age of onset of PD was found to be between 15 and 19 years of age (Von Korff et al., 1985). The age of onset in the present study was significantly lower in individuals with a family history of psychopathology.

Additional anxiety diagnoses were found both in this sample and in that studied by Noyes et al. (1992), who found that phobias of one kind or another accounted for over 30% of PD subject comorbidity, while anxiety accounted for 18% of comorbidity. In a twin study drawn from a general population sample (Kendler et al., 1992), 4.3% of twins who met a DSM-III-R diagnosis of GAD were comorbid with PD. In the present study, 21% of probands had a diagnosis of GAD, whereas an additional diagnosis of agoraphobia was found in 70% of probands. In agreement with the findings of Noyes et al. (1992), over 30% of our probands had a diagnosis of a simple social or school phobia. Insofar as we know, contrasts between referred and recruited PD patients have not previously been reported. In the present study, probands referred for treatment had lower ages of onset (24 yrs. vs. 29 yrs.) and more comorbid diagnoses than the advertised group (in part as a consequence of selection criteria). Referred subjects had significantly more comorbid depression, and a trend toward a greater prevalence of GAD diagnoses. Given the historical association between an early age of onset and comorbidity (Winokur et al., 1971), it might be argued that the reported differences between referred and advertised subjects might be solely the consequence of selection bias. In the present study, however, there was no correlation between depressive comorbidity and age of onset ($r=.06$, $p=.59$), nor between ages of onset and comorbidity with other anxiety diagnoses ($r=.005$, $p=.95$).

In the present study, it was also noteworthy that referred and recruited probands did not differ either with respect to a multigenerational family history of PD or any anxiety disorder, nor did they differ with regard to a multigenerational family history of substance abuse. There was a difference between groups with respect to MGFH of major affective disorder, and this was largely attributed to increased family loading in referred subjects comorbid with depression. Although no other comparisons between referred and recruited probands with PD could be found in the literature, other groups (Weismann et al., 1987; Leckman et al., 1983) have reported a positive association between depressive comorbidity and early age of onset of PD symptoms. The possibility that these multiple associations (early age of onset, depressive

comorbidity and increased family history of major affective disorder) are restricted to a subpopulation of the sample requires further investigation. The present study also found that 15% of families had a multigenerational form of PD. If verified statistically, a familial form of PD could be present in one-sixth of the PD population.

Patients with a lower age of onset are more often comorbid (Winokur et al., 1971). This comorbidity may increase the probability of seeking treatment , or may increase the probability of medical referral (du Fort et al., 1993). This is another important contrast between referred and recruited PD patients because drug studies often exclude patients with significant comorbidity (including GAD, MAD, SAD etc.). The possibility that these patients meet criteria for PD, but have a milder form of the illness, is important in assessing the generalizability of reported therapeutic effects. Unfortunately data on the severity of illness was not analyzed in the present study, but it was our clinical impression that the level of severity of PD symptoms varied significantly between subjects. In future studies, it would also be important to investigate the level of symptom severity in probands as a function of family history of PD or MAD.

Numerous studies have suggested not only that PD and depression are often comorbid but that they have a common genetic foundation. Next to agoraphobia, major affective disorder was the most common comorbid diagnosis. Major affective disorder was found in 40% of referred and less than 10% of advertised patients. Very low rates of alcohol and drug abuse were found in the probands, only 8% and 5% respectively. This is considerably lower than the rates of 15% to 25% cited in the literature (Thyer et al.,1986). Reasons for this large difference may be due to the fact that subjects were from a clinical sample and not part of a large catchment area network. In addition many PD patients may self medicate with alcohol and are never seen in the clinical population, or alternatively they may be seen in alcohol and drug abuse clinics.

A number of subjects were polymorbid (having two or more diagnoses). Being comorbid for one disorder (anxiety) was not correlated to being diagnosed with a second

(depression). This contradicts a number of studies on comorbidity where comorbidity is due to the artifact of Berkson's bias (Berkson 1946).

Due to the lack of a control group risks to relatives cannot be compared to the general population. As stated earlier, probands with comorbid depression had five times the rate of family histories of MG MAD than the non-depressed group. Probands comorbid for depression had only 41% of first-degree relatives and 36% of their second-degree relatives affected with a MAD, yet had a significantly higher proportion of family histories of MAD compared to the non-depressed group. Furthermore, the non depressed group had 32% of first degree and only 19% of second degree relatives affected with a MAD. From this data it may be hypothesized that the observed differences are due in part to the large number of affected second-degree relatives in the depressed group or alternatively, a small number of heavily affected families may skew the statistics. Therefore a small number of families have a large number of first and second degree relatives affected with MAD. It may be hypothesized that comorbidity of depression is an indicator of a family history of depressive disorder, rather than a family history of anxiety disorders.

Patients with comorbid depression did not have more family histories of PD or anxiety disorders. Having a MGFH of PD was not related to having a MGFH of MAD. Since the two groups, comorbid and not comorbid for depression, did not differ with respect to PD, it may well be that families of probands with comorbid depression are more likely to have a greater amount of psychopathology. These families are affected as much for PD as families of non-comorbid probands but in addition are also affected with large numbers of MAD. Family histories of substance abuse disorder were not related to comorbid SAD's in the proband.

This is not to say that psychopathology was not at times similar in families of comorbid probands. Indeed, a great deal of families did have a family history similar to the probands comorbid diagnosis, in fact these families often had family histories for a number of different illnesses (ie. MAD, SAD, and PD). In contrast there were probands who had every comorbid diagnosis but had rather nondescript family histories. The next step will be to look specifically

at the subset of families who have comorbid diagnoses in the proband and concurrent family histories. Unfortunately this study does not have the statistical power of the larger studies on PD, yet results reiterate a common theme in the literature that PD is in part a familial disease and that comorbidity of depression is often found in the families of comorbid probands.

Previous studies have shown PD to be a familial disease. This study defines PD as MG, 1-2 relatives affected and no relatives affected in order to categorize individuals into a group. Despite this method of organization, families differ significantly with respect to psychopathology. Therefore a family with MG MAD may have no PD and some SAD. Significant overlapping of illness occured in families, and as such, pure FH of one distinct disorder alone were seldom seen.

C. LIMITATIONS TO THE STUDY

There were four significant limitations to the study. First, no control group was included, and thus rates of psychopathology in relatives and probands cannot be contrasted to those in the general population. Second, family members were not directly interviewed. Therefore all diagnoses made for the family were based on information obtained from the proband. Many studies use a second or third informant for family history data to provide more concise information on the family. A family member's diagnosis is only as robust as the original information given to the informant. Therefore, by having more family members give a family history more information may be obtained (Andreasen et al.,1977, 1986; Thompson et al.,1982). This method of family history taking is prone to type II errors. When the diagnosis is known by the informant, especially if medical records are present, the interviewer may be reasonably certain of the validity of this diagnosis. When the interviewer is dependent upon the results of questioning the informant using a checklist the validity of the results may be less certain.

Third, only 73% of probands received a structured interview , as well as a clinical diagnosis. Structured interviews are especialiy helpful to obtain information on comorbid

diagnosis. These interviews also provide the common measure by which different researchers are able to define a given diagnosis in a similar structured format. Although a psychiatrist's diagnosis is robust, the additional diagnosis of a SCID insures validity as well as the ability to generalize (Shear and Maser., 1994). The patients diagnosed without a SCID are more likely to be missing secondary diagnoses than those using both diagnostic methods. The present study consisted of probands referred for treatment to a psychiatric clinic and individuals recruited for a drug study. Some of our population was excluded as it did not fit one of these two groups. Many individuals were seen who did not have a DSM III PD diagnosis but may have had panic attacks. The diagnostic instrument used in a study may also greatly affect the outcome. Kendler et al., (1993) stated:

> "Our ability to explore other diagnostic approaches was markedly limited by use of the 'skip-out' in the PD section of our diagnostic instrument. We collected no diagnostic information about individuals who reported a history of panic attacks but denied they had 4 in a 4 week period or at least one month of resultant anticipatory anxiety. Therefore we are unable to examine rigorously the category of panic attacks without PD, and its relationship to more classically syndromal PD." (p. 401)

It is to these two categories: referred and advertised that we can generalize our results and only within the province of Quebec; which brings in another confounding variable, the genetics of the Quebec population. Some probands were from French Canadian families originating from a small genetically distinct group, which has been proven to have a variety of familial forms of illness in certain areas of the province. The results of this study cannot be generalized to the PD population as a whole. All subjects were ascertained from an out patient clinic in psychiatry or by newspaper advertisement. If it is assumed that a large proportion of diagnoses are from specialized clinics, and not primary care centers like CLSC's then we may also assume that a large proportion of the PD population is not accounted for in the clinical

literature. This may explain some of the differences between a small clinical study and the results found in an ECA study.

Fourth, the small size of comorbid patient group (n=22) compared with non-comorbid patients (n=75), may have had an effect on the statistical analysis of the sample. This small sample size may in no way compare in power to the large twin and ECA studies on PD. Therefore great care must be taken in the overall generalizability of the results.

C. IMPLICATIONS AND FURTHER DIRECTIONS

Unfortunately not all subjects received a SCID diagnosis nor were family members personally interviewed. In future studies these two variables would be excluded and a larger amount of information obtained. We may now look at those families as they are grouped according to psychopathology to determine if perhaps there is a more familial form present in PD and if possible markers exist. A younger age of onset correlated with an increased level of family history in the proband. There may be other markers correlating to family history such as severity of symptoms in the proband. In conclusion, some but not all relatives had a family history of PD or anxiety. There is no normal distribution among relatives.

The new diagnostic category of the DSM IV called mixed-anxiety depression may recognize the large number of individuals whose clinical presentations do not meet full criteria for either an anxiety or mood disorder (Katon and Roy-Byrne,1991).

D. CLAIMS OF ORIGINALITY

The main findings described in this thesis are original. These findings may be summarized as follows:

1. Although PD is thought to be highly familial, only 15% of the subjects participating in the study had a MGFH of PD.

2. Proband referred for treatment have higher rates of comorbidity and lower ages of onset than probands advertised for in a drug study.

3. Subjects having a diagnosis of comorbid depression were five times more likely to have a multigenerational family history of major affective disorder than non depressed probands.

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APPENDIX 1: Diagnostic checklist

FAMILY HISTORY DATA SHEET

Subject: Name _____
Address _____
_____
Telephone Number_____
Sex, Year of Birth _____
Name, address of someone who will always know how to contact you:

Name of physician (if relevant)

Any other pertinent contact information

Marital/habitation status _____
Last year of school completed_____
Father's profession _____

Health: Known psychiatric diagnoses
Any major medical problems

Siblings (full brothers and sisters)

For each: First name
Sex
Year of birth (approximate if not known for sure)
State of mental/physical health
If deceased, cause of death and year of death

Parents of these children (The subject's Mother, Father)

Half-siblings (Half-brothers, half-sisters)

Step-mother, step-father

Mother's brothers and sisters

Their children (subject's maternal first cousins)

Mother's parents (subject's maternal grandparents)

The brothers and sisters of the maternal grandparents, if known

Great-grandparents on the mother's side, if known

Father's brothers and sisters

Their children (subject's paternal first cousins)

Checklist for FH-RDC

Panic

1. Recurrent (at least 4 within a month) attacks of intense anxiety not caused by a specific frightening situation
2. To be considered a panic attack, there must be physical symptoms present:
   - ....shortness of breath, smothering, choking
   - dizziness, faintness, numbness, tingling
   - ....palpitations, heart beating very fast
   - ....trembling, shaking
   - ....sweating, chills, hot flashes
   - ...nausea stomach cramps
   - ...chest pains feelings of having a heart attack
   - ....fear of dying or going crazy
3. Not explained by medical problem, eg. heart murmur, asthma, etc.

Agoraphobia

1. Persistent fear of going to places from which escape might be difficult
2. Phobic avoidance of these situations

Generalized Anxiety

1. Persistent (6 months or more), unrealistic and excessive worry about life situations which do not merit the degree of worry expressed
2. Symptoms: a) trembling, twitching, feeling shaky
   - b) muscle tension or aches
   - c) restlessness
   - d) tires easily
   - e) any of the symptoms of panic disorder no so severe as to cause of dying, having heart attack, going crazy
   - f) feeling keyed up or on edge
   - g) having difficulty concentrating
   - h) exaggerated startle response
   - i) irritability

Schizophrenia

1. Repeated hospitalization with a diagnosis of schizophrenia	10 pts
2. Recurrent treatment with antipsychotic medications	10 pts
3. Delusions:	2 pts
esp. feelings of persecution	
belief that you are controlled by imaginary person	
4. Hallucinations: esp auditory (hearing voices)	2 pts
5. Thought disorder: eg. saying things that make no sense and not realizing they make no sense; loose associations	3 pts
6. Catatonic behavior	2 pts
7. Flat or grossly inappropriate affect esp. feeling dead inside, saying personal things to complete strangers	2 pts

8. Inability to function at work or in social setting and to care for oneself 3 pts
9. Symptoms present recurrently or continuously for 6 mos
10. No known organic basis--eg. mental retardation, drugs, injury

ALCOHOLISM

	Never/Rarely	Sometimes	Frequently	Age
1. Treatment for alcoholism (hospitalization, detoxification, AA, Antabuse, etc)		Yes ____	No ____	
2. Legal problems—public intoxication		____	____	
—disorderly conduct		____		
—traffic violations		____		____
3. Marital, family problems due to drinking		____	____	____
4. Fired from job due to drinking		____	____	____
5. Health problems—cirrhosis, DT's, black outs, any other malnutrition from drinking, Korsakoff's		Yes ____	No ____	
6. Chronic absence from work or school		____		____
7. Loss of friends because of drinking		Yes ____	No ____	
8. Violence after drinking				
a. directed toward people	____	____	____	____
b. directed toward inantimate objects	____	____	____	____
9. Inability to stop drinking once started		Yes ____	No ____	

ANTISOCIAL PERSONALITY (CONDUCT DISORDER IF UNDER 18 YEARS OF AGE)

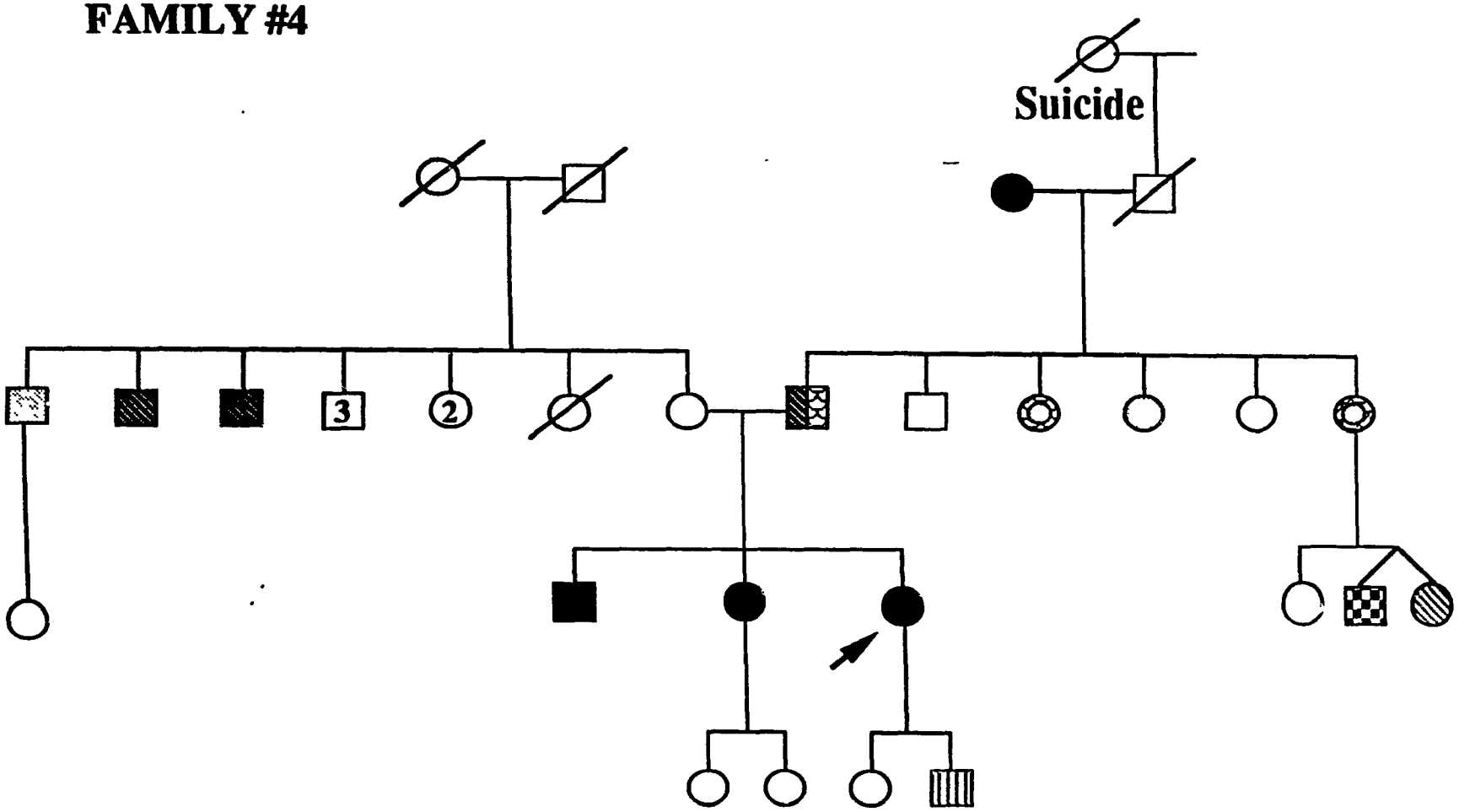
	Never/Rarely	Sometimes	Frequently	Age
1. Fighting	____	____	____	____
2. Stealing	____	____	____	____
3. Truancy	____	____	____	____
4. Ability to form close relationship	____	____	____	____
5. Expelled from school/loss of job for behavior problems	____	____	____	____
6. Many job changes or never worked		Yes ____	No ____	
7. Trouble with law—				
a. arrest	____	____	____	____
b. probation or imprisonment	____	____	____	____
8. Persistent and repeated lying	____	____	____	____
9. 2 or more divorces		Yes ____	No ____	
10. Deserted wife, children		Yes ____	No ____	
11. Aggressive and violent behavior (human)		____	____	____
(non-human)		____	____	____
12. Compulsive risk-taking behavior "living on the edge," sensation-seeking behavior	____	____	____	____

DEPRESSIVE DISORDER

	Never/Rarely	Sometimes	Recurrently	Age
1. Long-lasting or recurrent sadness	____	____	____	____
a. Of what duration were the episodes?				
b. How often did they recur? every year? once or twice?				
2. Treatment with anti-depressant medications		Yes	____ No ____	
3. Hospitalization for depression		Yes	____ No ____	
4. Loss of interest	____	____	____	
in activities previously enjoyed: Duration?				
5. Loss of energy or motivation (during episode)		Yes	____ No ____	
6. Feelings of worthlessness, guilt or reproach		____	____	____
7. Suicidal thoughts or behavior		____	____	____
8. Compulsive overeating? Severe loss of appetite?		Yes	____ No ____	
Insomnia? Sleeping much more than normal?		Yes	____ No ____	

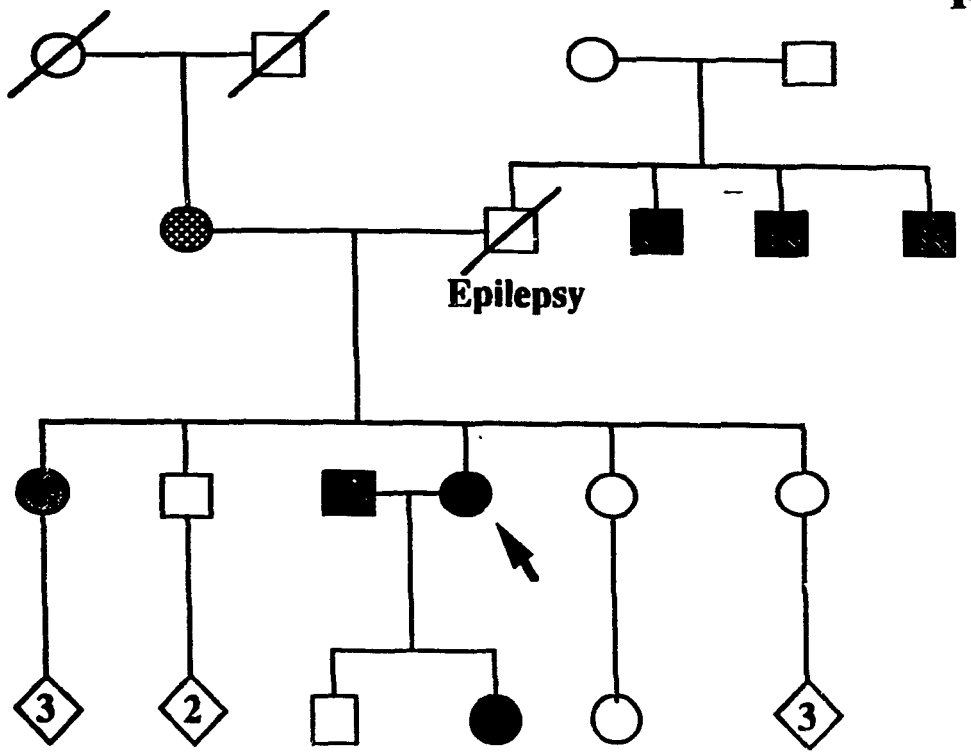
APPENDIX 2: pedigrees

FAMILY #4



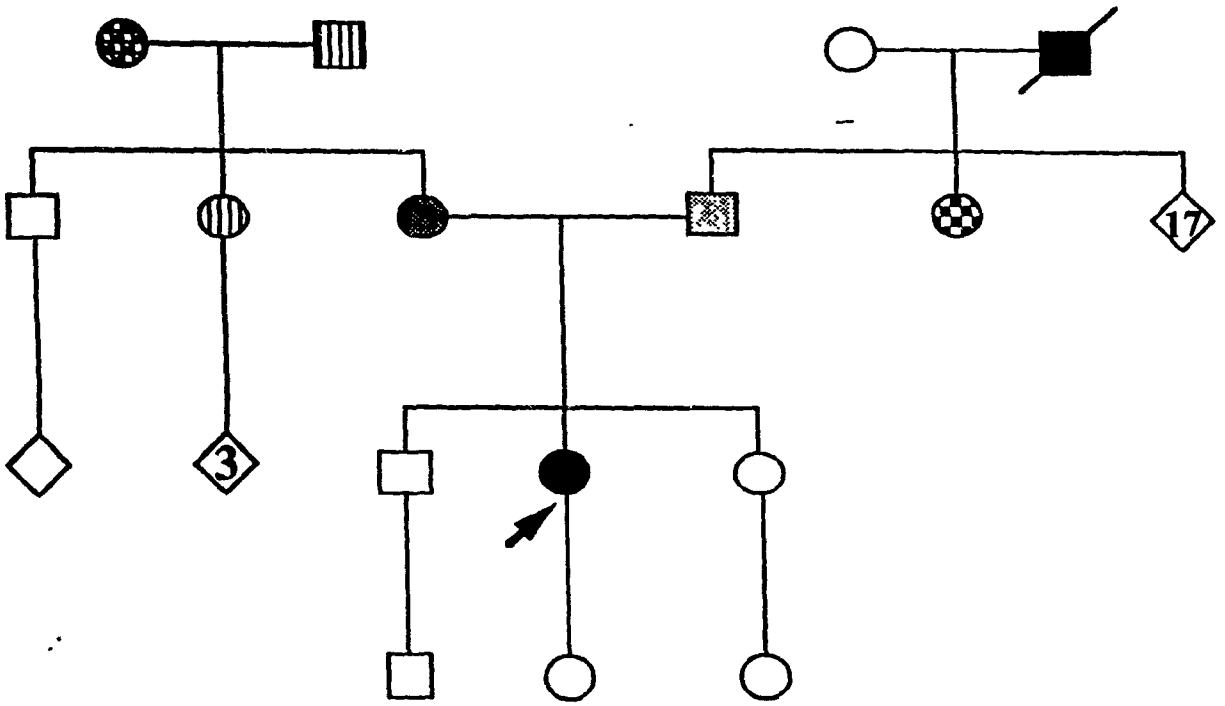
PROBAND	ALCOHOLISM
PANIC W/WO AGORAPHOBIA	ALCOHOL ABUSE
ANXIETY DISORDER	DRUG ABUSE
DEPRESSION	ADHD

FAMILY #5



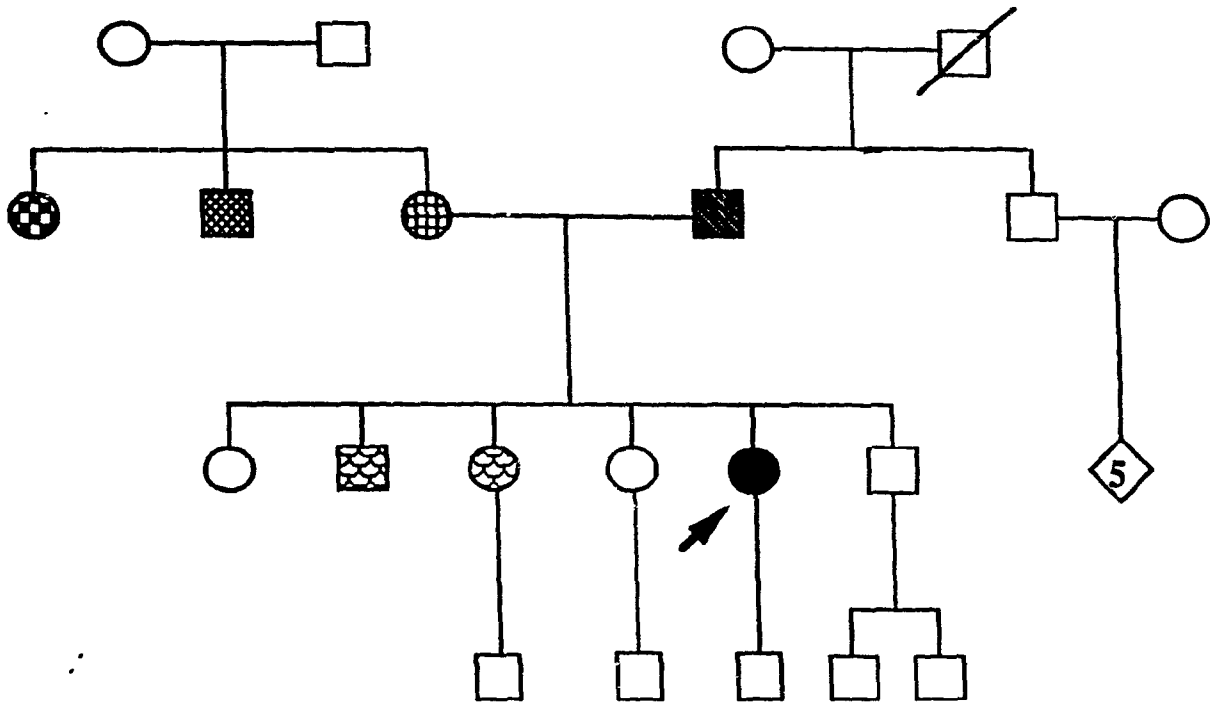
PROBAND	? AGORAPHOBIA
PANIC DISORDER	DEPRESSION, AGORAPHOBIA
AGORAPHOBIA	ALCOHOLISM

FAMILY #6



PROBAND	PANIC, ALCOHOLISM
PANIC DISORDER	ANXIETY, ALCOHOLISM
ANXIETY	PANIC, DEPRESSION
ALCOHOLISM	PSYCHOSIS

FAMILY #7



PROBAND

PANIC DISORDER

AGORAPHOBIA,DEPRESSION

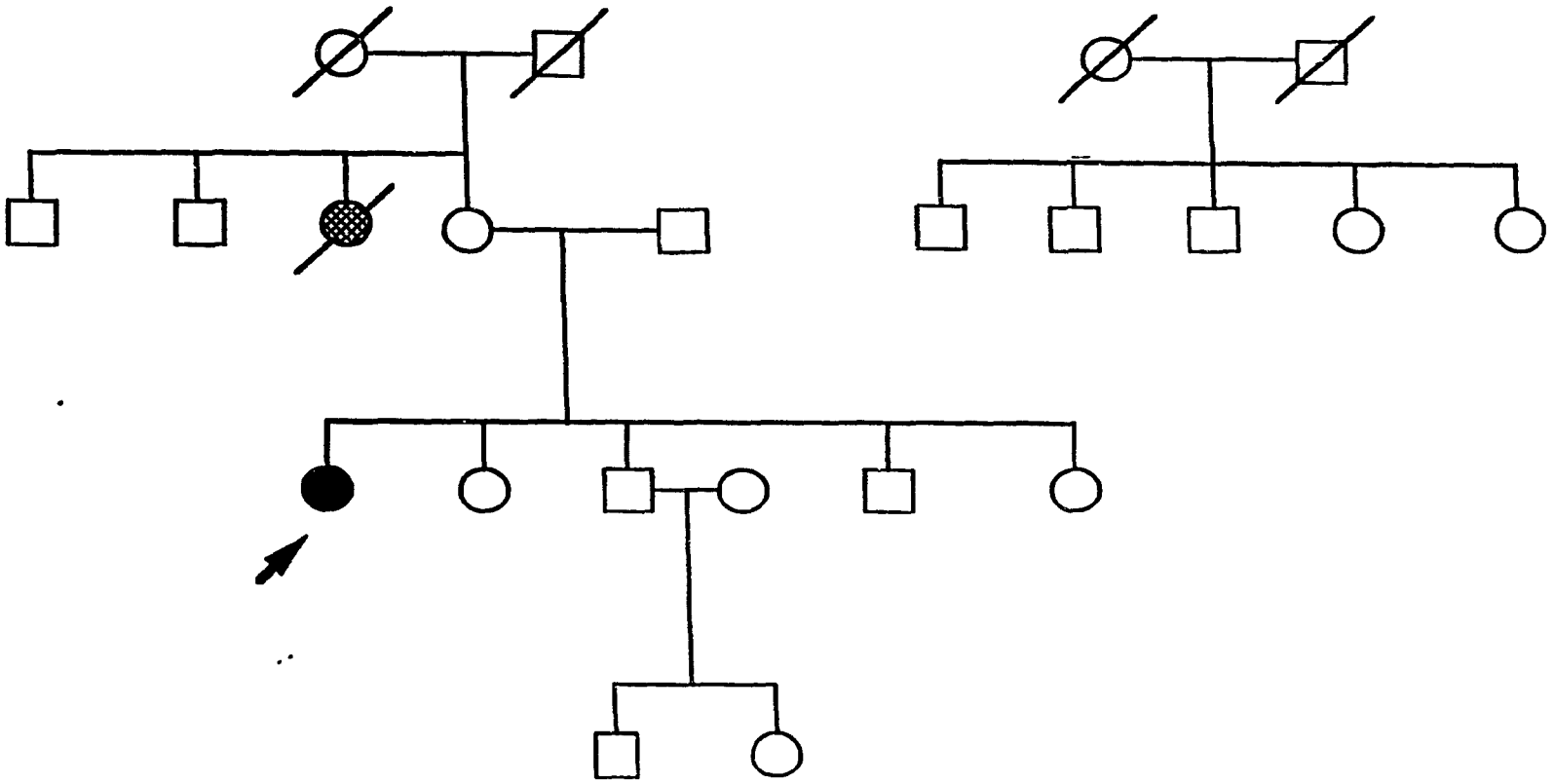
DEPRESSION

ANXIETY, DEPRESSION

ALCOHOLISM

ALCOHOLISM, DEPRESSION

FAMILY #16

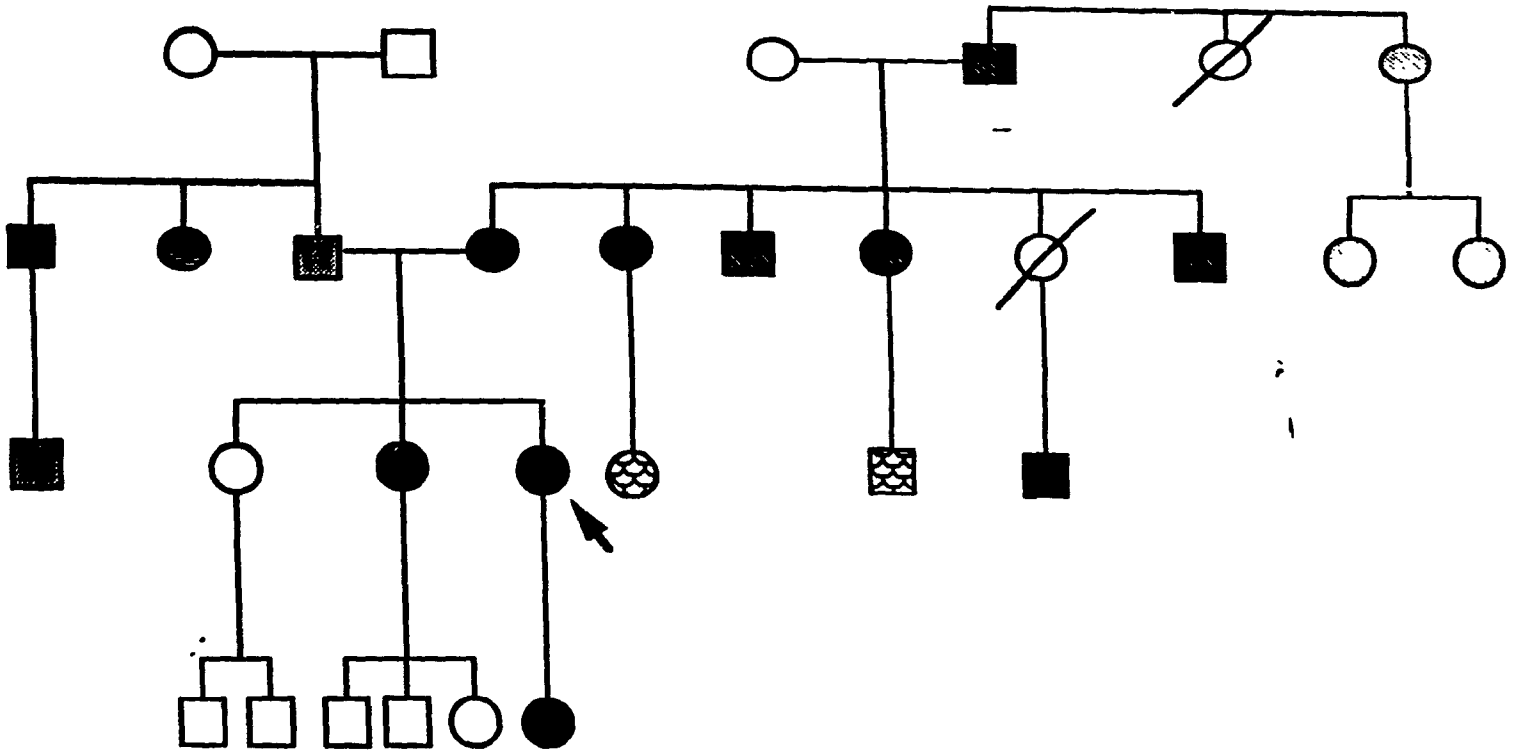


PROBAND

PANIC DISORDER, PAST DEPRESSION

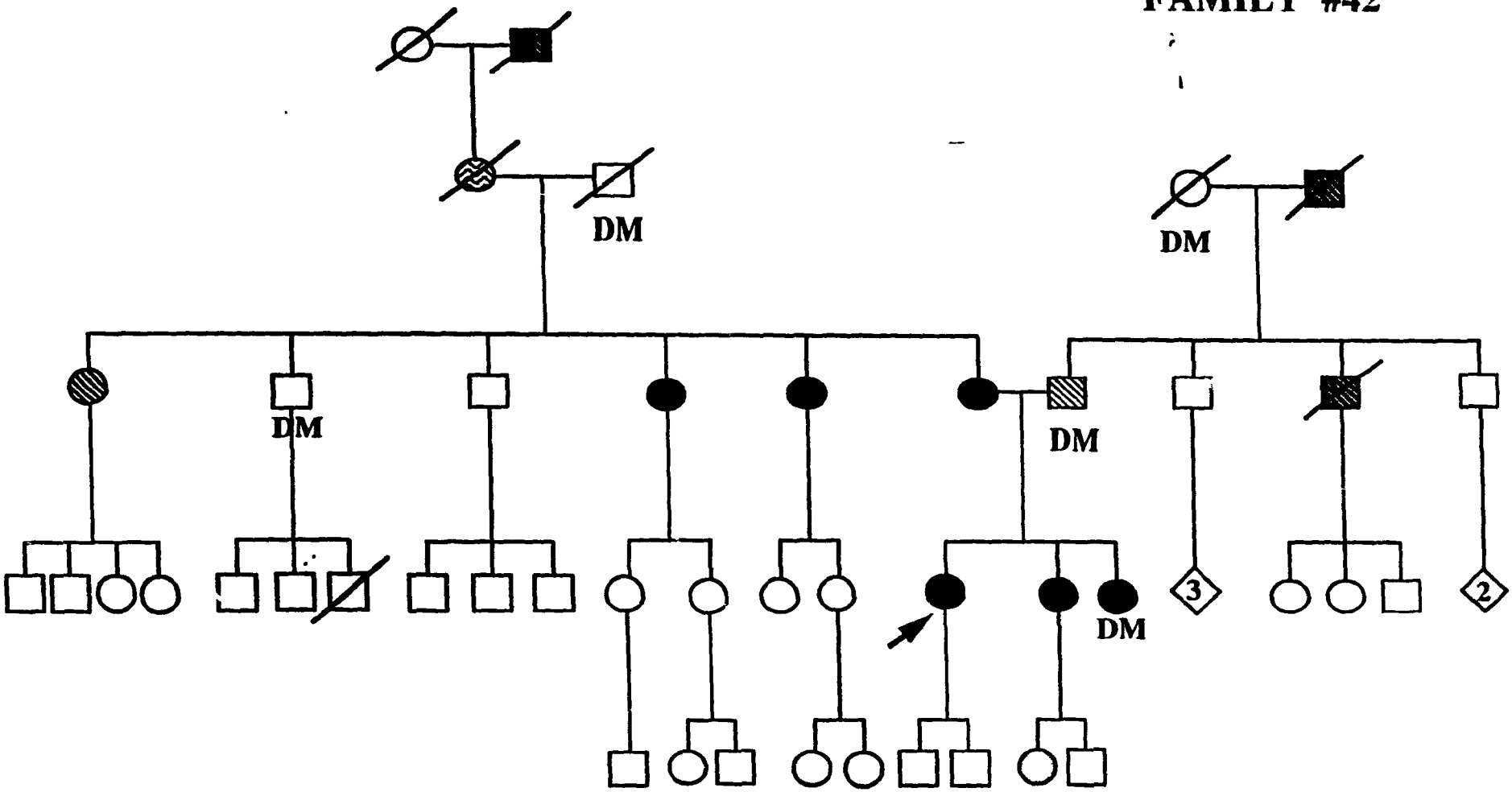
ALZHEIMER'S

FAMILY #40



PROBAND	PERSONALITY DISORDER
PANIC, AGORAPHOBIA	ALCOHOLISM
SYMPTOMS OF PANIC	DRUG ABUSE, SUICIDE
? ANXIETY	DEPRESSION

FAMILY #42



	PROBAND	DM	DIABETES MELLITUS
	PANIC W/WO AGORAPHOBIA		ALCOHOLISM
	AGORAPHOBIA		ALCOHOL ABUSE
	PERSONALITY DISORDER		PHOBIA

APPENDIX 3: Advertisements

Recherche Sur La Panique, la Phobie et l'Anxiété

L'hôpital St. Mary's méne présentement des projets de recherche sur le traitement médicamenteux du trouble panique se définit par les attaques de panique qui sont caractérisées par: l'étouffement, le coeur rapide, l'étourdissement, la peur, les nausés. La phobie sociale est vécue comme une forte anxiété durant des situations sociales menant à l'évitement de celles-ci. L'anxiété généralisée représente une inquiétude permanente accompagnée de tension.

Les participant(e)s à ces projets devront:
•être en bonne santé physique
•ne presendre aucun médicament actuellement
•être d'un âge entre 18 et 65 ans et,
•pratiquer une forme de contraception (pour les femmes d'âge fertile)

Si vous êtes intéressé(e) à être traité(e) dans le cadre d'un projet de recherche, veuillez remplir et adresser le questionnaire suivant à:

Lise Durand
Centre hospitalier St. Mary's
Section de psychopharmacologie
3830, avenue Lacombe
Montréal (Québec)
H3T 1M5

NOM: _____ **ÂGE**_____
ADRESSE: _____
NUMÉRO DE TÉLÉPHONE:_____

CHUS Centre Hospitalier
Universitaire de Sherbrooke

CLINIQUE D'ANXIETÉ DU SOUFFREZ-VOUS D'ATTAQUES DE PANIQUE?

La clnique est présentement à la recherche de personnes pour participer à une étude sur le traitement du trouble de apnique. Les symptômes centraux de trboule de panique sont des attaques soudaines d'angoisse accompagnées par au moins quatre symptômes physiques et/ou psychologiques.

Parmi ces symptômes se retrouvent
•une difficulté à respirer, une impression d'étouffer
•une sensation de chaud ou de froid
•des palpitations
•des nausées
•des douleurs au ventre, à l'estomac ou à la poitrine
•des étourdissements
•des tremblements
•un sentiment d'évanouissement
•une peur de perdre le contrôle, de perdre connaissance, de devenir fou ou de mourir.

Si vous avez coché plusieurs de ces symptômes, vous pourriez souffrir d'attaques et de troubles de panique et être séléctionné pour participer à une étude au niveau national d;un niouveau médicament pour le traitement de cette condition.
Si vous êtes intéressé à participer à cette étude, s'il vous plaît contacter l'infirmière responsable de la sélection des patients de cette étude Suzanne Frenette au 563-5555 poste 4899, les lundi, mercredi et jeudi.
Nous vous demanderons de consentir à venir à des rendez-vous réguliers, pendant 8 semaines, et à nous permettre de prélever des échantillons de sang et d'urine de temps à autre. Les médicaments à l'étude seront remis gratuitement. Tous les traitements seront prodigués par un médecin, assisté d'une infirmière autorisée.

Après votre participation à l'étude vous pourrez continuer d'être traité à la Clinique d'Anxiété, si vous le désirez.
S'il-vous-plaît, signaler le 563-5555 poste 4899 pour plus d'information.