

# Outcome of Panic Disorder

## Relationship to Diagnostic Subtypes and Comorbidity

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• Eighty-nine subjects with panic disorder, who had been naturalistically treated, and 46 nonanxious controls were followed up after 3 years. Although they remained symptomatic, most subjects with panic disorder reported relatively little distress or social maladjustment. The course of panic disorder was characterized by fluctuating anxiety and depressive symptoms. Panic subtypes (uncomplicated, limited phobic avoidance, and extensive phobic avoidance) and Axis I and II comorbidity (major depression and personality disorders) were highly predictive of symptoms and social adjustment after 3 years. Abnormal personality was, in fact, the strongest predictor of social maladjustment in both subjects with panic disorder and controls. The results showed that while panic disorder has a favorable outcome, the illness is a chronic one that may require continuing treatment. They also show that subtypes and comorbid disturbances are important predictors of outcome.

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To modify favorably the long-term course of illnesses, such as panic disorder, we need accurate information about outcome and factors that predict it. Follow-up studies of anxiety neurosis, a *DSM-II* forerunner of panic disorder, suggested that this illness was a chronic one, but that it had a favorable outcome.<sup>2,9</sup> Only a small minority of patients completely recovered, but more than half had mild symptoms and relatively little social impairment.<sup>10</sup> Recent studies that utilized *DSM-III*<sup>11</sup> criteria have, on the whole, suggested that the prognosis for patients with panic disorder and agoraphobia with panic attacks is equally good.<sup>12-18</sup> With the exception of Krieg et al,<sup>15</sup> who observed a chronic and severe course among patients who had been hospitalized, most studies of treated samples indicated that a substantial proportion recover and that the remainder do well despite residual symptoms. In fact, three studies reported recovery rates that ranged from 25% to 72% after 1 or 2 years.<sup>13,14,16</sup> However, recovery was variously defined in these studies to include patients with mild symptoms. Also, a number of the patients who were classified as having recovered subsequently relapsed. Therefore, we should not accept these optimistic assessments uncritically.

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Given the apparent chronicity of panic disorder, we need to concern ourselves with the course of the illness and the occurrence of complications. Agras et al<sup>19</sup> found that phobic disturbances in the community, including agoraphobia, were relatively unstable over time. Although they found little change in the group as a whole, individual subjects were often better or worse than they had been when they were first interviewed. Noyes et al<sup>18</sup> observed similar fluctuations in a group of patients with panic disorder who were followed up after 2½ years. Complications or comorbid conditions, such as depression and alcohol abuse, may also contribute to instability from one time period to the next. Among patients with *DSM-III* panic disorder and/or agoraphobia, between 24% and 91% have had one or more episodes of major depression, with the median for studies being about 50%.<sup>20-22</sup> Although the relationship between panic and major depression continues to be debated, there is evidence that depression occurs in more severely ill patients and that future episodes are more likely to occur in patients with a history of such episodes.<sup>23-27</sup> Likewise, alcohol abuse has been identified in 9% to 43% of patients with panic disorder, with the median for studies being about 17%.<sup>22</sup> The relationship between alcohol abuse and panic disorder appears to be complex, but many patients report that they use alcohol in an attempt to control symptoms.

Because panic disorder is a relatively recent addition to the diagnostic nomenclature, there has been little opportunity to examine the effect of Axis I and II comorbidity on its course and outcome.<sup>11,28</sup> However, there are several reasons why this may be an especially important issue for panic disorder. First of all, subtypes of the disorder (eg, agoraphobia) have been proposed, and the co-occurrence of Axis I and II disorders appears to be frequent.<sup>11,21,29</sup> Second, as has been said, panic disorder appears to be a chronic condition.<sup>18</sup> This means that associated disturbances have longer to interact with the primary illness and thereby undermine functioning. Third, comorbid disturbances are associated with social impairment of their own, apart from that caused by anxiety symptoms. Because the impairment associated with most anxiety disorders is relatively modest, the contribution of personality disorders or of depression may be disproportionately great.

Although *DSM-III-R* combines panic disorder and agoraphobia under a single heading, there is continuing debate over whether agoraphobia represents a variant of panic disorder

or a separate illness.<sup>28</sup> Agoraphobia is, after all, a unique and disabling symptom complex that responds to behavior therapy. Reflecting British tradition, Marks<sup>30</sup> included this illness in his classification of phobic disorders that was later incorporated into *DSM-III*.<sup>11</sup> However, influenced by the hypothesis of Klein<sup>31</sup> about the primacy of panic attacks, the work group charged with revising *DSM-III*<sup>32</sup> chose to establish a single category of panic disorder. According to the degree of avoidance, patients might be subdivided into those without phobic avoidance (uncomplicated), those with limited phobic avoidance, and those with extensive phobic avoidance (agoraphobia).

Data bearing on the question of classification have tended to support the unitary viewpoint. To begin with, there is a considerable overlap of anxiety and agoraphobic symptoms among patients with panic disorder and agoraphobia.<sup>33</sup> Beyond that, almost no distinguishing demographic or illness characteristics have been found, except for those reflecting severity.<sup>34,35</sup> In addition, agoraphobic patients who have never experienced spontaneous panic attacks are rarely encountered in clinical populations, although they may exist in the general population.<sup>36</sup> Further support for the unitary view comes from the observation that agoraphobic symptoms often develop after the onset of panic attacks, suggesting that agoraphobia is a conditioned reaction to the occurrence of unexplained attacks.<sup>37</sup> Finally, both drug and behavior therapies appear to reduce panic attacks, as well as agoraphobic symptoms, although direct comparisons have not been made.<sup>38</sup>

There is some evidence that personality disorders, which occur in 27% to 58%, influence the outcome of patients with panic disorder and/or agoraphobia.<sup>29,39-43</sup> Three studies have shown that the presence of a personality disturbance predicts a less favorable treatment response. For example, Tyrer et al<sup>44</sup> found a strong relationship between personality and clinical response to phenelzine in patients with anxiety and depressive and phobic neuroses. Only 3 of 16 responders had personality disorders compared with 29 of 44 nonresponders. Similarly, Mavissakalian and Hamann,<sup>45</sup> who treated agoraphobic subjects with combined drug and behavior therapy, found that only 1 of 11 responders had personality disorders compared with 5 of 10 nonresponders. Also, in a series of patients with panic disorder treated with benzodiazepines, Reich<sup>46</sup> found a less favorable outcome among patients with unstable (cluster B) personality disorders.<sup>28</sup> In addition, Favelli and Albanesi<sup>47</sup> found that personality measures predicted the outcome of agoraphobic patients who had been treated naturalistically.

With respect to Axis I comorbidity, depression is the syndrome that most frequently occurs in patients with anxiety disorders and that seems most likely to influence outcome. Several studies have shown that patients with panic disorder who have depression have a less favorable course and outcome than patients without. For example, Breier et al<sup>25</sup> and Lesser et al<sup>27</sup> found that those patients with current or past major depression had more severe anxiety and phobic symptoms when they were examined. Also, both Van Valkenburg et al<sup>24</sup> and Nutzinger and Zapotoczky<sup>26</sup> reported that patients with comorbid depression had worse outcomes than did patients without depression. In a similar vein, Buller et al<sup>28</sup> reported that patients with secondary depression were more likely to experience depression during a follow-up period. Although both Reich et al<sup>29</sup> and Zitrin et al<sup>48</sup> found that patients with panic disorder or agoraphobia who had major depression (current or past) responded less well to drug and/or behavior therapy, other investigators have not found depressed patients any more or less responsive to treatment.

This study examines the outcome of a large series of pa-

tients with panic disorder who were originally enrolled in an 8-week treatment study after which they were treated naturalistically and then followed up after 3 years. The study also looks at the relationship of diagnostic subtyping and Axis I and II comorbidity to the outcome of these patients.

## SUBJECTS AND METHODS

### Subject Selection

This study involved 97 subjects with panic disorder who were recruited via the news media and screened by using the Structured Clinical Interview for *DSM-III* developed by Spitzer and Williams.<sup>49</sup> All subjects met *DSM-III-R* (1985 working draft) criteria for panic disorder and had at least one panic attack in the week before being enrolled in a drug treatment study.<sup>32</sup> Subjects were excluded who had a history of psychosis, dementia, bipolar disorder, melancholia, or alcohol abuse (within the past 6 months). Subjects with major depression were included, providing the onset of depression began after the onset of the anxiety disorder. Subjects with distinctly abnormal laboratory values or uncontrolled physical disease were also excluded.

Subjects were enrolled in a double-blind, placebo-controlled study that compared the effects of alprazolam and diazepam. All had stopped taking psychotropic medication for at least a week before baseline assessment. At that time, information about a series of demographic and illness characteristics was obtained. Demographic variables included age, sex, educational level, occupational class, social class, income, marital status, social network, and religion. Educational level and occupational class were combined according to the Hollingshead Two-Factor Index of Social Position to give a measure of social class.<sup>50</sup> Social network was assessed by means of the Social Relationships Scale.<sup>51</sup> Illness characteristics included age at onset, duration of illness, occurrence of major depression (current or past), and subtyping according to the extent of phobic avoidance (uncomplicated, limited, or extensive).<sup>32</sup> Subtyping and screening for depression were accomplished by using the Structured Clinical Interview for *DSM-III*.

### Baseline Assessment

At baseline, the level of anxiety symptoms was measured by using the Hamilton Anxiety Rating Scale<sup>52</sup> and the Self-rated Anxiety Scale developed by Sheehan.<sup>53,54</sup> The frequency of panic attacks (three or more symptoms) was recorded for the preceding month on a panic attack scale that had been employed in a previous study.<sup>54</sup> Agoraphobic symptoms were rated by using a phobia scale on which fear (0 = not at all to 10 = extremely) and avoidance (0 = never to 4 = always) were rated separately for each item. This scale included seven agoraphobic symptoms that were summed separately.<sup>54</sup> The overall severity of phobic symptoms was rated on an 11-point scale (0 = no phobias present to 10 = extremely distressing or restricting). In addition, social impairment related to anxiety and phobic symptoms was rated on three 11-point scales (0 = not at all to 10 = very severely impaired) and a five-point global scale (1 = no complaints, normal activity to 5 = symptoms radically change or prevent normal work or social activities).<sup>54</sup>

Personality was assessed by means of the Structured Interview for *DSM-III* Personality (SIDP)<sup>55</sup> and the Personality Diagnostic Questionnaire (PDQ).<sup>56</sup> The SIDP was administered by two research assistants who had been trained in its use. This instrument is a 160-item, semistructured interview for the assessment of *DSM-III*, Axis I disorders. The interview takes 60 to 90 minutes to complete, and information is also obtained from a family member. Satisfactory reliability for the SIDP has been reported.<sup>57,58</sup> The PDQ is a 152-item, self-administered questionnaire designed to assess *DSM-III* personality disorders. The reliability of this instrument has also been reported.<sup>59</sup> Both instruments yield scores for individual personality disorders and, if the necessary criterion items are scored positively, a subject is said to meet criteria for one or more personality disorders.

### Treatment Study

The subjects of this investigation were randomly assigned to alprazolam (1-mg capsules), diazepam (10-mg capsules), or placebo capsules that were administered in a flexible dose for 8 weeks. If, at the end of this period, subjects were doing well, they could elect to

receive study medication (double blind) for 6 additional months. At that point, study medication was gradually discontinued, and subjects were treated naturalistically. Approximately half of the subjects responded well to study medication and chose to continue beyond 8 weeks (21 dropped out before 8 weeks). At the time of completion, the mean dose of alprazolam was 3.6 mg, of diazepam was 32.0 mg, and of placebo was 8.1 capsules. The results of this study will be reported elsewhere.

### Follow-up Assessment

Those participants in the treatment study who received at least one dose of study medication were followed up between 2 and 4 years after their initial enrollment. At this time, they were personally interviewed by a trained research assistant (J.C.) who was familiar with patients with anxiety disorders. Subjects were interviewed in their homes or, if they lived more than 150 miles from the University of Iowa Hospitals, Iowa City, by telephone. Each was given a structured interview and questionnaires that lasted 2 to 2 1/2 hours. The interview included the Social Adjustment Scale developed by Weissman et al<sup>59</sup> and the Global Assessment Scale<sup>61</sup>; questionnaires included the PDQ and a repeat of scales administered at the initiation of the treatment study.<sup>56</sup> The Social Adjustment Scale is an interview that consists of 42 items rated on five-point scales. Items cover the areas of work, social activities, family relationships, and marital adjustment. The interview yields scores for maladjustment in each of these areas, as well as for a series of factor analytically derived dimensions.<sup>62</sup> Also, a total score may be obtained by summing individual items. Retrospective, month-by-month ratings of panic/agoraphobic symptoms (0 = no symptoms to 5 = extreme symptoms), major depression (present or absent), and alcohol abuse (present or absent), were made for the follow-up period. To assist these ratings, a time chart with anchor points was used.

### Controls

Controls consisted of 48 relatives of patients with major depression who participated in the National Institute of Mental Health Collaborative Depression Study at the University of Iowa.<sup>63</sup> These relatives had been screened for psychiatric illness by using the Schedule for Affective Disorders and Schizophrenia-Lifetime version<sup>64</sup> and had provided demographic information 3 years earlier. They had also completed the Maudsley Personality Inventory.<sup>65</sup> Controls were selected who had no psychiatric illness (Research Diagnostic Criteria), unless that illness would not have excluded them from the panic disorder treatment study, and controls were matched as a group for age and sex with subjects with panic disorder. Three controls had minor depressive disorder, two had generalized anxiety disorder, and one had an unspecified psychiatric illness. Controls were interviewed in the same manner as were the subjects with panic disorder.

### Follow-up Populations

A total of 89 subjects (91.8%) with panic disorder were interviewed. Of the remaining 8, 3 could not be located, 3 chose not to participate, and 2 gave incomplete information. The follow-up interval ranged from 25 to 49 months, and the mean interval was 36.5 months (initiation of treatment to study follow-up). A total of 46 controls (95.8%) were interviewed; the 2 remaining did not wish to take part. The follow-up interval for controls ranged from 27 to 51 months, and the mean interval for this group was 35.5 months (initial interview to follow-up). Subjects with panic disorder and controls were closely matched: 57.3% and 54.3%, respectively, were women, and the mean ( $\pm$  SD) ages were  $38.7 \pm 10.6$  and  $38.0 \pm 9.6$ , respectively. Also, they were similar with respect to social class; the mean Hollingshead Two-Factor Index of Social Position scores were  $37.5 \pm 14.1$  and  $38.3 \pm 15.2$ , respectively.<sup>50</sup>

### Statistical Analyses

For the sake of simplicity, we report analyses by using the Self-rated Anxiety Scale rather than the Hamilton Anxiety Rating Scale. These scales were highly correlated ( $r = .78$  at baseline), and the findings using the two scales were similar; however, scores on the Self-rated Anxiety Scale showed stronger associations with most baseline and follow-up measures. For similar reasons, we included data obtained by using the SIDP in most analyses. Scores from the

SIDP and the PDQ were also highly correlated ( $r = .76$  at baseline), and the results using these measures were similar.

To examine the influence of certain baseline variables on outcome measures, we separated subjects into groups falling above and below the median of each distribution. Otherwise, standard statistical procedures were employed. Categorical frequencies were cross-tabulated in two-way tables and examined for independence by using  $\chi^2$  tests. For continuous measures, comparisons of means were carried out with  $t$  ratios (two way) or one-way analysis of variance and follow-up tests (Tukey's). The associations among continuous variables were examined by means of pairwise correlations. A stepwise, multiple-regression analysis was performed in which both continuous and categorical predictor variables were included. Models were constructed by using all subjects with panic disorder for each of three outcome measures. In constructing the models, we attempted to minimize colinearity in the selection of variables that relied on the usual  $R^2$  and mean square error criteria.

Personality measures were scored categorically for certain analyses and continuously for others. Subjects who met criteria for any personality disorder on the SIDP were so categorized. Also, the total number of abnormal personality traits identified by the SIDP and PDQ were summed for each subject. Because the PDQ was administered twice, we were able to examine change that had occurred between baseline and follow-up by using this instrument. For this purpose, we looked at scores that represented the sum of items contributing to individual personality disorders. Sample size for subjects with panic disorder varied from 88 to 90 because of incomplete information on three subjects.

## RESULTS

### Sample Characteristics and Outcome

Subjects with panic disorder who were followed up included 51 women with a mean ( $\pm$  SD) age of  $38.2 \pm 11.5$  years and 38 men with a mean ( $\pm$  SD) age of  $39.3 \pm 9.3$  years at the time they participated in the treatment study. Sixty-nine (77.5%) of the subjects were married. The age at onset, which ranged from 5 to 49 years, was a median of 24.0 years, and the duration of illness, which ranged from 3 months to 54 years, was a median of 9.5 years. The majority of subjects (65.2%) had been treated for panic disorder before taking part in the treatment study. Twenty-six subjects (28.6%) were classified as having uncomplicated panic disorder according to the October 5, 1985, draft of *DSM-III-R*.<sup>32</sup> These subjects reported "no significant phobic avoidance or intense anxiety." Twenty-nine (31.9%) were classified as having limited phobic avoidance, meaning that they had "significant phobic avoidance or endurance despite intense anxiety," and 36 (39.6%) had extensive phobic avoidance, defined as "generalized travel restrictions, often needing a companion away from home, or a markedly altered life style." Forty-one subjects (45.1%) reported one or more current or past episodes of major depression, and 40 (44.9%) were identified as having one or more personality disorders by using the SIDP. The rates of individual disorders are reported elsewhere.<sup>29</sup>

### Outcome of Subjects With Panic Disorder and Controls

At follow-up, subjects with panic disorder were asked to estimate the overall level of their panic/agoraphobic symptoms on a six-point scale (0 = no symptoms to 5 = extreme symptoms). As a result, 10.0% reported no symptoms, 36.6% reported minimal symptoms, 20.0% reported mild symptoms, 28.9% reported moderate symptoms, 3.3% reported severe symptoms, and 2.2% reported extreme symptoms. Table 1 shows baseline and follow-up scores on scales administered at both times. Statistically significant reductions were observed on all self- and observer-rated scales. The level of symptoms, as measured by the Hamilton Anxiety Rating Scale, was reduced by at least half in 48.4% of subjects, and 52.8% scored 10 or less at follow-up. The frequency of panic attacks was reduced by half in 89.9% of subjects, and 31.9% reported no attacks in the month preceding the follow-up assessment. Sixty-three subjects with panic disorder (69.2%) were taking medication for anxiety on a regular basis at the time of follow-up.

As is shown in Table 2, subjects with panic disorder were rated as having more social maladjustment than controls in the areas of work, social and marital adjustment, as well as total adjustment (sum of items making up the Social Adjustment Scale) at follow-up. With respect to overall social adjustment, as rated on a seven-point scale

Table 1.—Mean Scores Obtained at Baseline and Follow-up by Subjects With Panic Disorder

	Score		P<
	Baseline (n = 88)	Follow-up (n = 88)	
Observer-rated anxiety*	20.1	11.1	.0001
Self-rated anxiety†	54.4	30.3	.0001
Panic attacks (mean weekly)	6.4	1.3	.0001
Symptom-related disability‡	3.8	2.5	.0001
Overall phobia§	5.3	3.0	.0001
Global improvement	5.0	7.8	.0001
Personality Diagnostic Questionnaire (mean abnormal traits)	33.1	28.8	.01

\*Mean Hamilton Anxiety Rating Scale scores.

†Mean Self-rated Anxiety Scale scores (35 items rated on five-point scales).

‡Mean global social disability rated on a five-point scale (1 = normal activity to 5 = symptoms radically changed or prevent normal work or social activities).

§Mean global rating of phobic symptoms (0 = no phobias present to 10 = extremely distressing or restricting).

||Mean global rating of improvement by the clinician on an 11-point scale (0 = very bad, could not be worse, to 5 = no change to 10 = major improvement, back to normal).

Table 2.—Mean SAS and PDQ Scores for Panic Disorder and Control Subjects at Follow-up\*

		Score		
		Panic Disorder (n = 88)	Controls (n = 46)	P<
SAS				
Areas of functioning				
	Work adjustment	10.6	8.6	.001
	Social leisure adjustment	18.0	14.9	.001
	Family adjustment	11.4	10.6	NS
	Marital adjustment	15.4	12.7	.001
	Parental adjustment	6.5	6.3	NS
	Total adjustment	57.1	48.8	.0001
Dimensions of functioning				
	Work productivity	8.5	7.0	.001
	Interpersonal friction	11.7	10.0	.01
	Inhibited communication	11.7	10.0	.01
	Emotional dependence	3.7	2.9	.02
	Family bound	5.4	4.4	.01
	Anxious rumination	9.7	7.2	.0001
PDQ				
	Total PDQ	28.8	19.7	.001
	Impairment/Distress scale	1.6	0.8	.01

\*SAS indicates Social Adjustment Scale; PDQ, Personality Diagnostic Questionnaire; and NS, not significant.

(1 = no maladjustment to 7 = very severe maladjustment), subjects with panic disorder scored a mean of 2.55, and controls scored a mean of 1.78 ( $P < .0001$ ). On the Global Assessment Scale, subjects with panic disorder scored a mean of 72.3 (range, 45 to 91) compared with a mean of 84.2 (range, 56 to 94) for controls ( $P < .001$ ). Among subjects with panic disorder, 11.4% were rated as having no overall maladjustment; 37.5% had minimal maladjustment, 36.4% had mild maladjustment, and 14.3% had moderate maladjustment. By comparison, 30.4% controls were rated as having no overall maladjustment, 60.9% had minimal maladjustment, and 8.7% had mild maladjustment.

Also, at follow-up, subjects with panic disorder scored a mean of 28.8 on the PDQ compared with a mean of 19.7 for controls.

## Course and Complications

During the follow-up interval, the overall level of panic/agoraphobic symptoms showed a degree of fluctuation. In only 21.1% of subjects with panic disorder did the level remain constant; in 46.7%, the level varied one point; in 20.0%, it varied as much as two points; and in 12.2%, it changed three or more points on a six-point scale. The average level of symptoms for the follow-up period was higher among subjects who experienced more variation. The mean ranged from 1.8 for those whose level of symptoms remained constant to 3.0 for those varying as much as four points. No distinct patterns with respect to the level of anxiety symptoms were discernible within the subjects with panic disorder, or for the population as a whole. Most subjects showed irregular fluctuations but no overall change during the last 2 years of the follow-up period. No seasonal variation in symptoms was observed when mean symptom levels were compared with a 12-month interval. A small proportion of subjects (12.2%) achieved a symptom-free state for at least 1 month, and 44.4% achieved a state of minimal symptoms for 1 month or more.

During the follow-up period, 34.4% of the subjects with panic disorder experienced depressive symptoms that lasted a month or more. Symptoms that qualified for major depression ranged in duration from 1 to 42 months and lasted a median of 5 months. Twenty subjects reported a single episode, and 7 subjects reported two episodes of depression. In all but 4 subjects, these represented new episodes that arose in the follow-up period. The mean overall level of anxiety symptoms during periods of depression was 2.68 compared with 2.16 during the remainder of the follow-up period ( $P < .05$ ). Also, the mean level of anxiety symptoms throughout the follow-up period was 2.22 for subjects who experienced depression compared with 1.77 for those who did not ( $P < .05$ ). Nearly half of the subjects (47.5%) who experienced depression during the follow-up interval had a history of major depression compared with 26.0% of those who had not experienced depression ( $P < .02$ ). The mean Self-rated Anxiety Scale score at the time of original assessment for subjects who experienced depression was 62.3 compared with 49.9 for those who did not experience depression ( $P < .05$ ). Five subjects abused alcohol (or drugs) during the follow-up interval, and at such times, the mean level of anxiety symptoms was 2.71 compared with 1.94 when they were not abusing alcohol ( $P < .05$ ).

## Baseline Differences According to Subtype and Comorbid Disturbances

When they were subtyped according to *DSM-III-R* (draft of October 5, 1985), subjects with extensive phobic avoidance differed most from those with no phobic avoidance (uncomplicated panic disorder), and those with limited phobic avoidance fell in between.<sup>32</sup> As may be seen from Table 3, subjects with extensive phobic avoidance had an earlier age at onset, as well as a longer duration of illness. Also, subjects with extensive phobic avoidance had more severe symptoms, including more frequent panic attacks and symptom-related social disability, than subjects with limited or no phobic avoidance. Comorbid major depression (current or past) was most frequent in the extensive avoidance group, and coexistent personality disorders were identified most frequently in the extensive phobic avoidance subgroup.

When we compared subjects with major depression (current and past did not differ and were combined) with those subjects who had no history of depression at baseline (Table 3), we found that the former had more severe symptoms and more frequent coexisting personality disorders; also, a greater proportion belonged to the extensive phobic avoidance (agoraphobic) subgroup. Similarly, when we compared subjects with any personality disorder with those subjects who had no such disorder, we found that the personality-disordered group had more severe anxiety symptoms and symptom-related disability at baseline, had more current or past major depression, and more frequently belonged to the extensive phobic avoidance subgroup. Also, we found our baseline measures of personality and severity of symptoms to be closely related. The correlation between the total score (sum of items) on the SIDP and the total score for the Self-rated Anxiety Scale was .50 ( $P < .001$ ). However, there appeared to be little relationship between either symptom severity or personality and demographic variables at baseline.

Table 3. — Baseline Demographic and Illness Characteristics of Patients With Panic Disorder Grouped According to Subtype and the Presence or Absence of Comorbid Conditions\*

	Panic Disorder Subtypes†			Major Depression†		Personality Disorders‡	
	Extensive Avoidance (n = 36)	Limited Avoidance (n = 29)	Uncomplicated (n = 26)	Present (n = 41)	Absent (n = 50)	Present (n = 40)	Absent (n = 49)
Demographic features							
Mean age, y	39.2	38.0	37.2	40.5	36.4§	39.1	37.9
Sex, % F	69.4	55.2	52.0	58.5	61.2	48.8	63.0§
Social class	36.7	37.6	39.2	35.1	39.8	39.3	35.8
Illness characteristics							
Mean age at onset, y	22.7	25.2	28.5§	25.1	25.1	25.6	24.8
Duration of illness, y	16.4	12.2	8.4¶	15.2	10.8§	12.9	12.4
Self-rated anxiety#	62.7	54.0	43.2**	64.2	45.9††	65.1	45.4††
Panic attacks, mean/mo	34.4	21.8	18.4§	37.7	16.1**	25.8	26.2
Phobic symptoms‡‡	8.0	5.6	1.0§§	6.4	4.3**	5.9	4.9
Symptom-related disability	14.2	12.8	9.0**	13.9	10.9¶	14.2	10.6**
Comorbid conditions							
Panic subtypes, %†							
Uncomplicated	...	...	...	19.5	36.4	22.5	32.7
Limited avoidance	...	...	...	29.3	34.0§	30.0	34.7
Extensive avoidance	...	...	...	51.2	30.0	47.5	32.7
Major depression, %†	58.3	41.4	30.8§	...	...	57.5	36.7¶
Personality disorders, %‡	54.3	41.4	36.0	56.1	35.4¶	...	...

\*Percentages indicate the proportion of subjects listed at the top of the table that belong to categories listed at the left of the table.

†Classified according to *DSM-III-R* (1985 version) using the Structured Clinical Interview for *DSM-III*.

‡Identified as having one or more personality disorders using the Structured Interview for *DSM-III* personality.

§ $P < .10$ .

¶Mean Hollingshead, Two-Factor Index of Social Position scores.

¶ $P < .05$ .

#Mean Self-rated Anxiety Scale scores.

\*\* $P < .01$ .

†† $P < .001$ .

‡‡Mean Global Phobia Rating Scale scores.

§§ $P < .0001$ .

|||Mean sum of three social disability rating scales.

### Predictors of Outcome

Certain baseline measures were more predictive of symptoms, and others were more predictive of social adjustment at follow-up. However, demographic variables were relatively unimportant in this regard. Subjects of lower social class and less extensive social networks had less favorable social adjustment at outcome, but few of the remaining differences were statistically significant. Table 4 shows that, with the exception of panic attack frequency, ratings of symptoms at baseline were highly predictive of symptom severity, symptom-related disability, and social adjustment at outcome. For example, subjects who scored below the median on the anxiety scale (Self-rated Anxiety Scale) obtained scores on most symptom and symptom-related impairment scales at follow-up that were about half those obtained by subjects who scored above the median.

Differences in outcome according to diagnostic subtypes and comorbid conditions can be seen in Table 5. The most severe symptoms and symptom-related disability at follow-up were observed among subjects with extensive phobic avoidance, whereas the least severe symptoms and impairment were seen in the uncomplicated subjects. Similarly, subjects with current or past major depression had more severe symptoms and symptom-related disability at follow-up than did subjects without major depression. Neither the subtypes nor the comorbid depression appeared to be associated with differences in social maladjustment, however. By contrast, subjects with coexisting personality disorders showed greater social maladjustment at follow-up. These subjects had more severe symptoms as well. Subjects with a history of major depression, at baseline, were also more likely to experience depression during the follow-up interval (47.5%) than were those who had no history of depression (26.0%) ( $P < .02$ ).

### Relationships Among Predictors of Outcome

Three outcome measures were selected from a larger pool for the purpose of a multivariate analysis of potential predictors. These included the Self-rated Anxiety Scale (total and percent reduction from baseline) and the Social Adjustment Scale (total). Other measures of symptom severity and social maladjustment were highly correlated with one another and, for this reason, were not included. The relationships between continuous baseline variables and these outcome measures is shown in Table 6. The table shows that correlations between the percent change in anxiety symptoms and baseline variables, with the exception of duration of illness, were low. For both level of anxiety symptoms and social adjustment at follow-up, the baseline variables that showed the highest correlations were abnormal personality traits, the initial level of anxiety symptoms, and the duration of illness.

Stepwise, multiple-regression analyses were done, beginning with seven continuous and four categorical baseline variables. Continuous variables included age, income, social class, social network, duration of illness, level of anxiety (Self-rated Anxiety Scale), and abnormal personality traits (SIDP). Categorical variables included sex, marital status, panic disorder subtypes, and the presence or absence of major depression. The initial level of anxiety symptoms accounted for 25.0% of the variance and was the strongest predictor of the level of symptoms at follow-up ( $P < .0001$ ). The level of symptoms, together with duration of illness ( $P < .01$ ) and level of income ( $P < .05$ ), accounted for 37.0% of the variance in this measure. The sum of abnormal personality traits, accounting for 27.9% of the variance, was the strongest predictor of social maladjustment at follow-up ( $P < .0001$ ) and, together with duration of illness ( $P < .01$ ) and social class ( $P < .01$ ), accounted

Table 4.—Differences in Outcome of Subjects With Panic Disorder According to Baseline Severity of Symptoms and Symptom-Related Disability

Outcome Variables	Predictor Variables								
	Self-rated Anxiety		Panic Frequency		Phobic Avoidance			Illness-Related Disability	
	High	Low	High	Low	High	Medium	Low	High	Low
	(n = 43)	(n = 45)	(n = 43)	(n = 43)	(n = 36)	(n = 29)	(n = 25)	(n = 59)	(n = 29)
Anxiety and phobic symptoms									
Observer-rated anxiety*	14.6	8.3†	12.7	10.2	13.0	10.8	9.6	12.4	9.4
Self-rated anxiety‡	41.1	20.7†	34.3	27.5	38.2	29.0	21.4§	34.5	22.8§
Panic attacks, mean/mo	7.0	2.6§	6.8	2.6§	7.4	3.6	2.3§	5.9	2.5§
Phobic symptoms	3.6	2.4§	3.1	2.8	3.9	3.2	1.4¶	3.6	1.8¶
Overall severity of symptoms#	2.1	1.7	1.9	1.8	2.0	1.9	1.6	2.0	1.6
Illness-related impairment									
Work disability**	2.8	1.6§	2.6	1.7	3.0	2.5	0.6††	2.9	0.6†
Social disability	3.4	1.8††	3.0	2.1	3.4	2.9	0.8¶	3.4	0.9†
Family disability	2.5	1.0††	2.3	1.1§	2.4	1.7	0.7§	2.3	0.6†
Overall disability‡‡	2.9	2.2††	2.7	2.4	2.9	2.7	1.8¶	2.9	1.9†
Social maladjustment									
Work adjustment§§	11.3	9.9	11.1	10.2	10.8	10.9	9.8	11.1	9.4§
Social adjustment	19.1	17.0	18.1	17.9	18.3	18.1	17.4	19.0	16.0††
Family adjustment	12.2	10.6§	11.5	11.4	11.9	11.5	10.4	12.0	10.1††
Marital adjustment	17.2	13.7††	15.8	15.4	15.5	15.6	15.2	16.2	13.9
Overall adjustment	61.8	52.7††	58.1	56.6	58.6	57.8	54.1	60.1	51.0††

\*Mean Hamilton Anxiety Rating Scale scores.

† $P < .0001$ .

‡Mean Self-rated Anxiety Scale scores.

§ $P < .05$ .

||Mean Global Phobia Rating Scale scores.

¶ $P < .001$ .

#Mean global rating using a six-point scale.

\*\*Mean score on 11-point scales.

†† $P < .01$ .

‡‡Mean score on a five-point scale.

§§Mean score on items contributing to assessment of each area.

for 41.1% of the variance in this measure.

To examine the relationship between categorical predictor variables and outcome measures, we constructed tables in which the level of anxiety symptoms and social adjustment were calculated for each panic subtype (uncomplicated, limited phobic avoidance, and extensive phobic avoidance) according to whether major depression had been present or absent and whether any personality disorder had been present or absent. A table was also constructed that showed the same scores for subjects with and without major depression according to whether any personality disorder had been present or absent. Examination of these tables showed that the presence of a personality disorder was a strong predictor of social maladjustment, but that there was no relationship between panic subtypes or major depression and social adjustment at follow-up. On the other hand, all three of these Axis I and II variables (ie, panic subtypes, major depression, and personality disorder) independently predicted more severe anxiety symptoms at follow-up.

Relationships were also examined between baseline and follow-up measures for controls. Statistically significant negative correlations between social maladjustment at follow-up and the Extraversion scale of the Maudsley Personality Inventory and life satisfaction were observed, as were significant positive correlations between both the Neuroticism scale of the Maudsley Personality Inventory and social class and social maladjustment at outcome. A stepwise multiple-regression analysis was also done by using potential predictor variables for controls. Continuous variables included age, social class, life satisfaction, and the Extraversion and Neuroticism scales from the Maudsley Personality Inventory. Categorical variables included sex and marital status. The outcome measure used in this analysis was the Social Adjustment Scale (total). The Extraversion scale accounted for 38.7% of the variance in the measure ( $P < .0001$ ), and the

Neuroticism scale explained an additional 7.4% ( $P < .05$ ); together, these variables accounted for 46.1% of the variance in social adjustment at outcome.

## COMMENT

### Chronic Course but Favorable Outcome

Our findings confirm those of previous follow-up studies that showed that panic disorder is a chronic disturbance, but that it has a relatively favorable outcome.<sup>20,22</sup> After 3 years, only 10.0% of our subjects were free of symptoms, but an additional 25.6% reported minimal symptoms. The outcome of 68 patients with major depression who were available for comparison was different. After 3 years, 50.0% of these patients were free of symptoms, and an additional 19.1% had minimal symptoms (W.A.C., written communication, July 1, 1989). The authors of a recent study claimed that 43% of their patients with panic disorder had remitted after 1 year.<sup>16</sup> However, remitted patients were those who no longer met criteria for panic disorder (four panic attacks in the previous month). Two factors that we observed argue against expanding the definition of recovery to include patients with minimal symptoms. One is that this level of symptoms appears to be relatively unstable, and the other is that medication may be required to sustain it.

Our patients, who took part in a controlled treatment study and then were naturalistically treated for panic disorder, did well.<sup>18</sup> Nearly 80% of our patients claimed at least moderate improvement from the time that they entered the treatment

Table 5.—Outcome of Patients With Panic Disorder According to Panic Subtypes, Comorbid Conditions, and Illness Duration

Outcome Variables	Predictor Variables						
	Panic Disorder Subtypes			Major Depression		Personality Disorder	
	Extensive Avoidance (n = 36)	Limited Avoidance (n = 29)	Uncomplicated (n = 26)	Present (n = 41)	Absent (n = 50)	Present (n = 40)	Absent (n = 49)
Anxiety and phobic symptoms							
Observer-rated anxiety*	13.2	10.5	9.6	13.3	9.8†	13.9	9.4‡
Self-rated anxiety§	38.3	25.4	25.3†	38.6	24.3‡	37.1	25.9†
Panic attacks, mean/mo	7.6	2.1	3.7†	6.0	3.7	6.1	3.8
Phobic symptoms	4.1	2.4	1.9¶	3.6	2.5†	3.6	2.6†
Overall severity of symptoms#	2.1	1.7	1.7	2.0	1.8	2.1	1.7
Illness-related impairment							
Work disability**	2.9	1.8	1.6	2.6	1.8	2.7	1.8
Social disability	3.6	2.2	1.4‡	3.2	2.0‡	3.4	1.9‡
Family disability	2.4	1.6	0.9†	2.5	1.1†	2.4	1.1†
Overall disability††	2.9	2.5	2.1†	2.8	2.4†	2.8	2.5
Social maladjustment							
Work adjustment‡‡	10.6	10.6	10.6	11.1	10.1	11.9	9.6†
Social adjustment	18.6	17.4	17.9	18.5	17.6	20.5	16.3¶
Family adjustment	12.1	11.0	10.7	11.9	10.9	12.3	10.8†
Marital adjustment	15.1	16.3	14.8	15.5	15.4	17.1	14.0†
Overall adjustment	58.8	56.5	55.4	58.8	55.7	63.5	52.7§§

\*Mean Hamilton Anxiety Rating Scale scores.

† $P < .05$ .‡ $P < .01$ .

§Mean Self-rated Anxiety Scale scores.

||Mean Global Phobia Rating Scale scores.

¶ $P < .001$ .

#Mean global rating using a six-point scale.

\*\*Mean score on 11-point scales.

††Mean score on a five-point scale.

‡‡Mean score of items contributing to assessment of each area.

§§ $P < .0001$ .

study. In terms of severity, two thirds reported symptoms that were either absent, minimal, or mild, and one third claimed to have had no panic attacks in the past month. Regarding social adjustment, nearly half were rated as having maladjustment that was minimal or absent. Two factors are important in evaluating these findings. One involves the method of selection, and the other involves continuing drug treatment. With respect to the first, the subjects of this investigation were volunteers who were recruited through the news media. Such populations tend to have milder illnesses than those recruited from treatment facilities.<sup>66</sup> Also, for the sake of the treatment study, subjects with certain comorbid conditions (eg, current alcohol abuse, melancholia) were excluded. It is noteworthy that, despite the nearly 10-year average duration of illness, a third of our subjects had not been treated specifically for panic disorder before participating in the treatment study.

Subjects with panic disorder differed from controls with respect to social maladjustment. The comparison between these groups is important for gauging the impairment that is attributable to panic disorder itself. The mean difference between subjects and controls on the overall Social Adjustment Scale of 0.77 appeared to be clinically significant although relatively small. The majority of subjects with panic disorder were rated as being minimally or mildly maladjusted, whereas the majority of controls had minimal or no maladjustment. Also, the difference between subjects with panic disorder and controls was present in most of the important areas of social adjustment and all the dimensions of function-

ing measured by the Social Adjustment Scale. This was true despite the fact that subjects with panic disorder had been treated and were, for the group as a whole, moderately improved. These findings are consistent with our view that panic disorder is chronic, but that it has a good outcome.

#### Course 1 of Fluctuating Anxiety and Depressive Symptoms

The follow-up period was, for the most part, characterized by fluctuating symptoms. While the retrospective assessment of the level of symptoms on a month-by-month basis may not have been reliable, it revealed that nearly 80% of subjects had experienced some change in severity during a 2½-year interval. Within the changes, we were unable to identify any pattern either within subjects or groups of subjects. The reason for the fluctuation in symptoms that we observed is not known.<sup>18</sup> We observed no seasonal variation nor did stopping and starting of medications appear to account for much of the change. It is possible that stressful life events or circumstances influence the severity of panic symptoms over time although evidence for this is lacking.<sup>67</sup> Regardless of the cause, our findings suggest that intermittent treatment may be a reasonable alternative for some patients.

Depression was reported by a third of subjects during the follow-up period. Most subjects experienced a single episode, and the median duration of episodes was less than 6 months. Subjects who experienced major depression more often had histories of depression and had more severe anxiety symptoms, both at baseline and throughout the follow-up period. Also, during the time that they were depressed, they had



Table 6.—Correlations Between Continuous Baseline and Outcome Variables in Patients With Panic Disorder

Baseline Variables	Outcome Variables		
	Self-rated Anxiety*	Change in Anxiety†	Social Maladjustment‡
<b>Demographic variables</b>			
Age, y	0.02	−0.12	0.18
Educational level§	0.08	−0.01	0.08
Occupational class	0.15	−0.03	0.27¶
Social class#	0.14	−0.02	0.24¶
Income**	−0.20	0.09	−0.05
<b>Illness characteristics</b>			
Age at onset, y	−0.26¶	0.17	−0.11
Duration of illness, y	0.28††	−0.29††	0.30††
Personality traits‡‡	0.36§§	−0.03	0.53
Social network¶¶	0.01	−0.01	−0.23¶
<b>Severity of symptoms</b>			
Self-rated anxiety*	0.50	0.11	0.41
Agoraphobic symptoms##	0.21	0.09	0.07
Panic attacks (monthly)	0.27††	−0.02	0.05
Symptom-related disability***	0.16	0.16	0.24¶

\*Level of anxiety symptoms as measured by the Self-rated Anxiety Scale.

†Baseline score on the Self-rated Anxiety Scale minus the outcome score divided by the baseline score (percentage reduction).

‡Sum of items making up the Social Adjustment Scale.

§Educational level according to the Hollingshead Two-Factor Index.

||Occupational class according to the Hollingshead Two-Factor Index.

¶ $P < .05$ .

#Social class according to the Hollingshead Two-Factor Index.

\*\*Estimated household income in thousands of dollars.

†† $P < .01$ .

‡‡Sum of abnormal personality traits as measured by the Structured Interview for DSM-III personality.

§§ $P < .001$ .||| $P < .0001$ .

¶¶Size of social network as assessed by the Social Relationships Scale.

#Sum of fear and avoidance ratings for agoraphobic symptoms as measured by a phobia rating scale.

\*\*\*Sum of three symptom-related disability scales.

more severe anxiety symptoms. Thus, it is the more severely ill patients and those with histories of depression who are most likely to experience depression in the future. This is consistent with findings from a number of other studies and suggest that prevention may be possible in some patients either through early recognition of depressive symptoms or the use of maintenance antidepressant medication.<sup>23-25,27</sup> Some have claimed that anxious patients become depressed in reaction to worsening symptoms.<sup>31</sup> Our findings are consistent with this but might just as well be explained conversely; that is, more severe anxiety symptoms may be the result of depression. Subjects who abused alcohol also reported more severe anxiety symptoms during periods of heavy drinking. This also has been reported previously and suggests that, while alcohol may relieve anxiety symptoms acutely, it may have the opposite effect when used in excess or during periods of alcohol withdrawal.<sup>22</sup>

Our findings show rather clearly that patients with extensive phobic avoidance or agoraphobia have a more severe form of panic disorder. These subjects were more often women, had an earlier age at onset, a longer duration of illness, more severe symptoms, and greater illness-related disability, and they were more likely to have had Axis I or II comorbidity than were subjects with no phobic avoidance. Patients with limited phobic avoidance fell in between. In addition, agoraphobic subjects had a less favorable outcome with more severe symptoms and greater social maladjustment than subjects with limited or no phobic avoidance. These data confirm earlier findings of a similar kind, suggesting that the categories of no avoidance (panic disorder), limited avoidance, and extensive phobic avoidance (agoraphobia) fall on a continuum of severity.<sup>33</sup> Whether they represent distinct subtypes or not, the predictive value of this categorization seems clear. Our finding that agoraphobic patients had been ill longer than those with limited or no phobic avoidance would appear to support the hypothesis of Klein<sup>31</sup> that phobic avoidance develops over time from the repeated occurrence of spontaneous panic attacks. However, it is also possible that selection contributed to this difference.<sup>36</sup>

We found that subjects with panic disorder with secondary depression (current or past) were a more severely ill group. Those with depression had been ill longer and had more severe anxiety symptoms, more frequent panic attacks, and more extensive phobic avoidance, and they more frequently had personality disorders. These findings confirm those of Breier et al<sup>23</sup> and Lesser et al,<sup>27</sup> both of whom found that patients with panic disorder who had a history of depression had more severe anxiety and phobic symptoms. Our subjects with panic disorder with depression also had a less favorable outcome of their panic disorder than did subjects without depression. Our observation of more severe symptoms at follow-up in subjects with a history of depression confirms similar findings reported by Van Valkenburg et al<sup>24</sup> and Nutting and Zapotoczky.<sup>25</sup>

We also found that the presence of a personality disorder was associated with a greater initial severity of illness and less favorable outcome. The level of anxiety symptoms, as measured by the Hamilton Anxiety Rating Scale and Self-rated Anxiety Scale at baseline, was higher among those with personality disorders than among those without. Also, more subjects with personality disorders had extensive phobic avoidance and major depression (current or past). In addition to this, personality-disordered subjects had more severe symptoms and social maladjustment at the time of follow-up. As reported earlier, our patients with personality disorders responded less favorably to benzodiazepines administered in the placebo-controlled treatment study.<sup>46</sup> These findings are also consistent with those of Mavissakalian and Hamann<sup>45</sup> who reported that agoraphobic patients with few abnormal personality traits, as measured by the PDQ, responded better to combined drug and behavioral treatment than did those who had many such traits.

Thus, we found diagnostic categorization of patients, both on Axis I and on Axis II, to be strongly predictive of symptomatic distress and social maladjustment at follow-up. Subjects with extensive phobic avoidance (agoraphobia), major depression (current or past), and any personality disorder were doing less well after 3 years despite continuing treatment. In fact, the 13 subjects who qualified for all three of these categories scored more than twice as high on the Self-rated Anxiety Scale as those who qualified for none (mean, 47.8 vs 22.4,  $P = .02$ ). Our findings are similar to those of Faravelli and Albanesi<sup>47</sup> who reported that the variables that



made the greatest contribution to the variance in outcome among patients who had agoraphobia with panic attacks after 1 year were initial agoraphobia, similar scores on the Psychopathic Deviate and Hysteria scales from the Minnesota Multiphasic Personality Inventory, Extraversion as measured by the Maudsley Personality Inventory, and education level. These data show the importance of diagnostic subtyping and of Axis I and II comorbidity in predicting outcome.

Several points regarding the relationships that we observed between diagnostic categories and outcome should be noted. First, the relationship between an abnormal personality at baseline and severity of anxiety symptoms at follow-up already existed at the time of initial assessment. That is, patients with personality disorders had more severe symptoms at baseline. Had we measured social adjustment at baseline, we would probably have found that patients with personality disorders and more severe symptoms also had greater social maladjustment. Second, the diagnostic categories may, to some extent, have represented the very chronicity and severity that they appeared to predict. We found that both agoraphobia and major depression were associated with a longer duration of illness and that both contributed to the overall severity of the panic disorder. Third, the diagnostic variables, because of their categorical nature, were relatively weak predictors when compared with symptom scales, especially when scores on the same scale were being predicted. This is not surprising and does not entirely eliminate the predictive value of the diagnostic variables. Our multiple-regression analyses indicated that, across categories, our anxiety scale (Self-rated Anxiety Scale) behaved uniformly in predicting a specific outcome, namely, scores on the same scale. What these analyses do not tell us is how well other outcomes might have been predicted or how our diagnostic variables might have performed had we, as in the case of personality traits, made them continuous. A relative weakness among diagnostic predictors was a finding in earlier outcome studies.<sup>8</sup>

#### Relationship Between Abnormal Personality Traits and Panic Disorder

As mentioned, we observed abnormal personality traits more frequently among subjects with panic disorder than we did among controls. Scores for nearly all of the personality disorders, as measured by the PDQ, were significantly higher among subjects with panic disorder. Other investigators have also observed an excess, especially among the anxious (cluster C) personality disorders.<sup>40-42</sup> Such findings suggest that some personality disorders are manifestations of panic disorder

rather than independent disturbances that happen to be associated with a less favorable social outcome. In addition, we observed a change in the response to the PDQ from the time of initial assessment to the time of follow-up 3 years later. This improvement coincided with a reduction in anxiety and phobic symptoms that occurred among the patients with panic disorder as a whole. Although scores for most of the personality disorders were reduced at follow-up, the changes of greatest statistical significance occurred among the cluster C disorders. This change is similar to that observed by Mavissakalian and Hamann<sup>46</sup> and is another indication that such traits may be secondary to panic disorder and, for that reason, responsive to treatment.<sup>46</sup>

#### Limitations of This Study

This study has a number of limitations that need to be considered in interpreting the results. To begin with, the population studied was originally selected for participation in a controlled treatment study. Such a restricted sample may not be broadly representative of patients with panic disorder. Also, the treatment given these subjects after the controlled study was naturalistic. It is possible, therefore, that a lack of uniform treatment may have had an uneven effect on the outcome reported for various subgroups. Another limitation has to do with our control group. Relatives of patients with major depression have an increased risk for psychopathology and may even differ from the general population with regard to personality or other predisposing factors. The comparison between subjects with panic disorder and controls may have been influenced by this bias.

Additional limitations have to do with assessments made. Although this study was prospective in design, certain measures involving the interval between the initial and follow-up evaluations were retrospective. Consequently, the ratings of anxiety and depressive symptoms during this period may have been less reliable. Also, the research assistant (J.C.) who conducted follow-up interviews was not blind to the status of subjects (ie, panic vs control). She was, however, blind to all baseline measures, including the diagnostic assessments. In addition, baseline and follow-up evaluations differed to some extent. The Social Adjustment Scale was not administered at baseline, and neither the Structured Clinical Interview for *DSM-III* nor the SIDP were given at follow-up, thus limiting analyses. Finally, we restricted our study to certain comorbid syndromes and chose to ignore others that may have been present.

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