The Panic-Agoraphobic Spectrum: A Descriptive Approach to the Assessment and Treatment of Subtle Symptoms

Giovanni B. Cassano, M.D., Stefano Michelini, M.D., M. Katherine Shear, M.D., Elisabetta Coli, M.D., Jack D. Maser, Ph.D., and Ellen Frank, Ph.D.

Objective: *Psychiatric classification is still a topic of considerable discussion and debate in spite of major advances in the past two decades. The debate involves categorical versus dimensional approaches, cutoff numbers of symptoms to define a case, degree of impairment, objective diagnostic criteria versus more theoretically based criteria, episodic versus trait-like symptoms, and the role of atypical and subclinical symptoms. All of these issues have been raised for the anxiety disorders and depression. This article presents the conceptualization of a relatively novel and testable approach to the diagnosis and classification of panic and agoraphobia, the panic-agoraphobic spectrum, and pilot data on a new questionnaire to assess it.* *Method:* *Pilot testing of the Panic-Agoraphobic Spectrum Questionnaire was undertaken with 100 inpatients who had lifetime diagnoses of panic disorder, unipolar depression, comorbid panic and unipolar depressive disorders, or an eating disorder. The instrument emphasizes impairment related to 144 behaviors and experiences in seven panic-agoraphobic symptom domains.* *Results:* *Patients with panic disorder scored highest on the questionnaire, and those with comorbid depression showed even greater severity of illness. The scores of the patients with eating disorders and of the depressed patients differed from those of the other groups but also differed from 0.* *Conclusions:* *The spectrum model of panic and agoraphobia is a flexible and comprehensive means of describing this clinical complex. The proposed model, complementary to the categorical approach, presumably expresses a unitary pathophysiology. Its usefulness is discussed in terms of its value for patient-therapist communication, outcome measures, identification of subtle personality traits, and subtyping of patients for research and treatment.*

This article is in honor of the career of Melvin Sabshin, who has been a generative and driving force in American psychiatry for over four decades. Even as a young investigator (1954–1957), he evidenced versatility and breadth of interests. For example, the 12 publications of which he was the author or co-author during that period can be categorized into research on schizophrenia, emotion and anxiety, services, and psychophysiology. His energy, interests, and long service to the American Psychiatric Association have surely influenced the field of anxiety disorders, along with virtually the entire spectrum of psychiatric disorders.

Psychiatric classification has been a subject of intense interest over the past three decades. During this period much progress has been made in diagnostic reliability with the use of relatively uncomplicated prototypes. The complexity of clinical reality is acknowledged in these systems by several strategies. One is the use of polythetic diagnostic criteria. Another is the acceptance of the possibility of co-occurring diagnoses and symptoms. The multiaxial classification system that includes trait-like personality disorders, physical disorders, psychosocial stress, and overall functioning adds further recognition of complexity. Nevertheless, there remains a serious gap between clinical reality and the options provided by the official nomenclatures (DSM-IV and ICD-10). Thus, notwithstanding the profound innova-

From the Institute of Psychiatry, School of Medicine, University of Pisa, Italy; Western Psychiatric Institute and Clinic, University of Pittsburgh; and the Anxiety and Somatoform Disorders Program, NIMH, Rockville, Md.

The Spectrum Project is supported by Pfizer Inc., Roerig Division, Italy.

tions represented by the Research Diagnostic Criteria (1) and the DSMs, the lack of correspondence between the current classifications of mental disorders and the presentations of psychopathology in both community and clinical settings leads to an incomplete characterization of most patients. In particular, the current categorical systems fail to capture the continuum between the core symptoms of each disorder and the associated aura of prodromal, atypical, and subclinical psychopathology. We have adopted a "spectrum" model as an approach to conceptualizing and assessing this subtle psychopathology, the importance of which is typically underestimated. In this article, we present a descriptive approach—one that we believe has a number of potential advantages for etiologic understanding, clinical evaluation, and optimal treatment.

THE SPECTRUM MODEL

Other investigators have used the term "spectrum" to highlight relationships among clusters of symptoms and to place a group of defined syndromes in relation to one another (2–7). We use the term to refer to broad areas of psychiatric phenomena relating to a single mental disorder, including 1) core, atypical, and subclinical symptoms of the primary axis I disorder; 2) signs, isolated symptoms, symptom clusters, and behavioral patterns related to the core symptoms that may be prodromal, may represent precursors of a not yet fully expressed condition, or may be sequelae of a previously experienced full-fledged disorder; and 3) temperamental and/or personality traits.

To clarify further how different symptoms (isolated or clustered) and dimensions of psychopathology are related, we use the metaphor of a beam of white light, representing a DSM-IV diathesis. When it is refracted by a prism, we can see a spectrum of component colors (symptoms, traits, signs, etc.) that are clinically relevant. The metaphor emphasizes that such variable manifestations are derived from a common source.

A clinical example of the spectrum model of such a refracted diathesis is the case of a young man who, at the age of 20, experiences a few limited-symptom panic attacks. He seeks no treatment, but those symptoms change his life in certain ways. Before the onset of the attacks, he was described as energetic, open to new experiences, and socially outgoing. After the onset of panic symptoms, he becomes increasingly fearful, passive, dependent, socially avoidant, and worried about his health. Progressively, these features become stable and trait-like. At age 40, when he is seen by a clinician for treatment of a depressive episode, the panic symptoms have long been forgotten, and the patient presents as a fearful person, somewhat hypochondriacal and dependent on others to such an extent that he avoids remaining alone. If the clinician attempts to treat only the depressive episode, he or she will miss the primary reason for 20 years of fearfulness, dependency, avoidance, and hypochondriasis, which were initiated by a partial expression of panic disorder. As a consequence, although remission of the depressive symptoms may be achieved, the patient will continue to suffer from panic spectrum symptoms and remain dysfunctional. Recognizing that panic spectrum symptoms are also present permits the clinician to treat both the depression and the panic spectrum condition effectively.

In this example, focusing on the most prominent current symptoms and using only DSM-IV diagnostic criteria would have oversimplified the clinical description. The spectrum model makes manifest and gives clinical weight to low-severity and isolated symptoms co-occurring with the major disorder. In our experience, this presentation may have implications for clinical course similar to that of comorbid full-blown panic disorder and major depression. These implications include greater severity of the depressive illness, poorer prognosis, higher rates of chronicity, poorer adherence to the treatment regimen and responsiveness to treatment, poorer psychosocial functioning, greater risk of illness among family members, and higher risk of substance abuse and suicide attempts. If this hypothesis is correct, identification of spectrum symptoms should be a routine part of clinical assessment and should inform selection of treatment interventions (8).

The foregoing example is not an unusual one. Clinicians often face a complex array of co-occurring, isolated, or clustered symptoms that may be associated with one or more axis I or axis II conditions, giving rise to complex clinical situations. The DSM-IV approach treats such co-occurring symptoms as background noise, interfering with the primary task of matching symptoms to diagnostic criteria (9). Yet there is growing evidence that failure to acknowledge and address such symptoms leads to less than acceptable response to treatment. For example, Brown et al. (10) found that co-occurring symptoms of panic were associated with a significantly reduced probability of response to either nortriptyline pharmacotherapy or interpersonal psychotherapy among primary care patients being treated for depression. Similarly, Buysse et al. (manuscript submitted for publication) found that elderly patients with recurrent unipolar depression and prominent anxiety responded significantly less well to treatment with a combination of interpersonal psychotherapy and nortriptyline. Finally, Frank and colleagues (unpublished data) noted that middle-aged women with recurrent unipolar depression and high levels of somatic anxiety were significantly less likely to respond to interpersonal psychotherapy alone.

SPECTRUM AND NEUROTIC PERSONALITY

Research concerning the relationship among spectrum phenomena, trait-like syndromes, and comorbidity is of substantial clinical relevance. Some authors suggest that this relationship of categories and multiple temperament dimensions may constitute an apparent diagnosis of personality disorder (8, 11–13). Even patients themselves sometimes attribute symptoms to some personality dys-

function (12). The descriptive approach taken by the spectrum model reconceptualizes such dysfunctional traits and presumed personality disorders as a mosaic of recognizable and treatable manifestations of one or more axis I disorders. This view is consistent with that expressed by the Slaters (14), who considered "neurotic personality" to be composed of symptoms drawn from mood and anxiety disorders (15–17). Tyrer (18, 19) also identified the co-occurrence of different types of anxiety symptoms and depression and called this "general neurotic syndrome." Tyrer's hypothetical construct is that of a single nosological entity in which patients are distributed along a continuum that has predominant depressive symptoms at one extreme and predominant anxiety symptoms at the other. In contrast, we propose that this heterogeneous group of individuals with complex comorbidity is better understood if conceived of as suffering from spectra of distinct disorders, each likely to be responsive to specific treatments.

What is shared by the spectrum model and the theory of neurotic personality is the idea that an underlying diathesis, composed of phenomena such as residual symptoms and poor interpersonal, sexual, and social adjustment, leaves one vulnerable to the appearance of acute symptoms. The spectrum model essentially reverses the traditional European view of psychopathology, which holds that the predisposition to neurosis arises from a lifelong premorbid psychopathological personality (14, 20–23). Instead, we consider early-onset symptoms and subthreshold phenomena as manifestations related to a major disorder shaping the adult personality. Such symptoms, in themselves, are potentially morbid and incapacitating. In support of this position, by adopting the spectrum approach, we have also observed that the appropriate treatment of subthreshold phenomena was followed by substantial improvement in personality functioning.

SPECTRUM ASSESSMENT

Standardized and reliable assessment of DSM panic disorder (24–28) and scales rating the severity of various anxiety symptoms (29–36 and Shear et al., manuscript submitted for publication) are available. Further, Shear and Maser (37), responding to a recommendation by the National Institute of Health Consensus Development Conference on the Treatment of Panic Disorder (38), reported results of an assessment standardization conference. Clinicians were provided with essential, recommended, and optional measures for a comprehensive assessment of panic disorder. Although not discussed at this conference, appropriate use of these measures could result in detection of much of the phenomenology of panic disorder as conceived by the proposed spectrum model. We believe, however, that assessment of the panic spectrum can be better accomplished by using a specific instrument designed for this purpose.

Grounded in several years of clinical experience with mood and anxiety disorders, and with panic disorder in particular, clinical researchers working at the Institute of Psychiatry at the University of Pisa, Italy, began to evolve a systematic approach to the assessment and treatment of patients that is based on the spectrum model. This effort led to the first conceptualization of the panic-agoraphobic spectrum and systematic methods for its assessment (39, 40). The remainder of this article focuses on the panic-agoraphobic spectrum and the description of a pilot study with the first assessment instrument developed for validating the model.

PANIC-AGORAPHOBIC SPECTRUM DOMAINS

The seven domains of panic-agoraphobic symptoms assessed in the Panic-Agoraphobic Spectrum Questionnaire evolved from clinical experience in Pisa. The domains include panic symptoms, anxious expectation, phobic features, and sensitivity to reassurance, to substances, to general stress, and to separation. These domains, as well as the symptoms thought to constitute them, must be subjected to formal and rigorous testing to confirm their validity.

Panic Symptoms

The panic attack is the essential core manifestation required in the DSM-IV criteria for panic disorder (41–46). According to DSM-IV, at least four of 13 symptoms are required for the diagnosis of a panic attack. However, in agreement with the observation that limited-symptom panic attacks may produce impairment similar to that of full-blown attacks (47), we consider a great variety of isolated panic symptoms to be clinically relevant also.

Moreover, we have observed panic patients in whom the sudden onset of less common symptoms, not listed in DSM-IV, can be associated with intense anxiety, similar to that produced by classic panic symptoms. Such symptoms can be very distressing psychic experiences and may produce important changes in the patient's emotional life and behavior. Therefore, we include in this domain experiences, mostly associated with acute and intense anxiety, such as unstable balance, sudden numbness, a sense of disorientation, "jelly legs," tiredness, transient loss of sight or hearing, hypersensitivity to noises, light, or heat, and distress in the presence of an indefinite visual perspective such as may occur on a foggy day, on the open sea, or in snowy flat landscapes (appendix 1 provides a full list).

Anxious Expectation

This domain encompasses two subcategories: 1) anticipatory anxiety focused on the occurrence of typical or atypical panic symptoms and 2) a persistent general state of alertness, associated with a sense of insecurity, impotence, or impending menace with respect to physical and psychic integrity.

A few patients describe persistent apprehension and worries about symptoms in the apparent absence of

panic attacks, with the consequent adoption of a range of maladaptive behaviors as a response to these worries. Others experience concerns that may be associated with specific situations and linked to previous experience of panic symptoms, sometimes long forgotten by the patient. Anxious expectation can become the main source of intense suffering and marked interference with overall functioning (48).

Phobic and Avoidant Features

Although agoraphobia and panic disorder are considered independent syndromes in DSM-IV, in clinical practice they are clearly related. Some authors (43, 49–51) consider phobic/avoidant symptoms to be a complication of panic disorder, while others (52–54) point out that a subtle phobic/avoidant behavioral pattern may also precede the onset of other panic manifestations.

Avoidance primarily occurs as an attempt to cope with the distress related to panic symptoms and anticipatory anxiety. When extensive, such avoidance can be temporarily successful in blocking panic (49, 55, 56). More commonly, patients try to counteract their fears through efforts to confront feared situations and/or by dependence on a companion. For these patients, reports of mild distress when they are facing situations that commonly produce agoraphobic reactions should be considered clinically significant.

Most clinicians are familiar with the syndrome of claustrophobia, also common in patients with panic disorder. In a substantial number of patients, claustrophobia takes the form of intolerance of any perceived obstacles to breathing, including those related to constriction of airways (e.g., safety belts, ties, shirts, swallowing pills) or to perceived impairment in the quality of the air (e.g., stale air, humid air). These claustrophobic symptoms are considered to be manifestations of the panic spectrum. Such a view is consistent with Donald Klein's hypothesis of a malfunctioning suffocation alarm in panic disorder (57). However, we believe that such phobic manifestations are often misdiagnosed as simple phobias or labeled as "anxious-neurotic personality traits," and this may lead to inadequate treatment.

Some social phobias actually represent another common panic-related phobia (58, 59). It is important to recognize that social fears and avoidances may be the overtly recognizable manifestation of panic disorder. The fear may be one of being humiliated by the occurrence of panic symptoms during a public gathering. Alternatively, the arousal usually linked to a public performance can itself be experienced as frightening (60, 61). Such phobic anxiety may produce mild to severe avoidance that interferes with social and work relationships (54) and is not easily distinguishable from primary social phobia. The correct attribution of symptoms to the panic-agoraphobic spectrum is crucial in choosing an effective therapeutic approach, since the response of secondary social phobia to treatment with tricyclic antidepressants is similar to that of panic disorder, whereas primary social phobia seems to show poor response to these compounds (61).

Illness phobia is a third common type of panic-related phobia. Cognitive-behavioral theorists have drawn attention to the fact that misinterpretation of bodily sensations as catastrophic is virtually universal in panic patients (45, 62, 63). The panic spectrum model extends this observation to individuals who exhibit hypochondriasis and/or a full-blown illness phobia. Distortion of self-perceptions of health and hypochondriacal thinking are very common in panic disorder (64–68). Hypochondriacal concerns may be focused on the fear of having a potentially lethal disease. For example, isolated palpitations may be interpreted as signs of a heart attack and a sudden headache as a symptom of a stroke or a brain tumor; mild difficulty in breathing may be followed by intense fear of having a severe form of asthma or bronchitis. Patients with illness phobia may report feelings of distress or may engage in avoidance in response to medical situations. Even reading medical magazines or hearing conversations concerning medical topics may produce symptoms. Such individuals typically become anxious when undergoing laboratory testing or other medical diagnostic procedures.

Another manifestation of panic-related phobia is fear and avoidance of medications. Indeed, this may be a predictor of vulnerability to panic disorder. Some panic spectrum patients report having idiosyncratic "allergies" to all or almost all drugs. These individuals carefully scrutinize every word of the package insert that comes with prescribed medications and, terrified by the possibility of experiencing any of the adverse reactions described, fail to comply with the prescribed treatment. Sometimes the distress is focused only on psychotropic drugs, where the fear is that such medications will permanently change one's personality or cause loss of control.

Phobic reactions to sleep may occur and lead to delay in going to bed or refusal to go to bed. Sleep phobia may be related to worry about dying during sleep and/or fear of having a nocturnal panic attack. Fear of anesthesia or taking hypnotic drugs may be a related expression of the same phobia.

Another type of fear and avoidance centers on bad weather (thunderstorms, strong winds, snowstorms, etc.) or the anticipation of natural disasters such as earthquakes and volcanic eruptions. Because of this phobia about natural phenomena, persons with panic traits may be reluctant to go to specific places (e.g., areas of seismic activity) so as to avoid risking their lives in a natural disaster.

Sensitivity to Reassurance

Individuals with the panic diathesis often rely on reassurance from others as a means of coping with an overwhelming sense of insecurity and impotence (69, 70). Lacking a well-developed capacity for autonomous action, they continuously seek help from friends, relatives, and neighbors. In some individuals, the powerful need for reassurance may give rise to peculiar interpersonal behavior and increased dependency; in others, it may induce

manipulativeness and dramatic exaggeration of symptoms in order to obtain help and protection.

A specific form of help-seeking behavior involves patients' physicians. There may be repeated requests for medical examinations and laboratory or other diagnostic procedures, as well as unnecessary admissions to emergency care units and medical centers. Sometimes these patients attempt to establish close friendships with doctors, in order to feel free to contact them anytime, anywhere. Similarly, the attachment of such patients to a psychotherapist may be so strong that they are unable to terminate therapy even when the therapist indicates that further treatment is not warranted or unlikely to be of any value.

Quite often these patients do not limit their magical faith to doctors and companions; sensitivity to reassurance may be manifested as superstitious thinking about protective objects. Some individuals feel that they need to take with them talismans such as a bottle of water, a hat, sunglasses, a stick, a dog, a good luck charm, or anxiolytics. Sometimes another person serves this purpose, so that the panic patient becomes incapable of going places alone.

Sensitivity to Substances

Sensitivity to several chemicals and to psychotropic medications is a well-described feature of panic disorder (71–73). For these patients, one more cup of coffee, a single dose of a recreational drug (74), or small doses of tricyclic antidepressants (75, 76) may trigger a full-blown panic attack. This sensitivity also encompasses withdrawal symptoms, as well as symptoms associated with tranquilizer dose reduction. Conventional tapering schedules for benzodiazepines or alcohol during detoxification may be too rapid for persons with a panic diathesis (77).

Sensitivity to General Stress

Although panic patients were found not to be more reactive than normal subjects to specific laboratory stressors (78), several studies have revealed the vulnerability of panic patients to stressful life events (67, 79–83). However, panic symptoms may also occur in reaction to minor stressors such as day-to-day family problems, a brief period of sleep deprivation, or overwork. To protect themselves, these individuals typically ask to be kept away from any trouble, warning relatives and friends against giving them bad news. This attitude represents a general tendency toward harm avoidance. A paradoxical manifestation of this sensitivity to stress may be the onset of panic symptoms after relief from tension (e.g., onset of palpitations after driving off a busy highway or walking out of a crowded room).

Sensitivity to Separation

Whether separation anxiety disorder is, in fact, more frequent in patients with agoraphobia than in the general population remains a controversial issue (43, 84–86). Nevertheless, the separation sensitivity domain has been included in the panic-agoraphobic spectrum because in clinical practice, many adult panic patients show an enhanced sensitivity to separation, regardless of whether there was a full-blown separation anxiety disorder in childhood. Symptoms of separation anxiety, as part of the panic-spectrum phenomena, may first appear in children as school phobia and in adults as reluctance to leave home for vacations or for a job or as distress when sleeping alone or far from home. Such anxiety may persist into old age.

Separation-sensitive individuals often react dramatically to loss (or even to the anticipation of it), such as the end of a friendship or partnership, the news of severe illness, or the sudden death of a loved one or even a pet (87). Consequently, they tend to develop close and emotionally intense relationships characterized by dependency (58, 88–92) and often choose a partner on the basis of his or her high reliability as a companion.

TRANSITION FROM CLINICAL HYPOTHESES TO EMPIRICAL VALIDATION: THE SPECTRUM QUESTIONNAIRES

Following the initial work of Cassano et al. (39), Cassano and Michelini began work on the empirical validation of the spectrum model. This work commenced with the development of a structured interview to assess the panic-agoraphobic spectrum. In 1995 they were joined by a group of U.S. consultants, and the task force was extended to include other Italian psychiatrists supervised by two associate professors. The goal of this research project is to develop and test assessment instruments that can be used to study the spectrum model, its relation to current diagnostic categorical classifications, and its usefulness in facilitating more focused consideration of treatment choices and a more complete evaluation of the patient's quality of life.

Specifically, the project involves the development, psychometric testing, and validation of assessment instruments conceived as complementary to categorical nosologies. At present, the Panic-Agoraphobic Spectrum Questionnaire and the Structured Clinical Interview for the Panic-Agoraphobic Spectrum are the most fully developed. As is detailed below, the former has been administered to patients with several different axis I conditions. Preliminary versions of the bulimic-anorexic spectrum, the obsessive-compulsive spectrum, and social phobic spectrum assessment instruments have also been developed, and work has commenced on the mood disorders spectrum interview.

PILOT STUDY OF THE PANIC-AGORAPHOBIC SPECTRUM QUESTIONNAIRE

To test the questionnaire version of the panic-agoraphobic spectrum assessment, we undertook a study of its performance in various clinical populations. The hy-

TABLE 1. Sociodemographic Characteristics of Study Subjects Grouped by Diagnosis

Variable	Patients With Panic Disorder (N=30)		Patients With Unipolar Depression (N=20)		Patients With Panic Disorder and Unipolar Depression (N=20)		Patients With Eating Disorders (N=30)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age (years)[a]	36.4	13.3	50.3	15.4	44.3	12.9	22.9	3.8
	N	%	*N*	%	*N*	%	*N*	%
Sex[b]								
Male	16	53.3	7	35.0	2	10.0	1	3.3
Female	14	46.7	13	65.0	18	90.0	29	96.7
Race								
White	30	100.0	20	100.0	20	100.0	29	96.7
Other	0	0.0	0	0.0	0	0.0	1	3.3
Current marital status[b]								
Single	11	36.7	2	10.0	3	15.0	30	100.0
Married	16	53.3	14	70.0	13	65.0	0	0.0
Divorced	2	6.7	1	5.0	3	15.0	0	0.0
Widowed	1	3.3	3	15.0	1	5.0	0	0.0
Living children								
None	13	43.3	5	25.0	3	15.0	30	100.0
One or more	17	56.7	15	75.0	17	85.0	0	0.0
Education[c]								
None	1	3.3	0	0.0	1	5.0	0	0.0
Primary	5	16.7	13	65.0	7	35.0	7	23.3
Secondary	15	50.0	4	20.0	10	50.0	21	70.0
Tertiary	9	30.0	3	15.0	2	10.0	2	6.7
Main occupation[c,d]								
Housewife	3	11.1	5	31.3	8	47.1	0	0.0
Student	4	14.8	1	6.3	1	5.9	13	43.3
Unskilled/skilled worker	5	18.5	2	12.5	2	11.8	6	20.0
White collar worker	5	18.5	2	12.5	2	11.8	6	20.0
Manager/professional	9	33.3	4	25.0	3	17.6	1	3.3
Unemployed	1	3.7	2	12.5	1	5.9	4	13.3
Living arrangement[b]								
Alone	2	6.7	2	10.0	2	10.0	1	3.3
With relatives/friends	27	90.0	17	85.0	18	90.0	29	96.7
In institution	1	3.3	1	5.0	0	0.0	0	0.0

[a]Eating disorder group significantly different from the other groups ($p<0.0001$, ANOVA).
[b]Significant differences between groups for this variable ($p<0.0001$, chi-square test).
[c]Significant differences between groups for this variable ($p<0.005$, chi-square test).
[d]N=27 for the panic disorder group, N=16 for the unipolar depression group, and N=17 for the comorbid panic disorder/unipolar depression group for this variable.

pothesis was that scores on the Panic-Agoraphobic Spectrum Questionnaire would be highest among those who met the DSM-III-R criteria for panic disorder, as either a primary or a comorbid diagnosis. Patients with other DSM-III-R diagnoses (e.g., major depression, eating disorders) but no history of panic were expected to have lower scores on the questionnaire. The method and results of the Panic-Agoraphobic Spectrum Questionnaire validation study are described below.

Method

One hundred inpatients with a lifetime diagnosis of pure panic disorder (N=30), pure unipolar depression (N=20), comorbid panic disorder and unipolar depression (N=20), or an eating disorder (N=30), who were consecutively admitted to the Institute of Psychiatry at the University of Pisa were included in the study. Diagnoses were based on the Structured Clinical Interview for DSM-III-R—Patient Version (SCID-P) (26). For the eating disorder group, because of the difficulty in recruiting patients without depressive symptoms, a history of depressive episodes currently in full remission was allowed. All patients were in treatment.

After written informed consent was obtained, the patient underwent diagnostic assessment based on the SCID-P by a senior psychiatrist (G.B.C.) and then was randomly assigned to another rater (E.C., S.M.), blind to the subject's axis I diagnosis, for the administration of the Panic-Agoraphobic Spectrum Questionnaire. The questionnaire is a semistructured interview composed of four sections: 1) identification of the patient and the assessor; 2) general records and demographic information; 3) previous and current treatment; 4) 144 panic-agoraphobic spectrum items descriptive of the phenomena of panic disorder and grouped in the following domains (each including one or more subsections): panic attack symptoms; anxious expectation; phobic and/or avoidant features; reassurance sensitivity; substance sensitivity; general stress sensitivity; and separation sensitivity. The items were extrapolated from an initial pool that was developed by us on the basis of 15 years of clinical experience with panic disorder. Each item of the Panic-Agoraphobic Spectrum Questionnaire was rated by the interviewer as present or absent, and if it was present, a severity rating was given. Because our study was designed to investigate the presence of panic spectrum symptoms throughout the patient's lifetime, we decided to rate severity for "the worst period the patient had ever experienced" in relation to a specific symptom. Scores were calculated as a ratio: the sum of scores for each domain divided by the maximum score possible for that domain.

Results

Demographic characteristics of the subjects, grouped by axis I diagnosis, are shown in table 1. All but one of the enrolled subjects was Caucasian. There was a predominance of women (74%) over men (26%), mainly as a result of the high percentage of women in the eating disorder group. The mean age was 36.7 years (SD= 15.5); the eating disorder patients were significantly younger than the patients in the other groups. Patients living with relatives (N=91) outnumbered those living alone (N=7) or in an institution (N=2), a situation consistent with the demographic characteristics of the general population in Italy. The difference among diagnostic groups with respect to marital status was highly significant. The high proportions of unmarried patients and patients with no children in the eating disorder

TABLE 2. Panic-Agoraphobic Spectrum Questionnaire Scores of Study Subjects Grouped by Diagnosis

Measure	Group A: Patients With Panic Disorder (N=30) Mean	SD	Group B: Patients With Unipolar Depression (N=20) Mean	SD	Group C: Patients With Panic Disorder and Unipolar Depression (N=20) Mean	SD	Group D: Patients With Eating Disorders (N=30) Mean	SD	Significant Differences Between Groups (ANOVA)
Total score	27.5	12.0	19.2	14.0	41.4	14.8	12.1	8.5	A vs. D ($p<0.0001$); C vs. A ($p=0.002$), C vs. B ($p<0.0001$), C vs. D ($p<0.0001$)
Panic symptoms	28.3	14.5	19.6	12.5	46.7	17.5	13.8	11.9	A vs. D ($p<0.002$); C vs. A ($p=0.0003$), C vs. B ($p<0.0001$), C vs. D ($p<0.0001$)
Anxious expectation	48.5	23.0	23.7	26.9	62.2	20.9	12.4	12.7	A vs. B ($p=0.001$), A vs. D ($p<0.0001$); C vs. B ($p<0.0001$), C vs. D ($p<0.0001$)
Phobia/avoidance	29.8	14.4	19.2	18.6	44.8	18.4	11.1	8.5	A vs. D ($p<0.0001$); C vs. A ($p<0.009$), C vs. B ($p<0.0001$), C vs. D ($p<0.0001$)
Reassurance sensitivity	20.2	12.1	12.0	10.2	26.8	14.3	9.7	7.2	A vs. D ($p=0.005$); C vs. B ($p=0.0009$), C vs. D ($p<0.0001$)
Substance sensitivity	14.4	18.3	5.4	9.8	19.6	18.4	2.7	5.5	A vs. D ($p=0.02$); C vs. B ($p<0.02$), C vs. D ($p=0.001$)
General stress sensitivity	41.1	25.0	29.1	28.4	49.2	30.2	21.7	16.3	D vs. A ($p=0.03$), D vs. C ($p=0.03$)
Separation sensitivity	26.6	17.9	33.1	22.8	40.0	17.2	17.2	15.3	D vs. B ($p=0.03$), D vs. C ($p=0.0006$)

group can be partly explained by the lower mean age of those patients.

Table 2 shows the mean Panic-Agoraphobic Spectrum Questionnaire scores of the patients by diagnostic group. As expected, the patients with panic disorder showed higher total scores on the questionnaire than the patients with pure unipolar depression and the patients with eating disorders. Also as expected, the presence of comorbidity implied a more severe clinical picture; the patients with comorbid panic disorder and unipolar depression scored the highest. Similarly, the mean score obtained in the panic symptom domain was higher among the patients with comorbid panic disorder and unipolar depression than among those in the other diagnostic groups. The degree of anxious expectation seems to have been influenced mainly by the presence of a panic disorder diagnosis, with highly significant differences between the panic disorder group and the unipolar depression group, between the panic disorder group and the eating disorder group, between the comorbid panic disorder/unipolar depression group and the eating disorder group, and between the comorbid group and the unipolar depression group, but not between the comorbid and noncomorbid panic disorder groups. Patients in the comorbid panic disorder/unipolar depression group scored significantly higher than those in the other three groups in the domain of phobic and avoidant features. The differences among groups with regard to reassurance sensitivity and substance sensitivity were significant for comorbid or pure panic disorder versus eating disorder and for comorbid panic disorder/unipolar depression versus pure unipolar depression, with patients who had panic disorder scoring higher in all cases. Patients with eating disorders scored significantly lower than patients with pure or comorbid panic in the general stress sensitivity domain. No significant differences among the groups were found in the separation sensitivity domain, except that eating disorder patients scored lower than those with unipolar depression with or without comorbid panic disorder.

Discussion

Among the four diagnostic groups, the patients with axis I panic disorder scored highest on the panic spectrum. Comorbidity with depression enhances the severity of panic-agoraphobic symptoms and/or modifies the way in which the symptoms are experienced, supporting, once again, the clinical relevance of the presence of more than one disorder in the same patient. It is noteworthy that the patients with eating disorders and those with pure unipolar depression had scores on the Panic-Agoraphobic Spectrum Questionnaire that, though low in comparison with those of the panic patients, were substantially different from 0. According to the spectrum model, the detection of a panic diathesis in these patients is crucial for obtaining a more precise picture of their clinical condition, for selecting the correct therapeutic strategy, and, ultimately, for providing appropriate treatment. In the case of patients with full-blown panic disorder, the value of the Panic-Agoraphobic Spectrum Questionnaire is in monitoring treatment and follow-up. In pharmacological studies of panic patients, the Panic-Agoraphobic Spectrum Questionnaire could serve as a tool facilitating the development of more specific antipanic medications. In psychotherapy studies, identification of subtle symptoms could be used to develop more focused and refined treatment techniques.

UTILITY OF THE SPECTRUM APPROACH

The spectrum model is based on clinical observation and is essentially atheoretical. Nonetheless, it provides a flexible and comprehensive operational system for de-

scribing phenomena that are the presumed expression of an underlying unitary psychopathological process. The psychopathological continuum, either subclinical or subsyndromal, understood within the framework of the spectrum model acquires new clinical relevance, ranging from a vulnerability factor to a basis for prevention, improved treatment, and quality of life.

Other authors have described myriad clinical phenomena—such as soft signs; subclinical, subsyndromal, subthreshold, formes frustes, and atypical symptoms; subtle or limited-symptom attacks; and partial or incomplete manifestations—to denote polymorphic manifestations that may precede, accompany, or follow a major disorder. Such symptoms can lead to marked interference with overall functioning (47, 54, 67). Early-onset spectrum-like phenomena have been considered to be direct clinical expressions of temperament (15, 21, 23, 93–99), have been interpreted as constituting the primary basis of personality itself, and have been seen as vulnerability factors for a neurotic breakdown. Following this line of thinking, we contend that early-onset, often subthreshold spectrum manifestations of one or more major disorders may imprint cognitive style and drive learned behaviors that become what is currently thought of as a personality profile.

Without any pretense of having a proven theory of how spectrum conditions relate to other axis I and axis II disorders or to other spectrum conditions, we bring our clinical experience to bear in developing a project to test these spectrum concepts empirically. From the outset, the Panic-Agoraphobic Spectrum Questionnaire has shown excellent interrater reliability when it has been administered at the Institute of Psychiatry in Pisa. Its ability to discriminate among clinical populations in a logical fashion provides initial confirmation of its potential usefulness. Throughout several years of clinical application, the spectrum approach has also shown robust clinical justification, with a range of advantages that can be summarized as follows.

1. Enhancement of the clinician-patient relationship. The spectrum model constitutes an operational frame of reference for clinicians that may substantially improve the clinician-patient relationship. This comprehensive and analytical approach makes patients feel more fully understood and comfortable during diagnostic evaluations, since from the first contact, they recognize that the interviewer is familiar with their personal feelings and experiences. In turn, clinicians can adjust their communication style to the spectrum of the patient (e.g., adopt an appropriately reassuring style in the case of a patient who shows help-seeking behavior within the panic spectrum or adopt an extroverted style with a patient who has a hyperthymic temperament within the bipolar spectrum). In our experience, the resulting enhanced communication leads patients to adhere more readily and completely to the therapeutic plan.

2. Drug selection and treatment strategies. The enormous growth of the field of psychopharmacology during the 1970s was intertwined with the development of DSM diagnostic categories, which came to be thought of as monolithic entities. The 1980s brought the concepts of comorbidity and of the interepisode or lifetime presence of subtle symptoms and traits on a psychopathological continuum with a full-blown disorder. In the 1990s further conceptualizations of psychiatric illnesses are evolving. With the advent of atypical neuroleptics, selective antidepressants, and reversible monoamine oxidase inhibitors, it is increasingly possible to target discrete dimensions of psychopathology or clusters of symptoms. The increased specificity and the benign side effect profile of some of the new compounds have lowered the severity threshold for initiation of treatment and raised new interest in mild and subthreshold psychiatric conditions. Intervention at this level, considered by some to be application of "pharmacological cosmetics," is a logical part of the proposed model that aims to correct the spectrum manifestations which impair functioning, interfere with quality of life, and/or constitute ongoing vulnerability to occurrence of a full-blown disorder. Moreover, since use of the spectrum approach results in a more detailed description of the presenting psychopathology, treatment strategies—whether psychotherapeutic or pharmacotherapeutic—can be individually tailored.

We can illustrate this approach using examples from a collection of unpublished clinical reports gathered at the Institute of Psychiatry in Pisa. Consider the cases of two patients with what appears to be the same type and severity of major depressive episode diagnosed according to the DSM-IV or other categorical criteria. The clinician prescribes the same antidepressant (e.g., clomipramine) for both patients, starting and increasing the dosages at the rate usually recommended for the treatment of depression (100). After 15–20 days, one patient improves as expected, while the other, from the first days of treatment, evidences panic attacks and worsening of depression. When examined more closely, the patient who markedly improved shows subtle obsessive traits (e.g., perfectionism, "just-right" phenomena, stubbornness) that make clomipramine a good choice for first-line treatment; the patient who worsened instead shows panic-agoraphobic spectrum symptoms (e.g., mild claustrophobia, drug or illness phobia, separation sensitivity) that predispose to full-blown panic attacks, triggered by an inappropriate therapeutic regimen of clomipramine (too high initial doses and too rapid rate of increase). The adoption of the spectrum approach would have anticipated these opposite outcomes.

3. Outcome measures and monitoring of course of illness. The current spectrum questionnaire could also serve to monitor spectrum symptoms over short periods, allowing clinicians to follow prospectively the course of these symptoms during and after treatment. Such a precise assessment could provide a detailed picture of the degree of response, as well as an indication of when relapse may be imminent. This approach would result in a thorough and systematic identification of cognitive changes, persisting residual symptoms, or maladaptive behaviors emerging during the entire course of the illness. It should be possible to draw analytical profiles of the illness course

and flow charts of therapeutic response that track the persistence/emergence of spectrum symptoms in relation to treatment initiation and discontinuation.

4. Identification of subtle personality traits and enhancement of quality of life. A central premise of the spectrum model is that some trait-like behaviors may be considered manifestations of an illness diathesis (either prodromal or residual). If this is the case, major inroads could be made into the understanding and treatment of these maladaptive behaviors and, by extension, of personality disorders. Not surprisingly, the use of a treatment strategy that addresses early-onset symptoms, even in the absence of any clear-cut disorder, has been found to produce meaningful changes in the maladaptive lifestyle of a patient and, consequently, in the perceived quality of life. In contrast, failing to recognize and address such traits may leave the clinician puzzled as to why, if all of the axis I symptoms have remitted, the patient still reports feeling miserable or maladjusted.

5. Subtyping of patients for clinical research. The attempts made to investigate the causes of anxiety and/or mood disorders by using inclusion criteria based on sets of DSM-IV symptoms leads to an overly broad selection of subjects. It is widely appreciated that such a strategy results in a heterogeneous group of patients. The spectrum assessment could help to discriminate subgroups with specific patterns of symptoms, as well as premorbid personality and temperamental features. Such subtyping would allow investigation of more homogeneous groups, increase the chances of identifying specific pathophysiologic mechanisms, and improve the rates of response to efficacious interventions.

6. Fine-tuned assessment of psychopathology in primary care and addictive behaviors. The spectrum assessment can be fruitfully used for patients with the medical conditions known to coexist with mild forms of anxiety disorders (101–105). Moreover, since most drug addicts show other axis I comorbidity (106, 107), the spectrum model can serve to explore the subtle psychopathological features of these patients that may also enhance the risk of detoxification failure.

7. Educational features. Sir Martin Roth concluded a recent article (54) by stating that "practicing psychiatrists will for an indefinite time ahead have to be trained and equipped with a wide span of knowledge, experience, and skill to enable them to investigate and diagnose, but also to understand and empathize with, their patients." The spectrum model has been shown to be easily understood and successfully applied by inexperienced resident physicians; moreover, trainees report feeling more comfortable and confident in making diagnoses by using the spectrum model as an operational frame of reference rather than relying only on DSM-IV.

CONCLUSIONS

Since Kraepelin, Kretschmer, and Jaspers, the psychopathological continuum linking temperamental features to full manifestations of major disorders has been seen as clinically meaningful. In 1936 Lewis (108) stated that "a gross blatant psychosis may do less damage in the long run than some meager neurotic incubus: a dramatic attack of mania or melancholia, with delusions, wasting, hallucinations, wild excitement and other alarms, may have far less effect on the course of a man's life than some deceptively mild affective illness which goes on so long that it becomes inveterate. The former comes as a catastrophe, and when it has passed the patient takes up his life again . . . while with the latter he may never get rid of his burden."

In agreement with these authors, the spectrum approach considers as clinically relevant and potentially incapacitating not only the full-fledged disorder but also its early-onset, atypical, and attenuated presentations. Spectrum phenomena such as subtle symptoms of separation anxiety or soft signs of mood dysregulation may precede the full manifestation of a disorder by many years or may appear as sequelae revealing the continuity of the underlying psychopathological process. The spectrum model provides a complementary clinical tool for the current diagnostic and classification systems of mental disorders. The latter, by giving sharp prototypic group definitions, miss the aura that surrounds the core of mental disorders. Consequently, spectrum phenomena are often neglected by clinicians, even when these interfere greatly with the patient's overall functioning; their detection is even more difficult when they are perceived as ego-syntonic, passively accepted by the patient.

The spectrum model, and the systematic assessment approach that follows from it, is in an early stage of validation. As such, it is currently only a hypothetical model with theoretical advantages. We recognize that the process of validation may lead to changes in the specific form of some of the hypothesized features. Thus, the Panic-Agoraphobic Spectrum Questionnaire is presented here only in its main structure. A detailed description will be provided after full psychometric testing. We believe that spectrum assessment represents a formalized method for doing the kind of minute clinical assessment that experienced treating clinicians have always done in every branch of medicine. Preliminary results suggest the panic-agoraphobic spectrum instrument we have designed is effective in capturing clinically relevant phenomena. On the basis of the analyses of the data derived from our pilot study, our assessment methods have been further refined, leading to the development of the Structured Clinical Interview for the Panic-Agoraphobic Spectrum. This interview is currently being tested in a large multicenter study. We expect this iterative process to continue for some time. Further, it is our plan to involve a broad-based, multidisciplinary group of international investigators in the further validation and assessment of the spectrum model and related structured interviews. We consider our ultimate task to be the preparation and standardization of a single, comprehensive, practical, and usable instrument that will evaluate the wide range of spectrum phenomena of multiple common psychiatric conditions.

REFERENCES

1. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders, 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1978
2. Kety SS, Rosenthal D, Wender PH, Schulsinger F, Jacobsen B: Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic: a preliminary report based on psychiatric interviews, in Genetic Research in Psychiatry. Edited by Fieve R, Rosenthal D, Brill H. Baltimore, John Hopkins University Press, 1975, pp 147–165
3. Kety SS: The significance of genetic factors in the etiology of schizophrenia: results from the national study of adoptees in Denmark. J Psychiatr Res 1987; 21:423–429
4. Winokur G: Psychosis in bipolar and unipolar affective illness with special reference to schizo-affective disorder. Br J Psychiatry 1984; 145:236–242
5. Akiskal HS: The bipolar spectrum: new concepts in classification and diagnosis, in Psychiatry Update: The American Psychiatric Association Annual Review, vol 2. Edited by Grinspoon L. Washington, DC, American Psychiatric Press, 1983, pp 271–292
6. Andreasen NC, Arndt S, Alliger R, Miller D, Flaum M: Symptoms of schizophrenia: methods, meanings, and mechanisms. Arch Gen Psychiatry 1995; 52:341–351
7. Hollander E, Wong CM: Obsessive-compulsive spectrum disorders. J Clin Psychiatry 1995; 56(April suppl):3–5
8. Cassano GB, Michelini S: Pharmacological treatment of depression and comorbid anxiety disorders, in Depression and Mania: From Neurobiology to Treatment. Edited by Gessa GL, Fratta W, Pani L, Serra G. New York, Raven Press, 1995, pp 113–125
9. Maser JD, Weise R, Gwirtsman H: Depression and its boundaries with selected Axis I disorders, in Handbook of Depression, 2nd ed. Edited by Beckham EE, Leber WR. New York, Guilford Press, 1995, pp 86–106
10. Brown C, Schulberg HC, Madonia MJ, Shear MK, Houck PR: Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. Am J Psychiatry 1996; 153:1293–1300
11. Battaglia M, Przybeck TR, Bellodi L, Cloninger R: Temperament dimensions explain the comorbidity of psychiatric disorders. Compr Psychiatry 1996; 37:292–298
12. Andrews G: Comorbidity and the general neurotic syndrome. Br J Psychiatry 1996; 168(suppl 30):76–84
13. Maser JD, Cassano GB, Michelini S: Treatment implications of comorbid disorders, in Treatment Strategies for Patients With Psychiatric Comorbidity. Edited by Welzer S. New York, John Wiley & Sons (in press)
14. Slater E, Slater P: A heuristic theory of neurosis. J Neurol Psychiatry 1944; 7:49–55
15. Eysenck HJ: The Biological Basis of Personality. Springfield, Ill, Charles C Thomas, 1967
16. Duncan-Jones P: Modelling the aetiology of neurosis: long-term and short-term factors, in The Epidemiology of Psychiatric Disorders. Edited by Cooper B. Baltimore, Johns Hopkins University Press, 1987, pp 178–191
17. Roth M: TherRelationship between anxiety and depressive disorders and its implications for the concept of a "general neurotic syndrome," in Handbook of Anxiety, vol 5. Edited by Burrows GD, Roth M, Noyes R Jr. New York, Elsevier, 1992, pp 1–20
18. Tyrer P: Classification of Neurosis. New York, John Wiley & Sons, 1989
19. Tyrer PJ: The division of neurosis: a failed classification. J R Soc Med 1990; 83:614–616
20. Pavlov IP: Conditioned Reflexes and Psychiatry. Translated by Ganto WH. London, Lawrence & Wishart, 1941
21. Schneider K: Psychopathology, 6th ed. Stuttgart, Thieme, 1962
22. Jaspers K: General Psychopathology. Translated by Hoenig J, Hamilton MW. Manchester, England, Manchester University Press, 1963
23. Jaspers K: Casual and "meaningful" connections between life history and psychosis. J Neurol 1974; 141:154–263
24. DiNardo PA, Barlow DH: Anxiety Disorders Interview Schedule, Revised (ADIS-R). Albany, NY, Graywind Publications, 1988
25. Mannuzza S, Fyer AJ, Klein DF, Endicott J: The Schedule for Affective Disorders and Schizophrenia—Lifetime Version Modified for the Study of Anxiety Disorders (SADS-LA): rationale and conceptual development. J Psychiatr Res 1986; 20:317–325
26. Spitzer RL, Williams JBW, Gibbon M, First MB: Structured Clinical Interview for DSM-III-R—Patient Version (SCID-P). New York, New York State Psychiatric Institute, Biometrics Research, 1988
27. Robins LN, Helzer JE, Croughan J, Ratcliff KS: The National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. Arch Gen Psychiatry 1981; 38:381–389
28. Robins LN, Wing J, Wittchen HU, Helzer JE, Babor TF, Burke J, Farmer A, Jablenski A, Pickens R, Regier DA, Sartorius N, Towle LH: The Composite International Diagnostic Interview: an epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry 1988; 45:1069–1077
29. Marks IM, Mathews AM: Brief standard self rating for phobic patients. Behav Res Ther 1979; 17:263–267
30. Chambless DL, Caputo GC, Bright P, Gallagher R: Assessment of fear of fear in agoraphobics: the Body Sensations Questionnaire and the Agoraphobic Cognitions Questionnaire. J Consult Clin Psychol 1984; 52:1090–1097
31. Chambless DL: The relationship of severity of agoraphobia to associated psychopathology. Behav Res Ther 1985; 23:305–310
32. Reiss S, Peterson RA, Gursky DM, McNally RJ: Anxiety sensitivity, anxiety frequency, and the prediction of fearfulness. Behav Res Ther 1986; 24:1–8
33. Silove D, Manicavasagar V, O'Connell D, Blaszczynski A, Wagner R, Henry J: The development of the Separation Anxiety Symptom Inventory (SASI). Aust NZ J Psychiatry 1993; 27: 477–488
34. Peterson RA, Reiss S: Manual for the Anxiety Sensitivity Index, 2nd ed. Worthington, Ohio, International Diagnostic Services, 1992
35. Greenberg RL: Panic disorder and agoraphobia, in Cognitive Therapy in Clinical Practice: An Illustrative Casebook. Edited by Scott J, Williams JMG, Beck AT. London, Routledge & Kegan Paul, 1989, pp 25–49
36. Mizes JS, Crawford J: Normative values on the Marks and Mathews Fear Questionnaire: a comparison as a function of age and sex. J Psychopathology and Behavioral Assessment 1986; 8:253–262
37. Shear MK, Maser JD: Standardized assessment for panic disorder research: a conference report. Arch Gen Psychiatry 1994; 51:346–354
38. Wolfe BE, Maser JD (eds): Treatment of Panic Disorder: A Consensus Development Conference. Washington, DC, American Psychiatric Press, 1994
39. Cassano GB, Toni C, Musetti L: Treatment of panic disorder, in GABAergic Synaptic Transmission: Molecular, Pharmacological, and Clinical Aspects. Edited by Biggio G, Concas A, Costa E. New York, Raven Press, 1992, pp 449–460
40. Cassano GB, Savino M: Symptomatology of panic disorder: an attempt to define the panic-agoraphobic spectrum phenomenology, in Psychopharmacology of Panic. Edited by Montgomery SA. Oxford, England, Oxford University Press, 1993, pp 38–57
41. Klein DF: Delineation of two drug-responsive anxiety syndromes. Psychopharmacology (Berl) 1964; 5:397–408
42. Klein DF, Gittelman R, Quitkin FM, Rifkin A: Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children, 2nd ed. Baltimore, Williams & Wilkins, 1980, pp 502, 512, 513, 540, 585
43. Klein DF: Anxiety reconceptualized, in Anxiety: New Research and Changing Concepts. Edited by Klein DF, Rabkin JG. New York, Raven Press, 1981, pp 235–265
44. Klein DF, Rabkin JG (eds): Anxiety: New Research and Changing Concepts. New York, Raven Press, 1981, pp 297, 760
45. Barlow DH: Current models of panic disorder and a view from

emotion theory, in American Psychiatric Press Review of Psychiatry, vol 7. Edited by Frances AJ, Hales RE. Washington, DC, American Psychiatric Press, 1988, pp 10–28
46. Gorman JM, Papp L, Klein DF: Biological models of panic disorder, in Handbook of Anxiety, vol 3: The Neurobiology of Anxiety. Edited by Burrows GD, Roth M, Noyes R Jr. New York, Elsevier, 1990, pp 59–77
47. Johnson J, Weissman MM, Klerman GL: Service utilization and social morbidity associated with depressive symptoms in community. JAMA 1990; 267:1478–1483
48. Perugi G, Maremmani I, Deltito J, Simonini E: Social adjustment in agoraphobia with panic attacks with major depression. New Trends in Experimental and Clin Psychiatry 1986; 2:45–51
49. Sheehan DV: Current concepts in psychiatry: panic attacks and phobias. N Engl J Med 1982; 307:156–158
50. Garvey MJ, Tuason VB: The relationship of panic disorder to agoraphobia. Compr Psychiatry 1984; 25:529–531
51. Breier A, Charney DS, Heninger GR: Agoraphobia with panic attacks: development, diagnostic stability, and course of illness. Arch Gen Psychiatry 1986; 43:1029–1036
52. Marks IM: Behavioral aspects of panic disorder. Am J Psychiatry 1987; 144:1160–1165
53. Lelliot P, Marks I, McNamee G, Tobena A: Onset of panic disorder with agoraphobia: toward an integrated model. Arch Gen Psychiatry 1989; 46:1000–1004
54. Roth M: The panic-agoraphobic syndrome: a paradigm of the anxiety group of disorders and its implications for psychiatric practice and theory (festschrift). Am J Psychiatry 1996; 153(July suppl):111–124
55. Klein DF: Anxiety reconceptualized. Compr Psychiatry 1980; 21:411–427
56. Roth M: Agoraphobia, panic disorder, and generalized anxiety disorder: some implications of recent advances. Psychiatr Dev 1984; 2:31–52
57. Klein DF: False suffocation alarms, spontaneous panics, and related conditions: an integrative hypothesis. Arch Gen Psychiatry 1993; 50:306–317
58. Argyle N, Roth M: The relationship of panic attacks to anxiety states and depression, in Biological Psychiatry: Developments in Psychiatry. Edited by Shagass C. New York, Elsevier, 1986, pp 460–465
59. Argyle N, Roth M: The definition of panic attacks, part I. Psychiatr Dev 1989; 7:175–186
60. Liebowitz MR, Gorman JM, Fyer AJ, Klein DF: Social phobia: review of a neglected anxiety disorder. Arch Gen Psychiatry 1985; 42:729–736
61. Perugi G, Simonini E, Savino M, Mengali F, Cassano GB, Akiskal HS: Primary and secondary social phobia: psychopathologic and familial differentiations. Compr Psychiatry 1990; 31: 245–252
62. Clark DM: A cognitive approach to panic. Behav Res Ther 1986; 24:461–470
63. McNally RJ: Psychological approaches to panic disorder: a review. Psychol Bull 1991; 108:403–419
64. Barsky AJ, Barnett MC, Cleary PD: Hypochondriasis and panic disorder: boundary and overlap. Arch Gen Psychiatry 1994; 51: 918–925
65. Schmidt AJM: Bottlenecks in the diagnosis of hypochondriasis. Compr Psychiatry 1994; 35:306–315
66. Schmidt NB, Telch MJ, Ioiner TE Jr: Factors influencing health perceptions in patients with panic disorder. Compr Psychiatry 1996; 37:253–260
67. Fava GA, Grandi S, Canestrari R: Prodromal symptoms in panic disorder with agoraphobia. Am J Psychiatry 1988; 145:1564–1567
68. Benedetti A, Perugi G, Toni C, Simonetti B, Mata B, Cassano GB: Hypochondriasis and illness phobia in panic-agoraphobic patients. Compr Psychiatry (in press)
69. Bowlby J: Attachment and Loss, vol I: Attachment. New York, Basic Books, 1969
70. Bowlby J: Attachment and Loss, vol II: Separation: Anxiety and Anger. New York, Basic Books, 1973
71. Pitts FM, McClure JN: Lactate metabolism in anxiety neurosis. N Engl J Med 1967; 277:1329–1336
72. Charney DS, Heninger GR, Redmond DE Jr: Yohimbine induced anxiety and increased noradrenergic function in humans: effects of diazepam and clonidine. Life Sci 1983; 33:19–29
73. Dager SR, Holland JP, Cowley DS, Dunner DL: Panic disorder precipitated by exposure to organic solvents in the work place. Am J Psychiatry 1987; 144:1056–1058
74. McCann UD, Ricaurte GA: MDMA ("ecstasy") and panic disorder: induction by a single dose. Biol Psychiatry 1992; 32:950–953
75. Nutt DJ, Glue P: Clinical pharmacology of anxiolytics and antidepressants: a psychopharmacological perspective. Pharmacol Ther 1989; 44:309–334
76. Nutt D, Lawson C: Panic attacks: a neurochemical overview of model and mechanism. Br J Psychiatry 1992; 160:165–178
77. Michelini S, Cassano GB, Frare F, Perugi G: Long-term use of benzodiazepines: tolerance, dependence and clinical problems in anxiety and mood disorders. Pharmacopsychiatry 1996; 29: 127–134
78. Roth WT, Margraf J, Ehlers A, Taylor B, Maddock RJ, Davies S, Agras WS: Stress test reactivity in panic disorder. Arch Gen Psychiatry 1992; 49:301–310
79. Last CG, Barlow DH, O'Brien GT: Precipitants of agoraphobia: role of stressful life events. Psychol Rep 1984; 54:567–570
80. Andrews G: Stressful life events and anxiety, in Handbook of Anxiety, vol 2. Edited by Noyes R Jr, Roth M, Burrows GD. New York, Elsevier, 1988, pp 163–174
81. Argyle N, Roth M: The phenomenological study of 90 patients with panic disorder, part II. Psychiatr Dev 1989; 7:187–209
82. Wade SL, Monroe SM, Michelson LK: Chronic life stress and treatment outcome in agoraphobia with panic attacks. Am J Psychiatry 1993; 150:1491–1495
83. Lteif GN, Mavissakalian MR: Life events and panic disorder/agoraphobia: a comparison at two time periods. Compr Psychiatry 1996; 37:241–244
84. Gittelman R, Klein DF: Relationship between separation anxiety and panic and agoraphobic disorders. Psychopathology 1984; 17(suppl 1):56–65
85. Gittelman R, Klein DF: Childhood separation anxiety and adult agoraphobia, in Anxiety and the Anxiety Disorders. Edited by Tuma AH, Maser JD. Hillsdale, NJ, Lawrence Erlbaum Associates, 1985, pp 389–402
86. Deltito JA, Perugi G, Maremmani I, Mignani V, Cassano GB: The importance of separation anxiety in the differentiation of panic disorder from agoraphobia. Psychiatr Dev 1986; 4:227–236
87. Roy-Byrne PP, Geraci M, Uhde TW: Life events and the onset of panic disorder. Am J Psychiatry 1986; 143:1424–1427
88. Roth M: The phobic anxiety depersonalization syndrome. Proc R Soc Med 1959; 52:587–595
89. Buglass D, Clarke J, Henderson AS, Kreitman N, Presley AS: A study of agoraphobic housewives. Psychol Med 1977; 7:73–86
90. Reich J, Noyes R Jr, Troughton E: Dependent personality disorder associated with phobic avoidance in patients with panic disorder. Am J Psychiatry 1987; 144:323–326
91. Katschnig H: Discontinuation and long-term follow-up of panic disorder (PD) patients (abstract). Biol Psychiatry 1991; 29 (suppl):10S
92. Noyes R Jr, Woodman CL, Holt CS, Reich JH, Zimmerman MB: Avoidant personality traits distinguish social phobic and panic disorder subjects. J Nerv Ment Dis 1995; 183:145–153
93. Kraepelin E: Manic-Depressive Insanity and Paranoia. Translated by Barclay RM, edited by Robertson GM. Edinburgh, E & S Livingstone, 1921
94. Kretschmer E: Physique and Character. Translated by Miller E. London, Kegan, Paul, Trench, Trubner, 1936
95. Sjobring H: Personality Structure and Development: A Model and Its Application. Acta Psychiatr Scand Suppl 1973; 244
96. Gray JA: The Neurophysiology of Psychiatry. New York, Oxford University Press, 1982
97. Cloninger CR: A unified biosocial theory of personality and its role in the development of anxiety states. Psychiatr Dev 1986; 4:167–226

98. Kagan J, Reznick JS, Snidman N: Biological bases of childhood shyness. Science 1988; 240:167–171
99. Akiskal HS: Temperament, personality and depression, in Research in Mood Disorders: An Update. Edited by Hippius H, Stefanis C. Gottingen, Germany, Hogrefe & Huber, 1994
100. Depression Guideline Panel: Depression in Primary Care, vol 2: Treatment of Major Depression: Clinical Practice Guideline 5: AHCPR Publication 93-0551. Rockville, Md, US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, April 1993
101. Chignon JM, Lépine JP, Adès J: Etude du trouble panique chez des patients consultant en cardiologie. Encéphale 1994; 20: 319–326
102. Ehlers A, Breuer P, Dohn D, Fiegenbaum W: Heartbeat perception and panic disorder: possible explanations for discrepant findings. Behav Res Ther 1995; 33:69–76
103. Stein MB, Uhde TW: The thyroid and anxiety disorders, in The Thyroid Axis and Psychiatric Illness. Edited by Joffe RT, Levitt AJ. Washington, DC, American Psychiatric Press, 1993, pp 255–277
104. Roth M, Harper M: Temporal lobe epilepsy and the phobic anxiety-depersonalization syndrome, part II: practical and theoretical considerations. Compr Psychiatry 1962; 3:215–226
105. Stein MB, Asmundson GJG, Ireland D, Walker JR: Panic disorder in patients attending a clinic for vestibular disorders. Am J Psychiatry 1994; 151:1697–1700
106. Howens IG, Cantwell DP, Kiriakos R: Psychiatric comorbidity in hospitalized adolescent substance abusers. J Am Acad Child Adolesc Psychiatry 1994; 33:467–483
107. Perretta P, Nisita C, Zaccagnini E, Lorenzetti C, Nuccorini A, Cassano GB, McNair DM, Akiskal HS: Feasibility of pharmacotherapy in HIV-related affective spectrum disorders: an open trial with fluvoxamine. Eur Psychiatry 1996; 11:40–45
108. Lewis A: Prognosis in the manic-depressive psychosis. Lancet 1936; 2:997–999

APPENDIX 1. Atypical Symptoms Assessed in the Panic-Agoraphobic Spectrum Questionnaire[a]

Feeling confused, numb
Feeling of spatial disorientation
Sensation of walking on a velvet tread or foam rubber or as if legs were jelly
Feeling unstable, walking awkwardly or as if legs were stiff
Sensation of urinary or bowel incontinence
Onset of depressive symptoms
Feeling of losing control
Headache
Hypersensitivity to heat, stale air, or humid air
Hypersensitivity to perfumes or other odors
Hypersensitivity to light
Hypersensitivity to noises
Discomfort in the presence of blurred perspectives
Discomfort in the dark
Asthenia
Feeling as if something had broken inside the brain or the body
Feeling as if one had become blind or deaf

[a]Includes symptoms, either acute or persistent, that are not listed in the DSM-IV criteria for a panic attack.



With Mel Lipsett, M.D., Ben Jacobs, Donald Langsley, M.D., John McGrath, M.D., and Mayor Marion Barry at the groundbreaking ceremony for the new APA headquarters building (Washington, D.C., November 1980)