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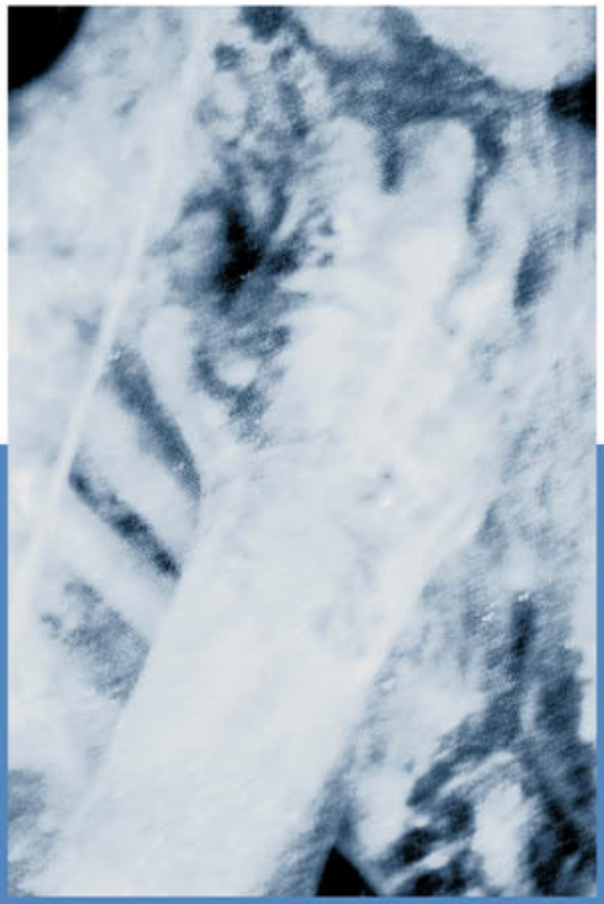
TEXTBOOK OF ANXIETY DISORDERS



EDITED BY

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Textbook of Anxiety Disorders

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Dan J. Stein, M.D., Ph.D.
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Preface

Anxiety is one of the oldest of subjects. The phylogenetic origins of anxiety date back to the origins of the animal kingdom, and philosophers and thinkers have long written about the centrality of anxiety to human life and experience. The experience of anxiety has a ubiquity and a universality that extends across times and across cultures.

At the same time, anxiety is one of the newest of subjects. Only in the past few decades have scientists and clinicians been able to develop rigorous diagnostic schemas, to appreciate the prevalence of different anxiety disorders, to understand the underlying psychobiology of anxiety disorders, and to develop effective pharmacotherapeutic and psychotherapeutic interventions.

Although the universality of anxiety and its disorders provides the justification for this book, it is these new advances that often have inspired our interest in the anxiety disorders and that have provided the immediate impetus for collecting a series of contributions at the cutting edge of anxiety disorder research and clinical practice.

Several of these advances are particularly worth emphasizing at the outset. First, it is not always appreciated that the anxiety disorders are not only among the most prevalent of the psychiatric disorders but also among the most disabling. Both the Epidemiological Catchment Area study and the National Comorbidity Survey found that the anxiety disorders are more common than either mood or substance use disorders.

Furthermore, it has been estimated that one-third of all costs of psychiatric disorders are due to the anxiety disorders; in particular, the anxiety disorders are associated with high indirect costs. Whereas the high direct costs of disorders such as the psychotic disorders are obvious, the high indirect costs of the anxiety disorders are less so and therefore require continued emphasis.

Unfortunately, however, the anxiety disorders continue to be misdiagnosed and undertreated. Perhaps the very universality of anxiety makes it more difficult for caregivers to appreciate the morbidity of anxiety disorders and for patients to seek help. Clinicians and advocacy groups have made important strides in increasing awareness, but further work remains to be done.

However, the psychobiology of anxiety disorders is indisputably one of the most interesting and rewarding areas of contemporary medical research. The specific neuroanatomy, neurochemistry, cognitive dysfunctions, and genetic and environmental contributions to each of the anxiety disorders is gradually being outlined. Data from disparate fields are being integrated into powerful and sophisticated models.

Indeed, anxiety disorders provide researchers and clinicians with a remarkable locus for integration. Animal models of fear conditioning, for example, provide fascinating parallels with clinical phenomena such as posttraumatic stress. Similarly, functional brain imaging has shown that pharmacotherapy and psychotherapy for obsessive-compulsive disorder are characterized by similar changes, providing a unique opportunity for the integration of brain and mind.

In this volume, we include sections on each of the main anxiety disorders (including chapters on their phenomenology, pathogenesis, pharmacotherapy, and psychotherapy). The introductory and concluding sections also consider several theoretical and clinical issues that cut across the different anxiety disorders.

We would like to express our gratitude to the colleagues who have helped support and guide us, to the patients who have taught us about themselves, and to our families for their love and encouragement.

Dan J. Stein, M.D., Ph.D.
Eric Hollander, M.D.

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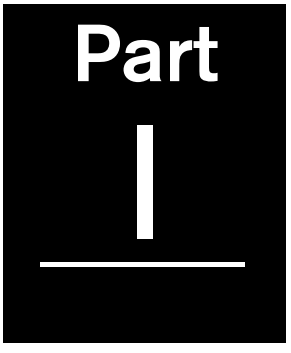

Approaching the Anxiety Disorders

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1

History of Anxiety Disorders

Michael H. Stone, M.D.

An Etymological Note

Anxiety goes back to our very beginnings. Perhaps it was because of the very universality of anxiety as part of the human condition that physicians in ancient times omitted it from their roster of mental illnesses. The Greeks of the classical age had words for mania, melancholia, hysteria, and paranoia (in fact, those were the Greek words, which we still use to this day). But they had no word for *anxiety*. In modern Greek, we confront the word *anesuchia*, whose root meaning is "not quiet" or "not calm." The Romans, however, in Cicero's time used the word *anxietas*, which indicated a lasting state of fearfulness. This contrasted with *angor*, which signified a momentary state of intense fear, akin to our concept of panic. Angor also meant strangling—and derives from the verb *ango:* to press something together, to strangle. The idea of narrowness is another connotation, as in the Latin *angustia* (narrowness), the French *angoisse* (anguish—a more acute, paniclike state), and the German *Angst* (fear) and *eng* (narrow). The *angr* root in Indo-European languages also gave rise to our *anger* (akin to Old Norse *angra:* grief) and *angina* (a term also used in Roman times to signify a crushing sensation in the chest and the accompanying dread).

Early Commentaries on Anxiety or Equivalent States

It is easy enough to understand the origins of our modern word because anxiety is often accompanied by a feeling of closeness; a feeling of pressure on the chest, such that one can scarcely breathe; or a feeling of pressure on the abdomen (Littre and Robin 1858).

Berrios and Link (1995) pointed out that although many references to anxiety-like states are found in older books such as Burton's *Anatomy of Melancholy* (1621), the term *anxiety* was not used as such in psychiatric parlance until later. Instead, the individual symptoms and manifestations were considered as separate diseases or conditions. That is, the difficulty breathing while in a state of anxiety would be ascribed to some pulmonary abnormality, what we call "butterflies in the stomach" would be understood as some gastric condition, and the dizziness that may accompany intense anxiety might be described as the "condition" of vertigo and seen as a function of a middle-ear problem. Symptoms of this sort would be manifestations of what Berrios and Link called the *objective* aspects of anxiety (p. 545). These include what we now call the psychosomatic illnesses that can arise in the context of intense anxiety, such as abdominal pain, palpitations, hot flushes, and breathlessness. The contrasting *subjective* aspects are those that answer more closely to modern conceptions of anxiety states or disorders, such as feelings of terror; pressing worries; phobias; stage fright; obsessive ruminations about dirt, disease, and death; and experiences of depersonalization or derealization. Burton (1621) hinted that some connection probably existed between the disturbances of the mind and those of the body:

> the Minde most effectually workes upon the Body, producing by his passions and perturbations, mirac-

> ulous alterations; as Melancholy, despaire, cruell diseases, and sometimes death itselfe. Inso much, that it is most true which Plato saith in his *Charmides*: omnia corpora mala ab anima procedere: all the mischiefs of the Body, proceede from the Soule. (p. 78)

But nowhere does Burton mention the term *anxiety* itself.

Anxiety, as we understand it, was, in medieval and Renaissance times, often conflated with the concept of melancholia. Just as contemporary clinicians seldom encounter seriously depressed patients who are not also anxious to a significant degree, "melancholic" persons in bygone times often were pathologically anxious at the same time. One common form of this mixed state was (and still is) lovesickness. Presumably, there was something special about lovesickness or doubting-with-compulsions that would attract the attention of a physician: persons with these conditions were dysfunctional. The lovesick nephew, for example, was wasting away in bed, lacking appetite, and lacking even the will to live. Someone expressing the same worry repeatedly and showing some repetitive behavior (such as hand washing) would likewise strike physicians and laypersons alike as "different" from an ordinary person. What was missing, and what did not become common medical currency until the nineteenth century, was the awareness that anxiety (of this more than "normal" sort) was the red thread that ran through a whole variety of conditions: lovesickness, obsessive-compulsive symptoms, fainting spells, hypochondriasis, and the like. At the same time, these anxiety disorders, as we would call them, usually fell short of necessitating institutional care. Hence, the medical literature from the first printed books (mid-fifteenth century) until this "red thread" was discovered was very sparse in its mention of these disorders.

Among the descriptions of such conditions in the seventeenth century was that of the English moral-tract writer, Richard Younge (?–1671). In his sketches of mental abnormalities (Younge 1638) are some that inspired the characterology of Richard Flecknoe's *Enigmaticall Characters*, written a generation later, by which time, as Hunter and Macalpine (1963) mentioned, psychiatric labels came to be attached (p. 116). Flecknoe wrote of "anxiety states" in which "one troubles herself with every thing," or else—the "irresolute person" (the contemporary obsessive-compulsive person) who "hovers in his every choice like an empty Ballance with no weight of Judgment to incline him to either scale… when he begins to deliberate, he never makes a end" (Hunter and Macalpine 1963, p. 116).

Eighteenth-Century Impressions About Anxiety

At some point in the early eighteenth century (one cannot be precise as to just when), the term *anxiety* came into medical writing about mental illness. We can hardly speak about "psychiatry" as yet because this word did not come into medical parlance until Johann Reil coined it in 1808. Use of the term *anxiety* also meant in effect that a distinction was now made between the "normal" levels average people experienced after love disappointments, financial worries, and so on and the excessive levels noticeable in persons who overreacted grossly to similar life events (as LePois [1618] had commented on a century earlier).

In England, Sir Richard Blackmore (1653–1729), in a treatise on "vapours," advocated "pacifick medicines" for what we would call anxiety states and other significant psychological disturbances: "If Inquietude be the Distemper, Quiet must be the Cure" (Blackmore 1725). The old term *vapours* was itself analogous in some respects to our concept of anxiety disorders: Aristotle had contended, for example, that the brain condensed vapors that emanated from the heart and that vapors were involved in various "nervous" (especially hysteric) states (Stone 1997a, p. 9). Blackmore believed that opiates in moderation were helpful in "hypochondriacal and hysteric" cases and did not lead to loss of appetite or mental dullness.

The first psychiatric textbook in English was that of William Battie (1703–1776), director of Bethlem Hospital in London, England, and later (in 1751), founder of St. Luke's Hospital, also in London.

Although his work concentrated on the more grave (we would say *psychotic*) disorders necessitating hospitalization, he distinguished between "madness" and "anxiety," writing of the latter in this vein:

> it may not be improper to take some notice of those two other disorders…which were excluded from our definition of Madness, viz., praeternatural Anxiety or Sensation too greatly excited by real objects, and its contrary Insensibility or Sensation not sufficiently excited by real objects.… Madness in its proper sense [is] very often preceded by or accompanied with the first and often terminates in the second of these two disorders.… Whatever may be the cause of Anxiety, it chiefly discovers itself by that agonizing impatience observable in some men of black November days, of easterly winds, of heat, cold, damps, etc. (Battie 1758, p. 33ff)

On the theoretical plane, Battie adhered to the view that anxiety was to be understood mainly in terms of

the body, more so than of the mind, insofar as it represented an "excess of sensation." Battie's awareness that many deluded persons (those with "madness") also at times experienced "anxiety," whereas many other persons showed "anxiety" without ever experiencing "madness" confused some of his colleagues, such as James Vere (1700–1779). Vere was a merchant of London and a governor of the Bethlem Hospital. In his view, nervousness (for which we can read *anxiety*) could be understood as the outcome of an internal war or conflict—between the "lower order of instincts" and the "moral instincts." The lower order of instincts were those concerned with the preservation and continuance of existence (for which we might read *sex and aggression*). This strikes the modern ear as very much in keeping with the Freudian tripartite model of the mind, in which the ego is seen as mediating between the impulses stemming from the id and the prohibitions imposed by the superego (Freud 1923/1961). In a similar prelibation of Freudian theory (here, the aspect dealing with the pleasure-pain principle), Vere (1778) also spoke of the "two great principles which actuate all animated bodies: appetite and desire [versus] aversion and dislike."

The Scottish neurologist Robert Whytt (1714–1766) focused, as Battie had done, on sensation and the peripheral nervous system in his writings on hysteria, hypochondriasis, and the "nervous disorders" (Whytt 1765). He mentioned that "The coats of the nerves may be obstructed, or inflamed, compressed by hard swellings, or irritated by acrid humours" (p. 85) and viewed abnormalities of this sort (perhaps because of his neurological background) as the root causes of the minor (i.e., nonpsychotic) afflictions he worked with. Whytt also wrote of *nervous exhaustion*—similar to the nineteenth century concept of *neurasthenia*. Allusions to what we would consider anxiety are found in Whytt's comments on palpitations, in which he states: "In those whose nervous system is easily moved, any sudden and strong passion, but especially fear, will produce palpitations, and an irregular motion of the heart, by rendering it more irritable" (p. 286).

In France, intense anxiety states were mentioned in the medical text of Boissier de Sauvages (1752), although not yet with the terms *anxiete* or *angoisse*. He spoke, for example, of "panophobia," a generalized state of anxiety that might express itself by turns as pavor nocturnus, intense shaking of the body, insomnia, or feelings of terror arising from the "working of the imagination" (p. 240). The concept of *panophobia* was echoed a century and a half later in Ribot's "pantophobia."

Thus far, as we have seen, the medical practitioners in the field of mental illness (they could be called *alienists* at this stage but not yet *psychiatrists*) concentrated on patients with delusions and other severe disorders requiring institutional care. The less serious disorders were seen as abnormalities of the nerves or of the brain to which the nerves were connected. This was a very "biological" view of mental illness. Although there was some awareness of the psychological underpinnings of some of these afflictions, these were seldom placed in the hierarchy of causative factors. One has the impression that ordinary people themselves were less aware of the psychological, interpersonal stresses that underlay their illnesses and that they tended to "somatize"—partly for this reason and partly for the reason that somatic conditions were the only conditions that their physicians were equipped to hear about and deal with. Contemporary conditions such *hwa-byung* (burning in the stomach) in Korea (Stone 1997a, p. 423) seem altogether analogous to the fainting spells of anxious women in the eighteenth and nineteenth centuries, who had little opportunity to escape psychologically intolerable situations except to develop some somatic condition.

This emphasis on the "nerves" is still discernible in the writings of the celebrated Scottish physician William Cullen (1710–1790), who coined the term *neurosis:* "I propose to comprehend, under the title of Neurosis, all those praeternatural affections of sense and motion, which are without pyrexia, and all those which…depend upon a more general affection of the nervous system" (Cullen 1807, p. 387).

The Nineteenth Century: The Early Years

The early years of the nineteenth century witnessed a shift, within the mental health field, from attention to the somatic causes or accompaniments of mental illness to the possible psychological causes. The German romantic period was in full swing, having been energized by works such as Goethe's *The Sorrows of Young Werther*, first published in 1774. Goethe's tale of hopeless love for an unavailable woman that led its protagonist to suicide precipitated a wave of suicides in Europe, earning the author the contumely of the English vicar Charles Moore (1743–1811), whose magnum opus on suicide (Moore 1790) condemned Goethe for his "lovesick tale."

Nevertheless, during this time (which lasted until about 1840), the first lengthy biographical sketches were written—in the medical literature—about the anxieties, conflicts, and general psychological problems of people in everyday life. Among the earliest of such sketches were those of Christian Spiess (1796), John Haslam (1809) in England, and the director of Berlin's Charity Hospital, Karl Ideler (1841).

These influences were not felt in America until some time later. Cullen's pupil Benjamin Rush (1746–1813), from Philadelphia, Pennsylvania, was still writing in his psychiatric text (Rush 1812) in a very "somatic" vein about anxiety disorders. "The objects of fear are of two kinds," he mentioned (p. 325): "the reasonable (death and surgical operations) and the Unreasonable (these are, thunder, darkness, ghosts, speaking in public, sailing, riding, certain animals, particularly cats, rats, insects and the like)." As for the one anxiety disorder easily recognizable to us as a type of *social anxiety* (speaking in public), Rush had no more to say about it than "The fear from speaking in public was always obviated by Mr. John Hunter, by taking a dose of laudanum [an opiate] before he met his class every day" (p. 332).

The year after Rush's book appeared, Landre-Beauvais (1813) in France used the term *angoisse* to designate anxiety states, defining it as "a certain malaise, restlessness, excessive agitation" that could accompany either acute or chronic conditions and either psychological or somatic expressions of anxiety (Berrios and Link 1995, p. 546). This state of intense fearfulness was still seen as an element in the clinical picture of melancholia (Georget 1820; Pinel 1801). Another label that indicated a condition involving severe anxiety was "monomania with fear." To show the equivalence of this term with our concepts of anxiety disorder, Alexander Morrison (1826) in his lectures on mental diseases appended etchings of typical patients. The caption to Plate VI reads as follows: "This plate is intended to give an idea of partial insanity with fear, what has been termed Panaphobia" (p. 136). The subject is female, although, from her dress, she rather gives the idea of a male. Delusive fear of every object and person keeps her in a state of perpetual distress: it is necessary to watch her closely, to prevent her from committing suicide.

The phrase *anxiety of mind* appeared shortly afterward in a book by the English physician Charles Thackrah (1831). Writing about the tribulations peculiar to each of the five social classes he outlined, he commented that the "health of doctors is impaired particularly by anxiety of mind." Thackrah ascribed this vulnerability to the physician's special need for study and research and (worst of all) for making night calls.

Although, in general, anxiety and "anguish" were now seen as manifestations of psychiatric disturbances of a severity intermediate between psychosis ("madness" or "lunacy" or "insanity") and normalcy, Prichard (1835) nevertheless claimed that care and anxiety, distress, grief, and mental disturbances were the most common causes of insanity.

Jules Angst (1995) mentioned a German physician, Otto Domrich, who wrote in the first half of the nineteenth century about anxiety attacks. These consisted of a combination of anxiety and cardiopulmonary symptoms, such as might be induced (as with the current posttraumatic stress disorder) by the terror of the battlefield.

Implicit in my comment above about German romanticism is that advances in theory about anxiety did come mostly from German-speaking authors throughout the first half of the nineteenth century. The German school went beyond the empiricism of the British and the French, who were still dwelling on the state of the "nerves" of anxious persons (and on the various anodynes that might soothe those nerves) rather than on the particularities of the individual persons who had various forms of anxiety. Friedrich Beneke (1798–1854), for example, argued that certain "ideas" or attitudes of mind could be symbolized within psychosomatic reactions (Beneke 1853). Along similar lines, Baron Ernst von Feuchtersleben (1806–1849) stressed the role of conflict, as Vere had done 50 years earlier, as central to the understanding of mental illness (von Feuchtersleben 1838, 1845). Again, the conflict was seen specifically as the battle between one's "irrational impulses" and one's more reasonable wishes and expectations. As to his "psychosomatic" views, von Feuchtersleben understood that intense anxiety and grief could lead to organic conditions of the heart and the digestive system (Berrios and Link 1995, p. 548). We also must credit the Viennese baron with a thought that may be seen as prefiguring Freud's famous dictum about freeing the psychoanalytic patient from neurotic misery—by making the unconscious conscious, by in effect helping the patient to master the anxiety from hidden sources by enabling those sources to reach the level of awareness.

We should also acknowledge the contribution of Jean-Etienne Esquirol (1772–1840), who did not write on the topic of anxiety per se but did provide detailed clinical examples of what we now call obsessive-compulsive disorder (OCD). Esquirol's descriptions (1838, p. 62ff) served as the inspiration for the even more detailed descriptions of Henri Le Grand du Saulle (1830–

1886), one of which I had translated in an earlier communication (Stone 1997b). Here, I give only some brief portions taken from the description of one of Esquirol's OCD patients:

> Miss F., aged 34, was raised in a merchant household from her earliest days. She feared that she would do wrong to others, and later on, when she handled the payments and receipts, feared that she would make a mistake in giving too little change to a customer.… Back in her parents' shop, she would fear that, in returning change to a customer, she might have retained in her fingers something of value.… She knew her anxiety was "absurd and ridiculous" but could do nothing to control her behavior. She ended up shaking her hands vigorously after touching nothing, to make sure that nothing stuck to her fingers that didn't belong to her. (Esquirol 1838, Vol. 2, pp. 63–64) (my translation)

The Nineteenth Century: The Later Years

By the second half of the nineteenth century, there was more widespread recognition that anxiety, in its more intense or persistent forms, deserved its own place within psychiatric nosology. As was typical of the French school, anxiety was seen as part of a "three-stage process," which began with inquietude, progressed to anxiety, and might end with anguish (*angoisse*) (Littre and Robin 1858). Feelings of "closeness" and "difficulty breathing" were noted in both anxiety and anguish.

In Germany, Wilhelm Griesinger (1817–1868) saw mental disease and somatic disease as one; neuropathology and psychiatry were in essence the same field. He realized that not all behavior was consciously determined and acknowledged the importance of temperament and personality. Although he thought that mental disease must stem from abnormalities of the brain cells (and thus had an "organic" basis), he nevertheless endorsed the idea from his romanticist predecessors that strong affects could induce mental illness. Such illness might come about, in Griesinger's (1861) view, because of conflicts involving the repression (*Verdraengung*) of sexual urges—a Freudian concept expressed a generation before Freud. Griesinger estimated that 1 in 10 patients who developed a psychosis ("insanity") did so with acute fear as the inciting agent.

A similar theory was espoused by Heinrich Wilhelm Neumann (1814–1884), a contemporary of Griesinger. Neumann saw mental illness as partaking of a dynamic process in which, under normal circumstances, a person succeeds in his or her development toward a freedom gained through self-mastery. In pathological circumstances, the perturbations of the drives, especially the sexual ones, disturb one's harmony. When the drives cannot be satisfied, anxiety appears. Furthermore, if certain life functions are threatened, the instinctual needs are apt to express themselves in consciousness as "perceptions" (Neumann used the Greek word *aistheses*) or "calls" that make the person aware of impending danger (Beauchesne 1781, p. 51). Neumann's theory here anticipates Freud's reworking of his anxiety theory in 1923, wherein he spoke of "signal anxiety."

Although psychiatry in the second half of the nineteenth century remained more biologically oriented, this was more true in France even than in Germany. Benedict Morel (1809–1873), to whom we owe the concept of *demence precoce* (Morel 1860) (which gave rise to the later concepts of dementia praecox and schizophrenia), believed that both the psychological and the somatic (subjective and objective) expressions of anxiety could lead to pathological changes in the autonomic nervous system (Berrios and Link 1995, p. 549).

Le Grand du Saulle (1878), a prominent and prolific psychiatrist at the Bicetre Hospital in Paris, France, wrote a monograph on the *peur des espaces* (fear of spaces), based on Westphal's (1872) article on agoraphobia. Le Grand du Saulle preferred the admittedly more vague designation rather than the term *agoraphobia* that the German school preferred because "although one may see now and again that these patients fear open spaces, they may experience the fear at the theater, at church, on an elevated storey of a building, or while inside near a window giving out to a large courtyard, or on a bus or boat or a bridge" (p. 6) (my translation). Although he was aware that psychological causes had been mentioned by other authors ("the too vivid emotions of a person sad by nature, an unexpected fright, the sudden death of a loved-one, the good luck to have escaped a great danger…, excessive intellectual efforts, insufficient sleep, or sexual excess"; p. 31), Le Grand du Saulle favored the etiological (and not at all psychological) factors of excess coffee or of heredity (and gave examples of each; pp. 32–35). The hereditary view was later endorsed by Dagonet (1894).

Earlier, Dagonet (1876), a professor of psychiatry in Strasbourg, France, had described several forms of anxiety under the broad heading of *lypemanie* (Esquirol's term for depression stemming from the Greek *lupeo*,

to grieve). He characterized hypochondriasis (*lypemanie hypochondriaque*) as beginning with mild symptoms, which progress in the usual "three stages" customary in all French nineteenth-century psychiatric texts. The patient is "anxious [inquiet], preoccupied, and begins to experience fears concerning his health; he inspects his body minutely…, observes scrupulously all the rules of hygiene; he reads books on medicine and is most eager to speak with physicians about his condition" (p. 25) (my translation). Dagonet also discusses *lypemanie anxieuse* (anxious depression), also known as *panophobia*, *angoisse morale* (anguished mood, or in German, *Gemuethsbeklemmung*), or *Angst*. Dagonet's case descriptions are those of a serious disorder, midway between our concept of generalized anxiety and OCD, bordering on delusion. The clinician encounters as the patient's predominant symptoms: "*les angoisses*, *les inquietudes vagues*, *les terreurs*, *des conceptions erronees*, *et un delire plus ou moins systematise*" (p. 239) ("feelings of dread, vague anxieties, terror, false ideas, and more or less systematized delusory ideas"). In the lengthier example Dagonet provided, the patient had a mentally ill grandmother, uncle, and five cousins (all by that uncle), which suggested to Dagonet that heredity was the principal causative agent.

Berrios and Link (1995, p. 551) gave a description of *vertigo* written by Leroux (1889) for a medical encyclopedia, which could serve well as a defining example of panic attack. In this connection, Berrios credits Le Grand du Saulle with realizing that the patient with "vertigo" did not have an inner-ear malady, as Benedikt was still suggesting in 1870, but was more likely troubled by a *fear* of falling.

The panophobia, or *lypemanie anxieuse*, of which the European psychiatrists of the period were speaking—similar to generalized anxiety disorder—was given the name *neurasthenia* (a weakness of the nerves) by the American neurologist George Miller Beard (1839–1883). Beard enjoyed considerable fame during his lifetime for his application of electrical treatments—"voltaic-galvanic stimulation" or "faradic stimulation"—to the cure of neurasthenia (Beard 1880; Beard and Rockwell 1875). The popularity of Beard's method in the waning years of the century can hardly be overestimated.

The *neurasthenia* concept was so popular that many mental health practitioners placed all types of anxiety-related conditions in this broad category. Sigmund Freud (1856–1939) objected to this tendency, writing: "It can be nothing but a gain to neuropathology if we make an attempt to separate from neurasthenia proper all those neurotic disturbances in which…the symptoms are more firmly linked to one another than to the typical symptoms of neurasthenia (such as intracranial pressure, spinal irritation, and dyspepsia with flatulence and constipation)" (Freud 1895/1962, p. 90). Freud went on to describe *anxiety neurosis*, a term first published in the 1895 paper, although he had used it in letters to Fliess 2 years earlier. Freud gave credit to Ewald Hecker (1893) for originating the concept (Freud was at first unaware of Hecker's paper), but Hecker had not gone so far as to discriminate between anxiety neurosis and neurasthenia, as Freud now was about to do. The clinical picture was composed, as Freud outlined, of the following elements: 1) general irritability; 2) anxious expectation (Freud gave an example of a woman who fears that her husband has pneumonia every time she hears him cough), which also may take the form of scrupulosity, pedantry, or doubting mania; 3) anxiety that is constantly lurking in the background; 4) rudimentary anxiety attacks; 5) waking up at night in a fright (pavor nocturnus); 6) vertigo; 7) phobias (*specific* fears) of snakes, darkness, vermin, and so forth but also agoraphobia; 8) digestive troubles; 9) paresthesias; and 10) chronic states, such as a constant feeling of lassitude (pp. 92–99).

Freud's description of anxiety neurosis was, as we can see from the list of its defining elements, a fairly broad concept. DSM-IV-TR (American Psychiatric Association 2000), for example, lists 13 anxiety disorders. Of these, panic attack (at least the type represented by pavor nocturnus), agoraphobia, specific phobia, and generalized anxiety disorder all would seem to fit within the borders outlined by Freud's "anxiety neurosis." Freud went on to disclose what he believed were the psychological underpinnings of the condition. In fact, all the various character disorders he and the psychoanalytic pioneers described may be seen as resting on a foundation of anxiety—now defined as a common but abnormal state, as distinct from fear, which requires no psychoanalytic uncovering to understand (i.e., fear of the tiger-in-the-room situation, which would be a universal and normal reaction). Still, the predominantly psychological explanation for anxiety neurosis was not universally accepted. The French neurologist Eduard Brissaud (1890), as Berrios and Link (1995) mentioned, could acknowledge that *anxiete* was cerebral in origin, but in his view, *angoisse* (here, to be understood as panic) was a brain-stem phenomenon—basically, a physical disorder expressing itself as a sensation of *suffocation* (in contrast to anxiety, which manifested itself as a feeling of *insecurity*).

The Early Twentieth Century

The tendency was still quite strong at the turn of the century and at the beginning of the twentieth century to assume that the main etiological factors behind anxiety were hereditary or strictly biological. Maurice De Fleury (1897), for example, divided the emotions into two groups: "Doubt, humility, sloth, fearfulness, sadness and pity are symptoms—to varying degrees—of cerebral exhaustion; Pride, foolishness, anger, egoism, courage, heroism, and cruelty are the manifestations of exaltation of the spirit" (p. 317) (my translation). Freud's original concept of anxiety also shared this notion that energy played a key role: dammed-up libido from ungratified drives led to an excess of energy accumulating in the nervous system, manifesting itself as anxiety. This mechanistic and closed-system model (in keeping with the physics of the last decade of the nineteenth century) gave way two decades later, when Freud modified his theory, such that anxiety was no longer measured as so many discreet packets of (ill-distributed) energy but rather as a signal warning (involving very little actual energy) of a threat to one's equilibrium and well-being.

The distinction between fear and anxiety (made, as Pichot [1990] pointed out, in the middle of the nineteenth century by Sören Aabye Kierkegaard [1813–1855]) was emphasized once again by Karl Jaspers (1913). Several varieties of anxiety disorder that had for many years been neglected began to receive attention. What we now call *social phobia*—the opposite side of the coin of avoidant personality (because anxiety is what the avoidant person would experience if forced into social situations)—was alluded to by other terms in earlier writings. Berrios and Link (1995) mentioned Hippocrates and Richard Burton in this connection. Paul Hartenberg (1901) wrote of *timidity*, a concept paralleling that of social phobia. Hartenberg singled out heredity, social or psychological defects, and (maladaptive) learning as contributing factors. Hartenberg was a student of Theodule Ribot (1839–1916), as was the prolific and long-lived Pierre Janet (1859–1947).

Janet was the founder of French dynamic psychiatry. Ribot had been the chairman of the department of experimental psychology at the College de France. Janet, in contrast, was less interested in either experimental methods or in statistics and pursued instead a more clinical path. Janet helped his patients to express the "fixed ideas" that he saw as the source of much of their psychological distress. Feelings, for Janet, were secondary mental states that guided the expression and termination of behaviors. Their effectiveness depended on their "energy" and on one's integrative capacity. Too little energy or too little integrative capacity led to a failure of feelings and to the emergence of primitive behaviors. Anxiety and *angoisse* were the main manifestations of such failure. In his book, Janet (1926) spoke of *tendencies* rather than of drives; also, he described "psychological tension": the capacity of a person to use his or her energy on some more or less elevated level (akin to the psychoanalytic concept of *sublimation*). According to Janet, a person's "dynamism" depended on the quality and quantity of this energy rather than on the conflicts and their respective forces that Freud placed at the center of his dynamic model.

Janet's case descriptions focus primarily on the here-and-now: the patient's current situation and feelings; only rare allusions are made to the details of early childhood and to the influence those early events may have had on the shape of the patient's anxious symptoms. In his 1926 book, however, Janet discussed at length the case of "Madelaine," a single, 40-year-old woman from a well-to-do family. It is quite possible that Madelaine represents a case of severe anxiety for which the predisposing factors were almost entirely constitutional. In addition to being episodically depressed since adolescence and experiencing obsessions with a delusional force, she was physically handicapped. We could not fault Janet for leaving us in the dark about conflictual or dynamic factors in her early family life—if these were absent or negligible. But Janet's description points out what is so often a tantalizing situation in case histories of anxious patients. Clinicians without a psychoanalytic background too often omit what may be crucial from a family dynamic standpoint. Equally true, psychoanalytic writers too often omit sufficient mention of possible hereditary and constitutional factors. The "complete picture" remains elusive. In any event, just as the experimentalist Ribot influenced the more descriptively oriented Janet, Janet influenced the great psychopharmacologist Jean Delay (1907–1987), whose work (and that of his successors) has brought us closer to an understanding of the neurochemical correlates of anxiety. The work of Delay, Deniker, and Pichot in the 1950s also helped validate the separateness of anxiety and depression, developing along the way anxiolytics and antidepressants (Delay and Deniker 1952).

Other notable work in the area of anxiety disorders in the early twentieth century includes that of Ribot (1896, 1911), who made clearer distinctions than were previously available between generalized anxiety disorder ("pantophobia") and the specific phobias of various

objects and animals. The major theoretician of behavior therapy, Burrhus Frederick Skinner (1904–1990), explained anxiety as a manifestation of conditioned response to some feared situation (1938). The English analyst Wilfred Bion (1897–1979) understood the developing infant as experiencing from birth a series of "psychotic" anxieties in relation to his or her primary caregivers—anxieties that can be reactivated later in various group situations. Bion (1967) had received his inspiration from Melanie Klein (1882–1960), who speculated (1975) that infants went through depressive and paranoid "positions" during early development. The problem with Kleinian theory with regard to anxiety is that it confuses substantive with substance. The infants' reactions are perhaps analogous to certain reactions of adult patients with a depressive or paranoid psychosis. But, as has become clearer through contemporary research in psychobiological psychiatry, the "chemistry" of psychotic patients and that of nonpsychotic infants or children is by no means the same. A similar problem confronts us when we examine the theoretical model of Harry Stack Sullivan (1892–1949). Sullivan saw anxiety as the "basic symptom" underlying all forms of psychopathology. Today, we feel that this is an overstatement. Most patients with severe psychiatric disorders do report more than their share of anxiety. But at the turn of this century, we are beginning to understand the biological correlates of intense anxiety and how certain "harm-avoidant" persons, in Cloninger's (1986) language, are temperamentally (i.e., innately) more prone to experience anxiety than are other people (e.g., persons with an "anxious-fearful cluster" personality). At the other end of the spectrum are persons with antisocial, especially psychopathic, personalities who are less prone to experience anxiety. Perhaps in the twenty-first century psychiatric advances will allow both the overly anxious and the not anxious enough to meet somewhere in a more comfortable middle ground. Likewise, we can hope that the various theories and practices concerning anxiety will be better integrated.

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2

Classification of Anxiety Disorders

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With the publication of DSM-IV (American Psychiatric Association 1994), 12 anxiety disorder categories now exist in the formal nomenclature: panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, social phobia, specific phobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder, and anxiety disorder not otherwise specified. A thirteenth category, mixed anxiety-depressive disorder, was considered for inclusion in DSM-IV but currently resides in the appendix of disorders in need of further study as a possible addition to DSM-V (Zinbarg et al. 1994). In addition to the creation of three new categories (acute stress disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder), the definitions of existing categories underwent numerous revisions in DSM-IV. Table 2–1 summarizes these revisions and provides an overview of key diagnostic features for the major anxiety disorder categories.

DSM-IV perpetuates the steady increase in the number of categories across its preceding editions and in other major classification systems for mental disorders (e.g., ICD-10; World Health Organization 1992). For instance, DSM-IV includes 12 anxiety disorders, whereas DSM-II (American Psychiatric Association 1968) included only 3 categories. This increase could be viewed as corresponding to expanding cumulative knowledge of the nature of psychopathology and in the classification of disorders. However, many researchers (e.g., Andrews 1996; Tyrer 1989) have expressed concern that the expansion of our nosologies has come at the expense of less empirical consideration of shared or overlapping features of emotional disorders that, relative to unique features of specific disorders, may have far greater significance in the understanding of the prevention, etiology, and course of disorders and in predicting their response to treatment.

Moreover, this expansion has led to questions of compromised discriminant validity; namely, whether our current classification systems are erroneously distinguishing symptoms and disorders that, in reality, are inconsequential variations of broader syndromes. For instance, many anxiety disorders share constituent *processes* (e.g., apprehension of situations or objects, protective or anxiety-reducing actions) and differ primarily (or solely) at the descriptive level in *content* or *focus* of apprehension (e.g., worry about rejection or embarrassment in social phobia, worry about contamination in obsessive-compulsive disorder, worry about several daily matters in GAD) or in the *form* of protective action (e.g., situational avoidance in agoraphobia, special phobia, and social phobia; compulsions in obsessive-compulsive disorder; safety behaviors in all anxiety disorders). Similarly, virtually all current cognitive-behavioral treatments of anxiety disorders contain the elements of exposure (situational, imaginal, and/or interoceptive), cognitive therapy, and between-sessions practice, varying primarily in content and process. Although differentiation may be helpful in conveying information about the

TABLE 2–1. Overview of key features and changes to the definitions of major anxiety disorders introduced in DSM-IV

Disorder	Key feature(s)	Changes in DSM-IV
Panic disorder	Recurrent, unexpected panic attacks	Elimination of panic severity specifiers (mild, moderate, severe)
	Persistent worry/concern about additional attacks or their consequences	Introduction of a panic typology (unexpected, situationally bound, situationally predisposed)
		"Recurrent" replaces requirement of history of at least four panic attacks in a 1-month period
		Increased emphasis on cognitive features (e.g., worry about panic, cognitive misappraisals)
		Criterion of "significant change in behavior related to the attacks" for coverage of "nonfearful panic disorder"
Panic disorder with agoraphobia	Meets criteria for panic disorder	See panic disorder
	Agoraphobia: fear/avoidance of situations in which panic attacks might occur	Elimination of agoraphobia severity specifiers (mild, moderate, severe)
Social phobia	Marked fear/avoidance of social situations because of possibility of embarrassment or humiliation	Diagnosis permitted in presence of unexpected panic attacks, if attacks confined to social situations (i.e., situationally predisposed attacks)
Specific phobia	Fear/avoidance of circumscribed objects or situations (e.g., heights, enclosed places, receiving injections)	Introduction of phobia types (animal, natural environment, situational, blood-injury-injection, other)
		Diagnosis permitted in presence of unexpected panic attacks, if attacks confined to phobic situation/object
		Previously named "simple phobia"
Generalized anxiety disorder	Chronic excessive, uncontrollable worry about a number of events or activities (e.g., job performance, finances)	Criterion of uncontrollable worry
		"A number of events or activities" replaces requirement of two or more worry spheres
		List of associated symptoms reduced from 18 to 6, primarily via elimination of autonomic symptoms
		Replaces category of "overanxious disorder" as a child/adolescent diagnosis
Obsessive-compulsive disorder	Recurrent, intrusive thoughts, images, or impulses (e.g., excessive doubting, thoughts of contamination)	Recognition of mental/covert compulsions
	Repetitive behaviors or mental acts aimed at reducing distress or to "neutralize" an obsession	Inclusion of differential diagnostic criterion involving boundary of obsessions and chronic worry
		Introduction of "with poor insight" specifier for cases in which obsessions and compulsions not recognized as excessive or unreasonable
Posttraumatic stress disorder	Persistent reexperiencing (e.g., dreams, flashbacks), distress, and avoidance of stimuli associated with prior exposure to extreme stress (e.g., rape, combat)	Traumatic event criterion revised to require subjective response (intense fear, horror, helplessness)
		Introduction of course specifier (acute, chronic)
		Introduction of a new category, acute stress disorder, for coverage of short-term extreme stress responses emphasizing dissociative symptoms

nature of the disturbance, the empirical question is whether these manifestations are sufficiently distinct (e.g., beyond variations in content) to warrant separation. The intent of this chapter is to review issues, extant empirical evidence, and future research directions bearing on the validity of the anxiety disorder categories.

Do the Anxiety Disorders Have Poor Discriminant Validity?

As noted in the previous section, the steady rise in the number of anxiety disorder diagnoses has led to questions about the discriminant validity of these categories. Findings of unfavorable diagnostic reliability (interrater agreement) and a high rate of co-occurrence of the anxiety and mood disorders are frequently cited as evidence in support of these concerns. Because most studies to date have approached these issues at the descriptive and diagnostic levels, diagnostic reliability and comorbidity data alone do not allow for firm conclusions about the extent or nature of overlap among the anxiety disorders (Brown and Chorpita 1996). Nevertheless, although alternative explanations are plausible (see the following sections), evidence of unsatisfactory reliability and high comorbidity among diagnoses is consistent with the hypothesis that the anxiety disorders do not represent distinct entities. In addition, data indicating that a wide range of emotional disorders respond similarly to the same psychosocial or medication treatment and evidence that the neurobiological underpinnings of these conditions often overlap have suggested that the similarities among diagnoses outweigh their differences.

Diagnostic Reliability

Diagnostic reliability refers to the extent to which two (or more) independent raters or interviewers agree on the presence or absence of a given diagnosis. The approach to studying diagnostic reliability of the anxiety disorders usually has taken one of two forms—test-retest or simultaneous—both involving the use of structured clinical interviews such as the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV; Di Nardo et al. 1994) and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al. 1996):

1. *Test-retest:* on two separate occasions, the patient is interviewed by different independent evaluators (e.g., Di Nardo et al. 1993, 1995).
2. *Simultaneous:* a diagnostic interview is video- or audiotaped and rated by an independent evaluator (e.g., Riskind et al. 1987; Skre et al. 1991).

In both approaches, the most widely used index of interrater agreement is the kappa statistic (κ; Fleiss et al. 1979), which ranges in value from 0 (poor agreement) to 1 (perfect agreement). Clearly, the strategy of interviewing patients on separate occasions is the more stringent approach to estimating diagnostic reliability because it introduces several potential sources of disagreement not found in the single-interview method (e.g., variation in patient report, change in clinical status). Although these issues could be viewed as limitations of this approach, the single-interview method also has been criticized for its potential of providing an overly optimistic estimation of diagnostic reliability (e.g., the independent evaluator's judgments may be strongly influenced by the nature and extent of follow-up questions asked by the initial interviewer; the evaluator may not address the short-term stability in symptoms or in patient report); these factors may bear on confidence in judgments of the presence or absence of a DSM diagnosis (Segal et al. 1994).

Although large-scale reliability studies on the DSM-IV anxiety and mood disorder categories are still in progress (e.g., Di Nardo et al. 1995), data based on DSM-III-R (American Psychiatric Association 1987) definitions suggest that these diagnoses are associated with differential levels of agreement (Di Nardo et al. 1993; Mannuzza et al. 1989; Williams et al. 1992). Results of three large-scale studies of the DSM-III-R anxiety and mood disorders are summarized in Table 2–2 for current diagnoses. All three studies used the test-retest method but differed on the structured interview used; Di Nardo et al. (1993) used the Anxiety Disorders Interview Schedule—Revised (ADIS-R; Di Nardo and Barlow 1988); Mannuzza et al. (1989) used the Schedule for Affective Disorders and Schizophrenia—Lifetime Anxiety version (SADS-LA; Fyer et al. 1985); and Williams et al. (1992) used the SCID. Based on guidelines often used in the interpretation of kappa ($\kappa \geq 0.75$, excellent agreement; $\kappa = 0.60$–0.74, good agreement; $\kappa = 0.40$–0.59, fair agreement; $\kappa < 0.40$, poor agreement; Shrout et al. 1987), results indicated that categories such as panic disorder with agoraphobia and obsessive-compulsive disorder had good to excellent reliability in at least two of the studies. However, certain categories (e.g., GAD, dysthymia) were associated with fair agreement at best.

Analyses of the sources of diagnostic disagreements indicate that the factors contributing to unreliability are wide-ranging (Chorpita et al. 1998b; Di Nardo et al. 1995; Mannuzza et al. 1989). The most prevalent reason for disagreements across studies has been "information variance" (patients provide different information to the two interviewers), a source that accounted for fully 51% of the discrepancies in the Mannuzza et al. (1989) study. Interviewer error has

TABLE 2–2. Summary of interrater reliability studies for DSM-III-R anxiety and mood disorders

	Di Nardo et al. (1993)		Mannuzza et al. (1989)		Williams et al. (1992)	
	n	κ	*n*	κ	*n*	κ
Panic disorder	44	.39	53	.79	—	—
Panic disorder with agoraphobia	53	.71	34	.81	35	.58[a]
Generalized anxiety disorder	108	.53	11	.27	8	.56
Social phobia	84	.66	51	.68	23	.47
Simple phobia	47	.63	30	.29	20	.52
Obsessive-compulsive disorder	24	.75	13	.91	27	.59
Posttraumatic stress disorder	8	.55	—	—	—	—
Major depression	46	.55	—	—	121	.64
Dysthymia	25	.35	—	—	23	.40

Note. *n* = number of cases in which diagnosis was assigned by one or both raters; κ = kappa; all kappas pertain to current clinical diagnoses (collapsing across principal and additional diagnoses).
[a]Panic disorder and panic disorder with agoraphobia were collapsed under the same category in this study.

been identified as another common source of disagreement (e.g., 26% in Mannuzza et al. 1989). In a reanalysis of the sample (*N*=267) originally reported on by Di Nardo et al. (1993), Chorpita et al. (1998b) identified three factors that were significantly associated with diagnostic unreliability: 1) presence or absence of additional diagnoses (comorbidity), 2) severity of disorder, and 3) presence or absence of overt defining symptoms (e.g., compulsions, phobic avoidance). Specifically, kappa statistics were significantly lower in cases involving more than one diagnosis, lower clinical severity, and no overt symptoms (e.g., presentations of obsessive-compulsive disorder with obsessions only).

The sources of unreliability identified by Chorpita et al. (1998b) correspond to important issues and problems in the classification of emotional disorders. The fact that clinical severity was significantly associated with unreliability (i.e., disagreements as to whether presenting symptoms are above or below the DSM threshold) speaks to the purely categorical approach of current classification systems. If one assumes that the constituent features of disorders (or the disorder constructs themselves) are dimensional and operate along a continuum (e.g., Vredenberg et al. 1993), then a certain degree of measurement error will be inherent to the classification system that imparts a categorical cutoff (i.e., variability in symptom expression is collapsed on either side of the dichotomy). Many researchers have noted difficulties with this approach and have championed alternative systems that incorporate a dimensional component to classification (Frances et al. 1990).

In addition, Chorpita et al. (1998b) found that comorbidity was significantly linked to discrepancies in diagnostic judgments. When two or more potential diagnoses are present, the risk for disagreement is heightened by the fact that interviewers may not agree as to whether the features of one disorder should be subsumed under another disorder (e.g., do the symptoms of social anxiety represent a social phobia, or are they better accounted for by panic disorder with agoraphobia—i.e., fear of negative evaluation or of having a panic attack in public?). Indeed, this has been identified as a common source of diagnostic disagreement (Di Nardo et al. 1995) and pertains to another major issue concerning the potential poor discriminant validity among emotional disorders—their high rate of co-occurrence.

Diagnostic Comorbidity

Consistent evidence of high comorbidity among anxiety and mood disorders is frequently cited in support of skepticism about the distinguishability of the emotional disorders (Andrews 1990; Tyrer 1989). Comorbidity studies typically indicate that at least 50% of the patients with a principal anxiety disorder have one or more additional diagnoses at the time of assessment (e.g., Brawman-Mintzer et al. 1993; Brown and Barlow 1992; Sanderson et al. 1990b). Results from a large-scale study (*N*=468) of the DSM-III-R categories, with patients presenting to an anxiety disorders specialty clinic, are summarized in Table 2–3 (Brown and Barlow 1992). It is important to note that this study, like others, probably yielded conservative estimates of diagnostic co-occurrence because of limits in generalizability, such as the nature of inclusion and exclusion criteria used (e.g., active substance use disorders and presence of suicidality were exclusion criteria) and its outpatient setting. Nevertheless, comorbidity rates for many categories were quite high. For instance, consistent with other findings (e.g., Brawman-Mintzer et al. 1993), more than 80% of the patients with a principal diagnosis of GAD had at least one additional diagnosis. In the Brown and Barlow (1992) study, GAD was the most commonly occurring additional diagnosis as well. These findings, in tandem with evidence that GAD is associated with poor to fair diagnostic reliability (Di

TABLE 2–3. Percentages of additional diagnoses among patients with anxiety and mood disorders

	DSM-III-R principal diagnosis							
Additional diagnosis	**PD (*n*=35)**	**PDA (*n*=197)**	**SOC (*n*=76)**	**GAD (*n*=38)**	**OCD (*n*=25)**	**SIM (*n*=25)**	**MDD (*n*=13)**	**Overall[a]**
Any diagnosis	37	51	45	82	56	20	61	50
Anxiety disorders								
PD			4	18	0	0	8	6
PDA			5	18	12	4	15	9
SOC	6	13		29	24	0	23	14
GAD	20	30	17		4	8	23	23
OCD	3	1	1	3		0	15	2
SIM	3	7	9	16	4	8	0	7
Mood disorders								
MDD	9	12	11	11	12	4		11
DYS	3	6	13	18	28	0	0	9
MDD or DYS	11	17	20	29	40	4	0	18

Note. PD = panic disorder; PDA = panic disorder with agoraphobia; SOC = social phobia; GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder; SIM = simple (specific) phobia; MDD = major depressive disorder; DYS = dysthymia.
[a]Overall frequency in which category was assigned as an additional diagnosis.
Source. Adapted from Brown TA, Barlow DH: "Comorbidity Among Anxiety Disorders: Implications for Treatment and DSM-IV." *Journal of Consulting and Clinical Psychology* 60:835–844, 1992. Copyright © 1992 by the American Psychological Association. Used with permission.

Nardo et al. 1993; Mannuzza et al. 1989; Williams et al. 1992), contributed to the debate during the preparation of DSM-IV of whether GAD should be moved to the appendix containing disorders in need of future study because of the uncertainty about its status as a distinct syndrome (see Brown et al. 1994 for a detailed discussion of this issue).

However, in part because of their descriptive nature, comorbidity data alone do not have substantial implications for establishing or refuting the discriminant validity of the emotional disorder constructs. The multiple conceptual explanations for diagnostic comorbidity are sufficiently wide-ranging to either support or invalidate current nosologies and conceptualizations of emotional disorders (Blashfield 1990; Frances et al. 1990). Accounts for comorbidity that challenge current classification systems include the possibility that disorders co-occur in part because 1) they share overlapping defining criteria, or 2) they represent inconsequential variations of a broader underlying syndrome that has been erroneously separated by the classification system. In regard to the first explanation, for example, as currently defined by DSM-IV, the associated symptom criteria for GAD overlap almost entirely with the defining features of major depression and dysthymia (e.g., sleep disturbance, fatigability, concentration difficulties, restlessness). This overlap could contribute to findings of a differentially high comorbidity rate of GAD and mood disorders (e.g., Brown and Barlow 1992; Sanderson et al. 1990a), although DSM-IV attempts to adjust for this with a hierarchy rule stating that GAD should not be assigned if its features occur exclusively during the course of a mood disorder. The second explanation is akin to arguments that classification systems may have become overly precise to the point of artificial separation of broader disorders (Tyrer 1989).

Explanations for comorbidity that do not suggest problems in the current nosologies include the possibility that disorders co-occur in part 1) because of artifacts such as their base rates of occurrence in the study setting, 2) because they emerge from the same diathesis, and 3) because the features of one disorder act as risk factors for another disorder (e.g., severe agoraphobia leads to mood disturbance due to hopelessness, restricted mobility, etc.). An illustration of the first explanation is that after GAD (23%), social phobia (14%) was the most frequently assigned additional diagnosis in Brown and Barlow's (1992) study. This result may have been more a reflection of the fact that social phobia was a prevalent diagnosis in this clinic as opposed to reflecting a potential boundary problem with this category. The second explanation is intriguing in terms of its alignment with current theories of emotional disorders, which assert that anxiety and mood disorders emanate from shared genetic, biological, and psychosocial vulnerabilities (e.g., Barlow et al. 1996). By these accounts,

which are discussed in detail later in this chapter, a certain amount of co-occurrence among disorders would be presumed because of their shared etiological roots.

Nevertheless, other aspects of extant comorbidity findings maintain questions about the discriminant validity of anxiety and mood disorders. Recent findings indicate that psychosocial treatment of a given anxiety disorder results in a significant decline in other anxiety or mood diagnoses that are not addressed in treatment (Borkovec et al. 1995; Brown et al. 1995a). For instance, Brown et al. (1995a) examined the course of additional diagnoses in a sample of 126 patients who were enrolled in a short-term (11-session) psychosocial treatment program for panic disorder with minimal agoraphobic avoidance. At pretreatment, 26% of the patients had an additional diagnosis of GAD. The rate of comorbid GAD declined significantly at posttreatment to 7%; this rate remained low at 2-year follow-up (9%). Although it might be tempting to attribute this decline to factors such as treatment generalization (e.g., elements of the treatment, such as cognitive restructuring, were powerful enough to reduce symptoms of both panic disorder and GAD), evidence of the resiliency of GAD to current psychosocial and drug treatments mitigates the plausibility of such an explanation (Brown et al. 1994). Rather, other factors such as a lack of independence between disorders, random measurement error (e.g., diagnostic unreliability), and systematic measurement error (e.g., demand characteristics to overreport symptoms at pretreatment or underreport at posttreatment) (Brown and Barlow 1992) might better explain the sharp decline in GAD.

However, an interesting pattern of results was obtained when overall comorbidity was examined (i.e., collapsing across all additional diagnoses). In this analysis, a significant pre- to posttreatment decline in overall comorbidity was still evident—40% to 17%. At 2-year follow-up, however, the rate of comorbidity had increased to a level (30%) that was no longer significantly different from that of pretreatment. This was despite the fact that, in the aggregate, patients maintained or improved on gains for panic disorder across the follow-up interval, indicating considerable independence between panic disorder symptoms and overall comorbidity. Although these findings are based on descriptive data and are highly speculative, they could be interpreted in accord with the explanation for comorbidity and theoretical models stating that disorders emerge from the same vulnerabilities. Specifically, although cognitive-behavioral treatment was generally effective in ameliorating the symptoms and maintaining the processes of panic disorder, perhaps the intervention did not substantially reduce the general predispositional features (e.g., trait negative affect), which left patients vulnerable to the emergence or resilience of other disorders.

Treatment Response Nonspecificity

Although the ability to draw conclusions about the validity of a disorder based on its treatment response is limited, the fact that numerous disorders respond similarly to the same psychosocial or drug treatment has been cited as further evidence of their overlap (e.g., Hudson and Pope 1990; Tyrer et al. 1988). Findings that a wide range of emotional disorders (e.g., major depression, dysthymia, obsessive-compulsive disorder, panic disorder) respond similarly to antidepressant medications has been interpreted as indicating overlap or a shared pathophysiology among these syndromes (e.g., Hudson and Pope 1990). In one of the largest studies bearing on this issue to date, Tyrer et al. (1988) treated 210 outpatients with GAD, panic disorder, or dysthymia with one of the following five interventions: diazepam, dothiepin, placebo, cognitive-behavioral therapy, or a self-help program. Although some treatment condition differences were noted at posttreatment (e.g., diazepam was less effective than dothiepin, cognitive-behavioral therapy, and self-help), no diagnostic group differences were found. In view of the lack of diagnostic group treatment response differences, Tyrer et al. concluded that differential diagnosis of anxiety and mood disorders did not provide a sound basis for treatment prescription. However, these conclusions are limited by several issues, including the absence of long-term outcome data and the fact that the study did not use treatments developed specifically for the key and maintaining features of the disorders in question (e.g., Brown et al. 1993; Craske and Barlow 1993; Young et al. 1993).

Limitations of Extant Studies of the Classification of Emotional Disorders

Although the literature reviewed in this chapter thus far provides clues about boundary issues among disorders and the validity of current nosologies of emotional disorders, most of these studies have design problems that limit their contribution to this area. Indeed, most studies that bear on the validation of the classification of

anxiety and mood disorders have been conducted at the diagnostic level (e.g., family and twin studies) (Andrews et al. 1990; Kendler et al. 1992a) or have examined dimensional features within a diagnostic category (e.g., psychometric evaluations of constituent features within a DSM disorder) (Marten et al. 1993). As we have discussed at length elsewhere (Brown 1996; Brown and Chorpita 1996), the categorical approach to analysis has many limitations (Costello 1992; Livesley et al. 1994). For instance, studies conducted at the diagnostic level (e.g., comorbidity, genetic or familial aggregation, across-diagnosis comparisons) are restricted by their adherence to the disorders defined by the classification system (i.e., by using diagnoses as the units of analysis, researchers are implicitly accepting or are bound to the nosology they are evaluating). Moreover, analyses at the diagnostic level rely largely on data that do not reflect the dimensional nature of psychopathological phenomena. Categorization of dimensional variables usually forfeits meaningful information by artificially (and often erroneously) collapsing variability above and below an arbitrary threshold (e.g., presence or absence of a DSM-IV disorder). In addition to reducing statistical power and limiting the ability to detect more complex uni- or multivariate relationships, this categorization often unnecessarily introduces additional measurement error. In the Chorpita et al. (1998b) study reviewed earlier in this chapter, a common source of unreliability was interviewer disagreements of whether the features of a disorder met or surpassed the DSM threshold. In another clear example of this phenomenon, in the large-scale study of the diagnostic reliability of the DSM-III-R anxiety disorders, Di Nardo et al. (1993) found considerable unreliability for DSM severity specifiers for agoraphobia (i.e., mild, moderate, severe), a finding that influenced the decision to eliminate these specifiers in DSM-IV. This was despite the fact that the zero-order correlation of the first and second interviewers' dimensional ratings of agoraphobic avoidance was quite high (r=.81). Thus, whereas considerable concordance was observed at the dimensional level, error was inflated when categorization was imposed on these ratings.

Conversely, if assessment were conducted at the dimensional level, the interrelationships among symptoms and syndromes could be examined, as could the extent to which the latent structure of these features corresponds to that specified by major classification systems such as DSM-IV. Methods of structural equation modeling could be used to examine the cross-sectional and longitudinal covariation of these latent factors, adjusting for measurement error and an error theory (e.g., extracting shared method variance from relationships or paths of interest).

Classification studies addressing multiple domains and dimensional features are beginning to appear in the literature on emotional disorders (Brown et al. 1998; Spence 1997; Zinbarg and Barlow 1996). Spence (1997) examined the structure of anxiety symptoms in 698 children (aged 8–12 years) with confirmatory factor analysis of a questionnaire on the frequency of symptoms from six DSM-IV constructs: panic disorder, separation anxiety disorder, social phobia, specific phobia, obsessive-compulsive disorder, and GAD. Compared with competing models in which disorders were collapsed or factors were constrained to be orthogonal, the six-factor model provided a superior fit to the data. Although factorially distinct, the six disorder factors were highly intercorrelated (r=.67–.88). However, the considerable covariance in these latent factors was satisfactorily accounted for by a higher-order model in which the six disorder factors loaded significantly onto a single second-order factor. This higher-order model is consistent with the underpinnings of the DSM-IV nosology, which asserts that panic disorder, separation anxiety disorder, social phobia, specific phobia, obsessive-compulsive disorder, and GAD, albeit distinct, belong to a common family of disorders. This higher-order model was replicated in a second cohort and was found to be consistent across sexes and age groups. Although this research was limited to some degree by its use of a single self-report measure and a nonclinical sample and by its failure to include a depression factor (i.e., mood disorders may be highly overlapping with some anxiety disorders such as GAD), the results are nonetheless encouraging with regard to the correspondence of the obtained latent structure with the nosology outlined in DSM-IV.

A recent example in the area of adult anxiety disorders is a study by Zinbarg and Barlow (1996). In this study, an exploratory factor analysis of various questionnaires on features of anxiety disorders produced a factor structure that was largely consistent with the DSM-III-R nosology (i.e., social anxiety, generalized dysphoria, agoraphobia, fear of fear, obsessions and compulsions, simple fears). Support for DSM-III-R also was provided by discriminant function analyses indicating that selected diagnostic groups (defined by principal diagnoses established by structured interviews) had characteristic profiles in factor scores generated from a higher-order factor analysis. Although encouraging, as noted by the authors, these findings were

limited by factors such as the preponderant use of self-report measures (e.g., method variance could account in part for the structure observed) and the fact that mood disorders were poorly represented (i.e., depressive symptoms were assessed by a single measure with a scale under psychometric development). Again, this latter limitation is noteworthy given evidence that mood disorders (i.e., major depression, dysthymia) may pose greater boundary problems for certain anxiety disorders than do other anxiety disorders (Brown et al. 1995, 1998; D.A. Clark et al. 1994; Starcevic 1995).

Conceptual Models and Evidence of the Structure and Pathogenesis of Anxiety and Mood Disorders

Traditionally, dimensional studies of anxiety and depression have noted considerable overlap in these constructs. For instance, intercorrelations among widely used self-report measures (e.g., State-Trait Anxiety Inventory, Beck Depression Inventory) and clinical rating scales (e.g., Hamilton Anxiety Scale and Hamilton Rating Scale for Depression) of anxiety and depression typically have exceeded .70 (L.A. Clark and Watson 1991; Kendall and Watson 1989). These findings, in tandem with the aforementioned studies conducted at the syndromal level, have led investigators to question whether clinical anxiety and depression are in fact empirically distinct phenomena. L.A. Clark and Watson (1991) addressed this issue and concluded, on the basis of literature review, that although anxiety and depression share a significant nonspecific component encompassing general affective distress and other common symptoms, the two constructs can be distinguished by certain unique features. L.A. Clark and Watson (1991) proposed a tripartite structure of anxiety and depression consisting of

1. *Negative affect*—symptoms of general distress, such as worry, irritability, and tension
2. *Positive affect*—defined as the level of pleasurable engagement with the environment, and characterized by features such as cheerfulness, sociability, energy, and enthusiasm
3. *Autonomic hyperarousal*—characterized by symptoms such as rapid heart rate, shortness of breath, and trembling

As originally proposed, the tripartite model asserts that negative affect is a shared feature of anxiety and mood disorders (i.e., symptoms of tension, worry, irritability, and so on are present in both anxiety and depression). However, autonomic hyperarousal is viewed as specific to anxiety. Conversely, an absence of positive affect (anhedonia) is regarded as a feature that differentiates mood disorders from anxiety disorders.

Sophisticated studies have emerged in support of the tripartite structure in adult and child samples (e.g., Chorpita et al. 1998a; Joiner et al. 1996; Watson et al. 1995a), although much of this work has been conducted with analog samples or clinical samples in which anxiety and mood disorders were not highly represented (e.g., Watson et al. 1995b). Although the initial principal intent of the tripartite model was to delineate the shared and unique features of anxiety and mood disorders, subsequent research has suggested that this model may have considerable relevance to the understanding of the pathogenesis of these conditions. Specifically, although no compelling evidence has been obtained for autonomic arousal, findings suggest that negative affect and perhaps positive affect represent trait vulnerability factors for the development of emotional disorders. For instance, negative affect shows considerable temporal stability (e.g., 12-year test-retest correlations>.70); is strongly heritable; and as a higher-order factor, accounts for covariance or communality in lower-order symptom dimensions (e.g., Costa and McCrae 1988; Tellegen et al. 1988; Watson and Clark 1984; see Watson et al. 1994 for a review). Although developed independently, the constructs of negative affect and positive affect coincide to a considerable degree with trait vulnerability constructs of other leading theories such as those of Gray (1987), Eysenck (1970), and Barlow et al. (1996). For instance, negative affect is a construct similar to behavioral inhibition, neuroticism, and anxious apprehension in the Gray, Eysenck, and Barlow models, respectively. The construct of positive affect is similar to behavioral activation and extraversion in the Gray and Eysenck models, respectively. Autonomic arousal has been considered to reflect a manifestation of the fight-or-flight system of the Gray (1987) model (Barlow et al. 1996; Fowles 1995).

These conceptualizations of the pathogenesis of anxiety and depression may have a strong bearing on issues in the classification of emotional disorders. For instance, these models posit that anxiety and mood disorders arise from shared vulnerability dimensions, a claim that is in accord with a potential account for the high co-occurrence of these conditions (i.e., anxiety and mood disorders are comorbid partially because they emerge from the same etiological sources). Recent ge-

netic evidence is consistent with this position. For example, in a study of 1,033 blindly assessed female-female twin pairs, Kendler et al. (1992a) concluded that GAD is a moderately familial disorder, with a heritability estimated at about 30% (the remainder of variance in GAD liability may result from environmental factors not shared by the adult twins). Further research in both all-female (Kendler et al. 1992b) and mixed-sex twin samples (Roy et al. 1995) has indicated that a clear genetic influence exists in GAD, and the genetic factors in GAD are completely shared with major depression. In addition, anxiety and mood disorders have been considered to share biological vulnerabilities. Although several neurotransmitter systems (e.g., γ-aminobutyric acid [GABA]-benzodiazepine, noradrenergic, serotonergic) and areas of the limbic system of the brain (e.g., septal-hippocampal system) have been implicated (Cowley and Roy-Byrne 1991; Gray 1987), this common biological vulnerability may be best characterized as an overactive neurobiological response to stress (Barlow et al. 1996).

In addition to negative affect, other psychosocial vulnerability constructs have been construed to be shared by anxiety and depression (e.g., attributional style, perceptions of control) (Alloy et al. 1990; Barlow et al. 1996). These diatheses are considered to operate on a continuum from no mental disorder to anxiety disorder to mood disorder (e.g., helplessness in anxiety, hopelessness in depression) (Alloy et al. 1990). Accordingly, depression has been posited as reflecting "end-state" anxiety (Barlow et al. 1996); that is, clinical anxiety may progress to depression depending on the extent of one's psychological and biological vulnerabilities, the severity of current life stressors, and the coping mechanisms at one's disposal. Although awaiting empirical verification, these models may account for the temporal sequence of comorbidity often observed between anxiety and mood disorders.

Findings and conceptualizations of shared genetic, biological, and psychosocial vulnerability in anxiety and depression could be taken as further indication of the poor boundaries of these conditions. Nevertheless, empirical and conceptual accounts suggest that this may not be the case. For example, Kendler et al. (1992b) found that GAD and major depression share the same genetic factors but that their environmental determinants appeared to be mostly distinct. These findings are consistent with conceptual models of emotional disorders (e.g., Barlow et al. 1996) that view the anxiety and mood disorders as sharing vulnerabilities but differing on important dimensions (e.g., focus of attention, degree of psychosocial vulnerability arising from environmental experiences) to the extent that differentiation of these psychopathological phenomena is warranted. Biologically or genetically based traits such as negative affect and behavioral inhibition may underlie social phobia and panic disorder; whether one or both conditions become manifest from these diatheses could depend on environmental determinants such as direct experiences with social humiliation or scrutiny, vicarious exposure (e.g., parental modeling) to shyness or introversion, and hypochondriacal behavior. Although anxiety and depression seem to have common vulnerability dimensions, unique diatheses may exist as well (e.g., low positive affect in depression) (Brown et al. 1998; L.A. Clark et al. 1994).

In summary, evidence and predictions emanating from the tripartite model (L.A. Clark and Watson 1991), genetic and biological studies (e.g., Kendler et al. 1992b), and comprehensive theories of emotional disorders (e.g., Alloy et al. 1990; Barlow et al. 1996; Gray 1987) align with the position that although most of the constructs underlying the DSM-IV anxiety and mood disorders are relatively distinct (Brown et al. 1998; Spence 1997; Zinbarg and Barlow 1996), salient overlap exists in these categories. This overlap may include features such as negative affect and behavioral inhibition, which represent expressions of common genetic and biologically or psychosocially based vulnerability dimensions. Of course, alternative explanations also may account to varying degrees for the overlap and high comorbidity among emotional disorders (e.g., erroneous splitting of a trivial variations of a broad syndrome into two or more categories; unnecessary overlap in diagnostic criteria); thus, extensive research is needed to determine the validity of these positions.

For instance, the debate continues as to whether the DSM-IV diagnosis of GAD represents a distinct syndrome (Brown et al. 1994). Although studies indicate that GAD can be distinguished from other anxiety disorders on measures of worry and symptoms of negative affect and tension (for a review, see Brown et al. 1994), this often has not been the case when GAD is compared with major depression and dysthymia (e.g., Brown et al. 1995b; Starcevic 1995). Indeed, emerging evidence of the poor discriminability of indices of worry and associated symptoms suggests that the mood disorders may pose greater boundary problems for GAD than do other anxiety disorders. Nevertheless, these findings could be viewed as being consistent with the tripartite model of anxiety and depression (L.A. Clark and Watson 1991). That worry and the associated symptoms of

DSM-IV GAD are considered symptoms of negative affect may explain why GAD and mood disorders cannot be differentiated on these features. Specifically, although negative affect is present to varying degrees in all anxiety and mood disorders, its level is highest in GAD and the mood disorders (Brown et al. 1998).

Similarly, although symptoms of autonomic arousal are posited by the tripartite model to be specific to anxiety disorders, this appears not to be true for GAD. Autonomic arousal symptoms (e.g., accelerated heart rate, shortness of breath) are endorsed with relatively low frequency by patients with GAD and are less correlated to measures of worry compared with symptoms of tension, negative affect, and so on (Brown et al. 1995b; Marten et al. 1993). Moreover, laboratory studies indicate that patients with GAD respond to psychological stress with autonomic suppression and inflexibility (Borkovec et al. 1993; Hoehn-Saric et al. 1989). Thus, unlike in other anxiety disorders such as panic disorder, autonomic arousal symptoms may not differentiate GAD from mood disorders. However, in accord with the tripartite model, emerging data suggest that GAD can be differentiated from depression on indices of low positive affect, although this distinction may be stronger for other disorders than for GAD (Brown et al. 1998). Nevertheless, the numerous similarities between GAD and the mood disorders have led some researchers to conclude that GAD represents a variant of or prodrome to depression. As noted earlier, DSM-IV acknowledges this boundary issue with the hierarchy rule, specifying that GAD should not be diagnosed if its features occur exclusively during a mood disorder.

The overlap of GAD with other emotional disorders also has been addressed by current conceptual models. For instance, Barlow (1988) referred to GAD as the "basic" anxiety disorder because its core features may represent the fundamental predispositional or maintaining processes (anxious apprehension, negative affect) of all emotional disorders. In addition to its association with high levels of negative affect, GAD usually has an early onset and precedes the disorders with which it co-occurs (Garvey et al. 1988; Nisita et al. 1990). Thus, a potential explanation for the high comorbidity rate associated with GAD (exceeding 80%; Brawman-Mintzer et al. 1993; Brown and Barlow 1992) is that its constituent features contribute to the predisposition for the development of other anxiety and mood disorders. Furthermore, studies have found that GAD is resilient to psychosocial and pharmacological interventions, a result that could be construed as consistent with a characterological or vulnerability conceptualization of this disorder (Sanderson and Wetzler 1991).

These arguments require empirical evaluation. Although GAD may indeed be best conceptualized as a trait or a general vulnerability (as opposed to an Axis I disorder), a substantial literature supports the construct and discriminant validity of the disorder. Yet, if negative affect and worry are vulnerability dimensions, the question remains as to why these characteristics act as a predisposition to other disorders for some persons (e.g., a prodrome to mood disorders), whereas these dimensions become sufficiently prominent to require a separate diagnosis (i.e., GAD) and a specialized treatment for others. From a purely classification standpoint, studies are needed to examine the relations and discriminability of the DSM-IV disorder constructs with key vulnerability dimensions (e.g., tripartite model constructs).

Although these issues would be best studied in longitudinal designs in which the extent of covariation and directionality of the relations of disorder and vulnerability constructs could be evaluated over time, a cross-sectional study of this nature recently examined the structural relations of dimensions of selected emotional disorders and dimensions of the tripartite model constructs (Brown et al. 1998). In a sample of 350 patients with DSM-IV anxiety and mood disorders who were assessed by a variety of questionnaires and clinician ratings, a confirmatory factor analysis of the latent structure of dimensions of key features of selected DSM-IV disorders (i.e., mood disorders, GAD, panic disorder/agoraphobia, obsessive-compulsive disorder, social phobia) supported the discriminant validity of DSM-IV for the five constructs examined. Relative to models that collapsed across all or various disorders, the five-factor model (i.e., mood disorders, GAD, panic disorder/agoraphobia, obsessive-compulsive disorder, social phobia) provided the best fit for the data. Notably, model fit was degraded significantly when indicators of GAD and mood disorders were collapsed into a single factor, thereby lending support for the differentiation of these features. However, the GAD latent factor was most strongly correlated with the mood disorder latent factor (r=.63), supporting contentions that the features of GAD have the most overlap with the mood disorders.

Also, this study comparatively evaluated several structural models of the relations among the five DSM-IV disorder latent factors and the three latent factors corresponding to the tripartite model of anxiety and depression (i.e., negative affect, positive affect, autonomic

arousal). Consistent with the tripartite model, superior data fit was associated with a model that specified negative affect and positive affect as higher-order factors to the DSM-IV disorder factors (with significant paths from negative affect to each of the five DSM-IV factors and significant paths from positive affect to the mood disorder and social phobia factors only) and that specified autonomic arousal as a lower-order factor (with significant paths from panic disorder/agoraphobia and GAD to autonomic arousal). For instance, all paths from negative affect to the DSM-IV disorder factors were statistically significant, in accord with predictions that negative affect is a shared and potentially dispositional feature of emotional disorders, which accounts for communality among them (i.e., the considerable zero-order correlations among DSM-IV disorder factors were well accounted for by negative affect and for two disorders by positive affect). Yet, the strongest paths from the higher-order factor, negative affect, to the various DSM-IV factors were to GAD and mood disorder (path coefficients = .74 and .67, respectively), consistent with arguments and evidence discussed earlier that GAD and depression are associated with the highest levels of negative affect.

Other noteworthy findings from the Brown et al. (1998) study included results involving the structural relations of the DSM-IV disorder factors and the latent factor of autonomic arousal. Counter to prediction and the tripartite model, paths from the DSM disorder factors obsessive-compulsive disorder and social phobia to autonomic arousal were nonsignificant. These results suggest that, although generally unrelated to mood disorders (i.e., results indicated no improvement in model fit with the addition of a path from depression to autonomic arousal), autonomic arousal symptoms may be weakly related to or of less discriminant value for certain anxiety disorders (e.g., discrete social phobias). Accordingly, the current findings highlight a possible refinement of the tripartite model with regard to autonomic arousal. Although autonomic arousal initially had been posited to be a discriminating feature for the entire range of anxiety disorders, these data suggest that the relevance of autonomic arousal may be limited to primarily panic disorder/agoraphobia. This interpretation is in accord with recent reconsiderations of the tripartite model (Mineka et al. 1998), which also now acknowledges the consistent finding of an association between positive affect and social phobia (Brown et al. 1998; Watson et al. 1988). Specifically, the unique relation of social phobia to positive affect relative to the other anxiety disorders has been interpreted as being based on the interpersonal character of low positive affect (e.g., low self-confidence, unassertiveness) (L.A. Clark et al. 1994).

Another interesting finding regarding the construct of autonomic arousal was the statistically significant negative path from GAD to autonomic arousal. In addition to aligning with the results of laboratory studies indicating that the features of GAD (i.e., excessive worry) are associated with autonomic suppression, this finding may point to another distinguishing characteristic of GAD relative to other anxiety disorders (although this distinction could be primarily limited to panic disorder because many other anxiety and mood disorders, although not linked to autonomic suppression, may be characterized by low autonomic arousal).

Directions for Future Research

The principal position outlined in the preceding section was that overlap in anxiety and mood disorders, although reflective of nosological concerns to varying degrees (perhaps with regard to GAD, in particular), may provide important clues to the understanding of the origins and maintenance of these syndromes. This position is consistent with one potential explanation of comorbidity that high co-occurrence of disorders at the descriptive level is the result of their common etiological roots. Clearly, these hypotheses await sophisticated, hypothesis-driven research. Several suggestions have been made throughout this chapter as important refinements for future research on the classification of emotional disorders. These suggestions included 1) increased emphasis on dimensional measures of psychopathological phenomena and disorders to better elucidate the latent structure and interrelationships of these features (which also mitigates the problem of being bound to the existing nosology if disorders are studied at the diagnostic level); 2) greater use of structural equation modeling approaches to data analysis, which have the advantages of adjusting for measurement error and an error theory, fostering statistical comparisons of models reflecting competing theories of classification or causality (e.g., models emanating from competing explanations for diagnostic comorbidity; Blashfield 1990; Frances et al. 1990), and evaluating paths or relations only in the context of good model fit (Bollen 1989); 3) increased within-study focus on a wider range of disorders given that issues pertaining to overlap and pathogenesis cut across the classes of syndromes (chapters) outlined in DSM-IV (e.g., although residing in

separate chapters in DSM-IV, potential boundary issues exist across the anxiety, mood, somatoform, and personality disorders); and 4) incorporation of multiple measures associated with theoretically salient vulnerability dimensions (e.g., negative affect, behavioral inhibition, perceived control) to examine issues such as the (differential) prediction of the emergence of diagnostic syndromes and the extent to which the defining features of emotional disorders overlap with these traits (e.g., are the features of GAD best subsumed under these traits, consistent with arguments that GAD simply reflects a nonspecific symptom or trait, or does GAD represent a distinct latent factor that, like other anxiety and mood disorders, is influenced by these higher-order traits?). This latter focus also would address suggestions made by researchers for increased empirical consideration of the common traits of emotional disorders that may hold strong predictive value to the prevention, etiology, course, and treatment response of emotional disorders.

It is hoped that these methodological refinements will be increasingly applied to two other important avenues of classification and pathogenesis research—genetic and longitudinal studies. Greater emphasis on dimensional assessment of psychopathology (e.g., latent disorder constructs) in twin studies, in tandem with the use of structural equation modeling approaches that are well entrenched in the behavioral genetics literature (Boomsma et al. 1989), could lead to important advances beyond evidence on the heritability and familial aggregation of disorders focused at the diagnostic (categorical) level (i.e., estimates of genetic liability are influenced by heightened measurement error and mitigated statistical power associated with collapsing dimensional variability above and below the DSM threshold). Increasingly, genetic studies of this nature are emerging in the literature (e.g., Kendler et al. 1987).

In addition, important potential avenues for longitudinal research include 1) study of at-risk or large nonclinical samples to identify the contribution of dimensions implicated as vulnerability factors (e.g., negative affect) in the prediction of emotional disorders (and whether these higher-order traits are more explanatory than vulnerability constructs suggested to be disorder-specific; e.g., cognitive vulnerabilities of depression, obsessive-compulsive disorder; Ingram et al. 1998; Salkovskis 1996); and 2) large-scale clinical studies addressing issues such as the temporal stability and covariation of disorders and their underlying constructs. This methodology is crucial to the better understanding of the direction of the relations among disorders and potential vulnerability constructs (e.g., theory-driven tests of selected conceptual accounts for comorbidity, such as the features of a disorder, serve as risk factors to another disorder). For instance, whereas the findings of Brown et al. (1998) were consistent with positions of the tripartite model that negative affect operates as a higher-order trait, the cross-sectional nature of this study precluded conclusions about the direction and the possible reciprocal nature of these relations. These questions await longitudinal study.

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3

Preclinical Models of Anxiety

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Many animal models of anxiety have been developed for two major purposes: to screen compounds for potential anxiolytic activity and to study the neurobiology of anxiety. One problem that arises when using animal models to study anxiety is the diversity of human anxiety disorders. In DSM-IV-TR (American Psychiatric Association 2000), generalized anxiety disorder (GAD), panic disorder, obsessive compulsive disorder (OCD), specific phobia, social phobia, and posttraumatic stress disorder (PTSD) are considered as separate diagnostic entities, and what conditions the different animal models correspond to is a matter of controversy. There is considerable comorbidity both among some of the anxiety disorders and between the anxiety disorders and the affective disorders. Both genetic and environmental factors are believed to play a role in the pathophysiology of most anxiety disorders.

One basic criterion a laboratory test for anxiety should fulfill is the ability to discriminate between drugs that are clinically effective in the treatment of anxiety disorders and those that are not. Moreover, a test should be able to detect agents that are known to be anxiogenic in humans. Indeed, most tests were developed on the basis of the effects of benzodiazepines and barbiturates. However, because many tests have failed to detect an anxiolytic action of partial serotonin type 1A (5-HT_{1A}) receptor agonists (i.e., buspirone and the related compounds gepirone, ipsapirone, and tandospirone), investigators have questioned whether these tests are valid models for anxiety or, alternatively, screening tests for benzodiazepines and related compounds.

In clinical trials, buspirone shows efficacy equal to that of benzodiazepines in the treatment of GAD. However, the onset of action of buspirone is much slower than that of the benzodiazepines, and the anxiolytic effects of buspirone are not clinically apparent until after several weeks of treatment have elapsed. This suggests that the anxiolytic action of buspirone is mediated through neurochemical changes in brain that develop after repeated administration of the drug rather than by its acute mechanism of action. Thus, the lack of an anxiolytic action of partial 5-HT_{1A} receptor agonists reported in several anxiety models may in part be a result of the fact that most investigators have studied the effects of such drugs only after acute administration. Several antidepressant drugs are also effective in the treatment of anxiety disorders, but several weeks of treatment are required before clinical improvement is observed. Thus, in this chapter, only the effects of chronic treatment with 5-HT_{1A} receptor agonists and antidepressant drugs in different anxiety models are included.

In this chapter, we include conditioned models, ethologically based models, and genetic models. We

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also include two models—adversely reared primates and maternal deprivation—that we have designated etiologically based models. Accumulating data from studies that used these models strongly indicate that they constitute valid animal models to study anxiety. The genetic and etiologically based models probably provide particularly good animal models to study the pathophysiology of anxiety because the animals show permanently increased anxiety, which may better reflect the chronic state of human anxiety disorders than the acute anxiety elicited in conditioned or ethologically based models. The paradigms that are included in this chapter are models that are generally considered to model GAD. Animal models specifically developed to study other anxiety disorders are not discussed here, and the reader is referred to other comprehensive reviews (e.g., Koob et al. 1998; Lister 1990).

Conditioned Models: Operant Conflict Tests

The operant conflict test is one of the most commonly used animal models of anxiety. This test was developed by Geller and Seifter (1960) and is therefore often referred to as the *Geller-Seifter test.* It is based on the approach-avoidance test of Masserman and Yum (1946). Approach behavior is induced by stimulating ingestive behavior by food deprivation but simultaneously reduced by punishment (an aversive event such as electric shock), which induces conflict in the animal. The conflict paradigm consists of two components in which freely moving rats are trained to press a lever for food reward. In one component, lever-pressing is reinforced with food after a variable interval of time (i.e., the "unpunished" period). In the second component, a short signal (a tone or a light) precedes the delivery of a mild electric shock in conjunction with food reward (i.e., the "punished" period). After several weeks of training, the animal presses the lever much less frequently when the signal is on because it is assumed that the animal is anxious about the impending delivery of the shock. Thus, the anxiety in this model is conditioned. Both benzodiazepines and barbiturates increase the response during the punished period (also called *anticonflict effect*); that is, the animal accepts significantly more electric shocks, which is taken to reflect anxiolytic properties of the drug under study (for reviews, see Iversen 1980; Pollard and Howard 1990). Modification of the Geller-Seifter paradigm by using incremental shock levels beginning at zero has provided a distinct improvement over the original paradigm and is most often used today. With this paradigm, drug effects were qualitatively similar to those reported with the original procedures.

A variant of the Geller-Seifter model of anxiety is Vogel's conflict test (Vogel et al. 1971). In this test, water-deprived naive animals are placed in an experimental chamber with a water tube, allowed to drink briefly, and then periodically punished with electric shocks for licking water, thus suppressing licking behavior. Benzodiazepines and barbiturates reverse this suppression. The advantage of this model over the Geller-Seifter test is that it is faster, is simpler, and does not involve training of animals. However, Vogel's original conflict test used unconditioned suppression of drinking and could not distinguish nonspecific effects, such as sedation or ataxia, which confounded the interpretation of the results. Consequently, this model has been further modified by the inclusion of an unpunished responding component and a tone signaling the onset of the shock, as well as training of animals to stable baselines (Ford et al. 1979). This model is often referred to as the *conditioned suppression of drinking* test. Comparisons with the Geller-Seifter test found that this test is equally sensitive to the antianxiety properties of benzodiazepines and barbiturates. In the remainder of the discussion, the effects of various drug treatments that use the Geller-Seifter test, Vogel's conflict test, or conditioned suppression of drinking test are described together.

Treatment with clinically effective anxiolytic drugs outside of the benzodiazepine or barbiturate class has produced inconsistent results in the operant conflict tests. Chronic treatment with antidepressants, which are effective in the treatment of panic disorder, resulted in a gradual increase in punished drinking behavior without affecting water intake (see Table 3–1). Remarkably, this effect parallels the slow onset of therapeutic effect observed in panic disorder patients receiving antidepressant treatment. An anxiolytic profile of 5-HT_{1A} receptor agonists has been observed in this test in chronic treatment in rats but not in mice (Table 3–2). Neither acute nor chronic treatment with propranolol affected punished responding in the conflict test.

Both compounds that block the γ-aminobutyric acid (GABA) receptor–coupled chloride channel and benzodiazepine inverse agonists were anxiogenic in the conflict tests, as shown by a decrease in punished responding, which is not surprising and is further evidence of the validity of the paradigm. Central administration of corticotropin-releasing factor (CRF), the peptide that coordinates the endocrine, autonomic, immune, and behavioral response to stress, suppresses both punished

TABLE 3–1. Effects of chronic treatment with antidepressant drugs in different animal models of anxiety

Model	Compound	Species	Effect	Reference
Operant conflict tests	Imipramine	Rats	+	Fontana and Commissaris 1988
	Desipramine	Rats	+	Fontana et al. 1989
	Amitriptyline	Rats	+	Fontana et al. 1989
	Phenelzine	Rats	+	Fontana et al. 1989
	Pargyline	Rats	+	Commissaris et al. 1995
Open field	Imipramine	Rats	–	Dwyer and Roy 1993
Elevated plus-maze test	Phenelzine	Rats	0	File 1995; Johnston and File 1988
	Imipramine	Rats	0	File and Johnston 1987
	Imipramine	Mice	0	Cole and Rodgers 1995
	Maprotiline	Mice	+/0	Rodgers et al. 1997b
	Mianserin	Rats	+	Rocha et al. 1994
	Cianopramine	Rats	+	Griebel et al. 1994
	Fluvoxamine	Mice	0	Rodgers et al. 1997b
	Paroxetine	Rats	+	Cadogan et al. 1992
Social interaction	Clomipramine	Rats	0	File 1985
	Imipramine	Rats	0	Pellow and File 1987
	Phenelzine	Rats	–	Johnston and File 1988
	Maprotiline	Mice	+/0	Cutler et al. 1997b
	Paroxetine	Rats	+	Lightowler et al. 1994
	Fluvoxamine	Mice	0	Cutler et al. 1997b
Isolation-induced ultrasonic vocalizations	Clomipramine	Rats	0	Winslow and Insel 1990
Maternal deprivation	Paroxetine	Rats	+	Ladd et al. 2000

Note. +=anxiolytic effect; 0=no effect; –=anxiogenic effect.

and unpunished responding. Both chlordiazepoxide and ethanol reverse the suppressive effect of CRF. CRF_1 receptor antagonists produce opposite effects to CRF, evidence of their anxiolytic properties (see, e.g., Arborelius et al. 1999).

The conflict test has several disadvantages. It is time-consuming to perform because the animals have to undergo long training periods and need to be deprived of food or water. It has been argued that drugs that directly affect hunger or thirst confound the interpretation of the results. Drug treatments also may affect motivation for these rewards. Indeed, animals treated with benzodiazepines increase both their intake of rewards and their rate of responding for rewards (for an extensive review on critics of this model, see Treit 1985).

Ethologically Based Models

Elevated Plus-Maze Test

The elevated plus-maze (or elevated X- or T-maze) test is one of the most popular of the currently available animal models for anxiety mainly because it is easy and quick to perform, requires only inexpensive equipment, and appears to detect both anxiolytic and anxiogenic effects. The apparatus consists of a plus-shaped maze, consisting of two open and two enclosed arms, and the whole construction is elevated from the floor. The animal is placed in the center of the maze and observed for a short period (usually 5 minutes). The proportion of entries to the open arms and the time spent in the open arms expressed as percentage of the total time spent in the maze are measured (Handley and Mithani 1984; Pellow et al. 1985). This test was developed from the observation by Montgomery (1955) that laboratory rats showed a greater fear response and therefore more avoidance behavior when exposed to an open maze alley than when exposed to an enclosed alley. Montgomery proposed that exposure to both the open and the enclosed alleys evoke the exploratory drive, but the former evokes greater fear in rodents. Thus, the elevated plus-maze test is considered a conflict test because it evokes an approach-avoidance conflict (i.e., a conflict between fear and an exploratory drive). If a treatment increases the time spent in the open arms without altering the total number of arm entries, this is

TABLE 3–2. Effects of chronic treatment with partial 5-HT_{1A} receptor agonists in different animal models of anxiety

Model	Compound	Species	Effect	Reference
Operant conflict tests	Buspirone	Rats	+	Amano et al. 1993
	Buspirone	Rats	+	Schefke et al. 1989
	Buspirone	Rats	+	Yamashita et al. 1995
	Buspirone	Mice	0	Martin et al. 1993
	Gepirone	Rats	+	Yamashita et al. 1995
	Tandospirone	Rats	+	Shimizu et al. 1987
Elevated plus-maze test	Buspirone	Rats	+	Söderpalm et al. 1993
	Buspirone	Rats	–	Moser 1989
	Buspirone	Rats	–	File 1995
	Buspirone	Mice	+	Cole and Rodgers 1994
	Buspirone	Mice	0	Rodgers et al. 1997a
	Gepirone	Rats	+	Motta et al. 1992[a]
	Gepirone	Rats	+	Maisonnette et al. 1993[a]
	Ipsapirone	Rats	0	Wright et al. 1992
Social interaction	Buspirone	Mice	+	Cutler 1991
	Buspirone	Mice	+	Gao and Cutler 1992
	Buspirone	Mice	0	Cutler et al. 1997a
Shock-induced ultrasonic vocalizations	Ipsapirone	Rats	+	Baudrie et al. 1993

Note. +=anxiolytic effect; 0=no effect; –=anxiogenic effect; 5-HT_{1A}=serotonin type 1A.
[a]Isolated animal.

interpreted as an *anxiolytic action*. Conversely, if a treatment decreases the animal's preference for open arms without altering the total number of arm entries, this is taken to reflect *anxiogenic action*.

The reluctance of rodents to explore the open arms of the maze reflects their natural aversion to open areas and the elevation of the maze. Physiologically, this was reflected by a greater rise in plasma corticosterone levels in animals exposed to open arms than in those exposed to enclosed arms (Pellow et al. 1985). Confinement to the open arms also was associated with more anxiety-related behaviors, such as increased freezing and defecation, than was confinement to the enclosed arms. Whether it is the novelty, openness, or height that is the predominant anxiogenic stimulus in the elevated plus-maze is unclear. Reducing the height of the plus-maze did not increase exploration of the open arms, and changes in light level generally did not alter the behavior of the animal on the elevated plus-maze. However, attaching a clear Plexiglas wall along one edge of one of the open arms increased the preference for this arm. Thus, it has been suggested that fear of open spaces is the predominant anxiogenic stimulus in the elevated plus-maze (Treit et al. 1993).

This test has been extensively evaluated pharmacologically and appears to be sensitive to both anxiolytic and anxiogenic drugs in both rats and mice. Thus, both acute and chronic treatment with clinically effective anxiolytics increased the percentage of time spent in open arms and open arm entries, whereas compounds known to be anxiogenic in both animals and humans reduced the percentage of time spent in and entries into open arms. However, exposure to acute stressors (immobilization or footshock), which normally increases fear in animals, did not increase the preference for the enclosed arms in the elevated plus-maze. In contrast, exposure to social stressors or a more severe stress (i.e., 1-hour restraint) increased open arm aversion. The anxiolytic effect of chronic treatment with antidepressants has been detected in the elevated plus-maze test in some, but not all, studies (see Table 3–1). Moreover, chronic treatment with clinically effective partial 5-HT_{1A} receptor agonists produced variable effects in the elevated plus-maze (Table 3–2). Thus, in mice, buspirone produces anxiolytic effects in high, but not low, doses, and in rats, buspirone or ipsapirone produces anxiolytic, anxiogenic, or no effects.

Indeed, one problem with the elevated plus-maze test is the great interlaboratory variability in pharmacological sensitivity, which has been reported for some compounds (see above), raising serious questions about the validity of the test as a model for anxiety. The vari-

ability of pharmacological responses in this test has been suggested to be attributed to either different characteristics of the maze, such as the material on the floor of the open arms and the use of transparent or opaque walls on the enclosed arms, or the test procedures used (i.e., prior handling of the animals, single- or group-housed animals, time of the day of testing, and presence of the experimenter during testing) (for extensive reviews, see Hogg 1996; Rodgers and Dalvi 1997).

Defensive Withdrawal Test

Laboratory rats have an innate fear of unfamiliar environments, particularly open areas, but subsequently they start to explore for possible resources (Blanchard et al. 1974). The defensive withdrawal test evolved from so-called timidity tests, in which latency to emerge or move from a sheltered environment is recorded (Archer 1973). The test consists of an illuminated 1-m^2 open field with a small enclosed chamber with one open end (Takahashi et al. 1989). The animal is placed in the chamber with the open end facing a corner and is observed for 10 or 15 minutes. The latency to leave the chamber, the number of passages between the chamber and the open field, and the total time spent in chamber are recorded. An untreated rat spends most of its time withdrawn in the chamber, shows a long latency before leaving the chamber, and makes few entries into the open field. If the same animal is tested a second time, defensive withdrawal behavior is decreased, as shown by a decrease in latency to leave the chamber and a decrease in total time spent in the chamber (Takahashi et al. 1989). CRF appears to be involved in the mediation of defensive behavior and in the adaptation to an unfamiliar environment. Thus, central administration of a CRF receptor antagonist decreases defensive withdrawal in rats and increases exploration of the open field; the usual increase in exploration observed when the animal is tested a second time in this model can be blocked by central pretreatment with CRF (Takahashi et al. 1989; Yang et al. 1990). Moreover, local injection of CRF into the locus coeruleus (LC), the origin of the main noradrenergic projections to the forebrain, increases defensive withdrawal, indicating that central noradrenergic systems also may be involved in this behavior. Exposure of rats to acute stressors, such as restraint stress or air-puff startle, markedly increases defensive withdrawal in this test (Engelmann et al. 1996; Yang et al. 1990). Such stress-induced increases in anxiety can be blocked by CRF receptor antagonists.

Not many of the clinically used anxiolytics have been tested in this model. The benzodiazepine chlordiazepoxide has anxiolytic effects in this model, as evidenced by a decrease in latency to leave the chamber and in time spent withdrawn in the chamber. β-Adrenergic antagonists (e.g., propranolol), which have some anxiolytic effects in humans, decrease defensive withdrawal as well as the anxiogenic effects induced by restraint stress. Conversely, β-adrenergic agonists increase anxiety in this test, providing further support for the involvement of noradrenergic systems in defensive withdrawal behavior.

Social Interaction Test

The social interaction test developed by File and colleagues is based on the observation that the time male rat pairs spent in active social interaction (e.g., sniffing and grooming) decreased as the illumination or unfamiliarity of the test arena increased. Because such manipulations have been suggested to be aversive or anxiogenic to rats, File and Hyde (1978) proposed that increased anxiety is also reflected in a decrease in social interaction. In this test, the time spent in active social interaction by a pair of male rats of similar weight (to avoid having one rat clearly dominant over the other) is measured in four different testing conditions: high light, unfamiliar; low light, unfamiliar; high light, familiar; and low light, familiar (see, e.g., File 1980). Drug-naive rats show the highest level of social interaction when the test area is familiar and has low light. Social interaction is lowest when the test area is brightly lit and unfamiliar. Locomotor activity is also measured during the test, which makes it possible to distinguish between sedative and anxiolytic effects and, thus, increase the specificity of the test. The test has been validated behaviorally, and it has been shown that the decrease in social interaction is correlated with an increase in more traditional behavioral measures of emotionality (i.e., defecation and freezing) and is not due to an increase in exploratory behavior when animals are tested in an unfamiliar environment. Plasma levels of corticosterone were higher in rats placed in unfamiliar environments than in rats placed in familiar environments and higher in rats tested under high-light conditions than in those tested under low-light conditions in an unfamiliar, but not a familiar, arena.

Some methodological details need special considerations when using this model. The light level where the animals are housed should be kept low because rats that are housed in bright light lose their aversion to this, and

changes in illumination no longer influence their social interaction. Moreover, stress decreases social interaction; therefore, repeated handling of the animals before testing is of great importance.

In the social interaction test, anxiolytic effects of benzodiazepines and barbiturates are observed only after subchronic treatment, when tolerance has developed to the sedative effects of such drugs (File 1980). Benzodiazepines increase the time spent in social interaction during conditions of high light and unfamiliarity of the test arena but have only minimal effects in low-light, familiar conditions, the least anxiety-provoking test condition. Propranolol did not have anxiolytic effects in the social interaction test (File 1980). Chronic treatment with the antidepressants clomipramine, imipramine, or phenelzine did not produce anxiolytic effects in this test (see Table 3–1). In fact, chronic treatment with phenelzine actually showed anxiogenic activity. In contrast, 3 weeks of treatment with the selective serotonin reuptake inhibitor paroxetine showed a clear anxiolytic profile, as indicated by a significant increase in social interaction under high-light conditions. Chronic treatment with the 5-HT1A receptor agonist buspirone has been reported to produce anxiolytic or no effects in this test (Table 3–2). Anxiogenic compounds reduce the time spent in social interaction without concomitant reduction in locomotor activity. Central administration of CRF significantly decreased social interaction, an effect that was prevented by pretreatment with a benzodiazepine.

Isolation-Induced Ultrasonic Vocalization in Rat Pups

Following social isolation, rat pups emit vocalizations that probably alert their mother to retrieve them. The biophysical properties of these sounds (i.e., very high frequency, 35–45 kHz) make them inaudible for most predators as well as for humans. These ultrasonic vocalizations are considered distress calls and have been proposed to reflect anxiety in the pup (for reviews, see Winslow and Insel 1991). Gardner (1985) first observed that ultrasonic vocalizations induced by tail-holding stress in rat pups were decreased by the anxiolytic drugs diazepam and chlordiazepoxide in doses that neither altered locomotion nor had sedative effects. Subsequent studies showed that isolation-induced distress calls were decreased by benzodiazepines, an effect that could be blocked by specific benzodiazepine receptor antagonists, and, conversely, anxiogenic compounds such as benzodiazepine inverse agonists increased the number and the power of such calls, giving further support to the notion that isolation-induced ultrasonic vocalizations in rat pups represent a useful anxiety model.

Based on these observations, it has been suggested that the benzodiazepine-$GABA_A$ receptor complex is involved in the physiological mediation of distress calls. Moreover, 25 minutes of isolation resulted in a decrease in benzodiazepine receptor binding in vivo, but not in vitro, in several brain regions, including the neocortex and hippocampus, suggesting the release of an endogenous benzodiazepine during isolation.

Additional evidence that isolation-induced ultrasonic vocalizations in rat pups represent anxiety, or increased emotionality, in the pups comes from studies of inbred rat strains. During isolation, pups from the Maudsley reactive (MR) rat strain, which is considered to be more emotional (see subsection "Maudsley Reactive and Nonreactive Rat Strains" later in this chapter), emit about five times as many ultrasonic calls as do pups from the less emotional Maudsley nonreactive (MNR) rat strain (Insel and Hill 1987). This finding also may imply that the large variability in the number of isolation-induced distress calls across litters that have been observed could, at least partly, be of genetic origin.

Several variables affect ultrasonic vocalizations in rat pups, including changes in body temperature, locomotion, and coordination. Thus, it is of great importance that the effects on these variables are monitored for each given drug treatment to avoid the confounds of putative anxiolytics in this test. Another confounding factor in this model is change in respiratory rate. The ultrasonic vocalizations are emitted during the expiratory phase of respiration, and, consequently, any drug-induced change in respiratory rate would predictably alter vocalizations.

The use of this model for studying drug effects during chronic treatment is limited because ultrasonic vocalizations are evident only in the first 2 weeks after birth. Moreover, chronic drug treatment may alter normal development. Another disadvantage of using infant animals to study drug effects is that changes in receptors, pharmacokinetic factors, and the permeability of the blood-brain barrier may occur during postnatal development. Thus, postnatal development of the density and the distribution of brain CRF receptors may explain the contradictory finding that central administration of CRF decreases but a CRF receptor antagonist increases ultrasonic distress calls in rat pups. The effect of chronic treatment with the tricyclic antidepressant clomipramine has been studied with this model (see Table

3–1). In contrast to the therapeutic effects of clomipramine, which usually are apparent only after 2–3 weeks of treatment, acute administration of clomipramine decreased ultrasonic vocalization in the rat pups. After 2 weeks of treatment, tolerance to this effect developed. The reason for these findings is not clear but may be related to the above-mentioned confounding factors associated with the use of immature rats for studying drug effects.

Defensive Behavior in Infant Rhesus Monkeys

Kalin and Shelton (1989) have pioneered the study of defensive behavior in infant rhesus monkeys in response to fearful stimuli. They observed that when a young monkey (6–12 months old) was briefly separated from its mother and placed in a cage, it became active and emitted distress calls ("coo" vocalizations). When a human stood outside the cage without eye contact with the infant monkey, a situation the monkey perceived as frightening, it became silent and froze, remaining completely still in one position. However, if the human stared at the infant, it started to bark and produced so-called threat faces. The cooing is thought to be activated by disruption of the attachment bond and helps the mother locate her infant. The freezing behavior is a common response to threat in many animal species, which reduces the likelihood to be attacked, and the aggressive barking serves the purpose of warding off an attack once the infant has been detected by a predator.

Based on their observation that freezing is elicited in a threatening situation, Kalin and co-workers (1998) have suggested that this behavior in infant rhesus monkeys is analogous to the responses observed in behaviorally inhibited children who are exposed to unfamiliar environments (Kagan et al. 1988). Because extremely inhibited children are at increased risk for developing anxiety disorders, fear-induced freezing may represent a model to study behavioral inhibition and the development of anxiety in monkeys. The propensity to freeze shows marked interindividual differences in infant rhesus monkeys, and these differences appear to be stable over time (Kalin and Shelton 1989). In a recent study (Kalin et al. 1998), basal plasma cortisol levels were positively correlated with freezing duration. It is noteworthy that elevated levels of salivary cortisol also have been reported in behaviorally inhibited children. Benzodiazepines have been shown to reduce freezing behavior in infant monkeys in response to a human intruder not engaged in eye contact with the solitary infant. Conversely, an inverse benzodiazepine agonist increases freezing in this situation, consistent with the anxiogenic effects of such drugs. These findings give further support to the notion that freezing may reflect anxiety in infant rhesus monkeys.

Genetic Models

Maudsley Reactive and Nonreactive Rat Strains

The MR and MNR rats were selectively bred in London, England, in the 1960s from Wistar rats on the basis of their high or low rates of defecation in the open field, respectively (Blizard 1981; Broadhurst 1975). Defecation rate in the open-field test has been suggested to indicate the level of emotionality of the animal, with the MR rats showing high levels of emotionality and the MNR rats showing low levels of emotionality (Blizard 1981). In a wide range of tests designed to measure anxiety or fear, or under stressful conditions, the MR rats showed greater levels of anxiety than did MNR rats, but not under basal conditions. Because results from early studies examining the differences between the strains are comprehensively reviewed elsewhere (Blizard 1981; Broadhurst 1975), we mainly review recent research on Maudsley rat colonies established in the United States in the 1960s.

The MR rats show less activity in the open-field test and accept less shock in conditioned suppression of drinking or feeding paradigms than do MNR rats. Moreover, MR rats spend less time in the open arms of the elevated plus-maze and show less exploratory (rearing) behavior in the staircase test than do MNR rats. In the infant separation test, MR rat pups show greater distress, manifested as an increased number of ultrasonic calls, compared with MNR rat pups. Interestingly, the latter study suggests that increased anxiety in the MR rats is apparent already early in development. However, the Maudsley rat strains do not differ in all animal models of anxiety or emotionality. In defensive burying behavior and active avoidance performance, no difference was seen between MR and MNR rats. Thus, the MR rat strain clearly differs from other emotional rat strains (i.e., the Roman low-avoidance rats, which were selectively bred for their poor performance in active avoidance) (see subsection "Roman High-Avoidance and Low-Avoidance Rats" below). In the forced swim test, the MR rats are more immobile than their less reactive counterparts, suggesting that the MR rats also may have depressive-like behaviors. Taken together, most studies support the view that the MR rats

have an increased level of emotionality and, thus, provide a valid animal model for studying genetically based anxiety. The increased anxiety in the MR rats does not appear to be linked to a learning deficit because they do equally well as or even better than MNR rats in learning tasks. However, the MR rats have a profound working memory deficit that appears to be correlated with lower muscarinic receptor binding in the central nervous system.

The Maudsley rat strains provide an excellent model for characterizing the physiological, neuroendocrine, and neurochemical basis for anxiety. However, no difference in basal or stress-induced plasma levels of corticosterone has been found between MR and MNR rats, which indicates that the two rat strains do not differ in hypothalamic-pituitary-adrenal axis activity. In contrast, a higher sympathetic tone is observed in the less emotional MNR rats (for review, see Blizard 1988). Thus, the MNR rats show higher tissue levels of norepinephrine in several peripheral organs, including the heart, adrenals, small intestine, and colon. However, in response to various stressors, the MR but not the MNR rats show an increase in plasma norepinephrine, which reflects norepinephrine release from peripheral nerve endings; plasma epinephrine concentrations increase in both strains in response to moderate stress. Central noradrenergic systems have also been extensively studied in the Maudsley rat strains. Although some results appear contradictory, the differences in central noradrenergic neuronal reactivity in MR rats compared with MNR rats are of interest in that the noradrenergic systems, especially the LC, have been implicated to play a role in fear and anxiety in animals and in humans. However, for a more complete validation of the MR rats as an animal model of anxiety, the effects of other anxiolytics (i.e., 5-HT_{1A} receptor agonists and antidepressants) and anxiogenic drugs must be studied in these animals.

Roman High-Avoidance and Low-Avoidance Rats

The Roman rat lines derive from Wistar rats and were psychogenetically selected based on their performance in active avoidance. The Roman high-avoidance (RHA) rats show unusually rapid acquisition of active avoidance on shock presentation in a shuttle box (a box divided into two equal-sized compartments connected by one opening), whereas the Roman low-avoidance (RLA) rats fail to acquire this behavior but show escape or freezing behavior on this test (for reviews, see Castanon and Mormède 1994; Driscoll and Bättig 1982). Numerous behavioral studies have suggested that RLA rats are more anxious and emotionally reactive than are RHA rats. Thus, RLA rats placed in an open field show signs of increased anxiety, such as decreased locomotion, decreased rearing, and increased grooming behavior and defecation, compared with RHA rats. The RLA rats also show increased anxiety in several other tests involving exposure to a novel environment, such as decreased feeding in the so-called hyponeophagia test; decreased head-dipping, which is a measure of exploratory behavior; and less frequent entering of the brightly illuminated center of a hexagonal tunnel maze than their RHA counterparts.

Physiologically, RLA rats have a greater increase in heart rate in unconditioned stressful situations than do RHA rats and a pronounced bradycardia in response to conditioned emotional stressors. The release of renin, which can be used as an indirect index of sympathetic reactivity, also has been reported to be higher in RLA rats than in RHA rats when tested in the open field (Castanon and Mormède 1994). Neuroendocrine activation during stress is another important measure of emotional state and, indeed, difference in activation of the HPA axis after stress has been described between the two rat lines. Thus, RLA rats have greater adrenocorticotropic hormone (ACTH), corticosterone, and prolactin responses to different stressors than do RHA rats. No difference in basal CRF messenger ribonucleic acid (mRNA) or stress-induced increases in CRF mRNA have been observed between the two rat lines; however, increased vasopressin mRNA was found in RLA rats.

Several neurochemical differences have been observed in the central nervous system of the two Roman rat strains. For example, impaired GABAergic transmission has been implicated in anxiety disorders based mainly on pharmacological evidence. Increasing GABAergic transmission produces anxiolytic effects, as evidenced by the well-known anxiolytic effects of benzodiazepines and barbiturates, whereas drugs that decrease GABAergic transmission increase anxiety. One study found lower [^{3}H]diazepam binding in several brain areas, including cortex, striatum, hippocampus, thalamic regions, and pons medulla, in RLA rats compared with RHA rats. Others have found a decrease in GABA receptor-effector coupling, but not in GABA or benzodiazepine receptor binding, in the cortex of RLA rats compared with RHA rats. Thus, a decrease in benzodiazepine binding sites and/or a decrease in GABA receptor function in RLA rats may, at least partly, account for their increased anxiety.

Diazepam or propranolol treatment reduced anxiety in the hyponeophagia test in both rat strains, and RLA rats were more sensitive to both drugs. Several different treatment paradigms have been found to increase the performance of RLA rats in the active avoidance test, such as an acute dose of pentobarbital, prenatal diazepam or perinatal flumazenil, neonatal handling, and extensive training. Neonatal handling also decreased anxiety and increased exploratory behavior in RLA rats.

RLA rats that have previously been exposed to an experimental stressor (i.e., the shuttle box) showed a marked decrease in locomotor activity and an increased ACTH response when subsequently tested in the open field. In contrast, RHA rats showed no difference in performance in the open field with or without previous testing in the shuttle box. Thus, RLA rats appear to be particularly vulnerable to stressors, and this rat strain may therefore serve as a good model of individuals with a genetic risk to develop anxiety disorders.

Uptight and Laid-Back Rhesus Monkeys

From extensive studies of individual behavior of rhesus monkeys, Suomi (1991) and co-workers have observed strong evidence for a hereditary anxiety trait present in about 20% of the monkeys found in both a self-sufficient breeding colony and the wild. These monkeys showed nervous, fearful, and anxiety-like behaviors when faced with challenge or novelty, which elicited interest and exploration from the other monkeys in the colony. Thus, the term *uptight* has been used to describe the behavioral characteristics of the fearful animals as opposed to the other animals that are more *laid back*. These differences in response to novelty or challenge appear very early in life and are apparently stable over the life span. Physiologically, the uptight monkeys showed a higher increase in heart rate when exposed to novelty than did the less reactive, laid-back monkeys. After some time in the novel environment, the heart rate of the less reactive individuals decreased, whereas the heart rate of the behaviorally reactive individuals showed little change with time. In addition, when subjected to novelty, uptight monkeys not only elicited a greater increase in plasma ACTH and cortisol levels, but these stress hormones remained elevated for a longer time than in laid-back monkeys. In contrast, during familiar, unchallenging conditions, no obvious differences in behavior or physiological reactions occurred between uptight and laid-back monkeys. Moreover, if the behaviorally reactive monkeys stayed in the novel environment for several hours or were repeatedly reintroduced to it, both their cardiac and their neuroendocrine functions normalized, and the behavioral distinction between the reactive individuals and the others diminished. Taken together, the characteristic behavioral and physiological responses to environmental challenge and novelty observed in the high-reactive, uptight rhesus monkeys resemble the human infants and children described by Kagan et al. (1988) as "behaviorally inhibited to the unfamiliar" (see subsection "Defensive Behavior in Infant Rhesus Monkeys" earlier in this chapter). Behaviorally inhibited children are believed to be at increased risk for developing anxiety disorders in adulthood.

When subjected to short-term separation from either parents or peers, the uptight monkeys showed depressive-like behaviors and a greater activation of the HPA axis, decreased cerebrospinal fluid norepinephrine levels, and increased cerebrospinal fluid levels of its metabolite MHPG (3-methoxy-4-hydroxyphenylglycol). In contrast, their more laid-back counterparts showed rapid adjustment to such separations. The behavioral, physiological, and biochemical changes observed in high-reactive individuals in response to separation can be reversed by treatment with tricyclic antidepressants and selective serotonins reuptake inhibitors. The observations that the more anxious and fearful monkeys are also more prone to develop depressive-like symptoms parallel the close relation between anxiety disorders and depression in humans (see Cameron and Schatzberg, Chapter 13, in this volume). These findings also are in line with a twin study that found that the liability to depression and GAD in women appears to be influenced by the same genetic factors (Kendler et al. 1992). Based on these findings, they proposed that "whether a vulnerable woman develops major depression or generalized anxiety disorder is a result of her environmental experiences" (p. 716).

Etiologically Based Models

Exposure to repeated early life stress has been proposed to constitute a model of anxiety primarily based on the relation between stress and the development of anxiety disorders. Although stress generally has been associated with the development of affective disorders, several studies have shown that adverse early life experiences, such as childhood abuse and neglect, also are associated with an increased risk for anxiety disorders in adulthood (see, e.g., Arborelius et al. 1999). Moreover, human anxiety disorders have been suggested to develop from

dysfunction of certain neuronal systems in brain, and a growing body of evidence now suggests that not only hereditary factors but also stressful early life events significantly affect the development of neuronal pathways.

Adversely Reared Primates

A primate model for adverse early life experience, which may resemble the adverse events hypothesized to predispose to human anxiety disorders, has been developed by Coplan et al. (1995). In this model, bonnet macaque infants are raised under different rearing conditions in which the mothers are confronted with different foraging demands. Mothers that have low foraging demands (LFD) can easily find food, whereas mothers that have consistently high, but predictable, foraging demands (HFD) must work to find food. A third group of mothers are exposed to variable, unpredictable foraging demands (VFD). The VFD paradigm appears to be the most stressful for the mother-infant dyad, and these mothers appear to be more anxious, presumably because of the uncertainty of the environment, and they are more neglectful of their infants. Infant monkeys raised by VFD mothers show several signs of increased anxiety—for example, they are more timid, less social, and more frightened by novelty than are LFD and HFD offsprings (Coplan et al. 1995). These behaviors seen in VFD offsprings have several similarities to those observed in young children identified as behaviorally inhibited, who are at increased risk for the development of anxiety disorders in adulthood (see subsection "Defensive Behavior in Infant Rhesus Monkeys" earlier in this chapter).

Several biochemical differences that indicate dysfunction of central neuronal systems have been observed in young adult monkeys raised by VFD mothers. The concentrations in cerebrospinal fluid of the dopaminergic metabolite homovanillic acid, the serotonergic metabolite 5-hydroxyindoleacetic acid (5-HIAA), and CRF were significantly elevated, whereas cortisol was decreased in VFD-reared monkeys compared with LFD- and HFD-reared subjects. Moreover, VFD-reared subjects showed a behavioral hyperresponsiveness after administration of yohimbine, an α_2-adrenoceptor antagonist that stimulates central noradrenergic activity. Interestingly, patients with panic disorder and PTSD experienced larger biochemical and cardiovascular effects after yohimbine administration than did healthy subjects as well as an increase in panic attacks and flashbacks. A reduced growth hormone response to the α_2-adrenoceptor agonist clonidine, a biological marker found in several anxiety disorders, has been found in VFD-reared monkeys. In contrast, VFD-reared monkeys showed hyporesponsiveness to the behavioral effects of the serotonergic agonist *m*-chlorophenylpiperazine (m-CPP), which has been shown to exacerbate the symptoms in patients with anxiety disorders, including panic disorder, obsessive-compulsive disorder, and PTSD. Taken together, these studies in nonhuman primates support the notion that early life stress permanently alters central noradrenergic and serotonergic functioning as well as CRF systems in brain. In view of the hypotheses that noradrenergic, serotonergic, and CRF (Arborelius et al. 1999) systems are altered in anxiety disorders, this may underlie the observed anxiety-like behaviors in adult monkeys reared under stressful conditions. The above-cited studies strongly suggest that early life stress in nonhuman primates may constitute a valid animal model for anxiety. However, for a more complete validation of this model, the effects of anxiolytic compounds should be assessed.

Maternal Deprivation

The maternal deprivation model has been suggested to constitute a model to study early life stress in the laboratory rat. In different separation paradigms, rat pups are subjected to various intervals of separations from their mothers during the first 2–3 weeks after birth. Maternally deprived rats may be compared with so-called handled rats, which are subjected to daily handling during the same period, or with facility-reared animals. As adults, maternally deprived rats showed several signs of increased anxiety, including decreased exploration in a novel open field, increased defensive withdrawal behavior, increased novelty-induced suppression of feeding, increased startle response, and a distinct alcohol preference compared with handled rats (Caldji et al. 2000; Ladd et al. 2000). Maternally deprived rats also showed an enhanced neuroendocrine response to an acute psychological, but not somatic, stressor, as evidenced by a larger rise in plasma ACTH and corticosterone levels than in nondeprived rats (Ladd et al. 2000). The hyperresponsiveness to stress may be related to the observed hypersecretion of hypothalamic CRF, coupled with the decrease in glucocorticoid receptor binding and expression in the hippocampus and medial prefrontal cortex, in maternally deprived rats. Moreover, changes in extrahypothalamic CRF systems have been observed in maternally deprived rats. Notably, CRF binding sites have increased

in both the dorsal raphe nucleus, the major site of origin of the widespread serotonergic innervation of the forebrain, and the LC, the origin of the noradrenergic innervation. Moreover, maternally deprived rats showed an increased release of hypothalamic norepinephrine in response to restraint stress and decreased α_2-adrenoceptor binding in the LC compared with handled rats. These findings are of particular interest in view of the possible involvement of these monoaminergic pathways in the pathogenesis of human anxiety. Decreased binding of $GABA_A$ receptors and benzodiazepine binding sites also has been found in several different brain regions, including the LC, in maternally deprived rats, which may contribute to the increased anxiety observed in such animals. In the central nucleus of amygdala, a brain region presumably involved in fear and anxiety, benzodiazepine binding sites are decreased and the gene expression of CRF is increased in maternally deprived rats (Caldji et al. 2000; Ladd et al. 2000). The effects of benzodiazepines have not yet been studied in maternally deprived rats. However, chronic treatment with the selective serotonin reuptake inhibitor paroxetine almost completely normalized stress-induced neuroendocrine hyperresponsivness, reduced anxiety behaviors in the elevated plus-maze test and the defensive withdrawal test in such animals, and reduced their alcohol preference (Ladd et al. 2000; P. M. Plotsky, unpublished observations, 1995).

Conclusion

The purpose of this chapter was to present a selection of different types of animal models of anxiety (i.e., conditioned models, ethologically based models, genetic models, and a new group that we designated etiologically based models). Overall, it is clear that the different types of anxiety models can serve different purposes to increase our understanding of anxiety disorders. Because human anxiety disorders are believed to result from genetic and environmental factors (one such factor is adverse early life experiences) and such disorders are often chronic in nature, the genetically and etiologically based models in which the animals showed permanently increased anxiety may serve as better models to study the pathophysiology of anxiety disorders than the conditioned and ethologically based models. However, a more complete pharmacological validation is needed for the genetic and etiologically based models because the effects of only a few of the clinically effective anxiolytic drugs have been studied. On the other hand, the conditioned and ethologically based models are important tools to study "state" anxiety. Moreover, these paradigms are necessary to evaluate the level of anxiety of animals in the genetic and etiologically based models. However, whether the inconsistent results with chronic treatment with partial 5-HT_{1A} receptor agonists and antidepressant drugs in these anxiety models are due to pharmacological factors, confounding factors, or the fact that the models do not really measure anxiety remains to be elucidated.

Interestingly, in the genetic models of anxiety, the animals showing high levels of anxiety respond with helpless behavior in certain situations, suggesting that these animals may also be at increased risk to develop depression. Moreover, because adverse early life experience is associated with increased risk to develop depression in humans, the etiologically based animal models have also been used to study the development of depression. This parallels observations in humans, in whom comorbid anxiety disorders and depression are common, and suggests that the genetic and etiologically based models also may be valid models to study mixed anxiety-depression in animals.

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4

Neural Circuits in Fear and Anxiety

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In this chapter, we review neural correlates of fear and anxiety and the clinical neuroscience of human anxiety disorders built on basic research. We make connections between neurobiology and functional neuroanatomy and the clinical and symptomatic presentation of patients with anxiety disorders. This work is ongoing, and many of the models proposed may be subject to modification and revision as our knowledge base in this exciting area continues to expand.

Development of a Model for the Neural Circuitry of Fear and Anxiety

There has been a long history of hypotheses related to the neurobiology of human anxiety. Early neuroanatomical studies showed that removal of the cerebral cortex of the cat, which left only subcortical regions including the amygdala, thalamus, hippocampus, and hypothalamus, resulted in accentuated fearful responses to potentially threatening or novel stimuli, accompanied by signs of diffuse sympathetic activation such as increased blood pressure, sweating, piloerection, and increased secretion of epinephrine from the adrenal medulla (Cannon 1927). This behavioral response became termed *sham rage* and led to the original hypothesis that subcortical brain structures above the level of the midbrain, such as the hypothalamus, hippocampus, cingulate, entorhinal cortex, and thalamus, mediate human anxiety responses (Kluver and Bucy 1937, 1939; Papez 1937; reviewed in LeDoux 1977). Maclean (1966) later added the amygdala to the "Papez circuit" of "limbic" brain structures, so called because of their relation to olfaction in evolution, which were hypothesized to play a role in fear and anxiety. More recent work by LeDoux (1993) and Davis (1992) has confirmed the important role of the amygdala in animal models of anxiety. More recently, clinicians have developed neuroanatomical hypotheses related to specific anxiety disorders, including panic disorder (Gorman et al. 1989) and posttraumatic stress disorder (PTSD) (Pitman 1989). Alterations in neurochemical and neurotransmitter systems, including norepinephrine (Redmond 1979; Uhde et al. 1984), cortisol, benzodiazepines (Guidotti et al. 1990), and other neurochemical systems (reviewed in Roy-Byrne and Crowley 1998), that mediate the stress response have been hypothesized to play a role in anxiety. Specific hypotheses related to respiratory system dysfunction in panic disorder were based on findings of panic provocation by sodium lactate in panic patients (Klein 1993).

Based on studies of the effects of stress on animals and emerging work in the clinical neuroscience of anxiety disorders, we have developed a working model for the neural circuitry of fear and anxiety (Bremner et al. 1999; Charney and Deutch 1996). The model extends and to some extent integrates prior models of panic disorder that are partially reviewed above. This model is preliminary and is subject to modification based on new

information, especially in the clinical neuroscience of anxiety disorders. The model needs to explain how information related to a threatening stimulus (e.g., someone approaches you with a gun in a dark alley) enters the primary senses (smell, sight, touch, hearing), is integrated into a coherent image that is grounded in space and time, activates memory traces of prior similar experiences with the appropriate emotional valence (necessary to evaluate the true threat potential of the stimulus), and triggers an appropriate motor response. Specific brain circuits that mediate these responses make up the neural circuitry of fear and anxiety.

In the development of human fear or anxiety, afferent sensory input enters through the senses of smell, sight, touch, and hearing; the body's own visceral information; or any combination of those. These sensory inputs are relayed through the dorsal thalamus to cortical brain areas, such as primary visual (occipital), auditory (temporal), or tactile (postcentral gyrus) cortical areas. Olfactory sensory input, however, has direct inputs to the amygdala and entorhinal cortex. Input from peripheral visceral organs is relayed through the nucleus paragigantocellularis and nucleus tractus solitarii in the brain stem to the locus coeruleus, site of most of the brain's noradrenergic neurons, and from there to central brain areas.

Information that reaches primary sensory areas is then processed by secondary cortical association areas (Jones and Powell 1970). These secondary areas are often physically adjacent to the primary sensory areas from which they receive information. For instance, the primary sensory area for vision is in the medial portion of the occipital lobe (Brodmann's area 17), which is in the posterior portion of the brain. Just lateral to this area is the visual association cortex (Brodmann's areas 18 and 19). Therefore, while the primary occipital cortex is responsible for determining, for example, the color of an object, the visual association cortex is responsible for forming a visual image. More complex visual processing involves recognition of faces, which is mediated by the lingual gyrus (posterior parahippocampal region), fusiform gyrus, and inferior temporal gyrus. These brain areas have projections to multiple areas, including the amygdala, hippocampus, entorhinal cortex, orbitofrontal cortex, and cingulate, that are involved in mediating memory and emotion.

Cognitive appraisal of potential threat is also an important aspect of the stress response. The cognitive response to threat involves placing the threatening object in space and time. Specific brain areas are involved in these functions. For example, the parietal cortex is involved in determining where an object is located in space. Posterior portions of the cingulate have connections to the parietal cortex, hippocampus, and adjacent cortex. This region plays an important role in visuospatial processing (Vogt et al. 1992). The prefrontal cortex also is involved in memory and cognition and, with the parietal cortex, has important dual reciprocal connections with all of the subcortical areas mentioned above (Selemon and Goldman-Rakic 1988). The dorsolateral prefrontal cortex has a range of functions, including declarative and working memory and planning of action, whereas the parietal cortex, as mentioned above, plays an important role in spatial memory (Goldman-Rakic 1988). The prefrontal cortex and parietal cortex probably work in concert in the alerting and planning aspects of the stress response that is critical for survival. Anterior cingulate (Brodmann's area 32) is involved in selection of responses for action as well as emotion (Devinsky et al. 1995). This area and other medial portions of the prefrontal cortex, including subgenual area (Brodmann's area 25) and orbitofrontal cortex, modulate emotional and physiological responses to stress and are discussed in more detail below.

Another important aspect of the stress response is incorporation of a person's prior experience (memory) into the cognitive appraisal of stimuli. For example, if one is approached in a potentially threatening situation, it is important to determine whether the person is someone familiar or is a stranger who may be more threatening. Also, it is important to place the situation in time and place. Entering a dark alley may trigger memories of being robbed, with associated negative emotions and physiological arousal. These memories may have survival value, in that the individual will avoid the situation in which the previous negative event took place. Finally, it is critical to effectively lay down memory traces related to a potential threat to avoid this type of threat in the future. Specific brain areas are involved in retrieval of memory.

The hippocampus, which is particularly vulnerable to stress, plays an important role in memory. The hippocampus and adjacent cortex mediate declarative memory function (e.g., recall of facts and lists) and have been hypothesized to play an important role in integration of memory elements at the time of retrieval and in assigning significance to events within space and time (Squire and Zola-Morgan 1991). The hippocampus also plays an important role in mediating emotional responses to the context of a stressor; for example, in animal studies, lesions of the hippocampus disrupted the formation of emotional memories of the context (i.e.,

the box) in which the stressor (i.e., electric foot shock) took place. High levels of glucocorticoids released during stress also were associated with damage to the CA3 region of the hippocampus (Sapolsky 1996) and related memory deficits (McEwen et al. 1992). Glucocorticoids appear to exert their effect through disruption of cellular metabolism and by increasing the vulnerability of hippocampal neurons to a variety of insults, including endogenously released excitatory amino acids. Factors other than glucocorticoids, such as nerve growth factor (NGF), may contribute to stress-induced hippocampal damage. These findings may be applicable to patients with PTSD and other anxiety disorders, as discussed below (see section "A Working Model for the Neural Circuitry of Anxiety Disorders" later in this chapter).

With long-term storage, memories are believed to shift from the hippocampus to the neocortical areas, where the initial sensory impressions take place (Squire and Zola-Morgan 1991). The shift in memory storage to the cortex may represent a shift from conscious representational memory to unconscious memory processes that indirectly affect behavior. *Traumatic cues*, such as a particular sight or sound reminiscent of the original traumatic event, will trigger a cascade of anxiety- and fear-related symptoms, often without conscious recall of the original traumatic event. In patients with PTSD, however, the traumatic stimulus is always potentially identifiable. Symptoms of anxiety in patients with panic or phobic disorder, however, may be related to fear responses to a traumatic cue (in individuals who are vulnerable to increased fear responsiveness, through either constitution or previous experience) when there is no possibility that the original fear-inducing stimulus will ever be identified.

The amygdala is involved in memory for the emotional valence of events. The paradigm of conditioned fear has been used as an animal model for stress-induced abnormalities of emotional memory (Davis 1992; LeDoux 1993). Conditioned fear, in which pairing of a neutral (conditioned) stimulus to a fear-inducing (unconditioned) stimulus results in fear responses to the neutral (conditioned) stimulus alone, has been used as a probe of amygdala function (Davis 1992; LeDoux et al. 1990). Lesions of the central nucleus of the amygdala have been shown to completely block fear conditioning while electrical stimulation of the central nucleus increases acoustic startle. The central nucleus of the amygdala projects to a variety of brain structures via the stria terminalis and the ventral amygdalofugal pathway. One pathway is from the central nucleus to the brain stem startle reflex circuit (nucleus reticularis pontis caudalis) (Davis 1992). Pathways from the amygdala to the lateral hypothalamus effect peripheral sympathetic responses to stress (Iwata et al. 1986). Electrical stimulation of the amygdala in cats resulted in peripheral signs of autonomic hyperactivity and fear-related behaviors seen in the wild when the animal is being attacked or is attacking, including alerting, chewing, salivation, piloerection, turning, facial twitching, arching of the back, hissing, and snarling, associated with an increase in catecholamine turnover (Hilton and Zbrozyna 1963). Electrical stimulation of the amygdala in human subjects resulted in signs and symptoms of fear and anxiety, including an increase in heart rate and blood pressure, increased muscle tension, subjective sensations of fear or anxiety (Chapman et al. 1954), and increases in peripheral catecholamines (Gunne and Reis 1963). These findings show that the amygdala plays an important role in conditioned fear and emotional responding and modulates peripheral stress responses. Also, connections between cortical association areas, thalamus, and amygdala are important in shaping the emotional valence of the cognitive response to stressful stimuli. In addition to thalamo-cortico-amygdala connections, there are direct pathways from thalamus to amygdala, which could account for fear responding below the level of conscious awareness (LeDoux et al. 1989; Romanski and LeDoux 1993).

Frontal cortical areas modulate emotional responsiveness through inhibition of amygdala function, and we have hypothesized that dysfunction in these regions may underlie pathological emotional responses in patients with anxiety disorders. The medial prefrontal cortex (Brodmann's area 25—subcallosal gyrus) has projections to the amygdala that are involved in the suppression of amygdala responsiveness to fearful cues. Dysfunction of this area may be responsible for the failure of extinction to fearful cues, which is an important part of the anxiety response (Morgan and LeDoux 1995; Morgan et al. 1993). This area is involved in regulation of peripheral responses to stress, including heart rate, blood pressure, and cortisol response (Roth et al. 1988). Finally, case studies of humans with brain lesions have implicated the medial prefrontal cortex (including orbitofrontal cortex—Brodmann's area 25 and anterior cingulate—Brodmann's area 32) in "emotion" and socially appropriate interactions (Damasio et al. 1994). Auditory association areas (temporal lobe) also have been implicated in animal studies as mediating extinction to fear responding (Romanski and LeDoux 1993). We found dysfunction of medial pre-

frontal cortex and auditory cortex with traumatic reminders in PTSD.

A final component of the stress response involves preparation for a response to potential threat. Preparation for responding to threat requires an integration between brain areas involved in assessing and interpreting the potentially threatening stimulus and brain areas involved in responding. For instance, the prefrontal cortex and anterior cingulate play an important role in the planning of action and in holding multiple pieces of information in working memory during the execution of a response (Goldman-Rakic 1988). The parietal cortex and posterior cingulate are involved in visuospatial processing, which is an important component of the stress response. The motor cortex may represent the neural substrate of planning for action. The cerebellum has a well-known role in motor movement, which suggests that this region is involved in planning for action; however, imaging studies are consistent with a role in cognition as well (Ashkoomoff and Courchesne 1992). Connections between parietal and prefrontal cortex are required to permit the organism to rapidly and efficiently execute motor responses to threat. It is therefore not surprising that these areas have important innervations to precentral (motor) cortex, which is responsible for skeletal motor responses to threat that facilitate survival. The striatum (caudate and putamen) modulates motor responses to stress. The dense innervation of the striatum and prefrontal cortex by the amygdala indicates that the amygdala can regulate both of these systems. These interactions between the amygdala and the extrapyramidal motor system may be very important for generating motor responses to threatening stimuli, especially those related to prior adverse experiences (McDonald 1991a, 1991b).

The organism must rapidly effect peripheral responses to threat, which are mediated by the stress hormone cortisol and the sympathetic and parasympathetic systems. Stimulation of the lateral hypothalamus results in sympathetic system activation, producing increases in blood pressure and heart rate, sweating, piloerection, and pupil dilatation. Stress stimulates release of corticotropin-releasing factor (CRF) from the paraventricular nucleus (PVN) of the hypothalamus, which increases peripheral adrenocorticotropic hormone (ACTH) and cortisol levels. The medial prefrontal cortex, as mentioned earlier in the chapter, also mediates increased blood pressure and pulse rate as well as elevated cortisol levels in response to stress. Striatum, amygdala, and bed nucleus of the stria terminalis also effect peripheral responses to threat through the lateral nucleus of the hypothalamus (Sawchenko and Swanson 1983a, 1983b).

The vagus and splanchnic nerves are major projections of the parasympathetic nervous system. Afferents to the vagus include the lateral hypothalamus, PVN, locus coeruleus, and amygdala. There are afferent connections to the splanchnic nerves from the locus coeruleus (Clark and Proudfit 1991). This innervation of the parasympathetic nervous system may relate to visceral symptoms commonly associated with anxiety, such as gastrointestinal and genitourinary disturbances.

Function of these brain areas is mediated by specific neurochemical systems that mediate the stress response. Increased release of glucocorticoids, catecholamines (norepinephrine, epinephrine, and dopamine), serotonin, benzodiazepines, and endogenous opiates is associated with acute stress exposure. We have hypothesized that long-term dysregulation of these systems, acting on brain areas outlined earlier in this chapter, mediates the symptoms of pathological anxiety (Bremner et al. 1999).

The hypothalamic-pituitary-adrenal (HPA) axis is an important component of the stress response system. This axis is involved in a negative feedback loop that regulates cortisol release (as well as regulatory feedback with the noradrenergic system, which is discussed in more detail later in this chapter). Cortisol has a variety of functions in the body, primarily regulating energy use, as well as bone resorption, reproduction, and immunity. The purpose of the functions of cortisol is to help the organism rapidly adapt to cope with stressors. In addition to the PVN of the hypothalamus, binding sites for cortisol and CRF are located in multiple central brain areas involved in fear and the stress response. Binding sites for glucocorticoids include the type I and type II receptor, which have varying affinities for cortisol and the other glucocorticoids (such as dexamethasone). The highest number of bindings sites for cortisol are in the hippocampus (McEwen et al. 1986). There are at least three CRF receptors, CRH_1, CRH_{2A}, and CRH_{2B}, each constituting seven putative spanning domains characteristic of G_s-coupled receptors (Chalmers et al. 1996). CRH_1 receptors are most abundant in neocortical, cerebellar, and sensory relay structures. CRH_2 receptors are generally localized to specific subcortical structures, most notably, lateral septal nuclei, choroid plexus, olfactory bulb, specific amygdaloid nuclei, and various hypothalamic areas. Within the pituitary, CRH_1 expression predominates over CRH_2 expression, suggesting that CRH_1 receptors may mediate corticotropin-releasing hormone (CRH)–induced changes

in ACTH release. CRF has been hypothesized to have direct behavioral effects in the brain that lead to anxiety. As described later in this chapter, one possibility is that CRF exerts behavioral effects during stress by stimulating other systems, such as norepinephrine.

Acute stress of many types results in release of CRF, ACTH, and cortisol. The mechanism responsible for transient stress-induced hyperadrenocorticism and feedback resistance may involve a downregulation of glucocorticoid receptors. High glucocorticoid levels (such as those elicited by acute stress) decrease the number of hippocampal glucocorticoid receptors, resulting in increased corticosterone secretion and feedback resistance. Following stress termination, when glucocorticoid levels decrease, receptor numbers increase and feedback sensitivity normalizes (Sapolsky et al. 1984).

The effects of chronic stress on ACTH and corticosterone secretion vary depending on the experimental paradigm. It has been reported that an adaptation to chronic stress may occur, resulting in decreased plasma ACTH and corticosterone levels compared with levels following a single stressor. However, other investigations have reported enhanced corticosterone secretion after chronic stressor regimens. Evidence also indicates that the experience of prior stress may result in augmented corticosterone responses to a subsequent stress exposure (Caggiula et al. 1989; Dallman and Jones 1973). It is not known which factors determine whether adaptation or sensitization of glucocorticoid activity will occur following chronic stress (Yehuda et al. 1991).

The HPA axis has important functional interactions with the norepinephrine system that facilitate a sophisticated range of responses to stress. Glucocorticoids inhibit stress-induced activation of catecholamine synthesis in the PVN. CRF increases activity of the locus coeruleus, and CRF injected into the locus coeruleus intensifies anxiety-related responses. These findings support the notion that CRF serves as an excitatory neurotransmitter in the locus coeruleus, which may represent the pathway for the behavioral effects of CRF.

Stressors early in life may have long-term effects on the HPA axis. Both prenatal (light and noise) (Fride et al. 1986) and early maternal deprivation stress (Levine et al. 1993; Stanton et al. 1988) and early manipulation stress (Levine 1962) resulted in increased glucocorticoid response to subsequent stressors. Prenatal stress was associated with a failure of habituation of glucocorticoid responsiveness to novel stimuli (Fride et al. 1986). Increased glucocorticoid responsivity to ACTH challenge in maternal deprivation stress suggested an increase in adrenocortical responsivity with early stress (Stanton et al. 1988).

Early postnatal adverse experiences altered hypothalamic CRF messenger ribonucleic acid (mRNA), median eminence CRF content, and stress-induced CRF release (Plotsky and Meaney 1993) and ACTH release (Ladd et al. 1996) in male rats. Maternally deprived rats had decreased numbers of glucocorticoid receptors, as measured by dexamethasone binding, in the hippocampus, hypothalamus, and frontal cortex. They also had increased norepinephrine levels in the PVN, as determined by microdialysis. The importance of locus coeruleus–CRH interactions was supported by increased CRH binding in the locus coeruleus (P. Plotsky, personal communication, December 8, 1996). These observations suggest that early adverse experience permanently alters the HPA axis. In nonhuman primates, early adverse experiences induced by variable maternal foraging requirements resulted in profound behavioral disturbances (more timid, less social, and more subordinate) years later. Adult monkeys raised in the variable maternal foraging environment also were hyperresponsive to yohimbine and had elevated levels of cerebrospinal fluid (CSF) and decreased CSF cortisol levels in adulthood, a picture that is closer to PTSD than depression (Coplan et al. 1996). These observations suggest that early adverse experience permanently affects the HPA axis.

Positive early life experiences during critical periods of development may have long-term beneficial consequences on an animal's ability to mount adaptive responses to stress or threat. An animal model that appears to be of use in studying this phenomenon is postnatal handling. Postnatal handling has important effects on the development of behavioral and endocrine responses to stress. For example, daily handling within the first few weeks of life (picking up rat pups and then returning them to their mother) resulted in increased type II glucocorticoid receptor binding, which persisted throughout life. This was associated with increased feedback sensitivity to glucocorticoids and reduced glucocorticoid-mediated hippocampal damage in later life (Meaney et al. 1988, 1989). These effects appear to be the result of a type of "stress inoculation" from the mother's repeated licking of the handled pups. Considered together, these findings suggest that early in the postnatal period, the naturally occurring brain plasticity in key neural systems may "program" an organism's biological response to threatening stimuli.

Coordinated functional interactions between the HPA axis and noradrenergic neuronal systems may be

critical in promoting adaptive responses to stress, anxiety, or fear. CRF increases locus coeruleus firing, resulting in enhanced norepinephrine release in cortical and subcortical areas throughout the brain. The PVN of the hypothalamus, site of most CRF-containing neurons in the hypothalamus, is an important site in effecting cardiovascular and neuroendocrine responses to stress. Norepinephrine increases CRF in the PVN of the hypothalamus. In chronically stressed animals, the locus coeruleus (as opposed to other norepinephrine neurons in the medulla) may be preferentially responsible for norepinephrine release in the PVN. High levels of circulating cortisol act through a negative-feedback pathway to decrease both CRF and norepinephrine synthesis at the level of the PVN. Glucocorticoid inhibition of norepinephrine-induced CRF stimulation may be evident primarily during stressor-induced cortisol release and not under resting conditions. High levels of cortisol likely inhibit the effects of norepinephrine on CRF release from the PVN, serving to restrain the stress-induced neuroendocrine and cardiovascular effects mediated by the PVN. Norepinephrine, cortisol, and CRF thus appear to be tightly linked in a functional system that provides a broad homeostatic mechanism for coping with stress.

Norepinephrine release in the brain is an important part of the stress response (reviewed in Bremner et al. 1996b, 1996c). Most noradrenergic cell bodies are located in the brain stem, in the locus coeruleus region of the pons, with axons that extend throughout the cerebral cortex and to multiple subcortical areas. Neurons in the locus coeruleus are activated in association with fear and anxiety states (Abercrombie and Jacobs 1987; Redmond 1987), and the limbic and cortical regions innervated by the locus coeruleus are those thought to be involved in the elaboration of adaptive responses to stress. Stressors such as a cat seeing a dog result in an increase in firing of neurons in the locus coeruleus and enhanced norepinephrine release in the hippocampus and medial prefrontal cortex. Exposure to chronic stress also results in a potentiation of norepinephrine release with subsequent stressors (reviewed in Bremner et al. 1996b, 1996c). Consistent with these findings, noradrenergic stimulation resulted in decreased metabolism in the hippocampus (consistent with high levels of norepinephrine release) and relative failure of activation in the medial prefrontal cortex in PTSD patients but not in subjects without PTSD. A relation between this metabolic response and increased panic or anxiety also was found (Bremner et al. 1997).

Acute stress increases dopamine release and metabolism in several specific brain areas (reviewed in Thierry et al. 1998). However, the dopamine innervation of the medial prefrontal cortex appears to be particularly vulnerable to stress. Sufficiently low-intensity stress (such as that associated with conditioned fear) or brief exposure to stress increases dopamine release and metabolism in the prefrontal cortex in the absence of overt changes in other mesotelencephalic dopamine regions. Low-intensity electric foot shock increases in vivo tyrosine hydroxylase and dopamine turnover in the medial prefrontal cortex but not in the nucleus accumbens or striatum. Stress can enhance dopamine release and metabolism in other areas receiving dopamine innervation, provided that stress is of greater intensity or longer duration. Thus, the medial prefrontal cortex dopamine innervation is preferentially activated by stress compared with mesolimbic and nigrostriatal systems, and the mesolimbic dopamine innervation appears to be more sensitive to stress than the striatal dopamine innervation is.

The effects of stress on serotonin systems have been studied less thoroughly than the effects on noradrenergic systems. Animals exposed to a variety of stressors, including foot shock, tail shock, tail pinch, and restraint stress, all produced an increase in serotonin turnover in the medial prefrontal cortex, nucleus accumbens, amygdala, and lateral hypothalamus, with preferential release during conditioned fear in the medial prefrontal cortex. Chronic electric shock, producing learned helplessness behavioral deficits, was associated with reduced in vivo serotonin release in the frontal cortex (Petty et al. 1992), probably reflecting a situation in which synthesis cannot keep pace with demand. Serotonin antagonists produce behavioral deficits resembling those seen following inescapable shock. Drugs that enhance serotonin neurotransmission (selective serotonin reuptake inhibitors) are effective in reversing learned helplessness (Petty and Sherman 1980). Preadministration of benzodiazepines or tricyclic antidepressants prevents stress-induced decreases in serotonin and the acquisition of behavioral deficits, whereas injection of serotonin into the frontal cortex after stress exposure reverses behavioral deficits. Chronic restraint stress results in a decrease in serotonin type 1A (5-HT_{1A}) receptor binding in the hippocampus. Animals exposed to social stress had decreased 5-HT_{1A} receptor binding in the hippocampus and dentate gyrus and decreased serotonin type 2 (5-HT_2) receptor binding in the parietal cortex. Administration of 5-HT_{1A} agonists such as buspirone results in a reversal of stress-induced behavioral deficits.

The effect of stress to activate serotonin turnover may stimulate a system that has both anxiogenic and anxiolytic pathways within the forebrain (Graeff 1993). A primary distinction in the qualitative effects of serotonin may be between the dorsal and the median raphe nuclei, the two midbrain nuclei that produce most of the forebrain serotonin. The serotonergic innervation of the amygdala and the hippocampus by the dorsal raphe is believed to mediate anxiogenic effects via 5-HT_2 receptors. In contrast, the median raphe innervation of hippocampal 5-HT_{1A} receptors has been hypothesized to facilitate the disconnection of previously learned associations with aversive events or to suppress formation of new associations, thus providing a resilience to aversive events (Graeff 1993). Chronic stress increases cortical 5-HT_2 receptors and reduces hippocampal 5-HT_{1A} receptors (Mendelson and McEwen 1991).

Endogenous benzodiazepines also play an important role in the stress response and anxiety (reviewed in Guidotti et al. 1990). Benzodiazepine receptors are present throughout the brain, with the highest concentration in cortical gray matter. Benzodiazepines potentiate and prolong the synaptic actions of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Central benzodiazepine receptors and $GABA_A$ receptors are part of the same macromolecular complex. These receptors have distinct binding sites, but they are functionally coupled and regulate one another in an allosteric manner. Administration of inverse agonists of benzodiazepine receptors, such as β-carboline-3-carboxylic acid ethyl ester (β-CCE), results in behavioral and biological effects similar to those seen in anxiety and stress, including increases in heart rate, blood pressure, plasma cortisol, and catecholamines. These effects are blocked by administration of benzodiazepines or pretreatment with the benzodiazepine antagonist flumazenil. Animals exposed to acute inescapable stress in the form of cold swim or foot shock developed a decrease in benzodiazepine receptor binding (density [B_{max}] but not typically affinity [KD]) in the frontal cortex, with mixed results for the cerebral cortex, hippocampus, and hypothalamus and no change in the occipital cortex, striatum, midbrain, thalamus, cerebellum, and pons. Chronic stress in the form of foot shock or cold swim resulted in decreases in benzodiazepine receptor binding in the cerebral cortex, frontal cortex, hippocampus, and hypothalamus, with mixed results for the cerebellum, midbrain, and striatum and no change in the occipital cortex or pons. Decreases in benzodiazepine receptor binding are associated with alterations in memory manifested by deficits in maze escape behaviors. Changes in benzodiazepine receptor function appear to be specific to uncontrollable stress, as opposed to controllable stress, and are prevented by preadministration of benzodiazepines. In addition, animals exposed to inescapable stress have decreased binding of the benzodiazepine receptor antagonist flumazenil, which is associated with deficits in learning, and decreased depolarization-induced release of GABA relative to control subjects. A decrease in benzodiazepine receptor binding has been found in the so-called Maudsley genetically fearful strain of rat in comparison to nonfearful rats in several brain structures, including the hippocampus.

Several neuropeptides also mediate the response to stress. Cholecystokinin (CCK), an anxiogenic neuropeptide present in the gastrointestinal tract and the brain, recently has been suggested as a neural substrate for human anxiety. CCK-containing neurons are found with high density in the cerebral cortex, amygdala, and hippocampus. They are also found in the midbrain, including the periaqueductal gray, substantia nigra, and raphe nuclei. Iontophoretic administration of CCK has depolarizing effects on pyramidal neurons, which suggests that it may serve as an excitatory neurotransmitter. CCK_{4-8} has stimulatory effects on action potentials in the dentate gyrus of the hippocampus. Activation of hippocampal neurons is suppressed by low-dose benzodiazepines. CCK agonists are anxiogenic in a variety of animal models of anxiety, whereas CCK antagonists have anxiolytic effects in these tests. Stress is associated with an increase in endogenous opiate release, with a decreased density of μ opiate receptors, which may mediate the analgesia associated with stress. Other neuropeptides under investigation that appear to play a role in the stress response are neuropeptide Y, somatostatin, and thyrotropin. Stress also has important effects on the immune system that are not reviewed here in detail.

Application of the Model of the Neural Circuitry of Anxiety and Fear to Anxiety Disorders

The primary goal in research related to the clinical neuroscience of anxiety disorders is to apply findings related to the effects of stress on the brain in animals (which are used as models of anxiety) to patients with anxiety disorders. Ideally, animal studies are used to measure the effects of chronic stress on neurochemical systems and brain areas that are particularly sensitive to

stress. This approach assumes that animal models of the anxiety disorders are directly applicable to human anxiety disorders. However, it can immediately be seen that this is not possible because different anxiety disorders are expressed in different ways (e.g., panic disorder has important symptomatic differences from PTSD). Animal models used for anxiety disorders (e.g., chronic stress) are also used as models for depression. If there is any validity to our differentiation of unique disorders of anxiety and depression, then it is not possible that, when it comes to animal models, "one size fits all."

However, given these limitations, animal models can be very useful in guiding research in the anxiety disorders. The animal model of chronic stress can go a long way in explaining many of the neurobiological changes associated with anxiety disorders (and possibly depression). We have posited that PTSD, panic disorder, and phobic disorders share many neurobiological and phenomenological characteristics and can benefit from the application of animal models of stress (Bremner et al 1996b, 1996c). Obsessive-compulsive disorder does not fit as easily with these disorders (and therefore is not discussed in depth in this chapter).

Neural circuits mediating symptoms of anxiety disorders can be studied by measuring neurotransmitter and hormone levels in blood, urine, and saliva; assessing behavioral and biochemical responses to pharmacological challenge to specific neurochemical systems; measuring brain structures with structural neuroimaging; provoking disease-specific symptoms in conjunction with functional neuroimaging; or using imaging to measure neuroreceptors.

Thus, for example, several replicated studies showed hippocampal atrophy with associated verbal memory deficits in PTSD. Considering the role played by the hippocampus in the integration of memory elements that have been stored in primary sensory and secondary association cortical areas at the time of retrieval, the findings suggest a possible neural correlate for symptoms of memory fragmentation and dysfunction in PTSD (Bremner et al. 1996a). Similarly, several studies showed alterations in hippocampus and adjacent cortex (parahippocampus) in panic disorder.

Similarly, studies have begun to use positron-emission tomography (PET) during pharmacological and cognitive provocation of PTSD symptom states to identify neural correlates of PTSD symptomatology and of traumatic remembrance in PTSD. We used PET and fluorine-18 2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) in the measurement of cerebral glucose metabolic rate after administration of the α_2 antagonist yohimbine and placebo in Vietnam combat veterans with PTSD and healthy control subjects. Increased noradrenergic function has been hypothesized to underlie many of the symptoms of PTSD. Administration of yohimbine, which stimulates brain norepinephrine release, resulted in increased PTSD symptoms and anxiety among the PTSD group. Norepinephrine has a U-shaped curve type of effect on brain function—lower levels of release cause an increase in metabolism, and very high levels of release actually cause a decrease in metabolism. We hypothesized that yohimbine would cause a relative decrease in metabolism in patients with PTSD in cortical brain areas that receive noradrenergic innervation. Consistent with this hypothesis, yohimbine administration resulted in a pattern of decreased metabolism in PTSD patients and a pattern of increased metabolism in control subjects in orbitofrontal, temporal, parietal, and prefrontal cortex. PTSD patients (but not control subjects) had decreased hippocampal metabolism with yohimbine (Bremner et al. 1997). These findings are consistent with an increased release of norepinephrine in the brain after yohimbine administration in PTSD patients. The findings are also consistent with PET metabolism studies showing an inverse-U relation between anxiety and cortical function (similar to the Yerkes-Dodson law), with low levels of anxiety causing an increase in cortical metabolism and high levels causing a decrease in cortical metabolism (Gur et al. 1987; Rodriguez et al. 1989).

These findings point to a network of related regions as mediating symptoms of PTSD. Two or more PET studies performed to date showed increased activation in the posterior cingulate and motor cortex, failure of activation in the anterior cingulate, and decreased blood flow in the subcallosal gyrus, hippocampus, middle temporal cortex, and visual association cortex with traumatic stimuli in PTSD. The posterior cingulate plays an important role in visuospatial processing (Devinsky et al. 1995; Vogt et al. 1992) and is therefore an important component of preparation for coping with a physical threat. The posterior cingulate has functional connections with the hippocampus and adjacent cortex, which led to its original classification as part of the "limbic brain" (Gray 1982). PTSD may represent a dysfunction in the brain's response to coping with stress and potential threat, which involves excessive recruitment in brain areas responsible for visuospatial processing, attention, and memory, in addition to attaching an affective valence to stimuli. Motor cortex activation may represent the neural correlate of preparation for action (i.e., fight or flight). The hippocampus is involved in declarative memory as well as contextual

fear. The motor, parietal, and visual association cortex and the posterior cingulate are involved in a functional network with connections to portions of the prefrontal cortex (middle frontal gyrus), which also showed increased activation in the current study. This network between the middle frontal gyrus portion of prefrontal cortex, motor cortex, parietal cortex, posterior cingulate, and visual association cortex mediates memory and visuospatial processing and may represent a neuroanatomical network mediating symptoms of PTSD.

Findings from imaging studies also may be relevant to the failure of extinction to fear responding that is characteristic of PTSD and other anxiety disorders. Following the development of conditioned fear, as in the pairing of a neutral stimulus (bright light—the conditioned stimulus) with a fear-inducing stimulus (electric shock—the unconditioned stimulus), repeated exposure to the conditioned stimulus alone usually results in the gradual loss of fear responding. The phenomenon, known as *extinction to conditioned fear*, has been hypothesized to be secondary to the formation of new memories that mask the original conditioned fear memory. The extinguished memory is rapidly reversible after reexposure to the conditioned-unconditioned stimulus pairing even up to 1 year after the original period of fear conditioning, suggesting that the fear response did not disappear but was merely inhibited. Recent evidence in fact suggests that extinction is mediated by cortical inhibition of amygdala responsiveness. The medial prefrontal cortex (Brodmann's area 25) or adjacent medial prefrontal regions (anterior cingulate—Brodmann's areas 24 and 32) have inhibitory connections to the amygdala that play a role in extinction of fear responding, an important component of the symptom profile of PTSD. The auditory association cortex (middle temporal gyrus) also has projections to the amygdala that seem to be involved in extinction. PET studies in PTSD reviewed earlier in this chapter showed decreased blood flow of the medial prefrontal cortex (Brodmann's area 25) and middle temporal gyrus, with failure of activation of the anterior cingulate and medial orbitofrontal cortex. Based on these findings, we previously argued that anterior cingulate (Brodmann's area 32) activation represents a "normal" brain response to traumatic stimuli that serves to inhibit feelings of fearfulness when no true threat is present. Failure of activation in this area and/or decreased blood flow in adjacent subcallosal gyrus in PTSD may lead to increased fearfulness that is not appropriate for the context, a behavioral response that is highly characteristic of patients with PTSD.

Fear conditioning has been used as a model for the occurrence of pathological anxiety responses to seemingly neutral stimuli. According to this model, the neutral stimulus was originally paired with a truly fearful stimulus, which now may be forgotten. Patients then begin to avoid these stimuli in their everyday life. These subcortical memory traces may be indelible and account for repetitive memories specific to PTSD that are often resistant to cognitively based therapies. Patients with anxiety disorders also have symptoms that reflect a continuous perception of threat. The inability to distinguish true threat from perceived threat in innocuous situations is in fact highly characteristic of the anxiety disorders. The animal model of contextual fear conditioning may represent a good model for these symptoms. Preclinical data suggest that the hippocampus (as well as the bed nucleus of the stria terminalis and the periaqueductal gray; see previous section) plays an important role in the mediation of contextual fear and that increased responding to a conditioned stimulus is due to hippocampal dysfunction. Hippocampal atrophy in PTSD, as described earlier in this chapter, therefore provides a possible neuroanatomical substrate for abnormal contextual fear conditioning and chronic feelings of threat and anxiety in PTSD. Interestingly, in light of studies showing abnormal noradrenergic function in PTSD, the bed nucleus of the stria terminalis has some of the densest noradrenergic innervation of any area in the brain.

Alterations in Neurochemical Stress Response Systems in Patients With Anxiety Disorders

Patients with anxiety disorders have long-term alterations in neurochemical systems that mediate the stress response and that have been shown to be sensitive to chronic stress (Tables 4–1, 4–2, 4–3). Alterations in HPA axis function have been reported in PTSD (reviewed in Yehuda et al. 1995). One possible explanation of clinical findings to date is an increase in neuronal CRF release, with resultant blunting of ACTH response to CRF, increased central glucocorticoid receptor responsiveness, and resultant low levels of peripheral cortisol caused by enhanced negative feedback. Interestingly, nonhuman primates with variable maternal foraging (a model for early life stress) had elevated CSF CRF and decreased CSF cortisol levels in adulthood, a picture that is closer to PTSD than depression (Coplan et al. 1996).

TABLE 4–1. Evidence for alterations in catecholaminergic function in anxiety disorders

	PTSD	Panic disorder
Increased resting heart rate and blood pressure	+/–	+/–
Increased heart rate and blood pressure response to traumatic reminders/panic attacks	+++	++
Increased resting urinary NE and epinephrine	+	++/–
Increased resting plasma NE or MHPG	–	–
Increased plasma NE with traumatic reminders/panic attacks	+	+/–
Increased orthostatic heart rate response to exercise	+	+
Decreased binding to platelet α_2 receptors	+	+/–
Decrease in basal and stimulated activity of cAMP	+/–	+
Decrease in platelet monoamine oxidase activity	+	?
Increased symptoms, heart rate, and plasma MHPG with yohimbine noradrenergic challenge	+	+++
Differential brain metabolic response to yohimbine	+	+

Note. – = one or more studies did not support this finding (with no positive studies), or the majority of studies did not support this finding; +/– = an equal number of studies supported this finding as studies that did not support this finding; + = at least one study supported this finding, with no studies not supporting the finding, or the majority of studies supported the finding; ++ = two or more studies supported this finding, with no studies not supporting the finding; +++ = three or more studies supported this finding, with no studies not supporting the finding; NE = norepinephrine; PTSD = posttraumatic stress disorder; MHPG = 3-methoxy-4-hydroxyphenylglycol; cAMP = cyclic adenosine monophosphate.

Studies showing decreased cortisol in chronic PTSD raise the question of how elevated cortisol can represent the etiology of hippocampal atrophy in PTSD. We have hypothesized that high levels of cortisol *at the time of the stressor* result in damage to hippocampal neurons, which may persist for many years after the original trauma, leading to reductions in hippocampal volume, as measured with magnetic resonance imaging. In this scenario, decreased cortisol characterizes the chronic stages of the disorder as a result of adaptation and long-term changes in cortisol regulation. Longitudinal studies of cortisol in sexually abused girls supports an elevation in cortisol around the time of the stressor, with decreased cortisol developing later in patients who develop chronic symptoms of PTSD (F. Putnam, personal communication, June 1, 1997). However, an alternative hypothesis for hippocampal atrophy is that small hippocampal volume, which is present from birth, is a risk factor for the development of PTSD—in this scenario, high levels of cortisol associated with stress would have nothing to do with hippocampal atrophy.

In patients with panic disorder, the responsiveness of the HPA system to a combined dexamethasone-CRF challenge test was higher than in healthy control subjects but lower than in depressed patients. The difference between panic disorder and depression may be due to overexpression of vasopressin in major depression, which is known to synergize the effect of CRF at corticotropes. The results of the combined dexamethasone-CRH test indicate that a substantial portion of patients with panic disorder have disturbed HPA system regulation. If sensitization by repetitive panic attacks is indeed responsible for progressive HPA dysregulation, and if progressive HPA dysregulation is indeed of decisive importance for the pathogenesis of panic disorder, then therapeutic strategies capable of dampening the hyperactivity of the HPA–locus coeruleus "alarm system" are indicated.

Release of glucocorticoids and/or catecholamines with stress may modulate the encoding of memories of the stressful event. Among the most characteristic features of anxiety disorders such as PTSD and panic disorder is that memories of the traumatic experience or original panic attack remain indelible for decades and are easily reawakened by all sorts of stimuli and stressors. The strength of traumatic memories relates, in part, to the degree to which certain neuromodulatory systems, particularly catecholamines and glucocorticoids, are activated by the traumatic experience. Evidence from experimental and clinical investigations suggests that memory processes remain susceptible to modulating influences after information has been acquired. Long-term alterations in these catecholaminergic and glucocorticoid systems also may be responsible for fragmentation of memories, hyperamnesia, amnesia, deficits in declarative memory, delayed recall of abuse, and other aspects of the wide range of memory distortions in PTSD.

A Working Model for the Neural Circuitry of Anxiety Disorders

Findings of the studies reviewed in this chapter are consistent with dysfunction of an interrelated neurochemical

TABLE 4–2. Evidence for alterations in CRF/HPA axis function in anxiety disorders

	PTSD	Panic disorder
Alterations in urinary cortisol	+/–[a]	+/–
Altered plasma cortisol with 24-hour sampling	+ (decreased)	+ (increased)
Supersuppression with DST	+	–
Blunted ACTH response to CRF	++	+/–
Elevated CRF in CSF	+	+
Increased lymphocyte glucocorticoid receptors	++	NT

Note. – = one or more studies did not support this finding (with no positive studies), or the majority of studies did not support this finding; +/– = an equal number of studies supported this finding as studies that did not support this finding; + = at least one study supported this finding, with no studies not supporting the finding, or the majority of studies supported the finding; ++ = two or more studies supported this finding, with no studies not supporting the finding; +++ = three or more studies supported this finding, with no studies not supporting the finding; NT = not tested (to our knowledge); CRF = corticotropin-releasing factor; HPA = hypothalamic-pituitary-adrenal; PTSD = posttraumatic stress disorder; DST = dexamethasone suppression test; ACTH = adrenocorticotropic hormone; CSF = cerebrospinal fluid.
[a]Findings of decreased urinary cortisol in older male combat veterans and Holocaust survivors and increased cortisol in younger female abuse survivors may be explainable by differences in sex, age, trauma type, or developmental epoch at the time of the trauma.

and neuroanatomical system in human anxiety disorders. PTSD and panic disorder have several biological and phenomenological similarities that allow them to be considered in relation to each other. Phobic disorders and generalized anxiety disorder are still in the early stages of investigation; although they are phenomenologically similar to PTSD and panic disorder, it is premature to include them in a model for human anxiety disorders. Obsessive-compulsive disorder is different in many ways from these other disorders and therefore has not been reviewed in this chapter. With the two anxiety disorders that are therefore the focus of subsequent discussion—PTSD and panic disorder—PTSD is more related to the deleterious effects of environmental stress, whereas panic disorder is not as clearly related to stress and may be more related to genetic variability in anxiety. Therefore, a model can be created that incorporates information from animal and clinical research relevant to these disorder, keeping in mind that working models are subject to modification with new information and that generalizations involving causality should be seen as merely speculative when derived from clinical studies that are, by their very nature, cross-sectional.

A biological model to explain pathological human anxiety should include both brain-stem circuits and cortical and subcortical regions involved in memory and modulation of emotion. The evidence reviewed in this chapter is consistent with chronically increased function of neurochemical systems (CRF and norepinephrine) that mediate the stress response in anxiety disorders. Although activity at the central portion of the HPA axis is increased, responses at other portions of the HPA axis, including the pituitary and adrenal, and long-term effects on the hormonal final product, cortisol, are less clear. Increased norepinephrine and CRF released in the brain act on specific brain areas (including the hippocampus; medial prefrontal, temporal, and parietal cortex; and cingulate) that are dysfunctional in human anxiety disorders. Other neurochemical systems, including benzodiazepines, opiates, dopamine, CCK, and neuropeptide Y, also play a role.

Hippocampal dysfunction may play a role in the pathological symptoms of anxiety. In stress-related anxiety disorders (i.e., PTSD), symptoms and cognitive dysfunction associated with PTSD may be linked to hippocampal dysfunction. Release of glucocorticoids or other stress-related factors (e.g., stress-induced decreases in brain-derived neurotrophic factor) may result in hippocampal damage, with lasting deficits in verbal declarative memory dysfunction in PTSD. Although hippocampal volume reduction appears to be specific to stress-related anxiety disorders, patients with panic disorder have had alterations of parahippocampal gyrus and other portions of extrahippocampal temporal lobe that may underlie declarative memory deficits also seen in panic disorder. Increased cortisol release with stress in both PTSD and panic disorder may result in amnesia and cognitive dysfunction associated with these disorders. Excessive release of norepinephrine with stressors in anxiety disorder patients will be predicted to result in decreased function of neurons, which may be related to both cognitive dysfunction and increased anxiety with stress. In addition, given the known role of the hippocampus in contextual fear, lasting damage to the hippocampus may contribute to excessive anxiety and fear responding in anxiety disorders. Finally, because the hippocampus is involved in inte-

TABLE 4–3. Evidence for alterations in other neurotransmitter systems in anxiety disorders

	PTSD	Panic disorder
Benzodiazepine		
Increased symptomatology with benzodiazepine antagonist	–	++
Opiate		
Naloxone-reversible analgesia	+	
Increased plasma β-endorphin response to exercise	+	
Increased endogenous opiates in CSF	+	
Serotonin		
Decreased serotonin reuptake site binding in platelets	++	
Decreased serotonin transmitter in platelets	–	
Blunted prolactin response to buspirone (5-HT_{1A} probe)	–	
Altered serotonin effect on cAMP in platelets (5-HT_{1A} probe)	–	
Thyroid		
Increased baseline thyroxine	+	
Increased TSH response to TRH	+	
Somatostatin		
Increased somatostatin levels at baseline in CSF	+	
Cholecystokinin (CCK)		
Increased anxiety symptoms with CCK administration	NT	++

Note. – = one or more studies did not support this finding (with no positive studies), or the majority of studies did not support this finding; + = at least one study supported this finding, with no studies not supporting the finding, or the majority of studies supported the finding; ++ = two or more studies supported this finding, with no studies not supporting the finding; NT = not tested (to our knowledge); PTSD = posttraumatic stress disorder; CSF = cerebrospinal fluid; 5-HT_{1A} = serotonin type 1A; cAMP = cyclic adenosine monophosphate; TSH = thyroid-stimulating hormone; TRH = thyrotropin-releasing hormone.

gration of individual aspects of memory at the time of memory retrieval, hippocampal dysfunction may lead to memory fragmentation and amnesia in anxiety disorders.

The medial prefrontal cortex also plays a prominent role in anxiety. Moving up in terms of species complexity, the most salient change in brain architecture is the massive increase in cortical gray matter, especially frontal cortex. It is therefore not surprising that the frontal lobe plays a role in the phenomenon uniquely associated with our species—that is, emotion. The medial portion of the prefrontal cortex seems to have an important role in human emotion and anxiety. The medial prefrontal cortex (Brodmann's area 25—subcallosal gyrus and Brodmann's area 32—anterior cingulate) has inhibitory inputs that decrease amygdala responsiveness and has been hypothesized to mediate extinction of fear responding. Brodmann's area 25 also stimulates the peripheral cortisol and sympathetic response to stress. Activation of this area has been shown to be a normal response to stress or increased emotionality. We have hypothesized that dysfunction in this area may mediate increased emotionality and failure of extinction to fear-inducing cues in anxiety disorders. Evidence to support this idea includes failure of normal activation in this area with yohimbine-induced provocation of anxiety in both PTSD and panic disorder and failure of activation/decreased blood flow with traumatic cue exposure in PTSD. Again, potentiated release of norepinephrine with stressors in PTSD and panic disorder is expected to be associated with a relative decrease in function of neurons in this area. Findings in anxiety disorders are consistent with a long literature, mostly from studies of lesions in human subjects, supporting a role for medial prefrontal cortex in emotionality.

Studies performed to date are encouraging in that many findings from animal studies have been successfully applied to human anxiety disorders. The past decade has seen an exciting expansion of research in human anxiety disorders. Future research must continue to apply findings from the revolution in neuroscience to understand human anxiety disorders.

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5

Evolutionary Concepts of Anxiety

Myron A. Hofer, M.D.

For the last century or more, psychiatry has been divided by a shifting alignment of opposing theoretical views on the nature and origins of mental illness. But recent developments in the field of evolution now offer the opportunity for psychiatry to be unified by a broadening of evolutionary theory that would integrate the social, psychological, and biological levels of organization. By exploring current concepts on the evolution of anxiety, I hope to illustrate how advances in our understanding of evolutionary processes may make such a cohesive integration possible. These new developments involve discoveries in several areas: in the fossil record of evolution and in the application of DNA mapping to phylogeny, in field studies documenting the ongoing process of rapid evolutionary change, in our understanding of the interaction between developmental and evolutionary processes, in the arrival of a new field of evolutionary studies—sociobiology, and in the discovery of laboratory models of anxiety in a range of organisms representing our phylogenetically distant ancestors.

In addition to the advances in the field of evolution, major changes have taken place in our concept of the emotions, changes that facilitate application of the new evolutionary concepts to anxiety. In traditional theory, emotions were considered as discrete entities, each defined by certain characteristic behavioral and physiological response patterns (Darwin 1872/1965; Izard 1977; Lewis and Brooks-Gunn 1979). In development and in evolution, emotions were believed to emerge as units and to follow the appearance of new cognitive advances or structures. The new view, in contrast, is a functional or transactional one (Campos et al. 1994; Lazarus 1991). Emotions are seen as processes existing at the interface of the organism and its transactions with the environment. They are defined in terms of particular characteristics of the functional relationships between the organism and the environment, serving to regulate (establish, maintain, or disrupt) these relationships. Different families of emotions can be defined in terms of the nature, dynamics, and adaptive role of those transactions rather than in terms of certain invariant features of the response. In development and in evolution, each family of emotions emerges gradually, together with its cognitive components, following growth in the complexity of the organism.

Thus, in this chapter, I view anxiety as an organized group of functions by which an organism senses, evaluates, and responds to cues of danger in its external (or internal) environment. In the first half, I review several advances in the concept of evolution as it applies to be-

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havior and specifically to anxiety. In the second half, I use these concepts to describe the organization of prototypical anxiety states in four very different contemporary species, representing major steps in the evolution of anxiety as we know it.

New Developments in Evolutionary Studies

To consider the evolution of any behavior or mental state, we must first deal with the skeptic's question: how can you even talk about the evolution of something like anxiety that leaves no fossil record? New evidence in the rapidly expanding fossil record (Eldredge and Gould 1972) and in DNA for the timing of divergence of vertebrate lineages (e.g., Kumar and Hedges 1998) has modified evolutionary theory in a way that allows us to use evidence from contemporary mammals to infer how anxiety manifested itself in our phylogenetic ancestors and how it evolved. This modification is a shift away from the view of evolution as having progressed with the slow, incremental effect of cumulative small changes. In the old "phyletic gradualism," no contemporary species was thought to resemble closely our distant ancestors. But extensive fossil evidence now shows that once a species has evolved, it rarely undergoes major change. The evolution of new species occurs only at intervals of many millions of years and in relatively rapid (20,000–40,000 years) spurts, occurring in a small subpopulation at the geographic border of the species range where selection pressures are likely to be the strongest. The new view has been termed *punctuated equilibria* (Eldredge 1989). It does not mean that we can simply assume that a rat, a marine invertebrate, or a microbe that we study in the laboratory today is a precise replica of a creature existing much earlier in phylogeny. But the conservative nature of evolution has resulted in a stability, over hundreds of millions of years, of numerous genes, cell structures, biochemical mechanisms, intercellular messengers, and major features of neural circuitry. Thus, by studying contemporary species, we are likely to obtain useful insights into the probable workings of our distant ancestors' adaptive responses, even of their brain states, the precursors of anxiety. The second section of this chapter illustrates such an approach in some detail.

The *existence* of evolution over millennia can only be supported by the geological and fossil record. However, the *mechanism* of evolution, natural selection, is primarily supported by contemporary evidence provided in the remarkable variation in domesticated species (Darwin 1868/1998), in the range of available laboratory animals resulting from selection by scientists (DeFries et al. 1981), and in the recent field studies of selection under the natural pressures of yearly climatic change (Grant 1986). Examples of rapid evolution under experimental selection for anxiety traits are described later in this chapter and in papers by Suomi (1997) and Brunelli et al. (1997). Because these forms of selection have been shown to alter behavioral and biological traits of small groups of animals in a rapid and powerful manner over a few generations, this constitutes the most direct evidence we have as to how the emotions, and anxiety itself, may have evolved over geological time.

In contrast to the evolution of new species (macroevolution), individual traits show rapid changes in intensity or form within species, under changing environmental pressures (microevolution). Variation produced in this manner can create extremes in a trait such as anxiety that form the basis for the evolution of human temperamental differences in vulnerability to anxiety disorders (Marks and Nesse 1994) (as described by Pollack et al. in Chapter 18 of this volume).

We know surprisingly little about the development of anxiety in the individual, but this may well be an area in which new evolutionary concepts can be helpful in gaining an understanding of human anxiety. For it is becoming evident that one of the most powerful mechanisms for producing rapid, major changes in evolution is through alterations in the developmental schedules of individual traits (McKinney and McNamara 1991). Each system within the organism and each behavioral trait has its own developmental schedule for expression, one strongly shaped by genetic timing mechanisms ("heterochrony"). When one of these timing genes or its regulatory components is altered by selection or mutation, the developmental schedule for that trait is shifted in relation to the others. A single mutation in a timing gene can have major effects on the phenotype that are nevertheless not lethal because of accommodation by other developing systems. Or, a minor change in the developmental schedule of one trait can have multiplier effects on the developing phenotype through the effects of this change in one system on other developmental schedules.

In this way, the newly appreciated principle of heterochrony serves to unite the processes of evolution with those of development and helps us understand the heterogeneity of the manifestations of anxiety over the course

of development and within individuals of a given age. For selection pressures tend to act on a single component of a trait and do so by altering the development of that component in relation to the development of other aspects of behavior in that subpopulation. An example of this can be found in selective breeding studies in mice (Gariepy 1990). Selection for low levels of aggression in adulthood shifted the whole course of the development of aggressive behavior by prolonging into adulthood the normal juvenile trait of a slow latency to attack, while leaving other aspects of aggression unchanged.

Such processes at work during hominid evolution, in response to a varied range of environmental demands at different ages, may help account for the great interindividual variability in the forms and manifestations of anxiety in today's population. For example, the appearance of stranger anxiety at about age 6 months in a broad range of human cultures and child-rearing practices has been related by Marks and Nesse (1994) to the appearance of the capacity for rapid crawling and exploratory behavior at that age that can expose the infant to potentially dangerous strangers. Infanticide by unrelated males is a widespread reproductive strategy in primates as well as other species (Hrdy 1977) and is likely to have been a strong selective force in human evolution. Thus, the appearance of particular forms of anxiety at different ages in contemporary patients may be traced to age-specific forces in our distant past.

The application of evolutionary concepts to our understanding of emotions, begun by Darwin (1872/1965) with the publication of *The Expression of the Emotions in Man and Animals*, strongly influenced many later developments in psychology, such as psychoanalysis and ethology. More recently, Haldane (1932/1993), Hamilton (1964), Trivers (1974), and finally Wilson (1975) brought about a synthesis of ethology, evolutionary biology, and population genetics, which Wilson called *sociobiology*. Comparative psychology has been transformed as a result, but the application of this thinking to psychiatric illness has been delayed by a reluctance within the field to accept the idea of genetic influences on aspects of human personality and/or by a concept of illness limited to the medical models of infectious, nutritional, and degenerative disease; environmental toxins; and sporadic single gene mutations. In the last few years, however, there are signs of an awakening of interest within medicine and psychiatry in particular to the usefulness of an evolutionary approach (McGuire and Troisi 1998; Nesse and Williams 1996). This movement is likely to grow with the rapid advance of genetics in medicine.

One of the major difficulties that psychiatrists have with evolutionary accounts of the origin of major mental illnesses is the obvious incapacitating effects of these conditions on their patients, effects that should have led to their disappearance from the gene pool in the more hostile environments of our prehistoric past. It is easy to contend that although evolution may have given us adaptive patterns of response, this cannot account for clinical conditions such as panic disorder. How can evolution account for such extreme forms of behavior, without the intervention of a recent gene mutation? This question has several possible answers, and one of them goes back to one of the principal lines of evidence used by Darwin (1859/1976) in the first chapter of *The Origin of Species by Means of Natural Selection* and presented in detail in the two volumes Darwin published a decade later (1868/1998) as the most compelling evidence for his theory. Overwhelming evidence indicates that when plants or animals are brought from their ecological niches in the wild into the conditions of domestication, a remarkable increase occurs in the degree of variation between individual members and the appearance of new traits, or the exaggeration of traits seen in the wild. Darwin reasoned that these new variants appeared because of the relaxation of the harsh and limiting selective pressures of their particular niches and because of the developmental effects of novel environments, such as high levels of nutrition, that (somehow) facilitated the expression of novel traits, although Darwin could suggest no mechanism at the time. Today, we know that such facilitation could be caused by the unmasking of latent genes that had remained unexpressed. With the pervasive relaxation of natural selective pressures brought about by civilization, and the novel environments thrust on humans by technological change, it appears likely that conditions are present for the expression of great variability in human traits. It is intriguing to speculate that patients with incapacitating anxiety may well represent one of the results of the increased variation of humans under the influence of civilization.

Another evolutionary process may allow us to understand how incapacitating mental illnesses such as schizophrenia, bipolar disorder, and panic disorder may have evolved. This is the property of evolution to operate through trade-off and compromise. A favorite example is the evolution of sickle cell anemia (a disease that occurs in only those who are homozygous for the trait) in an evolutionary trade-off for the resistance to malaria conferred on the far greater number who are heterozygous and therefore unaffected with the sickle

cell abnormality in their hemoglobin. In a similar way, evolution may have allowed the capacity for extreme forms of anxiety, such as those constituting clinical anxiety disorders, to evolve in some individuals as a trade-off for the advantage conferred by more moderate and adaptive levels of the same trait in most individuals.

New evidence from developmental studies has clarified the crucial importance of the changing environment, as well as the changing genome, in the evolutionary processes discussed above (Gottlieb 1987, 1992; Ho and Saunders 1984). Environmental stresses play a central role in the expression of anxiety and in the precipitation of episodes of mental illness. In fact, stress may best be defined as consisting of those major selection pressures under which humankind has evolved: those events that threaten our "reproductive fitness" (H. Weiner 1992). Furthermore, it has become increasingly clear in studies that behavioral responses to stress can be the "leading edge" of evolution, in the sense that the organism's behavior is often responsible for its moving into a new environment or using a new food source and that, in this way, modification of behavior often precedes the evolution of new structural and physiological traits (Grant 1986; J. Weiner 1994). Thus, the behavioral and emotional responses to stress, which in extreme forms constitute mental illness, may be at the center of the evolutionary story as initiators of evolutionary change, not simply as products. In this way, environmental change and the highly variable behavioral responses of organisms to it have been central actors in the evolution of anxiety.

Psychiatric opinion is divided at present along a continuum ranging from a belief that pathological genetic and environmental events of comparatively recent origin are primarily responsible for the clinical anxiety disorders to a view of these conditions as simply representing the extremes of evolved adaptive responses. The evidence described in this chapter is presented to show how an evolutionary perspective can illuminate both clinical and research approaches to the anxiety disorders and predicts that when the etiology of the anxiety disorders is finally understood, a major component, at least, will involve variation in individual vulnerability that is a legacy of our evolution (Hofer 1995).

Major Steps in the Evolution of Anxiety

Looking beyond the processes of evolution, we can see that we have shared with other species the problems in living, even more than the solutions. It is therefore illuminating to observe in present-day species that represent our phyletic heritage, different kinds of solutions to the common problem of avoiding danger. The role of specific signal cues, the importance of memory for the context of stressful events, the occurrence of anxiety in the setting of early separation, and the adaptive value of states of enhanced attention to clues of danger are all illustrated in the examples below. I have chosen a single-celled organism, a marine invertebrate, a common vertebrate mammal, and a nonhuman primate. With these examples, I hope to illustrate some of the aspects of anxiety that are likely to have evolved first and those that appear to be later acquisitions by species that occupy steps in evolution similar to those taken by our ancestors over hundreds of millions of years.

Minimal Necessary Conditions in Bacteria

The essential elements within which an anxiety state might evolve would consist of the following: a means to detect signals, a means to discriminate those that denote danger, and the capacity to initiate behavior that results in avoidance of that danger. Anxiety, as we currently understand it, occurs somewhere within the matrix of those capacities. Definitions of anxiety require several attributes in addition to these basic functions, but if we are looking within the whole phylogeny for when the simplest forms of anxiety first appeared, organisms with this sort of basic equipment would be the place to start. Because of our use of words such as *detect*, *discriminate*, and *initiate* to refer to our own conscious processes, these capabilities would appear at first glance to require the evolution of animals with complex brains. However, in reality, much simpler processes can be used to carry out the essential functions outlined, processes that can be found in single-celled organisms such as motile bacteria with thin, hairlike flagella. This places the starting point for our evolutionary search to the period between 2 billion and 600 million years ago (Margulis 1993) before the great Cambrian "explosion" of life in which the major animal phyla first appeared about 580 million years ago. The discovery of complex behavior in present-day typhoid and coliform bacteria and the elucidation of the underlying biochemical mechanisms by Daniel Koshland (1980) provides a vivid demonstration of the fact that adaptive behavior does not require consciousness or even a brain.

Motile bacteria are equipped with five to seven whiplike flagella that drive them forward through the fluids that surround them. These flagella are attached to the cell membrane in a way that permits them to

rotate like propellers. Koshland found that these cell membranes also contain up to 30 receptors. Flagella and receptors are both widely distributed over the surface of the cell membrane and are functionally linked through a series of intracellular biochemical pathways that are enzyme regulated. The receptors respond to specific molecules and control the actions of the flagella so that the bacterium can either move forward or stop. For example, in response to certain molecules in the water, acting at the membrane receptors, the flagella all rotate in the same direction, forming a tight bundle that effectively drives the bacterium forward with a single corkscrewlike action. In response to other molecules, the flagella alternately rotate clockwise and counterclockwise. This causes the flagella to fly apart and then exert inconsistent and discordant forces at the various individual flagellar attachment sites on the cell membrane so that the bacterium stops and then "tumbles" in place.

This simple system allows the bacterium to move forward in a relatively straight line, to stop, and then to move off again in what is likely to be a new direction determined randomly by the orientation of the bacterium at the moment that uniform flagellar rotation resumes. This allows the bacterium to approach sources of one kind of molecular signal (e.g., sugar) but also to stop and change direction when another kind of specific signal molecule (e.g., a toxin) binds to a receptor. By trial and error, it will thus gradually move away from the source of a signal that it is predisposed to avoid. The receptor, its transmembrane protein linkage, and its intracellular signaling mechanism embody the components that are familiar to us as the basis for communication within the brain by neurotransmitter molecules. In the bacterium, they directly control the behavior of the cell in which they exist. Koshland found that some of the membrane receptors are "constitutive" and do not change with the environment, whereas others are "inducible" by exposure of the bacteria to high concentrations of certain molecules. Nine genes play a role in the formation of receptor types. Thus, responses of the cell are affected by hereditary, environmental, and probabilistic factors in the life processes of cell division, mobility, and replication of the organism. For bacteria in a given culture can be shown to have highly individual response properties despite being identical in heredity and general environment, and these differences remain for the lifetime of the cell.

The presence of multiple receptors and time-dependent intracellular enzyme systems allows a limited degree of integration and flexibility in responses. For example, when both attractant and repellent molecules are present, bacteria respond as an algebraic function of both influences. After weak stimuli, a return to previous functioning is more rapid than after strong stimuli, and suppression of tumbling in response to positive (e.g., nutrient) gradients is long lasting, whereas initiation of tumbling in response to negative (e.g., toxic) gradients is extremely rapid in onset. However, the only form of learning appears to be habituation, and bacterial memory is extremely short (about half a second).

A single-celled organism clearly has evolved the machinery for an organized behavioral repertoire with some fairly sophisticated capabilities. It can approach weak stimuli that are beneficial and it can flee from very strong stimuli and those that signal danger. When it stops and tumbles in response to loss of a positive signal or the presence of a negative signal, is it anxious? Certainly, we would not want to say so, even though the mental picture of a tumbling creature with flagellar hairs standing on end may be intuitively persuasive. A change in behavioral state has taken place in the bacterium that differs from anxiety, primarily in the simplicity of the information and memory processes taking place and in the narrowness of the repertoire of responses available. We have a scaled-down, highly simplified prototype for anxiety, which is capable of producing some of the behaviors seen in anxious humans. The presence of these behaviors in so primitive an organism gives us an idea of how basic a state resembling anxiety has been for survival of life forms.

Two Types of Acquired Anxiety in an Invertebrate

Hundreds of millions of years after the first bacteria, the marine invertebrates emerged in the Cambrian period, 500 million years ago. Members of this order exist today in a physical form that has remained essentially unchanged, according to the fossil record. A modern representative of the class is *Aplysia californicus*, the sea hare studied with such success by Eric Kandel and his colleagues. Through the specialization of cellular function, the organization of groups of these cells into component organs, and the integration of organs into a self-contained system, evolution has enormously increased the variety of behaviors and the range of signals available. This complex organization now has different functional states that are specialized for responding to certain types of signals and for carrying out one or another set of behaviors. Examples of such states are hunger and sexual arousal. After some consideration, we may want to call these motivational or emotional states.

The range of signals has been expanded by a crucial new addition, the capacity to detect and represent the contingencies between signals and events, to learn, and to remember. Through the organization of groups of cells specialized for signal processing, this simple nervous system now can respond to an event in terms of its past experience as well as its current environmental input.

The sea hare normally flees from contact with its natural predator, the starfish, a response also carried out (less reliably and efficiently) by the typhoid bacillus in response to a similar chemical signal. Kandel and colleagues (reviewed in Kandel 1983) showed that a chemical stimulus that *Aplysia* normally ignored, shrimp juice, could be made a signal for an escape response by associating it repeatedly with electric shock, the laboratory equivalent of a starfish attack. But they went further by showing that after such an experience, shrimp juice, when encountered a second time, induced a state change in *Aplysia* during which other defensive responses (not involved in the original training) were enhanced, such as gill withdrawal and the release of protective clouds of ink. This state change also involved a reduction in appetitive behaviors such as feeding. An innocuous event had thus become a signal eliciting an anticipatory state in which responses to threat were exaggerated and what we might call pleasurable behaviors were inhibited; a simple form of anticipatory anxiety had been induced.

The sea hare in the previous experiments behaved normally after training when shrimp juice was not present. In the second procedure, a prototype of chronic anxiety was produced in which the animal showed a persistent state of altered responsiveness similar to that induced by shrimp juice but without requiring a danger signal. A series of unavoidable electrical shocks were used (sensitization), which produced a change in response repertoire over several weeks following the traumatic events. During this persistent state, defensive and escape responses were exaggerated, and responses to positive events were blunted; an abnormal behavioral repertoire had been established that resembled a form of chronic diffuse anxiety.

These two simple paradigms, one for anticipatory signaled anxiety and the other for chronic generalized anxiety, have become the focus of intense efforts to determine the neural and molecular mechanisms for the altered states and their novel behavioral responses. The neurotransmitter serotonin, the components of the biochemical cascade, and the enzyme protein kinase identified by these studies are all conserved by evolution and are key elements underlying brain activity in higher animals, including humans. In the *Aplysia*, the short- and long-term presynaptic facilitation that was found to underlie anticipatory and chronic anxiety-like states has become a particularly promising model for understanding the molecular mechanisms for memory. This is a turn of events that Freud would enjoy, considering his emphasis on the role of remembered states in human anxiety.

Separation Anxiety in a Small Mammal

Next we come to the age of the dinosaurs, 100–200 million years ago, when our ancestors, small terrestrial mammals, were found on dry land, scurrying through the undergrowth of the forest floor, out of sight of the great reptiles. Only the most adaptive of these survived the great extinction of species that brought an end to the age of the dinosaurs 65 million years ago. Of today's small mammals, one of the most successful orders is the rodents, and a domesticated strain, the laboratory rat, is the species of animal we know the most about next to the human. For this reason, and because it has been the subject of my own research, I have chosen this animal to represent an evolutionary innovation introduced by our early mammalian ancestors.

Paul MacLean has studied the probable evolution of the brain that accompanied the splitting off of mammals from reptilian ancestors 250 million years ago. He argues that the evolution of the limbic system of the brain in mammals distinguishes them from all modern reptiles, endowing mammals with a set of novel behaviors and brain structures. According to MacLean (1985), the three crucial behavioral attributes that evolved with the mammals are play, parental behavior, and the separation cry, all of which, he points out, are absent in most modern-day reptiles. MacLean provides neuroanatomical and neurophysiological evidence supporting his theory that the presence of these behaviors in modern-day mammals is made possible by the specialized neural networks of the limbic system and their connections to the cerebral cortex and the midbrain. The evolution of social relationships based on mutual attachment in mammals provides a new set of behaviors, motivational systems, and dangers within which a new variant of anxiety can evolve. The infant's separation cry is a communication to the mother with adaptive value; it is also a manifestation of a state of distress that may constitute the first innate anxiety state to evolve.

Here, the cues are not learned, as in the sea hare, for rat infants respond with loud (60–90 dB) calls, in the ul-

trasonic frequency range, to their first experienced separation. Evolution has endowed mammalian infants with a response to a set of cues (isolation from conspecifics) that represent the potential for several actual dangers. The uncertain nature of the dangers and the sudden loss of their familiar and responsive companions add new dimensions to this form of anxiety that were not present in the simpler forms of anxiety elicited in marine invertebrates in the previous subsection. Thus, the evolution of prolonged immaturity of offspring and the related period of close parental care created the basis for a new form of anxiety in this relatively primitive mammal, a form that seems to resemble the separation anxiety we are familiar with in children and even in adult humans.

In 1956, an Austrian ethologist, Wolfgang Schleidt, and his student Zippelius discovered that young mice emitted short bursts of very-high-frequency sound, similar to the then recently discovered ultrasonic pulses of bats that had provided an animal analogue for the sonar developed by the allies for antisubmarine patrol in World War II (Zippelius and Schleidt 1956). The emphasis of early research on this phenomenon was on the environmental events (such as cold, rough handling, altered substrate odor or texture, and novelty) to which rat or mouse infants were responding when they initiated calling and on the maternal search and retrieval behaviors elicited by these calls. I became interested in this behavior after I found that rat pups showed other behavioral and physiological responses to separation from their mother (reviewed in Hofer 1996a). In a series of studies, my colleague and I (Hofer and Shair 1978) first found that pups emitted these calls, even in the home cage nest, if all their littermates and mother were removed, showing that separation from social companions was a key element in eliciting these vocalizations. Next, we found that if pups were alone in an unfamiliar place, they would greatly reduce or cease calling when a littermate or their mother was placed with them, even if she was completely passive (anesthetized).

We now had a behavioral indicator for a state induced rapidly by separation, one that could be roughly quantified. And we had a means of rapidly terminating the state by what appeared to be a form of contact comfort. Because the separation-induced state depended on the effect social companions had on pups, we embarked on a search for the cues to which the pup was responding in this contact comfort response and the sensory pathways by which the pup was processing this information (Hofer and Shair 1980, 1991). We found that after the neonatal period, pups appeared to be responding to texture, odor, and temperature in a cumulative fashion, with contour and size as additional factors.

But as scientific skeptics, we wondered whether rat pups really experience separation negatively and whether the state induced by separation involves a change in the way the pup responds to new information, as was found during the state induced by sensitization in *Aplysia* and as is familiar to us from our own experiences with anxiety. Experiments by researchers interested in early learning have given affirmative answers to both of these questions. Isolated rat pups will learn difficult maze problems to get back to their mothers (Kenny and Blass 1977), and for a separated pup, merely experiencing short periods of contact with the mother acts as a powerful reinforcer (Amsel et al. 1977). Furthermore, cues associated with separation are strongly avoided when encountered subsequently (Smith et al. 1985). These findings show that rat pups dislike separation and are strongly predisposed to respond to cues associated with reunion. In addition, Norman Spear's group found a variety of associations, discriminations, and tasks that rat pups learned less well when they were separated from their home cages than when they were provided with familiar nest cues during the learning experience (summarized in Spear et al. 1985). This was not a simple generalized interference with functioning, however. As in human anxiety, rat pups form some associations *more* readily when isolated. They learn to associate novel tastes and odors with illness and then avoid those cues (taste aversion learning) two to three times more strongly when separated than when the learning took place in the home cage.

These striking effects of social isolation and of home cage contextual cues are not seen in older juvenile and adult rats. Thus, growing evidence indicates that altered information processing is specific to young rats. Perceptual and cognitive alterations characteristic of the state of anxiety are present in a simple form in the *Aplysia* (see previous section, "Two Types of Acquired Anxiety in an Invertebrate"), and involve more complex manifestations as we move on to animals such as the rodent and primate with more elaborate brains.

For those most interested in the neurobiological mechanisms of anxiety, studies on drugs and neuropeptide modulators have provided the most compelling evidence that the isolation distress state of young rats provides a useful animal model of anxiety. Studies over the past 5–6 years have found that most major classes of drugs that are useful in human anxiety have powerful

and selective inhibitory effects on isolation-induced ultrasonic calls in rat pups, usually without affecting other behaviors or inducing signs of sedation. Even more convincing is that synthetic compounds known to produce severe anxiety in human volunteers (such as pentylenetetrazol and the inverse agonist benzodiazepines) greatly increase the call rate in isolated pups and can even elicit calling in the home cage when the pup is with its familiar littermates (for reviews, see Hofer 1996a; Miczek et al. 1991).

The benzodiazepines were the first anxiolytics found to be effective for isolation distress in rat pups, and Insel et al. (1989) have autoradiographic evidence that an endogenous ligand at the γ-aminobutyric acid (GABA)-benzodiazepine receptor complex in the cerebral cortex and hippocampus may play a role in rat pup isolation distress. Morphine and more recently synthesized specific μ and δ opiate receptor ligands decrease calling, whereas a specific κ receptor ligand increases calling in isolated pups (Carden et al. 1991). κ opiate receptor activation even causes pups in the home cage nest to vocalize vigorously. Thus, endogenous opiates may play a role in both the initiation and the reduction of isolation distress. This possibility is strengthened by our finding that naltrexone, an opiate receptor blocker, prevents companion comfort response to littermates in young rats (Carden and Hofer 1990). This finding suggests that social companions exert some of their comforting effect by stimulating endogenous μ and/or δ opiate release in young that have become displaced from the nest.

Winslow and Insel (1990) showed that rat pups respond to clinically effective anxiolytic drugs that are active primarily on the serotonin system, such as the reuptake inhibitor clomipramine and the serotonin type 1A (5-HT_{1A}) receptor agonist buspirone. Neuropeptides such as cholecystokinin (implicated in human satiety), which are known to reduce anxiety in humans, reduce ultrasonic calling in young rats (Weller and Blass 1988). Insel (1992) proposed oxytocin as a neuropeptide underlying a broad range of affiliative behaviors. Oxytocin is present in maternal milk and may well be absorbed by nursing pups. When given to isolated rat pups, it reduces calling.

How did vocalization first evolve as a manifestation of the separation state, so that the mother's retrieval behavior could then act selectively to enhance survival of vocal young and establish this important mother-infant communication system? To answer this question, we should recall 1) the close natural association of cold temperature with displacement from the mother and home nest in small mammals and 2) that cold ambient temperature is a major cue for the elicitation of isolation calls in isolated rat pups.

We recently found more direct evidence for the evolution of the separation call from a physiological response to cold exposure. When rat pups were made severely hypothermic (25°C below normal) and recovered at room temperature (a routine surgical anesthesia procedure), we found to our great surprise that they started to emit ultrasonic vocalization when they were still comatose, at surgical levels of anesthesia (Hofer and Shair 1992). These hypothermic ultrasounds are produced by the same laryngeal mechanism as isolation calls and have similar acoustic properties. Although they are emitted at a slower tempo than isolation calls, because of the slow respiratory rates of pups at such low temperatures, rat mothers will respond to hearing these calls by searching and will use them as directional cues (Brunelli et al. 1994).

However, this behavior may not have originated, in evolution, as a signal to the mother but rather in a physiological role. We found that when hypothermic pups were devocalized and were no longer able to generate positive intrapulmonary pressure by breathing against a closed larynx, they did not rewarm nearly as fast as vocal pups, and developed pulmonary edema, failing to recover in some cases. These findings closely parallel the pulmonary edema that regularly occurs during rewarming from severe hypothermia in humans and the use of positive-pressure respiratory therapy in its treatment. They tend to support the hypothesis (Blumberg and Alberts 1990) that the communicatory aspects of infant vocalization represent an "exaptation," in which a physiological regulatory response (laryngeal braking and the high-pitched sound inadvertently produced) that originally evolved as an adaptation to cold later became co-opted by the evolutionary process to function in a new role as a signaling response in parent-infant communication. Our language today represents an ancient association of social separation and cold in phrases such as "left out in the cold" and the use of "warm" or "cold" to describe emotional closeness or distance. These terms may not be simply modern metaphors but testimony to an ancient role for the separation cry during periods in our evolution when thermal stresses were unavoidable and when the underlying laryngeal activity may have acted as a strong physiological selection factor promoting survival after severe hypothermia.

The nature of later evolutionary selection pressures is evident in the sensory and perceptual adaptations of rodent mothers to these ultrasonic vocalizations, physiological adaptations that underlie their sensitive and

specific search, retrieval, and caregiving responses (Ehret 1992). But the infant's isolation call also can attract predators, and certain predator odors dramatically suppresses ultrasonic vocalizations in isolated pups (Takahashi 1992). This seeming paradox is an example of what is known as an "evolutionary trade-off," a ratio of risk to benefit that is thought to have shaped many of our behaviors. The theory predicts that in environments with many predators, infants that show less isolation calling will gradually increase in the population. However, when nest disruption occurs frequently (e.g., through flooding) and fewer predators exist, high rates of isolation calling would be advantageous.

To explore these hypothetical evolutionary processes, we have been conducting an experiment in the laboratory that simulates them: selectively breeding rats that, as infants, had shown relatively high or relatively low rates of ultrasonic vocalization responses to isolation. We found that, in as few as five generations, two distinct subpopulations emerged that differed widely on this infantile trait (Brunelli et al. 1997). Clearly, this manifestation of early separation anxiety has a strong hereditary component. This laboratory study of evolutionary processes should allow us to ask some interesting questions. In the rodent families with high (and low) levels of vocal separation responses as infants, will their adult responses to anxiety-provoking situations be different, and in what ways? How will the neural substrates for isolation calling be altered in the two different strains? Will other responses of the infants to isolation (e.g., autonomic, adrenocortical) be increased (and decreased) along with the vocal responses? Studies like this one promise to help us understand basic questions about the relation between natural selection, development, and the evolution of vulnerability to extreme levels of anxiety.

If early experiences of separation constitute the first anxiety in our lives and if anxiety in adulthood reevokes this early experience, as Freud and others have supposed, then knowledge about this relatively simple form of anxiety in rat pups may help us understand the more complex forms and manifestations of anxiety in primates such as our own species. Already in the rat pup, this state involves a range of cognitive alterations, a communicative role for affect display, and a neural substrate involving all of the major neuromodulatory systems known to modulate clinical anxiety in humans.

Primate Anxiety

Looking back into our recent past, 10–20 million years ago, our ancestors were likely to have resembled modern-day Old World monkeys and apes. The brains and behavior of these animals, which share 90%–99% of our genes, are uncannily similar to those of humans. Studies on rhesus macaques, for example, have allowed us to verify clinically derived hypotheses relating the powerful effects of both environmental events and genetic constitution on the etiology of severe and crippling anxiety states in individual monkeys. They have documented, under natural conditions, the transition from evolutionarily adaptive forms of anxiety to lasting incapacitating states resulting in substantial mortality. This work, described in other chapters on animal models of individual disorders, extends the conceptual bridge that I have tried to portray in this chapter between evolution and clinical psychiatry, between normal and pathological anxiety.

Suomi and his colleagues (reviewed in Suomi 1997) described a subpopulation (20%) of rhesus monkeys living under natural conditions on an island in the Caribbean; these monkeys had most of the signs of a mild generalized anxiety disorder. As infants, they showed less exploratory behavior, and as juveniles, when the mother left for hours or days in the breeding season, they showed enhanced agitation, followed by lethargy, a fetal-like huddled posture, and social withdrawal. The great majority of their age-mates showed little response or actually increased their social interactions with peers in the mother's absence. Here, both anxiety and depressive behavior were enhanced in a subgroup of monkeys, as is found clinically in a subgroup of humans. As adolescents, males in the vulnerable subpopulation left their social group later than other males and were less able to establish new affiliations.

The anxiety-prone temperamental characteristics of this subgroup are greatly exaggerated by rearing conditions of inadequate mothering, as when they are experimentally reared with peers instead of their mother. Their physical, motor, and social-behavioral repertoires develop adequately, but their tendency toward anxious withdrawal and avoidance is so greatly enhanced that as young adults, they drop to the bottom of dominance hierarchies within the social structure of their group. These anxiety-prone characteristics are clearly heritable, as shown by selective breeding studies. But they are also sharply modified by variations in maternal behavior during rearing: If they are fostered to unusually nurturant and experienced mothers, then the expression of the anxious traits is prevented.

What do these findings in nonhuman primates tell us about evolutionary processes in the origin of clinical anxiety disorder in humans? First, heritable traits pre-

disposing to anxiety appear to be distributed within populations so as to leave an appreciable number of individuals at an end of the distribution that could be classified as an anxious phenotype. The variation of anxiety traits within a population allows a wide range for natural selection to act on, but anxious individuals are present in considerable numbers, even when living conditions are optimal for several generations. Second, in harsher conditions, the anxiety-prone subpopulation is likely to have a selective advantage, and these genes would then become even more common in the population. Third, inadequate mothering, which might occur under severe conditions (e.g., maternal death and rearing primarily by age-mates), serves to increase expression of the anxious genotype. This mechanism further amplifies the capacity of the population to adapt to chronically threatening conditions. Persistent anxiety (high levels of arousal, searching for cues for danger, and high levels of avoidance of potentially damaging encounters) confers an adaptive advantage over less anxious individuals under such conditions.

Evolutionary Clues Found in Human Panic Disorder

Evolutionary approaches to obsessive-compulsive disorder, panic disorder, and other human anxiety disorders have been reviewed recently by Stein and Bouwer (1997). The most fully described and best documented of these—panic disorder—has been found to have properties that suggest that it might have evolved from adaptive physiological response in our ancestors, similar to the hypothesized evolution of the separation call from an adaptive response to hypothermia in infant rats described earlier in this chapter. Klein (1993) has proposed that the precipitation of acute symptoms of anxiety in patients with panic disorder, and some persons without panic disorder, by carbon dioxide (CO_2) inhalation may represent an adaptive "suffocation alarm." Klein hypothesized that in some individuals the threshold level of this alarm system is lowered to the point that normal or even low levels of partial pressure of CO_2 (pCO_2) in the circulation can trigger acute anxiety, a "false suffocation alarm." This could be enhanced when other cues to possible suffocation, such as closed exits, crowds, or immobilization, are also present. When further sensitized, through genetic or environmental mechanisms, the alarm and the panic response may occur spontaneously. He proposed that panic may be more primitive than other forms of anxiety and that it also differs in being a response to an endogenous cue (pCO_2) rather than an external threat. Klein pointed out that the hyperventilation, frequent yawns, and sighs in patients between panic episodes may constitute tests monitoring for signs of rising blood pCO_2. If CO_2 is not rapidly lowered and symptoms eased as a result of these respiratory maneuvers, suffocation could be imminent. Klein suggested that another distinctive feature of panic attacks, the lack of adrenal cortical response, may derive from the maladaptive consequences of hypercortisolemia in hypoxic conditions, as would be found in suffocation.

The association of adult panic disorder with separation anxiety in childhood and with the precipitating conditions of separation and loss in adulthood is also interesting from an evolutionary point of view. A calling response of infants when isolated from familiar surroundings and companions is remarkably consistent across mammalian species. It is found also among birds, a parallel evolutionary line, in which parental care is a major feature of the evolved developmental plan. In those species in which this separation cry has been studied pharmacologically (guinea pigs, rats, mice, and monkeys), the evidence consistently supports a similarity between isolation calling and adult anxiety responses. Increased calling has been found in response to experimental anxiogenic compounds, and decreased calling has been found in response to clinically useful anxiolytic drugs (see subsection "Separation Anxiety in a Small Mammal" earlier in this chapter). The neural substrates for anxiety thus seem to appear early both in evolution and in development. One of the most effective classes of anxiolytic compounds (e.g., morphine) acts at the μ opiate receptor. At this brain site, decreased sensitivity to endogenous CO_2 and decreased responsiveness to exogenous cues such as social isolation both follow activation of the receptor by μ opioid compounds. Thus, separation and loss may involve a neural substrate that is also activated by endogenous and exogenous cues for impending suffocation and, thus, for panic attacks as well.

Conclusion

By examining the examples from widely diverse life forms described in this chapter, we can gain an appreciation of the differences that have evolved in how organisms successfully use a behavioral state, anxiety, in avoiding threats to their survival. Anxiety appears to represent a stage in the process by which an individual adapts to the presence of threats to its survival. This

stage is omitted in the rapid responses to imminent injury that are mediated by sensorimotor reflex pathways. As soon as animals evolved more than one kind of response to danger and receptors that could detect cues before imminent injury, it became advantageous for them to enter an intervening state between stimulus and response. In this state, information processing and response thresholds could be specialized for assessing and responding to those cues for danger. Thus, anxiety allowed individuals to respond in ways that were particularly well suited to a variety of dangers and timed to be maximally effective. The very early evolution of highly specific information-processing capability, in the form of the membrane receptors of bacteria, emphasizes the central role of evaluative processes as forerunners of altered cognitive processing in anxiety. With the advent of the marine invertebrates, a pattern of selective enhancement of certain behavioral responses, and inhibition of other behaviors, evolved as part of their intervening anxiety state. The very early appearance of learning and memory in the simple neural networks of the first marine animals is now widely appreciated.

This combination of capacities, both to learn and to enter a specialized information-processing and motor response state, was likely a basic prerequisite for survival from early stages of evolution. It marks the origin of the capacity for the state we call anxiety as very old indeed. One could say that all that has happened in the course of our own evolution has been the addition of massive degrees of complexity to each element in the simple invertebrate system outlined earlier in this chapter. But vast increases in complexity have a way of creating new emergent properties. The evolution of increasingly complex social structure has added a whole new host of dangers that are not present for bacteria or sea hares. The evolution of the limbic system of the brain has made possible an enormous amplification of the kinds of possible intervening emotional states, creating a variety of qualitatively different anxieties. The evolution of the cerebral cortex has vastly expanded capabilities for learning and memory so that long-past experiences, as well as recent ones, play important roles in eliciting anxiety and in shaping the information processing during the state. The extent of parallel processing that has become possible in the primate brain has increased the extent of self-regulation within the system to the point that self-awareness and what we call consciousness has emerged. This creates a whole new order of response to anxiety—namely, the inner subjective experience of it. Finally, the advent of symbolic communication in language has made it possible for us to communicate that experience to one another. This, in turn, has led to a wealth of verbal interactions that can alleviate or perpetuate anxiety and can avoid or create new dangers.

Insights into the evolution of anxiety can be clinically useful (Marks and Nesse 1994). Once a patient can be led to realize that his or her symptoms are part of the history of human nature, that these responses can even be advantageous in certain situations, and that the real problem lies in their occurrence at the wrong time and place, this understanding can provide the basis for a variety of psychotherapeutic interventions. Furthermore, an evolutionary perspective can help alleviate the confusion, shame, and hopelessness that burden so many patients with anxiety disorders.

As our understanding of genetic mechanisms involved in the expression of behavior and in predisposition to mental illness grows exponentially in the coming years, so will our insight into the evolution of the behaviors and states of mind that are the subject of this volume. We can begin to see the outlines of what lies ahead, but there is much more to be learned than we know today. I hope that we will continue to view this state of affairs with more curiosity and anticipation than anxiety.

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6

Cognitive Concepts of Anxiety

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Condition de l'homme: inconstance, ennui, inquietude [The state of man: inconstancy, boredom, anxiety].
Blaise Pascal, *Pensées* (1670), no. 127
***Bartlett's Familiar Quotations*, 16th Edition, p. 270**

It would be impossible to conceive of life without concerns for safety, well-being, and security at some point. These concepts all derive from a concern for consequence embodied in the cognitive issue of the "What if…?" phenomenon. In the biological realm, an important issue for any organism is the extent to which the nutrients needed for survival are obtained. In the emotional realm, the issue involves being free from assault or harm to one's physical being or sense of self-esteem. Maslow (1943), for instance, spoke of the need for meeting both the physiological and the safety needs as prerequisite to what he termed the "higher" needs of love, status, and self-actualization. The perception of safety, then, plays a critical role because without it, the organism would be in a constant state of anxiety or arousal and prepared for flight-or-fight responses. Psychoanalysts spoke of the defense mechanisms that protect the ego from assault. These ego defense mechanisms appear to have as their focus the protection of the individual from the anxiety wrought by a state of conflict. The area, unfortunately, that has been largely ignored over the years has been the cognitive realm.

Within the past three decades, however, this state of affairs has changed markedly. The field of psychology has witnessed a cognitive revolution (Beck 1991; Mahoney 1974; Meichenbaum 1977). This cognitive or, more accurately, cognitive-behavioral revolution has been fueled by the interaction between the needs of clinical practice and the experimental tradition of behavioral psychology. This vital interaction has produced several empirically supported treatments, a major part of which have been the development and refinement of cognitive-behavioral strategies and techniques. Although some debate remains about the relative primacy of behavioral or cognitive approaches (Beck 1991; Simon and Fleming 1985), the therapeutic mix is arguably dependent on the specific goals of therapy, the skills of the patient, and the skills of the therapist (Freeman et al. 1990).

Although the earliest roots of the role and importance of cognition in human behavior can be traced to Eastern, Greek, and Roman philosophers (Ellis 1989), there is little doubt that the theorizing of Albert Ellis (1962) and Aaron T. Beck (1967) has been perhaps the most influential source in guiding and nurturing the

cognitive movement. Basing their earliest observations and theories on unipolar depression, Beck (1967) and his associates extended the cognitive model, which now enjoys wide application to a variety of other disorders (Freeman and Simon 1989).

In this chapter, we outline and elucidate the cognitive theory and model of anxiety and its disorders. We address the definition of anxiety and anxiety disorders, basic assumptions of the cognitive theory of anxiety, the role of predisposing and precipitating factors, a cognitive case conceptualization derived from the cognitive model, and common misconceptions about cognitive theory. Where relevant, we use clinical research and case examples to illustrate our conceptual points.

Definition of Anxiety

Anxiety has a multitude of definitions. The common elements of the anxiety experience include the following descriptors: a tense emotional state characterized by a variety of sympathetic symptoms, including chest discomfort, palpitations, and shortness of breath; painful uneasiness of mind over an anticipated ill; abnormal apprehension or fear; self-doubt as to the nature of the threat; belief as to the reality of the threat; and lapses of weakness of coping potential. Under normal circumstances, the human nervous system is designed to prepare and mobilize the individual to respond in one of three ways to an objective and physically dangerous threat. We can fight (attack or defend against the feared force or object), flee (leave the field), or freeze (become paralyzed). The hallmark of the anxious patient, however, is the presence of a powerful perceived threat and the activation of the physiological concomitants in the absence of an objective real threat. In other words, the person with an anxiety disorder sees threat and reacts to threat when no real threat exists. To make this point, we differentiate between fear, which we define as a response to a stimulus that is consensually validated to be scary, and anxiety, which we define as a response that is more idiosyncratic. For example, an individual can be anxious about flying in a scheduled airliner. Many others may refuse to fly because of similar concerns, but refusal to fly would be considered an anxiety response inasmuch as many people do fly with greater or less difficulty.

Although anxiety is a universal human experience and is undoubtedly a common human emotion, its evocation does not necessarily imply the presence of a clinically significant disorder. DSM-IV-TR (American Psychiatric Association 2000) is quite explicit about the definition of a disorder that is conceptualized as a clinically significant behavioral or psychological syndrome or pattern—it is associated with present distress (a painful symptom) or disability (impairment in one or more important areas of functioning) or with significantly increased risk of death, pain, disability, or an important loss of freedom. In effect, a disorder implies a duration, frequency, number, and intensity of symptoms that are significant enough to interfere with a person's quality of life. Anxiety is not a single disorder but part of a spectrum of anxiety disorders.

Basic Assumptions

The cognitive model of anxiety makes several basic assumptions about anxiety, its evocation, its mediation, and significance (Beck et al. 1985; Wells 1997). These assumptions are crucial in understanding the phenomenon of anxiety and the nature of anxiety disorders from a cognitive perspective.

1. Fear is an emotional response that has adaptive significance for humans when evoked in response to objective danger. It is, in effect, a survival mechanism (Beck et al. 1985; Cannon 1929; Emery and Tracy 1987; Freeman and Simon 1989; Izard and Blumberg 1985; Lindsley 1952, 1957, 1960; Plutchik 1980; Wells 1997).
2. The evocation of anxiety in response to misperceived or exaggerated perceptions of danger, when there is no danger, is considered maladaptive (Beck and Greenberg 1988; Beck et al. 1985; Foa and Kozak 1986; Freeman and Simon 1989; Wells 1997).
3. Individuals with anxiety disorders are prone to precipitate false alarms that create a relatively constant state of emotional arousal, tension, and subjective distress. These "fire drills" keep the organism in a state of readiness (Barlow and Cerney 1988; Beck and Greenberg 1988; Beck et al. 1985; Freeman and Simon 1989; Wells 1997).
4. Cognitive, physiological, motivational, affective, and behavioral systems all are involved and interrelated during an individual's episode of anxiety (Freeman and Simon 1989; Persons 1989; Taylor and Arnow 1988; Wells 1997).
5. The cognitive system plays a vital and essential role in appraising danger and resources and activating the physiological, motivational, affective, and behav-

ioral systems, each of which serves important functions (Beck et al. 1985; Foa and Kozak 1986; Freeman and Simon 1989; Lazarus 1991; Wells 1997).

6. The cognitive system mediates its influence through repetitive, unpremeditated, and rapid involuntary thoughts and/or images of which the individual is unaware (unless attention is called to them) and which the individual accepts without question or challenge (Beck and Greenberg 1988; Beck et al. 1985; Emery and Tracy 1987; Freeman and Simon 1989; Wells 1997).
7. Automatic thoughts are derived from underlying deeper cognitive structures called schemas, which are underlying beliefs or assumptions (Emery and Tracy 1987; Foa and Kozak 1986; Freeman and Simon 1989; Kendall and Ingram 1987, Persons 1989; Wells 1997).
8. Automatic thoughts and schemas may be disorder specific and in individuals with anxiety, reflect themes of threat and danger as opposed to themes of loss, as is typically seen in depressed individuals (Beck and Rush 1975; Beck and Weishaar 1989; Beck et al. 1985; Foa and Kozak 1986; Freeman and Simon 1989; Hilbert 1984; Wells 1997).
9. Anxiety reactions and disorders may be more fully and parsimoniously understood by elucidating the individual's automatic thoughts, cognitive distortions, and underlying assumptions (Beck 1976; Butler and Matthews 1983; Deffenbacher et al. 1986; Freeman and Simon 1989; Freeman et al. 1990; Merluzzi and Boltwood 1989; Wells 1997).
10. In trigger situations, individuals with anxiety disorders tend to activate danger or threat schemas, by which they selectively screen in stimuli that indicate danger and screen out stimuli that are incompatible with danger (Beck 1976; Beck et al. 1985; Freeman et al. 1990; Freeman and Simon 1989; Wells 1997).
11. Individuals with anxiety disorders have impaired objectivity and ability to evaluate their threat-bound cognitions in a rational and realistic manner (Beck et al. 1985; Wells 1997).
12. Individuals with anxiety disorders show systematic errors in processing information by, for example, catastrophizing, selectively abstracting, thinking dichotomously, and making arbitrary inferences (Beck et al. 1985; Freeman and Simon 1989; Wells 1997).
13. Individuals with anxiety disorders may be classified as having a disorder of arousal caused by a limbic-based neurological hypersensitivity phenomenon (Everly 1989). A limbic-based neurological hypersensitivity phenomenon is essentially a "a lowered threshold for excitation and/or a pathognomonic state of excess arousal within the limbic circuitry or it neurological, neuroendocrine, and/or endocrine efferent limb" (p. 151).
14. A limbic-based neurological hypersensitivity phenomenon may result in an individual with anxiety disorder from a kindling process by which repeatedly stimulating the limbic structures results in a lowered threshold and increased likelihood of activation of these structures, evidenced by affect lability, autonomic nervous system hyperreactivity, and associated behavioral manifestations (Every 1989).
15. A limbic-based neurological hypersensitivity phenomenon in an individual with anxiety disorder may have several causes, resulting in repeated excitation of the limbic structures or acute stimulation of a traumatic nature. Among the causative agents are environmental events, cognitive-affective factors, and personality characteristics (Everly 1989).

Critical to this neurophysiological model is the cognitive appraisal of the individual about stressor events. The cognitive model of anxiety also makes explicit assumptions about the predisposing and precipitating factors that are associated with the onset of anxiety disorders. In the sections that follow, we discuss several predisposing and precipitating variables related to anxiety disorders. It is important to bear in mind that any combination of these factors may set the stage and provide the impetus for the development, onset, maintenance, and exacerbation of anxiety problems.

Predisposing Factors

According to the cognitive model of anxiety (Beck et al. 1985), five possible factors may predispose or make an individual potentially vulnerable and more prone to anxiety and anxiety disorders: 1) genetic heritability; 2) physical disease states; 3) psychological trauma; 4) absence of coping mechanisms; and 5) dysfunctional thoughts, beliefs, assumptions, and cognitive processing. We discuss each of these factors in detail. As a result of individual differences, an anxiety disorder may result from a unique combination of predisposing and precipitating variables (Beck et al. 1985).

Genetics

Within recent years, the role of possible genetic factors in certain psychopathological disorders has assumed

more importance. Anxiety disorders are no exception. Panic disorder, phobic disorders, and obsessive-compulsive disorder are more common among first-degree biological relatives of patients with these disorders. Nonetheless, the question about how heredity exerts an influence in anxiety disorders is important to consider in the cognitive conceptualization of anxiety. Heredity may manifest its influence by the existence of an easily aroused or labile autonomic nervous system (Barlow and Cerney 1988). In other words, in certain anxiety conditions, a family history of the disorder may make it more likely for a patient to have anxiety symptoms under the right set of conditions. Thus, the role of genetic vulnerability cannot be fully appreciated without considering the interactive role of environmental, psychological, and social factors (Barlow and Cerney 1988).

Physical Disease

The cognitive model also considers the possible role of physical factors in making an individual vulnerable to an anxiety disorder. Two issues must be considered here. First, possible physical causes that can mimic anxiety must be ruled out in assessing anxiety disorders. In many instances, treating the physical problem alone may resolve the symptoms. Second, the existence of a physical problem does not necessarily preclude the existence of an anxiety problem. A physical problem can coexist with an anxiety disorder, and both problems may need to be treated.

Psychological Trauma

Mental trauma experienced during development (Beck et al. 1985) may render an individual more vulnerable to experience anxiety in situations similar to the experience of the trauma. This may be a single trauma or, more likely, a series of traumatic experiences. The developmental traumas occurring in the context of high emotional arousal can result in an individual developing specific schemas about threat ("that situation is dangerous") or broader threat scripts. This latter concept refers to a series of schemas that meet two conditions: 1) they occur in a designated sequence, and 2) they are predictable. For example, the script might be as follows: "That is dangerous," "I cannot cope," "Given my inability to cope, I will be hurt," "If I am hurt, I may be damaged beyond repair," "If I run, I may be saved." Such schemas would presumably relate to the themes of danger in anxious patients and would be expected to become activated in situations that are similar to the circumstances in which the schema was originally learned. As Foa and Kozak (1986) noted, "A fear memory is accessed when a fearful individual is presented with fear information that matches some of the information structure in memory" (p. 23). According to their emotional processing model, fear is expressed as a memory network that incorporates information about the stimulus situations and responses and the meaning of the stimuli and responses. Fear structures, by definition, involve themes of danger.

Absence of Coping Mechanisms

Another predisposing factor in the development of anxiety disorders is a deficit in coping responses coupled with a negatively distorted view of ability to cope. Not only are the primary appraisals of situations more likely to result in perceptions of threat when no threat exists in anxiety-prone individuals, but their secondary appraisals of their resources to cope with threat more often show inability to cope. Patients with anxiety may have failed to learn adequate coping strategies or may have learned to use responses such as avoidance, which have served to strengthen their anxiety and preclude effective coping. As a result, they may find themselves more vulnerable to experience anxiety in the presence of life events or other daily stressors. The anxious individual makes primary, secondary, and tertiary evaluations and converts them into a rough ratio equation. This risk-to-resources ratio involves the perception of risk and the perception of available resources to effectively cope with the perceived risk. If the risk is viewed as outweighing the resources, then anxiety results. If, however, the resources are greater than the risk, no anxiety results.

Irrational Thoughts, Assumptions, and Cognitive Processing Errors

The cognitive model of anxiety places primary emphasis on the role of cognitive factors in predisposing individuals to anxiety disorders. In individuals with anxiety disorders, underlying unrealistic beliefs about threat or danger are presumed to be activated by trigger events or situations that have elements that the individual believes are similar to situations during which these schemas were learned. When these schemas are activated, they fuel the patient's thinking, behavior, and emotion, all of which can serve to reciprocally reinforce one another and the underlying schema. When the anxiety is stimulated, the individual moves to a response that is egocentric, global, and involuntary. The effort is geared to survival, even though the trigger event is realistically devoid of objectively threatening stimuli.

Precipitating Factors

The cognitive model of anxiety (Beck et al. 1985) posits several possible factors that may precipitate anxiety: physical disease or toxic substances, severe external stressors, long-term stress, and stressors affecting a specific emotional vulnerability of an individual.

Physical Problems or Toxic Substances

Anxiety can be precipitated by the onset of a physical problem that does or does not mimic anxiety. For example, the development of anxiety after the onset of a physical problem is not an uncommon reaction during an individual's attempt to adjust to illness. Physical problems may cause symptoms such as fatigue or depression that could compromise or overtax the individual's ability to tolerate or manage even normal, everyday stressors. As a result, previously handled stressors may overburden the individual's resources. In addition, a physical problem may present an individual with an array of symptoms that are viewed as signs of a serious problem when the problem actually is relatively benign. Some anxious patients seem to be hypervigilant about normal bodily reactions that they interpret in a threatening manner (Wells 1997).

Respiratory difficulties may lead to a disruption of the oxygen and carbon dioxide balance. This may manifest as anxiety-like symptoms.

In some instances, individuals ingest a psychoactive substance that produces some physical effect that is interpreted as threatening. Everly (1989) discussed the notion of biogenic stressors or substances such as caffeine and amphetamine that are capable of precipitating a stress response by circumventing the cognitive appraisal mechanism. Of course, cognitive appraisal of the stress response can serve to exacerbate the response. Another pharmacological source of anxiety-like symptoms involves the use of prescription drugs that are stimulants. Certain decongestants or bronchodilators have the effect of increasing the heart rate and causing light-headedness. These symptoms also may be interpreted as threatening and cause anxiety, creating a vicious cycle. In summary, many substances can be classified as biogenic stressors, which circumvent the cognitive appraisal system and act directly on the nervous system (Everly 1989). However, cognitive appraisals may exacerbate even those symptoms precipitated by the biogenic stressor.

Severe External Stressors

The occurrence of a severe stressor or life event, such as loss of a loved one or loss of a job, is another possible precipitant of anxiety. The role of life events (Last et al. 1984) in precipitating anxiety reactions is well known.

Long-Term Stress

Stressors may be cumulative over a long time and, in a sense, may piggyback on each other. The result may be a situation in which a person's coping resources are exhausted and overwhelmed.

Stressors Affecting Vulnerability and Threshold

Circumstances, situations, or areas of deficit have the effect of decreasing an individual's ability to effectively cope with life stressors. With a single factor or the cumulative effect of several factors combined, the individual may either lose options or fail to see available options for actions, feelings, or thoughts and become threatened as a result. Coping ability can be thought of on a continuum from 0 to 100. The normal exigencies of life may be no more than 60, so that if an individual's threshold is 75, there is still a "cushion" until the limit is reached. The vulnerability factors serve to lower the patient's threshold or tolerance for life stress situations so that experiences that were previously easily tolerated or that were easily coped with now become overwhelming. Alone or in combination, the increased level of vulnerability may serve to increase the patient's difficulty in several areas, including marital discord, chronic pain, substance abuse, suicidal behavior, generalized anxiety disorder, depression, eating disorders, personality disorders, problems of the elderly, social anxiety, sexual abuse, physical and emotional abuse, or problems in occupational functioning. The cognitive therapist needs to evaluate the various vulnerability factors because they may have contributed to the current difficulty, may exacerbate the difficulty, may increase the patient's resistance to therapy, or may predispose the patient to future difficulty.

Other Precipitating Factors

Acute health impairment may range from severe and debilitating health issues that require medical intervention or hospitalization to more transient illnesses such as headaches, viral infections, or colds, which may be treated by self-medication. Chronic health problems may decrease one's ability to confront stressors, leading to feelings of overwhelming anxiety. Aging individuals

may have a loss of activity because of the body's inability to perform up to the expectations appropriate at other times in one's life. Anxiety and stress reactions may result from the individual's inability to handle situations dealt with more easily in the past. In a similar fashion, fatigue decreases both problem-solving strategies and the energy stores needed to handle events. With the death of a significant other or divorce or separation, individuals often see themselves as having reduced options or a lack of caring for what happens to them. Certain individuals may have impaired problem-solving ability, which may not be obvious until the individual is placed in situations of great stress. Being able to deal with minor problems may never truly test the individual's ability. New life circumstances (changing jobs, marital status, homes, or family status) are also stressors that are vulnerability factors. Assessment of the vulnerability factors may help to explain anxiety reactions and predict the possibility of bouts of such. Stressors also may strike at an individual's particular emotional vulnerability. What may precipitate anxiety in one person may not do so in another. To partially account for this, we would infer and test whether an individual has a particular vulnerability. For example, consider an individual who believes that to be worthwhile, one must be loved by everyone. As long as this individual receives acceptance from others, we may not expect him or her to become symptomatic. The rejection by a lover may reliably precipitate an emotional reaction.

Theory and Cognitive-Behavioral Case Conceptualization

The relation between cognitive theory and case conceptualization is clearly provided by Persons (1989), Freeman (1992), and Needleman (1999). Theory should guide clinicians in assessing, planning, implementing, and evaluating treatment. In this section, we use Persons's (1989) model to highlight how the cognitive model and theory of anxiety can be helpful.

> Ms. A, a 75-year-old woman, had a 15-year history of panic disorder. Following the cognitive model and Persons's formulation model, the following areas were identified: problem list, behavioral factors, cognitive factors, hypothesized mechanisms, relation between mechanisms and problem, current precipitants, and predicted obstacles to treatment. This conceptualization emphasizes the interaction between the predisposing and the precipitating factors.

I. Problem List

A. Feelings: 1) *panic attacks:* Ms. A was experiencing the sudden onset of intense fear and accompanying panic attacks several times a week at the beginning of therapy. These attacks were interfering significantly with the quality of life and provoked a great deal of fear. 2) *generalized anxiety:* Ms. A also had a chronic sense of generalized anxiety characterized by anticipation of the next attack. She lived in anticipation of experiencing fear-provoking thoughts. 3) *depression:* Ms. A was experiencing a dysthymia secondary to her panic problems. She was constantly aware of the demoralizing effect that the panic attacks had on her quality of life. There was also a sense of loss and guilt related to her view that she had changed from the person everybody knew and was now a burden on her family.

B. Behavior: 1) *fear-provoking situations:* Ms. A showed no avoidance of situations, but she was fearful of being alone at times. She also was fearful about the possibility of having an attack in the presence of her family. This created a great deal of anticipatory anxiety. 2) *difficulties in relationships with family members:* A significant source of distress was the negative effect that her problems had on her family. Family members believed that all she wanted was attention and attributed her problems to the fact that she did not want to live alone There was also some indication of resentments toward her family that she was unable to verbalize. 3) *lack of assertiveness:* Ms. A had assertiveness deficits that seriously undermined her ability to obtain social reinforcement. Her dependent features also interfered with her ability to assert herself for fear of alienating family members on whom she was dependent.

C. Cognitive: 1) *cognitive distortions:* Ms. A had a variety of cognitive distortions, especially catastrophizing. She tended to misinterpret her symptoms as a cause for threat to her mental status. She also had a variety of other distortions such as selective abstraction and jumping to conclusions. These distortions typically escalated her anxiety symptoms to panic proportions and also fueled her dysthymia. 2) *suicidal ideation:* Ms. A reported thoughts at times of wishing that she were dead and demoralization about her ability to cope with the panic for the rest of her life. She openly reported these thoughts and was willing to discuss them. On several occasions, a thorough suicide assessment was negative. 3) *decreased self-efficacy:* Ms. A had little belief in her ability to do what she could do to resolve her problems. This may have been her reason for choosing medication initially. She had been treated with medication for such a long time that her attributions about improving were externalized.

II. Hypothesized Mechanisms

A. Cognitive: Ms. A had a variety of underlying schemas that fueled her problematic thoughts, feel-

ings, and behaviors. Some examples of her core schema were as follows: 1) *vulnerability:* Something terrible will happen to me at any moment, and I will lose control and go crazy. I will forget who I am and forget my family. If I experience too much anxiety, I will lose my identity. 2) *dependence:* I am unable to cope on my own. If I do not please others, they will abandon me. 3) *view of self, environment, and future:* I'll never improve. I'm inadequate. My problem is so bad that no one can help me.

B. Social: Although Ms. A viewed herself as an independent person, it was very clear from her social history that she was extremely dependent on her husband. She apparently never had to rely on herself because he did everything for her. She was socialized in a society that placed women in her age group in a dependent role.

C. Biological: A possible underlying biological mechanism in Ms. A is suggested by the fact that one of her daughters had panic disorder. This finding suggests some possible genetic vulnerability to panic in the face of stressors.

III. Relation Between Mechanisms and Problem

Ms. A's panic attacks may have been precipitated by a variety of mechanisms, including several stressful life events, a possible biological vulnerability, and the activation of strongly held beliefs about her vulnerability to threat. She appeared to be a rather dependent woman with low self-efficacy about her ability to cope. Her extreme dependence on her husband buffered her against the effects of stress. Following his death, a major stressor, basic schemas about her vulnerability were probably activated and fueled her negative thoughts, feelings, and behaviors and increased the likelihood of a panic attack. When she experienced this attack, she was extremely frightened by it and interpreted it as a sign of her vulnerability to losing control and going crazy. Her distorted style of processing information exacerbated her anxiety, fueled her anticipation and generalized anxiety, demoralized her, and precipitated anxiety in certain situations. The patient found herself in a vicious cycle of precipitating the very symptoms she feared. Probably as a result of her low self-efficacy, she sought a pill to solve her problems. Her initial physician prescribed a low-potency benzodiazepine of questionable efficacy, which may have contributed to her depression. She also had several depressogenic assumptions that fueled her depression, undermined her hopefulness, and precipitated suicidal thinking. Ms. A's difficulties with her family related to her underlying beliefs about pleasing others and inability to assert herself.

IV. Current Precipitants

The original precipitant of Ms. A's panic related to a situation in which she misinterpreted a benign experience as a sign of an impending catastrophe. One might hypothesize that Ms. A was socialized as a dependent, weak person who is unable to cope on her own.

V. Predicted Obstacles to Treatment

Several factors were hypothesized to interfere with treatment. First, evidence showed that the patient did not maintain her appointments for her medical visits. Second, her view of medication and externalization of sources of improvement could have undermined her participation in therapy.

Misconceptions About the Cognitive Model of Anxiety

Various common misconceptions exist about the cognitive model of psychiatric disorders (Freeman et al. 1990) and anxiety in general. Next, we address each of these misconceptions and provide a more accurate description of what the cognitive model implies.

1. *Faulty cognitions cause anxiety disorders.* This misconception is perhaps the most commonly cited unjustified criticism of the cognitive model. The cognitive model does not assume that thoughts cause anxiety disorders. Rather, this model proposes that a variety of predisposing and precipitating factors, including cognitive patterns, may coexist with and relate to the development of anxiety disorders. Cognitions and cognitive processing are not the only important elements but do represent a useful focus for intervening.
2. *The cognitive model is simply a variant of the Norman Vincent Peale's power of positive thinking approach.* The cognitive model of anxiety assumes that individuals with anxiety disorders tend to perceive threat when no danger exists. Anxiety patients have unrealistic thinking and are unlikely to respond to positive, reassuring thoughts. Numerous individuals, including family, friends, and even their physicians, have encouraged positive thinking in many of these patients to no avail. The model proposes that patients must learn to evaluate the triggers for anxiety in a realistic, valid manner.
3. *The cognitive model denies the importance of behavioral principles, such as exposure, in overcoming anxiety.* Although the cognitive model of anxiety views that the cognitive apparatus of the patient has a basic problem, it is simply untrue that the model overlooks the importance of behavioral principles. In fact, Free-

man and Simon (1989) noted that the model might more appropriately be referred to as the *cognitive-behavioral-emotive model.* The model does place primary emphasis on the cognitive aspects but most certainly does not ignore the importance and role of behavior and emotion. Cognitive therapists freely use techniques that are designed to modify behavior (e.g., assertiveness training) and emotions (e.g., relaxation therapy).

4. *Applying the cognitive model is simply a matter of talking patients out of their fears and worries.* The cognitive approach actively relies on the principles of collaborative empiricism and guided discovery. The model assumes that the Socratic approach, through which patients are led through questioning to examine and alter faulty cognitions and underlying beliefs, teaches the patient a process that he or she can take with him or her. Cognitive therapists do not talk patients out of their problems by persuading or cajoling them to adopt a new perspective. Rather, cognitive therapists talk to patients in ways that help them guide themselves to think, act, and feel more realistically and adaptively.

Conclusion

In summary, from our perspective, the cognitive model of anxiety appears to be both a viable and a useful vehicle for furthering our understanding of the complex phenomenon of anxiety and the onset, development, exacerbation, and treatment of anxiety-related disorders. Continued clinical research designed to further test and refine the hypotheses of the cognitive theory of anxiety is warranted. Likewise, we await further research aimed at more carefully delineating and clarifying the possible role of cognitive factors in the treatment of anxiety disorders.

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7

Psychodynamic Concepts of Anxiety

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Psychoanalytic concepts and psychodynamic techniques are important to a well-rounded understanding of patients with anxiety disorders. These ideas can enhance therapeutic strategies distant from psychoanalysis. The purpose of this chapter is to acquaint the reader with some of these ideas. In addition, uncontrolled evidence is accumulating that psychodynamic psychotherapy can be an effective treatment for anxiety disorders, including panic disorder.

In 1991, Milrod and Shear found 35 patients described in the literature with DSM-III-R (American Psychiatric Association 1987) panic disorder that had been successfully treated with psychodynamic psychotherapy or psychoanalysis alone. Information about duration of treatment was available for 17 of the 35 patients. Thirteen of these 17 received treatment for less than 4 months, 2 other patients were given therapies described as "long term," and the remaining 2 patients received treatments described as "brief." Since then, other successful psychodynamic treatments of panic disorder have been reported (Busch et al. 1996; Milrod 1998; Milrod and Shear 1991; Milrod et al. 1996; Renik 1995; Stern 1995; Wiborg and Dahl 1996). These reports suggest that psychodynamic treatment alone can bring symptomatic relief, often as rapidly as psychopharmacological or cognitive-behavioral interventions. Although clinical reports do not address the issue of treatment efficacy, this nonetheless provides clinical evidence that psychodynamically informed treatments can be effective in panic symptom relief.

Brief Historical Overview

Many psychoanalytic scholars have described important aspects of the dynamics of anxiety because of its central position in psychoanalytic theory. It is beyond the scope of this chapter to summarize these thoughtful contributions. (See Kessler 1996 for an excellent summary of some of the highlights of these theories.) Here, we outline three important historically important dynamic formulations of anxiety that continue to be of ongoing clinical relevance.

1. Freud (1926/1959): Two types of anxiety were delineated by Freud: 1) *traumatic anxiety*, in which the ego, which is the psychic apparatus that organizes perception, defenses, cognition, anxiety and mood regulation, as well as other mental functions, is overwhelmed by psychologically meaningful danger: an "excitation, whether of internal or external origin, which cannot be dealt with" (Freud 1926/1959, pp. 137, 166). Overwhelming, traumatic, or "automatic" anxiety results, and the ego cannot function or defend itself; and 2) *signal anxiety*, which is posited to be an intrapsychic mechanism that generates smaller doses of anxiety to alert the ego to the presence of psychologically meaningful dangers and to act as a stimulus to mobilize defenses. Signal anxiety prevents the experience of overwhelming, or traumatic, anxiety. Traumatic anxiety is experienced during what we now label panic episodes.

In addition to distinguishing between traumatic and signal anxiety, Freud described a developmental progression of central anxious fears in children. He believed that the psychologically meaningful, internal dangers that can potentially lead to the eruption of anxiety change with phase of life. He outlined these traumatic or dangerous situations to be the *fear of the loss of the object* (e.g., a loved parent)—also described as separation anxiety, *fear of the loss of the object's love*, *fear of castration*, and *superego fear* or, in simple terms, fear of a guilty conscience. In clinical situations with adult patients, several or all of these developmental situational fears commonly operate simultaneously, but one or two areas often assume clinical ascendance.

2. Helene Deutsch (1929): She succinctly described the way in which unconscious angry and ambivalent aspects to intense love attachments can result in agoraphobia and the need for a phobic companion (the ambivalently held love object), partly in an unconscious attempt to prevent symbolic destruction of the love object from hostile, destructive fantasies.
3. Bertram Lewin (1952): He described the wishful aspects to what he labeled "the phobic facade," or the repetitive terrifying scenarios with which phobic patients are preoccupied.

Clinical Psychodynamic Approach to the Anxious Patient

The ideas elaborated in this section will be further expanded throughout the course of this chapter. Symptoms of anxiety may contain specific symbolic information about the particular set of unconscious conflicts that are intolerable to the patient. Anxiety can be a final common pathway of many unconscious conflicts. These conflicts are important in the presence and persistence of the anxiety disorder. The initial focus in any psychodynamically informed treatment of an anxiety disorder is to gain the information necessary to delineate specific unconscious fantasies and feelings underlying the symptoms. For this reason, when confronted with an anxious patient, the psychodynamically informed clinician must obtain a very detailed psychological history of the patient and of other symptoms and feelings associated with the anxiety that can help to delineate underlying conflicts and fantasies. A goal of the treatment will be for the patient to become consciously aware of these conflicts and to begin to handle them in different, verbally mediated rather than somatically mediated ways.

Much has been written about the underlying meaning of panic symptoms (Kessler 1996). Clinical observations indicate that fantasies surrounding separation and independence are common areas of conflict for panic patients. Several epidemiological studies provide indirect support for this finding (Leonard and Rapoport 1989; Rosenbaum et al. 1988; Weissman et al. 1984). Clinical observations also suggest that patients with panic disorder have intense difficulty tolerating and modulating angry feelings and thoughts (Busch et al. 1991; Shear et al. 1993). Additionally, although panic attacks often occur in the setting of conflicted hostility, for some patients the attacks take on an exciting significance of their own, beyond the commonly manifested panic about being ill, dying, or becoming "crazy." Some patients report a frightening or arousing inherent excitement associated with the attacks, often closely tied to sadomasochistic sexual conflicts (Milrod 1995; Milrod et al. 1996). Panic attacks can serve a self-punitive function, with which patients unconsciously atone for guilty transgressions, as is illustrated in the clinical example about Ms. D later in this chapter. Finally, the panic experience can represent a specific unconscious fantasy or memory (Freud 1895/1955).

The following case example illustrates the underlying meaning of panic symptoms in a woman who was getting married.

> Ms. B, a 25-year-old newly married woman, presented in a constant state of severe panic and agoraphobia, which made it impossible for her to leave her apartment without a companion. She was unable to eat, had lost 15 pounds, and was sleeping only several hours each night in intermittent spurts. She had failed several medication trials, including benzodiazepines, tricyclics, selective serotonin reuptake inhibitors, and finally chlorpromazine.
>
> Ms. B reported having been well until 3 months before her marriage, the day she tried on her wedding dress after it had been made. Her most prominent symptoms during panic attacks were severe nausea, although she had never vomited, and dizziness, symptoms she described as "being like the first trimester of pregnancy." Because of the nature of her symptoms, she had been given pregnancy tests on numerous visits to medical emergency rooms, all of which had negative results.

Ms. B's panic and agoraphobia ultimately remitted after 6 months of thrice-weekly psychodynamic psychotherapy. Nonetheless, from the information presented in this case example, which was obtained during the first

10 minutes of her first contact, the following important dynamic information became clear simply as a result of focus on the time and place of her initial symptoms and a brief discussion of what her fantasy was about the meanings of her symptoms: 1) Ms. B had some mixed feelings of which she was not aware about getting married, and 2) Ms. B also thought of her panic attacks as being like the first part of a pregnancy. Given that these two ideas co-occurred with the onset of her illness, it seemed highly likely that one of the elements of her strong unconscious mixed feelings about getting married concerned her new potential to become pregnant once she was married. These dynamisms in fact proved to be of central importance later in her treatment and in the remission of her symptoms and formed the starting place for the therapist to approach the patient.

In working psychodynamically with patients who have severe symptoms like those described in Ms. B, clinicians must refrain from joining in patients' severe anxiety and must impart the idea that symptoms are understandable psychological phenomena. The goal of psychodynamically informed psychotherapy for the treatment of anxiety disorders is to determine how the symptoms make sense as psychological phenomena and, thus, to help patients to recognize their own feelings and thoughts in a more complete way than they had been able to before.

Basic Psychodynamic Concepts That Inform Our Understanding of Anxiety

The psychodynamic principles and common psychodynamic conflicts found in anxious patients described in this section have general applicability in any clinical treatment undertaken with patients who have anxiety, regardless of therapeutic modality chosen.

To clearly outline psychodynamic concepts as they pertain to the anxiety disorders, several basic psychoanalytic ideas about mental life must be defined.

From a psychodynamic point of view, all of mental life exists on two levels: both within the realm of consciousness and within a more inaccessible realm described as the unconscious (Freud 1895/1955). Psychic or emotional symptoms arise from aspects of mental life that are at least in part unconscious.

Anxiety is central in mental life. Anxiety usually represents the failure of other less painful psychological defenses. Under ordinary circumstances, people who do not have anxiety disorders become conscious of some degree of psychological danger before overwhelming anxiety takes over, which serves as a warning or signal that permits them to ward off severe anxiety by activating psychological defenses. When defenses fail, anxiety becomes overwhelming and becomes a symptom (Freud 1926/1959). Some emotionally engendered symptoms bind what has been described as "free floating anxiety" (Freud 1895/1955, 1917/1961). What this means is that the presence of psychic symptoms (e.g., conversion symptoms, phobias) can function to lessen the degree of distress that the patient experiences.

Nonetheless, all psychic symptoms do not bind anxiety. For instance, panic disorder, initially described by Freud (1895/1962), has been viewed by many clinicians and researchers as being a genetically mediated, neuropsychiatric syndrome (Gorman et al. 1995), in part because identifiable triggers for panic attacks are thought to be characteristically absent. However, many studies suggest that acute stressors, described in the literature as "life events," frequently occur just prior to panic onset (Faravelli 1985; Last et al. 1984; Roy-Byrne et al. 1986) despite the DSM-IV-TR description of panic attacks coming "out of the blue" (American Psychiatric Association 2000, p. 431). Certain individuals are vulnerable to life events triggering panic. In a dynamic view, the meaning of the event to the individual, both conscious and unconscious, and affects triggered in response to these events play a central role in the development of panic attacks.

Patients with panic are overwhelmed by anxiety much of the time. From a psychodynamic perspective, panic symptoms are indicative of specific, intense unconscious conflicts, the understanding of which forms the cornerstone of psychodynamically based treatments of panic. Although panic attacks as symptoms do not effectively bind anxiety, from a dynamic perspective, they nonetheless represent the least unpleasurable solution to the intrapsychic conflictual situation at hand. The need to avoid unconscious conflicts and disturbing ideas is more distressing for patients in fantasy than in reality. Patients' fantasies about the terrifying things that might occur if they were to acknowledge warded off feelings and wishes seem more catastrophic when they are avoided. Bringing these previously unconscious wishes and fantasies into consciousness in psychotherapy has the effect of decreasing anxiety and imparting greater control. For example, in unconscious mental life, the fantasy of having to confront homicidal fantasies toward one's mother is more distressing than the panic attacks that come to symbolize and disguise this fantasy.

People unconsciously avoid "unpleasure," and ideas that produce unpleasure are screened from consciousness by processes we call *defense mechanisms* (Freud 1911/1958). Defense mechanisms are also unconscious processes. Clinically, the degree to which "unpleasure" is avoided varies from patient to patient.

Anxiety symptoms per se represent a failure of more adaptive defenses against unacceptable unconscious fantasies and also represent episodes of threatened breakthrough of unconscious fantasy (Shapiro 1992) into consciousness. Persistent unconscious fantasies often underlie people's psychological symptoms, dreams, personalities, and important life choices. When unconscious fantasies are important underpinnings in symptoms such as anxiety, it may be useful for psychologically based treatments to help patients articulate them in order to effect symptomatic change.

Many aspects of mental life, including symptoms (such as anxiety), dreams, fantasies, and various aspects of character, are the result of *compromise formations* (Freud 1895/1955). In brief, a compromise formation symbolically represents a compromise between a forbidden wish and the defense against the wish.

In the course of development, individuals form an internalized representation of both external objects (people with whom they have significant relationships) and themselves. Psychic symptoms come to play a part in the way these representations change during development. Current relationships with other people are at least in part a repetition of old relationships that continue to exert compelling unconscious influence. Therefore, a cornerstone of psychodynamic theory and practice is the psychological phenomenon of *transference*. Transference is a universal psychological phenomenon in which aspects of important and formative relationships (such as with parents and siblings) are unconsciously ascribed to unrelated current relationships (Freud 1905/1953). This fundamental unconscious process also occurs in relationships between therapists and patients. In clinical practice, it can prove helpful to patients to recognize underlying fantasies that surround the therapeutic relationship regardless of the type of treatment in which the patient is engaged or the therapeutic orientation of the therapist. From a psychodynamic perspective, the transference situation has far-reaching effects and necessarily influences therapeutic outcome. Patients with anxiety disorders commonly experience tremendous distress at times of separation from the significant people in their lives, including their treating therapists. For this reason, anxiety symptoms commonly worsen at times that ongoing psychiatric treatment, regardless of the modality, is temporarily or permanently discontinued.

The following case example illustrates how severe and disabling symptoms can serve a protective function in permitting a patient to avoid unacceptable fantasies and feelings:

> Ms. C, a 25-year-old highly devout Baptist, presented for twice-weekly psychodynamic psychotherapy for her multiple daily panic attacks and crippling agoraphobia, which was so severe that she could not leave her house unaccompanied and had to remain within several blocks of her apartment, even with a companion. Her claustrophobia was so severe that she could not wear makeup or nail polish because of fantasies of being suffocated.
>
> Ms. C reported that she had been sexually molested by an uncle when she was 6 years old. The details of the abuse remained obscure because Ms. C said that she "didn't want to" remember them. The patient had otherwise had a very traumatic childhood, marked by many tragic separations, abandonments, and disappointments with important attachment figures, emotional issues that continued to affect her in her adult life. Additionally, her boyfriend of 2 years chose to break up with her at the time that she entered treatment.
>
> Ms. C had had a significant melancholic major depression following a breakup with a boyfriend in the past, and she worried that she might become too "depressed" if she focused too much attention on the feelings of abandonment that plagued her during what had been prearranged as a time-limited treatment. Nonetheless, she spent a significant portion of her time in her therapy talking about how lost, injured, and frightened she had felt throughout much of her life and again now since her boyfriend had left her and as she confronted the limitations of time-limited psychotherapy. Although Ms. C hated to be angry, she was able to acknowledge some of her rage toward her mother and her boyfriend, for example. One area that Ms. C could not permit herself to think about at all, however, was the sexual abuse.
>
> Ms. C became panic free after the second session of her treatment, when the therapist began to focus the patient's attention on the connection between her overwhelming rage and disappointment with the irresponsible adults in her life and her panic attacks. As Ms. C's 24-session treatment neared its end and she became much less agoraphobic and able to travel to most places alone, including out of town, she began to talk for the first time since her initial revelation to her therapist about her thoughts about the abuse.
>
> Therapist: "I'm sure that we've both noticed by now that you can't seem to think about what happened to you with your uncle."

Ms. C: "I cannot go there at all. I cannot permit myself to even think of the room, or him, or what he did. I don't know what happened to me, even though I was wide awake, and I remember the next day perfectly, it's stuck in my mind forever: me sitting on the swings trying not to think about anything, kicking my feet in the air. I was in terrible pain. Some day I'm going to let myself remember it, but I have to be at a point where I don't feel so worried about myself."

Therapist: "Worried in what way?"

Ms. C: "I have no idea what I would think if I really remembered what happened. I'm sure I couldn't forgive him, that much is for sure, and my religion says I have to be a forgiving person."

Therapist: "There are things you can't permit yourself to think about or feel, just like there used to be places you couldn't go because of your agoraphobia."

Ms. C: "It's true, these things have to be connected, I know that now for sure. Better to stay close to home and not know… [*pause*, *Ms. C bursts into tears*]. I really think I might kill him if I let myself think about it, and I'd turn out to be no better than my mother in the end."

The following case example illustrates anxiety symptoms that represent a compromise formation, or a symbolic representation of both a forbidden wish and the defense against the wish:

Ms. D, an 18-year-old woman, was driving from one city to another to attend her eighteenth birthday party when she experienced her first panic attack. The attack was so severe that she had to drive off the road and call her mother in the city to which she was driving to ask her mother to pick her up on the highway. It took her mother several hours to find another person to drive with her who could also drive the car back, and, in the meantime, Ms. D's party had to be canceled.

At the moment that she experienced the attack, Ms. D had found herself thinking that her eighteenth birthday was very important to her: it symbolized her "total independence" from her family and a new ability "to get rid of them." In unraveling the onset of her illness later in psychotherapy, it became clear that in her fantasy, turning 18 and being "independent" represented the emotional equivalent of killing off her parents and siblings, all of whom enraged her. The fantasy was so full of conflict for her that she had her first panic attack, in this case with the wish to be rid of her family. The panic symptom represented both the *wish* to be alone (suddenly, Ms. D found herself in fantasy feeling entirely alone and unable to function) and the *defense* against this wish—a sudden-onset, severe illness that made her "independence" from her family (and the very existence of her birthday celebration) impossible and effectively immobilized her in her escape/fantasy murder plan. Additionally, the panic represented a real way in which she effectively punished herself for her homicidal (and unacceptable) thoughts: now she could never be free of her family.

The following case example illustrates panic symptoms that signify the symbolic representation of an unconscious fantasy:

Ms. E, a 24-year-old woman with panic disorder, lived with the persistent unconscious fantasy/wish that she would become closer to her beloved and physically impaired brother, which she imagined would happen if she became ill, impaired, and "pathetic" herself. Many aspects of Ms. E's life, including her severe panic disorder, served to reinforce a cherished image of herself as ill and pathetic and, hence, united with her rejecting brother. This fantasy was severely challenged when she was accepted to a prestigious graduate school, at which time she experienced profound, "unaccountable" depression and an exacerbation of her panic symptoms.

In the session after her acceptance, which also happened to be the session following her "remembering" important material that she had "forgotten" (that her brother had had a serious medical disorder throughout their childhood), she had a panic attack in the street on the way to her therapist's office and needed her father to pick her up and bring her to her appointment. In the office, she said that she was furious at her father "because now the fact that I needed him to come and get me will make him think that he has license to treat me like I'm a pathetic, sick child."

The therapist pointed out to Ms. E that she had just been discussing "another sick, pathetic child in our last session." "Oh, right," she said. "So you mean to tell me that you think this stuff about me forgetting that my brother was sick is somehow connected to my panic?"

Ms. E's panic symptoms disappeared after she was able to consciously acknowledge the way in which she clung to and identified with her ill brother through her own anxiety symptoms.

The following case example illustrates the centrality of the transference phenomenon in forms of psychiatric treatment distant from psychodynamic psychiatry. A psychopharmacologist who specializes in the treatment of panic disorder reported the following case:

Ms. F, an older patient with panic disorder who had been receiving treatment from the psychopharma-

cologist for years, had been taking very high doses of benzodiazepines. She and her physician had been engaged in a very slow and gradual taper of the drug because her panic attacks had remitted. She was in the middle of this taper, continuing a substantially high dose of benzodiazepines, and had been tolerating the taper well. The pharmacologist lowered her dose again in a "microscopic decrement" before *leaving for a vacation.* Ms. F had "the worst panic attack in my life," for which she still has "not forgiven" him, years later.

Benzodiazepine taper is well known to be difficult in this patient population because withdrawal syndromes and rebound anxiety are common. Thus, benzodiazepine tapers are best accomplished over a period of months. Nonetheless, in the Cross-National Collaborative Panic Study discontinuation phase, most of the patients who had received alprazolam experienced their most severe withdrawal syndromes and rebound anxiety at the very end of the drug discontinuation phase or during the first week in which they were medication free (Pecknold et al. 1988). Ms. F was in neither situation. However, this patient was experiencing another equally common panic-related phenomenon: anxiety when being separated from the important objects in her life—in this case, her psychopharmacologist. Even in the context of a pharmacological treatment, some degree of focus on the transference situation probably could have prevented the panic attack.

Clinicians who routinely treat panic disorder may want to consider incorporating some psychodynamic understanding of the panic syndrome, as described in this chapter, into their treatments.

Combining Psychodynamic Treatments With Medication

Psychodynamic psychotherapy for panic disorder can be an effective treatment alone (Milrod 1995; Milrod and Shear 1991; Milrod et al. 1996; Renik 1995; Stern 1995), even though it is only now being submitted to clinical trials (Milrod et al. 2000). Nonetheless, medication treatment is known to be efficacious (American Psychiatric Association 1998), and the two treatment approaches can be effectively combined (Milrod and Busch 1998; Wiborg and Dahl 1996).

Some patients who present with severe anxiety symptoms find their symptoms so intolerable that they want to begin antianxiety medication immediately. Given the overall discomfort that patients often experience, this situation is less common than might be expected because anxious patients are often frightened to take medicine (Cross-National Collaborative Panic Study 1992).

Whereas the initial goal of psychotherapy alone is to control acute anxiety through reassurance and early exploration, which permits patients to begin to understand underlying meanings connected with symptoms and thereby to gain control of feelings, the goal of combined treatment is to curtail acute anxiety with medication to help patients calm down enough to work productively in psychotherapy. In a psychodynamically based treatment, the therapist and patient must begin to understand some of the underlying significance and meaning of the symptoms whether medication is being used or not. If medication is used, the meaning of taking it also must be explored before a successful taper can be expected. After this work has been accomplished, medication can frequently be tapered successfully (Milrod and Busch, in press).

Psychoanalytic Perspectives on Nonpanic Anxiety Disorders

Psychoanalytically oriented clinicians more commonly focus on underlying characterological difficulties and pervasive unconscious fantasies rather than on specific symptomatic presentations. Thus, the current DSM nosology, which differentiates the anxiety disorders on the basis of specific symptom pictures, generally is not reflected in the large volume of psychoanalytic thinking or literature about anxiety. DSM-IV-TR differentiates Axis I anxiety syndromes primarily on the basis of specific symptom profiles and temporal criteria. This taxonomy has helped investigators in systematic research to determine the efficacy of treatment approaches to specific psychiatric syndromes. Nonetheless, some researchers have criticized this approach for encouraging the separation of syndromes into what may be artificially discrete categories with limited clinical relevance (Andrews et al. 1990; Tyrer 1986; Tyrer et al. 1992). Accordingly, there has been an increasing recognition of comorbidity.

Many aspects of the general psychodynamic understanding of anxiety as it has been described thus far in this chapter are applicable to a psychoanalytic view of the other anxiety disorders, but we were unable to locate specific psychodynamic literature that addresses psychodynamic treatment of generalized anxiety disor-

der, for example. However, a large psychoanalytic and psychodynamic literature pertains to what we now call posttraumatic stress disorder, beginning with Freud's (1920/1955) discussion of the "traumatic war neuroses" in 1920. For a review of psychodynamic perspectives on posttraumatic stress disorder, which is beyond the scope of this chapter, and a highly organized approach, see Marmar et al. (1995). The central psychodynamic principles outlined in the earlier discussion (the idea of unconscious conflicts giving rise to symptoms) apply to the psychodynamic approach to posttraumatic stress disorder as well.

Review of Psychodynamic Research in Anxiety Disorders

No studies have shown the efficacy of psychodynamic psychotherapy as a sole treatment for any specific anxiety disorder because this treatment approach has not been subjected to randomized controlled trials. Nonetheless, two types of clinical evidence provide preliminary support for the need to continue active work in this area and, in particular, to submit psychodynamic psychotherapy for panic disorder to a credible controlled trial: 1) the existence of so many successful reports of these treatments for panic (Kessler 1996; Milrod 1995; Milrod and Shear 1991; Milrod et al. 1996; Renik 1995; Stern 1995), which constitutes inferential suggestive data that psychoanalysis or psychodynamic psychotherapy may well be helpful, and 2) initial outcome data, which are presented below.

Some aspects of the psychodynamic model presented in this chapter have been systematically studied. Many panic researchers believe that personality traits predispose individuals to panic in the context of particular life stressors. Marks (1970) reported that most agoraphobic patients had been described as "soft, anxious, shy, and dependent" before the onset of panic disorder (p. 541). D. F. Klein (1964) determined that half of the patients in his early study "seem to have suffered from a chronically high separation anxiety level throughout life and to have developed panic attacks under conditions where they were peculiarly vulnerable" (pp. 405–406). Personality traits, including dependence and difficulty in being assertive, appear to predispose to the onset of panic that may be triggered by particular life stressors (D.F. Klein 1964; Kleiner and Marshall 1987).

A pilot study was conducted to gain further information about the role of predisposing psychological factors in vulnerability to panic and meaningful life events connected with panic onset (Busch et al. 1991). Nine consecutive subjects with DSM-III-R panic disorder who presented to the Anxiety Disorders Clinic of the Payne Whitney Clinic in New York City were videotaped during psychodynamic interviews conducted by two experienced training analysts, members of the Cornell University faculty. An independent rater with psychoanalytic training reviewed the videotapes to assess life events preceding panic onset, capacity to tolerate anger, conflicts about sexuality, descriptions of parents, and behaviors and attitudes apart from symptoms of panic disorder.

Identifiable, psychologically meaningful stressors appeared to precede onset of panic in all the subjects. All stressors involved a loss or alteration in the level of expectations placed on the patients. Reported loss events involved physical or emotional separations from a significant person in the subjects' lives. Changes in expectations usually reflected subjects being asked to take on increased responsibilities in their occupations. Further exploration in the interviews suggested that the subjects linked these events to frightening childhood experiences and viewed them as representing threats to important attachment figures. Seven of the nine subjects had difficulty acknowledging angry feelings. Every subject described significant problems in interpersonal relationships, and seven of the nine reported occupational difficulties.

Shear et al. (1993), in a further review of the interviews, found that the patients revealed themes of early life anxiety and shyness, unsupportive parental relationships, and a chronic sense of feeling trapped and troubled by frustration and resentment. In the formulation of these authors, patients with panic disorder either have a neurophysiological vulnerability to panic, manifested in early life as what Kagan et al. (1990) defined as "behavioral inhibition to the unfamiliar," or experience traumatic developmental events. In either scenario, Shear and colleagues hypothesize, the child becomes angry at what he or she perceives to be his or her parents' rejecting or frightening behavior. He or she becomes fearful of loss and terrified that his or her angry fantasies will destroy the parent on whom he or she depends. A vicious cycle arises in which rage threatens the all-important tie to the parent, increasing the child's fearful dependency. Immaturity or failure of the ego's signal anxiety function leads to the uncontrollable onset of panic levels of anxiety. This cycle is repeated in adulthood, when threats to attachment reawaken these early conflicts.

In the Busch et al. (1991) study, when patients began to explore specific psychological sources related to their panic onset during the interviews, they reported that this process relieved their anxiety. This does not validate a psychodynamic model, but it does indicate that grappling with psychological events in this manner can have the effect of calming patients.

The field of psychodynamic psychiatry lags behind the general psychiatric community in the area of systematic outcome research, in part because of the very specific individual nature of psychodynamic treatment; because of the focus on detailed individual case presentations in psychoanalytic training, practice, and literature; and because of the relative underemphasis on systematic research in the psychoanalytic community. To obtain efficacy data for psychodynamic psychotherapy or for any other form of psychotherapy, the treatment must be described in manual form so that it can become a *reliably reproducible* treatment for the purpose of the performance of meaningful clinical trials. Four research groups are currently at various stages in this process (Milrod et al. 1997 and Wiborg and Dahl 1996 for panic disorder; Crits-Christoph et al. 1995 and Luborsky 1984 for generalized anxiety disorder; and Marmar et al. 1995 for posttraumatic stress disorder). Adherence measures must be developed to determine whether psychodynamic psychotherapists and psychoanalysts are performing treatments according to treatment manuals. Therapists must be reliably trained in the administered treatments. Only after the groundwork has been laid in this manner—as it already has been for outcome research in other psychotherapeutic techniques, most notably for cognitive-behavioral therapy and interpersonal therapy (Agras et al. 1995; Barlow and Craske 1989; Clarkin et al. 1999; Craske et al. 1989; Klerman et al. 1984; Luborsky 1984; Mufson et al. 1993; Sandler et al. 1980)—can we hope to learn how effective these forms of treatment are under which specific circumstances and for which particular patients.

Panic Disorder

Treatments that focus on individual fantasies underlying the panic symptoms appear to be an effective psychodynamic approach to the treatment of panic disorder (Kessler 1996; Milrod 1995; Milrod and Shear 1991; Milrod et al. 1996, 1997, 2000; Renik 1995; Stern 1995). Because the manner in which psychodynamic psychotherapy and psychoanalysis are actually practiced in the community varies greatly, and because psychodynamic psychotherapy is generally designed to elicit and address specific individual fantasies that underlie patients' symptoms via focus on the transferential situation, which necessarily varies from patient to patient, it is difficult to pinpoint general therapeutic interventions that have been found to be most helpful, despite a wealth of available clinical material. Nonetheless, many aspects of therapeutic interpretive work have been described (Kessler 1996). In this section, we summarize issues surrounding research in this area and describe the findings that pertain to psychodynamically based treatments for panic disorder.

Background

The psychodynamic view of panic disorder describes panic as a three-part problem:

1. The syndrome has a genetic or constitutional backdrop, often described in early life as "shyness" or "inhibition to the unfamiliar" (Kagan et al. 1990).
2. Life events and important relationships can aggravate genetic predisposition or can create a similar picture acting alone. Ambivalent attachments to parents and difficulty in experiencing and acknowledging angry feelings because of terrifying fantasies about the meaning of rage, as well as difficulty permitting oneself to be autonomous because of fears of abandonment, are central dynamisms in this view.
3. Stressors in current life symbolically represent the core conflicts described in the second point above and reawaken these chronic conflicts, leading to the onset of panic disorder.

New Directions in Psychodynamically Oriented Research for Panic Patients

Some efficacy data on psychodynamic interventions in panic patients are available. Wiborg and Dahl (1996), in the only published randomized controlled trial in which panic patients were serially assessed with standard measures and treated with a manualized form of psychodynamic psychotherapy, showed in a pilot study that weekly psychodynamic psychotherapy for 26 weeks in addition to clomipramine significantly reduced relapse rates at 6- and 18-month follow-up among patients with panic disorder in comparison to patients treated with clomipramine alone (9% relapse in the combined treatment group vs. 91% in the clomipramine alone group). This study did not control for frequency of therapist contact.

In an attempt to study a psychodynamic approach in a systematic manner, other investigators have developed clearly defined, panic-specific psychodynamically

based treatments to facilitate outcome research. Panic-focused psychodynamic psychotherapy (PFPP), for example, is a modified form of psychodynamic psychotherapy that maintains the central psychodynamic principles of the importance of unconscious mental dynamisms and fantasies, free association, and the centrality of the transference, and the therapist focuses attention on all of these processes as they are connected to the patient's experience of panic (Milrod et al. 1997). General principles of psychological dynamisms that are common to most panic patients, such as their difficulty with separations, are used to inform interpretive efforts. As in other psychodynamic psychotherapies, techniques of clarification, confrontation, and interpretation inside and outside the transference are used.

An open trial of panic-focused psychodynamic psychotherapy was recently completed (Milrod et al. 2000) in which standard panic assessment measures were used, as recommended by the National Institute of Mental Health consensus development conference (Shear and Maser 1994). Twenty-one patients with panic disorder were entered into a trial of twice-weekly, 24-session psychodynamic treatment. Sixteen of these 21 experienced remission of panic and agoraphobia. Treatment completers with depression also experienced remission of depression. Symptomatic and quality-of-life improvements were substantial and consistent across all measured areas. Symptomatic gains and improvements in quality of life were maintained over 6 months. The results of this trial indicate that psychodynamic psychotherapy is a promising nonpharmacological treatment for panic disorder. The study was not designed to assess efficacy.

Much remains to be learned about the effects of this arena of interventions on patients with panic disorder because outcome research is in its infancy in this field.

Posttraumatic Stress Disorder

Psychotherapy process and content, as they relate to phase-specific outcome criteria, are being studied in psychodynamically oriented group therapy for Vietnam veterans with posttraumatic stress disorder (Kanas et al. 1994; Marmar 1990). The treatment approach used is very clearly described in a manualized and reliably teachable form (Weiss and Marmar 1993). Thus far, outcome data have not been published from this initiative.

Mixed Anxiety Disorders

No systematic outcome studies of psychodynamically based treatments for any single anxiety disorder other than for panic disorder exist. Nonetheless, several studies of psychodynamic treatments for mixed disorders, including some patients with anxiety disorders, are in progress; we review one in this section.

In an interesting but uncontrolled study, Vaughan et al. (2000) examined DSM diagnoses determined by the *Structured Clinical Interview for DSM-IV* in a sample of 24 patients who entered psychodynamic psychotherapy twice a week ($n=15$) or psychoanalysis four times a week ($n=9$) at the Columbia University Center for Psychoanalytic Training and Research in New York, NY. In this setting, no patients with primary anxiety disorders entered psychoanalysis, and 7 patients (29.2% of the total sample) with DSM anxiety disorders (1 with panic disorder, 4 with social phobia, 1 with obsessive-compulsive disorder, 1 with simple phobia, and 1 with generalized anxiety disorder [one of the patients had been diagnosed with two different anxiety disorders]) entered psychodynamic psychotherapy. Assignment to treatment condition was not random.

Patients were assessed before starting treatment and after 1 year of ongoing treatment with the Spielberger State-Trait Anxiety Inventory. During the year of psychodynamic treatment, 2 patients who previously had not had anxiety disorders developed the symptoms of generalized anxiety disorder; the authors hypothesized that the treatment acted to mobilize warded-off affects and generate more anxiety that had been inaccessible to consciousness.

Interestingly, in this sample of patients, both the lack of psychological-mindedness and the sense of locus of control being located *externally* were positively correlated with higher degrees of anxiety. Because both psychological-mindedness and a sense of locus of control being located *internally* have been thought to be good predictors of patients' ability to make use of dynamically oriented psychotherapies, these data might imply that highly anxious patients may not be among the best candidates for these forms of therapy. However, these hypotheses may equally well *not* be predictors of who will or will not respond to psychodynamic psychotherapy because they have not yet been empirically tested. This hypothesis contradicts what was found in the large, retrospective outcome study of 735 psychodynamic treatments (psychodynamic psychotherapy and psychoanalysis) in the child and adolescent population at the Anna Freud Centre (Fonagy and Target 1994; Target and Fonagy 1994a, 1994b), in which patients with anxiety disorders were found to benefit more than patients in any other diagnostic category from these treatment modalities.

The 24 patients experienced an average of a 13-point drop (24%) on the Spielberger State-Trait Anxiety Inventory between their initial evaluations before beginning treatment and their evaluations after having received 1 year of treatment.

Two important studies in the area of child and adolescent psychiatry indirectly document some of the salutary effects of psychodynamic treatment on patients with anxiety disorders, although additional research is necessary in this area. Heinicke and Ramsey-Klee (1986) evaluated the relative effects of once-weekly and four-times-weekly psychodynamic psychotherapy or psychoanalysis on 15 boys aged 7–10 years with DSM-III (American Psychiatric Association 1980) overanxious disorder and problems at school. Patients were systematically evaluated before treatment, at treatment termination, and at 2-year follow-up. Both groups showed significant improvements in levels of anxiety, but those receiving four-times-weekly therapy experienced additional important characterological and coping skills gains.

Fonagy and Target (1996) performed a retrospective review of the Anna Freud Case Center's 196 child and adolescent patients who had diagnoses of anxiety disorders and assigned DSM-III-R diagnoses to patients from detailed clinical reports. Patients received psychoanalysis four or five times a week or psychodynamic psychotherapy once or twice a week. By treatment termination, average children's Global Assessment Scale scores (a measure of overall functioning scored from 0 to 100) improved 13.7 points, indicating a significant overall average improvement in level of functioning. A positive correlation was found between frequency of treatment and degree of clinical improvement, despite the fact that children who were initially evaluated as being more impaired were assigned to the more intensive treatment condition.

Conclusion

The field of psychodynamic psychiatry awaits efficacy studies to determine the effect of psychodynamic interventions, alone or in combination with other antianxiety treatments, on anxiety disorders. It is unfortunate that this important area of psychiatry has such a wide disjunction between clinical practice and systematic research. It is fortunate that several groups of researchers are in the process of assembling the necessary tools to accomplish this work. The first step in this process is to clearly define relatively homogeneous patient populations for systematic study. The DSM-IV-TR definitions of specific anxiety disorders provide useful parameters in this regard.

Another focus of fruitful research in the area of psychodynamic treatments for anxiety disorders will be to systematically determine, with the use of audio- or videotapes, which types of interpretive interventions are most useful for the relief of which specific symptoms. Several projects of this nature also are currently under way (C. Klein et al., in press; Luborsky 1984; Vaughan et al., submitted; Weiss and Marmar 1993). In the absence of controlled studies, numerous reports from many sources, including clinical cases and the uncontrolled pilot data in the panic-focused psychodynamic psychotherapy study (Milrod et al. 2000, in press), justify an intense effort to determine whether psychodynamic psychotherapy for specific anxiety disorders can be sufficiently effective and safe to warrant a place among standard treatments.

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8

Combined Treatment for Anxiety Disorders

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Since our earliest written records, people have struggled to comprehend the relation between the energies that animate us and the material that is animated. The despair of Gilgamesh trying to comprehend the departure of life from the body, the authoritative voice of Plato on the relation between ideas and things, St. John's Gospel on "the Word made flesh," and Descarte's proclamation of mind-body dualism all respond to the same problem. Despite the natural existence of each person as an integrated organism, medicine often has concerned itself more with the mechanical prerequisites for life than with what flows through us to set the "machine" in motion. In the field of mental health, this compartmentalized approach to understanding the living organism is reinforced by the trend for clinicians to specialize in areas characterized predominantly as psychological or biological.

This push toward specialization has been supported by an increasing refinement in both biological and psychological treatments during the past two decades. A proliferation of new medications and new indications for their uses has developed at the same time that psychotherapy outcome research has generated a growing number of empirically validated, disorder-specific treatment protocols. Psychotherapists may lack awareness of recent advances in pharmacotherapy, and many pharmacotherapists lack familiarity with the recent developments in the cognitive-behavioral therapy (CBT) approaches.

Paradoxically, discoveries from each treatment approach reinforce the concept of an essential unity of mind and body. Patients whose anxiety disorders are treated with serotonergic antidepressants, for example, report associated psychological effects of unexpected range and subtlety, affecting characteristics such as patience, temper, procrastination, self-confidence, sexual desire, and absentmindedness. Anxious persons who were thought to be without clinical depression have reported that these agents enhanced "brightness of mood" and optimism (Kramer 1993). Conversely, psychological interventions have been shown to affect "biological" processes and conditions in several models (Kandel 1998). Group therapy has been shown to enhance survival in women with breast cancer (Fawzy et al. 1993; Spiegel et al. 1989), meditation has been shown to lower blood pressure (Benson 1975), and psychosocial interventions have been shown to enhance immune functioning (Kiecolt-Glasser et al. 1985, 1986). Positron-emission tomography (PET) scan imaging studies have reported that response prevention techniques used with obsessive-compulsive patients resulted in changes in brain physiology similar to those produced by pharmacotherapy with a selective serotonin reuptake inhibitor (Schwartz et al. 1996).

All this points to a psychobiology of behavior that demands a more unitary conceptualization. The anxiety disorders present a particularly appropriate opportunity to think in terms of mind-body unity. The experience of anxiety involves a host of familiar, pronounced physical processes, such as changes in respiration and heart rate, increased muscle tension, alteration of skin

conductivity, and redistribution of blood flow. At the same time, anxiety serves psychological functions, shaping and intensifying one's response to external and internal influences (McCarter 1996). Learned associations, cognitive appraisals, beliefs, expectations, mental representations of danger, self-representations, and self-esteem all reciprocally interact with the biological aspects of anxiety to create a unified personal experience.

Numerous studies have documented the beneficial effects of psychotherapeutic treatment, usually cognitive behavioral, on each anxiety disorder represented in this text. Pharmacological monotherapy also has been an effective treatment for each of these disorders, except specific phobia and possibly posttraumatic stress disorder (PTSD). A smaller body of studies addresses the effects on anxiety disorders of a combined treatment that includes both psychotherapy and pharmacotherapy. As McCarter (1996) discussed, simply providing pharmacotherapy and psychotherapy at the same time is not the same as coordinating the two to provide an integrated and unified treatment. We use the term *combined* to describe any treatment including both therapies and reserve the word *integrated* to describe the latter approach. Thus far, research has predominantly examined the simple combination of treatments rather than their integration. In this chapter, we summarize the currently available results of combined treatment studies and the preliminary recommendations that can be generalized from them. Following additional discussion of the interactions of pharmacotherapy and CBT, we make recommendations for the delivery of integrated treatment.

Studies of Combined Treatment

Anxiety disorders have been treated with a varied and extensive range of medications, including benzodiazepine and nonbenzodiazepine anxiolytic agents, antidepressants, mood regulators, and even antipsychotic agents. In studies of combined treatment, however, there is a distinct lack of variety among the medications used. Except for the use of a monoamine oxidase inhibitor (MAOI) in some early panic disorder studies and one social phobia study and the use of a selective serotonin reuptake inhibitor in one published combined treatment study of obsessive-compulsive disorder (OCD), combined treatment studies of anxiety disorders have relied on the use of tricyclic antidepressants (TCAs) or high-potency benzodiazepines. The forms of CBT used in combined treatment studies vary greatly. Early studies used primarily variations of exposure or relaxation. Only a few have used the sophisticated, disorder-specific forms of CBT described in this book.

Panic Disorder With Agoraphobia

Panic disorder with agoraphobia is the most frequently examined disorder in studies of combined treatment. (For a discussion of psychodynamic interventions, see Spiegel and Hofmann, Chapter 21, in this volume.) Most studies of combined treatment have used exposure therapy, although a few have used cognitive therapy or more complex CBT. The medications used fall predominantly into two classes—the antidepressants and the benzodiazepines. Because the findings have differed between these classes, they are discussed separately.

Following two early antidepressant combined treatment studies that used MAOIs (Lipsedge et al. 1973; Solyom et al. 1981), imipramine emerged as the usual antidepressant in such studies. The preponderance of evidence favors the conclusion that imipramine has specific antipanic and antiphobic effects and that it acutely enhances the therapeutic effects of exposure (Mavissakalian 1991). The strongest evidence that imipramine enhances the effect of exposure came from a study (Mavissakalian and Michelson 1986a) of patients with panic disorder with agoraphobia who received imipramine or placebo combined with flooding or programmed practice. Imipramine contributed statistically significant benefits beyond programmed practice, an effect accounted for by patients who had received higher doses of imipramine (150–200 mg/day). These effects were not attributable either to alleviation of depressive symptoms or to increased programmed practice among the imipramine patients. Imipramine added to the acute effects of exposure in several earlier studies of agoraphobic patients (Telch et al. 1985; Zitrin et al. 1980, 1983) as well, but Marks and colleagues (1983) found no significant benefit when imipramine was added to self-exposure homework in a group of patients with chronic agoraphobia. The presence of exposure also appears quite clearly to add to the effects of imipramine. Telch et al. (1985) showed that patients who were given imipramine and antiexposure instructions did not improve significantly until the antiexposure instructions were removed.

Whether imipramine's beneficial effects are sustained over the longer term following discontinuation

is controversial. At 6-month follow-up, Zitrin and colleagues (1983) noted a higher rate of relapse among imipramine-treated than among placebo-treated patients. One 2-year follow-up (Mavissakalian and Michelson 1986b) found a statistically nonsignificant trend for worsening of symptoms after discontinuation of imipramine among patients who received imipramine and exposure, compared with those who received placebo and exposure. Another follow-up study (Cohen et al. 1984) found no such problem. A commonsense interpretation of these findings suggests that imipramine's therapeutic effects cannot be expected to persist long after the medication has been discontinued.

Given the current predominant use of serotonergic antidepressants rather than TCAs or MAOIs, it is clear that further research on the combination of such drugs with CBT is greatly needed. The one study that addressed antipanic effects of combination treatment with exposure and the serotonergic antidepressant fluvoxamine (de Beurs et al. 1995) reported beneficial effects of the combined treatment significantly exceeding those of either treatment alone. Unfortunately, the data addressed only short-term follow-up, leaving unresolved the important question of pharmacotherapy's effects on longer-term outcome.

The combined use of benzodiazepines with CBT raises complex questions about treatment priorities. Despite effective acute alleviation of symptoms, some authorities believe that benzodiazepines can detract from the benefits of CBT (Brown and Barlow 1995; Marks et al. 1993). Other experts warn about the potential for dependence, abuse, or tolerance with benzodiazepines, although abuse appears to occur primarily among individuals with a personal or family substance abuse or dependence history, and tolerance to the anxiolytic effects is considered unusual (Spiegel and Bruce 1997).

Oei et al. (1997) found that preexisting treatment with antianxiety medication or antidepressant medication did not adversely affect the long-term outcome of brief intensive group CBT for panic disorder, but considerable other evidence suggests that the initial relief of symptoms from a combination of CBT with a high-potency benzodiazepine may be counterbalanced by a later increase in relapse risk. Hafner and Marks (1976) administered diazepam or placebo to agoraphobic outpatients receiving group exposure treatment. Although the diazepam significantly reduced discomfort during the group exposure treatment, it did not facilitate a better eventual outcome than placebo. Marks and colleagues (1993), in an important and frequently cited collaboration (the "London/Toronto Study"), showed that the combination of alprazolam and exposure therapy was initially as effective as either treatment alone but that patients who received the combination experienced a high relapse rate following alprazolam discontinuation. At a limited 3.5-year follow-up assessment, the alprazolam appeared to have added no significant long-term benefit to exposure therapy (Kilic et al. 1997). This study has been criticized on the basis of sample composition, attrition rate, treatment design, and lack of a treatment effect on panic attacks (Spiegel et al. 1993) and for the simultaneous termination of both treatment modalities but nonetheless raises very important issues. It appears that the combination of CBT with a high-potency benzodiazepine may expose the patient with panic disorder with agoraphobia to an increased risk of relapse on discontinuation of the benzodiazepine and that perhaps the benzodiazepine detracts from the patient's ability to make full use of the CBT.

Several groups have found that CBT can facilitate the discontinuation of a benzodiazepine in patients with panic disorder, indicating that the sequence in which treatment components are administered and discontinued is an important dimension of the integration of treatment modalities. Otto and colleagues (1993) combined CBT with a moderately slow taper of benzodiazepine (alprazolam or clonazepam) medication. Seventy-six percent of the CBT/slow-taper patients but only 25% of the no CBT/slow-taper patients were able to successfully discontinue medication. Most CBT patients remained benzodiazepine free at 3-month follow-up. Spiegel and colleagues (1994) similarly reported the use of CBT to facilitate successful slow taper of alprazolam in outpatients with panic disorder and agoraphobia. At 6-month follow-up, half of the patients who discontinued alprazolam without CBT had relapsed and resumed alprazolam treatment, whereas none of those who received CBT had done so. Oei and colleagues (1997) showed that the addition of brief intensive group CBT to preexisting antianxiety or antidepressant regimens was associated with numerous patients (44%) reporting no current use of medication at long-term follow-up (mean follow-up period, 3.2 years).

A further reason for adding CBT to pharmacotherapy for panic disorder was reported by Pollack and colleagues (1994), who found that some panic patients resistant or only partially responsive to apparently adequate pharmacotherapy could be converted to treatment responders by adding CBT to their pharmaco-

therapy regimen. These patients were primarily receiving high-potency benzodiazepines, although some concurrently were using imipramine, desipramine, fluoxetine, or lithium.

Taken as a whole, the research on combined treatment of panic with benzodiazepines brings into sharp relief the difference between simply combining treatments and systematically integrating them. When benzodiazepines have been combined with CBT without any effort at coordination, as in the London/Toronto study, adverse effects, such as increased risk of relapse, are likely. However, when methods have been used that involved coordination of the two treatments, as in the work of Otto or Spiegel and their colleagues, it appears that patients may be offered the rapid relief associated with a benzodiazepine while also receiving the long-term benefits associated with CBT.

Obsessive-Compulsive Disorder

A few studies of combined behavioral and pharmacological treatment of OCD have been published. Evidence for superiority of a combined approach is weak, and no study yet allows definitive conclusions about the additive or interactive effects of the treatment components on specific symptoms or the effects of combined treatment on relapse rate following treatment discontinuation.

A study by Foa et al. (1992) examined the combination of imipramine with CBT in patients with OCD and comorbid depression. Although imipramine did not enhance CBT's effects, it reduced depressive symptoms. With the increasing dominance of potent serotonergic antidepressants in pharmacotherapy for OCD, this study's results have become less relevant.

In a very small study, Amin et al. (1977) found that the combination of clomipramine plus behavior therapy was superior to either treatment alone. Marks et al. (1980) compared the combination of clomipramine or placebo with either exposure or relaxation in a larger population. The addition of clomipramine to behavior therapy enhanced compliance with exposure or relaxation and aided the early improvement of rituals, mood, and social adjustment in patients who initially also had a depressed mood. Cessation of clomipramine was frequently associated with relapse. Exposure was concluded to be the treatment of choice in nondepressed ritualizers. This study was later criticized for the low doses of clomipramine used and the brief trial of clomipramine alone (Sherman et al. 1996). Furthermore, it is clear from other studies that clomipramine alone can exert a specific antiobsessional effect that is independent of its antidepressant effect (Mavissakalian et al. 1985; Thoren et al. 1980).

A subsequent study by Marks et al. (1988) reported a therapeutic effect of self-exposure to which clomipramine added a transient improvement (first 8 weeks of treatment only) in rituals and depression more than did placebo. The combination of clomipramine with anti-exposure instructions, however, led to very poor outcomes. Six-year follow-up of most of these patients linked better long-term outcome with improvement at the end of treatment, a lengthier initial course of exposure therapy, and better compliance with the exposure therapy homework but not with clomipramine treatment (O'Sullivan et al. 1991).

A partially consistent result was reported by Cottraux et al. (1990), who found that behavior therapy or fluvoxamine produced similar reductions in OCD symptoms acutely and after 6 months and that the only advantage of combined treatment was a slightly greater acute improvement in depression, a difference not evident at follow-up.

A multicenter study in progress is comparing the combination of clomipramine and unguided self-exposure with either exposure with response prevention or the combination of clomipramine and exposure with response prevention (Greist 1994). Although final results have not yet been published and the investigators have expressed caution about generalizing from the preliminary results (Liebowitz et al. 1995), early data have suggested a better response and a reduced subsequent rate of relapse with exposure with response prevention or the combination treatment regimen as compared with clomipramine and unguided self-exposure. Interestingly, the onset of improvement was faster for exposure with response prevention with or without clomipramine than for clomipramine alone. The combination treatment was associated with use of lower clomipramine dosages. Attrition rates were similar among the treatment groups.

Several studies of CBT for OCD have drawn on populations in which all or most of the subjects also were taking medication (Lucey et al. 1994; March et al. 1994; Orloff et al. 1994) and have uniformly found that the combined treatment was effective. None of these studies used a design that allowed for differentiation of the relative contributions of pharmacotherapy or psychotherapy. March et al. (1994) noted that the treatment effects they observed were greater than those typically reported for medication alone. Their data also suggested that CBT may help prevent relapse after

medication is discontinued. March (1995) reviewed 32 reports (mostly single case studies) on the use of CBT for OCD in children and concluded that in some cases combined treatment may work best.

Taken together, these studies offer a limited rationale for combined treatment as compared with CBT alone. Obstacles such as patient acceptance and therapist unavailability may make the addition of CBT to pharmacotherapy impractical, but this combination appears to produce a better result than pharmacotherapy alone and improves the quality of outcome after medication discontinuation. The addition of pharmacotherapy to CBT may facilitate a patient's confrontation of anxiety-provoking circumstances (Spiegel 1992) or improve response when a comorbid depression or other Axis I or Axis II disorder is present (Sherman et al. 1996).

Social Phobia

Although various monotherapeutic approaches have been evaluated for the treatment of social phobia (see Blanco et al., Chapter 24, and Turk et al., Chapter 25, in this volume), only limited data are available regarding the efficacy of combined therapy. Gelernter et al. (1991) compared CBT with pharmacotherapy by assigning 65 patients to one of four treatment conditions: 1) cognitive-behavioral group treatment (CBGT), 2) alprazolam with self-directed exposure, 3) phenelzine with self-directed exposure, or 4) placebo with self-directed exposure. Because this study included two groups of patients who received both an active medication and a form of behavior therapy (self-directed exposure), some information about combined therapy can be gleaned. Neither of the medication with self-directed exposure groups fared significantly better than the group receiving only CBGT. Also of note, the phenelzine group performed better than the alprazolam group on a measure of work and social disability, which was not administered to the CBGT group. At follow-up 2 months after treatment discontinuation, the phenelzine group maintained gains, the CBGT patients showed some improvement, and the alprazolam patients showed a higher relapse rate. In another study comparing CBGT with phenelzine, Liebowitz and colleagues (1999) found that phenelzine may be faster acting but that CBGT was associated with fewer relapses.

A study of performance anxiety among musicians assigned subjects to four treatment groups: five-session CBGT with buspirone or placebo, buspirone alone, or placebo alone (Clark and Agras 1991). Buspirone added no significant benefit to CBGT, but this medication is not considered an effective monotherapy for social phobia (van Vliet et al. 1997), although it may have a role in augmentation of selective serotonin reuptake inhibitor treatment of that condition (Van Ameringen et al. 1996).

A recent multicenter study that compared CBT with phenelzine, pill placebo, and psychosocial placebo is anticipated to yield further data that will compare the combination of CBT and phenelzine with either CBT or phenelzine provided separately (Barlow and Lehman 1996). In view of these data, the treatment of social phobia with either pharmacotherapy or CBT alone might be entertained. The finding of a high relapse rate among alprazolam with self-exposure patients following medication discontinuation suggests the need for prolonged pharmacotherapy in such patients, although an important question to explore is whether CBT might facilitate benzodiazepine discontinuation in patients with social phobia as it has in patients with panic disorder.

Generalized Anxiety Disorder

Generalized anxiety symptoms are prevalent in primary care settings (Fifer et al. 1994). These symptoms are a source of considerable morbidity (Barlow et al. 1996) and are often responsive to either pharmacotherapeutic or psychotherapeutic interventions (see Sussman and Stein, Chapter 11, and Huppert and Sanderson, Chapter 12, in this volume). Combined therapeutic approaches are often recommended, yet scant data support this conclusion at present. The early studies of combined treatment of generalized anxiety disorder (GAD) are by and large of limited current relevance in light of subsequent refinements in both the pharmacotherapeutic and the psychotherapeutic treatment approaches to this condition (Fontaine et al. 1988; Lorr et al. 1963; Podobnikar 1971; Rickels et al. 1966).

In two combined treatment studies of GAD, the psychotherapeutic treatment component was behavioral or cognitive behavioral. Lavallee and colleagues (1977) combined electromyographic feedback or control (no feedback) with diazepam or placebo in treating a group of chronically anxious patients. The combination of active treatments had additive anxiolytic effects during treatment, but diazepam-treated patients had a worse outcome following treatment, an effect that might have been caused by rebound anxiety or withdrawal (Beaudry 1991). Power and colleagues (1990), in a dif-

ferent study, showed that CBT with diazepam was somewhat more effective than CBT with placebo, which was more effective than diazepam alone at posttreatment assessment of a group of GAD patients.

Early reports asserted the value of relieving acute or intolerable anxiety symptoms to facilitate a patient's participation in psychotherapy. However, Lavallee's report raised the same concern with generalized anxiety that was apparent from studies of several other anxiety disorders that benzodiazepine treatment might help initially but lead to a poorer long-term treatment outcome. Apparently, no study has examined the effect on GAD of combining CBT with either buspirone or a serotonergic antidepressant, so research in this area lags far behind current clinical practice. Further studies are needed to determine whether one of these more current combinations might be more efficacious than either treatment modality alone.

Posttraumatic Stress Disorder

With the exception of one case report that showed how flooding sessions were aided by concurrent use of a trazodone/carbamazepine regimen in one PTSD patient (Mirabella et al. 1995), no published studies of combined treatment of PTSD were located. This lack of studies is unfortunate because the issues most relevant to combined treatment of PTSD may differ somewhat from those that guide treatment choices with other anxiety disorders. Furthermore, PTSD is not a homogeneous syndrome, and the results of studies that find treatment effects in a specific population may not be generalizable to other patient populations. The most relevant clinical distinctions in this respect may be between civilian and military PTSD and between acute and chronic PTSD (see McFarlane, Chapter 27, in this volume).

Among the various therapies that have been shown to alleviate various PTSD symptoms, both psychotherapies and pharmacotherapies are represented (Solomon et al. 1992). Effective pharmacotherapeutic alleviation of intrusive PTSD symptoms has been documented with several agents (Davidson 1997; Reeves and Ellison 1996; van der Kolk 1987; van der Kolk et al. 1994). Such symptomatic relief may diminish anxiety or depression sufficiently to allow a patient greater ease in and compliance with psychotherapy. When pharmacotherapy serves to make remote memories more available to the conscious mind (Robertson 1997), it may do so by rendering the associated affect less intolerable, thereby reducing the resistance to recovering the memories. Such new recollections, handled appropriately, can in some cases fuel the progress of psychotherapy.

In some settings, the pharmacotherapist also is able provide a therapeutic "holding environment." As a general rule, however, the treatment of PTSD with medication alone is not recommended. A supportive context for pharmacotherapy is especially needed during the potentially stressful evaluation process, when drugs were a component of the patient's prior trauma, when substance abuse has been present, and when the patient may be "triggered" by the experience of pharmacologically altered somatic sensations (Reeves and Ellison 1996). The use of medication frequently will stir intense reactions in PTSD patients, requiring the pharmacotherapist's attention to dynamic factors such as transference, countertransference, and the symbolic meaning of medications (Bridges 1996; Southwick and Yehuda 1993). Clearly, more studies are needed to address the advantages and drawbacks of combined treatments for PTSD.

Specific Phobia

Recent years have seen the development of highly effective cognitive-behavioral treatments of specific phobia (Öst et al. 1997). One study indicated that benzodiazepine treatments helped patients move more quickly up their exposure hierarchies (Marks et al. 1972), but in general pharmacotherapy has not been considered effective in treating specific phobias alone or in enhancing the psychotherapeutic treatment of this disorder unless comorbid disorders such as depression, social phobia, agoraphobia, or panic disorder are present (Zitrin et al. 1983).

Rationale for Combining Treatments

To provide a context for discussing combined treatment for the anxiety disorders, it is useful to review the advantages and disadvantages of the two component approaches: pharmacotherapy and CBT.

Advantages and Disadvantages of Pharmacotherapy

The main advantages claimed for pharmacotherapy are that it brings significant and relatively rapid relief, requires less from the patient in terms of effort and capability, and takes less investment of time on the part of both clinician and patient to achieve its effects. How-

ever, several disadvantages are frequently cited for pharmacological monotherapy for anxiety disorders. Undesirable side effects are perhaps the most frequent reason for aborted therapeutic trials. Pharmacotherapy, delivered alone, also may evoke negative cognitions in some patients, particularly when the patient experiences pharmacotherapeutic gains as the product of an external agent. A patient who experiences improvement as linked to "dependence" on medication rather than as a personal achievement may feel confirmed in a sense of weakness and shame. Finally, for several anxiety disorders, patients who receive pharmacological monotherapy are exposed to a significantly greater risk of post-treatment relapse than are patients who receive CBT.

Advantages and Disadvantages of Cognitive-Behavioral Therapy

An immediate advantage of CBT is that it has no usual adverse physical side effects. Furthermore, its effects are achieved by the acquisition of skills and the facing and mastery of fears, often resulting in a greater sense of ownership of treatment results. These achievements lead to long-term, robust changes in the individual's internal organization and repertoire of tools for future coping. CBT is associated with a lower rate of subsequent relapse at long-term follow-up (Brown and Barlow 1995; Hiss et al. 1994; Liebowitz et al. 1999). Perhaps more readily than with pharmacotherapy, CBT produces enhanced self-esteem and an increased sense of agency.

Among the disadvantages of CBT, however, are the relatively greater amount of time and effort required from both patient and clinician and the often lengthier wait for significant anxiety relief. "Homework" assignments take time and must be done regularly. Exposure exercises can be uncomfortable and arduous and must be carried out persistently. In a review of exposure-based treatments, Jansson and Öst (1982) found a median dropout rate of 12%, whereas other investigators reported even higher numbers (Kozak et al., unpublished). Because of the amount of effort required to maintain many CBT techniques, patients may let them lapse. Although this accounts for some relapses among successful responders to CBT, such patients usually retain their knowledge of how to perform CBT techniques and are able to reinstate them with just a few "booster" sessions.

Another disadvantage of CBT is that it may be difficult to find clinicians to deliver it. The high reported success rates are associated with refined protocols developed at research-oriented specialty clinics located in major population centers. The availability of comparably effective treatments at other sites is uncertain, although treatment manuals or self-help workbooks for many of these protocols are now available (e.g., Baer 1991; Barlow 1993; Barlow and Craske 1994; Craske et al. 1992; Steketee and White 1990). Psychiatric training in CBT approaches has been scant, so many psychiatrists refer patients to CBT-trained clinicians rather than invest the extra effort required to learn how to deliver these therapies themselves. The time required of clinicians to administer CBT also has been a deterrent for psychiatrists to learn and provide this treatment.

Also problematic is the time required for treatment to take effect. Patients receiving CBT can derive some immediate benefit from simply being educated about their disorders and from the hope associated with being in treatment, but, with a few exceptions, it usually takes weeks to months for the treatment to produce its full effects. The exceptions are some of the specific phobias, for which effective exposure-based treatment can sometimes be done in a single extended session (Öst et al. 1997). In the treatment of complex PTSD, by contrast, treatment may take years (Herman 1992).

Advantages and Disadvantages of an Integrative Treatment Approach

When pharmacotherapy and psychotherapy are thoughtfully integrated, their differing advantages can complement each other and compensate for some of the disadvantages associated with either monotherapy. Telch and Lucas (1994) identified three ways in which the two therapies can complement each other:

1. The set of primary disorder symptoms targeted by each approach is unique, resulting in a more comprehensive additive effect.
2. Pharmacotherapy facilitates psychotherapy by treating a comorbid disorder or reducing the paralyzing acute level of anxiety that would make participation in CBT otherwise impossible.
3. Psychotherapy facilitates pharmacotherapy by increasing compliance, addressing the symptoms of a comorbid personality disorder, or facilitating withdrawal from a benzodiazepine.

Each of these advantages has been confirmed in the studies cited, yet the potential advantages of a combined treatment are also associated with some difficulties, including the greater time required, the greater ex-

pense often associated with the extra treatment, and the need for clinicians to collaborate when treatment is shared.

Interactions of Cognitive-Behavioral Therapy and Pharmacotherapy

Despite the many different protocols for treating various anxiety disorders with CBT, two important components are shared by all: psychoeducation and exposure.

Psychoeducation

Almost all patients will benefit from information that helps them develop increased understanding of their anxiety disorders. The information must be imparted in language they can use and discuss in a collaborative way, resulting in a shared understanding. Beginning with the nature of the problem and its development, this discussion should proceed to a shared rationale for treatment and a related, mutually acceptable plan. For two or more treatment modalities to be combined, let alone effectively integrated, it is vital that the psychoeducation provide the patient with a unified model of the problem, from which compatible rationales may be derived for both pharmacological and psychological interventions. This may require special care when the two components are provided by different clinicians.

As the rationale for each component of treatment is presented, the clinician should be wary of language that may explicitly or implicitly undermine the complementary component. For instance, sometimes clinicians introducing pharmacotherapy will speak of an underlying chemical deficit or imbalance and compare the pharmacotherapy for certain anxiety disorders to the use of insulin for diabetes. Although the intent of such a comparison is to reduce the patient's feelings of shame and character weakness associated with taking the medication, such an analogy can lead the patient to embrace a too exclusively biological model of etiology and treatment, one in which the importance of psychological factors may be minimized. Similarly, clinicians introducing patients to the notion that thought processes may influence anxiety will sometimes offer a unidirectional model of causality, as if negative thoughts always preceded and caused anxious arousal, rather than constituting one part of a reciprocal relationship that includes physical factors and biological responses.

It will often be important to include the family system in the psychoeducational process. Significant others can do a great deal to either help or hinder the effectiveness of both pharmacotherapy and CBT. Several of the patient manuals now available contain chapters written for the patient's family, which are good models of the type of communication that is useful here (e.g., Baer 1991; Otto et al. 1995). In some cases, it may be appropriate to enlist a family member as a "coach" to help the patient carry out the exposure homework component of CBT. In other cases, it may be necessary to overcome family system resistance to the patient's recovery or to address family values opposed to the use of medication.

Exposure

As subsequent chapters in this book discuss, different types of exposure have been found to work for different disorders. They all share one principle, however, and this has crucial implications for integrative treatments: the exposure must evoke distress bearing a meaningful resemblance to that associated with the patient's actual symptoms. Unless the relevant dimensions of the patient's symptomatic anxiety are evoked, and at meaningful levels, therapeutic effects will be incomplete or nonexistent.

Effects of Pharmacotherapy on Exposure

Effective integrative therapy depends on coordinating pharmacotherapy with psychotherapy so that the effects of medication facilitate rather than block the effects of exposure. Benzodiazepines, for example, seem to interfere with exposure, through interference with acquisition and retention of new information, state-dependent learning that might impair recall of learned techniques in a drug-free state, interference with acquisition of the "toughening up" process by which an individual becomes tolerant to anxiogenic stimuli, or interference with development of the levels of anxiety or motivation necessary to take advantage of CBT (Spiegel and Bruce 1997). In addition, as Marks et al. (1993) described, pharmacotherapy has been associated with a higher relapse rate in patients who received combined treatment but attributed their improvement to the use of medication (even when receiving placebo). Medication best facilitates exposure when it reduces anxiety to meaningful yet manageable levels without blocking it entirely. To optimize this potential contribution, it will be useful for the clinician to have a model of the ways in which pharmacotherapy can facilitate exposure:

1. By enhancing mood and motivation, medication may increase the likelihood that patients will engage

in exposure, especially self-directed exposure between sessions (Telch 1988; Telch et al. 1985). This effect may operate independently of any primary anxiolytic action of the medication. It also may operate in patients who are not clinically depressed.

2. By slowing the escalation of arousal, medication use creates new opportunities to introduce mediating cognitive or behavioral responses that may help curtail further arousal.
3. By reducing anxiety without eliminating it, medication creates an intermediate state, which may be more amenable to the incorporation of skills from nonanxious states. In CBT without pharmacotherapy, an optimal level of anxiety is sought through the use of exposure hierarchies. At times, however, logistical constraints such as a patient's reactivity make attainment of a sufficiently low level of anxiety nearly impractical. Medication, in such cases, offers an additional tool for finding the optimal level of arousal for the patient's exposure activity.
4. By reducing the level of arousal associated with a given exposure activity, medication may enhance the probability of the patient's engaging in and completing the task. The result will be a greater likelihood of compliance with exposure.
5. Finally, antidepressants actually may alter the capacity of some patients to benefit during exposure itself. One way they may do this is by enhancing the positive tone of the self-evaluative cognitive processes that take place during the exposure, allowing the patient to have a greater sense of achievement and self-efficacy (Telch et al. 1985). In addition, clinical experience suggests that the antiobsessive effects of some antidepressants may enhance the capacity of patients to learn from exposure. For some patients, they may increase cognitive flexibility and the ability to take in positive outcomes and modify negative beliefs and self-perceptions. Again, this effect may operate even in patients whose symptoms do not meet diagnostic criteria for OCD.

Effects of Exposure on Pharmacotherapy

Barlow (1988) persuasively argued that, when long-term gains from pharmacotherapy persist beyond medication discontinuation, these were mediated by the de facto exposure facilitated by the pharmacotherapy. In patients studied by Telch and colleagues (1985), instructions to refrain from exposure to anxiety-provoking situations during pharmacotherapy almost completely eliminated medications' therapeutic effects.

If this argument is accurate, then, in a sense, all effective pharmacotherapy is de facto combined therapy in that it depends on associated exposure, whether deliberate or accidental, for its lasting effects. It seems likely to us that implicit cognitive restructuring is a routine component of effective pharmacotherapy as well. All of this is just another way of saying that, when medication works, it has enabled the patient to engage in new ways of thinking and acting, resulting in a reorganization that is able to take on a life of its own and carry over after pharmacotherapy is done. With this in mind, it may be useful for all clinicians delivering pharmacotherapy for the anxiety disorders to think of themselves as engaged in combined therapy. Conducting the therapy with attention to the techniques and principles discussed in this chapter will enable them to take advantage of the cognitive and behavioral opportunities inherent in the treatment process.

Single Provider Compared With Collaborative Approaches

Integrative treatment can be delivered by a single clinician or collaboratively. When the same clinician has expertise in both pharmacotherapy and psychotherapy, a single provider approach may be most practical. Under some circumstances (e.g., a skilled CBT therapist is unavailable, or the patient is unwilling to engage in a second treatment relationship), a single provider may be compelled to provide both CBT and pharmacotherapy despite a lack of CBT expertise. When treatment approaches are combined, it is often preferable to divide the approaches between two clinicians, but guidelines are offered also for the single provider of both treatment modalities.

Guidelines for the Single Provider

The pharmacotherapist who lacks expertise in CBT but who wishes to serve as a single provider of combined treatment faces a hierarchy of choices. Supervision with a qualified CBT provider is often the most rigorous way to proceed. A second option is to use one of the growing number of treatment manuals and patient workbooks now available. Whatever approach the single provider of pharmacotherapy and CBT chooses, the following set of general principles will maximize the opportunities for psychoeducation, cognitive restructuring, and exposure inherent in pharmacotherapy:

1. Empower patients by presenting a biopsychosocial model in which their thoughts and behaviors are important factors in the treatment.
2. Engage patients in a collaborative examination of the ways in which their cognitive processes foster or reduce their anxiety, and help them construct positive ways of framing their experiences.
3. Educate patients about the role of exposure in their treatment and encourage them to engage in exposure in a way that feels meaningful yet manageable.
4. Engage patients in the collaborative titration of medication to facilitate rather than block exposure.
5. Discontinue medication gradually.
6. Continue regular contact with patients until adaptive cognitive and behavioral functioning have been consolidated in the medication-free state.
7. Treat patients as active partners in treatment, a stance that has been termed *collaborative empiricism* (Hollon and Beck 1979).
8. Attend to the effect of the disorder and of the treatment process on how patients see themselves. Foster their sense of ownership over the process of change by calling attention to the ways in which it is a product of their active efforts and learning of skills.
9. Build relapse prevention into the termination process by discussing possible conditions under which symptoms might return, distinguishing between a slip and a relapse, and discussing coping strategies.

Guidelines for the Collaboration of Two Clinicians

A combination of treatments often is effectively delivered by a collaboration of providers, but collaboration requires something more than mere combination. Most psychiatrists and psychologists engage in collaborative treatment (Woodward et al. 1993), yet it continues to stir considerable professional ambivalence among residency directors (Riba et al. 1993) and practicing psychiatrists (Goldberg et al. 1991) as well as psychologists (Bascue and Zlotowski 1980). Regular communication between collaborating clinicians is widely accepted as a principle (e.g., American Psychiatric Association 1980; Bradley 1990; Chiles et al. 1991; Pilette 1988; Primm et al. 1989; Vasile and Gutheil 1979; Woodward et al. 1993) but may not be so often practiced (e.g., Hansen-Grant and Riba 1995). Collaborating therapists must be aware of the multiple opportunities that exist for supporting or undermining a complementary treatment modality and clinician. The more clinicians involved, the more important it becomes to understand the ground rules of the collaboration as well as the mechanics of effective collaborative communication.

Collaboration, too, does not necessarily mean successful integration of treatment modalities. An integrative treatment requires that each therapist have a sufficiently integrated view of the disorder and the patient to allow successful combined treatment and collaboration. To accomplish the integration of treatment modalities, clinicians must 1) communicate actively; 2) take the trouble to understand the basics of the other's treatment modality; 3) take the trouble to understand each other's formulation of the patient and to work through any differences and arrive at a shared formulation; 4) keep each other posted on important developments; 5) confer, as much as possible, before taking action that will affect the other's work; and 6) respect each other and convey that respect to the patient. Complaints about the other clinician should be listened to in a way that conveys respect for both patient and clinician, and direct communication of the complaints to the other clinician should be encouraged and supported. Ideally, every effort should be made to maintain the triad as a three-way team. Conflicts that might tend to align any two members against a third should be resolved as collaboratively as possible.

The pharmacotherapist engaged in collaborative treatment should be guided by the same rules outlined earlier for single provider treatment. Of course, design and implementation of major cognitive and behavioral interventions will be left to the CBT provider but should still be supported by knowledgeable inquiry as to how they are progressing and how medication is affecting them. Including the patient collaboratively in the process of dose titration to achieve optimal arousal levels during exposure is necessary and will enhance the patient's sense of ownership of the pharmacotherapy. Use of CBT devices such as self-monitoring forms during medication taper will further contribute to this sense of ownership and to the patient's sense of a unified treatment as well.

The Harvard Risk Management Foundation recently recommended an approach to collaboration that emphasizes the importance of communication between prescribing clinician and psychotherapist (Sederer et al. 1998). The Harvard Risk Management Foundation guidelines encourage collaborators to discuss a shared patient early on, assessing the context and circumstances of a collaboration request. At the outset, clinicians should engage in an initial discussion about treatment approach and goals; when they have not worked together previously, they also should discuss their cre-

dentials and experience. Respective treatment roles and a communication plan for emergencies should be developed. General guidelines for ongoing communication also should be discussed, including confidentiality issues. The patient's informed consent to ongoing communication is sought and in general should be a condition of treatment.

After this initial discussion, ongoing communication is necessary to support the alliance and facilitate treatment. The psychotherapist who becomes aware of a patient's concerns about pharmacotherapy (Primm et al. 1989) must feel empowered and respected by the prescribing clinician if helpful discussion is to take place. Conversely, the prescribing clinician, who may be accustomed to being in authority and acting unilaterally (see, e.g., Vasile and Gutheil 1979), must attempt to understand and support (or at the least discuss with the psychotherapist) the goals of the psychotherapy so far as possible without providing extraneous psychotherapy.

Conclusion

Anxiety disorders are pervasive and persistent conditions that require a comprehensive, integrated approach to treatment. As we attempt to integrate somatic and behavioral aspects of care, further research is needed to clarify the advantages and disadvantages of combining pharmacotherapy with CBT. On the basis of currently available studies, we can draw some preliminary conclusions, generalizing to some degree from studies of panic disorder with agoraphobia to the other anxiety disorders. The addition of pharmacotherapy to CBT appears to provide faster relief, enhance participation in CBT, and treat comorbid mental disorders. The addition of CBT to pharmacotherapy may achieve a more robust long-term outcome, improve medication compliance, promote a greater sense of ownership of treatment gains, and facilitate medication discontinuation, especially when medication is discontinued before CBT. Combined treatment, particularly when the pharmacotherapeutic component is a high-potency benzodiazepine rather than an antidepressant, may increase the subsequent risk of relapse after medication discontinuation. Panic disorder with agoraphobia has been studied the most extensively, and studies of GAD, social phobia, and PTSD are now particularly needed. Future research efforts should attempt to clarify whether and in what ways combined treatment is superior to monotherapeutic approaches; whether differential, additive, or synergistic effects can be determined; under what conditions the two treatments might interfere with each others' efficacy; and how the sequencing of treatments can affect outcome. We expect that future well-designed studies will confirm what experience already suggests to many clinicians: that for many patients, thoughtfully integrated treatment is the treatment of choice.

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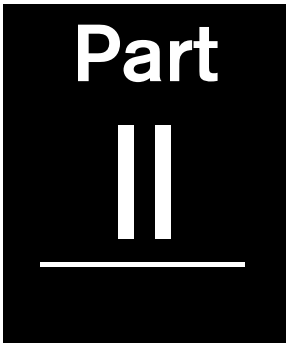

Generalized Anxiety Disorder

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9

Phenomenology of Generalized Anxiety Disorder

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Generalized anxiety disorder (GAD) is a disabling, chronic condition that is common in many medical settings. Nevertheless, to this date, GAD remains one of the least researched anxiety disorders. The reasons are numerous. First, because the diagnostic category of GAD was first introduced in DSM-III in 1980 (American Psychiatric Association 1980), studies conducted before that date have limited relevance and questionable validity. Second, because treatment resistance in GAD is not uncommon, patients and therapists are reluctant to engage in the prolonged and frequently unsuccessful therapeutic process that could yield the much-needed information. Third, because the varied symptoms of GAD can mimic a series of medical conditions, these patients usually are seen by non–mental health specialists; psychiatric referral, if ever made, is frequently delayed. Finally, because "pure" GAD without comorbid conditions is less common, the interpretation of studies with heterogeneous comorbid samples is difficult. These factors, compounded by the stigma generally attached to mental illness, have resulted in the relative sparsity of data on GAD.

Even more striking is the absence of information on GAD in populations with special needs, such as children, elderly persons, and women. A possible explanation is the reluctance of both investigators and relatives to "expose" the elderly, children, and women of childbearing potential to research. However, regulatory agencies, yielding to public demands, have begun to emphasize the need to include these patient groups in research studies. The recognition that GAD accounts for a very sizable proportion of all mental illness, coupled with the finding that comorbid GAD complicates almost half of all psychiatric and medical conditions (Judd et al. 1998; Maser 1998; Olfson et al. 1997), should mobilize the field.

Diagnosis

First described in DSM-III, GAD, along with atypical anxiety disorder, was considered a residual category reserved for disorders not meeting criteria for any other anxiety disorder. According to DSM-III, patients with generalized anxiety had a persistent, increased level of diffuse anxiety of at least 1 month's duration and manifested symptoms from three of four categories: motor tension, autonomic hyperactivity, apprehensive expectation, and vigilance and scanning.

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DSM-III-R (American Psychiatric Association 1987) extended the duration of symptoms necessary to meet criteria for GAD from 1 to 6 months, emphasized the importance of excessive or unrealistic worry, and required the presence of at least 6 of 18 anxiety symptoms. DSM-III-R also eliminated some of the hierarchical rules and allowed the diagnosis of GAD in the presence of other Axis I disorders.

The DSM-IV-TR (American Psychiatric Association 2000) diagnostic criteria for GAD are listed in Table 9–1. DSM-IV-TR defines GAD as at least 6 months of excessive and uncontrollable anxiety associated with somatic symptoms such as restlessness, fatigue, irritability, muscle tension, sleep disturbance, or difficulty concentrating. The criteria for somatic symptoms have been simplified, and the emphasis has shifted to the pervasive and uncontrollable nature of the worry. The anxiety impairs functioning and is not limited to another Axis I disorder or due to substance use or a medical condition. In evaluating the excessive nature of the worry, the sociocultural context, including the age and sex of the person, is emphasized.

Parallel with the changes in the consecutive DSMs, the anxiety categories in the *International Classification of Diseases* (ICD) have been revised as well. Although ICD-9 (World Health Organization 1977) acknowledged only generic "anxiety states" under the category "Neurotic Disorders," ICD-10 (World Health Organization 1992) is fully compatible with DSM-IV (American Psychiatric Association 1994) terminology.

The strict phenomenological approach first implemented in DSM-III represented a conscious effort to steer clear of theoretical debates concerning the etiology of anxiety. Although subsequent DSMs continue to set the standard for clinical research, neuroscience has made considerable progress in understanding the biological basis of anxiety over the past decade. It has become feasible to select symptoms of an anxiety disorder such as fear or worry and examine their neuroanatomy and neurochemistry (LeDoux 1996). Because these symptoms frequently cut across diagnostic categories, future DSMs may have to accommodate a dimensional diagnostic thinking.

TABLE 9–1. DSM-IV-TR diagnostic criteria for generalized anxiety disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).

B. The person finds it difficult to control the worry.

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months). **Note:** Only one item is required in children.

   (1) restlessness or feeling keyed up or on edge
   (2) being easily fatigued
   (3) difficulty concentrating or mind going blank
   (4) irritability
   (5) muscle tension
   (6) sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)

D. The focus of the anxiety and worry is not confined to features of an Axis I disorder, e.g., the anxiety or worry is not about having a panic attack (as in panic disorder), being embarrassed in public (as in social phobia), being contaminated (as in obsessive-compulsive disorder), being away from home or close relatives (as in separation anxiety disorder), gaining weight (as in anorexia nervosa), having multiple physical complaints (as in somatization disorder), or having a serious illness (as in hypochondriasis), and the anxiety and worry do not occur exclusively during posttraumatic stress disorder.

E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

F. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder.

Source. Reprinted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000, p. 476. Used with permission.

Diagnosis in Youths

The diagnosis of GAD in children and adolescents has been controversial. The DSM-III term for GAD in patients younger than 18 years was *overanxious disorder*. Defined as excessive or unrealistic worry (DSM-III-R) or generalized and persistent anxiety (DSM-III) lasting 6 months or longer, overanxious disorder was diagnosed in the presence of any four of seven possible symptoms: 1) excessive or unrealistic worry about future events; b) excessive or unrealistic worry about the appropriateness of past behavior; c) excessive or unrealistic worry about competence in one or more areas (e.g., athletic, academic, social); 4) frequent somatic complaints, such as headaches or stomachaches, for which no physical basis can be established; 5) marked self-consciousness; 6) excessive need for reassurance about a variety of concerns; and 7) marked feelings of tension or inability to relax.

In contrast with DSM-III, DSM-III-R allowed those younger than 18 to be given diagnoses of either overanxious disorder or GAD, but in those older than 18, GAD took precedence when patients met criteria for both disorders. DSM-III-R allowed overanxious disorder to be diagnosed after age 18 as well, providing that the patient's symptoms did not meet criteria for GAD.

In DSM-IV, overanxious disorder was subsumed under the diagnosis of GAD. Thus, the criteria for GAD in children are now the same as for adults, with one exception: children are required to endorse only one of six symptoms (vs. three of six for adults) in addition to excessive worry.

Diagnosis in the Elderly

Our diagnostic system has not yet developed separate criteria for GAD in the elderly. However, it is becoming clear that the current criteria are frequently inadequate to characterize this population. Diagnosing anxiety in the elderly can be difficult. Comorbid psychiatric conditions that can mask and/or produce anxiety in the elderly include mood disorders and dementia (Alexopoulos 1991; Reisberg et al. 1987). A further complication is that a primary medical condition (e.g., endocrine abnormality, nutritional deficiency, secreting tumor) may be causal (McCullough 1992).

Evidence indicates that clinically significant anxiety problems in the elderly often elude identification by conventional methods and are actually more prevalent than in the young. First, surveys that focus on anxiety symptoms rather than anxiety disorders indicate steadily increasing rates of anxiety as individuals age (Sallis and Lichstein 1982). Second, use of anxiolytic drugs increases with age (Rifkin et al. 1989; Salzman 1985), with some studies showing that as many as 20% of the noninstitutionalized elderly and 30% of the medically hospitalized elderly use benzodiazepines (Parry et al. 1973; Salzman 1991; Shaw and Opit 1976). Also, 20%–25% of the elderly experience insomnia "often" or "always." Research indicates that anxiety is the factor most often associated with insomnia in the elderly (Morgan et al. 1988); therefore, a significant proportion of nighttime benzodiazepine use in elderly patients may reflect anxiety in addition to a sleep problem. Finally, the elderly are subjected to an increasing number of real-life stressors (e.g., illness, disability, widowhood, financial decline, and social isolation) that are known to foster anxiety (Hassan and Pollard 1994). These stressors have been shown to predict ill health among the elderly, particularly stress-related disorders such as headache, gastrointestinal distress, hypertension, and cardiovascular disease (Deberry 1982). Often, the ill health brings the elderly patient to the attention of the medical practitioner. The concomitant or underlying anxiety disorder is frequently overlooked (Turnbull 1989).

Epidemiology

Prevalence data based on DSM-IV criteria have not been reported yet. However, given the more inclusive definition in DSM-IV, higher prevalence rates are expected compared with those based on earlier DSMs.

The largest survey of DSM-III GAD was conducted in 1983–1984 as part of the Epidemiologic Catchment Area (ECA) study (Blazer et al. 1991b). The 1-year prevalence rate for GAD excluding other disorders was 3.8%. Given the high rate of comorbidity, the rate dropped to 2.7% when comorbid depression and panic were excluded and to 1.7% when all other comorbid conditions were excluded. The ECA data also showed that GAD was about twice as prevalent in women. Without comorbid panic and depression, GAD was found to be more prevalent in African Americans. When no exclusions were made, prevalence was highest in people younger than age 30 years.

Five other community-based studies examined the prevalence of DSM-III GAD. In the United States, the point, 1-year, and lifetime prevalence rates were 2.5%, 4%, and 6.4%, respectively (Uhlenhuth et al. 1983; Weissman et al. 1978). Current prevalence of 1.5% and

1-year prevalence of 5.2% were reported from Europe (Angst and Dobler-Mikola 1985), whereas two studies from Asia (Hwu et al. 1989; Lee et al. 1990a, 1990b) found that the 1-year prevalence of GAD ranged from 3.4% to 8.6%, and the lifetime prevalence ranged from 2.9% to 10.5%. Rates were lowest among city dwellers. As in the ECA study, Asian women with GAD outnumbered men 2 to 1. In contrast to the United States study, however, age comparisons in the Asian samples showed increasing rates of prevalence over time (2.9% for those aged 18–24 vs. 4.3% for those aged 45–65 years).

One of the first studies of DSM-III-R GAD was conducted by Faravelli et al. (1989) in Florence, Italy. A community sample of 1,110 adults was assessed for both DSM-III and DSM-III-R anxiety disorders. GAD was the most frequent disorder, but prevalence rates declined significantly when the more stringent DSM-III-R criteria were used. The lifetime prevalence rates for DSM-III and DSM-III-R GAD were 5.4% and 3.9%, respectively, and the point prevalence rates were 2.8% and 2.0%, respectively. Overall, rates were lower than those reported in other surveys. Possible explanations are the use of psychiatrists as diagnosticians rather than lay interviewers and the use of a hierarchical diagnostic model, which allowed only one possible diagnosis per case.

Wacker et al. (1992) used both DSM-III-R and ICD-10 criteria to compare the prevalence of GAD in a survey of residents of Basel, Switzerland. They found that the lifetime prevalence of DSM-III-R GAD was 1.9%. The ICD-10 prevalence rate was 9.2%, more than four times greater. The discrepancy may be attributed, in part, to the higher symptom thresholds required by DSM-III-R. The ICD-10 system, for example, requires four symptoms (as opposed to six in DSM-III-R) and does not require worries to be excessive or unrealistic. Rates with DSM-IV criteria should be comparable to those based on ICD-10 criteria.

The largest study of DSM-III-R GAD was conducted by Wittchen et al. (1994). They used data collected from the United States National Comorbidity Study (NCS), which included 8,098 community-based respondents between ages 15 and 54 years. The current prevalence of GAD was 1.6%, the 1-year prevalence was 3.1%, and the lifetime prevalence was 5.1%. Lifetime prevalence according to ICD-10 criteria was higher (8.9%), similar to the findings of Wacker et al. (1992). Consistent with previous surveys, GAD was twice as common in women as in men. In addition, GAD was more common in those who were unemployed, separated, divorced, widowed, and older than 24 years. Ninety percent of those with lifetime GAD reported at least one other lifetime DSM disorder (most often, depression and panic), and 65% of those with current GAD reported current comorbid disorders (most commonly, depression, panic, and agoraphobia).

Epidemiology in Youths

Prevalence studies in children and adolescents have found that overanxious disorder and GAD are relatively common. Anderson et al. (1987) examined DSM-III disorders in 792 11-year-old New Zealand children. They found a 1-year prevalence of overanxious disorder of 2.9%, with a male-to-female ratio of 1.7:1. Overanxious disorder was more common in this sample than was simple phobia (2.4%), depression (1.8%), and social phobia (0.9%) but was less prevalent than separation anxiety disorder (3.5%). Four years later, overanxious disorder became the most prevalent disorder (5.9%) in the same cohort (McGee et al. 1990), and the sex ratio was reversed (female-to-male, 1.9:1).

Whitaker et al. (1990) examined the lifetime prevalence of DSM-III GAD in 356 adolescents aged 14–17 (disregarding the DSM-III minimum age requirement of 18 years) and found an incidence of 3.7%, with a male-to-female ratio of 1.8:4.6, consistent with the adult literature. GAD was more prevalent than panic (0.6%) but less common than major depression (4.0%) or dysthymia (4.9%).

Studies that used DSM-III-R criteria found incidence rates similar to those in studies that used DSM-III criteria. In a large sample of Canadian adolescents, the lifetime prevalence of overanxious disorder was 3.6% (Bowen et al. 1990), nearly identical to the rate found by Whitaker et al. (1990). In a clinic sample of 188 children aged 5–18 years with anxiety disorders, 13% had DSM-III-R overanxious disorder (9.6% had panic, 27% had separation anxiety disorder, 19.7% had simple phobia, and 15% had social phobia). The mean age at onset for overanxious disorder was 8.8 years in this group. Rates in males and females did not differ significantly (Last et al. 1992).

One of the largest surveys of DSM-III-R overanxious disorder in adolescents came from the Virginia Twin Study of 2,762 white twins aged 8–16 years (Simonoff et al. 1997). This survey found a 3-month prevalence of overanxious disorder of 4.4%, the most common disorder along with simple phobia (also 4.4%). Overanxious disorder in this sample was almost twice as common in girls as in boys (5.6:3.1). The study also

found that prevalence rates increased with age; the rate was 2.6% among 8- to 10-year-olds, 4.4% among 11- to 13-year-olds, and 10.7% among 14- to 16-year-olds. Sixty-eight percent of the overanxious disorder cases were comorbid with one other disorder, and 14% were comorbid with two or more. Phobias were the most common co-occurring disorders (57%), followed by separation anxiety disorder with depression (14%) and depression (13%).

Epidemiology in the Elderly

Studies generally agree that GAD is the most common anxiety disorder (other than phobias) in the elderly (Blazer et al. 1991a). In a large majority of elderly patients with another anxiety disorder diagnosis, GAD is a frequent comorbid condition (Brawman-Mintzer et al. 1993; Brown and Barlow 1992; Hassan and Pollard 1994). Taken together, these findings suggest that the rate of clinically significant anxiety problems may be as high as 20% among elderly individuals (Sheikh 1992).

Uhlenhuth et al. (1983) found a 1-year prevalence of DSM-III GAD of 7.1% in 442 subjects aged 65–79 years. This rate was lower than that for those aged 50–64 (8.6%) but higher than that for those aged 18–34 (5.8%) and 35–49 (4.7%). The same study found that GAD was the most common disorder in elderly patients: more than triple the rate for panic and phobias and 20% more common than major depression.

Another survey (Copeland et al. 1987) examined a sample of 841 subjects (about half in the United Kingdom and half in the United States) aged 65 years and older and found much lower incidence rates (0.7% in New York City and 1.1% in London). However, they used a non-DSM-III, computer-based diagnostic system that employed a strict diagnostic hierarchy and included the older "anxiety neurosis" category as opposed to GAD. Lindesay et al. (1989) surveyed 890 low-income elderly people (65 years or older) living at home in London with a generalized anxiety scale constructed for their study. They found a 1-month prevalence rate of 3.7% for generalized anxiety (2.5% in men and 4.5% in women).

Blazer et al. (1991a) examined data from the Durham, NC, site of the ECA study, which included 2,993 community-dwelling subjects aged 18 and older. They found 6-month and lifetime prevalence rates for DSM-III GAD of 1.9% and 4.6%, respectively, for those aged 65 and older (vs. 3.1% and 6.7% for those aged 45–64). These rates were greater than those for panic (0.04% and 0.30%), social phobia (1.3% and 2.6%), and obsessive-compulsive disorder (1.84% and 1.98%) but lower than those for simple phobia (9.6% and 16.1%) and agoraphobia (5.2% and 8.4%).

The high rate of variability in reported prevalence rates for GAD in elderly patients may be the result of methodological factors such as differences in survey methods, case definition, and hierarchical versus nonhierarchical approaches to diagnosis (Flint 1994). Underreporting of anxiety disorders may be caused by diminished recall ability, higher rates of anxiolytic medication use, and institutionalization.

Symptomatology

The symptoms of GAD are numerous and highly variable. Signs of motor tension, autonomic hyperactivity, and hyperarousal are frequently the presenting problems. Patients complain of restlessness, inability to relax, and fatigue. The motor tension results in frequent headaches and chronic muscle pain in the shoulder, neck, and lower back.

Pathological worry has been identified as the pathognomonic feature of GAD. The nature of pathological worry, however, has been subjected to research only recently. Therefore, only limited data are available on the characteristics of worry in actual clinical samples. GAD patients consistently report a greater number of worry areas compared with patients with other anxiety disorders and nonanxious control subjects, but the particular patterns of worry content are highly variable and do not consistently identify patients with GAD (Roemer et al. 1997). Studies show that patients with GAD share the same concerns as do nonanxious control subjects, such as concerns about family and interpersonal relationships, work, school, finances, and health (Craske et al. 1989; Roemer et al. 1997; Sanderson and Barlow 1990).

Some investigators suggest that the manifest content of the worry is unimportant. They argue that the worry simply is a distraction and serves to protect patients from their "real" problems. Indeed, GAD subjects do believe that worry serves to distract them from more emotional topics (Borkovec and Roemer 1995). The role of emotional trauma in the pathogenesis of GAD also may be supported by the finding that these patients have more exposure to potentially traumatizing events in their pasts than do nonanxious control subjects (Roemer et al. 1996). This hypothesis, akin to the "unconscious conflict" paradigm of psychodynamic thinking, needs further support.

GAD worry has been distinguished from "normal" worry by being perceived as significantly more uncontrollable and unrealistic. Patients with GAD spend more of the day worrying than do nonanxious control subjects (60% vs. 18%). Reliance on the perception of control alone, however, may be misleading. An objective measure of thought suppression has shown that although patients with GAD have significantly less mental control over intrusive thoughts concerning their "main worry" than they do over their own neutral cognitions, contrary to expectation, they have no more actual "main worry" intrusions than do nonanxious control subjects (Becker et al. 1998).

The one content area that has consistently distinguished GAD patients from others is excessive worry over minor matters (e.g., daily hassles and time management) (Craske et al. 1989; Roemer et al. 1997; Sanderson and Barlow 1990). This criterion has proven to be a necessary, if not sufficient, feature for a diagnosis of GAD. A negative answer to the question "Do you worry excessively about minor matters?" effectively ruled out the diagnosis of GAD in subjects (0.94 negative predictive power vs. 0.36 positive predictive power) (DiNardo 1991).

GAD patients do not lack problem-solving *skills* but do have poorer problem orientation (i.e., response set involving sense of control, problem-solving confidence, and approach vs. avoidance) and have significantly more difficulty tolerating ambiguity compared with control subjects (Davey 1994; Ladouceur et al. 1998). They also show a cognitive bias for threat-related information. Studies that used the modified Stroop Test, in which a subject's speed at naming the colors that different words are printed in is measured, consistently found that patients with GAD were slower than nonanxious control subjects in color-naming negative or threat-related words (Martin et al. 1991; Mathews and MacLeod 1985; Mogg et al. 1989, 1995).

Course

The course of GAD is chronic with fluctuating severity and symptom patterns. The onset is in the early 20s, but because of the overwhelmingly retrospective data, much controversy remains. Although most agree that onset beyond age 60 is rare, some investigators believe that the onset could be much earlier than in the 20s. Patients with onset of GAD before age 10 may represent a separate category with a more malignant type of the disorder. Although questions remain whether these types are sufficiently distinct, late-onset GAD usually is characterized by rapid onset following a clearly identifiable major stress. Early-onset GAD is more likely to have gradual onset, comorbid depression and other Axis I and Axis II disorders (Shores et al. 1992), and a more chronic course. These patients have a frequent history of childhood fears, school problems, and behavioral inhibition. Middle-aged patients report an average of 20-year history of significant baseline anxiety with frequent exacerbations. Untreated, prolonged remission is unusual. The long-term outcome of GAD is variable. Severity is dependent on several factors, including comorbid Axis I and Axis II disorders, environmental support, the biology of the disorder, and the duration of the illness.

Interrater Reliability

The interrater reliability of diagnosing GAD is low compared with most anxiety disorders. The sources of poor reliability for current GAD are inconsistent ratings of the anxiety symptoms, poor and inconsistent recall by patients, and disagreements on the nature of GAD worry. With κ statistics ranging from 0.27 to 0.57 (DiNardo et al. 1993; Mannuzza et al. 1989), estimates of the stability of the GAD diagnosis are clearly compromised. More recently reported κ statistics (0.83) have indicated much better reliability of GAD diagnoses with no significant effect of coexistent depressive disorders (cited in Barlow and Wincze 1998). The most common reason for interrater disagreement is related to severity as opposed to the presence or absence of GAD.

Because of controversy surrounding the diagnostic agreement, several investigators have questioned the validity of the GAD category. However, emerging consensus based on distinct course, specific treatment response, and family studies showing a higher risk of developing GAD in first-degree relatives of patients with GAD confirms the legitimacy of the diagnosis. Data from two large national surveys also suggest that the magnitude of role impairment from GAD is comparable to that of depression and that GAD-related disability occurs independently from comorbid depression or other comorbid conditions (Kessler et al. 1999). Although not yet supported by biological data, field trials and clinical experience also suggest that GAD is a distinct anxiety disorder (see Brown, Chapter 2, in this volume).

Several rating scales have been used to assess the severity of anxiety symptoms and to monitor treatment

outcome in both research and clinical settings (Shear et al. 2000). These rating scales are not diagnostic instruments and do not discriminate among the various anxiety disorders or between anxious depression and an anxiety disorder. For the most part, efforts to provide a distinct measure of anxiety independent of other psychopathology such as depression have been largely unsuccessful. Most ratings of anxiety show substantial correlation with measures of depression.

Considering the current controversy over DSM criteria for GAD, the inclusion of an assessment package containing several rating instruments is well justified. This approach will allow the collection of data on subjects who are defined as anxious according to psychometric criteria but ruled out by DSM criteria or vice versa. It also will lead to refined and more realistic diagnoses. Because understanding the course and phenomenology of GAD depends on interrater and test-retest reliability, further improvement in this area is a priority.

Differential Diagnosis

Substantial levels of comorbidity and diagnostic uncertainty are the two main challenges in the differential diagnosis of GAD. The symptoms of generalized anxiety are present in most anxiety and mood disorders, but only about 20% of the patients with depression and 10% of those with another anxiety disorder meet the criteria for the full syndrome of GAD. At the same time, more than two-thirds of the patients with the principal diagnosis of GAD have an additional Axis I disorder, with social phobia and dysthymia leading the list (Borkovec et al. 1995; Wittchen et al. 1994). A recent survey among primary care patients showed that 89% of those with GAD met criteria for a comorbid psychiatric disorder as well (Olfson et al. 1997).

Nonpathological Anxiety

Of the anxiety disorders, GAD is probably the most similar to "normal" anxiety. As described in DSM-IV-TR, the anxiety of patients with GAD is more pervasive and involves routine daily activities resulting in functional impairment. Nonpathological anxiety, on the contrary, usually is facilitating and does not manifest as disabling physical symptoms and catastrophic cognitive processes. As described earlier in this chapter, research on the nature of GAD worry has begun to delineate the phenomenology of pathological worry.

Depression

Unquestionably, the most difficult and most controversial differential diagnosis is between depression and anxiety. Depression, particularly dysthymia, and GAD share many features: insidious onset, protracted course with periodic exacerbations, and chronic dysphoric affect. The symptoms frequently represent the prodromal phase to major depression or panic disorder. Severe depressive symptoms, suicidality, and hopelessness are more characteristic of depression, whereas high ratings on vigilance, scanning, and somatization, specifically respiratory symptoms, indicate anxiety disorder. Although similar personality factors have been described in the two disorders, the suggestion that they may explain the overlap has not been substantiated. For the many cases when differentiation seems impossible, the category of mixed anxiety-depression can be applied.

Hypochondriasis

Another challenging diagnostic task is to distinguish between the health concerns of a patient with GAD and the disease conviction of a patient with hypochondriasis. In the absence of clear hierarchical rule, when disease conviction is present and the patient meets criteria for GAD, both conditions should be diagnosed.

Panic Disorder

The most obvious distinguishing mark is the presence of panic attacks in panic disorder. The age at onset is similar, but there is a sharp contrast between the sudden, unexpected panic attack marking the beginning of panic disorder and the insidious, vague complaints at the onset of GAD. Patients with panic disorder are more disabled by their symptoms than are patients with GAD and seek treatment earlier. Patients with panic disorder complain more about fearful, catastrophic thoughts, focusing on acute cardiopulmonary symptoms, whereas GAD manifests as less specific, chronic discomfort involving multiple organ systems.

Personality Disorders

Compared with the average rate of personality disorders of 10% in the general population, the rate of personality disorders in patients with GAD is close to 50%. Treatment resistance in GAD may be associated with an even higher rate of comorbid personality disorder. Although no specific personality disorder has been identified as typically comorbid with GAD, avoidant,

dependent, and obsessive-compulsive personality disorders and traits are common in patients with GAD. Some theories suggest that these personality disorders are complications of the anxiety disorder or represent a vulnerability to develop an anxiety disorder. However, a prospective study found no difference in the rate of baseline personality disorder between patients who later developed depression and those who developed an anxiety disorder. This finding would suggest that premorbid personality disorders do not predispose to anxiety disorders. However, personality traits frequently improve with anxiety disorder–specific treatments, suggesting that some personality disorders may be secondary to an anxiety disorder. These treatment results also challenge the validity of strictly differentiating Axis I and Axis II diagnoses.

Substance-Related Disorders

Self-medication is the most frequently suggested paradigm to explain the high rate of comorbidity between anxiety and substance use. Although anxiety disorders, including GAD, are common in alcoholic patients, patients with GAD are much less likely to self-medicate with alcohol and other substances than are patients with panic disorder and social phobia. However, up to two-thirds of the patients receiving treatment for alcohol problems report clinically significant anxiety, including GAD. In most cases, however, GAD develops after the alcohol problem. Alcohol and other substance withdrawal states are indistinguishable from the autonomic symptoms of GAD. Prolonged exposure to alcohol and other substances can lead to the same gastrointestinal, acid-base, and sleep disturbances described by patients with GAD.

Conclusion

GAD is a challenging diagnostic and treatment dilemma. Epidemiological surveys using ever-refined diagnostic criteria suggest that the disorder is one of the most prevalent psychiatric conditions. While clinicians continue to identify response patterns, course, and predictors of response in rigorous double-blind studies with patients whose symptoms were diagnosed according to DSM criteria, neuroscientists focus on the neurochemistry and neuroanatomy of select features of DSM categories, such as the excessive worry in GAD. The synthesis of the results of basic and clinical neuroscience and DSM-based treatment and epidemiological studies will likely improve our understanding of the nature of GAD and will lead to better treatment.

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10

Pathogenesis of Generalized Anxiety Disorder

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Generalized anxiety disorder (GAD) is a relatively new diagnosis, first defined in DSM-III (American Psychiatric Association 1980), the cardinal symptom of which is chronic anxiety. Worrying is experienced as a chain of thoughts and images that are laden with negative affect and are relatively uncontrollable (Borkovec et al. 1983). Many GAD patients' worries are uncued or at least appear to be. These patients also report an inability to control or reduce their worry (Craske et al. 1989). Although the content of their worries is familiar—family, finance, work, and illness (Barlow 1988)—anxiety patients tend to predict that there is a high probability that they will have a negative outcome (G. Butler and Mathews 1987). Throughout this chapter, we discuss GAD as a discrete entity; however, many of the symptoms of GAD are shared with other anxiety disorders. This commonality has made GAD one of the more controversial diagnoses. Indeed, some have proposed that it is not a discrete disorder but instead a personality trait or a misdiagnosed anxiety or depressive disorder.

The combination of chronic worry and somatic tension, which is diagnostic of GAD, lends itself to postulating both biological and psychosocial contributions to this disease; therefore, we review the literature in both of these broad fields. The biological factors section focuses on developments in genetics, neurochemistry, and neurophysiology, and the psychosocial factors section explores intrapsychic, social, and learning models of GAD. In this chapter, we attempt to integrate these main areas to provide an etiological model of GAD.

Biological Factors

Genetics

GAD may have a familial and genetic basis. Noyes et al. (1987) found that 19.5% of the first-degree relatives of GAD patients also had the disorder, compared with only 3.5% of the control subjects' families. Twin studies have found mixed results. One study found no significant difference in the concordance rates between monozygotic and dizygotic twins (Andrews et al. 1990), whereas another study found that the heritability of GAD was 30% in pairs of female twins (Kendler et al. 1992a). A study that may begin to explain these opposing views found that GAD was inherited only in cotwins who also shared a history of a mood disorder, and Skre et al. (1993) proposed that the genes involved in anxiety and mood disorders may be linked. Whether this relation may be attributed to different expressions of the same abnormal gene or two abnormal genes that lie on the same chromosome is unclear. Regardless, several studies have shown that a large percentage of patients with GAD have a comorbid mood disorder. Wittchen et al. (1994) found that 62.4% of the patients with

GAD also met criteria for major depression, and another 10.5% had bipolar disorder. Thus, there appears to be a genetic susceptibility to GAD that is shared with the mood disorders.

Evidence indicates that genetic factors may significantly contribute to the pathogenesis of GAD. However, a genetic diathesis toward GAD is insufficient for the development of all cases. In addition, the significance of these findings is limited because they could well be attributed to a shared environment and not shared genes, so further research with methods such as adoption studies and chromosomal analysis is required at this point.

Neurochemistry

Norepinephrine

The main norepinephrine nucleus in the brain, the locus coeruleus, is activated by stress (Chrousos and Gold 1992) and has been implicated in animal fear behavior. The locus coeruleus/norepinephrine system also has been postulated to play a role in vigilance and attentional processes (Aston-Jones et al. 1997). Thus, norepinephrine has been the focus of neurochemical studies in GAD.

Studies of peripheral norepinephrine function in GAD have had inconsistent findings. One study found that patients with GAD had higher plasma catecholamine levels than did control subjects (Mathew et al. 1980); however, a subsequent study (Mathew et al. 1982a) failed to show differences in resting plasma catecholamine levels, a finding the authors attributed to venipuncture-induced stress in the first study. Another study in which an indwelling catheter was used found no significant difference in norepinephrine levels between control subjects and patients with GAD (Munjack et al. 1990). Likewise, no difference was found between control subjects and patients with GAD in plasma levels of the catecholamine degradation enzymes catechol-O-methyltransferase, dopamine β-hydroxylase, and monoamine oxidase (Khan et al. 1986). However, several studies reported an increase in noradrenergic activity in GAD. Sevy et al. (1989) found that patients with GAD had an increased level (compared with control subjects and patients with major depression) of plasma norepinephrine and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG). This study also found that in GAD, the number of α_2 adrenoreceptors was decreased, implying chronic activation of this system. Levels of another norepinephrine metabolite, vanillylmandelic acid, also were increased in patients with GAD, and increases in urine excretion of this metabolite correlated with increased anxiety levels (Garvey et al. 1995).

All these studies failed to address the source of the norepinephrine. A study that examined patients with pheochromocytoma, a tumor of the adrenal medulla that releases massive amounts of norepinephrine, found that a source of catecholamines outside the central nervous system was not sufficient to elicit anxiety. The authors concluded that the elevated levels of catecholamines in anxiety patients reflect sympathetic activation caused by the anxiety and are not the underlying cause of this anxiety (Starkman et al. 1990). Therefore, to further understand the role of norepinephrine in GAD, assessment of norepinephrine function in the central nervous system has been necessary.

Most studies involving norepinephrine have focused on the inhibitory α_2-adrenergic receptor. Inhibition of this receptor on inhibitory presynaptic norepinephrine neurons in the locus coeruleus results in increased noradrenergic activity and anxiety behaviors in animals (Redmond 1987). Although human studies with the α_2-adrenergic antagonist yohimbine found that patients with panic disorder and posttraumatic stress disorder were abnormally sensitive, this finding did not generalize to GAD (Charney et al. 1989). Another set of studies used clonidine, an α_2-adrenergic receptor agonist that decreases locus coeruleus firing and has anxiolytic properties, and yohimbine to quantify the relative number of α_2-adrenergic receptors in GAD patients and control subjects. Both of these studies were interested in the α_2 binding sites on platelets (platelets have many of the same receptors found in the brain, and their receptor binding properties are thought to reflect this activity in the brain). These studies found that the patients with GAD had fewer α_2-adrenergic receptors than did control subjects (Cameron et al. 1990; Sevy et al. 1989). Another study noted a blunted growth hormone response to clonidine in patients with GAD, suggesting that these patients have decreased postsynaptic α_2-adrenergic receptor sensitivity (Abelson et al. 1991). This decrease in catecholamine receptors could reflect that GAD is characterized by chronic high levels of catecholamines, leading to downregulation of the presynaptic α_2-adrenergic receptors (Sevy et al. 1989). These data suggest that the locus coeruleus is overly active in GAD.

Overall, the results of studies of norepinephrine in GAD have been inconsistent. Several studies found that GAD is associated with elevated norepinephrine, and downregulation of postsynaptic α_2-adrenergic recep-

tors consistent with overactivation of the norepinephrine system is evident. However, this finding may be the result of GAD and might not indicate that abnormal norepinephrine function causes GAD. These data, together with the efficacy of tricyclic antidepressants such as imipramine in the treatment of GAD, however, imply that the norepinephrine system may play some role in perpetuating the symptoms of GAD.

Serotonin

Another neurotransmitter implicated in the etiology of GAD is serotonin. Potentially threatening situations appear to increase synaptic serotonin, and cortical and limbic regions possibly use this input to assess and react to the situation (Handley 1995). However, studies with serotonin synthesis inhibitors, such as *p*-chlorophenylalanine (PCPA), have inconsistently found that these agents are anxiolytic and that decreased serotonergic activity also is associated with anxiety (Brody 1970; Geller and Blum 1970). Hence, serotonin levels in themselves may not explain the onset of anxiety. Cell bodies of the major serotonin pathways arise in the raphe nucleus and innervate the hypothalamus, thalamus, and limbic system, particularly the septohippocampal system and the amygdala (Dubovsky and Thomas 1995). Four main classes of serotonin receptors have been identified: serotonin type 1 (5-HT_1), serotonin type 2 (5-HT_2), serotonin type 3 (5-HT_3), and serotonin type 4 (5-HT_4). In animal studies, serotonin receptor subtypes 5-HT_{1A} (Gammans et al. 1992), 5-HT_{2A} (Deakin 1989), and 5-HT_3 (Costall and Naylor 1992) have been implicated in fear behavior and, consequently, have been of most interest in human anxiety disorders such as GAD.

Studies in humans also support the role of serotonin in GAD. Garvey (1995) found that elevated urinary levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) predicted higher anxiety levels in GAD, implying increased serotonin metabolism in more anxious patients with GAD. Conversely, another study found that the serotonin synthesis inhibitor PCPA was anxiogenic in humans, implying an association between decreased serotonin levels and anxiety. Hence, the relation between serotonin levels and anxiety has been inconsistent, so attention should focus on receptor subtypes. Preclinical trials have supported the role of 5-HT_{2C} and 5-HT_{2A} receptor subtypes in GAD (Kahn et al. 1991). Furthermore, patients with GAD have shown hypersensitivity to the mixed postsynaptic 5-HT_2/5-HT_{2A} agonist/antagonist *m*-chlorophenylpiperazine (m-CPP) (Germine et al. 1992).

Several serotonergic agents are efficacious in the treatment of GAD. Imipramine, trazodone, and venlafaxine inhibit the reuptake of serotonin and appear to be effective in treating GAD (Davidson 1998; Rickels et al. 1993). 5-HT_{1A} agonists, such as the partial agonist buspirone, also have been shown to be anxiolytic, and this anxiolysis has been associated with the serotonergic property of the drugs (Eison et al. 1986). However, the 5-HT_3 antagonist ondansetron has had only limited efficacy in the treatment of GAD (Freeman et al. 1997). Hence, clinical studies in humans support the role of serotonin in GAD.

The role of serotonin in the etiology of GAD remains unclear. The finding of increased serotonin metabolites in patients with GAD supports a serotonin overactivation model of GAD, whereas similar findings with the serotonin synthesis inhibitor PCPA support a serotonin underactivation model of GAD. Thus, the relation between serotonin levels and anxiety remains unclear; however, direct findings with m-CPP and indirect clinical evidence indicate that the serotonin receptor subtypes may play a potentially significant role in the etiology of GAD.

γ-Aminobutyric Acid

γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter found in most parts of the brain. The benzodiazepines, anxiolytics that are agonists at the receptor-associated benzodiazepine site, increase the affinity of GABA for its binding site and cause the $GABA_A$ receptor complex to be more responsive to available GABA. One study found that the number of benzodiazepine receptors in the hippocampus and cortex decreased in animals following stress (Farabollini et al. 1996). In humans, most of the work examining the relation between GAD and GABA has focused on the effects of administering benzodiazepines. Because of the link between antianxiety treatments and GABA, the GABA/benzodiazepine system has been a logical focus of research into the pathophysiology of anxiety.

Benzodiazepines were the standard medication for the treatment of GAD until buspirone was released in 1987. Consequently, abnormalities in the benzodiazepine receptor have been a topic of interest in GAD. Patients with GAD appear to have a decreased density of platelet benzodiazepine binding sites, but after chronic administration of diazepam, the receptor density increased (Weizman et al. 1987). Similar results were found with lymphocytes, in which the benzodiazepine receptor density also is decreased in GAD patients before treatment but normalizes following diaz-

epam (Ferrarese et al. 1990; Rocca et al. 1991). However, peripheral and central benzodiazepine receptors are distinct, so it is difficult to conclude what significance to assign to findings in these studies (Brawman-Mintzer and Lydiard 1997). Central benzodiazepine receptor function can be studied by measuring the velocity of saccadic eye movements, which are under the control of central benzodiazepine receptors in the superior colliculus and pons. Patients with GAD have a reduced sensitivity of saccadic eye movements, implying downregulation of these receptors (Cowley et al. 1991). However, this abnormality is nonspecific and is also found in obsessive-compulsive disorder and panic disorder (Roy-Byrne et al. 1996). Another study of the central benzodiazepine receptors found that benzodiazepine binding is significantly decreased in the left temporal pole of patients with GAD, and the density distribution of these cerebral benzodiazepine receptors is more homogeneous than is found in control subjects (Tiihonen et al. 1997). Thus, both preclinical and clinical data implicate decreased benzodiazepine function in GAD. This would be consistent with impairment in the capacity of GAD patients to respond to endogenous anxiolytic ligands that activate the benzodiazepine receptor. Whether this is a state or trait abnormality remains to be determined.

The GABA system may play a significant role in the pathogenesis of GAD. This system may influence anxiety levels by mediating the release of other neurotransmitters (e.g., norepinephrine, cholecystokinin [CCK], and serotonin). Biological and benzodiazepine treatment studies of GAD implicate benzodiazepine receptor/GABA dysfunction in the initiation and/or propagation of this disorder. Further assessment of the GABA neuronal system, molecular genetics, and neuroimaging techniques is warranted to determine the precise nature of benzodiazepine/GABA dysfunction in GAD.

Cholecystokinin

CCK is one of the most abundant peptide neurotransmitters in the brain. A high density of CCK receptors is found in the hippocampus, the brain stem, and regions implicated in fear behavior in animals (the limbic system, basal ganglia, and cortex). There are several different CCK peptides, but the neurotransmitters CCK_4 and CCK_8 have been of most interest (Lydiard 1994). Two types of CCK receptors have been described: CCK_A and CCK_B. CCK_A is found in the viscera and some brain regions, whereas CCK_B is widely distributed in the brain and appears more directly involved in animal models of anxiety (Harro et al. 1993). CCK_B antagonists block the anxiogenic properties of CCK agonists in animal fear paradigms (Woodruff and Hughes 1991).

Studies of the CCK_B receptor have implicated it in the pathogenesis of anxiety. A CCK_B agonist, pentagastrin, induced a panic attack in 71% of GAD patients (vs. 14% of control subjects) (Brawman-Mitzer et al. 1995). This finding, however, is not specific because similar findings have been obtained in panic disorder and social phobia, suggesting that CCK dysfunction may contribute to anxiety proneness. Moreover, human studies of CCK_B antagonists in GAD have been disappointing. Receptor binding alone, however, does not convey the entire story. The administration of CCK_8 in animals stimulates the release of adrenocorticotropic hormone (ACTH) and cortisol (Kamilaris et al. 1992), and a study in humans found that these two stress reactants became elevated after administration of the mixed $CCK_{B/A}$ agonist pentagastrin (Abelson et al. 1994). However, increased CCK_8 binding is also associated with chronic treatment with diazepam, and CCK_8 may be involved in anxiety regulation but perhaps in an antagonistic manner to the role of CCK_4 (Harro et al. 1993). The CCK system, thus, appears to be involved early in the processes of anxiety induction.

The CCK system also may indirectly modulate anxiety in GAD through its interactions with other systems. For instance, CCK may contribute to anxiety through its influence on the noradrenergic system. CCK activates neurons in the locus coeruleus via peripheral CCK receptors in vagal afferent pathways (Monnikes et al. 1997). Selective destruction of noradrenergic nerve terminals in the locus coeruleus results in an increased CCK receptor density in the frontal cortex and hippocampus, two regions that receive input from the locus coeruleus (Harro et al. 1993). In addition, the CCK system may influence anxiety through its interaction with the GABA system. CCK is localized in GABA-synthesizing neurons in the cortex, hippocampus, and basolateral amygdala (Harro et al. 1993). Benzodiazepines selectively antagonize CCK_8-induced activation of rat hippocampal pyramidal cells, but the benzodiazepine antagonist flumazenil does not appear to antagonize the effect of CCK_4 in healthy subjects (Bradwejn et al. 1994). Bradwejn and colleagues theorized that both benzodiazepines and the CCK system act on GABA in opposing but separated mechanisms.

Endocrine Function in Generalized Anxiety Disorder

The multiple components of the endocrine system modulate the body's metabolism. One of the many roles

of the endocrine system is to respond to stress and reestablish homeostasis; hence, it is not surprising that the endocrine system, especially the hypothalamic-pituitary-adrenal (HPA) axis, has been a major interest with respect to human anxiety disorders such as GAD.

Corticotropin-releasing factor (CRF), which is released from the paraventricular nucleus of the hypothalamus (CRF is found in other regions as well), modulates ACTH release and has been implicated in stress and fear behaviors. Both acute and chronic stress increase CRF levels in the locus coeruleus and periventricular hypothalamic areas (P.D. Butler et al. 1990). CRF-secreting neurons are modulated by neurotransmitters such as norepinephrine and serotonin, which potentiate release of CRF. Rodents administered CRF decrease exploration and increase activities such as sniffing, indicating an increase in arousal (Chrousos et al. 1992). In humans, however, cerebrospinal fluid levels of CRF are not significantly different among persons with GAD, panic disorder, obsessive-compulsive disorder, and no psychiatric diagnosis (Fossey et al. 1996), suggesting that these disorders have no tonic abnormality of CRF secretion. However, CRF may be episodically hypersecreted and may initiate fear responses in some contexts. Levels do not reflect localized CRF function in the brain, and these regional differences may be significant in anxiety disorders. The findings in animal studies support the role of CRF in the induction of anxiety, but the human data, thus far, have been negative. Further studies in humans must be done before this agent is ruled out as a contributor to anxiety. The development of specific CRF-1 antagonists by industry may offer new tools to probe CRF in GAD and other disorders.

The stress reactant cortisol also has been a focus of research in GAD. A.H. Rosenbaum et al. (1983) found no significant difference in 24-hour urinary-free cortisol levels between patients with GAD and control subjects. However, several other studies implied that patients with GAD have elevated cortisol levels. Between 27% and 38% of patients with GAD are nonsuppressors on the dexamethasone suppression test (Avery et al. 1985; Tiller et al. 1988). Although these findings must be viewed in the light of the high comorbidity of GAD and depression, Tiller and associates' finding that all these patients reverted to suppressors after successful nondrug treatment (behavior therapy) of their GAD supports the view that patients with GAD have chronic hypercortisolemia. This finding is further supported by the observation that rats exposed to chronic stress or exogenous steroids showed a decrease in hippocampal corticosteroid receptor density. Corticosteroid receptors in the hippocampus inhibit the secretion of stress-induced glucocorticoids by the HPA axis (Jacobson and Sapolsky 1991). Hence, chronic stress leads to a heightened stress response to future dangers. In conclusion, the HPA axis appears overactivated in GAD and possibly plays a role in perpetuating the disorder.

Another endocrine system that has been evaluated in relation to the pathogenesis of GAD is the thyroid axis. Patients with thyroid dyscrasias often present with anxiety that may be mistaken for GAD. However, thyroid function does not appear to differ between patients with or without GAD (Munjack et al. 1988), nor is the level of thyrotropin-releasing factor significantly different between these groups (Fossey et al. 1993). Thus, so far no evidence supports a role for the thyroid axis in GAD.

Carbon Dioxide and Lactate in Generalized Anxiety Disorder

When faced by danger, one of the body's responses is hyperventilation. One adaptive reason behind this reflex may be to exhale carbon dioxide (CO_2), induce a respiratory alkalosis, and compensate for the metabolic acidosis being created by rising levels of lactate. Clinical studies have shown that simulating this situation by infusing lactate (Pitts and McClure 1967) or hyperventilating is panicogenic in anxiety patients (Bass et al. 1987). Patients who inhale CO_2 have similar results (Gorman et al. 1988). These anxiogenic techniques, hence, can be useful tools in the study of anxiety disorders.

Both CO_2 and lactate are used to provoke anxiety symptoms and have played an important role in differentiating GAD from panic disorder. Studies by Mathew and Wilson (1987), Gorman et al. (1988), and Holt and Andrews (1989) found that many patients with panic disorder had panic attacks while inhaling 5% CO_2, but patients with GAD did not. However, Verburg et al. (1995) found that when inhaling 35% CO_2, GAD patients had less anxiety and fewer panic attacks than did patients with panic disorder but that both groups had a similar increase in somatic symptoms. Conversely, another study in which the subjects were infused with sodium lactate found that patients with GAD were more likely than patients with panic disorder to report increased anxiety, although those with panic disorder continued to have a higher rate of panic attacks (Cowley et al. 1988). The results of these challenges show that GAD and panic disorder not only are discrete dis-

orders but also share a common sensitivity to certain physiological stressors. These findings also imply that both of these disorders might derive from a dysregulation of the self-preserving response and have led to the development of theories, such as the suffocation alarm (D.F. Klein 1993), that attempt to explain the role of CO_2 in the etiology of GAD.

Miscellaneous

No current data support the involvement of other systems in GAD. Studies of the central cholinergic system (Rapaport et al. 1991) and the adenosine receptor (Stein et al. 1993) failed to identify any relation with anxiety. Investigations that used the phosphodiesterase inhibitor caffeine have had mixed results. Bruce et al. (1992) found that patients with GAD were abnormally sensitive to caffeine based on both self-rating and physiological markers of arousal. However, other studies found that patients with anxiety disorders did not have an increase in anxiety or panic symptoms and did not appear to be any more anxious after caffeine use than control subjects were (Mathew and Wilson 1990). Both patients and control subjects, however, did have a significant decrease in cerebral blood flow, as is seen at times of high anxiety, and this alteration in blood flow could play a role in the anxiogenic properties of caffeine. Thus, no available data support the involvement of another particular transmitter system in GAD, but findings such as altered blood flow could imply the involvement of factors that have not yet been adequately investigated.

Neurophysiology

GAD has been associated with alterations of respiratory and cardiovascular function. In a study of women with GAD, resting respiratory rate, pulse rate, and blood pressure measurements did not differ significantly from those of control subjects (Hoehn-Saric et al. 1989). This finding was supported by other data that after the administration of yohimbine, no difference was found in the blood pressure or heart rate between patients with GAD and control subjects (Charney et al. 1989). However, another study reported that patients with GAD have lower systolic blood pressure than do control subjects after standing (Cameron et al. 1990), suggesting subtle autonomic dysfunction in GAD. In addition, Astrom (1996) reported that worry shortens interbeat intervals on an electrocardiogram (ECG) and decreases the mean differences of cardiac interbeat differences. In this study, patients with GAD had shorter interbeat intervals on an ECG than did control subjects. Anstrom theorized that patients with GAD have lowered cardiac vagal control. Whether this alteration is a cause or an effect of GAD is unclear, because, as in all biological studies of GAD, the study patient often enters the protocol already in the anxious state. In a separate paper, Brawman-Mintzer and Lydiard (1997) suggested that patients with GAD had autonomic inflexibility. They theorized that these patients have a weakened response to stress and require longer to recover from a stressor. Overall, the data support the idea that the chronic worry of GAD is accompanied by specific chronic alterations in the autonomic system.

Patients with GAD also have abnormal electroencephalogram (EEG) findings, and these changes may imply a relation to other syndromes. The EEG sleep profile of GAD indicates a decrease in slow-wave sleep (primarily Stage IV) but none of the rapid eye movement (REM) sleep disturbances characteristic of major depression. This same sleep profile is seen in dysthymia and may indicate a relation between these two chronic disorders (Arriago and Paivat 1990–1991). Note, however, that the low-voltage alpha-wave changes seen in many of the anxiety disorders, including GAD, are seen in a large variety of medical, neurological, and psychiatric disorders (Spiegel et al. 1986). The EEG findings in GAD, therefore, imply some underlying biological abnormality but at this time are not specific enough to help define that disturbance.

Studies measuring other parameters have found other possible physiological differences in patients with GAD. Several studies have found an increased startle reflex in posttraumatic stress disorder and panic disorder, and anecdotal evidence indicates that patients with GAD also may have this increased sensitivity (Grillon et al. 1997). The skin conductance of GAD patients is similar to that of control subjects but takes longer to return to baseline following a stress (Hoehn-Saric et al. 1989), a finding that supports the autonomic inflexibility theory discussed earlier in this chapter. Other studies, however, have found some concerning differences. Patients with GAD have higher cholesterol and triglyceride levels than do patients with mixed anxiety-depression, presumably because patients with GAD are exposed to increased noradrenergic activity (E. Klein et al. 1995).

Neuroimaging Studies in Generalized Anxiety Disorder

Both hemispheres of the brain appear to be involved in anxiety disorders. Following a lesion to the left hemi-

sphere, patients were more likely to develop a combination of anxious and depressed symptoms, whereas those patients with right hemisphere lesions developed only anxiety (Astrom 1996). Positron-emission tomography (PET) showed that anxiety scores correlate with changes in glucose metabolism in the limbic system and basal ganglia, although no significant difference was found between the right and left parahippocampal gyrus. PET scans of GAD patients showed a relative increase in glucose metabolism in parts of the occipital, right posterior temporal lobe, left inferior frontal gyrus, cerebellum, and right precentral frontal gyrus (Wu et al. 1991). Glucose metabolism is decreased in the basal ganglia, temporal lobe, and cingulate gyrus. In this same study, Wu et al. found that during vigilance tasks, patients with GAD had a relative increase in basal ganglia and right parietal metabolism, with decreased metabolism in the right temporal and occipital lobe. Benzodiazepine administration did not normalize this pattern; thus, stimulus processing may be dysfunctional in GAD, contributing to the cognitive bias toward chronic worrying. In addition, studies of EEG patterns have supported the role of the centroparietal and the occipital regions in anxiety (Grillon and Buchsbaum 1987). Thus, imaging studies imply that multiple regions of the brain contribute to GAD and that the basal ganglia and the occipital and temporal lobes have been implicated most consistently.

In a normal brain, function and blood flow are closely coupled, and increased arousal is associated with an increase in cerebral blood flow (Mathew et al. 1982b). Hence, those with GAD might be expected to have abnormal increased cerebral blood flow. However, one study found that people with low baseline anxiety had an increase in cerebral blood flow as their level of anxiety increased, whereas those with high baseline anxiety had a decrease in cerebral blood flow as they became more anxious, perhaps consistent with loss of the capacity to mount an adaptive stress response (Gur et al. 1987). Benzodiazepines also decrease cerebral blood flow (Mathew et al. 1991), but this effect was more likely the result of decreased metabolic rates in the cortex, the limbic system, and the basal ganglia by these drugs (Wu et al. 1991). However, this finding of a decrease in blood flow in anxiety patients under stress has been inconsistent. An earlier study by Mathew et al. (1982b) indicated that no differences were seen in cerebral blood flow patterns between patients with GAD and control subjects without anxiety. In a later study, Mathew and Wilson (1991) found that the decreases in cerebral blood flow in patients with GAD did not correlate with the patients' level of anxiety, but later they found that the response to CO_2 and epinephrine in patients with GAD distinguished their degree of cerebral blood flow from others. Those patients with the most severe anxious response to 5% CO_2 and epinephrine had less of an increase in cerebral blood flow than did those with less of an anxious response (Mathew et al. 1997). Similar to Brawman-Mintzer and Lydiard's (1997) autonomic inflexibility theory, Mathew attributed this difference to the more severely anxious patients having a pronounced sympathetic response, which limits hypercapnic cerebral vasodilation. These findings support the view that cerebral blood flow may be altered in GAD and that paradoxically these hyperaroused individuals have a decrease in flow during stress.

Imaging studies of GAD are still in their infancy but already show that a complex pattern of interactions occurs between brain regions in patients with GAD. The inconsistent findings of measures such as metabolic activity and blood flow among studies indicate that variables such as anxiety level at the time of the scan may have profound effect. Another possibility is that the inconsistent participation of regions such as the occipital and left inferior frontal lobes reflect different manifestations of worry, such as visual versus verbal cues for anxiety. Also, method differences could be important in this newly developing field. Although a great deal remains to be learned, imaging studies have been fruitful in illustrating aberrant brain metabolism in GAD. Possible future directions in neuroimaging are studying the sequence of metabolic changes in GAD, better delineating the quality of the anxiety state with the regions involved, and comparing pre- and posttreatment scans of patients receiving medications that work at different receptors.

Psychosocial Factors

Whatever role biology may hold in the hierarchy of contributors to GAD, the patient's own internal process, experience, and means of coping with a chronic state of anxiety certainly play a major role in maintaining, if not precipitating, this disorder. In this section, we highlight several findings about the life experiences, personality traits, cognitive processing, and coping skills of patients with GAD (note that psychodynamic theories are not discussed because Chapter 7 in this volume, by Milrod et al., is dedicated to this subject). A unifying belief among many of the psychological theo-

ries of GAD is that the dysfunctional worries can stem from early experience.

Childhood/Developmental Issues in Generalized Anxiety Disorder

Behavioral inhibition in childhood may indicate an increased risk for developing an anxiety disorder as an adult. *Behavioral inhibition* is defined as a childhood temperament characterized by a tendency to be shy and timid in novel situations (Hirshfeld et al. 1992). Children with behavioral inhibition have higher rates of childhood anxiety disorders, and behavioral inhibition also may be a potential predictor of later anxiety disorders (J.F. Rosenbaum et al. 1993). Although several authors have proposed theories of how childhood behavioral inhibition may manifest as an anxiety disorder in adulthood, longitudinal studies still need to be performed to prove these theories.

Some investigators have examined parenting factors in relation to GAD. Retrospective studies of adults with GAD have consistently found that they viewed their parents as rejecting and controlling, where *controlling* is defined as overinvolvement of a parent (Rapee 1997). The obvious limitation to these studies is that they were done retrospectively and may reflect more the patient's perception of his or her child rearing than his or her actual experiences. However, psychiatric symptoms may be more significantly influenced by the perception than the realities of child rearing (Parker 1983). Studies that question anxious children about their parenting have been less consistent, but other work indicates that anxious children's families are less cohesive and more enmeshed compared with control subjects' families (Rapee 1997). Rapee proposed that excessive protection from a parent conveys to the child that the world is a dangerous place and reduces the child's opportunity to explore and learn otherwise.

The effect of trauma and its possible contribution to GAD also has been a subject of great interest. The idea that a child who experiences some catastrophic event will grow up more fearful and apprehensive than his or her peers seems intuitively obvious. However, not all studies support this. Raskin et al. (1982) found that GAD and panic disorder patients did not differ in the amount of childhood abuse or separation. This finding implies that traumatic events do not contribute to the development of chronic worry. However, others found a significant association between physical and sexual abuse and the development of adult psychiatric disorders, particularly GAD (Windle et al. 1995). These two studies are not necessarily contradictory in that other factors aside from the trauma may determine who will develop chronic anxiety and who will develop severe, episodic anxiety. Another study found that many Cambodian refuges with posttraumatic stress disorder had GAD, indicating that childhood trauma can lead to worries that persist into adulthood (Hubbard et al. 1995). Trauma, therefore, likely contributes to the onset of GAD.

Personality and Generalized Anxiety Disorder

One perspective of GAD is not viewing it as a disorder as much as a constellation of maladaptive personality traits. Trait anxiety could be defined as a relatively stable disposition to respond to a wide range of situations with state anxiety (Spielberger 1972). Some investigators argue that GAD can be considered a manifestation of a high anxiety trait. The tendency to worry is highly correlated with trait anxiety (Borkovec et al. 1983) but not necessarily state anxiety (Saklofske and Eysenck 1983). Trait anxiety also is associated with an elevated estimate of threat, a phenomenon with implications that are discussed later (G. Butler and Mathews 1987). Although Rapee (1985) stated that GAD arises from a trait disposition, he acknowledged that GAD in some cases did not occur until after childhood. He theorized that adult-onset anxiety arises from a life stressor causing anxiety characteristics to become more severe or from a change in life that might lead to attitude changes. Following an attitude change, he proposed, what was once seen as a way of life could become viewed as a problem. Thus, GAD could be envisioned as the result of a coping style that enlists high arousal and worry at the least stresses.

Patients with GAD appear to differ from others in both coping styles and approach to potentially threatening situations. The above authors suggest that, in contrast to the disease model of GAD, these differences can be best explained by shared personality traits that reflect long-standing characteristics of these individuals. A weakness of this theory is that these studies have observed a limited number of characteristics and assumed that the unique features seen in GAD patients explain the etiology of the disorder when, in fact, these same characteristics could have been a consequence of the disorder.

Cognitive-Behavioral Theory

Cognitive-behavioral theory proposes that patients with GAD have developed a set of catastrophic, auto-

matic thoughts that are self-reinforcing and prevent the person from approaching novel situations without great trepidation. The patient's focus of worries cascades, and the person finds it progressively difficult to cope with his or her concerns about the future. The anxious patient overestimates the probability or severity of feared events, and this overestimation is responsible for maintaining the anxiety disorder. The anxious patient overattends to potentially threatening stimuli, and this biased attention propagates his or her feeling of being in danger. Patients engage in avoidance or escape behaviors, which prevent them from encountering evidence that would contradict their pessimistic predictions; hence, patients continue to hold these beliefs (D.M. Clark 1988). Although selective attention to emotionally laden material may be characteristic of a normal state of heightened arousal, in anxiety disorders, the attention appears to be more intensely focused and often centers on some idiosyncratic belief (Martin et al. 1991). Thus, selectively focusing on threatening stimuli appears to propagate the symptoms of GAD. Other theorists have emphasized the role of automatic cognitions in anxiety and mood disorders (Beck et al. 1985). These automatic cognitions are recurrent thoughts that the patient either has throughout the day or reverts to in stressful situations. Beck proposed that these automatic cognitions involve anticipated harm or danger to personal domain. In depressed patients, these thoughts tend to focus on loss or failures (Beck et al. 1988), whereas in anxious patients, these automatic thoughts tend to be more situational, future-oriented, and probabilistic (Beck and Clark 1988). These cognitions about harm and danger are particularly predictive of developing anxiety (D.A. Clark et al. 1989).

The cognitive-behavioral perspective proposes that patients with GAD selectively focus and ruminate on potentially threatening situations; therefore, these patients should improve if these ruminations are challenged and if the patient is educated about the inaccuracy of the level of danger perceived in a situation. Several studies support this view that therapy based on these tenets improves the symptoms of GAD (Harvey and Rapee 1995). Thus, the efficacy of treatment based on cognitive-behavioral theory supports the validity of this theory. Cognitive-behavioral theory proposes that automatic, pessimistic thoughts are a mechanism by which the chronic worry of GAD persists. Although this theory does not explain what leads to the development of these ruminations, it does provide a theoretical framework for treatment of the persisting symptoms of GAD that appears to be effective.

Information Processing in Generalized Anxiety Disorder

One role of the brain is to filter out unnecessary information and to develop a memory based on the remaining data. In the previous section, we focused on how anxious patients appear to overfocus on anxious memories. However, another approach would be to determine how anxious patients process the information. Information-processing theories of anxiety disorders are concerned with which data are not filtered out and how that leads to the development of anxious memories.

Patients with GAD appear to process threatening information differently from other people. Studies found that patients with GAD allocate extensive attentional resources to threatening stimuli and detect such information rapidly and effectively (MacLeod et al. 1986). One study found that GAD patients consistently write down the threatening version of a homophone (e.g., "die" instead of "dye"), and this tendency to use the threatening spelling correlated with trait but not state anxiety (Mathews et al. 1989). Another study required that control subjects and GAD patients memorize a word list and later recall it. The GAD patients tended not to remember the threatening words, suggesting that some inhibitory process interfered with proper storage of memory of threat (Mogg et al. 1987). Mathews and colleagues (1989) argued that this inhibitory processing may be somewhat voluntary and helps to prevent extensive elaboration. In this same paper, Mathews et al. reported that trait anxiety is not correlated with threat bias on word stem completion tasks but is correlated with threat bias on cued recall. This finding suggests that patients with GAD allocate extensive attentional resources to potential threats, so even ambiguous conditions are more likely to be interpreted as threatening.

Barlow (1988) proposed another model of attentional narrowing in anxiety disorder. He suggested that negative life events trigger stress-related neurobiological reactions. This leads the person to focus on life events, even minor ones, and to react to these events with a negative affect. This negative affect derives from stress-related neurobiological reactions and a belief that events are proceeding in an unpredictable, uncontrollable fashion. This, in turn, leads the person to shift his or her focus from the task at hand to self-evaluation, which only leads to further arousal. The person will begin a spiral of further vigilance and narrowing of attention to the focus of concern and how he or she is unable to cope with it. This theory is supported by a recent

finding that erroneous interpretation of information correlates with the pathogenic effect of CCK_4 in anxious patients (Aluoja et al. 1997). However, other studies do not support this theory. Lack of control alone appears to be insufficient to develop distress (England and Dickerson 1988). Rapee (1991) theorized that the coupling of this lack of control with a focus on potential threats leads to distress in GAD patients. What both of these theories support, however, is that the symptoms of GAD are potentiated by a persistent focus on worries.

In summary, patients with GAD appear to both attend to and process information in a manner that potentiates, and possibly initiates, the disorder. This area of research is only in its early stages yet may be a fertile link between the previously discussed biological findings and the clinical presentation of GAD.

Affect Theory and Generalized Anxiety Disorder

As discussed earlier in this chapter, mood disorders frequently are comorbid with GAD. The distinction between mood and anxiety symptoms often can be blurred, and these two categories of disorders may share a similar etiological basis. Based on this idea, another hypothesis to explain the etiology of GAD proposes that this syndrome is a disorder of affect.

Watson and Tellegen (1985) proposed a two-dimensional model of affect composed of positive and negative affect. They defined positive affect as the extent to which a person feels a zest for life and negative affect as the extent to which a person feels upset or unpleasantly aroused. Their theory holds that people with high negative affect experience more negative emotion and have negative views of the world, causing them to focus on negative aspects of self, others, and the world. Those with negative affect also ruminate about their mistakes and failures. Watson et al. (1988) argued that anxious patients have a high degree of negative affect, and their degree of positive affect fails to play the sort of role that it plays in depression, in which the low positive and high negative affects result in this disorder. Tellegen (1985), however, proposed that both disorders result from an aberration of negative affect. If the negative affect has a strong fear component, the person will become anxious, and if sadness and fatigue are more evident, then depression will develop. This "fear component" also can be conceptualized as a "orienting or questioning mode," which leads the anxious person to focus on the uncertainties of future events and circumstances. These theories share a good deal in common with cognitive-behavioral models and likely have similar clinical implications.

Self-Efficacy in Generalized Anxiety Disorder

Implicit in the act of worrying is the belief that the focus of concern is so overwhelming that it is beyond one's ability to deal with it. In earlier sections of this chapter, we discussed how patients with GAD selectively attend to and process stressful stimuli. However, the degree to which someone worries about a particular stressor is subjective. The level of threat may be determined not only by the stimuli and how they are processed but also by how well the person believes he or she can deal with this situation. Self-efficacy is concerned with the patient's beliefs about his or her ability to exercise control over events. In a disorder in which worry is the cardinal symptom, GAD may result from low self-efficacy.

Self-doubt may underlie many of the symptoms of GAD. Individuals who doubt their capability to complete a task have reduced effort and often settle prematurely on mediocre solutions (Bandura 1989), thereby reinforcing their belief that they could not adequately handle the situation. Bandura also noted that those who believe that they are incapable of managing threatening situations tend to perceive the situation as more perilous than it is and dwell on their own inadequacies to deal with it. This leads to higher levels of stress and anxiety. In anxious patients, their perception of self-efficacy is closely related to their degree of distress in a given situation (Kent and Gibbons 1987). These findings suggest that GAD may be disorder of self-efficacy.

The phenomenon of relaxation-induced anxiety also might be explained by the GAD patient's low self-efficacy. *Relaxation-induced anxiety* is the term used to describe the finding that techniques such as progressive relaxation, biofeedback, and meditation can initiate or exacerbate anxiety in some individuals (Heide and Borkovec 1984). These authors theorized that because generalized anxiety states result from a fear of loss of control, relaxation techniques that entail relinquishing this control leave the anxious person without whatever active coping skills he or she had developed. These same coping skills, however, may be the source of the constant tension and anxiety experienced by those with GAD. Interestingly, these authors found that the specific techniques that provoked relaxation-induced anxiety differed among individuals. GAD, thus, might not only be a disorder of poor self-efficacy but also stem from maladaptive coping strategies.

Etiological Models of Generalized Anxiety Disorder

Both biological and psychosocial factors appear to contribute to the initiation and propagation of GAD. Several researchers, including Barlow, whose ideas were discussed earlier in this chapter, have proposed models that attempt to integrate these factors into theories that can account for the findings previously discussed.

Kendler (1996) emphasized the interaction of inheritance and the environment. He proposed that the genetic influences for the development of GAD and major depression are identical. Therefore, the environment determines which disorder the patient will develop. His theory is supported by studies that propose that events such as facing danger and pregnancy are distinctly associated with developing anxiety; in contrast, facing great loss is associated with developing depression. A limitation of this theory is that both major depression and GAD have disorders with which they are comorbid, and this theory does not support data to explain why a patient develops one disorder versus another, nor does it adequately explain the neurophysiological differences among these disorders.

An alternative theory integrating this information hypothesizes a *behavioral inhibition system* (Gray 1988). This theory proposes that the septohippocampal area is responsible for processing threat-relevant stimuli. The presence of danger activates the behavioral inhibition system, resulting in increased arousal and inhibition of all regular behaviors. Noradrenergic and serotonergic stimulation of the septohippocampal region further activates this system. Gray proposed that this increased state of vigilance is analogous to GAD. Therefore, drugs that reduce noradrenergic or serotonergic input into the septohippocampal area will treat the anxiety. A weakness of this theory is that some drugs that have been helpful in the treatment of GAD, such as buspirone and the selective serotonin reuptake inhibitors, increase serotonin function with chronic administration.

Another model of anxiety proposed by Goddard and Charney (1997) focuses on the central role of the amygdala in the regulation of anxiety. Electrical stimulation of the amygdala elicits fearlike behaviors in animals and is associated with several physiological changes consistent with anxiety (Kaada 1972). Anatomically, the amygdala's extensive network of afferent and efferent pathways provides access to the other areas of the brain involved with anxiety. The theory proposes that sensory input is processed in the cortices, entorhinal cortex, limbic area (amygdala and hippocampus), and brain stem structures (nucleus paragigantocellularis and locus coeruleus). When faced by a threatening stimulus, this stimulus is processed in the context of past and present experiences, and the processing areas of the orbitofrontal cortex and the amygdala choose an anxiety response. Next, this response is implemented by the locus coeruleus, the hippocampus, the dorsal motor nucleus of the vagus, the parabrachial nucleus, the trigeminal nucleus, the facial motor nucleus, the striatum, and the periaqueductal gray. The strength of this theory is its ability to integrate the numerous areas implicated in the development of anxiety. A limitation of this theory is that it fails to address which factors predispose someone to a specific disorder. However, additional research into the role of specific neural structures is required before this question can be answered. The amygdala model of anxiety, however, offers a model by which the neural structures initiate and propagate anxiety disorders.

Cloninger (1986) proposed a model in which inherited abnormalities in neurotransmitter systems cause personality traits that could manifest as GAD. Cloninger focused on three aspects of personality—novelty seeking, harm avoidance, and reward dependence—that he argued are determined by monoamine activity. Several studies support the idea that novelty seeking is associated with low basal dopaminergic activity, whereas harm avoidance is seen in individuals with high serotonergic activity, and reward dependence results from low basal noradrenergic activity (Cloninger 1986). Cloninger used the Tridimensional Personality Questionnaire to draw several conclusions about the relation of these traits and the development of chronic anxiety. In particular, he hypothesized that extremely high or low levels of harm avoidance predispose individuals to chronic anxiety because low harm avoidance increases the risk of aversive events (such as trauma), and the person learns that the world is not a safe place, whereas high harm avoidance predisposes individuals to always overestimate the risk and leads them to constantly feel that they are in danger. Cloninger further suggested that specific combinations of these traits led to "somatic anxiety" or "cognitive anxiety." Those with somatic anxiety have high novelty seeking, but not harm avoidance, whereas those with cognitive anxiety have low novelty seeking and low reward dependence. Cloninger proposed that GAD is the result of chronic cognitive anxiety. In one study, harm avoidance was slightly elevated and reward dependence slightly low-

ered in GAD patients, but their novelty seeking was not different from that of control subjects (Starcevic et al. 1996). This assertion is also supported by a study that found an association between a polymorphism in a region that regulates the expression of the serotonin transporter and anxiety-related personality traits, particularly harm avoidance (Lesch et al. 1996). Assuming that Cloninger's ideas about specific monoamines being associated with traits are correct, this study supports the idea that norepinephrine and serotonin play some role in GAD, whereas dopamine does not (and hence, dopamine has not been of much interest for study).

Conclusion

GAD is characterized by chronic worry and somatic tension. In this chapter, we explored the range of biological and psychosocial theories and integrated these ideas into potential etiological models to explain the initiation and propagation of this disorder.

Biological factors seem to play a significant role in GAD. Genetic factors appear to predispose to development of GAD but do not yet account for all cases. Several studies have found aberrations in the norepinephrine system, suggestive of norepinephrine overactivity in GAD. The serotonin system also has been an area of interest. GABA plays a significant regulatory role throughout the brain, and its role in mediating the release of several neurotransmitters (including CCK) may be important in the initiation and propagation of GAD. The CCK system also may be involved early in the induction of anxiety and potentially acts on the GABA system in a way that opposes benzodiazepines.

Patients with GAD appear to have other pathophysiological lesions. The HPA axis tends to be overactivated in GAD, but the thyroid axis appears unaffected. These patients also have shorter interbeat variability on ECG, which may be the result of an inflexible response to stress and a requirement for a prolonged time to recover from a stressor. Neuroimaging studies also demonstrate differences between GAD patients and control subjects.

Psychosocial factors such as child rearing, trauma, temperament, and information processing may play roles in the initiation and propagation of this disorder. Inasmuch as GAD is influenced by both biological and psychosocial factors, several authors have proposed models that combine these facets. Barlow proposed that negative life events led to neurobiological reactions, which led to anxious patients limiting their focus to only potentially threatening stimuli. Kendler theorized that major depression and anxiety have identical genetic causes and that significant life events determine which disorder will develop. Gray proposed a behavioral inhibition system, which theorizes that anxiety results when norepinephrine and serotonin overstimulate the septohippocampal region. Charney et al. proposed that the amygdala is the central structure in anxiety and that stimuli are processed and cognitively responded to via pathways that all communicate with the amygdala. Lastly, Cloninger proposed a set of neurochemically driven personality traits that, in concert, lead to the development of GAD. At this point, none of these models can sufficiently explain the development of GAD. More research is required in the genetics, biochemistry, anatomy, stimulus processing, and premorbid history of GAD before a more definitive model can be generated.

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Pharmacotherapy for Generalized Anxiety Disorder

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In this chapter, we focus on pharmacotherapy for generalized anxiety disorder (GAD). For much of recorded history, chronic anxiety has been treated with pharmacological agents. Starting with alcohol in prehistoric times and extending through the nineteenth century with the use of bromides, chloral hydrate, and paraldehyde and into the twentieth century with the synthesis of barbiturates, antihistamines, and benzodiazepines, there have been effective pharmacological treatments for such symptoms. Indeed, more treatments are probably available for GAD than for any of the other anxiety disorders because many classes of drugs have anxiolytic effects.

However, many of these early agents had disadvantageous side-effect profiles, and more recent advances in pharmacotherapy for GAD have included the use of serotonin type 1A (5-HT_{1A}) receptor agonists, tricyclic antidepressants, and more specific antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs). Here, we briefly review the assessment and evaluation of patients with GAD from the viewpoint of the psychopharmacologist; consider some of the early work in which benzodiazepines were used for GAD; and then review work on buspirone, tricyclic antidepressants, and the newer antidepressants.

Assessment and Evaluation

Previous chapters in this volume have discussed some of the controversies surrounding the construct of GAD. Not only may there be some conceptual difficulties in separating chronic anxiety from normal or trait anxiety (Akiskal 1985), but also patients with GAD frequently have comorbid major depression and other psychiatric disorders. From the viewpoint of the psychopharmacologist, it is crucial to establish target symptoms for intervention and to determine the range of psychopathology that may respond to medication. Although DSM-IV-TR (American Psychiatric Association 2000) criteria are of course crucial to assess, it is worth noting that most pharmacotherapy studies of chronic anxiety are not based on such criteria. Target symptoms for pharmacotherapy may include psychic anxiety, somatic symptoms, and functional impairment. Furthermore, comorbid diagnoses may be crucial in determining intervention; for example, comorbid major depression or substance use disorders are likely to point the clinician toward the use of an antidepressant agent rather than a benzodiazepine.

In addition to assessing the type and severity of GAD symptoms per se, it is important to assess the patient within the broader context of his or her expecta-

tions and motivations. In many patients, symptoms have been present for years. This is not a cause for pessimism, but change may occur relatively gradually, and treatment may need to be relatively chronic. Certainly, medication discontinuation in GAD may be followed by symptom relapse. Similarly, given that symptoms may have affected a range of different areas of life, supportive or specific psychotherapeutic measures may need to be included to address such dysfunctions. Relatively little empirical work has directly compared pharmacotherapy with cognitive-behavioral interventions or their combined use in GAD, but in clinical practice, it would seem reasonable to treat patients with flexibility and eclecticism as needed.

There are other reasons for adopting a clinically grounded and practically cautious approach to pharmacotherapy for GAD. GAD symptoms may wax and wane over time, and controlled pharmacotherapy trials often have found rather high placebo rates. Confounding effects in past trials include the use of outdated definitions of the disorder and the effect of prior benzodiazepine use on responses to comparator drugs. Patients should be encouraged to cope with low levels of anxiety without medication, reserving medication for when it is clearly needed. In selecting a drug, it is important of course to consider the risk-benefit ratio for the patient; unfortunately, few medications have passed rigorous regulatory requirements for the treatment of GAD, and relatively few postmarketing studies of medications in the treatment of GAD have been conducted.

Benzodiazepines

Benzodiazepines have been extremely widely used for the treatment of GAD and chronic anxiety symptoms. The popularity of these agents derives from their rapid anxiolytic activity, their relative safety compared with previously available agents such as barbiturates, and their ease of use. Benzodiazepine γ-aminobutyric acid (GABA) agonism is associated with a decrease in anxiety, an increase in sedation, cognitive slowing, anticonvulsant activity, and muscle relaxation. Certainly, a range of controlled trials has shown the efficacy of these agents in the treatment of chronic anxiety. Different types of benzodiazepines at equivalent doses appear equally effective, although a relation between plasma benzodiazepine concentrations and clinical response has not been established.

The widespread use of benzodiazepines has been controversial (Lader 1994). Although the benzodiazepines are occasionally associated with abuse, more worrisome is the association with dependence (physical and psychological symptoms increase when the agents are withdrawn) (Hollister et al. 1961), even with the discontinuation of relatively low doses (Covi et al. 1973). Benzodiazepines with short durations of therapeutic action require more frequent dosing, have more pronounced peaks and troughs, have more anterograde amnesia, and have more rapid withdrawal. Clinical characteristics, such as residual levels of anxious and depressive symptoms, also appear to predict withdrawal severity (Schweizer and Rickels 1998).

In addressing this debate about the ultimate value of benzodiazepines, we begin by emphasizing again the chronicity of GAD symptoms. After acute benzodiazepine treatment, symptom relapse and/or rebound anxiety (i.e., return of anxiety to a level above the pretreatment baseline) frequently occur (Schweizer et al. 1995). Furthermore, benzodiazepines have been shown to effect sustained remission of anxiety symptoms without dose escalation over 6 months and longer (Schweizer et al. 1995). Such considerations would suggest the usefulness of relatively long-term benzodiazepine treatment.

However, several unresolved questions about the efficacy and safety of benzodiazepines remain (Woods et al. 1992). These agents have persistent attentional, psychomotor, cognitive, and memory effects that may be associated with significant morbidity and even mortality (Thomas 1998). Benzodiazepines also may exacerbate hostility and impulsivity in some patients (Cowdry and Gardner 1988; Dietch and Jennings 1988). Other concerns about the chronic use of these agents have been raised, and although additional empirical evidence is needed, it is interesting to note that patients taking other antianxiety medications may ultimately achieve better responses (Rickels and Schweizer 1990). Finally, the effectiveness of benzodiazepines over the long term ultimately appears unclear (Schweizer et al. 1995).

Indeed, given the potential difficulties of having to taper patients from benzodiazepines, many clinicians would argue that benzodiazepines should not be used as first-line agents in the treatment of GAD. Some patients may, however, require long-term pharmacotherapy with these agents. In such cases, the symptoms of a chronic and disabling disorder may be reduced without dose escalation. Furthermore, even in such cases, using gradual tapering regimens, switching to a benzodiazepine with a longer half-life, or using other interventions for the management of benzodiazepine withdrawal ultimately may be successful (Schweizer and Rickels 1998).

Buspirone

Buspirone, an azapirone derivative, is a partial 5-HT_{1A} receptor agonist that has been effective at doses of 20–40 mg in several clinical trials of GAD (Napoliello 1986; Wheatley 1982). Although other 5-HT1A agonists also appear effective in GAD, none has yet come to market.

Buspirone has been argued to be comparable to benzodiazepines in efficacy for GAD in head-to-head studies (Cohn et al. 1989), and a meta-analysis of buspirone-controlled trials in GAD (but excluding patients with major depression) also suggested that buspirone may be as effective in patients with more depressive symptoms (Gammans et al. 1992). Nevertheless, several negative trials of this agent also exist (e.g., in a study of venlafaxine and buspirone in GAD), and the 5-HT_{1A} agonists in general have been disappointing because no other members of this class have reached the market to date. Furthermore, buspirone has a slower onset of action than do the benzodiazepines, and some evidence indicates that patients who have received these agents believe that buspirone is less effective (Schweizer et al. 1986).

The side-effect profile of buspirone has significant advantages over that of the benzodiazepines. Buspirone has no cognitive or psychomotor impairing effects, has no alcohol potentiation, and is well tolerated during maintenance treatment (Rakel 1990). Furthermore, buspirone-treated patients do not experience rebound anxiety or withdrawal symptoms. Indeed, after 6 months of buspirone or clorazepate, patients with GAD treated with buspirone had a lower relapse rate at 3 years posttreatment (Rickels and Schweizer 1990).

Thus, particularly in patients who do not demand immediate relief of symptoms, who do not have comorbid major depression, and who have not previously been given benzodiazepines, buspirone may be considered one option in the pharmacotherapy for GAD. Its favorable adverse-effect profile is particularly attractive.

Hydroxyzine

Hydroxyzine is a histamine (H_1) receptor antagonist that has not been found to induce dependence in animals or humans. Early clinical trials found that hydroxyzine has anxiolytic effects, but these studies predated the introduction of GAD as a diagnostic entity.

More recent controlled trials that used DSM-IV (American Psychiatric Association 1994) criteria for GAD found that hydroxyzine (50 mg) was superior to placebo on a range of measures from the first week (Ferreri and Hantouche 1998). Efficacy was maintained not only through the duration of the trial but also after abrupt discontinuation, confirming the lack of a rebound effect.

In a controlled trial against lorazepam, both agents showed comparable anxiolytic efficacy, but hydroxyzine showed greater and more rapid cognitive improvement (Ferreri and Hantouche 1998). The most frequent side effect was sleepiness, although most patients reported improvement in this problem over the course of the treatment.

Antidepressants

Perhaps nowhere is the misleading effect of traditional classification of drugs more evident than in the categorization of drugs as antidepressants or antianxiety drugs. With the exception of the relatively selective noradrenergic antidepressants bupropion, desipramine, and maprotiline, most agents first approved as treatments for depression have shown efficacy as treatments for GAD or GAD-like symptoms (Rickels et al. 1993). Although not all antidepressants have been systematically studied for their effectiveness in treating GAD, these agents certainly decrease anxiety symptoms in depression, and they appear to have antianxiety effects even in patients without overt depression.

Thus, early studies found that anxious patients with subsyndromal levels of depression had better responses to tricyclic antidepressants than to benzodiazepines (Johnstone et al. 1980; Kahn et al. 1986). More recent studies confirmed these findings; for example, in a study comparing imipramine, trazodone, and diazepam for patients with GAD, diazepam was the most effective medication during the first 2 weeks, but imipramine was most effective after 6–8 weeks. Furthermore, a subanalysis of patients with more depressive symptoms found lowered efficacy for diazepam and increased efficacy for the antidepressants (Rickels et al. 1993). In contrast, some investigators have suggested that certain benzodiazepines (such as alprazolam) have antidepressant properties (Rimon et al. 1991), but emergence of depressive symptoms during benzodiazepine treatment has been documented (Lydiard et al. 1987).

More recent studies have explored the use of novel antidepressant classes in GAD. The SNRI venlafaxine was the first antidepressant to receive regulatory approval for GAD treatment. Promising short-term pla-

cebo-controlled studies, short-term comparative studies (with buspirone and diazepam), long-term efficacy studies, and a relapse prevention study have been conducted with this agent. More recently, the SSRI paroxetine has also been approved on the basis of short-term, placebo-controlled studies demonstrating efficacy.

It is important to emphasize that most of the disorders that are comorbid with GAD respond to antidepressants, some better than others. For example, obsessive-compulsive disorder and major depression respond well to SSRIs. Even SSRIs that have initial activating effects do have anxiolytic properties with continued administration. Serotonin antagonist and reuptake inhibitors, such as nefazodone, and the noradrenergic and serotonin selective antagonist mirtazapine may have pronounced early anxiolytic effects.

Nevertheless, despite their reasonable tolerability, the side-effect profiles of antidepressants are not ideal. Depending on the drug, side effects such as anticholinergic and cardiovascular effects (tricyclic antidepressants), sedation (serotonin antagonist and reuptake inhibitors), weight gain (noradrenergic and serotonin selective antagonists), and sexual dysfunction (SSRIs) may complicate long-term compliance with treatment. Future pharmacotherapy studies of GAD should include pharmacoeconomic and quality-of-life variables to address the overall cost-benefit ratio and effectiveness of the antidepressants in the treatment of GAD.

Antipsychotics

An early body of literature supports the concept that antipsychotic agents have anxiolytic actions, and it has been suggested that these agents are intermediate in efficacy between the benzodiazepines and placebo for GAD (Rickels et al. 1993). The availability of the new atypical antipsychotics, with their low incidence of extrapyramidal side effects, had led to the use of these agents in refractory obsessive-compulsive disorder and nonpsychotic disorders. However, to date, no evidence supports the efficacy of these agents in GAD, and no careful documentation of the risk-benefit ratio associated with their use exists (El Khayat and Baldwin 1998).

Treatment Resistance

Failure to respond to any standard treatment of GAD should prompt a reassessment of the patient. Because generalized anxiety can be part of many medical or psychiatric disorders, a broad differential diagnosis should be considered. Other anxiety disorders, substance-induced anxiety disorders, mood disorders, and mental disorders secondary to general medical conditions must be considered.

The database on the pharmacotherapeutic management of symptoms that have not responded to a benzodiazepine or buspirone and to an antidepressant is extremely sparse. However, in such patients, combination therapy may arguably be prescribed. The combination of an SSRI and buspirone may be useful in some patients with treatment-refractory depression and could certainly be considered.

In particularly resistant cases, other classes of medication can be used, including atypical antipsychotic agents and anticonvulsants such as valproate and gabapentin. However, this area demands further research before empirically based recommendations can be made.

Conclusion

In contrast to prevailing thinking, empirical data suggest that GAD is neither mild nor a variant of another Axis I disorder. Whether GAD is merely associated with depression, panic disorder, and other anxiety disorders or whether it predisposes to the development of these comorbid disorders is not clear. Chronicity, functional impairment, high health care use, and relatively poor treatment response (Woodman et al. 1999) all characterize GAD. Thus, development of effective and safe pharmacotherapy for this condition is an important goal.

Although several effective agents have long been available for GAD, many medications that are commonly used in GAD have unfavorable side-effect profiles. The long-term use of benzodiazepines in GAD, for example, is controversial. A number of agents have now received regulatory approval for DSM-IV-TR GAD, but many questions remain unanswered by the current empirical database. In particular, relatively little work has been done on issues such as maintenance pharmacotherapy, combination with psychotherapy, and pharmacotherapy for the treatment-refractory patient.

Indeed, there is relatively little consensus on the algorithm for pharmacotherapy for GAD. The disparate drugs that are used as treatments of GAD are reflected in the many different "first choices" that are available. Nevertheless, given the high degree of comorbidity, compelling reasons suggest that antidepressants should be considered as first-line agents over benzodiazepines

over the long haul. Although they work more slowly, the antidepressants have a broader spectrum of action, are easier to discontinue, and are not subject to misuse. Some patients are unresponsive to or intolerant of conventional agents; in these cases, use of strategies that rely on compounds approved for other indications may be necessary.

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Psychotherapy for Generalized Anxiety Disorder

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As discussed in previous chapters in this volume, generalized anxiety disorder (GAD) is a relatively common disorder that is associated with significant distress and functional impairment. Fortunately, advances in both pharmacotherapy and psychotherapy have resulted in a greater likelihood of providing effective treatment. Unfortunately, many more inroads remain to be made to clarify what works for whom and how. In this chapter, we concentrate on what we do and do not know about psychosocial treatments for GAD. First, we describe the psychological aspects of GAD that appear to be involved in the maintenance of the disorder and, thus, must be addressed in treatment. Then, we review the outcome literature relevant to GAD. Finally, we discuss empirically supported psychological treatment strategies and suggest potential directions for future clinical research.

Psychological Aspects of Generalized Anxiety Disorder

GAD is a relatively new diagnosis, changed from a "wastebasket" diagnosis pertaining to anyone with anxiety whose symptoms did not fit into another anxiety disorder listed in DSM-III (American Psychiatric Association 1980) to a discrete entity, more "carved at its joints" in DSM III-R and DSM-IV (American Psychiatric Association 1987, 1994).

Worry

GAD consists of two major components: worry and somatic symptoms associated with hyperarousal (e.g., muscle tension, sleep disturbance, feeling keyed up). Clearly, worry is the major cognitive component of GAD and may be considered the cardinal feature of the disorder. People who have GAD tend to worry most of the day, nearly every day (Brown et al. 1993). However, worry in itself is not pathological. It is an attempt to predict future danger and/or an attempt to gain control over events that appear uncontrollable (and usually negative or dangerous) (Rapee 1991). Under appropriate circumstances, worry may lead one to take positive actions. In fact, some researchers posit that worry usually facilitates problem solving and that difficulties are attributed to lack of confidence in solutions, as opposed to lack of ability in solving problems (Davey 1994). However, it is clear that pathological worry is dysfunctional in that it is, by definition, excessive and/or unrealistic. As a result, patients overpredict the likelihood of negative events and exaggerate consequences if the events were to occur (Brown et al. 1993).

Patients with GAD and control subjects appear to worry about similar topics (Sanderson and Barlow

1990), although patients with GAD tend to worry more frequently about minor matters (Brown et al. 1994). Spheres of worry endorsed by patients with GAD include concerns about family, health, social matters, finances, work, and world events. The topics of worry may change with age and life situation.

Two main aspects of *pathological worry* (which have been elucidated through a combination of descriptive studies and information-processing studies) differentiate it from normal worry (for a review, see Mathews 1990). First, pathological worry appears to be uncontrollable. In a study by Abel and Borkovec (1995), 100% of the patients with GAD described their worry as uncontrollable compared with none of the nonanxious control subjects. Second, pathological worry is excessive for a given situation, in that patients overestimate the threat in their environment, especially when interpreting ambiguous cues (Mathews 1990). In fact, these two features may be the result of GAD patients' intolerance of uncertainty, leading to more excessive and uncontrollable worry (Dugas et al. 1998). In addition, anxious subjects tend to selectively attend to threatening, personally relevant stimuli (Mathews 1990). The overprediction of danger may lead patients with GAD to worry more often than others because they perceive the environment as more threatening. Frequently, the implied belief is that worry will make the world more controllable and predictable. For example, one patient stated, "When I fly in an airplane, I worry that the plane will crash. If I stopped worrying about it, it probably would crash." Consistent with this, worriers report five major functions of worry: 1) superstitious avoidance of catastrophes, 2) actual avoidance of catastrophes, 3) avoidance of deeper emotional topics, 4) coping preparation, and 5) motivating devices (Borkovec 1994).

Research supports the idea that pathological worry has a functional role for patients with GAD. Ironically, worry inhibits autonomic arousal in patients with GAD when they are shown aversive imagery (Borkovec and Hu 1990). Worrying may cause the avoidance of aversive imagery, which is associated with an even greater emotional state (Borkovec et al. 1991). Thus, worry may be maintained by both the avoidance of certain affective states and the reduction of anxious states through the decrease in arousal that occurs along with worry. Counterintuitively, relaxation has been shown to increase the amount of worry in some patients with GAD (Borkovec et al. 1991). In these patients, relaxation may signal a lack of control, triggering an increase in anxiety, or these patients may sit quietly with their thoughts, causing greater exposure to their worries.

Somatic Symptoms

In addition to worry, patients with GAD experience unpleasant somatic sensations. Although both the worry and the somatic sensations usually increase during the course of a worry episode, they can be described as relatively persistent and pervasive. The most common somatic symptom reported by patients with GAD is muscle tension. Often associated with worry and tension are other symptoms including irritability, restlessness, feeling keyed up or on edge, difficulty sleeping, fatigue, and difficulty concentrating.

Characteristics of Patients With Generalized Anxiety Disorder

GAD has been shown to be a relatively chronic disorder with an onset in childhood (Brown et al. 1994). In view of these and other data, some argue that, in contrast to other anxiety disorders, a subtype of GAD (chronic, pervasive symptoms since childhood) may be better conceptualized as an underlying personality trait that increases one's vulnerability to developing anxiety disorders per se (Sanderson and Wetzler 1991). GAD typically starts in childhood, but often, a major stressor will exacerbate symptoms. One clinical example that we have seen several times is having a child. It appears that the increased responsibility and the desire for perfectionism in child rearing may extend these traits to the point of interference and distress. This may be partially because of the increased reports of childhood trauma in patients with GAD (Borkovec and Whisman 1996). In addition, new conceptualizations of GAD have started to focus on interpersonal deficits that may have developed in childhood (Borkovec 1994; Crits-Christoph et al. 1996). Research (Wells 1994) and our clinical experience with GAD have led us to believe that patients with GAD are often driven toward being perfectionistic, feel a greater need for control in their environment, have difficulty tolerating ambiguity, and feel increased personal responsibility for negative events that occur or are predicted to occur in their environment.

Differentiating Generalized Anxiety Disorder From Other Disorders

Accurate diagnosis is an essential first step in providing the appropriate treatment for a particular disorder. In fact, differentiating GAD from other anxiety disorders can be extremely complicated. First, worry is a relatively generic feature of anxiety disorders (i.e., worry about panic attacks, worry about embarrassing oneself).

In addition, a high level of comorbidity exists among the anxiety disorders, and GAD in particular, which requires one to consider diagnosing multiple disorders as well as making differential diagnoses (Sanderson and Wetzler 1991). The primary distinction between GAD and other anxiety disorders is the focus of the patient's concern. Patients with GAD experience uncontrollable worry about several different areas in their life. In fact, they often worry about their worrying (known as *meta-worry;* Wells 1994). In contrast, the focus of concern for patients with other anxiety disorders is specific to their respective disorder.

Panic Disorder

Patients with panic disorder are worried about having a panic attack or the consequences of experiencing certain bodily sensations. Their focus is on internal states. What makes the differential diagnosis particularly confusing is that the worry experienced by patients with GAD can lead to a panic attack. However, unlike patients with panic disorder, patients with GAD are concerned primarily about some future event, not about having a panic attack or the symptoms of anxiety per se. Another distinction is the course of onset of worry compared with that of panic. Some patients with GAD are focused on the physical symptoms of their anxiety, and this can lead one to think that the preoccupation with bodily sensations is a sign of panic disorder. However, the onset of a panic attack is sudden, and its peak typically lasts for several minutes, whereas the onset and course of GAD-related anxiety are usually longer and more stable.

Social Phobia

Because social concerns are a common area of worry for patients with GAD, they are often given diagnoses of comorbid social phobia (Sanderson et al. 1990). However, some guidelines for differentiating the two disorders are available. The basic distinction is that GAD concerns are more global, focused on several different areas that may include social situations. In contrast, patients with social phobia are specifically concerned with being evaluated, embarrassed, or humiliated in front of others.

Obsessive-Compulsive Disorder

Although the differentiation between obsessive-compulsive disorder and GAD seems obvious because of the behavioral rituals that are unique to obsessive-compulsive disorder (Brown et al. 1994), some cases still can be extremely difficult to differentiate. This is especially true of patients with obsessive-compulsive disorder who do not have compulsions or who have only mental rituals. Obsessions and worries can be differentiated by assessing the focus of concern. Obsessions are focused on overexaggerated or unrealistic expectations and are usually short lived (e.g., "If I don't seal this envelop correctly, my kids will be injured on the way home from school"). In addition, obsessions often take an "if-then" form (e.g., "If I do or don't do something, then something bad will happen") or include vivid imagery (Wells 1994). Worry, on the contrary, usually is focused on future negative events that are not caused by the patient. According to nonanxious subjects, it lasts longer and is more distracting (Wells and Morrison 1994). Worry also is usually predominantly verbal thoughts as opposed to images (Wells and Morrison 1994). The thought content of a worry may be specified in a "what if" fashion, without a consequence being stated ("What if I get ill?"). Another difficult aspect of the differentiation of GAD and obsessive-compulsive disorder is that patients with GAD may engage in reassurance-seeking behaviors that can be somewhat ritualistic and superstitious. Patients with GAD may report feeling compelled to act to neutralize this worry (Wells and Morrison 1994) (e.g., to call one's wife at work to lessen a worry about something happening to her). However, these behaviors are not as consistent, methodical, or ritualized as compulsive behaviors in patients with obsessive-compulsive disorder.

Mood Disorders

The final differentiation is between GAD and mood disorders, especially major depression and dysthymia. According to DSM-IV-TR, if GAD symptoms are present only during the course of a depressive episode, then it is not diagnosed as a comorbid disorder. More often than not, anxiety symptoms occur within the context of depression, and thus GAD is diagnosed as a separate disorder only when the symptoms have occurred at least at some point independent of depression. However, regardless of DSM exclusionary criteria, the nature of cognitions associated with each disorder can be distinguished: ruminations (common in depressive disorders) tend to be negative thought patterns about past events, whereas worries (associated with GAD) tend to be negative thought patterns about future events. This is consistent with theoretical conceptualizations of anxiety and depression, which posit that depression is a reaction to uncontrollable, inescapable negative events, leading to feelings of hopelessness and helplessness and

deactivation, whereas anxiety is a reaction to uncontrollable negative events that the person attempts or plans to escape from (for a more detailed explanation, see Barlow et al. 1996).

Review of Treatment Outcome Studies

Since 1990, several reviews have been written about the treatment of GAD (Barlow et al. 1997; Borkovec and Whisman 1996; Butler and Booth 1991; Chambless and Gillis 1993; Durham and Allan 1993). These reviews have focused on cognitive and behavioral techniques for alleviating worry and tension and have concluded that these techniques generally are effective. In fact, the Task Force of the Division of Clinical Psychology of the American Psychological Association, involved with identifying empirically supported treatments, found that only techniques used in cognitive-behavioral therapy (CBT) meet criteria to be included as empirically supported treatments for GAD (Chambless et al. 1998; Woody and Sanderson 1998). Preliminary evidence (Crits-Christoph et al. 1996; Durham et al. 1994) suggests that both long- and short-term psychodynamic treatments for anxiety disorders may be effective, but adequate controlled studies have yet to be conducted. Therefore, consistent with the literature, our review emphasizes CBT.

Previous Reviews

In a review of the outcome literature on psychotherapy for GAD, Butler and Booth (1991) concluded that 1) CBT, behavior therapy, and nondirective psychotherapy were all better than no treatment, and 2) gains made at posttreatment appear to be maintained at follow-up evaluation. Thus, GAD appears to be responsive to psychosocial treatments. The authors also stated that CBT is better than behavior therapy at least in retaining patients and retaining treatment gains.

In a meta-analytic review of the literature, Chambless and Gillis (1993) reviewed nine studies evaluating the effectiveness of cognitive therapy for GAD. Most studies used a treatment protocol composed of a combination of cognitive therapy for anxiety (A.T. Beck et al. 1985) with behavioral relaxation techniques, such as progressive muscle relaxation (Bernstein and Borkovec 1973). Seven investigations reported that CBT was more effective than placebo or wait-list control. Follow-up studies showed that gains were maintained. However, because of the number of nonresponders who sought further treatment, follow-ups could not be compared using wait-list or control conditions. Chambless and Gillis reported that the overall effect size for cognitive therapy for GAD was very large (1.69), on average, based on a mean of self-report and evaluator ratings. However, they concluded that these effects were clinically modest and that improvements in treatment were still warranted.

In another review, Durham and Allan (1993) reported that approximately 50% of the patients given a diagnosis of GAD achieved high end-state, or normal, functioning following a trial of CBT. They analyzed 11 studies through 1991 and found that there was a 25% improvement on the "State" section of the State-Trait Anxiety Inventory (Spielberger et al. 1983), which remained at follow-up. On the Hamilton Anxiety Scale (Hamilton 1959), a clinician-rated scale, there was an average of 50% improvement, which was maintained at follow-up. These change scores were significantly different from those of wait-list control subjects. However, the relative efficacy of different therapies was inconsistent. Posttreatment results indicated that 57% of the patients who received CBT had recovered to normal range, whereas 22% of the patients who received behavior therapy alone had recovered. Studies that showed the greatest effects were those that included patients who were not taking any medications. In addition, patients appeared to make greater treatment gains if they were recruited outside of psychiatric settings (e.g., by primary care physicians, newspaper advertisements) (Durham and Allan 1993). The authors also concluded that patients with coexisting Axis I or Axis II disorders were likely to improve less and that patients' negative expectations about treatment also predicted poor outcome.

A comprehensive review and meta-analysis of treatment outcome studies for GAD conducted by Borkovec and Whisman (1996) outlined a variety of important strengths and limitations. Their primary conclusion was that all psychosocial treatments evaluated to date were more effective than no treatment. Four of six studies found no difference between behavior therapy and CBT at posttreatment, but three of four studies evaluated showed long-term maintenance and gains for the CBT group only. Borkovec and Whisman (1996) used meta-analytic procedures that differed slightly from those of Chambless and Gillis (1993) (analyzing composite data for the former, analyzing individual measures common across studies for the latter) and concluded that CBT appears to be the most effective

treatment for GAD. They reported large effect sizes ranging from 0.94 to 3.63 for CBT and 0.69 to 2.76 for behavior therapy. Nonspecific treatment and cognitive therapy also were reported to have large effect sizes. However, the conclusion was based on only one or two studies, as opposed to the six studies used for CBT and behavior therapy.

In a review of the same literature, Barlow and Lehman (1996) and Barlow et al. (1997) concluded that the most effective psychosocial treatment components for GAD are a combination of applied relaxation and cognitive therapy for anxiety disorders (i.e., CBT). Although Borkovec and Whisman (1996) and both reviews by the Barlow group noted that studies have shown that patients who met DSM-III-R criteria for GAD also were likely to meet DSM-IV criteria, they did not comment on the fact that 5 of the 11 studies they evaluated were published in 1988 or before, predating the use of DSM-III-R (DSM-III criteria were markedly different from DSM III-R and DSM-IV criteria). Because these studies have been previously reviewed, we focus our attention on the most contemporary studies. Thus, our review presents data and discusses only studies that used DSM-III-R, DSM-IV, or current Research Diagnostic Criteria.

Newer Studies

Several studies have been conducted since DSM-III-R was published (Table 12–1). Most studies used CBT and at least one other treatment group, a minimum of a 6-month follow-up assessment, and a variety of outcome measures, usually a combination of self-report and clinician-rated measures. We calculated percentage improvement by subtracting posttreatment averages from pretreatment averages and then dividing by the pretreatment averages. Data were gathered from information provided in published or presented reports of the research. Self-report and clinician-rated measures were separated because each type of information can be substantially different (i.e., a clinician may see improvement when a patient does not, or vice versa). Whether authors noted improvement, no change, or relapse during follow-up periods is noted next in the table. Finally, dropouts are presented in the last column. It is important to note that most percent improvement scores are treatment completer analyses and could be substantially different as intent-to-treat analyses.

Possibly because the eight studies used a variety of different methodologies and outcomes measures, a relatively wide range of improvement was found across the studies. Percent improvement was rated consistently greater by blind clinicians than by patients' self-reports. Clinician-rated improvement was between 34% and 68% for patients who participated in CBT, and self-report measures yielded between 16% and 71% improvement. In addition, four of six studies showed further improvement at follow-up, whereas two showed no change. Behavior therapy or relaxation yielded slightly lower effects, with clinician ratings ranging between 17% and 61% and self-report measures showing between 11% and 42% change. Two studies showed continued improvement, two showed maintained gains, and one reported deterioration at follow-up. The only other group reported in several of the studies was wait list, which had either no change or deterioration at both posttreatment and follow-up. See Table 12–1 for more details.

Six studies have not been covered in previous reviews and, thus, are discussed in more detail because they provide important information about the treatment of GAD. The study by Durham et al. (1994) is the only study that has evaluated both cognitive and psychodynamic therapies for GAD and is the first study discussed here. Second, Crits-Christoph et al. (1996) conducted an open trial examining the effects of short-term psychodynamic therapy for GAD. Third, follow-up reports from White and Keenan (1992, 1997) and White (1998a, 1998b) showed that treatment gains were maintained in a short-term, group format of CBT. Fourth, Ladouceur et al. (2000) recently reported preliminary results of a new variant of CBT for GAD. The final two studies (Borkovec et al. 1995; Sanderson et al. 1994a) addressed issues of comorbidity of Axis I and Axis II disorders, respectively.

Durham et al. (1994) compared CBT with anxiety management (a behavioral technique) and psychodynamic therapy. One hundred ten patients with DSM-III-R GAD diagnosed with a structured interview were divided into five groups: 1) brief cognitive therapy (average of 9 sessions), 2) extended cognitive therapy (average of 14 sessions), 3) brief analytic therapy (average of 8 sessions), 4) extended analytic therapy (average of 16 sessions), and 5) anxiety management training (average of 8 sessions). Patients who received CBT improved the most, patients who received relaxation strategies also improved but not as much, and patients who received psychoanalytic psychotherapy improved the least. Patients who received psychoanalytic treatment deteriorated on three measures, although not significantly, whereas patients in the CBT and behavior therapy groups improved on all measures at posttreatment

TABLE 12–1. Generalized anxiety disorder treatment studies that used DSM-III-R or DSM-IV criteria

Reference; follow-up period	Conditions *(n)*	Measures	% Improved	Follow-up	Dropouts
Butler et al. 1991; 6 months	CBT (19) BT (19) WTL (19)	BAI, STAI, Leeds, SelfA, HamA, AssessA, SelfD, AssessD, DAS, CCL, BDI, SPQ	CBT Cl: 49.7 SR: 39.7 BT Cl: 17.0 SR: 16.1 WTL Cl: 8.5 SR: –0.7	+ +	0 1 0
Barlow et al. 1992; 24 months	CBT (12) AR (16) CT (17) WTL (20)	HamA, HamD, STAI, CSAQ, EPI, BDI, FQ, SSS, monitoring	CBT Cl: 34.9 SR: 28.8 AR Cl: 50.7 SR: 33.4 CT Cl: 45.8 SR: 18.8 WTL Cl: –13.8 SR: 0.7	0 0 0	1 4 6 10
White 1998a, 1998b; White and Keenan 1992, 1997; 6 months, 2 years, 3 years, 8 years	CBT (26) BT (31) CT(26) PL (10) WTL (11)	STAI, DAS, FSS, BDI, MSPQ, SelfA	All SR CBT: 20.3 BT: 26.7 CT: 27.5 PL: 21.6 WTL: –3.4	+ + + – –	5 4 5 0 0
Borkovec and Costello 1993; 12 months	CBT (22), AR (23), ND (21)	HamA, HamD, BDI, AssessA, Relax, STAI, Zung, PSWQ, monitoring	CBT Cl: 68.2 SR: 39.3 AR Cl: 61.5 SR: 42.9 ND Cl: 42.1 SR: 23.2	+ – +	4 5 2

TABLE 12–1. Generalized anxiety disorder treatment studies that used DSM-III-R or DSM-IV criteria *(continued)*

Reference; follow-up period	Conditions *(n)*	Measures	% Improved	Follow-up	Dropouts
Durham et al. 1994; 6 months	CBT short (20) CBT long (15) BT short (16) PSA short (15) PSA long (14)	AssessA, SAS, HamA, BSI, STAI, BAI, BDI, DAS, SES, monitoring	CBT Cl: 41.3 Short SR: 16.0 CBT Cl: 43.1 Long SR: 19.3 AR Cl: 35.2 SR: 11.3 PSA Cl: 35.8 Short SR: 13.8 PSA Cl: 27.4 Long SR: 3.3	+ + 0 – +	1 4 9 10 6
Sanderson et al. 1994a	CBT w/o PD (16) CBT w/PD (16)	BAI, BDI	w/o PD: 71.8 w/PD: 62.7	NA	3 7
Crits-Christoph et al. 1996	SEP (26)	HamA, HamD, BAI, BDI, PSWQ, IIP	SEP Cl: 47.2 SR: 35.4	NA	3
Ladouceur et al. 2000; 6 months, 12 months	CBT (14) WTL (12)	PSWQ, WAQ, BAI, BDI, ADIS-IV, SORS	CBT Cl: 58.6 CBT SR: 47.2	0	0

Note. ADIS-IV = Anxiety Disorders Interview Schedule for DSM-IV; AR = applied relaxation; BT = behavior therapy; CBT = cognitive-behavioral therapy; CT = cognitive therapy; ND = nondirective therapy; PD = personality disorders; PL = placebo; PSA = psychoanalytic therapy; SEP = supportive-emotive psychodynamic therapy; WTL = wait list; 0 = no change; - = negative change; + = positive change; Cl = clinician ratings average; Sr = self-report average; AssessA = assessor rating of anxiety; AssessD = assessor rating of depression; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BSI = Brief Symptom Inventory; CCL = clinicians' checklist; CSAQ = Cognitive Somatic Anxiety Questionnaire; DAS = Dysfunctional Attitudes Scale; EPI = Eysenck Personality Inventory; FQ = Fear Questionnaire; FSS = Fear Survey Schedule; HamA = Hamilton Anxiety Scale; HamD = Hamilton Rating Scale for Depression; IIP = Inventory of Interpersonal Problems; Leeds = Leeds Scale for Self-Assessment of Anxiety and Depression; MSPQ = Modified Somatic Perception Questionnaire; NA = not assessed; PSWQ = Penn State Worry Questionnaire; Relax = Reactions to Relaxation and Arousal Questionnaire; SAS = Social Adjustment Scale; SORS = Significant Others Rating Scale; STAI = State-Trait Anxiety Inventory; SelfA = self-rating of anxiety; SelfD = self-rating of depression; SES = Self-Esteem Scale; SPQ = Subjective Probability Questionnaire; SSS = Subjective Symptom Scale; WAQ = Worry and Anxiety Questionnaire; Zung = Zung Self-Rating of Anxiety Scale.

and follow-up. Consistent with previous findings, patients continued to improve after CBT was terminated. However, note that fewer than 10% of each group was considered "better," or fully recovered (a conservative measure of improvement), at posttreatment and at follow-up. About 60% of those patients who received CBT were considered in the normal range of functioning (within one standard deviation of normal on various measures) at follow-up, whereas approximately 30% of the applied relaxation group and approximately 20% of the psychoanalytic group achieved the same status. Finally, the authors reported that patients who received only half the number of sessions of treatment fared as well as those who received a full course of treatment.

This study had several strengths. First, the authors measured patients' expectancies of recovery through therapy, which showed that patients in both CBT and relaxation training had greater expectations of improvement than did those in the psychoanalytic groups after the third treatment session. In addition, they used well-trained therapists who were strong believers in their theoretical perspectives, thus eliminating experimental bias for any one treatment. However, the study had several weaknesses as well. The researchers did not use treatment manuals and did not conduct adherence or competency ratings to ensure that the therapists in fact provided the said treatment components. Also, the reliability of the diagnosis of GAD was not confirmed. Finally, pretreatment levels of severity were higher for psychoanalytic treatment groups (a reported statistical trend), but this was not adjusted for in statistical analyses.

Crits-Christoph et al. (1996) conducted an open clinical trial of their newly developed short-term psychodynamically oriented treatment for GAD. Because this was the only trial that used treatment manuals, adherence ratings, and carefully trained therapists for a psychodynamic treatment focused specifically on GAD, it is considered here in detail despite the fact that we endorse randomized clinical trials before making any firm conclusions about its efficacy. Crits-Christoph et al. described the treatment as supportive-expressive psychodynamic therapy (SEP). SEP is grounded in psychodynamic theory, suggesting that anxiety is related to conflictual interpersonal attachment patterns and incomplete processing of past traumatic events. The authors cite Borkovec (1994), indicating the relevance of current research supporting this notion. The treatment focused on conflicts in relationships through examining the interpersonal desires of the patient, reactions of others to these desires, and consequences of these reactions. Relationships explored included current and past relationships as well as the therapeutic alliance. In SEP, the proposed mechanism of change is through working with the patient on exploring alternative methods of coping with feelings and interpersonal conflicts. SEP orients the therapist to deal with hypothetically specific GAD-oriented wishes, mechanisms of defense, and resistances. In addition, the influence of termination on the patient is explored in depth.

A total of 26 patients with GAD (diagnosed by structured interview) were treated by five therapists trained in SEP. Three patients dropped out. Posttreatment measures indicated significant improvement in all areas. Seventy-nine percent of the patients did not meet criteria for a diagnosis of GAD at posttreatment. Overall effect sizes were similar to those calculated for CBT and nondirective psychotherapy by Borkovec and Whisman (1996). Crits-Christoph et al. (1996) found that expressive techniques were more related to change than supportive techniques were. Thus, preliminary data suggest that this new, innovative psychodynamic therapy may be effective for patients with GAD.

Ladouceur et al. (2000) reported on a new variant of CBT, which was shown to be effective compared with a wait-list control group. This treatment was designed to target a primary feature of GAD: the inability to tolerate uncertainty (see Dugas et al. 1998 for a detailed description of the model). Topics of worry were dichotomized into either immediate concerns or remote concerns. Immediate concerns were challenged with problem solving and cognitive restructuring (decatastrophizing and realistic estimation of probability; techniques described below). Remote concerns were treated with worry exposure and worry behavior prevention (described below). At posttreatment, 20 of 26 (76.9%) subjects no longer met criteria for GAD, and 14 (53.8%) subjects met criteria for high response status and high end-state functioning. At 6- and 12-month follow-ups, 20 patients did not meet criteria for GAD. Twelve patients met criteria for both high response status and high-end state functioning at 6 months, and 14 patients met these criteria at 14 months. Effect sizes appeared to be somewhat higher than in previous studies. This treatment appears to be a promising extension of the work on CBT for GAD; thus, further investigation is warranted.

White (1998a, 1998b) presented follow-up results to his 1992 randomized clinical study demonstrating that treatment gains were maintained at 2-, 3-, and 8-year follow-ups. Essentially, their active treatment was group CBT conducted didactically in six 2-hour sessions. Throughout treatment, patients were encour-

aged "to be their own therapists." The authors stated that they have been conducting such treatment with as many as 60 people in a group and believe that a self-help model for treating anxiety may be effective, especially for populations in which access to mental health services is limited or psychotherapy is stigmatized. In light of the current health care environment, a notable aspect of this treatment is that it provides standard CBT strategies in a cost-effective manner, with results comparable to those of individual treatments. White and Jones (1997) also are attempting to create a computer-based service delivery system, which has facilitated positive change in patients, and a self-help procedure known as *Stresspac* (White 1998b). As the authors themselves note, this type of treatment may be useful for many patients but probably would not benefit more severe or disorganized patients often seen at outpatient mental health clinics. Certainly, determining which patients may respond to a short-term, focused approach administered by oneself or computer is an area worthy of further evaluation.

Effect of Comorbidity on Outcome of Generalized Anxiety Disorder

Although some of the studies described in the previous sections included patients with a variety of comorbid diagnoses, only four published studies have examined the effect of comorbid disorders on the treatment of GAD. Borkovec et al. (1995) found that comorbid anxiety disorders tended to remit when treatment focused on GAD. Of 55 patients with a principal diagnosis of GAD, 23 (41.8%) were rated as having at least one clinically significant comorbid Axis I diagnosis (patients with major depression had been ruled out of the study, thus decreasing the overall rate of comorbidity). At 12-month follow-up, only two patients retained a clinically significant comorbid diagnosis, suggesting that in many cases comorbid anxiety disorders may not need to be addressed directly. Furthermore, Ladouceur et al. (2000) reported that their sample of 26 patients had multiple comorbid diagnoses, most commonly specific phobia and social phobia. At pretreatment, patients had an average of 1.6 additional diagnoses, while at posttreatment and follow-up, they had significantly fewer (an average of 0.4) additional diagnoses.

Sanderson et al. (1994a) examined the influence of personality disorders on outcome and found that CBT treatment effects were equivalent for GAD patients with and without personality disorders. However, patients with personality disorders were more likely to drop out of treatment. Thirty-two patients with diagnoses of GAD were separated into two groups, with (n=16) and without (n=16) personality disorders. Of the 10 dropouts, 7 were given a diagnosis of a personality disorder. Effect sizes of treatment completers in both groups were similar to those mentioned by Borkovec and Whisman (1996). In light of these data, it appears that attention should be paid to issues related to dropout in patients with personality disorders (e.g., difficulties forming relationships).

In a study that focused on treating patients with principal diagnoses of panic disorder, Brown et al. (1995) reported that GAD remitted when the focus of treatment was on panic attacks in patients with a comorbid diagnosis of GAD. Of 126 patients with panic disorder, 32.5% received an additional diagnosis of GAD. Comorbidity did not appear to influence completer status but did appear to influence initial severity of panic. Of the 57 patients available for follow-up analyses, 26.3% were given diagnoses of GAD at pretreatment, whereas only 7.0% were given such diagnoses at posttreatment, 8.8% at 3-month follow-up, and 8.8% at 24-month follow-up. Thus, 11 of 15 (73.3%) patients did not meet criteria for a clinical diagnosis of GAD at posttreatment, and gains were maintained throughout follow-up assessments. Considering that the strategies used in CBT for panic disorder are similar for GAD, it is not surprising that the treatment would generalize to other anxiety symptoms as well (Sanderson and McGinn 1997).

Psychosocial Techniques for Generalized Anxiety Disorder

Several techniques are involved in the treatments in the above-mentioned studies that appear to have positive additive influence to treatment outcomes. (For detailed descriptions of these techniques, see Brown et al. 1993; Craske et al. 1992.) These techniques include psychoeducation, self-monitoring, cognitive restructuring, relaxation, worry exposure, and worry behavior control. Of course, these techniques should be delivered in the context of a good therapeutic alliance. Each is discussed below.

Psychoeducation

As in most cognitive-behavioral treatments, psychoeducation about GAD is an important aspect of therapy. A number of rationales exist for starting treatment with education about anxiety and worry. First, we believe

that knowledge is an important factor in change. Many patients who have come in for treatment have never been told their diagnosis and frequently have misconceptions about their disorder (e.g., that anxiety will lead to psychosis) and misunderstandings about common responses (e.g., physiological, emotional) to worry and stress (e.g., that all worry is bad or that increased heart rate means that you are more likely to have a heart attack). In addition, some patients want a greater understanding of why they are anxious and what they can do about it. Although educating patients about the biopsychosocial model of anxiety (Barlow et al. 1996; Borkovec 1994) will not result in a "cure," some patients experience great relief in knowing that their experiences are not uncommon, that considerable knowledge exists about the etiology and phenomenology of GAD, and that treatments are available designed specifically for their difficulties. Finally, providing education about GAD is a way to review the treatment rationale and, thus, may facilitate treatment compliance.

We recommend that psychoeducation be provided first in a written form (e.g., via a brochure such as the "Generalized Anxiety Disorder Brochure" available through the Anxiety Disorders Association of America) and then followed up in a session. During the session, questions are answered and the information is reviewed in a manner making the information personally relevant to the patient.

Self-Monitoring

Self-monitoring is one of the most basic, yet essential, parts of cognitive-behavioral treatment. Monitoring is used as both an assessment procedure (to identify the context and content of worry) and a treatment strategy (becoming aware of patterns and focusing on worry and anxiety may lead to reduction in worry and anxiety). The basic concept of monitoring is that each time the patient feels anxious, he or she should record when and where the anxiety began and the intensity of the experience, including symptoms that were present. The patient can monitor his or her experience on a full sheet of paper that contains the entire week or record one situation or day at a time. The amount of information gathered may vary with each patient, according to each individual's abilities and needs. It should be noted that avoidance of monitoring is seen as detrimental to treatment because of the likelihood that the patient is avoiding anxiety. Thus, we prefer to simplify and problem solve to attain compliance rather than eliminate the monitoring altogether.

To enhance compliance, the therapist should inform the patient of the reasoning behind the monitoring: to help elicit specific patterns that occur and lead to worry episodes, to obtain a good estimate of current symptoms, to be able to notice effects of treatment on symptoms, and to further examine worry (e.g., cognitions, behaviors). The basic aspects of worry monitoring are date, time began, time ended, place, event (trigger), average anxiety (from 1 [minimal] to 8 [extremely distressing]), peak anxiety (1–8), average depression (1–8), and topics of worry. Once cognitive restructuring is introduced, monitoring the specific thought process involving worries is added.

Cognitive Therapy: Restructuring the Worry

As stated earlier, worry is a predominantly cognitive process, thereby making cognition an important aspect to address. Cognitive therapy is an effective strategy for this purpose. Patients with anxiety disorders, and with GAD in particular, overestimate the likelihood of negative events and underestimate their ability to cope with difficult situations (A.T. Beck et al. 1985). These "cognitive distortions" can play a major role in the vicious cycle of anxiety, and they accentuate the patient's feelings of danger and threat. Thus, cognitive therapy targets the faulty appraisal system and attempts to guide the patient toward more realistic, logical thinking.

The idea of cognition and its influence on anxiety is reviewed in the introduction to therapy and the psychoeducation discussion. Threaded throughout the whole biopsychosocial model is the fact that cognition plays a major role in eliciting and perpetuating the cycle of anxiety. Cognitive restructuring (J.S. Beck 1995) is introduced in detail by discussing the concepts of automatic thoughts, anxious predictions, and the maintenance of anxiety through unchallenged/unchecked negative predictions about the future.

Automatic thoughts are described as learned responses to cues that can occur so quickly that they may be outside of one's awareness. However, these cognitions can create, maintain, and escalate anxiety if their content contains information with a danger-related theme. Thus, the patient is taught to observe his or her own thoughts at the moment of anxiety (or immediately after) and to assess what cues may have brought on the feeling and to elaborate on what thoughts were going through his or her mind. The goal is to bring the thoughts into awareness. Initially, the thoughts are not immediately challenged but collected as data to determine common thoughts that occur during worry. In ad-

dition to self-monitoring during anxiety episodes, anxious cognitions are accessed within the therapy session through Socratic questioning (asking questions to lead the patient to uncover his or her thoughts during anxiety-provoking situations), role-playing (if worry occurred during a social interaction, playing the role of the friend and replaying the event in the session), and imagery (trying to visualize a worry-provoking event to access thoughts and fears). Increases in levels of anxiety either in or outside of the session are opportune times to monitor "hot" cognitions. This often needs to be modeled by filling out a thought record and helping the patient elicit thoughts (e.g., "I won't be able to do the homework right") in session before patients can accurately monitor their thoughts for homework. It is often helpful to warn patients that monitoring thoughts can provoke anxiety because one is focusing on anxious cognitions. It should be explained that exposure to such thoughts, while uncomfortable, is necessary for change.

Once thoughts have been monitored sufficiently to determine frequency and themes, categories of distorted thinking are introduced. Several cognitive distortions have been identified as common in patients with GAD, the three most common being probability overestimation, catastrophizing, and all-or-none (black-and-white) thinking (A.T. Beck et al. 1985; Brown et al. 1993).

Frequently, many distortions may exist in one statement. In our clinical experience, it can be very helpful to address all of the distortions in each statement. This will help the patient have a "fully loaded armamentarium" against anxious thoughts. A patient may remain anxious after challenging a thought focus on a single type of distortion because he or she is still apprehensive because of another distortion. Thus, we believe that the most effective strategy is to thoroughly process all cognitive distortions. For example, a patient presents with a worry statement that he is not going to be able to pay the rent on time because he thinks that his paycheck will come in the mail late. We would have the patient evaluate the probability that he will not pay the rent based on past experiences of receiving his paycheck, evaluate the consequences of his paying the rent late, and evaluate his belief that if he is 1 day late with the rent, it is as if he will never pay it. Thus, the one worry may contain all three categories of distortions. Challenging in this fashion focuses on automatic thoughts. This may be sufficient for some patients, but for others, it may be necessary to examine core beliefs (i.e., consistent thought patterns about oneself, the environment, or the future) (J.S. Beck 1995).

Relaxation

Relaxation exercises are an important component of most CBT-oriented treatments for GAD. The function of the relaxation exercises is to reduce the physiological correlates of worry and anxiety by lowering the patient's overall arousal level. Relaxation clearly reduces arousal, but it may play other roles as well. First, relaxation may help broaden the focus of one's attention. Anxiety tends to narrow attentional focus (Barlow et al. 1996); thus, as a result of its anxiety-reducing property, relaxation may widen the scope of attention and, therefore, increase the patient's ability to consider more alternatives in an anxiety-provoking situation. In addition, relaxation may serve as a distraction. As a sole method, distraction is not effective because by constantly avoiding anxious cognitions, patients are subtly supporting their belief that their thoughts are threatening and/or harmful. However, distraction can be an effective tool when the GAD patient is "stuck" in a worry pattern and needs to break the perseverating thoughts. Finally, contrary to the above concepts and conventional wisdom that view relaxation solely as a coping strategy, relaxation may at times facilitate the activation of anxious thoughts that are otherwise not being processed (Borkovec and Whisman 1996), thereby assisting in exposure to the anxious thoughts. This may explain why some patients describe becoming *more* anxious when initially engaging in relaxation exercises. Specifically, because worrying prevents processing of more fearful information (see Borkovec and Hu 1990) and relaxation helps reduce the "protective" worry, it may ultimately aid in exposure to fearful thoughts, ideas, or images that were not fully processed through or the result of worry.

Whether it be for any of the above reasons or alternatives not discussed here, relaxation clearly helps patients with GAD. Most recent methods of relaxation have adapted a flexible concept of teaching relaxation rather than insisting on any particular method. Thus, although progressive muscle relaxation techniques are emphasized for most patients and have the most empirical support, if a patient prefers another method and is able to use it effectively, then we recommend continued use of that strategy. At times, a combination of relaxation techniques is also encouraged, depending on the needs of the patient. Thus, yoga, transcendental or other types of meditation, and tai chi are all acceptable, especially if the patient is already engaged in such activities and/or if progressive muscle relaxation does not appear effective.

There are a couple of caveats to be noted about conducting progressive muscle relaxation. First, the goal is to have the patient feel relaxed. Although similar procedures are used to help patients with insomnia, the goal here is not to have the person fall asleep. Second, this procedure is similar to those used in initiating a hypnotic trance; because of this, patients may react to the procedure with anxiety, fearing a "loss of control." It is important to explain to the patient the difference between hypnosis and relaxation as used in CBT for GAD is that in progressive muscle relaxation, the focus is on awareness of bodily sensations. Hypnosis has the goal of distracting to the point of reaching a trance state. This would be counterproductive in treating GAD because these patients already are distracted from aversive states through worry. Our goal is facilitated exposure to worry-provoking stimuli, not avoidance.

Worry Exposure

Another technique that recently has been developed but has not gained empirical support to date is worry exposure. As noted above, perpetuation of worry in GAD patients may be caused by ineffective processing, which is a result of avoiding concentration on the worry itself. Instead of focusing on a worry, patients attempt to avoid fully processing the worry through various behaviors (discussed below), as well as through constant shifting of worries. Thus, Brown et al. (1993) described a technique in which patients purposely expose themselves to both worry and images associated with the worry for an extended period. The concept is to have the patient activate the worst possible outcome in order to process it and habituate to the anxiety associated with it. Habituation of the anxiety is facilitated through cognitive challenging after the patient focuses on the image for 20–30 minutes. Borkovec et al. (1983) developed a similar technique referred to as *stimulus control.* In this technique, patients are asked to postpone worrying when it begins to occur, make a list of the worries that occur, and then set aside an hour in the evening to worry. The two procedures have subtle differences, but the basic mechanism of action may be the same. If, as suggested earlier in this chapter, the function of worry is similar to agoraphobia or compulsions, then repeated exposure will cause extinction.

Worry Behavior Control

Many patients who worry may behave in ways to try to avoid it. As stated earlier in this chapter, uncontrollable worry, although an aversive experience, may serve the function of avoiding an even more intolerable experience (i.e., by focusing on the worry instead of the other experience). Behaviors that facilitate the avoidance of the worry itself may then result in avoidance of both the anxiety created by worry and the experience avoided through worrying. According to this rationale, the patient's preoccupation with worry and its reduction distracts him or her from the original source of the negative state (e.g., fear, depression). Therefore, eliminating worry behaviors allows the patient to fully experience and process the worry.

To prevent worry behaviors, the patient carefully monitors what he or she does when he or she notices the onset of worry. Both subtle and explicit variants of these avoidance behaviors are detected through careful monitoring, assessment, and questioning. Then, similar to the technique of response prevention used in the treatment of obsessive-compulsive disorder, the patient is asked to refrain from these behaviors and instead to use the techniques described earlier to cope with the worry. If many behaviors are involved or if the patient is too anxious to just give up the worry behaviors, hierarchies are created to assist the patient in systematically giving up the behaviors, starting with easier ones and moving on to more difficult behaviors, making the task considerably less overwhelming (e.g., checking the child's forehead once daily, then every other day, and so on).

Future Directions

As noted in this chapter, the concept of challenging worries through problem solving, cognitive restructuring, and worry exposure is not sufficient for all patients with GAD. If we conceptualize worry as a reaction to an underlying affective state, then elimination of worry will be helpful to only those patients who have sufficient coping skills and strategies to deal with whatever states the worry exposes them to. That is, just as exposure is helpful in agoraphobia, most cognitive-behavioral treatments of panic work by providing coping skills that will be used instead of avoidance strategies. If some patients with GAD are avoiding affect (Yamas et al. 1997), then simply eliminating the worry through relaxation and cognitive techniques will not work unless they are taught other strategies to deal with the triggers for the affect. Borkovec (1997) recently proposed that interpersonal strategies (i.e., Safran and Segal 1990) be tested in addition to cognitive techniques to determine whether processing of interpersonal diffi-

culties facilitates activation and modification of affective structures (Foa and Kozak 1986).

In a similar notion, we have recently been working on applying schema-focused therapy to those patients who have not responded to traditional CBT (McGinn et al. 1994). This approach focuses on addressing underlying "early maladaptive schemas," which theoretically influence current symptomatology. Schemas are defined as persistent beliefs one develops about the self, based on formative experiences (which are often recurrent). Negative or faulty interpretations of positive and negative life experiences may lead to lifelong cognitive, behavioral, and emotional patterns of interacting with others and the environment. Based on our observations of patients with GAD, we hypothesize that they may have schemas that include unrelenting standards (the belief that one needs to be the best or perfect at everything he or she does), vulnerability to harm (the belief that the world is a dangerous place and one can easily be hurt in it), and emotional inhibition (the belief that expressing one's emotions is dangerous to the self or others and must be prevented). We have previously hypothesized that CBT nonresponders may be patients who fit into the characterological model of GAD, and, thus, an approach that focuses on these core issues may be warranted (McGinn et al. 1994). However, it is important to note that at this point, this is based on our clinical experience and not research data. Our recommendation for treating GAD is to begin with the standard CBT approach and to apply the schema-focused approach to those patients who have not responded.

Conclusion

A considerable amount of progress has been made in the treatment of GAD, especially considering that it only recently became a formal Axis I disorder. The progress is in part a result of the refinement in the diagnosis through the development of DSM III-R and DSM-IV, which has allowed for more accurate diagnosis. In addition, advances in the understanding of the nature and function of worry have allowed investigators to develop treatments that directly target these mechanisms. Some of the most innovative work to further increase the effectiveness of CBT is focusing on facilitating emotional and interpersonal processing of information. The direction of the future appears to be initially treating patients with CBT and then following up with interpersonal and affective techniques in nonresponders. If assessment allows for prediction of nonresponders, alternative methods of combination may be fruitful. At present, we await the data to make conclusions about these promising methods.

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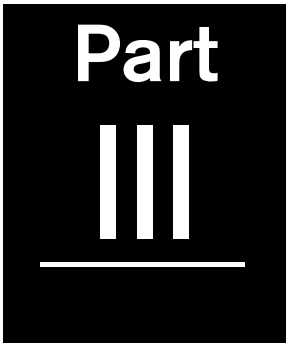

Mixed Anxiety-Depressive Disorder

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13

Mixed Anxiety-Depressive Disorder

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Mixed anxiety-depressive disorder, a diagnostic category proposed in DSM-IV (American Psychiatric Association 1994) for further study, is characterized by dysphoria combined with other depressive and anxiety symptoms that are subthreshold for a diagnosis of a primary affective or anxiety disorder (see Table 13–1). This diagnosis follows the lead of the World Health Organization (WHO), which included a similar subsyndromal diagnosis with anxious and depressed features, mixed anxiety-depressive disorder, in ICD-10 (World Health Organization 1992a). Mixed anxiety-depressive disorder reflects a fresh attempt to address several clinical truisms that have been underrecognized in recent DSMs: anxiety and depression frequently co-occur; patients' disorders do not always fit neatly into the primary diagnostic categories, such as major depression and generalized anxiety disorder (GAD); and subsyndromal symptoms may be clinically significant.

Prior to DSM-III (American Psychiatric Association 1980), the concept of mixed anxiety-depressive disorders had been widely accepted, as evidenced in diagnostic labels such as anxiety-depressive neurosis (Shammas 1977), psychoneurotic depressive illness with associated anxiety or anxiety-depressive syndromes (Houck 1970), anxiety masquerading as depression, or depression with prominent features of anxiety (Verner 1969). The use of earlier psychopharmacological agents (benzodiazepines and tricyclic antidepressants [TCAs]) with seemingly more specific effects for anxious or depressive symptoms and the emphasis in DSM-III on differential categorical classification encouraged an exaggerated dichotomy between the two broad diagnostic categories that has persisted to date.

Despite somewhat successful attempts to separate a variety of anxiety and depressive syndromes, the distinction between GAD and major depression has never been clear-cut, and genetic evidence suggests that these two disorders are outcomes of the same underlying diathesis (Kendler 1996; Kendler et al. 1992). Although, as characterized in DSM-IV, mixed anxiety-depressive disorder reflects symptomatology below diagnostic thresholds for existing anxiety and mood diagnoses (except the residual categories of anxiety disorder not otherwise specified and depressive disorder not otherwise specified), it appears to have clinically important implications for patients' distress and disability and potentially for their treatability. However, the inclusion of mixed anxiety-depressive disorder does not resolve the issue of overlap between anxiety and depression (in particular, GAD and major depression). Rather, it describes a syndrome with milder symptoms of this overlapping construct. We review the development of this new category (about which many research questions remain unresolved, including course, prognosis, and appropriate treatment) in the context of the long-standing debate about the distinction between anxiety and depressive disorders, particularly GAD and major depression.

TABLE 13–1. DSM-IV-TR research criteria for mixed anxiety-depressive disorder

A. Persistent or recurrent dysphoric mood lasting at least 1 month.
B. The dysphoric mood is accompanied by at least 1 month of four (or more) of the following symptoms:

(1) difficulty concentrating or mind going blank
(2) sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)
(3) fatigue or low energy
(4) irritability
(5) worry
(6) being easily moved to tears
(7) hypervigilance
(8) anticipating the worst
(9) hopelessness (pervasive pessimism about the future)
(10) low self-esteem or feelings of worthlessness

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.
E. All of the following:

(1) criteria have never been met for major depressive disorder, dysthymic disorder, panic disorder, or generalized anxiety disorder
(2) criteria are not currently met for any other anxiety or mood disorder (including an anxiety or mood disorder, in partial remission)
(3) the symptoms are not better accounted for by any other mental disorder

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History of Combined Anxiety-Depressive Syndromes

1960s–1970s: The Development of Specific Psychopharmacological Agents

Anxiety and Depression as Overlapping Constructs

Anxiety and depression were not as stringently differentiated in the era prior to DSM-III, when it was widely accepted that many patients presented for treatment with symptoms of both disorders. For example, Roth and his colleagues (1972) noted that "a wide range of workers drawn from many schools of thought have (explicitly or implicitly) upheld the view that anxiety states and depressive disorders merge insensibly with one another or belong to different parts of a single continuum of affective disturbance" (pp. 147–148).

Dichotomization of Anxiety and Depression

The concept of two separate classes of disorders was increasingly accepted by clinicians during the 1960s and 1970s. Roth and his colleagues (1972) in a seminal study investigated the ability to differentiate depressed and anxious patients and found that they could be distinguished despite areas of overlap. Factor analysis of symptoms suggested that two factors appeared to depict patients with either panic disorder or major depression with melancholia, and a third residual factor corresponded to GAD and depression. Historical data and social functioning indicated that the anxious group was more disturbed and disabled by their symptoms. This study led to incorporation of the distinction between panic disorder and major depression in DSM-III. It did not, however, help to resolve the debate regarding the existence of a mixed anxiety-depressive disorder.

The development of pharmacological agents with relatively specific antidepressant or anxiolytic effects, particularly TCAs and benzodiazepines, supported the dichotomization of depression and anxiety. Initial confusion over whether benzodiazepines should be considered an antidepressant class of drugs gave way over time to evidence that they were primarily and specifically useful for anxiety symptoms. In contrast, TCAs were primarily useful for depressive symptoms and for endogenous or severe depression, although data did emerge as to their effectiveness in panic disorder as well.

Rickels and Downing (1972) and Rickels et al. (1970) found that depressed outpatients classified on relative degrees of depression and anxiety differed in their treatment responses to a TCA, a minor tranquilizer, a combination, or placebo. Patients with high depression and high anxiety responded best to a combined regimen of amitriptyline and chlordiazepoxide, whereas amitriptyline alone was indicated for patients with high depression and low anxiety, and chlordiazepoxide was most effective for patients with low depression and high anxiety. Patients with low depression and low anxiety showed no difference between the three active treatments and placebo (Rickels et al. 1970). Neurotic outpatients with low depression and low anxiety suggest the newly proposed category of mixed anxiety-depressive disorder.

Two decades ago, we (Schatzberg 1978; Schatzberg and Cole 1978) reviewed the efficacy of benzodiazepines and TCAs in the treatment of depressive disorders. We suggested then the need to differentiate endogenous from nonendogenous depression, noting that nonendogenous depressive syndromes resemble neurotic anxiety disorders. *Endogenous depression* was defined as depression with symptoms including diurnal variation; terminal insomnia; decreased interest, pleasure, and energy; psychomotor retardation; and lack of reactivity to the environment. *Nonendogenous depression* was considered more heterogeneous but could include histrionic behavior, anxiety, anger, obsessionality, reversed diurnal variation, early insomnia, and variable responses to external stimuli. This latter syndrome is less easily distinguishable from anxiety states, which also are frequently accompanied by mild depressive symptoms. We suggested a continuum ranging from anxiety states to endogenous depression, with nonendogenous depression being intermediate between the two, and concluded that TCAs should be the drug of first choice for either type of depression or a mixed type. Benzodiazepines could be considered as an initial adjunctive treatment for specific symptoms, such as difficulty falling asleep, or for side effects of TCAs, such as agitation.

The Advent of DSM-III and Changes in DSM-III-R: Categorical Classification

Multiple Models of the Possible Relation Between Generalized Anxiety and Depression

Today, several models of the relation between anxiety and depression exist (Stahl 1993; Stavrakaki and Vargo 1986). The unitary position suggests that they are aspects of the same disorder but differ quantitatively or temporally. According to the pluralistic model, anxiety and depression are distinct disorders. A third position states that mixed anxiety and depression is distinct from both primary anxiety and primary depression. A major issue in developing such models is the frequent comorbidity among anxiety disorders and between anxiety and depression. Anxiety and depression can be comorbid in a variety of ways: comorbidity of full-syndrome disorders; one full-syndrome condition with significant subsyndromal overlay from the other; or a residual category of mixed, subsyndromal symptoms.

Wetzler and Katz (1989), in a study of comorbidity, discussed the problems of differentiating anxiety and depression. They distinguished two conceptual stances: a dimensional approach and a categorical approach. The dimensional approach considers anxiety and depression as separate, continuous constructs, whereas the categorical approach views anxiety and depression as syndromes that characterize different groups of patients. They noted that different questions are raised and different statistical techniques would be used to analyze questions flowing from these contrasting approaches. In addition, they noted that attempting to separate depression and anxiety is a somewhat artificial undertaking given their frequent co-occurrence. They studied a multivantaged approach, combining self-report data with nurses' and doctors' ratings of anxiety and depressed mood and found that different vantage points yielded different results for the distinction between these syndromes. Doctors' ratings were best able to distinguish anxiety and depression among severely depressed patients, whereas patients' self-reports reflected temporal distinctions in improvement within symptom clusters in response to treatment. Given the complexity of the relation between anxiety and depression, multiple vantage points have the potential to increase validity in psychological measurement of these two constructs.

DSM-III, DSM-III-R, and Comorbidity

Changes in classifications from DSM-II (American Psychiatric Association 1968) through DSM-IV have reflected then-current views and further influenced our conceptualizations of anxiety, depression, and their overlap. DSM-III contained a more elaborate system for classifying anxiety and depressive disorders than did DSM-II, with more subtypes under each broad syndrome and more specific criteria for each diagnostic category. DSM-III also implemented exclusion criteria

that prioritized diagnoses of depression over diagnoses of anxiety. DSM-III-R (American Psychiatric Association 1987) eliminated this hierarchy for anxiety disorders, thereby making it easier for comorbid anxiety and mood disorders to be diagnosed as such. Despite such efforts, a debate remains about the differentiation of GAD and major depression, which is only heightened by the somewhat arbitrary criteria. For example, the difference in duration of symptoms required for diagnosis of the two disorders (6 months for GAD vs. 2 weeks for major depression) still makes it difficult to assess the true extent of overlap in symptom presentation. In fact, GAD and major depression, as defined in DSM-IV, could easily be applied to the same clinical presentation if both dysphoria and worry were present, except for the distinction in duration of symptoms.

The DSMs, despite efforts to include dimensional constructs, as reflected in Axis V, have primarily used a categorical approach to psychopathology. Residual categories, such as depressive disorder not otherwise specified, and the recently proposed mixed anxiety-depressive disorder and minor depressive disorder offer a method for recognizing clinically significant distress or impairment occurring at lower levels of symptom severity within a diagnostic group. However, it remains to be seen whether a more truly dimensional approach would more accurately and usefully reflect psychiatric phenomena.

Generalized Anxiety Disorder Differentiation

Maser (1998), in his review of the literature on GAD and comorbidity, noted the shifting diagnostic criteria for GAD over time, with respect to both the duration of symptoms (1 month in DSM-III, yielding a 45% prevalence of GAD in a probability sample; 6 months in DSM-III-R and DSM-IV, yielding a 9% prevalence) and the hierarchical rules disallowing GAD from being diagnosed as a comorbid disorder with other anxiety and depressive disorders present in DSM-III but gradually eliminated in subsequent DSMs. Epidemiologic Catchment Area data indicated a 1-year prevalence of GAD alone of 1.30%–2.23%; GAD in the presence of other disorders was diagnosed in 3.42%–4.94% of the sample. In addition, the number of symptoms used to define GAD changed from DSM-III-R to DSM-IV, again with the likelihood that prevalence rates and comorbidity findings will be affected. However, Carter et al. (2001) studied German adults and found only minor differences in prevalence and comorbidity rates for DSM-IV GAD versus DSM-III-R GAD.

Maser (1998) further noted that obtaining comorbidity data from clinical samples confounds questions about the nature and frequency of comorbidity with the fact that treatment-seeking populations are more likely to be experiencing comorbidity and are more likely to be relatively severe cases. With these limitations in mind, he reviewed studies that found that 91% of the clinic patients with GAD had at least one comorbid condition. In this sample, 41% of the clinic patients with GAD had a mood disorder (usually dysthymia). In other clinical samples, rates of comorbid mood disorders ranged from 9% to 45% for major depression and from 29% to 69% for mood disorders defined more broadly (e.g., including dysthymia).

Alternative Conceptualizations

Evidence From Psychometric Studies of Self-Report Instruments: Affect Dimensions

Increasing evidence indicates that depression and anxiety do have common dimensional features or risk factors (e.g., genetics), although discriminating characteristics also may exist. Clark and Watson (1991) and Watson et al. (1988) investigated a tripartite model, in which measures of negative affect, positive affect, and hyperarousal were used to differentiate depression and anxiety. Studies have shown that low state positive affect is a specific feature of depression, whereas positive affect is largely unrelated to anxiety. Hyperarousal or autonomic arousal corresponds to the physiological symptoms of anxiety, such as pounding heart, feelings of constriction, and light-headedness. It is highly relevant to panic disorder and is less clearly temperamental. Negative affect is a common risk factor for both depression and anxiety, and it may reflect, in part, the overlap in phenomenological distress between these two disorders.

Findings From Genetic Studies

Kendler (1996; Kendler et al. 1992) examined genetic and environmental contributions to the frequent comorbidity of GAD and major depression. Lifetime diagnosis was used for the first study, and 1-year follow-up prevalence was used for the second. In a sample of approximately 1,000 female twin pairs, Kendler and colleagues (1992) found that GAD (diagnosed according to modified DSM-III-R criteria) and major depression (DSM-III-R criteria) share a common genetic diathesis. Furthermore, shared environmental experiences, such as shared aspects of family environment, played no role in the etiology of major depression or

GAD. Instead, individual-specific experiences were responsible for whether the genetic diathesis was expressed as major depression or GAD. Kendler (1996) replicated these findings and suggested that different stressful life events might be responsible for the occurrence of major depression and GAD.

Generalized Anxiety Disorder as Anxious Temperament Type

Akiskal (1998) suggested that GAD could be reconceptualized as the extreme manifestation of an anxious temperament type, called generalized anxious temperament. This constellation of traits represents a vigilant stance focused on harm avoidance and is considered narrower in scope than either neuroticism or negative affectivity. It may be associated with increased risk for depression and other disorders (e.g., phobias, substance use). Evidence in support of this view includes the finding that GAD symptoms (e.g., worry, nausea) are lifelong and traitlike, rather than acute, for many individuals. Acute life events may, therefore, provoke a more severe episode (GAD) in the context of long-standing symptoms (generalized anxious temperament).

Advent of Selective Serotonin Reuptake Inhibitors

The development of selective serotonin reuptake inhibitors and other new compounds has provided clinicians with access to treatments that are safer and better tolerated than older categories of antidepressants. Over time, evidence has accumulated that these drugs are effective in treating depression, anxious depression, and panic, and, more recently, GAD. The ability of these drugs to address a range of symptoms facilitates their use in primary care settings, where clinicians may not have the time to clarify complex differential diagnoses. However, this may have negative repercussions for accumulating clinical data on questions such as differential course and prognosis of different presentations of anxiety and depression and may reduce the apparent need for referrals to psychiatrists and other mental health specialists. This broad applicability of newer pharmacological agents may raise questions about distinctions in the underlying biochemical dysregulation of anxiety and depression.

Are Generalized Anxiety Disorder and Major Depression Distinct Presentations of the Same Disorder?

In conclusion, patients often experience symptoms of both anxiety and depression, although our diagnostic system is still evolving toward characterizing these syndromes in a conceptually meaningful and clinically useful way. The use of categorical diagnoses and somewhat arbitrary criteria for diagnoses may hinder our ability to capture the nuances of the relations between these two broad symptom areas. However, research on comorbidity, affect dimensions, genetics, course of illness, and psychopharmacology is contributing to our understanding of the relation between depression and anxiety.

The Development of DSM-IV and the Introduction of Mixed Anxiety-Depressive Disorder

Changes in DSM-IV

Two changes to DSM are reshaping our conceptualization of the relation between generalized anxiety and depression (Stahl 1993). First, GAD was redefined from its former status as a residual anxiety diagnosis (i.e., diagnosed only in the absence of any other anxiety disorder) to a generalized anxiety syndrome with symptoms of mild depression that are less severe than the symptoms of anxiety. Thus, GAD has become more explicitly a mixed disorder. In addition, GAD, since DSM-III-R, has been defined as a chronic disorder, with a minimum of 6 months' duration to warrant the diagnosis. Second, mixed anxiety-depressive disorder has been introduced and defined as a stable core of subsyndromal symptoms that do not reach the threshold for diagnosis of GAD, major depression, or any other full-syndrome disorder. It is unclear whether this syndrome is in fact a stable disorder or whether under stress, it can be exacerbated, leading to an overt anxiety or depressive disorder.

The DSM-IV-TR (American Psychiatric Association 2000) criteria for mixed anxiety-depressive disorder are somewhat different from the ICD-10 criteria. ICD-10 defines mixed anxiety-depressive disorder as having symptoms of both anxiety and depression, with neither more salient than the other and neither at a level that would warrant a separate diagnosis (World Health Organization 1992a). The ICD-10 clinical descriptions (World Health Organization 1992b) offer further specificity by requiring that autonomic symptoms be present and that a significant life change not be associated with the onset of symptoms (in which case, the diagnosis should be adjustment disorder). Finally, the ICD-10 research criteria suggest that researchers may wish to develop their own criteria within the guidelines described above (World Health Organization 1992c).

Effect of Subsyndromal States on Functioning

Many researchers have documented the effect of subsyndromal states on disability. Johnson and his colleagues (1992) used an epidemiological survey and found that threshold diagnoses of major depression or dysthymia resulted in increased service use and social morbidity (medication use, impaired physical and emotional health, time lost from work, and attempted suicide). However, the presence of subthreshold depressive symptoms resulted in higher levels of service use and social morbidity as well, and on a population basis, subthreshold symptomatology resulted in greater social impairment and service cost than did diagnosable disorders. Other researchers (Gotlib et al. 1995; Wells et al. 1989) have obtained similar findings, and Roy-Byrne (1996) concluded that despite a tendency to view GAD as mild, GAD and mixed anxiety-depressive disorder are associated with significant social impairment and role functioning limitations.

Preparations for DSM-IV

The recognition of high levels of comorbidity of full-syndrome anxiety and depressive disorders as well as the ICD-10 inclusion of a subsyndromal, mixed disorder prompted the planners of DSM-IV to consider several questions related to revising existing diagnoses or adding new ones. The work group charged with considering the possibility of including a mixed anxiety-depression diagnosis in DSM-IV delineated two relevant issues (Moras 1989, as cited in Moras et al. 1996). The first issue was whether to include a diagnosis that would correspond to the ICD-10 diagnosis of mixed anxiety-depressive disorder. The second issue was whether DSM-IV diagnoses should be altered to better reflect the overlap between anxiety and depression or whether a new diagnosis should be included to reflect empirical knowledge about comorbid anxiety and depressive disorders. Literature reviews were undertaken to answer these questions.

Evidence for a Subsyndromal Category

Katon and Roy-Byrne (1991) examined literature based on community samples, primary care samples, and psychiatric samples to determine whether a patient population with clinically important symptoms of anxiety and depression that fell below the thresholds for specific DSM-III-R diagnoses (consistent with the ICD-10 description of mixed anxiety-depressive disorder) existed. With respect to community samples, their review found that diagnosable mood disorders occurred in 3%–8% of the population (based on Epidemiologic Catchment Area data), that subsyndromal depression occurred in 13%–20% of the population, and that community members who had depressive symptoms were more likely to have mixed anxious-depressive profiles than more purely depressive profiles.

In their review of studies that used primary care samples, they found higher rates of distress (40%) than diagnosable disorder (25%), suggesting a 15% prevalence of subsyndromal, distressed patients in these settings. Furthermore, the patients with mixed-symptom profiles in this setting did have deficits in functioning.

Finally, a review of studies of psychiatric populations found a subgroup of patients with chronic anxiety and depression (general neurotic syndrome) that was stable, except that increased stress could result in acute exacerbations that led to diagnosable levels of symptoms.

Taken together, these findings suggested that a subsyndromal, mixed-symptom disorder does exist, that it results in meaningful functional impairment, and that it represents a higher risk of developing more severe disorders. Unresolved questions included determination of appropriate criteria, the possibility of lowering the threshold on existing diagnoses to capture this group, and resolution of issues of course and prognosis.

Diagnosis Based on the Tripartite Model

As described above, Clark and Watson (1989, as cited in Moras et al. 1996) presented a new dimensional model for characterizing depressive and anxious syndromes, based on patients' symptomatology with respect to the dimensions of negative affect, positive affect, and hyperarousal. The mixed anxiety-depression category proposed by Clark and Watson represents a more severe symptom profile than the mixed anxiety-depression category currently proposed in DSM-IV-TR. Other authors have called this type of symptom mixture panic-depressive disorder or mixed mood disorder (Akiskal 1990; Moras et al. 1996).

A Possible Comorbid Diagnostic Category

Moras (1989, as cited in Moras et al. 1996), in his review of the literature on comorbidity, focused on concurrent comorbidity rather than lifetime comorbidity. He selected major depression and dysthymia from the mood disorders and included a range of anxiety disorders, such as agoraphobia, panic disorder, GAD, obsessive-compulsive disorder, social phobia, simple phobia, and posttraumatic stress disorder. He found that comorbidity rates varied but that, generally, patients with

anxiety disorders were more likely to have a concomitant depressive diagnosis than were depressed patients to have an anxiety disorder. He concluded that the data did not support the creation of mixed diagnoses that would reflect current understandings of comorbidity.

The work group concluded that field trials should be conducted for the proposed mixed-symptom, subsyndromal disorder; that existing diagnoses should not be changed to reflect comorbidity; and that research should be conducted on the Clark and Watson tripartite model of depression and anxiety to prepare for DSM-V revisions.

Field Trial for Mixed Anxiety-Depressive Disorder

The DSM-IV field trial (Zinbarg et al. 1994) for mixed anxiety-depression was designed to answer four questions: 1) Do patients with subsyndromal symptoms and functional impairment exist? 2) Does medical pathology, rather than psychopathology, account for their functional deficits? 3) What is the breakdown of this population with respect to anxiety symptoms, depressive symptoms, or mixed symptoms? and 4) What is the best way to operationalize the criteria for any subsyndromal diagnosis?

Patients ($N=666$) were studied at five primary care medical sites and two mental health sites, chosen to yield a range of demographic characteristics of the patient population. Patients presenting to primary care clinics were screened for subjective distress with the General Health Questionnaire and the Medical Outcomes Study/Rand Short-Form General Health Survey. Those whose scores were at or above the cutoff and half as many patients whose scores were below the cutoff were interviewed in depth. Every patient presenting to the psychiatry clinics was interviewed. In-depth evaluations included the Anxiety Disorders Interview Schedule—Revised, the mixed anxiety-depression field trial revision of the Hamilton Anxiety Scale and the Hamilton Rating Scale for Depression, and the chronic disease score.

In addition to DSM-III-R diagnoses with previously established criteria sets, diagnoses of anxiety disorder not otherwise specified and depressive disorder not otherwise specified (i.e., sufficiently distressed or impaired to be considered a probable or definite "case" but not better fitting another diagnostic category) were identified. Patients with not otherwise specified diagnoses constituted 11.7% of the patients surveyed, making that group the third largest diagnostic group after panic disorder (29.1%) and GAD (20.2%), just ahead of major depression (11.6%). They were characterized by high levels of impairment or distress (80% met criteria for definite caseness).

A principal components analysis of the Hamilton symptom ratings (anxiety and depression) on all patients yielded three factors, which the investigators labeled *anxiety* (e.g., tension, apprehension), *physiological arousal* (e.g., tachycardia, choking), and *depression* (e.g., helplessness, diminished libido). These components were used to define symptom scales. A fourth symptom scale was constructed of items loading on both the anxiety and the depression components. This scale was labeled *negative affect* and included items such as irritability and fatigue. (It is important to note that this symptom scale does not equate to the trait construct *negative affect*, but the investigators considered their findings to be consistent with Clark and Watson's work identifying three factors [negative affect, positive affect, and hyperarousal] that underlie the constructs of anxiety and depression as measured by self-report instruments.)

Patients in the largest diagnostic groups (anxiety or depression not otherwise specified, panic disorder with agoraphobia, GAD, major depression, and no diagnosis) were analyzed with the symptom scales described earlier. These analyses indicated that the patients with anxiety or depression not otherwise specified could be identified with the negative affect scale. Profile analyses suggested that this negative affect scale characterized the subsyndromal group and differentiated it from the other groups of more established disorders. Although altering the criteria for GAD or major depression would be an alternative that would include many of these patients in existing categories, mixed anxiety-depressive disorder was seen as a more accurate and useful category for these patients. First, mixed anxiety-depressive disorder makes the mixed-symptom profile these patients present with explicit, and second, it increases the likelihood that a diagnosis will be made in these patients. Thus, a proposed criteria set for DSM-IV included symptoms reflective of the overlap between depression and anxiety.

Investigators concluded that at least as many patients had subsyndromal affective symptoms (defined as meeting criteria for anxiety disorder not otherwise specified or depressive disorder not otherwise specified) as had certain well-delineated diagnostic categories; that these patients had meaningful levels of functional impairment; that nonspecific, mixed-symptom profiles were the most common pattern of subsyndromal disorder; and that these patients could be distinguished from patients with GAD, major depression, and panic disorder with agoraphobia.

What Do We Know About Subsyndromal Mixed Anxiety-Depressive Disorder?

Given the decision to include mixed anxiety-depressive disorder as a proposed category in DSM-IV and given the ongoing debate over how to account for comorbidity and overlap between anxiety and depression, epidemiological data and data on clinical course are needed. Although defining a subsyndromal diagnosis of mixed anxiety-depressive disorder does not resolve the big questions about continuity between risk factors, symptoms, and syndromes or about the appropriateness of considering anxiety and depression to be separate or overlapping constructs, it potentially affords an opportunity to characterize a distressed and impaired group that is not currently a focus of attention. However, at this point, little has been established about mixed anxiety-depressive disorder patients. Information on sex, age at onset, chronicity, course, and treatment is scarce or nonexistent. We do have some information on the prevalence of mixed anxiety-depressive disorder (based on different criteria sets) in various settings (see Table 13–2).

Wittchen and Essau (1993) reported results of the Munich Follow-Up Study, including data from a general population sample. They assessed depression and dysthymia, as well as panic disorder, agoraphobia, and simple and social phobias, but not GAD. They found that the prevalence of mixed anxiety-depressive disorder, based on the ICD-10 definition (i.e., the presence of subsyndromal anxiety and subsyndromal depression), was 0.8% in their epidemiological sample, less than that of pure subsyndromal categories (21.9% subsyndromal anxiety and 2.4% subsyndromal depression). In addition, they found that comorbid depression and anxiety, whether above or below diagnostic thresholds, were associated with subjective suffering, functional impairment, and higher health service use than were pure disorders.

Roy-Byrne et al. (1994) used data from the field trial to describe the sample of 267 patients drawn from five primary care settings in the United States, France, and Australia. A brief screen followed by a structured interview found that 5.1% of the patients had subsyndromal symptoms of anxiety and depression (defined as depression not otherwise specified or anxiety not otherwise specified, based on DSM-III-R criteria), accompanied by functional impairment. This prevalence rate was comparable to the prevalence of mood disorders in this sample and about one-fourth the prevalence of anxiety disorders. In addition, the subsyndromal patients had functional impairments comparable to those of the anxiety and mood disorder groups.

TABLE 13–2. Prevalence of mixed anxiety-depressive disorder in specific settings[a]

Reference	Sample type	*N*	Prevalence (%)
Wittchen and Essau (1993)	Epidemiological	1,366	0.8
Roy-Byrne et al. (1994)	Primary care	267	5.1
Sartorius and Üstün (1995)	Primary care	25,916	1.3
Stein et al. (1995)	Primary care	501	2.0

[a]Definitions of mixed anxiety-depressive disorder vary; see text.

Stein and colleagues (1995) studied 501 primary care patients who denied having a current psychiatric diagnosis or receiving current psychiatric treatment. Of these, 78 (15.6%) were systematically interviewed after screening positive for distress on the Beck Depression Inventory (BDI) and/or the Beck Anxiety Inventory (BAI). Of the patients interviewed, 12.8% met the authors' criteria for mixed anxiety-depressive disorder (2.0% of the larger sample). In contrast to DSM-IV requirements, patients with previous diagnoses of anxiety or mood disorders were not excluded from the mixed anxiety-depressive disorder category. In contrast to the ICD-10 definition, autonomic symptoms were not required for a diagnosis of mixed anxiety-depressive disorder. For comparison, 44.9% of the interviewed sample met criteria for any depressive or anxiety diagnosis (7.0% of the larger sample). Mixed anxiety-depressive disorder patients reported levels of disability comparable to those of full syndrome anxiety or mood disorder patients.

Another investigation of the prevalence of mixed anxiety-depressive disorder, as defined in ICD-10, was conducted by Sartorius and Üstün (1995); they used a large data set of 25,916 patients in general health care facilities in 14 countries. A sample of 5,379 patients, including those who scored high and low on the General Health Questionnaire, received in-depth evaluations. In this sample, the rate of depressive disorders was 11.8% and the rate of anxiety disorders was 10.2%. The prevalence rates of subthreshold depression and subthreshold anxiety were 6.5% and 5.0%, respectively. Although there was some variability from country to country, the overall rate of mixed anxiety-depressive disorder was 1.3%.

Boulenger and colleagues (1997), in their review of the literature, estimated that the prevalence of mixed anxiety-depressive disorder ranges from 0.8% to 2.5%

in epidemiological studies and from 5% to 15% in primary care settings. Furthermore, they concluded that longitudinal evidence supports the conceptualization of mixed anxiety-depressive disorder as a risk factor for full syndrome depressive and anxiety disorders.

Controversy About Adding Mixed Anxiety-Depressive Disorder Category

Several authors have addressed the need for and potential problems with adding a new category of mixed anxiety-depressive disorder (Boulenger et al. 1997; Katon and Roy-Byrne 1991; Roy-Byrne 1996; Wittchen and Essau 1993). Beyond providing for compatibility with ICD-10, several arguments for adding mixed anxiety-depressive disorder to the DSM classification have been offered:

- Mixed anxiety-depressive disorder is seen in primary care settings, particularly because anxious and depressed patients tend to present somatic symptoms to their physicians. Identifying this group of patients may help physicians identify patients in need of intervention and reduce excessive or inappropriate medical use. Providing appropriate treatment is particularly important because subthreshold symptomatology can have a marked effect on distress and disability.
- Mixed anxiety-depressive disorder may represent a prodromal or residual phase of a more severe disorder, so identifying this at-risk group may facilitate the development of secondary preventive interventions.
- Mixed anxiety-depressive disorder may be a more appropriate diagnosis than adjustment disorder for some patients, who do not identify a precipitating stressor or who may be particularly reactive to stress (Liebowitz 1993).

Potential problems with the diagnosis of mixed anxiety-depressive disorder have been raised as well. Mixed anxiety-depressive disorder may increase the risk of trivializing distress that is severe enough to affect functioning (Stahl 1993), may overlap too much with adjustment disorder or other DSM diagnoses (Liebowitz 1993), or may become a wastebasket category and discourage more careful diagnosis. This could ultimately impede research and reduce the identification of major depression and other diagnoses requiring prompt, serious, and specific intervention (Liebowitz 1993; Preskorn and Fast 1993). In addition, mixed anxiety-depressive disorder may be an unstable diagnosis leading to episodes of traditional affective or anxiety disorders. Minor depression may provide a subsyndromal diagnostic category adequate to meet clinical needs (Liebowitz 1993). Other authors essentially argue that more effort should be put into distinguishing anxious from depressed patients rather than combining them into one category and offer strategies for making the appropriate primary diagnosis (Clayton 1990; Preskorn and Fast 1993).

Primary Care

It has long been recognized that anxiety and depression are associated with somatic symptoms influencing medical use (Roth et al. 1972). Primary care providers currently prescribe the majority of anxiolytic and antidepressant medications. Negative publicity about benzodiazepine dependence may have reduced the willingness of primary care providers to treat anxiety. Somatic symptoms may be seen as an acceptable route for seeking treatment for anxiety. In contrast, depression may be considered more legitimate and more treatable. It will be important to continue to gather evidence about somatization and medical use among patients with mixed anxiety-depressive disorder.

Clinical Course and Treatment

As alluded to earlier in this chapter, an important and unresolved question about patients meeting criteria for mixed anxiety-depressive disorder has to do with the stability of the diagnosis versus its status as a risk factor for more severe psychiatric illness.

In addition, appropriate and efficacious treatments for mixed anxiety-depressive disorder need to be established. Drawing on the treatment literature for major depression and anxiety disorders, selective serotonin reuptake inhibitors are effective for symptoms of both anxiety and depression. Beginning in the 1980s, the treatment of unipolar conditions has shifted from short-term to continuation therapy to maintenance therapy. If mixed anxiety-depressive disorder proves to be a chronic disorder that responds to selective serotonin reuptake inhibitors, then maintenance therapy is likely to be indicated.

Boulenger and colleagues (1997) suggested that patients who are in a residual phase of symptoms following a previously diagnosable disorder should conform to existing approaches to chronic conditions. According to DSM-IV criteria, these patients would not receive a diagnosis of mixed anxiety-depressive disorder in any event. However, Boulenger et al. pointed out that it is less clear how to treat mixed anxiety-depressive disorder in patients who have never had a psychiatric diag-

nosis in the past. Given the lack of research, particularly with DSM-IV criteria, they suggest that treatments used for mild anxiety and depression be considered.

Despite the lack of conclusive findings on treatment of mixed anxiety-depressive disorder, Zajecka and Ross (1995) and Boulenger et al. (1997) offered tentative recommendations. First, all of the major groups of antidepressants can be considered because they all have some degree of anxiolytic and antidepressant effects. Second, buspirone may be useful because it may have antidepressant effects at higher doses than are typically given for GAD. It is more effective with the psychological than the somatic symptoms of anxiety, and psychological symptoms are more typical in mixed anxiety-depressive disorder. Third, there may be a role for benzodiazepines in treating mixed anxiety-depressive disorder, but they may be insufficient if depressive symptoms are severe and rebound and withdrawal effects are a concern. These authors further reviewed evidence that benzodiazepines are less effective for mild anxiety than for severe anxiety. Finally, combination treatments may be warranted, and cognitive-behavioral psychotherapeutic approaches, including anxiety management, applied relaxation, and cognitive restructuring, that have been established as beneficial in treating GAD may be applicable to mixed anxiety-depressive disorder. Treatment should continue after symptoms have abated, and patients should be monitored for the development of full syndrome disorders.

Other authors have investigated the use of psychotherapy in patients with mixed-symptom profiles. For example, Moras and her colleagues (1993) described two case studies of treatment for comorbid GAD or anxiety disorder not otherwise specified and major depression. They adapted and integrated existing treatments for panic disorder (cognitive-behavioral therapy; Barlow and Craske 1989, as cited in Moras et al. 1993) and major depression (interpersonal therapy; Klerman et al. 1984, as cited in Moras et al. 1993) and found that the approach was promising in one case and less so in the other. Other researchers are investigating the effectiveness of an integration of cognitive-behavioral approaches for depression and anxiety among distressed primary care patients.

Conclusion

We have traced the historical progression of conceptualizations of the diagnostic distinctions between anxiety and depression over the last 30 years, focusing on GAD and depression. Early on, anxiety neurosis was redefined as either panic disorder or GAD, and both anxiety and depression have given rise to more differentiated and more specifically defined disorders. As hierarchical diagnostic rules were relaxed, researchers began to investigate and document the high rates of comorbidity between anxiety and depression. However, shifting criteria for GAD, in particular, have contributed to difficulties in combining findings from studies conducted under different DSMs.

Following the lead of ICD-10, a mixed-symptom, subsyndromal diagnostic category of mixed anxiety-depressive disorder was included in DSM-IV for further study. This reflects our increasing recognition of the common occurrence and disabling effect of subsyndromal states as well as the consistent observations of co-occurring symptoms. However, many questions remain unanswered about mixed anxiety-depressive disorder, including the demographic breakdown of patients with mixed anxiety-depressive disorder; the course, stability, and prognosis associated with the mixed anxiety-depressive disorder diagnosis; and the optimal treatment for mixed anxiety-depressive disorder. Researchers need to address these questions. In addition, fundamental questions of continuity between GAD and major depression must be resolved. These questions have implications for the issue of whether categorical or dimensional approaches best describe the clinical syndromes of anxiety and depression. The subsyndromal diagnosis of mixed anxiety-depressive disorder may facilitate research on these questions of continuity and discontinuity.

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Part

IV

Obsessive-Compulsive Disorder and Related Disorders

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14

Phenomenology of Obsessive-Compulsive Disorder

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Obsessive-compulsive disorder (OCD) is an intriguing and often debilitating syndrome characterized by the presence of two distinct phenomena: obsessions and compulsions (Table 14–1). Although these symptoms have been described for more than a century (Freud 1895/1962, 1909/1955), OCD was considered a relatively rare disorder until the past decade. Fueled by the findings from several epidemiological surveys conducted in the 1980s, which documented surprisingly high prevalence rates of OCD, there has been tremendous interest and a rapid growth in the understanding of the clinical features and treatment of this disorder.

Much of the progress in the epidemiology of OCD over the last decade has centered on confirmation of the high prevalence rates of OCD that were initially reported in the National Epidemiologic Catchment Area (ECA) Survey (Myers et al. 1984; Robins et al. 1984). The ECA prevalence figures have been verified by other studies that used improved methodology (Flament et al. 1988; Rapoport 1989) and by cross-cultural studies that confirmed that the unexpectedly high prevalence of OCD is a worldwide phenomenon (Hwuh and Chang 1989; Orley and Wing 1979; Vaisaner 1975).

Knowledge of the clinical features of the disorder also has expanded significantly in the last 10 years. Treatment centers specializing in OCD have succeeded in enrolling many patients, allowing more sophisticated analyses of phenomenology and comorbidity and the relation of these variables to treatment outcome. Areas receiving attention include range of insight; comorbidity with other disorders, particularly schizophrenia; the relation between OCD and compulsive personality disorders; and the prevalence of mental compulsions. Prospective observational studies of the longitudinal course of OCD have led to further insights into the clinical characteristics and prognosis of the illness. Improvements in methodology, such as the use of control groups, blind clinical assessments, structured interviews, reliable and valid diagnostic criteria, and better database management systems, have aided these analyses. Finally, significant progress has been made in identifying homogeneous subgroups of OCD patients, which should assist in unraveling the etiology of OCD (Jenike 1990) and in the development of more specific and effective treatment strategies. In this chapter, we review the current state of knowledge of the epidemiology and clinical features of OCD. We focus on the phenomenological heterogeneity of OCD and its comorbidity with other Axis I and Axis II disorders.

Epidemiology

The psychiatric literature has contained striking descriptions of patients with debilitating obsessions and compulsions since the fifteenth century. However, until

TABLE 14–1. DSM-IV-TR diagnostic criteria for obsessive-compulsive disorder

A. Either obsessions or compulsions:

Obsessions as defined by (1), (2), (3), and (4):

(1) recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress
(2) the thoughts, impulses, or images are not simply excessive worries about real-life problems
(3) the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action
(4) the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion)

Compulsions as defined by (1) and (2):

(1) repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly
(2) the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive

B. At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable. **Note:** This does not apply to children.
C. The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.
D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an eating disorder; hair pulling in the presence of trichotillomania; concern with appearance in the presence of body dysmorphic disorder; preoccupation with drugs in the presence of a substance use disorder; preoccupation with having a serious illness in the presence of hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a paraphilia; or guilty ruminations in the presence of major depressive disorder).
E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify if:

With poor insight: if, for most of the time during the current episode, the person does not recognize that the obsessions and compulsions are excessive or unreasonable

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the mid 1980s, OCD was considered extremely rare. This perception was based on a epidemiological study by Rudin (1953), who estimated OCD prevalence to be 5 in 10,000 in the general population. Several studies in the 1950s and 1960s conducted to examine the frequency of psychiatric diagnoses in inpatient and outpatient settings reinforced the notion that OCD occurred rarely; OCD made up a small minority (1%–4%) of the total patient pool (Ingram 1961; Kringlin 1965; Pollitt 1957). Some investigators believed that Rudin's figures were probably an underestimate, realizing that patients often did not come to treatment because of fear or shame. In a more recent study, Hantouche et al. (1995) found that 9.2% of 4,364 psychiatric outpatients had a diagnosis of OCD, and 17% had obsessive-compulsive symptoms. These higher figures most likely represent a combination of improved recognition by clinicians and increasing numbers of patients coming into treatment.

The results of a large psychiatric epidemiological study, the National ECA Survey, conducted in the United States in 1984, painted a very different picture of the prevalence of OCD. In this study, OCD was the fourth most common psychiatric disorder, following the phobias, substance use disorders, and major depression, with a 6-month point prevalence of 1.6% and a lifetime prevalence of 2.5% (Myers et al. 1984; Robins et al. 1984).

The same instrument that was used in the ECA survey was used in studies in diverse cultures, including Puerto Rico, Canada, Germany, Taiwan, New Zealand, and Korea, as part of the Cross-National Collaborative Group (Weissman et al. 1994). The lifetime (range,

1.9%–2.5%) and annual (range, 1.1%–1.8%) prevalence rates of OCD were remarkably consistent, with the exception of Taiwan. The prevalence rates in Taiwan were substantially lower than those in all the other sites, paralleling Taiwan's low rates for other psychiatric disorders. Tadai et al. (1995) measured the prevalence of OCD in 424 Japanese students with the Maudsley Obsessional-Compulsive Inventory and found that 1.7% had symptoms that met DSM-III-R (American Psychiatric Association 1987) criteria for OCD.

Although the ECA study has been criticized as having overestimated the prevalence of OCD, some studies in adolescent populations have supported the ECA findings. Flament and colleagues (1988) screened 5,000 high school students with a modified Leyton Obsessional Inventory. Students who scored above a predetermined cutoff on the scale were interviewed by a psychiatrist who was an expert in childhood OCD. Fifteen (0.3%) of the total 5,000 students were given DSM-III-R diagnoses of OCD. The average age of the subjects was 15.4 years, whereas the average age at onset of the disorder is around 20 years. When an age correction was applied, the point prevalence estimate for the general population was 1%. In a similar two-stage study, Valleni-Basile et al. (1994) screened 3,283 adolescents with a self-report screening questionnaire followed by the Schedule for Affective Disorders and Schizophrenia for School-Aged Children. The 1-year incidence rates of OCD and subclinical OCD were 0.7% and 8.4%, respectively. Douglass et al. (1995) found that the 1-year prevalence rate of OCD in 930 18-year-olds, as measured by the Diagnostic Interview Schedule, was 4%. In a similar epidemiological study, Apter et al. (1996) studied 861 Israelis aged 16 years during preinduction military screening. Eight percent of the sample reported spending more than an hour daily on obsessions and/or compulsions.

Some studies have failed to support the ECA findings. Degonda et al. (1993) investigated the longitudinal course of OCD and obsessive-compulsive symptoms over an 11-year period in a Swiss cohort. The prevalence of DSM-III (American Psychiatric Association 1980) OCD in the study was considerably lower than 1%. When a lower diagnostic threshold based on obsessive-compulsive symptoms and social impairment was used, the weighted lifetime prevalence rate for OCD at age 30 was 5.5%. Distinguishing between subthreshold OCD and full criteria OCD is critical in determining the prevalence of OCD in both epidemiological and clinical studies. After screening 861 Israeli military recruits aged 16 years, Apter et al. (1996) concluded that obsessive-compulsive phenomena appear to form a continuum, with few symptoms and minimal severity at one end and many symptoms and severe impairment at the other end. In that study, patients with OCD and subclinical OCD differed significantly from patients without OCD, but not from each other, in distress and mean number of symptoms. Rachman and DeSilva (1978) reported that a high percentage of the non-OCD population have some obsessions and compulsions. Most children also go through developmental stages characterized by obsessive-compulsive or superstitious behavior. Determining the relation between subthreshold OCD (minor obsessions and compulsions) and full criteria OCD (i.e., symptoms cause significant distress or impairment in functioning) is key in identifying homogeneous groups for assessing course, prognosis, treatment response, familial transmission, and prevalence.

Clinical Features

Demographic Features

Sex Distribution

Women appear to develop OCD slightly more frequently than do men. In the DSM-IV (American Psychiatric Association 1994) field trial, 51% of the 431 subjects with OCD were women (Foa and Kozak 1995). In our clinic population, 55% of the 830 subjects with DSM-III-R OCD evaluated over the past 10 years were women. Patterns of comorbidity may affect sex ratios. A study that assessed the presence of comorbid disorders characterized by psychosis (schizophrenia, delusional disorder) or psychotic-like features (schizotypal personality disorder) in 475 patients with OCD found a different sex ratio. Of the OCD patients without one of these comorbid disorders, 56% were women, whereas 85% of those with one of these comorbid psychotic disorders were men (Eisen and Rasmussen 1993).

A predominance of males also has been observed in child and adolescent OCD populations. In a National Institute of Mental Health study of 70 subjects with OCD between ages 6 and 18 years, 47 (67%) were males (Leonard et al. 1989). This finding may be a result of the fact that males develop OCD at a younger age than do females. Genetic data have shown a significantly higher frequency of OCD in relatives of patients who develop OCD before age 14, suggesting that in addition to sex distribution, there are differences between pediatric OCD and adult OCD (Bellodi et al. 1992; Nestadt et al. 2000).

Marital Status

In a study of 250 subjects with OCD, 43% were never married, 52% were ever married, and 5% were ever divorced (Rasmussen and Eisen 1991). In our clinic sample of 830 adults with OCD, 48% were never married. A study comparing marital status in OCD patients with that in a matched group of patients with major depression found no significant differences between the two groups (Coryell 1981). Although marital status was not found to be a predictor of course in several follow-up studies, a recent prospective study of 107 subjects with OCD found that being married significantly increased the probability of partial remission, with married patients more than twice as likely to remit as unmarried ones (Steketee et al. 1999).

Course and Natural History

Age at Onset

In our study of 250 patients, the mean age at onset of OCD was 20.9±9.6 years. Men had a significantly earlier onset of illness: 19.5±9.2, compared with 22.0±9.8 for women ($P<0.003$) (Rasmussen and Eisen 1998). Sixty-five percent of the patients studied experienced the onset of significant symptoms before age 25, whereas fewer than 15% had onset of the disorder after age 35. Most patients described minor symptoms (i.e., obsessions and/or compulsions that do not cause significant distress or impairment) prior to the development of full criteria for OCD. Although OCD usually begins in late adolescence, prepubertal onset is not rare: 21% of the 830 patients in our database had onset of OCD before age 14, and 11% had onset before age 12.

Some evidence suggests that age at onset may be significant in terms of familial transmission. In a study that examined the frequency of OCD in the first-degree relatives of 100 probands with OCD, 82% of the probands reported onset of OCD before age 18 (Pauls et al. 1995). In this study, the rate of OCD and subthreshold OCD among relatives of the probands with onset of OCD before age 18 was approximately twice as high as the rate of OCD in relatives of OCD probands with late onset.

Age at onset of OCD also may be a predictor of course. The vast majority of patients endorse having a chronic course once OCD occurs (see next subsection). However, Swedo and colleagues (1998) described a subtype of OCD that begins before puberty and is characterized by an episodic course with intense exacerbations. Exacerbations of OCD symptoms in this subtype have been linked with group A β-hemolytic streptococcal infections, leading to the subtype designation of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. Whether the course of illness in patients with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections continues to be episodic into adulthood or, as is the case with postpubertal onset, chronic is not yet known.

Course of Illness

DSM-IV describes the course of OCD as typically chronic with some fluctuation in the severity of symptoms over time (American Psychiatric Association 1994). Although terminology and definitions vary from study to study, overall, this appears to be supported, both by studies conducted retrospectively and by more recent follow-up and prospective studies.

In follow-up studies with a retrospective design, investigators generally identified patterns of course of illness in OCD as falling into the following categories: complete absence of obsessions and compulsions (remission), symptoms unchanged or worsening, symptoms much improved, and symptoms minimally improved with poor functioning. In these studies, it is often unclear whether patients described as "much improved" would nevertheless still meet criteria for the disorder. Another approach has been to determine the episodicity of OCD (i.e., whether this illness is characterized by distinct periods of illness and remission similar to major depressive disorder). These follow-up studies are compared in Table 14–2, with the caveat that different measures were used to assign patients to categories of course of illness. For the sake of comparison in Table 14–2, subjects considered mildly improved but with poor functioning were combined with subjects classified as having obsessive-compulsive symptoms that were minimally improved, were unchanged, or had worsened.

These early phenomenological and follow-up studies of OCD had several methodological limitations, including retrospective study design, small sample size, lack of standardized criteria to determine diagnosis, hospital-based samples not representative of the spectrum of the disorder found in the population as a whole, biases in inclusion and exclusion criteria, chart review rather than personal interview, absence of structured interviews, and lack of consensus on the definition of relapse, remission, and recovery. In reviewing these studies, Goodwin et al. (1969) concluded that the course of OCD usually is chronic but variable with fluctuations in severity of symptoms. He described depres-

TABLE 14–2. Retrospective follow-up studies of obsessive-compulsive disorder (OCD)

Reference	*N*	Mean follow-up (years)	Well (%)	Much improved (%)	Minimally improved, unchanged, or worse (%)	Comments
Lewis 1936	50	>5	32	14	44	10% episodic course
Pollitt 1957	67[a]	3.4	24	36	37	Mostly outpatients
Ingram 1961	29	5.9	7	21[b]	72	Inpatients
Kringlin 1965	80	13–20	0	24	76	Inpatients
Grimshaw 1965	100	5	40	24	35	Inpatients
Lo 1967	88	3.9	23	50	27	In- and outpatients, diagnostic heterogeneity
Coryell 1981	44	≥0.5	22	55	22	Inpatients
Thomsen 1995	47	6–22	28	47	25	Childhood OCD

[a]Leukotomized.
[b]One patient nonleukotomized; five patients leukotomized.

sion as being the most common psychiatric disorder to develop after the onset of OCD and found that the subsequent development of schizophrenia occurs rarely if it is adequately excluded at baseline.

In follow-up studies conducted since 1980, course of illness has been evaluated with different criteria from those used in the earlier studies described above. Patients were retrospectively assigned to "continuous," "waxing and waning," "deteriorative," and "episodic with full remissions between episodes" categories. Rasmussen and Tsuang (1986) conducted a study in which patients were selected based on current enrollment in an outpatient OCD clinic. Most of the 44 patients (84%) described the course of OCD as chronic or "continuous"; 6 subjects (14%) had a deteriorating course, and only 1 (2%) had an episodic course. The average duration of illness at time of assessment was more than 15 years, again suggesting the chronicity of the disorder. Because these subjects were acquired through the process of clinic referral and course was assessed retrospectively, no former OCD patients who had already recovered and remained well were included. Patients who developed other major psychiatric disorders (e.g., schizophrenia) also were unlikely to be represented in this cohort of patients in an OCD clinic.

Two studies used control groups to compare course of illness with an OCD cohort. Coryell (1981) compared the course of illness following hospitalization in 44 inpatients with OCD and 44 inpatients with major depression. He observed that although 55.6% of the patients with OCD had some improvement at follow-up, this cohort was significantly less likely to experience remission after discharge (22%) than the comparison cohort of depressed patients (64%). However, suicide occurred significantly less frequently in the cohort of patients with OCD compared with patients with depression.

In a cross-sectional follow-up study, Thomsen (1995) interviewed 47 patients with OCD 6–22 years after they had been treated for OCD as children and compared their characteristics with those of a group of non-OCD psychiatric control subjects. All subjects were at least 18 years old at the time of the follow-up interview. The majority of the subjects had either no OCD symptoms (27.7%) or only subclinical obsessive-compulsive symptoms (25.5%) at follow-up. Ten subjects (21.3%) had a chronic course of OCD. This study also assessed outcome by measuring Global Assessment Scale scores (Endicott et al. 1976). Although the difference was not statistically significant, males with childhood-onset OCD appeared to have a poorer outcome than did females: 9 of the 10 patients with Global Assessment Scale scores below 50 at follow-up were males.

More recent studies have used the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), a scale designed to measure severity of obsessive-compulsive symptoms, and assessed course by assigning patients to groups by percent improvement on the Y-BOCS (Goodman et al. 1989). In a study conducted by Orloff et al. (1994), most of the 85 subjects assessed 1–3 years after baseline evaluation were much improved at follow-up based on chart review; 33% had a greater than 75% decrease in Y-BOCS score. The mean follow-up Y-BOCS score was in the range of mild to minimal obsessions and compulsions that did not cause interference with functioning (Y-BOCS score=10.1±7.0). This improvement in obsessive-compulsive symptoms compared with

baseline symptomatology may be the result of the availability of effective behavioral and pharmacological treatments for OCD, such as exposure and response prevention techniques and selective serotonin reuptake inhibitors (SSRIs). In fact, 99% of the subjects had received at least a 10-week trial of an SSRI, and 45% had received some behavior therapy (although only 16% received at least 20 hours of behavior therapy). Of note is that most patients were still taking medication at the time of follow-up, with clear relapses in those patients who discontinued medication, suggesting that maintenance of improvement in obsessive-compulsive symptoms over time may require continued treatment.

Another follow-up study conducted in Austria assessed 62 inpatients who met ICD-9 (World Health Organization 1977) criteria for OCD after structured interviews (Demal et al. 1993). This study had findings consistent with those of earlier studies: episodic course with complete remission (11.3%), episodic with partial remission (24.2%), deteriorative (9.7%), continuous and unchanging (27.4%), and continuous with improvement (24.4%). The authors used the Y-BOCS to rate current obsessive-compulsive symptom severity and found that 29.1% had Y-BOCS scores in the normal range, 20.9% had scores in the subclinical range (8–15), and 50.0% had scores in the clinical range (16–40).

A prospective naturalistic study of course of OCD in adults was conducted, in which data were collected on 66 subjects over 2 years (Eisen et al. 1995). Of the subjects who started the study meeting full criteria for OCD, 57% still met full criteria for OCD after 2 years. Although some of these subjects had considerable improvement in the severity of their obsessive-compulsive symptoms, they nonetheless had continued significant impairment because of obsessions and/or compulsions. Twelve percent had minimal or no symptoms (Y-BOCS scores<8). The remainder of the subjects (31%) had obsessions and compulsions that persisted but did not meet full criteria and might be classified as being in partial remission or much improved. Statistical analysis involving survival analysis reported a 47% probability of achieving at least partial remission during the 2-year study period. However, if more stringent criteria were used to define remission (i.e., patients had only occasional or no obsessions and compulsions for 8 consecutive weeks), the probability of achieving remission was only 12%. Almost half the patients (48%) who achieved partial or full remission subsequently relapsed. These findings are consistent with those of most previous studies of OCD, which found that most people who meet full criteria for this disorder continue to have obsessions and compulsions, even though they may have considerable improvement in both the intensity of their symptoms and the corresponding degree of impairment.

Over the past decade, several studies on course of illness in childhood-onset OCD have been conducted in which a prospective design was used. In one of these studies, all students in a high school were screened for the presence of obsessions and/or compulsions. Fifty-nine of the 5,596 high school students screened were identified as having OCD, subclinical OCD, other psychiatric disorders with obsessive-compulsive symptoms, or obsessive-compulsive personality disorder (Flament et al. 1988). These teenagers were reinterviewed 2 years after the initial interview by raters blind to the baseline diagnosis (Berg et al. 1989). Of the 12 subjects with initial diagnoses of OCD, 5 (42%) still met full criteria for OCD. Those subjects with initial diagnoses of OCD at baseline and subclinical OCD at the 2-year interview (8%) might be analogous to the subjects described in other studies as being much improved or in partial remission. Only 1 subject with an initial diagnosis of OCD had no diagnosis after 2 years. Of interest is the development of psychiatric symptoms in the 15 students with subclinical OCD at baseline: at follow-up, 27% met full criteria for OCD, 27% continued to have subclinical OCD, 27% developed other psychiatric disorders with obsessive-compulsive features, and only 1 subject had no diagnosis.

Another study of OCD in children conducted prospectively assessed 25 children with OCD 2–7 years after initial evaluation (Flament et al. 1990). The majority of subjects (68%) still met criteria for OCD at follow-up, and 28% were considered completely well with no obsessions or compulsions. More than half of the subjects had a lifetime history of major depression, and 44% had another anxiety disorder in addition to OCD (e.g., social phobia or separation anxiety). Five patients had obsessive-compulsive personality disorder. Two patients developed psychotic symptoms (diagnosed as atypical psychosis or schizophreniform disorder).

A third study of course of illness in children with OCD assessed the effect of treatment on course. Fifty-four children and adolescents were reinterviewed 2–7 years after participation in a controlled trial of clomipramine and a variety of interim interventions (Leonard et al. 1993). At follow-up, most patients were only mildly symptomatic, and obsessive-compulsive symptoms were more severe in only 10 subjects at reassessment, so that, as a whole, the cohort had improved.

However, only 3 subjects (6%) were considered to be in true remission (defined as no obsessions or compulsions and no medication), and 23 subjects (43%) still met full criteria for OCD. In addition, most patients were taking medication at follow-up, which suggests that ongoing maintenance of improvement in OCD may require ongoing pharmacological intervention.

To synthesize findings from varied studies on course of illness in adults and children, it may be important to separate the best possible outcome (full remission or symptom free) from what is described as much improved or improved, which may indicate persistent symptoms in the abatement phase of chronic waxing and waning illness. The episodic pattern of full remission (and sometimes later occurrence), when it is clearly identified as such, appears to occur in about 10%–15% of OCD patients, although this proportion may increase somewhat as follow-up is extended for several years. In most studies, a smaller proportion (6%–14%) seems to follow a deteriorating course. Most presumably follow a course marked by chronicity, with some symptom fluctuation over time, but without clear-cut remissions or deterioration. Those fortunate subjects who experience complete remission of their obsessive-compulsive symptoms are very much in the minority.

Symptomatology

Obsessions (intrusive, inappropriate, and disturbing ideas, thoughts, or images) and compulsions (repetitive behaviors to reduce anxiety) constitute the core clinical symptoms of OCD. Descriptions of obsessions and compulsions beginning with scrupulosity and continuing into the twentieth century in the writings of Janet and Freud are strikingly consistent with current clinical presentations of OCD. Several investigators have systematically characterized obsessions and compulsions based on the content of the obsession or the specific compulsive behavior. Hodgson and Rachman (1977) developed the Maudsley Obsessional-Compulsive Inventory, a 30-item true-false questionnaire about obsessive-compulsive symptoms. This inventory focused predominantly on checking and cleaning compulsions. Goodman and colleagues (1989) developed the Yale-Brown Symptom Checklist, a symptom checklist of specific obsessions and compulsions. This checklist includes 60 specific obsessions and compulsions and organizes them into 15 categories. The obsession categories are aggressive, sexual, religious, somatic, symmetry, contamination, hoarding, and miscellaneous. The compulsion categories are checking, ordering and arranging, counting, repeating rituals, cleaning, hoarding and collecting, and miscellaneous.

The most common obsession is fear of contamination, followed by pathological doubt, somatic obsessions, and need for symmetry (see Table 14–3). The most common compulsion is checking, followed by washing, counting, need to ask or confess, and symmetry and precision (see Table 14–3). Children with OCD present most commonly with washing compulsions, which are followed by repeating rituals (Rapoport 1989).

TABLE 14–3. Obsessive-compulsive symptoms on admission (N=560)

Obsessions	%	Compulsions	%
Contamination	50	Checking	61
Pathological doubt	42	Washing	50
Somatic	33	Counting	36
Need for symmetry	32	Need to ask or confess	34
Aggressive	31	Symmetry and precision	28
Sexual	24	Hoarding	18
Multiple obsessions	72	Multiple compulsions	58

Most adults and children with OCD have multiple obsessions and compulsions over time, with a particular fear or concern dominating the clinical picture at any one time. The presence of pure obsessions without compulsions is unusual. Patients who appear to have obsessions alone frequently have reassurance rituals or unrecognized mental compulsions (such as repetitive, ritualized praying) in addition to their obsessions. Pure compulsions are extremely rare. In the DSM-IV field trial, 91% of the 411 patients with DSM-III-R OCD were classified as having "mixed obsessions and compulsions," 8.5% were classified as having "predominantly obsessions," and 0.5% were classified as having "pure compulsions" (Foa and Kozak 1995). With the Yale-Brown Symptom Checklist, the findings were more striking: only 2.1% had obsessions without compulsions, and 1.7% had compulsions without obsessions. Pure compulsions, although unusual in adult patients, do occur in children with OCD, especially in the very young (e.g., ages 6–8 years) (Swedo et al. 1989).

Subtypes

To advance the understanding of etiology, genetics, and treatment of OCD, there has been an effort to identify

meaningful subtypes of this disorder. Proposed strategies for subtyping include identification of comorbidity specifically with the tic disorders and identification of subtypes by clinical presentation. Two studies have analyzed data collected with the Yale-Brown Symptom Checklist to identify groups of obsessions and compulsions that cluster together on factor analysis. Baer (1994; Baer et al., in press) applied principal components analysis to 107 patients with OCD who competed the symptom checklist of the Y-BOCS and examined the correlations between the factor scores and the presence of comorbid tic or personality disorders. They found three independent symptom subtypes or factors: 1) *symmetry/hoarding*, which had high factor loading from symmetry and saving obsessions and ordering, hoarding, repeating, and counting compulsions; 2) *contamination/checking*, which had high factor loading from contamination and somatic obsessions and cleaning and checking compulsions; and 3) *pure obsessions*, which had high factor loading from aggressive, sexual, and religious obsessions. The symmetry/hoarding factor was the only factor found to be related to comorbid Tourette's disorder or chronic tic disorder. Patients who scored high on this factor had a relative risk 8.5 times higher for having a chronic tic disorder than did those who scored low on this factor.

A second study that used a similar methodological approach of factor analysis of the Yale-Brown Symptom Checklist in two independent groups of patients identified four factors: 1) obsessions and checking, 2) symmetry and ordering, 3) cleanliness and washing, and 4) hoarding (Leckman et al. 1997). As in the previous study, patients with chronic tic disorders scored significantly higher on symmetry and ordering factors in the total study group.

Another approach to identify meaningful subtypes in OCD based on symptoms has been developed by Rasmussen and Eisen (1998). They hypothesized that this disorder has three core features: 1) abnormal risk assessment, 2) pathological doubt, and 3) incompleteness. These features cut across phenomenological subtypes, such as checking, washing, and the need for symmetry, although some symptom subtypes are more closely associated with one core feature than another.

The core features appear to relate to both the clinical features of OCD and their relation to comorbid disorders. Patients with abnormalities in risk assessment have high levels of anxiety associated with their symptoms. In addition, they are more likely to have comorbid Axis I panic disorder, generalized anxiety disorder, or social phobia; avoidant and dependent personality features; and a family history of an anxiety disorder. In contrast, patients with incompleteness are more likely to manifest low levels of anxiety, to have comorbid multiple tics or habit disorders such as trichotillomania or onychophagia, and to have compulsive personality features. Further empirical validation of this proposed subtyping according to core features is necessary and may have important implications for diagnosis and treatment. Some evidence already indicates that patients with treatment-resistant OCD and tic spectrum disorder are particularly responsive to dopaminergic antagonists (McDougle et al. 1994). These patients also are more likely to have incompleteness.

The following descriptions of some common obsessions and compulsions illustrate the clinical presentation of these symptoms.

Contamination

Contamination obsessions are the most frequently encountered obsessions in OCD. Such obsessions usually are characterized by a fear of dirt or germs. Contamination fears also may involve toxins or environmental hazards (e.g., asbestos or lead) or bodily waste or secretions. Patients usually describe a feared consequence from contacting a contaminated object (e.g., spreading disease or contracting an illness themselves). However, the fear is occasionally based not on a fear of disease but on a fear of the sensory experience of not being clean. The content of the contamination obsession and the feared consequence commonly changes over time—for example, a fear of cancer may be replaced by a fear of a sexually transmitted disease.

Many patients with contamination fears use avoidance to prevent contact with contaminants, in addition to excessive washing. The fear structure for contamination is similar to that seen in specific phobias: precipitation by a specific external trigger, high level of anxiety, and a well-developed and coherent cognitive framework. In some cases, a specific feared object and associated avoidance become more generalized, a pattern also described in specific phobias. Unlike specific phobias, patients with contamination obsessions usually worry that they will inadvertently cause others to be harmed or become ill rather than themselves.

Washing is the compulsion most commonly associated with contamination obsessions. This behavior usually occurs after contact with the feared object; however, proximity to the feared stimulus is often sufficient to engender severe anxiety and washing compulsions, even though the contaminated object has not been

touched. Most patients with washing compulsions perform these rituals in response to a fear of contamination, but these behaviors occasionally occur in response to a drive for perfection or a need for symmetry. Some patients, for example, repeatedly wash themselves in the shower until they "feel right" or must wash their right arm and then their left arm the same number of times.

Pathological Doubt

Patients with pathological doubt are plagued by the concern that they will be responsible for a dire event as a result of their carelessness. They may, for example, worry that they will start a fire because they neglected to turn off the stove before leaving the house. Such patients often describe doubting their own perceptions. Excessive doubt and associated feelings of excessive responsibility frequently lead to checking rituals. Patients may spend several hours checking their home before they leave. As is the case for contamination obsessions, pathological doubt also can lead to marked avoidance behavior. Some patients become housebound to avoid the responsibility of leaving the house potentially unlocked.

Pathological doubt also is embedded in the cognitive framework of several other obsessions. Patients with aggressive obsessions may be plagued by the doubt that they inadvertently harmed someone without knowing that they did so.

Patients may adopt several strategies to limit the time they spend checking, including counting the number of times they check or involving a family member to observe the checking ritual so that the patient can be reassured later that he or she actually completed the checking task.

Need for Symmetry

Need for symmetry is a drive to order or arrange things "perfectly," to do and undo certain motor actions in an exact sequence, or to perform certain behaviors symmetrically or in a balanced way. Patients describe an urge to repeat motor acts until they achieve a "just right" feeling that the act has been completed perfectly. These patients can be divided into two groups: 1) those with primary magical thinking and 2) those with primary obsessive slowness. Individuals with primary magical thinking report obsessional worries about feared consequences to their loved ones. They perform certain ordering and arranging compulsions to prevent harm to loved ones from occurring. Patients who have primary obsessive slowness take an inordinate amount of time to complete even the simplest of tasks (Rachman and Hodgson 1980). Unlike most patients with OCD, those with obsessive slowness may not experience their symptoms as ego-dystonic. Instead, they seem to have lost their goal directedness in favor of completing a given subroutine perfectly. The basal ganglia control motor planning and therefore coordinate motor subroutines as well as what MacLean (1985) termed the *master routine*. It is, therefore, tempting to speculate that these patients have some frontal–limbic–basal ganglia dysfunction that interferes with their goal directedness, rendering them incapable of distinguishing the importance of subroutines and overall goal-directed behavior.

Patients with symmetry obsessions and compulsions often describe feeling uneasy or unsettled rather than fearful or anxious when things are not lined up "just so" or "perfectly." In that sense, these patients can be seen as at the extreme end of the spectrum of compulsive personality, in which the need for every detail to be perfect or just so is greatest. Their description of rising tension followed by relief after the act is more similar to the subjective sensory experience of patients with tics than to the anxiety experienced by other patients with OCD without comorbid tic disorders. These patients with obsessional slowness and/or extreme perfectionism may not respond to behavior therapy interventions, which may be related to this lack of subjective anxiety.

The desire to "even up" or balance movements may be present in patients with tapping or touching rituals. Patients may, for example, feel that the right side of the chair must be tapped after the left side has been tapped. Such urges and behaviors also are frequently seen in patients with comorbid tic disorders (Holzer et al. 1994; Leckman et al. 1994; Miguel et al. 1995, 1997), who may, for example, describe an urge to have a tic on the right side of their body after experiencing a tic on the left side.

Somatic Obsessions

Somatic obsessions (i.e., the irrational and persistent fears of developing a serious life-threatening illness) may be seen in a variety of disorders, including OCD, hypochondriasis, major depression, and panic disorder. Several features may be useful in distinguishing OCD with somatic obsessions from hypochondriasis. Patients with OCD usually have other past or current classic OCD obsessions; are more likely to engage in classic OCD compulsions, such as checking and reassurance seeking; and generally do not experience somatic and

visceral symptoms of illness. Somatic obsessions are more easily distinguished from somatization disorder, in that patients with somatic obsessions usually focus on one illness at a time and are not preoccupied with a diverse, apparently unrelated array of somatic symptoms.

In contrast to many patients with contamination obsessions, patients with somatic obsessions usually are worried about their own health rather than the well-being of others. Until recently, the most common somatic obsessions consisted of a fear of cancer or venereal disease. However, a fear of developing acquired immunodeficiency syndrome (AIDS) has become increasingly common. Checking compulsions that consist of checking and rechecking the body part of concern, as well as reassurance seeking, are commonly associated with this fear.

Sexual and Aggressive Obsessions

Patients with sexual or aggressive obsessions are plagued by fears that they might commit a sexually unacceptable act, such as molestation, or harm others. They often fear not only that they will commit a dreadful act in the future but also that they have already committed such an act. Patients usually are horrified by the content of their obsessions and are reluctant to divulge them. It is quite striking that the content of these obsessions tends to consist of ideas that patients find particularly abhorrent.

Patients with these highly distressing obsessions frequently have checking and confession or reassurance rituals. They may report themselves to the police or repeatedly seek out priests to confess their imagined crimes. An unsolved murder case in the media may cause tremendous anxiety and lead to extensive reassurance rituals. Patients may repeatedly tell their therapist, spouse, or close friend some terrible thought or deed that they feel they have committed as a way of seeking reassurance that they really are not capable of doing what they are worried about. Sometimes they leave the therapist's office after having sought reassurance for the whole hour, only to call back later to add an insignificant detail they earlier omitted confessing. Guilt and anxiety are the dominant affective symptoms. Patients may think that they should be jailed for their thoughts (both to protect them from what they think they might do and because they feel they deserve to be punished).

Patients also may use extensive avoidance to prevent obsessions (e.g., removing all sharp implements, such as scissors and knives, from the house or avoiding all television programs with references to violence, such as the news).

Mental Compulsions

Traditionally, obsessions have been considered mental events (e.g., thoughts, images), whereas compulsions have been thought of as observable behaviors (e.g., washing or checking). More recently, the prevailing concept is that obsessions are mental events that cause distress, and compulsions are either behavioral or mental acts that are performed to neutralize or reduce obsessional distress. Mental compulsions, therefore, are neutralizing thoughts such as mental counting or praying, which decrease anxiety caused by obsessions. Mental rituals were the third most common type of compulsion after hand washing and checking in the DSM-IV field trial (Foa and Kozak 1995). In that study of 431 subjects with OCD, almost 80% reported having both behavioral and mental compulsions. However, fewer than 1% reported having only mental compulsions.

It is particularly important to take a careful inventory of mental rituals and distinguish these from obsessions when the patient is engaged in exposure treatment. Behavior therapy uses different techniques for these symptoms; exposure is used for obsessions, and response prevention is used for compulsions. In addition, because mental rituals and avoidance often take the place of overt motor behavior, the patient may extinguish his or her overt rituals with no significant improvement in outcome.

Insight

Interest in the role of insight in OCD has been increasing over the past 5 years. Traditionally, awareness of the senselessness or unreasonableness of obsessions (often referred to as *insight*) and the accompanying struggle against the obsessions (referred to as *resistance*) has been generally accepted as fundamental to the diagnosis of OCD. However, numerous descriptions of OCD patients who are completely convinced of the reasonableness of their obsessions and need to perform compulsions have appeared in the psychiatric literature during the past century (Kozak and Foa 1994). In 1986, Insel and Akiskal described several such patients and presented the hypothesis that patients with OCD have varying degrees of insight and resistance, with "obsessive-compulsive psychosis" at one extreme of a hypothesized continuum. They also noted a fluidity between neurotic (i.e., associated with insight) and psychotic states in these patients.

The range of insight in OCD has been investigated systematically in several studies. Eisen and Rasmussen (1993) found that 14% of 475 patients with DSM-III-R

OCD also had psychotic symptoms. Six percent had lack of insight and high conviction about the reasonableness of the obsessions as their *only* psychotic symptom. Lelliott et al. (1988) used an interview that evaluated several insight-related parameters, including fixity of beliefs underlying the obsession, bizarreness, resistance, and degree of control. The fixity dimension included several constructs: strength of the belief in the feared situation, how the patient thought others viewed the belief, and the patient's response to evidence that contradicted the belief. A full range of responses was found in the 43 patients assessed, which led the authors to conclude that good insight in OCD is not necessarily present and that insight spans a spectrum from good to absent (i.e., delusional thinking).

More recently, insight in OCD was assessed during the DSM-IV field trial (Foa and Kozak 1995); patients were asked if they feared consequences other than anxiety if they did not perform their compulsions. Fifty-eight percent believed that harmful consequences would occur. The degree of certainty that their obsessions were reasonable ranged across the entire spectrum of insight: most were uncertain whether they actually needed to perform their compulsions to avoid harm; however, 4% were certain, and 25% were mostly certain.

To reflect the results of these various studies, DSM-IV established a new OCD specifier: *with poor insight*. This specifier applies "when, for most of the time during the current episode, the individual does not recognize that the obsessions or compulsions are excessive or unreasonable" (American Psychiatric Association 2000, p. 458). In addition, DSM-IV-TR acknowledges that the beliefs that underlie OCD obsessions can be delusional and notes that in such cases, an additional diagnosis of delusional disorder or psychotic disorder not otherwise specified may be appropriate.

Although these changes were made in DSM-IV, no generally accepted, reliable, and valid method is available to differentiate degrees of insight. To address the need for a scale that measures insight in OCD and other psychiatric disorders, Eisen et al. (1998) developed the Brown Assessment of Beliefs Scale (BABS), a seven-item semistructured interview with specific probes and anchors that measure various dimensions of delusionality. Items include conviction, perception of others' views of the belief, explanation of differing views, fixity, rejection of views, and insight. This scale, which has established reliability and validity, may prove useful in phenomenological, prognostic, and treatment studies of OCD. Eisen et al. (1997b) found that 30% of a group of untreated patients with OCD had limited insight into their obsessions, but no patients with OCD were categorized as delusional with the BABS, compared with 24% of patients with body dysmorphic disorder who were considered delusional.

Whether insight is an important predictor of prognosis and treatment response in OCD is an intriguing question that has received very little investigation. The available literature on insight as a predictor of response to behavior therapy is conflicting. One study found that patients with overvalued ideas did not respond as well as patients with good insight to behavior therapy (Foa 1979). Another study found that patients with high conviction about their obsessions and need to perform compulsions responded just as robustly as did patients with good insight to behavioral intervention (Lelliott et al. 1988).

A more recent study examined insight before and after open treatment with sertraline in 71 patients with OCD, with the BABS and Y-BOCS as outcome measures. At baseline, 1 patient (1.4%) had delusional OCD and 14 patients (19.7%) had poor insight as defined by the BABS (Eisen et al., in press). No correlation was found between the degree of insight in OCD at baseline and response to sertraline. Patients with poor insight at baseline were just as likely to respond to sertraline as were patients with better insight.

Comorbidity

The coexistence of mood disorders, other anxiety disorders, and psychotic symptoms with obsessive-compulsive symptoms was reported in the early psychiatric literature (Kringlin 1965; Pollitt 1957; Stengel 1945). Depressive symptoms have been the most common comorbid syndrome both in clinical studies completed before 1985 without the benefit of standardized diagnostic criteria or reliable structured instruments and in more recent studies that assessed comorbidity more systematically. In a study of 100 patients with primary OCD being seen in an OCD clinic, 67% had a lifetime history of major depression, and 31% met criteria for current major depression (Rasmussen and Eisen 1988). Over the course of their illness, most patients reported that depression developed *after* their OCD symptoms occurred; thus, they were classified as having secondary depression. A minority (8%) of the patients had concurrent onset of their obsessive-compulsive symptoms with their depressive episodes. Although it may be difficult to distinguish a primary from a secondary diagnosis, some patients with OCD view

their depressive symptoms as occurring secondary to the demoralization and hopelessness accompanying their OCD symptoms and report that they would not be depressed if they did not have OCD. However, other patients view their major depressive symptoms as occurring independently of their OCD symptoms. OCD symptoms may be less severe when these patients cycle into an episode of major depression because they feel too apathetic to be as concerned with their obsessions and too fatigued to perform compulsions. However, OCD symptoms intensify in some patients during depressive episodes.

The temporal relation between development of depression and OCD was assessed by Welner et al. (1976), who compared the clinical pictures via chart review before, during, and after hospitalization of 150 patients with OCD. Their sample was divided into the following subgroups: 1) OCD only (20%); 2) OCD followed by depression (developing an average of 14 years later) (38%); 3) concurrent onset of OCD and depression (13%); 4) primary depression with subsequent development of OCD (11%); and 5) OCD associated with other disorders. Depressive symptoms developing long after OCD onset was the predominant pattern. Patients with this history had an earlier age at OCD onset, longer duration of illness, and less frequent and shorter remissions than did patients who had depression complicated by subsequent development of OCD and patients who had concurrent onset. Patients with OCD only also had an earlier onset of OCD than did the concurrent onset group. The "primacy" of OCD over depression therefore was associated with earlier onset and greater chronicity, whereas the "primacy" of depression over OCD, which might include concurrent onset of both, was associated with a more episodic course, as one might predict given the seemingly different course characteristics of OCD and depression.

It has been noted that obsessive-compulsive features are rarely, if ever, seen in mania. Gordon and Rasmussen (1988) reported a case of OCD in a bipolar patient whose obsessions and compulsions worsened in direct proportion to the severity of his depression and completely disappeared during episodes of mania. No systematic data existed on the frequency of obsessive-compulsive symptoms in a bipolar population until recently. Chen and Dilsaver (1995) found that 21% of the patients with bipolar disorder, 12.2% of the patients with unipolar depression, and 5.9% of the patients with other disorders had OCD in the ECA sample. Kruger et al. (1995) found that 35% of both bipolar and unipolar depressed patients had an obsessive-compulsive syndrome.

Other anxiety disorders also frequently coexist with OCD. Several studies have assessed the frequency of OCD in patients in treatment for other anxiety disorders. In a study of 60 patients with panic disorder diagnosed with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version modified for anxiety disorders and personal interviews, Breier et al. (1986) found that 17% had DSM-III OCD. Subsequent studies by Mellman and Uhde (1986) and Barlow (1988) confirmed these initial findings of the overlap between panic disorder and OCD. In the Harvard Anxiety Research Project, a prospective study of course in 711 patients with panic disorder, social phobia, and/or generalized anxiety disorder, 11% had comorbid OCD at baseline (Steketee et al. 1999).

This comorbidity also has been assessed by reporting the frequency of other anxiety disorders in clinical OCD samples. Relatively high lifetime rates of social phobia (18%), panic disorder (12%), and specific phobia (22%) were reported in a sample of 100 subjects with primary OCD (i.e., those who sought treatment for OCD) (Rasmussen and Eisen 1988). This high frequency of current and lifetime anxiety disorders suggests that OCD patients are vulnerable to many types of anxiety. The high prevalence of anxiety states in these patients may be caused by common developmental and temperamental traits whose phenotypic expression is secondary to shared genotypic and psychosocial factors. Of particular interest in this regard is the high lifetime prevalence of separation anxiety in this group of patients (12%), a finding that also has been well documented in panic disorder (Lipsitz et al. 1994).

Attention has been focused on the relation between tics and OCD. Patients with Tourette's disorder have a high rate of comorbid OCD and obsessive-compulsive symptoms, with 30%–40% reporting obsessive-compulsive symptoms (Leckman et al. 1993). Conversely, approximately 20% of patients with OCD have a lifetime history of multiple tics and 5%–10% have a lifetime history of Tourette's disorder (Leckman et al. 1994). This subgroup has an earlier age at onset and family pedigrees that are loaded for both Tourette's disorder and OCD (Pauls et al. 1995). In addition to genetic comorbidity data linking OCD and tic disorders, some evidence suggests that these disorders are linked phenomenologically, as noted earlier in this chapter; certain OCD symptoms such as symmetry and ordering are more common in patients with OCD and tic disorders than in patients with OCD alone.

Several studies have examined the comorbidity of anorexia nervosa and OCD. In one study, 17% of 100

OCD subjects were found to have a lifetime history of an eating disorder (Rasmussen and Eisen 1988). Conversely, in a series of 93 subjects with an eating disorder, 37% met criteria for comorbid OCD, with Y-BOCS scores of 16 or higher (Thiel et al. 1995). Rastam et al. (1995) also reported a high rate of OCD in 16-year-old girls with anorexia nervosa.

Several recent studies have examined the frequency of OCD in patients with schizophrenia. Frequencies ranged from 7.8% to 40.5% (Berman et al. 1995; Eisen et al. 1997a; Fenton and McGlashan 1986; Porto et al. 1997). Differences in the findings may be based on criteria used to define OCD and obsessive-compulsive symptoms. Regardless of this range, it seems clear that a subgroup of patients with schizophrenia has co-occurring obsessions and compulsions. Assessment of prognosis and neuropsychological testing are two approaches that have been used to characterize this subgroup. Fenton and McGlashan (1986) found that 10% of the schizophrenic patients in a Chestnut Lodge (Rockville, MD) follow-up study had prominent obsessive-compulsive symptoms. These "obsessive-compulsive schizophrenics" tended to have a more chronic course and a greater frequency of social or occupational impairment compared with a matched sample of schizophrenic patients without obsessive-compulsive features. A study that conducted neuropsychological testing in two groups of patients with schizophrenia—those with and those without OCD—found that the group with comorbid OCD performed worse in visuospatial skills, delayed nonverbal memory, and cognitive shifting abilities—cognitive areas thought to be impaired in OCD (Berman et al. 1998).

Comorbidity between these two disorders also has been assessed by examining the frequency of psychotic symptoms in a group of patients with primary OCD cross-sectionally and in follow-up. Retrospective follow-up studies examining the subsequent development of schizophrenia in patients with OCD have produced varying results, with rates ranging from 0.7% to as high as 12.3% (Ingram 1961; Kringlin 1965; Lo 1967; Muller 1953; Pollitt 1957; Rosenberg 1968). These studies were, however, methodologically limited in that none of them were prospective, diagnoses were made by chart review, and standardized diagnostic criteria were not used, which probably resulted in the inclusion of affective psychoses. In reviewing this literature, Goodwin et al. (1969) concluded that subjects with OCD were at no greater risk for developing schizophrenia than is the general population. In a study with a cross-sectional design, Eisen and Rasmussen (1993) identified 67 of 475 (14%) OCD subjects as having psychotic symptoms. These 67 subjects were quite heterogeneous: 18 (4% of the larger cohort) had comorbid schizophrenia, 8 (2%) had comorbid delusional disorder unrelated to OCD, and 14 (3%) had comorbid schizotypal personality disorder. In the remaining 27 patients (6% of the larger cohort), the only psychotic symptom was a delusional conviction about the reasonableness of the obsessions (i.e., delusional OCD, or OCD without insight). Of interest, the 27 subjects without insight were similar to the OCD patients without any psychotic symptoms (i.e., OCD with insight) in terms of epidemiological and clinical features such as course of illness. Similarly, treatment studies of patients with OCD and comorbid schizotypal personality disorder have shown a poorer prognosis and poorer response to psychotropic medications for the comorbid group (Jenike et al. 1986). Thus, it appears important to differentiate OCD plus a comorbid psychotic disorder, which may have a relatively poor outcome, from delusional OCD, which may be more similar to OCD with insight and without comorbid psychosis.

Finally, comorbidity between Axis II disorders and OCD has been reported. The most commonly encountered personality disorder diagnoses in OCD are dependent, avoidant, passive-aggressive, and obsessive-compulsive. Schizotypal, paranoid, and borderline personality disorders are found less commonly in OCD but appear to be associated with poor outcome (Baer et al. 1992). Research on the coexistence of OCD and personality disorders was hampered initially by the lack of structured diagnostic instruments and subsequently by relatively poor interrater reliability for Axis II disorders. In a study of 96 subjects in which a structured interview with adequate interrater reliability (the Structured Interview for the DSM-III Personality Disorders [SID-P]) was used, 36% met criteria for one or more DSM-III personality disorders (Baer et al. 1990). Dependent (12%), histrionic (9%), and obsessive-compulsive (6%) personality disorders were diagnosed most frequently. Other comorbid personality disorders were schizotypal, paranoid, and avoidant (5% each).

The comorbidity between obsessive-compulsive personality disorder and OCD is of particular interest. Janet (1904) viewed all obsessional patients as having a premorbid personality causally related to pathogenesis of the disorder. However, as described above, several studies found that a significant percentage of OCD patients do not have premorbid compulsive personalities. In seven studies reviewed by Black (1974), marked ob-

sessional traits were found in 31% of 254 obsessional patients, moderate traits were found in 40%, and no obsessional traits were found in 29%. All of these studies were completed before the introduction of DSM-III, so comparisons among studies are difficult because of variations in methodology and sample selection.

Studies completed after the introduction of DSM-III also have reported varied rates of comorbidity of obsessive-compulsive personality disorder and OCD. In a study that used DSM-III-R criteria, obsessive-compulsive personality disorder was found in 25% of the subjects with OCD; the higher rate of obsessive-compulsive personality disorder found with DSM-III-R criteria may reflect changes in the criteria set between DSM-III and DSM-III-R (Baer et al. 1990). Even the DSM-III-R rate shows that the comorbidity of OCD and obsessive-compulsive personality disorder is relatively low, a finding that is at odds with earlier literature postulating that OCD and obsessive-compulsive personality disorder are closely related disorders on a continuum of severity. This is partially the result of the arbitrary nature of how many of the criteria need to be met to make the diagnosis. In a study that used the SID-P in 114 patients with DSM-III OCD, most patients had difficulty with perfectionism and indecisiveness (82% and 70%, respectively) (Eisen and Rasmussen 1991). In contrast, the other traits constituting obsessive-compulsive personality disorder (i.e., restricted ability to express warmth, rigidity, and excessive devotion to work) were not seen frequently (32%, 32%, and 18%, respectively). In fact, these traits were no more common in OCD patients than in non-OCD control subjects, suggesting that these traits are not developmental antecedents for OCD.

Ample evidence from recent studies now supports the discontinuity of obsessive-compulsive personality disorder and OCD (Baer 1998; Baer et al. 1990, 1992; Eisen and Rasmussen 1991). The classic distinction of compulsions being ego-syntonic in obsessive-compulsive personality disorder as opposed to ego-dystonic in OCD is useful but not absolute. Some patients with cleaning or hoarding compulsions and those with the need for symmetry and precision or obsessive slowness who strive for perfection or completeness find their rituals ego-syntonic until they begin to impair social and occupational function. Whether these patients should be classified as having obsessive-compulsive personality disorder or subthreshold OCD is a subject for further empirical study.

The relative validity of each of the criteria also needs further empirical validation. Although personality disorders are considered to be stable over time, a study found that of 17 patients with OCD and a personality disorder, 9 of the 10 treatment responders no longer met criteria for a personality disorder after successful pharmacotherapy, raising the question of whether the apparent personality disorder was actually a manifestation of or a result of chronic OCD (Ricciardi et al. 1992).

Conclusion

The past decade has seen tremendous strides in knowledge about the etiology, epidemiology, and treatment of OCD. We now know that OCD is a common psychiatric disorder not only in the United States but also globally. Research regarding phenomenological aspects of OCD has focused on various areas, including identification of subtypes, investigation of the role of insight, and patterns of comorbidity. Several studies that examined the course of illness in OCD found that the course is usually chronic in adults. However, increasing evidence indicates that there may be a subtype of OCD that is characterized by an episodic course, and current research is focusing on delineating that subtype more specifically. Another hypothesized subtype involves patients with both OCD and chronic tic disorders. Certain obsessions and compulsions are more common in patients with these two disorders, adding evidence to the familial transmission and treatment data suggesting that this pattern of comorbidity may identify a meaningful subtype.

Another area of focus over the past 10 years has been the role of insight. Evidence that patients with OCD have a range of insight has been increasing. It remains to be seen whether patients with poor insight have a different treatment response and/or different course than patients with better insight.

Finally, comorbidity between OCD and schizophrenia has been a recent area of interest. Evidence is emerging that obsessions and compulsions are more common in patients with schizophrenia than was previously thought. The effect of obsessions and compulsions on schizophrenia in terms of both treatment response and course is currently being investigated.

Despite tremendous advances in treatment of this potentially debilitating disorder, a significant percentage of patients have symptoms that do not respond to standard treatment. Continued research to identify meaningful subtypes in OCD is necessary to unravel important questions about etiology and to develop specific treatment strategies for refractory patients.

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Pathogenesis of Obsessive-Compulsive Disorder

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Obsessive-compulsive disorder (OCD) is a heterogeneous entity. One of the more important concepts to emerge in the past two decades of OCD research is the realization that the obvious clinical variability associated with the diagnosis likely reflects neurobiologically meaningful subtypes or dimensions of disease, in terms of both etiology and pathophysiology. In this chapter about the pathogenesis of OCD, we review several etiological and pathophysiological models, emphasizing the ways in which disparate data may well reflect real differences among OCD subtypes. Likewise, we extend the discussion to other diagnostic entities that may share common pathogenetic features with OCD and thus implicate a neurobiologically based obsessive-compulsive spectrum of disease. In this context, it is interesting that OCD remains categorized among the anxiety disorders despite accruing evidence that it appears to be more closely related to an array of other disorders that are scattered across DSM-IV-TR (American Psychiatric Association 2000).

We begin this chapter by reviewing family genetic data that support a genetic vulnerability to develop OCD and that suggest a relation between one subtype of OCD and Tourette's disorder. We present a brief heuristic model of OCD and related disorders that is based on phenomenological characteristics and informed by neuroanatomical considerations. We next outline the relevant functional anatomy of cortico-striato-thalamo-cortical (CSTC) circuitry and review data that implicate different elements of this system in different subtypes of OCD as well as other candidate obsessive-compulsive spectrum disorders. In this context, the issue of an immunological etiology for OCD and related disorders is discussed as a putative mechanism leading to striatal pathology. Finally, we review neurochemical models of OCD, emphasizing the role of serotonergic systems. In closing, we attempt to provide an integrated view of pathogenetic models as they pertain to OCD and related disorders and conclude by foreshadowing future research directions in this field.

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Genetics of Obsessive-Compulsive Disorder and Related Disorders

To the extent that OCD has a genetic origin, it is foreseeable that the gene or genes responsible for conferring increased risk ultimately will be identified and fully characterized. To date, however, genetic linkage and allelic association studies of OCD and related disorders have been few, and they have yielded little insight regarding pathogenesis thus far (see Samuels and Nestadt 1997). One large linkage study failed to find markers for Tourette's disorder or tic-related OCD (Pauls et al. 1990). Similarly, no significant relation has been found between candidate genes for tryptophan oxygenase, the serotonin type 1A (5-HT_{1A}) receptor, or the dopamine D_2 receptor and OCD or related conditions (Brett et al. 1995; Novelli et al. 1994). One preliminary study suggested that polymorphisms in the D_4 receptor gene distinguished OCD patients with and without comorbid tics (Nicolini et al. 1996), but this finding requires replication.

Similarly, few twin studies of OCD and related disorders have been done. Inouye (1965) reported obsessive-compulsive symptom concordance rates of 80% (8 of 10) in monozygotic twin pairs compared with 50% (2 of 4) in dizygotic twin pairs; Carey and Gottesman (1981) reported rates of 87% (13 of 15) and 47% (7 of 15), respectively, in another series. Analogous concordance rates for chronic tic disorders from several studies were approximately 75%–90% for monozygotic compared with 10%–20% for dizygotic twins (see Alsobrook and Pauls 1997). If OCD or Tourette's disorder were solely dependent on genetic factors, one would predict about 100% concordance among monozygotic twins and about 50% concordance among dizygotic twins; conversely, if these disorders were wholly attributable to epigenetic or nongenetic factors, one would expect little disparity between the rates for monozygotic and dizygotic twin pairs. Hence, despite the limited data from these twin pair case series, they are consistent with a substantial genetic component in the etiology of OCD and chronic tic disorders.

In addition, several family genetic studies of OCD and Tourette's disorder have been conducted; however, relatively few of them have entailed a high standard of diagnostic ascertainment (e.g., direct assessment of relatives [see Samuels and Nestadt 1997]). Black et al. (1992) used rigorous methods and found that the age-corrected morbid risk of "broadly defined OCD" (i.e., OCD plus subsyndromal OCD) was significantly greater in the parents of OCD probands than in the parents of psychiatric non-OCD control subjects (15.6% vs. 3.0%). Furthermore, the lifetime prevalence of generalized anxiety disorder, but not major depression, was higher among the first-degree relatives of OCD than among the first-degree relatives of control subjects (21.7% vs. 12.4%).

More recently, Pauls and colleagues (1995) performed several exemplary family genetic studies of OCD and Tourette's disorder. In 1995, they compared prevalence rates in first-degree relatives of OCD probands with rates in first-degree relatives of psychiatrically normal control subjects; significant differences were found with respect to OCD (10.3% vs. 1.9%), subthreshold OCD (7.9% vs. 2.0%), OCD plus subthreshold OCD (18.2% vs. 4.0%), and tics (4.6% vs. 1.0%). Moreover, the risks to relatives were higher when the probands had early-onset OCD (i.e., before age 19 years). Similarly, Leonard et al. (1992) studied children and adolescents with OCD and found an earlier age at OCD onset in probands who developed comorbid Tourette's disorder and an elevated lifetime prevalence of tics in their first-degree relatives (14%). Conversely, family genetic studies found a significantly greater prevalence of OCD in first-degree relatives of probands with Tourette's disorder, regardless of OCD comorbidity in the probands (Pauls et al. 1986, 1995). In two studies of probands with Tourette's disorder, Pauls and colleagues (Pauls and Leckman 1986; Pauls et al. 1990) used segregation analysis and found that familial patterns of Tourette's disorder, chronic tics, and OCD were consistent with an autosomal dominant mode of transmission with incomplete penetrance. Two subsequent studies have ostensibly replicated these findings (Eapen et al. 1993; van de Wetering 1993). Across studies, the penetrance rates have ranged from 0.5 to 0.9 for males and 0.2 to 0.8 for females (see Alsobrook and Pauls 1997).

Taken together, current data suggest that the risk of developing OCD is often inherited. Specifically, there appear to be at least two familial forms of OCD—one that is characterized by an early age at onset and an association with chronic tic disorders (including Tourette's disorder) and one that is not tic related (Alsobrook and Pauls 1997; Pauls et al. 1995). Thus, pathogenetic models of OCD and related disorders must account for an inherited component together with epigenetic influences on expression. Moreover, in the case of tic-related OCD, pathogenetic models should explain the spectrum of clinical presentation, in terms of both phenomenology and treatment response. Finally, in a third group of patients with OCD, no familial relationship is evident. These sporadic cases may well

represent phenocopies of the disorder attributable to various etiologies, including unrecognized general medical causes (e.g., infarction, tumor); consequently, this third group is likely to reflect a high degree of pathophysiological heterogeneity as well.

Heuristic Model of Obsessive-Compulsive Disorder and Related Disorders

In broad terms, the shared phenomenology of obsessive-compulsive spectrum disorders is fundamentally characterized by intrusive events leading to repetitive behaviors (Miguel et al. 1995; Rauch and Jenike 1997; Rauch et al. 1998b). In the case of OCD, the intrusive events are of a cognitive nature (obsessions), which prompt intentional repetitive behaviors (compulsions) that serve to neutralize the cognitive intrusions themselves as well as accompanying anxiety. In an analogous fashion, the tics of Tourette's disorder typically are performed in response to sensory intrusions (Leckman et al. 1993; Miguel et al. 1995); in those few cases in which the tics occur spontaneously, they can be conceptualized as motor intrusions. By extension, the phenomenology of trichotillomania may be more reminiscent of a tic disorder, whereas body dysmorphic disorder (BDD) may be more akin to OCD.

According to this heuristic model, the shared pathophysiology of obsessive-compulsive spectrum disorders should entail some basis for intrusive events, whereas the distinctions among the various disorders should reflect the differential involvement of sensorimotor and cognitive representations. Moreover, there must be some explanation for why the repetitive behavior ultimately leads to a temporary waning of the intrusive symptoms and consequently a temporary decrement in the drive to perform the repetitive behavior.

Neuroanatomy and Pathophysiology of Obsessive-Compulsive Disorder and Related Disorders

Relevant Normal Neuroanatomy

Contemporary neuroanatomical models of OCD and related disorders have emphasized the role of CSTC circuitry. In a series of classic articles, Alexander and colleagues (1986, 1990) introduced and reviewed the organization of multiple, parallel, segregated CSTC circuits. Briefly, each CSTC circuit involves projections from a variety of cortical zones to specific corresponding subterritories of striatum, which send projections via other intermediate basal ganglia targets to ramify within the thalamus. These circuits are ultimately closed via reciprocal projections from the thalamus back to the same prefrontal cortical regions from which the corticostriatal projections originated. Several levels of complexity must be considered with regard to the anatomy and function of these circuits to appreciate their role in the pathophysiology of OCD and related disorders. Therefore, we begin by describing the key elements of these circuits, as well as their functional significance (Rauch et al. 1998b).

Prefrontal Cortex

The prefrontal cortex mediates a variety of cognitive functions, including response inhibition, planning, organizing, controlling, and verifying operations. Consequently, prefrontal dysfunction is associated with disinhibition, disorganization, inflexibility, perseveration, and stereotypy (Otto 1990). The prefrontal cortex comprises several functional subterritories. Dorsolateral prefrontal cortex plays a role in learning and memory as well as planning and other complex cognitive (i.e., executive) functions. Ventral prefrontal cortex can be further subdivided into two functional domains: the posteromedial orbitofrontal cortex and the anterior and lateral orbitofrontal cortex. Posteromedial orbitofrontal cortex is a component of the paralimbic system and plays a role in affective and motivational functions, as discussed in the next subsection (Mesulam 1985). Anterior and lateral orbitofrontal cortex represent the structural and functional intermediaries between the lateral prefrontal and paralimbic prefrontal zones. For instance, anterior and lateral orbitofrontal cortex seem to play a role in response inhibition and regulation of behavior based on social context as well as other affectively tinged cognitive operations (Mesulam 1985; Zald and Kim 1996).

Paralimbic System

The *paralimbic system* is the name given to a contiguous belt of cortex that forms the functional conduit between other cortical areas and the limbic system proper. The constituents of the paralimbic belt include posteromedial orbitofrontal cortex, as well as cingulate, anterior temporal, parahippocampal, and insular cortex (Mesulam 1985). This system is believed to integrate abstracted representations of the outside world with inner

emotional states, so that appropriate meaning and priority can be assigned to information as it is processed. Convergent data from recent human neuroimaging studies, together with previous animal and human research, suggest that the paralimbic system plays a critical role in mediating intense emotional states or arousal; in particular, this system has been implicated in anxiety (Rauch and Shin 1997; Rauch et al. 1994, 1995a, 1996, 1997a). Furthermore, it has long been appreciated that paralimbic elements serve to modulate autonomic responses, including heart rate and blood pressure, that represent the somatic manifestations of intense affects or heightened arousal (Mesulam 1985).

Striatum

The striatum comprises the caudate nucleus, putamen, and nucleus accumbens (also called the ventral striatum). Historically, the basal ganglia, including the striatum, were thought to play a circumscribed role, limited to the modulation of motor functions. More recently, however, a much more complicated scheme has been adopted, which recognizes the role of the striatum in cognitive and affective functions as well (Houk et al. 1995).

Cortico-Striato-Thalamo-Cortical Circuits

Parallel, segregated CSTC circuits differ from one another on the basis of their distinct projection zones within cortex, striatum, and thalamus and, thus, the particular type of functions each subserves. For the purposes of this review, four of these CSTC circuits are emphasized: 1) the circuit involving projections from sensorimotor cortex via the putamen subserves sensorimotor functions; 2) the corticostriatal circuit involving projections from paralimbic cortex via the nucleus accumbens subserves affective or motivational functions; 3) projections from anterior and lateral orbitofrontal cortex via ventromedial caudate nucleus constitute the ventral cognitive circuit, which is thought to mediate context-related operations and response inhibition; and 4) projections from dorsolateral prefrontal cortex via dorsolateral caudate nucleus constitute the dorsal cognitive circuit, which is thought to mediate working memory and other executive functions.

The CSTC circuits have two major branches: 1) the corticothalamic branch provides a reciprocal excitatory monosynaptic communication between the cortex and the thalamus that purportedly mediates consciously initiated output (corticothalamic) and consciously accessible input (thalamocortical) streams, and 2) the cortico-striato-thalamic branch represents a collateral pathway that serves to modulate transmission at the level of the thalamus. Purportedly, the function of the striatum in this context is to process information automatically and without conscious representation. Hence, the healthy striatum, via exerting a balance of suppression and/or enhancement at the level of thalamus, serves to 1) filter out extraneous input; 2) ensure refined output; and 3) mediate stereotyped, rule-based processes without necessitating the allocation of conscious resources (Graybiel 1995; Houk et al. 1995; Rauch and Savage 1997; Rauch et al. 1995b, 1997b; Wise et al. 1996). In this way, the striatum regulates the content and facilitates the quality of information processing within the explicit (i.e., conscious) domain by fine tuning input and output. In addition, the striatum enhances the efficiency of the brain by carrying out some nonconscious functions, thereby reducing the computational load on conscious processing systems.

The "direct" and "indirect" cortico-striato-thalamic pathways represent a third level of complexity. Each cortico-striato-thalamic collateral consists of both a direct and an indirect pathway (Albin et al. 1989; Alexander et al. 1990). These two systems operate in parallel, with opposing ultimate influences at the level of the thalamus. The direct system is so-named because it involves direct projections from the striatum to the globus pallidus interna, with a net excitatory influence on the thalamus. Conversely, the indirect system involves indirect projections from the striatum via the globus pallidus externa to the globus pallidus interna and has a net inhibitory effect at the level of the thalamus. Although these two systems share many features in common, they are characterized by important neurochemical differences. Specifically, the direct system uses the neuropeptide substance P as a transmitter, but the indirect system uses enkephalin.

There are additional levels of complexity regarding the heterogeneity of cellular characteristics within striatal subterritories (i.e., the patch-matrix level of organization [Gerfen 1992; Graybiel 1990]). However, those concepts are tangential to the focus of this review.

Corticostriatal Hypothesis of Obsessive-Compulsive Disorder

For the past two decades, neurobiological models of OCD have emphasized the role of the frontal cortex and the striatum (Baxter et al. 1990; Cummings 1993;

Insel 1992; Modell et al. 1989; Rapoport and Wise 1988; Rauch and Jenike 1993, 1997; Rauch et al. 1998b; Salloway and Cummings 1996). The scheme of corticostriatal circuitry fits well with emerging data implicating the elements of those circuits. Convergent results from neuroimaging studies indicated hyperactivity of the orbitofrontal cortex, anterior cingulate cortex, and (less consistently) caudate nucleus at rest, and attenuation of these abnormalities with effective treatment (for a review, see Rauch and Baxter 1998). Neuropsychological studies were consistent with subtle deficits involving frontostriatal functions (for review, see Rauch and Savage 1997). Neurosurgical procedures that interrupted this circuit appeared to reduce OCD symptoms (see Cosgrove and Rauch 1995; Mindus et al. 1994). Furthermore, cases of other diseases characterized by documented striatal pathology had OCD symptoms or similar clinical manifestations (Cummings 1993; Salloway and Cummings 1996; Weilburg et al. 1989; Williams et al. 1988). There was also heuristic appeal to the hypothesis that positive feedback loops between the cortex and the thalamus might mediate circular, repetitive thoughts, whereas the striatum might mediate fixed action patterns in the form of repetitive behaviors or compulsions (Baxter et al. 1990, 1992; Insel 1992; Modell et al. 1989; Rauch and Jenike 1993; Rauch et al. 1998b).

Although this model had several early versions, each posited an overdriven corticothalamic reverberating circuit. Modell et al. (1989) proposed that a hyperactive caudate nucleus might be the cause of net excitation of the thalamus; Baxter et al. (1990) hypothesized that the apparent hyperactivity in caudate represented insufficient compensation for intrinsic striatal dysfunction, such that inhibition of the thalamus via the cortico-striato-thalamic collateral was inadequate. As researchers came to appreciate the ramifications of the direct and indirect systems within the cortico-striato-thalamic collateral branch, the models evolved. A revised version suggested that in healthy individuals, an appropriate balance between the direct and the indirect systems enabled the collateral to optimally modulate activity at the thalamus, whereas in OCD, a shift toward dominance of the direct system could result in excitation or disinhibition at the thalamus, thereby overdriving the corticothalamic branch. Insel (1992) provided a complementary model of OCD, which focused on the role of orbitofrontal cortex as the primary component of a "worry circuit." Thus, the corticostriatal models of OCD accommodated much of the available data as of 1993 (Cummings 1993; Rauch and Jenike 1993).

Striatal Topography Model of Obsessive-Compulsive Disorder and Related Disorders

Baxter and colleagues (1990) were the first to clearly articulate what has come to be known as the *striatal topography model* of OCD and related disorders (Leckman et al. 1992; Rauch and Baxter 1998; Rauch and Jenike 1997; Rauch et al. 1998b). As the phenomenological, familial, and neurobiological relations between OCD and Tourette's disorder became appreciated, Baxter et al. hypothesized that the two disorders might share a fundamental pathophysiology, whereby the clinical manifestations of each disease are governed by the precise topography of dysfunction within the striatum. Baxter et al. suggested that different corticostriatal circuits might mediate different symptoms and therefore define a spectrum of different disease entities. Originally, they proposed that ventromedial caudate and accumbens involvement might mediate obsessions, dorsolateral caudate dysfunction might mediate compulsions, and putamen involvement might mediate the tics of Tourette's disorder. Subsequently, based on results of symptom provocation studies, we proposed that the paralimbic system (including posteromedial orbitofrontal cortex) mediates affective manifestations, including the anxiety of OCD or BDD and the "urges" of Tourette's disorder or trichotillomania, whereas the ventral cognitive circuit comprising anterior and lateral orbitofrontal cortex and ventromedial caudate mediates obsessional symptoms (Rauch and Baxter 1998; Rauch et al. 1998b). Further support for the striatal topography model comes from recent imaging studies that indicate structural abnormalities involving the caudate in OCD (see Jenike et al. 1996; Rauch and Baxter 1998; Robinson et al. 1995; Scarone et al. 1992; but see also Aylward et al. 1996) and the putamen in Tourette's disorder (Peterson et al. 1993; Singer et al. 1993) and trichotillomania (O'Sullivan et al. 1997).

Cortico-Striato-Thalamo-Cortical Dysfunction and the Implicit Processing Deficit Hypothesis

The striatal topography model has further implications when elaborated via a cognitive neuroscience perspective. One scheme for understanding information processing, in the context of learning and memory, distinguishes between explicit (i.e., conscious) and implicit (i.e., noncon-

scious) operations (Rauch et al. 1995b, 1997b; A.S. Reber 1989, 1992; P.J. Reber and Squire 1994; Schacter and Tulving 1994). Apparently, these various information-processing functions are performed by distinct and dissociable brain systems. Explicit learning and memory are primarily mediated via dorsolateral prefrontal cortex and medial temporal structures, such as the hippocampus (Schacter et al. 1996; Squire 1992; Ungerleider 1995). There are several types of implicit learning and memory. Classical conditioning (especially with regard to aversive stimuli) is mediated in part by the amygdala. Implicit learning of procedures, skills, or stereotyped serial operations is purportedly mediated via corticostriatal systems (see Mishkin and Petri 1984; Mishkin et al. 1984; Rauch and Savage 1997, 2000). Therefore, if obsessive-compulsive spectrum disorders are fundamentally referable to striatal dysfunction, their phenomenology might best be understood as a consequence of implicit processing deficits (Rauch and Savage 2000; Rauch et al. 1998b).

From the cognitive neuroscience perspective, it is plausible that the intrusive events that are the hallmark of OCD and related disorders represent failures in filtering at the level of the thalamus, attributable to deficient modulation via the cortico-striato-thalamic collateral pathway. In other words, information that is normally processed efficiently via corticostriatal systems, outside of the conscious domain (i.e., implicitly), instead finds access to explicit processing systems because of striatal dysfunction. This theory could explain the cognitive intrusions of OCD (or BDD) and the sensorimotor intrusions of Tourette's disorder (or trichotillomania). Furthermore, it makes sense that these symptoms persist or recur until they are effectively "put to rest." The manner and inefficiency with which this end is achieved may depend both on the degree of dysfunction and on the nature of compensatory processes.

In fact, imaging studies have shown that the striatum is reliably recruited during learning of sequential behaviors (Rauch et al. 1995b). Patients with OCD do not show this normal pattern of striatal activation when confronted with an implicit sequence learning task and instead show recruitment of medial temporal structures typically associated with conscious information processing (Rauch et al. 1997b).

Repetitive Behaviors and the Modulation of Thalamic Overdrive

For an individual with a given pattern of striatal dysfunction, the most adaptive means for producing striatothalamic modulation might be via performance of highly ritualized thoughts or behaviors that activate adjacent, intact, striatothalamic networks. In this way, compulsions or tics may represent a compensatory, but relatively inefficient, method for recruiting the viable remnants of the cortico-striato-thalamic collateral. Thus, these repetitive behaviors actually serve to facilitate gating at the level of the thalamus. This would explain why these behaviors sometimes require numerous repetitions before the precipitating intrusive symptoms are put to rest.

This model also provides an explanation for the correspondence between intrusive symptoms and the repetitive behaviors performed in response to them. By this scheme, the pairing should principally be related according to the topography or interconnections of the neural systems involved. Within the putamen, it makes sense that these relations would be somatotopic, such that sensory intrusions that involve a given somatic distribution (e.g., the right shoulder) should prompt repetitive behavior in the same or a nearby somatic distribution (i.e., a shoulder or arm tic). In the case of cognitions, this mapping is less obvious and certainly not yet empirically established. It is plausible, however, that networks that mediate cognitive representations of contamination, for instance, might be topographically nearby or linked with neural networks that mediate cleaning procedures. Furthermore, this model would provide an explanation for why some patients develop mental rituals and also why some patients have intrusions but never develop ritualistic behaviors, because presumably in those cases, no behaviors evolve that effectively ameliorate the intrusive symptoms.

Again, in the context of an implicit sequence learning paradigm, recent functional imaging studies have shown a characteristic pattern of thalamic deactivation in association with striatal recruitment (Rauch et al. 1998). These findings have been interpreted as one illustration of thalamic gating; moreover, such paradigms represent potential tools for characterizing dysfunction within this system in patients with OCD and related disorders.

Cortical Excitability in Obsessive-Compulsive Disorder and Tourette's Disorder

The striatal topography model of OCD and related disorders focuses on subcortical dysfunction, but primary cortical pathology may be the cause in some subtypes of

these disorders. Transcranial magnetic stimulation (TMS) is a noninvasive means of inducing regional neuronal activity in humans. TMS can be used to assess the degree of neuronal inhibition in the cerebral cortex. The technique involves activating cortical motor output cells with magnetic pulses produced by a scalp electromagnetic coil. The resulting motor evoked potentials are reduced when subthreshold TMS pulses precede suprathreshold stimuli by several milliseconds. This phenomenon of intracortical inhibition is thought to be the result of activation of inhibitory interneurons by the subthreshold pulse. One recent study found that intracortical inhibition was defective in patients with Tourette's disorder (Ziemann et al. 1997); findings from an analogous study of OCD likewise found an intracortical inhibition deficit (Greenberg et al. 1998). These results implicate insufficient local cortical inhibition as one possible mechanism underlying the intrusive phenomena characterizing obsessive-compulsive spectrum disorders.

The cortical excitability model of OCD and related disorders is consistent with the observed efficacy of agents that facilitate intracortical inhibition. For instance, clinical trials have suggested that benzodiazepines are therapeutic for both OCD and Tourette's disorder (Hewlett 1993). Furthermore, preliminary clinical data suggest that gabapentin, a neutral γ-aminobutyric acid (GABA) analog, also may be effective in OCD (Beauclair et al. 1996). Interestingly, preclinical data (Gellman and Aghajanian 1993) indicate that serotonin may act within the frontal cortex by augmenting GABA transmission (see subsection "Serotonin and the Pathogenesis of Obsessive-Compulsive Disorder" later in this chapter). This implies that modulation of cortical serotonin transmission via serotonin reuptake inhibitor (SRI) administration may ultimately ameliorate symptoms of OCD by enhancing intracortical inhibition.

An Autoimmune Etiology for Obsessive-Compulsive Disorder and Related Disorders

Over the past two decades, a fascinating scientific story has emerged regarding the potential role of autoimmune mechanisms in the pathogenesis of OCD and related disorders. It had long been appreciated that Sydenham's chorea, one manifestation of acute rheumatic fever, is accompanied by neuropsychiatric symptoms reminiscent of OCD and Tourette's disorder. Unlike OCD or Tourette's disorder, however, much about the pathogenesis of Sydenham's chorea has been known since the mid 1970s. In particular, a study by Husby and colleagues (1976) suggested that the damage to the basal ganglia, characteristic of Sydenham's chorea, is mediated by antineuronal antibodies as part of an autoimmune response to group A β-hemolytic streptococcal (GABHS) infection. Hence, it was proposed that a similar process might cause OCD and/or Tourette's disorder in a subset of cases (Swedo et al. 1994). Critical clinical research initiated in the late 1980s found that OCD symptoms were common among children with Sydenham's chorea and that these symptoms often preceded motor manifestations of the disease (Swedo et al. 1989a, 1993). A series of studies involving children with OCD and Tourette's disorder showed that antineuronal antibodies were present in a subset of patients (Leonard et al. 1992; Rettew et al. 1992; Swedo et al. 1989b). Longitudinal study of a number of such patients indicated characteristic features of abrupt onset and discrete episodes of symptom exacerbation that are often associated with demonstrable GABHS infection (Allen et al. 1995; Ayoub and Wannamaker 1966; Berrios et al. 1985; Swedo et al. 1998). Interestingly, a few longitudinal cases have been reported in which serial neuroimaging data showed acute changes in striatal volume that parallel the clinical course (Giedd et al. 1995). Taken together, these findings led to the designation of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Specific criteria have been developed based on research to date and include 1) presence of OCD and/or a tic disorder, 2) prepubertal onset, 3) episodic course of symptom severity, 4) association with GABHS infection, and 5) association with neurological abnormalities (Allen et al. 1995; Swedo et al. 1998). Autoimmune mechanisms of pathogenesis in this subtype of OCD and related disorders suggest new possibilities in terms of early diagnosis and treatment, including prophylaxis with antibiotics and plasmapheresis (Swedo et al. 1998).

A vulnerability to rheumatic fever, and hence PANDAS, may be inherited as an autosomal recessive trait (Gibofsky et al. 1991). A monoclonal antibody against the B-lymphocyte antigen D8/17 appears to serve as a genetic marker for susceptibility to rheumatic fever; preliminary studies have indicated significantly greater D8/17 binding in cases of OCD and Tourette's disorder (T.K. Murphy et al. 1997; Swedo et al. 1997). Because PANDAS cases bear striking similarity to previously unselected cases of early-onset and tic-related OCD as well as Tourette's disorder, it is tempting to consider

that PANDAS may account for a substantial proportion of childhood-onset cases of OCD and related disorders. In fact, the relative frequency of OCD and Tourette's disorder attributable to PANDAS is unknown. However, it is interesting that family genetic data suggest a different inheritance pattern for PANDAS than has been observed in the large pedigrees of OCD and Tourette's disorder studied to date.

Neuroanatomical Correlates of Factor-Analyzed Symptom Dimensions

Although PANDAS provide the potential for identifying one subtype of obsessive-compulsive spectrum conditions with a homogeneous etiology, optimal strategies for characterizing obsessive-compulsive spectrum subtypes based on pathophysiology and phenomenology have yet to be established. Several strategies have been used for subtyping OCD and related disorders based on symptomatology. The approach of factor analysis has been used to determine clusters of intercorrelated OCD symptoms that can be treated as orthogonal factors for describing clinical presentation (Baer 1994; Leckman et al. 1997). Because these factors are independent of one another, it is reasonable to hypothesize that each one reflects a separate underlying aspect of pathophysiology. This modular approach to the characterization of OCD was recently tested by seeking neuroanatomical correlates of symptom severity for each factor with positron-emission tomography (Rauch et al., in press). In this preliminary study, the symptom factors used included 1) checking and religious, aggressive, and sexual obsessions; 2) symmetry and ordering; and 3) washing and cleaning (Baer 1994; Leckman et al. 1997). Of note, factors 1 and 2 had previously been associated with tic-related OCD. Interestingly, Rauch and colleagues (in press) found that during a nominally neutral state, factor 1 was positively correlated with bilateral striatal activity, factor 2 was negatively correlated with right caudate activity, and factor 3 was positively correlated with orbitofrontal and anterior cingulate cortical activity. These results, although preliminary, suggest that different symptom dimensions are associated with activity within different modules of the CSTC circuits of interest. In fact, the three key findings may correspond to 1) increased activity within striatal neurons that participate in the direct system, 2) decreased activity within striatal neurons that participate in the indirect system, and 3) increased activity within the relevant prefrontal cortical zones. This constellation of findings resonates with the range of substrates hypothesized in the earlier sections on the neuroanatomy of OCD and related disorders and underscores the potential pathophysiological heterogeneity of these conditions.

Neurochemistry and the Neuropharmacology of Obsessive-Compulsive Disorder and Related Disorders

Neurotransmitters mediate communication among the cells that compose the neuroanatomical constructs discussed earlier in this chapter. Furthermore, the neurochemistry and molecular biology of neuronal events form the basis of neuropsychiatric health and disease. In this section, we review the role of serotonergic and dopaminergic systems in OCD and related disorders.

Serotonin and the Pathogenesis of Obsessive-Compulsive Disorder

Serotonin is a neurotransmitter that is released from neurons whose cell bodies are located within the raphe nuclei of the midbrain. Serotonergic projections from the raphe are widespread. Moreover, numerous different serotonergic receptor subtypes exist, each with its own profile in terms of distribution in brain, location on neurons, effector mechanisms (e.g., second messengers), and influences on neuronal firing (Hoyer et al. 1994). Consequently, dissection of the serotonergic system is a complex and challenging enterprise.

A serotonergic hypothesis of OCD was prompted originally by the observed differential efficacy of SRIs in alleviating OCD symptoms (Fernandez and Lopez-Ibor 1967; Greist et al. 1995; Insel et al. 1983; Leonard et al. 1989; Thoren et al. 1980; Zohar and Insel 1987). There was instant appeal to the concept that SRIs might have antiobsessional effects by correcting some fundamental abnormality in the serotonergic system. However, the fact that medications with serotonergic action serve as effective antiobsessional agents does not necessarily mean that the serotonergic system is fundamentally dysfunctional in OCD. Rather, SRIs may act via modulation of an intact system to compensate for underlying pathophysiology in OCD that is otherwise unrelated to serotonin function. Thus, it is critical to distinguish between these different concepts; some

research efforts may speak to the hypothesis of a primary serotonergic abnormality in patients with OCD, whereas others more directly address how and where SRIs confer their beneficial antiobsessional effects.

Methods for probing the serotonergic system in brain are necessary for directly testing a serotonergic hypothesis of OCD pathophysiology. With the advent of functional imaging receptor characterization techniques, such studies are now feasible. However, the current array of serotonergic selective radioligands amenable to use in neuroimaging studies is limited. Consequently, advances in radiochemistry and pharmacology are necessary to enable a comprehensive dissection of the central serotonergic system in OCD and other disorders. In fact, no serotonergic receptor characterization imaging studies of OCD have been published to date.

In lieu of more direct means of assaying central serotonergic function, a considerable literature has accrued based on indirect measurements. Numerous studies of peripheral receptor binding in the blood or concentrations of serotonin metabolites in cerebrospinal fluid have been performed but have yielded disappointingly inconsistent results (for reviews, see Barr et al. 1992; Marazziti et al. 1994). Furthermore, these measures do not necessarily represent accurate indicators of serotonergic function within the brain. Pharmacological challenge studies provide another indirect approach (for reviews, see Barr et al. 1992; Gross-Isseroff et al. 1994; Marazziti et al. 1994; D.L. Murphy et al. 1996). By administering serotonergic agents and measuring endocrine or behavioral variables, investigators have attempted to assess central serotonergic sensitivities. These paradigms have likewise proven problematic because the pharmacological probes are nonspecific and the dependent variables assayed are typically mediated by a complex interplay of different neurochemical systems. Therefore, the serotonergic hypothesis of OCD remains not only unproven but largely untested.

In contrast, considerable pharmacological research has begun to clarify the therapeutic mechanisms of SRIs. Animal studies indicate that antidepressants can potentiate serotonergic transmission (Blier and de Montigny 1994). In the case of SRIs, potentiation of serotonergic transmission appears to be mediated by autoreceptor desensitization (Blier and Bouchard 1994; Blier et al. 1988). The time course of these receptor changes parallels the observed delay between initiation of SRIs and onset of therapeutic response. In an important study, Mansari and colleagues (1995) showed that SRI-induced changes in serotonergic transmission occur more quickly in lateral frontal cortex than in medial frontal cortex of rodents. This corresponds with the observation that the antidepressant effects of SRIs tend to occur sooner than do the antiobsessional effects (Fineberg et al. 1992), given current models of mediating anatomy suggesting that lateral prefrontal areas are involved in the pathophysiology of major depression, whereas medial frontal (i.e., orbitofrontal) cortex has been implicated in the pathophysiology of OCD. The ultimate neuropharmacological effects of SRIs on frontal cortex and other relevant territories remain to be fully delineated. Likewise, the relative role of different receptor subtypes (see Pineyro et al. 1994), as well as downstream effects on second messengers and genetic transcription factors (see Lesch et al. 1993), requires further study.

In summary, very limited evidence supports a serotonergic hypothesis of OCD pathophysiology, but modulation of serotonergic systems clearly plays a role in effective pharmacotherapy with serotonergic agents for OCD. Emerging data suggest that SRIs might have their beneficial effects, following a delay of several weeks, by downregulating terminal autoreceptors ($5\text{-}HT_{1D}$) in orbitofrontal cortex, thereby facilitating serotonergic transmission in that region (Mansari et al. 1995). Advances in radiochemistry and pharmacology, together with contemporary in vivo neuroimaging methods, should soon provide an opportunity to directly test the serotonergic hypothesis of OCD pathophysiology. Additional studies will be necessary to clarify the precise mechanisms that underlie the antiobsessional effects of SRIs, as well as other effective treatments, including nonpharmacological modalities.

Finally, it is not clear how this information generalizes to other related disorders. SRIs appear to be of modest therapeutic benefit for BDD and trichotillomania but typically are not effective for reducing the tics of Tourette's disorder (although they can be helpful for addressing other associated affective or behavioral manifestations). Thus, a model of SRI action in OCD and related disorders must explain the observed differential efficacy across this spectrum of disorders. Given the data at hand, SRIs may have their effects by modulating corticostriatal systems at the level of cortex and with prominent effects within medial and lateral prefrontal zones. Hence, obsessive-compulsive spectrum disorders that entail dysfunction within the cognitive and affective corticostriatal circuits might be preferentially responsive to SRIs; chronic tics involving sensorimotor cortex may be unresponsive to such interventions.

Dopaminergic Systems and the Pathogenesis of Tourette's Disorder

Complementing the above discussion of serotonin and its role in OCD, dopamine antagonists are effective for reducing the tics of Tourette's disorder as well as the manifestations of other hyperkinetic movement disorders. Conversely, dopamine agonists exacerbate tics and other adventitial movements. Unlike the serotonergic hypothesis of OCD, however, considerable data implicate primary dopaminergic abnormalities in Tourette's disorder.

The cell bodies of dopamine-containing neurons are principally concentrated in midbrain and tegmentum and project rostrally, forming the nigrostriatal pathway, as well as the mesolimbic and mesocortical systems. It has long been presumed that the therapeutic effects of dopamine antagonists in hyperkinetic movement disorders follow logically from the well-established role of dopamine in mediating motor control via the nigrostriatal system.

A series of studies have identified striatal dopamine receptor abnormalities in Tourette's disorder. A comparison of postmortem tissue from patients with Tourette's disorder and control subjects showed higher binding rates for a dopamine transporter site ligand in the striatum (Singer et al. 1991). An analogous in vivo neuroimaging study (Malison et al. 1995) reported increased binding capacity for dopaminergic reuptake sites in the striatum of patients with Tourette's disorder compared with matched control subjects, indicating an elevated density of available transporter sites in Tourette's disorder. In a study of twins concordant for Tourette's disorder but discordant for tic severity, Wolf and colleagues (1996) found decreased binding capacity for dopaminergic postsynaptic receptors in the striatum of the more severely affected twins. These results imply that more severe Tourette's disorder is associated with either higher levels of ambient dopamine or a reduced density of postsynaptic dopamine receptor sites. Taken together, the findings from these three studies suggest that patients with Tourette's disorder do have abnormalities of the dopaminergic system within the striatum. These preliminary findings should be interpreted cautiously, however, because the sample sizes were small and the subjects in these studies were not neuroleptic naive. Therefore, some of the observed abnormalities may be a consequence of past exposure to antidopaminergic medications or other differences between the groups that are unrelated to the Tourette's disorder diagnosis. Nonetheless, these data provide initial evidence supporting a dopaminergic hypothesis of Tourette's disorder. Specifically, Tourette's disorder appears to be associated with fundamental dopaminergic abnormalities within the striatum, and tic symptoms can be exacerbated by exposure to dopamimetic agents and attenuated by treatment with dopamine antagonist medications.

Neurochemistry Across the Obsessive-Compulsive Spectrum

Pathophysiological heterogeneity may explain why some subtypes of OCD are responsive to SRIs alone and others to SRIs plus dopamine antagonists, whereas others are wholly unresponsive to either of these interventions. For instance, tic-related OCD appears to be relatively SRI refractory and preferentially responsive to the combination of SRIs plus dopamine antagonists (e.g., McDougle et al. 1994a, 1994b). One possibility is that non-tic-related OCD and BDD involve primary orbitofrontal dysfunction or pathophysiology, whereas tic-related OCD and Tourette's disorder involve primary striatal pathology. Hence, serotonergic modulation at the level of orbitofrontal cortex might be sufficient for antiobsessional effects in non-tic-related OCD or BDD, whereas dopaminergic modulation within the striatum synergizes with orbitofrontal serotonergic modulation to relieve tic-related OCD, and pure Tourette's disorder responds to dopamine modulation at the level of the striatum but not to serotonergic modulation at the orbitofrontal cortex.

Integrating Perspectives on the Pathogenesis of Obsessive-Compulsive Disorder and Related Disorders

We have reviewed etiological and pathophysiological models that reflect current concepts regarding the pathogenesis of OCD and related disorders. It is clear that no single model explains the full spectrum of clinical and neurobiological phenomena associated with obsessive-compulsive spectrum disorders. On the contrary, accruing evidence implicates a multiplicity of etiologies and a true pathophysiological spectrum of disease. Consequently, a sophisticated understanding of

OCD and related disorders requires an integration of the various pieces of this puzzle. We propose that neurobiologically and clinically relevant schemes for subtyping OCD, as well as for defining and subdividing populations with obsessive-compulsive spectrum disorders, are critical to advancements in our understanding of these diseases.

CSTC loops represent an anatomical framework within which to describe the pathogenesis of OCD and related disorders. One perspective emphasizes which circuits are involved: dysfunction within the orbitofrontal-caudate circuit may represent a final common pathway for OCD symptoms; analogous dysfunction within the sensorimotor-putamen pathway may underlie chronic tics. Another perspective emphasizes the locus of primary pathology within these circuits: we have reviewed data that implicate striatal subterritories as primary sites of pathology (by virtue of both observed volumetric abnormalities and one feasible etiological scenario via autoimmune mechanisms); TMS data suggest that defective inhibition within cortex could be primary in some cases. A third perspective acknowledges the neurochemistry superimposed on the anatomy: serotonergic medications appear to act at the level of cortex to ameliorate OCD symptoms but not Tourette's disorder; dopaminergic medications are purported to have their principal action within striatum and are effective as primary treatments in Tourette's disorder but only as augmentors of SRIs in a subgroup of patients with tic-related OCD. A fourth perspective focuses on the issue of etiology: genetic factors appear to play a role in most cases of OCD and Tourette's disorder; however, the essence of what is inherited to confer increased risk is unclear, as are the critical epigenetic factors that influence expression, including penetrance.

PANDAS represent a prime example in which these various perspectives can be integrated to describe a phenomenological spectrum, whose genesis likely can be found in an inherited vulnerability for autoimmune destruction of striatum in the face of GABHS infection. Presumably, the topography and extent of striatal damage largely governs the clinical presentation, as well as the efficacy of conventional treatments. PANDAS are such a valuable example not only because they bridge the above perspectives but also because they underscore the potential benefits derived from delineating pathogenesis: once the etiology and pathophysiology of a disease are better understood, the scientific community is better equipped to rationally pursue superior interventions and even prophylaxis or cure.

Future Research

Advances in the genetics of obsessive-compulsive spectrum disorders could be most important. Once genes that confer risk are identified, the potential to study subjects at risk longitudinally will be enhanced, thereby enabling the investigation of pathogenesis. Furthermore, with identification of at-risk individuals, early diagnosis and thus early intervention or prophylactic strategies become feasible. Although a map of the human genome has been completed, genetic studies are ultimately reliant on valid determinations of phenotype. Hence, establishing phenotypic designations based on convergent data, including phenomenological, physiological, and etiological factors, is crucial.

Evolving brain imaging techniques represent the most powerful tools for characterizing in vivo human neuroanatomy, neurophysiology, and neurochemistry at modest temporal and spatial resolution. Categorical approaches will aim to identify discrete subtypes of patients based on the above measures as well as symptomatology and treatment response. Dimensional approaches will aim to consider these as continuous variables. Only time will tell which of these approaches is superior for describing the obsessive-compulsive spectrum. Prospective imaging studies can generate and test hypotheses regarding the elements of neuroimaging profiles that predict treatment response for medications, behavior therapy, or other therapies. Simultaneously, phenomenological characteristics can be correlated with both brain imaging indices and treatment outcomes. Thus, by triangulating across such multifaceted data sets, it should be possible to achieve a robust and valid clinical-neurobiological basis for diagnosis and subtyping across the obsessive-compulsive spectrum.

As various pathophysiological entities are dissected, the hope is that each one will give way to specific treatments. Basic pharmacological research will continue to explore the receptor changes and, perhaps more important, the downstream molecular effects of currently available therapies. Such research will progressively illuminate the salient changes that are necessary to ameliorate symptoms in each of the subtypes of the obsessive-compulsive spectrum. Once these targets are established, it will be possible to rationally design new and hopefully better treatments. Although this paragraph implies a focus on pharmacotherapy, in fact an analogous process is required to advance nonpharmacological treatments, including behavior therapy.

These are exciting times in psychiatric neuroscience, as the field moves closer to the promise of a diagnostic scheme that reflects pathophysiology. In this context, OCD is a model disorder: despite its historical placement among the anxiety disorders, with which OCD does share many phenomenological similarities, contemporary research is clarifying that at least one subtype of OCD is closely related to a movement disorder, and perhaps another is associated with an autoimmune etiology. Although technical advances in neuroimaging, genetics, and pharmacology have provided new tools with which to elucidate the pathogenesis of OCD, there should be renewed enthusiasm for the essential contribution of careful phenomenological characterization. It should already be clear that OCD, as defined in DSM-IV, is not one disease but several; conversely, in some cases, OCD and Tourette's disorder may not be different diseases pathogenetically but rather different faces of the very same one.

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Pharmacotherapy for Obsessive-Compulsive Disorder

Wayne K. Goodman, M.D.

Not long ago, obsessive-compulsive disorder (OCD) was viewed as refractory to conventional therapies. Traditional talk therapy based on psychoanalytical principles was rarely successful in reducing the severity of obsessions or compulsions. The success rate with a range of different medications was just as disappointing. The 1980s witnessed renewed optimism about the prognosis of OCD as new, more effective forms of behavior therapy and pharmacotherapy were introduced and subjected to rigorous testing. The form of behavior therapy that has been most effective in OCD is referred to as *exposure and response prevention*. Exposure consists of confronting the patient with situations that evoke obsessional distress; response prevention consists of instructing the patient how to resist performing compulsive rituals (see Greist and Baer, Chapter 17 in this volume, for an in-depth discussion of the use of behavior therapy in OCD). At present, the mainstay of the pharmacotherapy for OCD is a trial with a serotonin reuptake inhibitor (SRI).

Serotonin Reuptake Inhibitors

The modern era in the pharmacotherapy for OCD began in the late 1960s with the observation that clomipramine, but not other tricyclic antidepressants, relieved obsessive-compulsive symptoms. Clomipramine, the 3-chloro analogue of the tricyclic imipramine, is unique among the tricyclics in its marked potency for blocking serotonin reuptake. These distinctive clinical and pharmacological properties of clomipramine led to the hypothesis that serotonin might be involved in the pathophysiology of OCD. To date, the bulk of the evidence supporting a role for serotonin in OCD is based on drug response data (i.e., the preferential efficacy of SRIs) (Goodman et al. 1990). As discussed throughout this chapter, a trial with an SRI is the cornerstone of pharmacological management. Unfortunately, because clinical response is not always satisfactory, a major portion of this chapter is devoted to biological approaches to SRI nonresponders.

The superiority of clomipramine over placebo and nonserotonergic antidepressants (e.g., desipramine) has been confirmed in numerous double-blind trials (Clomipramine Collaborative Study Group 1991). Clomipramine was the first medication to receive U.S. Food and Drug Administration (FDA) approval for OCD. Desmethylclomipramine, a major metabolite of clomipramine, potently blocks reuptake of both serotonin and norepinephrine. During chronic treatment, des-

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methylclomipramine attains higher plasma levels than its parent compound. Most side effects of clomipramine can be predicted from its receptor binding profile. Like other tricyclic antidepressants, side effects typical of anticholinergic blockade (e.g., dry mouth and constipation) are common. Many patients complain of sedation and weight gain, likely the result of antihistaminic (H_1) binding. Orthostatic hypotension is thought to be caused by α-adrenergic blockade. Nausea and tremor also are common with clomipramine, as with other SRIs. Impotence and anorgasmia occur with clomipramine. Safety concerns include prolongation of the Q-T interval and seizures; the risk of seizures increases significantly at dosages greater than 250 mg/day. Intentional overdoses with clomipramine can be lethal.

In the last decade, trials have been conducted in patients with OCD with a newer generation of antidepressants—the selective serotonin reuptake inhibitors (SSRIs): fluvoxamine, paroxetine, sertraline, fluoxetine, and citalopram. Unlike clomipramine, none of these medications loses its selectivity for blocking serotonin reuptake in vivo. Also in contrast to clomipramine (and other tricyclics), these drugs lack significant affinity for histaminic, cholinergic, and α-adrenergic receptors. All potent SRIs tested to date have proved efficacious in OCD. An FDA indication for OCD in adults has been granted for fluvoxamine, fluoxetine, paroxetine, and sertraline. Another potent SSRI, citalopram, was recently introduced for the treatment of depression in the United States, and a double-blind controlled trial in OCD reported efficacy. The anti-OCD efficacy of fluvoxamine and sertaline have been confirmed in children. SSRIs generally are well tolerated. The most common side effects associated with SSRIs are nausea, somnolence, insomnia, tremor, and sexual dysfunction (anorgasmia). There are few significant safety concerns, and the risk with overdose is small.

It is noteworthy that antidepressants that do not significantly block serotonin reuptake (e.g., desipramine) generally are ineffective in treating OCD. As was previously shown for clomipramine, fluvoxamine was more effective than desipramine in reducing obsessive-compulsive symptoms (Goodman et al. 1990). In this respect, OCD contrasts sharply with depression and panic disorder, two psychiatric illnesses that, in most studies, respond equally well to antidepressants with differing profiles of monoamine reuptake affinity. Furthermore, potent SRIs generally are less effective in OCD than in depression or panic disorder. Indeed, the response of depression or panic disorder to treatment is often all-or-none, whereas OCD is more likely to show a graded and incomplete response to treatment. Based on conservative outcome criteria, approximately 40%–60% of the patients with OCD experience a clinically meaningful response to a trial with an SRI.

Acute blockade of serotonin reuptake appears to be the critical first step in a chain of neural events leading to anti-OCD efficacy. Based on their electrophysiological studies in laboratory animals, Blier and de Montigny (1998) proposed that enhancement of serotonin neurotransmission in the orbitofrontal cortex during chronic SRI administration is related to the mechanism of action of these agents in OCD.

Now that several potent SRIs are available, an important clinical question is whether significant differences exist in the anti-OCD efficacy of these drugs. A meta-analysis comparing published multicenter trials found that clomipramine was significantly superior to fluoxetine, sertraline, and fluvoxamine (Greist et al. 1995). However, meta-analyses are subject to several limitations, including the possibility that the apparent differences in drug efficacy actually reflect underlying differences in patient characteristics. The early multicenter clomipramine trials were conducted at a time when no effective alternatives to clomipramine were available, whereas in subsequent studies, many patients resistant to other medications (including clomipramine) were included. The best way to determine the comparative efficacy of treatments is a randomized, head-to-head, double-blind comparison. The results of several such studies comparing clomipramine with SSRIs have been published recently (Flament and Bisserbe 1997; Koran et al. 1996; Zohar and Rajinder 1996). By and large, these studies have failed to find evidence for the superiority of clomipramine over the SSRIs tested thus far. With regard to side effects, the outcome is different: SSRIs generally are better tolerated and associated with fewer serious side effects compared with clomipramine.

Acute Pharmacological Management

The recognition and accurate diagnosis of OCD are the first steps in the proper treatment of this condition. If the diagnosis of OCD is overlooked, then inappropriate treatment may be prescribed. For example, patients with OCD often present with symptoms of depression or anxiety, but not all antidepressants and few, if any, anxiolytic medications are effective antiobsessional agents. Likewise, treatments that have proven effective for OCD may be of little value in treating the symp-

toms of other disorders, such as the delusions of schizophrenia or the character traits of obsessive-compulsive personality disorder.

The first line in the pharmacotherapy for OCD is a 10- to 12-week trial with an SSRI at adequate doses. It is difficult to justify beginning with clomipramine given the superior tolerability and safety of SSRIs and their comparable efficacy. Which SSRI to prescribe initially is based on the expected side-effect profile and pharmacokinetic considerations. However, in the individual patient, it is quite difficult to predict the best fit with a particular agent. In the early stages of treatment, the primary objective is to promote compliance. Although patients may be experiencing marked distress and functional impairment, most have had symptoms for years before presenting for treatment. The dose of SRI can be increased incrementally every 3–4 days in outpatients (even faster in inpatients), but this dose escalation should be reduced if the patient is troubled by side effects, particularly nausea. Fluoxetine, paroxetine, and sertraline can be given as a single daily dose. The package inserts recommend initiating clomipramine and fluvoxamine therapy on a twice-daily regimen, but in most cases these drugs can be given as a single daily dose, usually at night because they tend to be sedating. In contrast, fluoxetine tends to be activating and is best administered in the morning so that sleep is not disrupted. If the patient reports insomnia while taking fluvoxamine, then the schedule should be reversed such that the bulk (or all) of the dose is taken in the morning.

Experts agree that the duration of an adequate medication trial must be between 10 and 12 weeks, but opinion is less uniform with regard to what constitutes an adequate dose. Some, but not all, fixed-dose trials of SSRIs indicate that higher doses are significantly superior to lower doses in the treatment of OCD. In the case of paroxetine in OCD, 20 mg/day was no different from placebo; the lowest effective dose was 40 mg/day (Wheadon et al. 1993). By and large, studies of fluoxetine treatment in OCD suggest that 60 mg/day is more effective than 20 mg/day but that 20 and 40 mg/day are still more effective than placebo (Tollefson et al. 1994). Because the 60-mg daily dose of fluoxetine is associated with more side effects than are lower dosages, the preferred clinical practice is to administer 40 mg for about 8 weeks before increasing the dose further in patients with OCD. In the final analysis, the criteria for an adequate trial must be defined in terms of the medication(s) in question. Adequate trials in OCD of clomipramine, fluvoxamine, fluoxetine, sertraline, and paroxetine would be 10–12 weeks of treatment with a minimum mean daily dosage of 150 mg, 150 mg, 40 mg, 150 mg, and 40 mg, respectively, for at least 8 weeks. Although a trial of fluoxetine at 40 mg/day for 10 of 12 weeks might be deemed adequate, a nonresponder to such a trial should probably not be labeled as fluoxetine resistant until the dosage was increased to 80 mg/day as tolerated.

Based on the multicenter trial of fluvoxamine in children (8 years or older) and adolescents with OCD (Riddle et al. 2001), it is advisable to start fluvoxamine in patients in this age range as a 25-mg dose at bedtime. This dose should be continued for approximately 3 days and then increased by 25-mg increments every 3–4 days until a maximum daily dose of 200 mg is achieved. Fluvoxamine should be given twice daily for daily doses of 75 mg or greater, with the larger dose given at bedtime. In general, lower maximal dosages of SRIs should be used in the elderly and in patients with hepatic insufficiency.

Long-Term Treatment

Important clinical questions remain unanswered regarding the long-term management of patients who have responded to an acute drug trial. Compared with an ample database on long-term treatment of depression, little is currently known about how long medication should be continued in OCD. In clinical practice, most patients continue taking medications for at least 1 year; some seem to require indefinite treatment. The relapse rate with abrupt discontinuation of medication is high in OCD—as much as 90% in some studies (Pato et al. 1990). It has not yet been established in a controlled study whether a gradual taper of medication over a longer period (e.g., 6 months or more), as is usually done in clinical practice, produces a lower relapse rate. An alternative to outright discontinuation is a dose reduction to a new stable level. Both clinical experience and a recent report (Ravizza et al. 1996) suggest that patients with OCD can be maintained successfully at lower doses than those required to produce an initial treatment response.

Adverse events have been associated with abrupt discontinuation of clomipramine and the SSRIs paroxetine, fluvoxamine, and sertraline. Relatively fewer reports of withdrawal syndromes following abrupt cessation of fluoxetine may reflect the long half-lives of the parent drug and its metabolite norfluoxetine. The constellation of symptoms reported with the SSRIs is

somewhat variable but has most frequently included flulike symptoms, vertigo/dizziness, insomnia, vivid dreams, irritability, and headaches lasting from several days to more than a week. No medically significant events have been documented, but patients often describe marked discomfort. To reduce the risk of a discontinuation syndrome, a gradual taper is recommended for all SRIs except fluoxetine.

Definitions of Treatment Resistance

Various terms have been used to describe patients who have failed treatment, but there is no universal agreement on a recommended nomenclature. For the purposes of this review of biological therapies, the term *treatment resistant* is generally applied to those patients who have not shown a satisfactory response to adequate trials of at least two SRIs. The terms *treatment refractory* or *intractable* connote greater degrees of treatment resistance, as reflected in failure to respond to a variety of anti-OCD treatment strategies (including combinations of agents) as well as behavior therapy.

The classification of patients as treatment failures is critically dependent on the definition of response that is used. Most recent studies have used change scores on the 10-item Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al. 1989a, 1989b) (range=0 [no symptoms] to 40 [extreme symptoms]) as the primary outcome measure. Most large-scale drug trials have used a 25% or greater decrease from baseline in Y-BOCS score to define a responder. The clomipramine multicenter trials set a higher threshold of a 35% reduction in Y-BOCS score to meet response criteria. Some studies have required responders to achieve a "much" or "very much improved" rating on the Clinical Global Impression Scale in addition to meeting Y-BOCS criteria. Nevertheless, a problem with using "change" criteria alone is that a patient who is classified as a responder still may have clinically significant symptoms of OCD at the conclusion of the trial. For example, a patient who started out with very severe symptoms (baseline Y-BOCS score=30) may be counted as a responder when a 35% reduction in Y-BOCS scores is used but still have moderate symptoms (Y-BOCS score=19.5). The patient in this example might be better categorized as a "partial responder," reserving the category "responder" for those who achieve an endpoint below a preestablished severity level (e.g., Y-BOCS score=16).

Reasons for Treatment Resistance

Different factors may account for the nonresponse of OCD to a potent SRI. First, the adequacy of the acute drug trial must be evaluated. Was the duration of the trial long enough or the dose sufficient? Some estimate of compliance is helpful in determining whether the trial was adequate, as indicated by drug plasma levels or pill counts. Patients with OCD generally are quite compliant except when their obsessive-compulsive symptoms interfere. One patient refused to take his medication because he thought that the bottle was contaminated; another would not follow the prescription of three pills a day because "odd" numbers were "bad." Clinical trials have not found a direct relation between SRI plasma levels and response in OCD. However, as discussed later in this chapter, it may be advisable to monitor clomipramine plasma levels when used in combination with some other drugs. Once the adequacy of a trial has been established, other explanations should be sought for cases of treatment resistance. Possible reasons for variability in drug response include effects of comorbid conditions, differences in underlying pathobiology, and psychosocial factors that can affect treatment. Evidence indicates that certain comorbid conditions are associated with a lower treatment response rate. OCD patients with schizotypal personality disorder appear to have a relatively worse outcome (Jenike et al. 1986). Most studies indicate that the response of obsessive-compulsive symptoms to SRIs generally is independent of the presence or severity of coexisting depression. Another study suggested that the response rate to SRI monotherapy is lower in OCD patients with a chronic tic disorder (McDougle et al. 1993). Patients with a clinical subtype of OCD referred to as *primary obsessional slowness* (Rachman and Hodgson 1980)—characterized by pervasive slowness in performing routine activities, pathological doubting, and checking—seem to be less responsive to treatment.

A careful differential diagnostic assessment should precede a drug trial. It is especially important to distinguish between OCD and the Axis II condition obsessive-compulsive personality disorder because there is little evidence that the latter responds to pharmacotherapy. Even apparently classic and uncomplicated cases of OCD have a variable response to SRI monotherapy. Variability in drug response raises the possibility that the pathogenesis of OCD is heterogeneous. Accidents of nature furnish direct evidence for this premise. Numerous clinical reports document that in-

jury to structures of the basal ganglia can produce obsessive-compulsive symptoms (Goodman et al. 1990). At present, however, one cannot rely on putative clinical subtypes of OCD to predict whether an individual patient will respond to SRI treatment. Even patients with obsessive-compulsive behavior secondary to an acute brain insult may show symptomatic improvement with SRI treatment.

Dosage Escalation and Switching Antidepressants

If a patient has had a limited response but few side effects while taking an SRI, the next logical step is to increase to the highest recommended dose. Fortunately, the SSRIs are generally safe even at high doses. In contrast, clomipramine should not be administered in doses above 250 mg/day without careful medical monitoring (e.g., serial electrocardiograms) and unless clinically indicated. The anti–obsessive-compulsive efficacy of supramaximal (above-recommended) doses of SSRIs has not been formally studied, although case reports have shown beneficial results with this approach (Byerly et al. 1996).

Several authors of literature reviews on pharmacotherapy for OCD have advocated changing to a different SRI if there has been no improvement at all following an adequate trial with one SRI. If there have been partial gains, a combination treatment approach is generally recommended instead. Naturally, if the patient does not tolerate one SRI, it is advisable to try a different one, selected on the basis of expected side-effect profile. Sometimes two or more SRIs need to be tried to identify the agent that is most effective for that particular patient.

The starting point for most pharmacological treatments is a trial with an SSRI rather than with the nonselective SRI clomipramine. Based on recent head-to-head studies, clomipramine shows no advantage in efficacy over SSRIs; whereas the SSRIs generally are better tolerated than clomipramine. Given equivalent efficacy and the superior safety and tolerability of SSRIs, it is difficult to justify commencing treatment with clomipramine unless the patient has a history of a good response to this drug. These practical considerations notwithstanding, I believe that some patients respond preferentially to clomipramine and, therefore, that no patient should be summarily declared treatment refractory in the absence of a clomipramine trial.

Based on some intriguing case reports (Jenike et al. 1983), a trial with a monoamine oxidase inhibitor (MAOI) showed promise in OCD patients with comorbid panic disorder. More recently, Jenike tested the hypothesis that comorbid anxiety may predict response to an MAOI in a 10-week double-blind, placebo-controlled trial of phenelzine (60 mg/day) versus fluoxetine (80 mg/day) (Jenike et al. 1997). Fluoxetine was significantly superior to both placebo and phenelzine in this trial. Phenelzine was no more effective than placebo, even in the subset of patients with prominent anxiety symptoms. I believe that MAOIs should be reserved as a distant second-line approach in treatment-refractory OCD.

Several novel medications have been introduced for the treatment of depression, but their value in the treatment of OCD has not been established. Venlafaxine inhibits the reuptake of both serotonin and norepinephrine without significant affinity for muscarinic, histaminergic, or noradrenergic receptors (Nierenberg et al. 1994b). Case reports and open-label studies support the efficacy of venlafaxine in OCD (Ananth et al. 1995; Grossman and Hollander 1996; Rauch et al. 1996; Zajecka et al. 1990). In contrast, venlafaxine was not significantly better than placebo in a double-blind trial of 30 patients with OCD (Yaryura-Tobias and Neziroglu 1996). The relatively short 8-week duration of treatment was a limitation of this study. Together, these published reports seem to warrant additional testing of venlafaxine in OCD under double-blind conditions for 10–12 weeks of treatment.

Nefazodone is structurally related to trazodone but has a somewhat different pharmacological profile and less propensity for inducing sedation (Fontaine et al. 1994). Early pilot studies of nefazodone in OCD were suspended, apparently because of lack of efficacy (T. Pigott, W.K. Goodman, S.A. Rasmussen, unpublished data, October 1991). The use of nefazodone was implicated in the emergence of obsessive-compulsive symptoms in a patient being treated for depression (Sofuoglu and Debattista 1996).

Combination Strategies: Adding Another Treatment to the Serotonin Reuptake Inhibitor

The patient who has had a partial response to SRI monotherapy or failed to show any improvement following two consecutive trials with different SRIs is a candidate for combination treatment.

Serotonin Reuptake Inhibitor Plus Behavior Therapy

Although a combination of an SRI and exposure and response prevention is believed to be the most broadly effective treatment for OCD, support from double-blind, placebo-controlled studies remains sparse (for review, see van Balkom et al. 1994). In fact, few studies have adequately addressed the question of whether a potent SRI plus behavior therapy is superior to either treatment alone. The studies that have examined this question either had methodological shortcomings that cloud interpretation or did not show clear advantages of combined SRI and behavior therapy over SRI therapy alone.

Serotonin Reuptake Inhibitor Plus Agents That May Alter Serotonin Function

To date, the rationale for most drug combination strategies has been to add agents that may modify serotonergic function, such as tryptophan, fenfluramine, lithium, or buspirone, to ongoing SRI therapy. The addition of clonazepam, trazodone, pindolol, or another SRI also is discussed in this section.

Tryptophan

The addition of tryptophan, the amino acid precursor of serotonin, has been reported helpful in a patient with OCD taking clomipramine (Rasmussen 1984). Adverse neurological reactions resembling the serotonin syndrome seen in laboratory animals have been reported when tryptophan is used in combination with fluoxetine (Steiner and Fontaine 1986). At present, oral tryptophan supplements are not routinely available in the United States because of evidence linking some of these preparations to a serious and potentially fatal hematological/connective tissue illness (Hertzman et al. 1990). Blier and Bergeron (1996) of McGill University (Montreal, Quebec, Canada), where tryptophan is not restricted, described the benefits of adding tryptophan to a subgroup of patients with OCD taking a combination of an SRI and pindolol (see subsection "Pindolol" later in this chapter).

Fenfluramine

In open-label studies, both *d,l*-fenfluramine (Pondimen) (Hollander et al. 1990) and dexfenfluramine (Redux) (Heninger et al. 1983) have been reported beneficial when used as adjuncts in cases of OCD unresponsive to SRIs. Both drugs are serotonin releasers and reuptake blockers used in the past as anorectic agents. In September 1997, the manufacturer (Wyeth-Ayerst) of Pondimen and Redux voluntarily removed these products from the market worldwide after reports of serious cardiac complications (carcinoid-like valvular changes) (Connolly et al. 1997).

Lithium

Coadministration of lithium is a proven method for enhancing the thymoleptic action of antidepressants in depressed patients (Heninger et al. 1983). Lithium has been hypothesized to potentiate antidepressant-induced increases in serotonin neurotransmission by enhancing presynaptic serotonin release in some brain regions (Blier and de Montigny 1992). Despite several earlier encouraging reports, the efficacy of lithium addition has not been corroborated in controlled trials (McDougle et al. 1991; Pigott et al. 1991). Although the overall yield is low in OCD, individual patients, particularly those with marked depressive symptoms, may benefit from lithium augmentation.

Buspirone

In open-label studies, addition of the serotonin type 1A (5-HT_{1A}) agonist buspirone to ongoing fluoxetine treatment in patients with OCD led to greater improvement in obsessive-compulsive symptoms than did continued treatment with fluoxetine alone. These initially encouraging findings were not confirmed in three subsequent double-blind trials (Grady et al. 1993; McDougle et al. 1993; Pigott et al. 1992).

Clonazepam

The benzodiazepine clonazepam generally is not considered a serotonergic agent. However, evidence from studies in both animals and humans indicates that clonazepam may have serotonergic properties not shared by other benzodiazepines (Wagner et al. 1986). Some clinicians maintain that addition of clonazepam to ongoing SRI therapy is helpful in reducing symptoms of OCD, but substantiation by published reports is limited (Jenike 1998). Although existing literature furnishes limited support for the anti–obsessive-compulsive efficacy of adjuvant clonazepam, it seems worthwhile to conduct additional studies with longer durations of combined treatment.

Trazodone

In addition to weakly inhibiting serotonin reuptake, the antidepressant trazodone and its major metabolite,

m-chlorophenylpiperazine, are active at several different neuroreceptors, including several serotonin receptor subtypes and α-adrenergic receptors. In clinical practice, low-dose trazodone is often prescribed as a sedative-hypnotic in conjunction with activating SRIs such as fluoxetine (Nierenberg et al. 1994a). Whether this combination confers any direct anti–obsessive-compulsive benefit remains to be established in controlled studies.

Pindolol

Studies in laboratory animals suggested that antidepressant-induced enhancement of serotonin neurotransmission does not occur immediately because of serotonin autoreceptor–mediated inhibition of firing rate and release. Artigas et al. (1994) hypothesized that the addition of an agent that blocks somatodendritic 5-HT_{1A} autoreceptors might accelerate or augment the action of antidepressants in humans. According to some studies, the β antagonist pindolol acts as a 5-HT_{1A} antagonist at presynaptic sites. In depressed patients, addition of pindolol to antidepressants has been reported to potentiate or hasten response in some (Artigas et al. 1996; Blier and Bergeron 1995) but not all studies (Berman et al. 1997).

In OCD, experience with adjunctive pindolol also has been mixed. An open-label study by Koran et al. (1996) combined pindolol with an SRI in eight patients with OCD who did not show a satisfactory response to the SRI alone. Only one of the eight responded. In another open-label trial, Blier and Bergeron (1996) added pindolol (2.5 mg three times a day) to ongoing SRI treatment in 13 patients with OCD who had not improved with SRIs alone. Four weeks of combined pindolol and SRI treatment had an antidepressant effect in patients with depressive symptomatology but did not reduce severity of obsessive-compulsive symptoms, as reflected in mean scores on the Y-BOCS. Examination of individual Y-BOCS score data did identify clinical improvement in obsessive-compulsive symptoms in 4 of the 13 patients, but overall, the pindolol addition had no significant group effect.

Addition of tryptophan to the SRI and pindolol combination was associated with significant improvement in obsessive-compulsive symptoms after 4 weeks of treatment. These encouraging results with triple therapy (SRI-pindolol-tryptophan) need to be verified in double-blind, placebo-controlled trials.

Byerly and Goodman (1997) reported preliminary findings from an ongoing double-blind, placebo-controlled study of 12 weeks of fluoxetine with or without pindolol. Treatment-resistant patients were excluded from this trial because the main objective was to assess whether pindolol hastened response to fluoxetine. Analysis of the first 12 patients showed a trend toward a more rapid response and greater reduction in obsessive-compulsive symptoms in the fluoxetine plus pindolol group.

It is noteworthy that pindolol showed agonist (not antagonist) effects at the 5-HT_{1A} autoreceptor in a recently published study (Clifford et al. 1998). If confirmed, these findings imply that pindolol is not the appropriate agent to be testing the hypothesis of Artigas et al. (1996).

Another Serotonin Reuptake Inhibitor

In clinical practice, some SRI-resistant patients with OCD receive simultaneous treatment with two SSRIs. However, this strategy has scant empirical or theoretical support. The advantage of dual SSRI therapy over a higher dose of a single agent is difficult to explain based on our current understanding of their pharmacodynamic properties (i.e., common mode of action via inhibition of serotonin transport). Suitable empirical studies would require a control group taking high-dose SRI monotherapy under double-blind conditions.

A more heuristically appealing strategy is the combination of an SSRI and clomipramine. There have been encouraging case reports of coadministering clomipramine with fluoxetine (Browne et al. 1993; Simeon et al. 1990) to minimize unwanted clomipramine-induced side effects. Combining clomipramine and fluvoxamine may offer special advantages as well as risks (Szegedi et al. 1996). Fluvoxamine, a potent inhibitor of cytochrome P450 1A2, inhibits the *N*-demethylation of clomipramine to desmethylclomipramine and thereby reverses the ratio of desmethylclomipramine to clomipramine such that the concentration of the parent exceeds that of its metabolite. Under normal circumstances, plasma concentrations of desmethylclomipramine exceed that of clomipramine during chronic drug administration. Clomipramine, a more potent blocker of serotonin transport than desmethylclomipramine, is also thought to be more potent as an anti-OCD agent; however, given the absence of adequate efficacy studies and possible risks (i.e., seizures and cardiac conduction delays), combined clomipramine and fluvoxamine treatment should be reserved for severe and highly treatment-refractory cases. If the combination is used, clomipramine and desmethylclomipramine levels

should be monitored, an anticonvulsant such as clonazepam should be prescribed prophylactically, and serial electrocardiograms should be obtained.

Serotonin Reuptake Inhibitor Plus Norepinephrine Reuptake Inhibitor

Some authors have suggested that clomipramine's dual inhibition of serotonin and norepinephrine transport may contribute to its anti-OCD efficacy. If true, then one might predict that a combination of an SSRI and a selective norepinephrine reuptake inhibitor (such as desipramine) would mimic the effects of clomipramine. Barr and colleagues (1997) investigated the addition of desipramine or placebo in a double-blind fashion to 23 fluvoxamine-, fluoxetine-, or sertraline-treated OCD patients whose symptoms did not respond to 10 weeks of monotherapy with the SSRI. No significant overall differences were found between the two treatment groups in either obsessive-compulsive or depressive symptoms.

Serotonin Reuptake Inhibitor Plus Antipsychotic

Conventional Antipsychotics

Monotherapy with conventional antipsychotics is not indicated in OCD, but evidence suggests that conjoint SRI and antipsychotic treatment may be beneficial in a subset of patients (McDougle et al. 1994). To date, the putative subgroup that has received the most attention has been OCD with a comorbid chronic tic disorder. This strategy has been based on evidence linking some forms of OCD with Tourette's disorder, coupled with the efficacy of standard antipsychotics in suppressing tics (Leckman et al. 1995).

Results from a double-blind, placebo-controlled study of haloperidol addition to fluvoxamine-refractory patients with OCD support the efficacy of this combination treatment strategy (McDougle et al. 1994). Thirty-four patients who had an unsatisfactory response to 8 weeks of fluvoxamine monotherapy were randomized to either 4 weeks of haloperidol (n=17) or placebo (n=17) in addition to a fixed daily dose of fluvoxamine. The mean daily dose of haloperidol at the end of the 4-week trial was 6.2±3.0 mg. The fluvoxamine and haloperidol combination was significantly superior to the fluvoxamine and placebo combination. As predicted, most of the benefit of haloperidol addition to fluvoxamine occurred in the OCD patients with a coexisting chronic tic disorder. It should be emphasized that none of these patients was psychotic. The benefit of antipsychotics in patients with OCD and schizotypal personality disorder has not been established.

Newer Antipsychotics

Because of the limited effectiveness and tolerability of conventional antipsychotics in Tourette's disorder, clinicians have turned to a new generation of antipsychotics that have been introduced for the treatment of schizophrenia. Risperidone, a member of a class of antipsychotics that blocks both dopamine and serotonin receptors, is being widely used by clinicians to treat tic disorders as positive reports emerge in the literature (Bruun and Budman 1996; Lombroso et al. 1995; Stamenkovic et al. 1994; van der Linden et al. 1994). Several preliminary publications suggested that risperidone might alleviate obsessive-compulsive symptoms when added to ongoing SRI therapy (Giakas 1995; Jacobsen 1995; Lombroso et al. 1995; McDougle et al. 1995b; Saxena et al. 1996). Specific clinical features predictive of response to a risperidone and SRI combination remain to be established. The impression, however, is that the response may not be restricted to patients with comorbid tics. Experience with other newer generation antipsychotics such as olanzapine is too early to draw conclusions about indications for use in OCD. The prototypic atypical antipsychotic clozapine was found ineffective when given alone to 12 patients with treatment-resistant OCD (McDougle et al. 1995a).

Novel and Experimental Drug Treatments

A variety of alternative drug treatments have been used in OCD. Of those considered here, intravenous clomipramine is the only treatment supported by a reasonable degree of empirical evidence. Several open-label trials suggested that intravenous administration of clomipramine may be helpful in patients refractory to oral clomipramine (Fallon et al. 1992; Thakur et al. 1991; Warneke 1989). Two double-blind trials (Fallon et al. 1994; Koran et al. 1997) lent support to the efficacy of intravenous clomipramine in treatment-refractory patients. Disadvantages of this experimental technique are its availability at only a few research settings and limited information on its long-term benefits.

The possible role of hormones and neuropeptides in the treatment of OCD has begun to be explored, but

preliminary findings are not reassuring. Four weeks of adjuvant triiodothyronine treatment was ineffective in 16 patients with OCD who had had a partial response to clomipramine (Pigott et al. 1991). Preclinical studies suggested that the neuropeptide oxytocin mediates several behavioral effects that may be related to obsessive-compulsive behavior in humans (Leckman et al. 1994), including inhibiting the acquisition of aversive conditioning. Ansseau et al. (1987) reported a case of OCD in which 4 weeks of intranasal administration of oxytocin led to improvement in obsessive-compulsive symptoms, but the side effects were profound, including memory disturbances, psychosis, and osmotic abnormalities. In another publication, oxytocin was ineffective in reducing symptoms of OCD (Den Boer and Westenberg 1992). In a small study of females with OCD, the antiandrogen cyproterone acetate seemed to exert an anti-OCD effect, but it was not sustained (Casas et al. 1986). An attempt by another group to replicate this finding in a woman with severe OCD was unsuccessful (Feldman et al. 1988).

Recent studies on the therapeutic use of the second-messenger precursor inositol have been extended to OCD. The design was based on the successful inositol treatment of depression and panic disorder under double-blind, placebo-controlled conditions. Fux and colleagues (1996) entered 15 patients with OCD (who had failed to respond to previous treatment with clomipramine or SSRIs) into a double-blind, controlled crossover trial of 18 g/day of inositol or placebo for 6 weeks each. No side effects were reported, and 13 patients completed the protocol. Y-BOCS scores were significantly lower when subjects were taking inositol compared with when they were taking placebo. The mechanism of action of inositol is unclear but warrants continued interest and replication.

Addition of the steroid suppressant aminoglutethimide to fluoxetine led to significant improvement in a case of treatment-refractory OCD (Chouinard et al. 1996). The rationale for this approach was based on evidence that steroids contribute to the maintenance of the depressed mood state and that steroid suppressant agents may be useful in cases of treatment-resistant depression.

Some cases of childhood-onset OCD may be related to an infection-triggered autoimmune process similar to that of Sydenham's chorea, a late manifestation of rheumatic fever (Swedo et al. 1994). More than 70% of the patients with Sydenham's chorea have obsessive-compulsive symptoms (Swedo et al. 1989). The etiology of Sydenham's chorea is thought to involve the development of antibodies to group A β-hemolytic streptococcal infection that cross-react with basal ganglia and other brain areas (Murphy et al. 1997). Swedo coined the term *PANDAS* (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) to describe cases of childhood-onset OCD that resemble Sydenham's chorea with respect to acute onset following a group A β-hemolytic streptococcal infection, accompanying neurological signs, and an episodic course (Swedo et al. 1994). Various trials with immunomodulatory treatments (e.g., prednisone, plasmapheresis, intravenous immunoglobins) or antimicrobial prophylaxis (e.g., penicillin) are under way at the National Institute of Mental Health and elsewhere for putative PANDAS cases. This exciting new avenue of research undoubtedly will be the subject of intense investigation over the next few years.

Nonpharmacological Biological Approaches

Nonpharmacological biological treatments of OCD have included electroconvulsive therapy (ECT), neurosurgery, sleep deprivation, phototherapy, and repetitive transcranial magnetic stimulation (rTMS). ECT, regarded as the gold standard for treating depression, generally is viewed as having limited benefit in OCD despite isolated reports of its success in treatment-resistant cases (Husain et al. 1993; Rudorfer 2000). In some instances, the favorable response to ECT was short-lived. Khanna et al. (1988) described nine treatment-refractory patients with OCD (without depression) who underwent ECT, resulting in a decline in global OCD ratings exceeding 20%. However, all had returned to their baseline illness by 4 months. ECT certainly should be considered in the treatment of depressive symptoms in the treatment-refractory patient with OCD at risk for suicide.

Modern stereotactic surgical procedures should not be equated with the relatively crude neurosurgical approaches of the past (Mindus et al. 1994). Recent evidence suggests that stereotactic lesions of the cingulum bundle (cingulotomy) or anterior limb of the internal capsule (capsulotomy) may produce substantial clinical benefit in some patients with OCD without causing appreciable morbidity. In a retrospective follow-up study of 33 patients with OCD who underwent cingulotomy, Jenike et al. (1991) found that 25%–30% of the patients experienced substantial benefit according to conservative criteria. In a more recent prospective study, Baer et al.

(1995) evaluated 18 patients with OCD before and 6 months after bilateral cingulotomy. Five patients (28%) met conservative criteria for treatment response. A few unanswered questions about neurosurgical treatment of OCD remain: 1) What is the true (placebo-corrected) efficacy of surgery? 2) Which procedure (i.e., cingulotomy, capsulotomy, limbic leukotomy) is best? 3) What is the optimal placement of lesions? and 4) Can we predict who are the best candidates for surgery? At present, stereotactic neurosurgery should be viewed as the option of last resort in the gravely ill patient with OCD who has not responded to well-documented adequate trials over a 5-year period with several SRIs (including clomipramine), exposure and response prevention, at least two combination strategies (including combined SRI and behavior therapy), an MAOI, a novel antidepressant (e.g., venlafaxine), and ECT (if depression is present).

rTMS provides a relatively noninvasive probe of cortical function. In rTMS, a pulsatile high-intensity electromagnetic field emitted from a coil placed against the scalp induces focal electrical currents in the underlying cerebral cortex. Cortical activity can be stimulated or disrupted by rTMS. Its primary application to date has been investigations of the relation between regional cortical activity and function in health and disease, but some studies suggest that rTMS may have therapeutic value in depression (George et al. 1995) and perhaps OCD (Greenberg et al. 1997). In a preliminary controlled study, Greenberg et al. (1997) reported that a single session of rTMS applied to the right prefrontal cortex produced a transient reduction in compulsive urges. The anti-OCD effect of rTMS may have stemmed from its interference with ongoing neuronal activity mediating the compulsive urges. rTMS is not without risk; seizures have been reported in at least 6 of more than 250 subjects undergoing the procedure (Wasserman 1997). Local discomfort from activation of scalp musculature and nerves also occurs. Further evaluation of rTMS as an investigative and therapeutic tool in OCD seems justified.

Conclusion

The mainstay of the pharmacological treatment of OCD is a 10- to 12-week trial with an SRI. For most patients, treatment should be initiated with one of the SSRIs (e.g., fluvoxamine, sertraline, or paroxetine). Clomipramine remains the benchmark for OCD drug treatment but is difficult to justify as a first-line agent given the superior tolerability and safety of SSRIs and their equivalent efficacy. Despite advances in pharmacotherapy and behavior therapy for OCD, some patients experience little or no significant improvement. Options in dealing with the SRI-resistant OCD patient include switching to a different SRI, combining another medication (or behavior therapy) with the SRI, considering novel or experimental drug treatments, or using nonpharmacological biological approaches such as ECT or neurosurgery in rare cases. Of the SRI combination approaches, the only one confirmed in double-blind studies is the addition of a low-dose antipsychotic in patients with comorbid tic disorders. Additional research is needed to identify subtypes of OCD with distinctive treatment response characteristics. In many cases, combined SRI and behavior therapy may be the most broadly effective treatment for OCD. An algorithm for the medical management of OCD is shown in the Appendix to this chapter.

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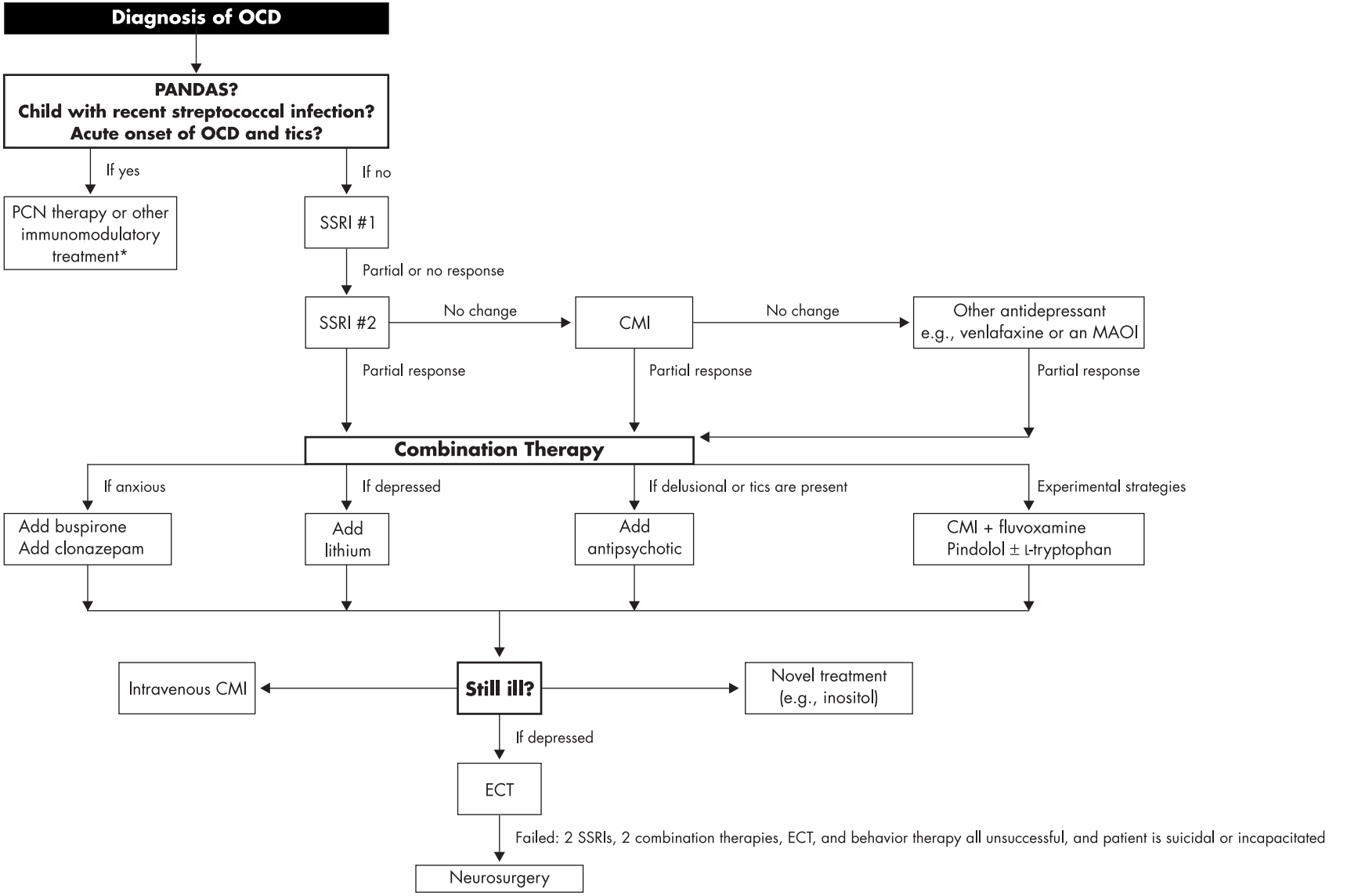

APPENDIX. Algorithm for medical management of obsessive-compulsive disorder (OCD).

Note. *At present these treatments are experimental. PANDAS= pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; SSRI=selective serotonin reuptake inhibitor; CMI=clomipramine; MAOI=monoamine oxidase inhibitor; PCN=penicillin; ECT=electroconvulsive therapy.

17

Psychotherapy for Obsessive-Compulsive Disorder

John H. Greist, M.D.
Lee Baer, Ph.D.

In common with all psychiatric disorders, obsessive-compulsive disorder (OCD) involves thoughts, feelings, and behaviors. The boundaries between normal and pathological phenomena remain somewhat blurred, but distress and dysfunction of such proportions that individuals seek, and clinicians offer, treatment is a useful dividing line across all of clinical medicine. Ideally, a clear understanding of causes will guide the selection of specific therapies to correct those causes. Understanding of the etiological factors underlying abnormalities in thoughts, feelings, and behaviors remains incomplete, but each field of therapy has its own paradigms that may constrain or expand its effectiveness.

Behavior therapists strive to change behaviors and thereby reduce distressing thoughts, feelings, and dysfunction. By contrast, psychotherapists first seek changes in thoughts and feelings, which are followed by changes to more functional behaviors. Pharmacotherapists manifestly modify neurotransmitters and neuromodulators to affect thoughts, feelings, and behaviors. Neurosurgeons create lesions in specific structures to effect reductions in distress and dysfunction. Each of these treatment approaches has a rich heritage of theories regarding OCD. Sir Clifford Allbutt (1915) put the facile theory enterprise into proper perspective:

> Our path is cumbered with guesses, presumptions, and conjectures, the untimely and sterile fruitage of minds which cannot bear to wait for the facts, and are ready to forget that the use of hypotheses lies, not in the display of ingenuity, but in the labor of verification. (p. 154)

Or as an anonymous authority said more simply, "When theory and facts disagree, the facts must be discarded." The paradigm problem elucidated by Kuhn (1962) in *The Structure of Scientific Revolutions* certainly operates in medical science and has led to generations of therapists practicing throughout their careers what they

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This chapter is revised, updated, and expanded from Greist JH: "New Developments in Behaviour Therapy for Obsessive-Compulsive Disorder." *International Clinical Psychopharmacology* 11 (Suppl 5):63–73, 1996. Copyright 1996 Lippincott Williams & Wilkins. Used with permission. The chapter also includes two brief segments from Baer L, Minichiello WE: "Behavior Therapy for Obsessive Compulsive Disorder," in *Obsessive-Compulsive Disorders: Practical Management*, 3rd Edition. Edited by Jenike MA, Baer L, Minichiello WE. St. Louis, MO, CV Mosby, 1998. Used with permission. Dr. Greist acknowledges literature research by Bette Hartley, M.L.S., of the Obsessive Compulsive Information Center and manuscript preparation by Lynn Tobias, both at Healthcare Technology Systems.

were preached as students. At this stage in our understanding of the psychopathophysiology of OCD, theories provide only crude pointers to useful treatments, and our best guidance comes from controlled empirical trials and commonsense clinical observations (Greist 1994). The dual cornerstones of effective treatment for OCD are potent serotonin reuptake inhibitors (SRIs) and behavior therapy. In this chapter, we focus primarily on behavior therapy and the merits of a combination of these treatments.

The apparent simplicity of behavior therapy for OCD can be misleading, as the following two examples indicate. Two neuroimaging studies at the University of California at Los Angeles (Baxter et al. 1992; Schwartz et al. 1996) have proven this seemingly simple treatment as the first nonsomatic intervention to result in neurophysiological changes that mirror the observable clinical improvements. In a similar vein, Professor Isaac Marks has lectured on the vital importance of spreading simple medical information. He notes that, despite all the money spent on high-technology medical and imaging equipment, the following simple instructions from the World Health Organization (WHO) to mothers in Third World countries have saved many more lives:

> The instruction is for the mother to boil a cup of water, put into it a pinch of salt lifted with three (not 2 or 4) fingers, stir it, taste it, and if it's no saltier than tears and not too hot to spoon it to her baby, who is likely to absorb it without vomiting. Behind that simple instruction are 200 years of Western scientific endeavor concerning the nature of dehydration and blood osmolarity and how to correct it. With that instruction one can do away with the need for intravenous fluid and all the paraphernalia it entails. Mums can treat their babies in the bush. (I.M. Marks, personal communication, 1995)

The simple rules of behavior therapy are similar to the WHO instructions in that both are behavioral instructions and both rely on the individual accepting the advice as worthwhile, nondangerous, and effective.

Efficacy of Behavior Therapy

Janet (1925) not only described the phenomenology of OCD with great precision but also expounded on his observation that the enforced discipline associated with joining the army or the clergy often reduced obsessions and compulsions in individuals with OCD. At a time when no effective treatments for OCD were available, he devised a form of behavior therapy emphasizing the essential element of exposure:

> The guide, the therapist, will specify to the patient the action as precisely as possible. He will analyze it into its elements if it should be necessary to give the patient's mind an immediate and proximate aim. By continually repeating the order to perform the action, that is, *exposure* [italics added], he will help the patient greatly by words of encouragement at every sign of success, however insignificant, for encouragement will make the patient realize these little successes and will stimulate him with the hopes aroused by glimpses of greater successes in the future. Other patients need strictures and even threats and one patient told [me], "Unless I am continually being forced to do things that need a great deal of effort I shall never get better. You must keep a strict hand over me." (Janet 1925, pp. 978–979)

In the late 1950s, Wolpe's (1958) systematic desensitization techniques reactivated interest in behavior therapy for phobias, although the benefit of this approach in OCD was slight, probably because of its emphasis on specific techniques that were either inert (relaxation) or only weakly effective (exposure in imagination or fantasy) (Beech and Vaughn 1978; Cooper et al. 1965). It was not until Meyer (1966) reported that sustained prevention of anxiety-reducing rituals also could lead to a reduction in obsessions that the modern era of effective behavior therapy for OCD began. Subsequent controlled trials (Boersma et al. 1976; Emmelkamp et al. 1985, 1988, 1989; Foa 1994; Foa and Goldstein 1978; Foa et al. 1983, 1984, 1992; Hoogduin and Hoogduin 1984; Julien et al. 1980; Marks et al. 1975, 1988; Rabavilas et al. 1976; Roper et al. 1975) confirmed the efficacy of behavior therapy in the treatment of OCD and have identified specific effective components: exposure for obsessions and response prevention for rituals (now explained more simply to patients as *ritual prevention*). Exposure in vivo is more effective than exposure in fantasy, although the latter technique is useful for situations where exposure in vivo would be dangerous or impractical to arrange (e.g., thunderstorms) (Foa et al. 1985a). Debate remains about the advantage of exposure in imagination or fantasy. In 23 patients who received either self-help exposure in vivo or the same exposure in vivo plus exposure in imagination, the imaginal component did not improve outcomes (Ito et al. 1995). A meta-analysis (Abramowitz 1996) found the combination of in vivo and imaginal exposure superior to in vivo exposure alone in reducing *symptoms of anxiety*. The same meta-analysis found that therapist-supervised exposure was more effective than self-controlled exposure and that complete ritual prevention yielded improved outcome over partial or no ritual prevention.

A composite picture of the effectiveness of exposure and ritual prevention for OCD was provided by Foa and colleagues (1985b), who pooled the results of exposure in vivo and response prevention in 273 patients treated by different therapists in different countries. A reduction in obsessions and rituals of at least 70% was obtained in 51% of the patients, and reductions between 30% and 69% occurred in another 39% of the patients. Thus, 90% of the patients who underwent behavior therapy had at least a 30% reduction in obsessions and compulsions. Foa et al. (1985b) also reported that 76% of the patients remained at least moderately improved (30%–69% symptom reduction) months to years after treatment had ended. More recently, Foa and Kozak (1996) described comparable results from a larger series of 12 studies including 330 patients: 83% of the patients were much or very much improved following initial treatment. Long-term results from 16 studies including 376 patients showed that at a mean follow-up of 29 months, 76% of the patients were very much or much improved. Differences in protocols and outcome measures in these studies emphasized the robustness of exposure in vivo and response prevention. Children also respond to cognitive-behavioral therapy for OCD (March 1995; Wever and Rey 1997).

The Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al. 1989a, 1989b) has become the standard scale for rating severity and change in treatment studies of OCD. Table 17–1 lists efficacy studies of behavior therapy in OCD in which Y-BOCS scores were used to measure outcome (de Araujo et al. 1995; Fals-Stewart et al. 1993; Foa 1994; Freund et al. 1991; Hiss et al. 1994; Krone et al. 1991; Lucey et al. 1994; McKay et al. 1996; Pato et al. 1995; Piacentini et al. 1994; Schwartz et al. 1996; Van Oppen et al. 1995). The range of improvement found across these studies was from 3.2 to 17.7, with a weighted arithmetic mean Y-BOCS improvement of 12.2 (calculated by multiplying the mean difference between baseline and endpoint Y-BOCS score by the number of subjects per study divided by total number of subjects). These improvements are larger than those obtained by potent SRIs (clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline; Table 17–2). For these five medications, the range of improvement was from 4.5 to 10.2, with a weighted mean of 7.5 (Greist et al. 1995; Wheadon et al. 1993). For this calculation, the *best dose* was used when available in fixed-dose studies. Placebo response was *not* subtracted from the drug response. This comparison has been confirmed in several meta-analyses published over the last 10 years (Abramowitz 1997; Christensen et al. 1987; Cox et al. 1993; Kobak et al. 1998; van Balkom et al. 1994), with at least a numeric advantage for behavior therapy over selective SRIs in five of six meta-analyses.

TABLE 17–1. Yale-Brown Obsessive Compulsive Scale (Y-BOCS) improvement for behavior therapy in obsessive-compulsive disorder

Study	*N*	Baseline	Endpoint	Improvement
Freund et al. 1991	9	24.0	9.0	15.0
Krone et al. 1991	17	20.4	17.2	3.2
Fals-Stewart et al. 1993	31	20.0	13.0	7.0
	30	22.0	12.0	10.0
Foa 1994	10	25.0	11.0	14.0
Hiss et al. 1994	8	23.1	7.9	15.2
Lucey et al. 1994	50	27.2	9.9	17.3
Piacentini et al. 1994	3	26.7	11.7	15.0
de Araujo et al. 1995	23	28.8	16.6	12.2
	23	27.4	14.0	13.4
Pato et al. 1995	13	23.7	13.1	10.6
van Oppen et al. 1995	29	25.4	17.3	8.1
McKay et al. 1996	21	30.2	15.0	15.2
Schwartz et al. 1996	6	24.3	12.5	11.8
	6	22.3	13.5	8.8
	3	28.3	20.0	8.3
	3	27.0	22.0	5.0
Freeston et al. 1997	28	23.5	10.8	12.7
Dewan 1997	9	22.0	12.0	10.0
Lindsay et al. 1997	9	28.7	11.0	17.7
Total	331		Mean change = 11.9	

Although such comparisons may suggest that behavior therapy is more efficacious in the treatment of OCD than are potent SRI medications, the patient populations in trials of these different treatment modalities may have had important differences. Few head-to-head comparisons have been reported. Pitting these therapeutic approaches against each other may be unwise and unnecessary. Combination approaches, however,

TABLE 17–2. Yale-Brown Obsessive Compulsive Scale (Y-BOCS) improvement for potent serotonin reuptake inhibitors in obsessive-compulsive disorder

Study	N	Baseline	Endpoint	Improvement
Greist et al. 1995				
Clomipramine	260	26.2	16.0	10.2
Fluoxetine	90	24.4	17.8	6.6
Fluvoxamine	160	22.9	18.5	4.4
Sertraline	80	23.5	17.3	6.2
Wheadon et al. 1993				
Paroxetine	85	25.3	18.0	7.3
Total	67		Mean change = 7.5	

have been evaluated in a few controlled and several open studies. These studies have uniformly found benefit in this combination, either of a statistically significant magnitude or of a numerical superiority, suggesting a trend toward statistical significance (de Haan et al. 1998; Foa 1994; Hohagen et al. 1998; Lucey et al. 1994; March 1995; Marks et al. 1980, 1988; Neziroglu et al. 2000; Orloff et al. 1994).

Maintenance of Gains

Marks (1981) reviewed eight studies with follow-up data collected at least 1 year after completion of behavioral treatment. In all these studies, improvements at the end of treatment were maintained or strengthened at follow-ups of 1–5 years. Hiss and associates (1994) reported encouraging results of a relapse prevention program following intensive behavioral treatment of OCD. Eighteen patients (17 with cleaning and/or checking rituals) were treated with 3 weeks of intensive imaginal and in vivo exposure for their cleaning and checking symptoms, including home practice and two home visits by the therapist. Patients were then randomly assigned to either a relapse prevention condition (consisting of four 90-minute sessions over 1 week) or a control condition (consisting of relaxation training and associative therapy). Based on a 50% improvement on the Y-BOCS as the criterion for treatment response, 75% of the patients assigned to the relapse prevention condition were responders after initial treatment, and 75% were responders at 6-month follow-up. However, 70% of the patients assigned to the control condition were responders after initial treatment, but only 33% were responders at 6-month follow-up. Although there were few statistically significant results because of the small sample size, this study suggested that a brief relapse prevention program, including brief telephone contacts, may help prevent relapse, at least in cleaning and checking rituals.

Technique

Behavioral Assessment

Essentially, the therapist helps the patient to identify specific triggers for obsessions, compulsions, rituals, and discomfort. Triggers are arranged in hierarchies from the least to the most distressing, which guides patient and clinician in selecting appropriate targets for treatment. Other comorbid conditions that may complicate treatment (see section "Behavior Therapy Combined With Pharmacotherapy" later in this chapter) are identified and treatment plans for their management established. Although behavioral assessment focuses on obsessive-compulsive psychopathology, the therapist also learns a great deal about the context in which OCD occurs and the complications it causes, as well as precipitants and alleviating elements.

Some patients with OCD may be reluctant to disclose socially charged obsessions and the rituals that diminish them, or they may have carried them out so long and so often that they are no longer recognized as abnormal. The use of a list of common obsessions and compulsions, such as the Yale-Brown Obsessive Compulsive Checklist, often helps patients describe their disorder more completely. Another approach is to ask patients to identify anything they are avoiding because it may cause discomfort, the onset of obsessions, or the urge to ritualize. Patients may be asked to take a figurative "trip through their day" to note avoidance or triggers of discomfort, obsessions, or compulsions. More formally, this can be undertaken over several days, and patients are asked to write down their experiences and their feelings about those experiences. Identifying all of the situations or people avoided is a key to designing effective behavior therapy programs. The behavioral assessment also should elicit information about involvement of family, friends, and co-workers in the patient's rituals because this is quite common (Hollander 1996). Specific techniques have been developed to guide those caught up in the patient's disorder to help the patient overcome the disorder by serving as co-therapists (see subsection below).

Education

Patients need an understanding of OCD, an explanation for how exposure in vivo and ritual prevention can lead to habituation, and an outline of the general plan of treatment. Clinicians need to learn about the patient's experiences with naturalistic exposure and ritual prevention, preferences regarding speed of treatment, time available for treatment, effects of anxiety or other discomfort, and availability of co-therapists and other supporters while behavior therapy is proceeding. Recognizing that learning occurs from within, for both patients and clinicians, and that rapport results from clear mutual understandings and agreements, time spent at the outset elaborating a thoughtful treatment plan covering the topics listed below will shorten the overall treatment time and improve outcomes.

Intensity and Length of Exposure Sessions

Setting specific goals for exposure and ritual prevention is a joint task for the patient and therapist. After hierarchies have been prepared, agreement is reached on the first trigger to be treated. It is best to focus initially on a single target and to fine tune treatment for that goal so that the lessons learned can be incorporated into the approaches to subsequent targets. A scale of discomfort should be developed to aid both patient and clinician in deciding which trigger to tackle, how much distress the exposure and ritual prevention sessions produce, and how long it takes for habituation to occur. Several discomfort scales can be used, such as the Subjective Units of Distress Scale (SUDS; Wolpe and Lazarus 1966) or an abbreviated numerical scale ranging from 0 (no distress) to 2 (mild distress), 4 (moderate distress), 6 (marked distress), and 8 (extreme distress). If this latter scale is used, the best starting point for treatment is probably a goal with a distress rating between 5 and 7. Goals with lower scores may not yield worthwhile improvements, whereas those with a score of 8 may be too distressing as the first target of treatment.

Patients often ask how long an exposure and ritual prevention session lasts. The answer is difficult to specify precisely until one has experience of the patient's rate of habituation when exposed to triggers of discomfort, obsessions, or rituals. In general, the session lasts until the patient's discomfort has diminished significantly. A reduction of 2 or more points on the 0–8 scale indicates significant habituation and might occur in as little as 15 minutes, although it can take a few hours. In our practice, patients are asked to set aside at least 1 hour for an exposure and ritual prevention session with the understanding that we will learn, together, how much time is needed, recognizing that some triggers may require more time, and others less, for habituation. Patients can be helped to understand that exposure and ritual prevention need not fully occupy the time that they have allocated to the task. Thus, a patient could touch a "contaminated" doorknob, which triggers a compulsion to wash, but resist the urge to carry out that ritual for an hour or longer while carrying on other activities. It is important, however, that the individual does not use other activities to distract him or her from the discomfort initiated by exposure because this would be a form of avoidance.

Progress Through a Hierarchy

After a patient has largely mastered his or her first target of treatment, the experience and confidence gained can be used to overcome the next triggers and rituals in the hierarchy. After a patient has reduced the maximum distress rating to a level between 0 and 2 for 3 or more consecutive days, it is appropriate to add goals to deal with other triggers of discomfort, obsessions, and rituals. It is important to continue, from time to time, with exposure and ritual prevention for the initial trigger as a form of relapse prevention (see subsection "Consolidating Gains" later in this chapter). No one speed or duration of exposure and ritual prevention is right for all patients. One can proceed very gradually or very rapidly and at all rates in between. Patients often can be helped to understand this by a simple analogy; if one is removing adhesive tape from one's body, it can be taken off one hair at a time or all at once. The total amount of discomfort is approximately the same, but the choice is up to the person. The essential element is to engage in exposure and then to reduce, defer, or eliminate rituals that decrease discomfort so that habituation may occur and replace rituals as the method for controlling discomfort. For a successful outcome, most target triggers and corresponding goals must be dealt with directly by exposure and ritual prevention; however, it is often possible to bundle specific triggers together to make progress more efficient.

Managing Anxiety During Sessions

Rituals evolve to control discomfort after exposure to triggers, and ritual prevention removes this source of solace. At the beginning of therapy, therefore, short-term transient increases in obsessions and discomfort may occur as rituals are prevented. Coping tactics can be planned to enable patients to continue exposure until habituation occurs without resorting to ritual behav-

iors. For example, patients can write down on cards specific things that they can say to themselves and do until habituation has relieved their distress, such as "This distress is uncomfortable but not unbearable, and it will diminish if I continue exposure without giving in to my ritual. When discomfort occurs because of exposure, my task is to continue the exposure until habituation occurs." Some patients may even wish to "beard the lion in its den" with a coping tactic such as "When discomfort mounts during exposure and ritual prevention, I will try to heighten it further by repeating the exposure." Coping tactics should be individualized but always have a goal of maintaining exposure and ritual prevention until habituation occurs.

Therapist Involvement

From Janet's time onward, it has been widely agreed that the therapist serves as a "guide" or coach. How this guidance is achieved remains a topic of debate. Some feel that the therapist must assist the patient by encouraging and modeling the exposure and ritual prevention and that this should be carried out at the actual site where triggers cause distress and rituals are used to relieve it. Recently, emerging data suggest that such a costly approach often may be unnecessary. Those who advocate self-help exposure and ritual prevention hold that habituation occurs within the patient and not in the therapeutic dyad. van Balkom et al. (1994) reviewed the evidence on therapist assistance versus self-help exposure and ritual prevention and concluded "that the treatment effect of self-controlled exposure in vivo is not enhanced by therapist or spouse involvement" (p. 373).

The therapist-intensive approach to behavior therapy is unquestionably quite effective and remains one standard against which other therapist involvement models can be compared. A recent illustration of the therapist-intensive approach was given by Foa (1994). Two treatment planning sessions were followed by 15 sessions of 2-hour duration over 3 weeks. Each of the 2-hour sessions included exposure in imagination (45 minutes), exposure in vivo within the session (45 minutes), and homework assignments (15 minutes). There were also 2 days of home visits, totaling 8 hours of therapist time in the home, and 8 weekly 1-hour maintenance sessions after the initial 3-week treatment had ended. This approach produced a 14-point decrease in Y-BOCS score. The affordability of 50 hours of therapist involvement is a substantial problem. Whether less intensive therapist involvement will yield lesser improvements is still be studied.

Group Therapy

Group therapy is more cost-effective than individual therapy, and many patients do as well in a group setting as when seen alone (Fals-Stewart et al. 1993; Kobak et al. 1995). Patients participating in groups soon learn that they are not alone and may serve as co-therapists for one another in designing and carrying out exposure and ritual prevention.

"Pure Obsessionals"

Clearer recognition of the frequency of mental rituals, often mistaken for obsessions because they are not visibly apparent behaviors, has substantially reduced estimates of the proportion of patients with only obsessions. However, 1%–2% of obsessive-compulsive individuals seem to have no visible, or even mental, rituals. For them, ritual prevention is impossible, and the only available behavioral technique is extensive exposure using massed practice. Here, the person repeatedly writes out the obsession, says it aloud, or records it on a continuous-loop audiotape and then plays it back repeatedly on a portable audiocassette player (Salkovskis and Westbrook 1989). These approaches may work through the phenomenon of semantic satiation (Marks 1987), by which even a word such as *murder* loses its distressing effect and even its meaning if repeated rapidly for long enough.

Cognitive Therapy

Individuals with OCD often hide their rituals because they know that others would find them unusual or even bizarre. Patients call their obsessions stupid, crazy, ridiculous, insane, or other synonyms proving preservation of insight. They tell themselves repeatedly that their cognitions are incorrect but cannot turn their attention from them. Cognitive therapies aimed at changing faulty cognitions about risk and responsibility seem logical, but most studies have not found them effective (James and Blackburn 1995). Two recent trials (Cottraux et al. 2000; van Oppen et al. 1995), however, did find cognitive techniques as effective as exposure and response prevention. The van Oppen et al. trial was significant because it was the first to tailor cognitive techniques to the specific cognitive errors of OCD patients. Further evaluations of these techniques are currently ongoing to determine whether cognitive therapy will provide a useful second-line or potentially first-line treatment for OCD. At this point, however, exposure and response prevention remains the first-line psychosocial treatment for OCD.

Rituals by Proxy

As rituals become the chosen way for managing discomfort, patients usually are discomfited by the "failure" of those around them to conform to their rituals. Ultimately, they may ask others to carry out certain rituals to decrease their discomfort. A patient with concerns about contamination may ask family members to take off their shoes as they enter the house, or at least the patient's living space. If the family acquiesces, the next request may include a distinction between "outside" and "inside" clothing, again on the obsessive-compulsive rationale that "contamination" may thereby be avoided.

Examples of involving others in proxy rituals are common and after being carried out for some time may no longer be viewed as abnormal but simply as "the way we do things." The most common kind of proxy ritual is a request for reassurance regarding risks or behaviors that are thought of as being dangerous by the obsessive-compulsive individual. The patient may ask, "Did I lock the door?," to which the family member might reassure, "Yes, you locked the door." The patient feels reassured, momentarily, but soon obsesses and worries aloud and repeats the request for reassurance, "Are you sure I locked the door?" These reassurance rituals usually are repeated many times and, as with all rituals, have only a limited benefit in relieving distress.

The correction for this proxy ritual is for the family member to do ritual prevention. In the illustration in the preceding paragraph, the family member would learn and role-play, saying, "Doctor's instructions are I'm not to reassure." This "broken-record" ritual prevention response, given in a monotonic manner with the patient's prior approval, is quite effective in reducing and then eliminating what is an annoying and counterproductive part of the relationship with someone who has OCD.

Record Keeping

Monitoring of exposure and ritual prevention therapy sessions by written record is a powerful tool in behavior therapy. Not only does it help guide the patient when the therapist is not present, but a failure to keep written records predicts a poor outcome. A simple form can be prepared to help the patient monitor his or her progress. The design of the form is not important, but its development by the patient and therapist in a manner that is useful to them, followed by its consistent use, is very valuable.

Consolidating Gains

Although most patients maintain the benefits they achieve during short-term treatment for many months and years, it is prudent to consolidate those gains and to anticipate possible future problems. Probably the best protection comes from establishing a lifestyle directed toward reasonable risk taking, which counteracts the inappropriate risk aversion present in OCD. This *way of life* can be codified and practiced so that it becomes second nature.

During the first stages of exposure and ritual prevention, one would expect uncertainties, inefficiencies, failures, and the need to adjust techniques to a range of triggers. This process is analogous to learning to drive a car with a standard transmission. At the beginning of therapy, some "grinding of gears" occurs, but soon the patient learns to smooth out the process and continue to carry out exposure and ritual prevention as second nature.

OCD is a disorder with some migration of symptoms and signs (e.g., from obsessions about contamination to those of doubt and, correspondingly, from washing rituals and cleaning to checking). This normal variability of OCD should not be seen as a failure of behavior therapy but rather as an occasion for extension of behavior therapy techniques (i.e., from washing to checking rituals).

At times of increased situational stress, and sometimes without obvious reason, obsessions and corresponding rituals may increase transiently. These *lapses*, as Foa has called them, should alert the patient to a need for greater structure and systematic application of behavior therapy to regain control. Often, no therapist intervention is needed. *Relapses*, however, with a return toward baseline levels of severity of obsessions, discomfort, and rituals, suggest a need for therapist evaluation to assess for factors that may explain the loss of benefit (see section "Behavior Therapy Limitations" later in this chapter). Finally, planned booster treatments improved long-term outcome in one study (Foa 1994).

Self-Help Books

Behavior therapy is not widely available, and even when a therapist can be found, it is often helpful for patients to have a self-help book that may answer their questions when the therapist is not available. These books also provide a structured plan for carrying out behavior therapy, which the therapist may instruct the patient to follow so that they both have a clear indication of the goals toward which they are working.

Behavior Therapy Combined With Pharmacotherapy

About 25% of patients with OCD refuse behavior therapy (Lucey et al. 1994; McDonald et al. 1988) usually on the grounds that exposure and ritual prevention would make them too anxious. They also may fear that the risks of not carrying out their rituals are too great and that they would feel responsible if the things they obsess about were to happen as a result of not performing their rituals. These individuals are logical candidates for a trial of cognitive therapy, although no systematic test of this logic has yet been made. Some of these patients will accept treatment with medication as an alternative to behavior therapy.

Conversely, approximately a quarter of patients dislike the thought of taking medications that they view, globally, as "contaminants." Some can be helped to take effective medication through a graduated exposure paradigm in which they are exposed first to small doses of medication and later to effective pharmacological doses of potent SRIs. Medication improves compliance with behavior therapy (Marks et al. 1980), whereas behavior therapy conveys longer-lasting gains after treatment is discontinued (O'Sullivan et al. 1991). Benefits of potent SRIs are rapidly lost after they are discontinued (Leonard et al. 1991; Pato et al. 1988, 1991). Several studies (de Haan et al. 1998; Hohagen et al. 1998; Lucey et al. 1994; March et al. 1994; Neziroglu et al. 2000; Orloff et al. 1994) support the commonsense conclusion that a combination of these two independently effective treatment modalities is more effective than either treatment alone. The major problem with the combination is the difficulty of finding effective behavior therapy.

Behavior Therapy Limitations

It would be ideal to predict those who will and will not respond to behavior therapy *before* treatment begins. Probably the most potent predictor of good outcome is compliance with treatment during the first week of therapy (de Araujo et al. 1996), and the best predictors of compliance were being employed during treatment and living with one's family (Buchanan et al. 1996). Buchanan et al. (1996) also found that clinical improvement was predicted by these two variables, in addition to never having been treated previously, having observable rituals, and having contamination fears. Weaker predictors of clinical improvement were absence of prior treatment, fears of contamination, presence of overt rituals, and absence of depression. Keijsers et al. (1994) found that higher initial severity of symptoms and higher depression predicted poorer outcome for compulsive behavior, whereas these two variables, along with longer problem duration and poor motivation for treatment with the therapeutic relationship, predicted poorer outcome for obsessive fears. Several studies (de Araujo et al. 1996; de Haan et al. 1997) have shown that good outcome at the end of treatment predicts good outcome at follow-up. However, some who fail to respond at the end of treatment improve later, apparently needing longer for benefit to emerge (de Haan et al. 1997; Minichiello et al. 1987). Personality pathology, particularly from the odd or eccentric Cluster A disorders (paranoid, schizoid, and schizotypal), predicts poorer response in some (de Haan et al. 1997) but not all studies (Dreessen et al. 1997). Severity of symptoms may delay onset of improvement (de Haan et al. 1997) but seldom prevents benefit (de Araujo et al. 1996).

However, some studies have shown beneficial changes in personality pathology in patients treated effectively with anti–obsessive-compulsive medications (Baer et al. 1992) or behavior therapy (McKay et al. 1996). Additional factors associated with poorer outcomes of behavior therapy are described below.

Depression

Marked depression can interfere substantially with behavior therapy, as it does with psychotherapy for all disorders. Mild to moderate levels of depression that are commonly found in OCD do not interfere with behavior therapy (Basoglu et al. 1988; Foa et al. 1984; Hoogduin and Duivenvoorden 1988; Mavissakalian et al. 1985; Steketee 1987, 1993), which should proceed without modification. If depression is pronounced, a potent SRI antidepressant often provides effective treatment for OCD as well as depression. Other antidepressant treatments, including electroconvulsive therapy (Steketee 1993) and cognitive-behavioral therapy or interpersonal psychotherapy (Elkin et al. 1989), also are appropriate, remembering that psychotherapies are less effective as depression becomes more severe. Medications or electroconvulsive therapy would then be the treatment of choice.

Delusions

Preservation of insight is one of the hallmarks of OCD. Although many obsessions and the rituals evolved to

answer them seem inappropriate or even bizarre to the patient and clinician, very few patients with OCD become deluded. Even children who lack formal insight usually hide their rituals from classmates for fear of being scapegoated. After the disorder has been present for many years, some patients drift into overvalued ideas that appear quasi-delusional or become so accustomed to carrying out their rituals that they no longer see them as abnormal. Despite these slippages toward apparent psychosis, even patients with extreme obsessions and rituals often respond well to behavior therapy, and it is unwise to prejudge response before a trial of behavior therapy.

Some individuals have both OCD and schizophrenia, and, interestingly, even here the OCD may be responsive to behavior therapy (Lelliott and Marks 1987). Schizophrenic delusions and hallucinations seldom change during behavior therapy. Even patients with extreme obsessions and rituals retain insight and make clear the risk-avoidant nature of their response to obsessional fears. By contrast, deluded individuals may engage in risky behaviors, believing that they are thereby reducing risk of harm.

Depressants of Central Nervous System Function

State-dependent learning caused by central nervous system (CNS) depressant drugs can interfere with behavior therapy. What animals learn in one CNS state may not be accessible in another CNS state. Thus, benzodiazepines can interfere with habituation, possibly through a phenomenon of anterograde amnesia or CNS depression (Jensen et al. 1989). It is best to avoid CNS depressants in patients undergoing behavior therapy. Potent SRIs do not appear to cause state-dependent learning.

Noncompliance

Failure of patients to undergo behavior therapy is a major limitation of this treatment modality. About 25% of patients either refuse behavior therapy outright or undermine its effectiveness by poor adherence to important therapy components (Lucey et al. 1994; McDonald et al. 1988). For example, patients may spend insufficient time in an exposure and ritual prevention session to permit habituation to occur, may spread sessions so far apart that benefits attenuate before they accumulate sufficiently to become worthwhile, or may undo the benefit of apparent exposure through covert mental rituals.

Even more troubling than patient noncompliance is clinician noncompliance. Despite two decades of awareness that behavior therapy is an effective treatment of OCD, and attempts by proponents to persuade and train clinicians, behavior therapy is not widely available (Greist 1989). Many clinicians remain reluctant to ask patients to engage in activities (exposure and ritual prevention) that may *increase* discomfort over the short term, even though the possibility of long-term gains is great. Risk estimation is a problem for clinicians as well as patients.

Self-help books (Baer 1991; Foa and Wilson 1991; Greist 2000; Marks 2001; Neziroglu and Yaryura-Tobias 1991; Steketee and White 1990) are sometimes sufficient, although many patients come to the behavior therapist having read one or more of these books. The large gap between the need for behavior therapy (Greist 1989) and behavior therapists trained to provide therapy has led to consideration of computer-administered behavior therapy programs to meet at least part of the need for this effective treatment. Behavior therapy programs have been shown to be successful in treating phobias (Carr et al. 1988) and mild to moderate depression (Selmi et al. 1990).

BT STEPS™

Because behavior therapy is an effective treatment for OCD but not widely available, Marks and colleagues (1998) developed BT STEPS, a comprehensive, computer-administered self-help behavioral treatment program for OCD. The program uses interactive voice response technology. BT STEPS includes a workbook to guide the treatment process and permits the patient to place 12 distinct telephone calls (several are used repeatedly), which contain more than 1,000 phrases or "frames" with branching between them based on responses in present and previous calls. The program helps patients assess their OCD and then design and implement their self-help treatment program of exposure and ritual prevention with support and monitoring provided by the program.

Forty patients in three remote sites participated in a 12-week study. Of the 17 who completed two or more exposure and ritual prevention sessions, 75% said that they were much improved or very much improved (Mundt et al. 1998). Twenty-three additional United Kingdom patients awaiting hostel treatment also improved (Marks et al. 1998). A larger random-assignment, relaxation-controlled study involving 218 patients has recently been completed. Findings indicated that clinician-administered behavior therapy achieved

somewhat better results than BT STEPS and that both of these treatments were more effective than relaxation control. For example, after 2 weeks of treatment, reduction in time spent on obsessions and compulsions each day decreased by 3.44, 3.36, and 0.61 hours for clinician-administered therapy, BT STEPS, and relaxation control, respectively.

Conclusion

Behavior therapy is a highly effective treatment for OCD. Exposure in vivo and ritual prevention are essential elements in behavior therapy, and gains achieved in short-term treatment often are maintained for years. Of those offered behavior therapy, about 25% decline either directly or indirectly through poor compliance. A larger contribution to the compliance problem is that the proportion of clinicians who have learned effective behavior therapy techniques and are actively providing them is small. Self-help books are useful for some patients, and promising initial results have been obtained with BT STEPS. Alone or in combination with potent SRIs, behavior therapy offers those who use it an opportunity to substantially ameliorate the difficult obsessions, compulsions, rituals, and discomfort of OCD.

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Part

V

Panic Disorder and Agoraphobia

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18

Phenomenology of Panic Disorder

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Diagnostic Considerations

Panic disorder is a common, distressing, and often disabling condition in which patients experience recurrent unexpected panic attacks followed by at least 1 month of persistent concerns about having additional attacks (i.e., anticipatory anxiety), worry about the implications of the attack, or a significant change in behavior (e.g., avoidance) related to the attacks (Table 18–1) (American Psychiatric Association 2000). In order for the diagnosis of panic disorder to be made, the panic attacks cannot be due to the physiological effects of a substance or a medical condition or better accounted for by anxiety episodes occurring in conjunction with other psychiatric disorders such as social phobia, specific phobia, posttraumatic stress disorder, or depression.

Panic attacks are periods of intense fear, apprehension, or discomfort that develop suddenly and reach a peak of intensity within 10 minutes of the initiation of symptoms. The DSM-IV-TR criteria (see Table 18–2) require that 4 of 13 symptoms be present to diagnose a panic attack. Of note, most of the symptoms (i.e., 11 of 13) of a panic attack are physical rather than emotional; this may contribute to the frequent presentation of patients with panic disorder in general medical settings and increased rates of use of medical services among affected patients (Katon 1984; Katon et al. 1986; Margraf et al. 1987; Simon and VonKorff 1991). The sudden onset of panic attacks and their episodic nature distinguish them from the more diffuse symptoms characterizing anticipatory or generalized anxiety.

Panic attacks are not unique to panic disorder and may occur on exposure to feared events in any of the anxiety disorders (Barlow et al. 1985). Moreover, panic episodes are reported, albeit infrequently, in individuals without anxiety disorders. As compared with panic attacks occurring in the context of panic disorder, these nonclinical panic episodes are less likely to involve fears of dying, having a heart attack, and losing control and tend to occur during stressful situations such as public speaking and interpersonal conflicts and before tests and examinations (Norton et al. 1985, 1986, 1992).

Given the ubiquity of panic attacks, differential diagnosis is aided by diagnostic revisions made in DSM-IV (American Psychiatric Association 1994) that emphasize fears of recurrent panic attacks as a core feature of panic disorder. In DSM-III-R (American Psychiatric Association 1987), panic disorder was defined, in part, by the number of attacks (i.e., four) occurring over a 4-week period. In DSM-IV, this criterion was changed to emphasize fears of panic attacks as defined by 1 month or more of persistent concerns about having additional attacks, worry about the implications of attacks, and/or a significant change in behavior (e.g.,

TABLE 18–1. DSM-IV-TR diagnostic criteria for panic disorder without agoraphobia

A. Both (1) and (2):

(1) recurrent unexpected panic attacks (see p. 432)
(2) at least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:
  (a) persistent concern about having additional attacks
  (b) worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, "going crazy")
  (c) a significant change in behavior related to the attacks

B. Absence of agoraphobia (see p. 433).
C. The panic attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).
D. The panic attacks are not better accounted for by another mental disorder, such as social phobia (e.g., occurring on exposure to feared social situations), specific phobia (e.g., on exposure to a specific phobic situation), obsessive-compulsive disorder (e.g., on exposure to dirt in someone with an obsession about contamination), posttraumatic stress disorder (e.g., in response to stimuli associated with a severe stressor), or separation anxiety disorder (e.g., in response to being away from home or close relatives).

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TABLE 18–2. DSM-IV-TR symptoms of a panic attack

(1) Palpitations, pounding heart, or accelerated heart rate
(2) Sweating
(3) Trembling or shaking
(4) Sensations of shortness of breath or smothering
(5) Feeling of choking
(6) Chest pain or discomfort
(7) Nausea or abdominal distress
(8) Feeling dizzy, unsteady, lightheaded, or faint
(9) Derealization (feelings of unreality) or depersonalization (being detached from oneself)
(10) Fear of losing control or going crazy
(11) Fear of dying
(12) Paresthesias (numbness or tingling sensations)
(13) Chills or hot flushes

Source. Adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000, p. 432. Used with permission.

avoidance) associated with the attacks. This diagnostic change placed central attention on a patient's phobic responses to the panic attacks themselves and their perceived consequences ("I'm having a heart attack," "I may lose control," "I may faint"). In contrast, other disorders may be characterized by panic responses that accompany feared responses to *other phobic events*, such as exposure to a social situation in social phobia, to a trauma cue in posttraumatic stress disorder, or to an obsessional concern (e.g., contamination) in obsessive-compulsive disorder.

Panic attacks that occur with fewer than 4 of the 13 panic symptoms specified by DSM-IV-TR are referred to as *limited symptom attacks*. Many patients with panic disorder have a combination of full and limited symptom attacks. For some individuals, the early phases of treatment may be characterized by a decrease in full symptom attacks with a transient increase in limited symptom attacks, as treatment begins to become effective. Although limited symptom attacks are associated with fewer symptoms, they still may be quite distressing and associated with significant impairment and increased treatment-seeking behavior (Klerman et al. 1991).

The severity and frequency of panic attacks vary; some patients experience episodes once or twice a week,

and others experience multiple attacks on a daily basis. The frequency of panic attacks may be a misleading indicator of the true severity of the condition because some patients may reduce the frequency of attacks by avoiding situations that trigger them (i.e., agoraphobic avoidance). Thus, a consensus conference on the assessment of panic disorder recommended broadening the domain of symptoms evaluated to include not only panic attack frequency and severity but also phobic anxiety, avoidance, and interference with function (Shear and Maser 1994). The Panic Disorder Severity Scale (PDSS; Shear et al. 1997) is a validated instrument increasingly used to assess these aspects of the panic disorder syndrome and their change with treatment.

The presence of agoraphobia frequently complicates panic disorder (see Table 18–3). In clinical settings, more than three-quarters of the patients with panic disorder report at least mild agoraphobic avoidance (Breier et al. 1986). The diagnosis of agoraphobia refers to a patient's fear or avoidance of situations from which escape might be difficult or embarrassing or in which help may not be readily available in the event of having a panic attack. Agoraphobic situations may include being alone; traveling in public transportation; going over bridges; being in elevators, tunnels, or grocery stores; and standing on long lines; agoraphobia also may occur in any situation in which the patient previously experienced a panic attack. Despite their fear, some patients may push themselves through the agoraphobic situation, whereas others avoid the situations or can face them only in the presence of a trusted companion. Some patients become literally homebound, unable to venture beyond their doorstep, for fear of having a panic attack outside of the perceived relative safety of their home. For some patients, the avoidance behavior may be cued by interoceptive or internal stimuli, such as rapid heart rate, which may occur in the context of physical exercise or sexual arousal. Through conditioning, these stimuli may trigger a cognitive cascade of alarm and result in patients' avoidance of physical exertion or other situations that cause autonomic arousal.

Relation Between Panic Disorder and Agoraphobia

In DSM-IV-TR, agoraphobia is a condition that may occur in the context of two disorders: panic disorder with agoraphobia and agoraphobia without history of panic disorder. In both disorders, however, agoraphobia is described as occurring in response to panic attacks (panic disorder with agoraphobia) or paniclike symptoms (agoraphobia without history of panic disorder). This view of agoraphobia as a consequence of panic has evolved from both theoretical considerations and clinical observations (Klein 1981). However, it is not universally held and remains the subject of one of the more interesting controversies in psychiatric nosology (Ballenger and Fyer 1996).

TABLE 18–3. DSM-IV-TR diagnostic criteria for panic disorder with agoraphobia

A. Both (1) and (2):
   (1) recurrent unexpected panic attacks (see p. 432)
   (2) at least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:
      (a) persistent concern about having additional attacks
      (b) worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, "going crazy")
      (c) a significant change in behavior related to the attacks

B. The presence of agoraphobia (see p. 433).

C. The panic attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).

D. The panic attacks are not better accounted for by another mental disorder, such as social phobia (e.g., occurring on exposure to feared social situations), specific phobia (e.g., on exposure to a specific phobic situation), obsessive-compulsive disorder (e.g., on exposure to dirt in someone with an obsession about contamination), posttraumatic stress disorder (e.g., in response to stimuli associated with a severe stressor), or separation anxiety disorder (e.g., in response to being away from home or close relatives).

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Broadly speaking, two descriptions of the panic disorder–agoraphobia connection have been most prominent. The prevailing view in American psychiatry, as reflected in DSM-IV-TR, has been that agoraphobia is almost always a complication of panic disorder. Klein and Klein (1989) reviewed evidence that agoraphobia usually develops after the onset of spontaneous panic attacks and represents the fear and avoidance of situations in which help may not be readily available should a panic attack recur. An alternative view, more closely allied with European psychiatry and reflected in ICD-10 (World Health Organization 1992), is that agoraphobia is a distinct disorder that may or may not follow the onset of panic attacks (Marks 1987). In ICD-10, the diagnosis of panic disorder with agoraphobia is given only if a primary diagnosis of agoraphobia has been excluded. Which view is better supported by the available data? Three types of studies—epidemiological, clinical, and family and genetic studies—bear on this question, but the answers they provide are inconclusive.

Epidemiological Studies

The common comorbidity of panic disorder and agoraphobia has been well documented in community surveys around the world, in which the lifetime prevalence of agoraphobia among those with panic disorder has ranged from 22.5% to 58.2% (Weissman et al. 1997). Agoraphobia is up to 20 times more common among individuals with panic disorder than among those without it (Weissman et al. 1997). However, data from the largest epidemiological surveys of psychiatric disorders in the United States seem to provide strong evidence that agoraphobia is not typically a consequence of panic disorder.

In the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area (ECA) study of approximately 15,000 individuals examined at five centers in the United States, the overall lifetime prevalence of agoraphobia without panic disorder was 5.6%, whereas the lifetime prevalence of panic disorder was only 1.6% (Eaton 1995; Regier et al. 1988). In the National Comorbidity Survey (NCS) conducted by Kessler and colleagues (1994), the lifetime prevalence of agoraphobia was 6.7%, whereas the lifetime prevalence of panic disorder was 3.5%, and only a minority (36%) of those diagnosed with agoraphobia reported ever having had an unexpected panic attack (Eaton et al. 1994; Magee et al. 1996). These prevalence rates, however, were based on lifetime diagnoses made at the time of a cross-sectional community survey and, as such, could be subject to recall biases. However, Eaton and Keyl (1990) also found that the incidence of agoraphobia without panic disorder was higher than the incidence of agoraphobia following panic disorder in a prospective study of the ECA sample. Their study included the 11,756 individuals who were interviewed in wave 1 of the ECA and, again, 1 year later and who reported no history of any agoraphobia-related fear at the initial interview. The 1-year incidence of agoraphobia was 2.2%, and at least two-thirds of the new patients reported no history of a panic attack. In community studies, then, agoraphobia occurs commonly in those with panic disorder, but most individuals with agoraphobia do not have panic disorder.

Clinical Studies

Evidence from clinical investigations paints a very different picture. Based on these studies, the diagnosis of agoraphobia without a history of panic is quite rare and, in several studies, nonexistent (Goisman et al. 1995; Lelliott et al. 1989; Noyes et al. 1987; Pollard et al. 1989; Thyer and Himle 1985). For example, in one series of 55 patients with agoraphobia, 54 (98%) reported onset of agoraphobia following the onset of panic attacks (Breier et al. 1986). Other investigators who compared patients who have panic disorder with those who have panic and agoraphobia found few differences in terms of clinical or demographic variables, concluding that panic disorder and agoraphobia are manifestations of a single underlying disorder (Noyes et al. 1987; Thyer et al. 1985). Because the presence of agoraphobia was associated with earlier age at onset, greater symptom severity, and more chronicity, these studies have suggested that panic disorder with agoraphobia is a more severe variant of panic disorder (Noyes et al. 1987).

Although most clinical studies have supported the hypothesis that agoraphobia is a sequela of panic, this finding has not been universal. In one study of patients with panic disorder with agoraphobia, Fava and colleagues (1988) reported that 18 of 20 patients (90%) reported the onset of phobic avoidance before their first panic attack. In a clinical sample of 472 children and adolescents, Biederman and colleagues (1997) found that agoraphobia had a higher prevalence than panic disorder (15% vs. 6%) and an earlier mean age at onset.

Family and Genetic Studies

Family and genetic studies can be powerful methods for delineating boundaries between disorders (Smoller and Tsuang 1998). For example, if relatives of probands

with either panic disorder or agoraphobia are at elevated risk for both disorders, then this would lend support to the hypothesis that these disorders can be expressions of a common genetic diathesis. In one study (Noyes et al. 1986), familial risk of panic disorder was elevated in relatives of probands who had either panic disorder or agoraphobia with panic attacks; however, the risk of agoraphobia was elevated only among relatives of probands with agoraphobia. These results were interpreted as indicating that agoraphobia is a more severe variant of panic disorder, although they are not inconsistent with the possibility that agoraphobia is separately transmitted. In a more recent study, however, relatives of probands with agoraphobia did show an elevated risk of agoraphobia without panic disorder (Horwath et al. 1995). The results of these studies provide some support for the position that panic disorder and agoraphobia are expressions of a single underlying disorder. Because DSM-IV-TR defines agoraphobia as a response to panic or paniclike symptoms, the phenotypes of panic and agoraphobia have become linked by definition so that future family and genetic studies may have difficulty testing whether they can be independent.

Discussion

Unfortunately, the causal and clinical relation between panic disorder and agoraphobia has not been conclusively resolved. Several explanations have been offered for the striking discrepancy between the results of epidemiological and clinical investigations, including differences in diagnostic criteria, methods of assessment, and sampling techniques. With the exception of the prospective ECA study, almost all available data are based on retrospective reports, which can be subject to recall bias. When asked to provide a retrospective account of the development of agoraphobia, patients, like clinicians, may seek an explanation for these symptoms. The experience of an initial panic attack is so salient that it may dominate an individual's memory of anxiety symptomatology (Lelliott et al. 1989). Clinical studies also may overestimate the association between agoraphobia and panic disorder because of the phenomenon of Berkson's bias (Berkson 1946). If both panic attacks and agoraphobia independently contribute to treatment seeking, then individuals with both features will be overrepresented in clinical settings.

Alternatively, epidemiological studies may have underestimated the presence of panic symptoms or panic disorder among individuals with agoraphobia. In large studies, such as the ECA and NCS, diagnoses were obtained via fully structured interviews administered by lay interviewers. Some have argued that these methods may have misclassified respondents with respect to panic disorder and/or agoraphobia. As a test of this hypothesis, Horwath and colleagues (1993) studied 22 subjects from the ECA study who had been given diagnoses of agoraphobia without panic disorder or panic attacks. These subjects were reinterviewed with a semistructured clinical interview (Schedule for Affective Disorders and Schizophrenia—Lifetime Anxiety version [SADS-LA]) by master's level social workers or psychologists who were blind to the ECA diagnoses. This clinical interview allowed a diagnosis of simple phobia to be made for individuals who fear crowds, tunnels, bridges, public transportation, or going out of the house alone. After clinical reappraisal, only one case of agoraphobia without panic remained. The other subjects were rediagnosed as having either agoraphobia with panic (2 subjects), simple or social phobia (12 subjects), or no phobia or panic (7 subjects). Although based on a small sample, these results are consistent with the hypothesis that the ECA study overestimated the prevalence of agoraphobia without panic.

Although areas of uncertainty remain, the available evidence does support a few inferences: 1) in clinical settings, agoraphobia most often appears to be associated with panic, and most patients who present clinically report that initial panic attacks preceded or coincided with the onset of agoraphobia; 2) panic attacks are a strong risk factor for the development of agoraphobia, and panic generally precedes agoraphobia in patients with panic disorder with agoraphobia; 3) community studies and a clinical study of children provided consistent evidence, however, that agoraphobia does not always arise as a consequence of panic attacks or panic disorder; and 4) the presence of both panic disorder and agoraphobia is associated with a more severe and chronic course of anxiety symptoms than is seen in panic disorder alone. The remaining ambiguities may succumb to further epidemiological, clinical, and genetic investigation. Of particular interest clinically is determining why some patients with panic disorder develop agoraphobia but others do not. The identification of factors involved in the vulnerability to agoraphobia could provide an important focus for preventive efforts.

Epidemiology

Panic disorder was not defined as a discrete disorder until the publication of DSM-III (American Psychiatric

Association 1980); therefore, few, if any, specific data are available on its epidemiology before that point. The lifetime prevalence rates of panic attacks and panic disorder have been estimated through a series of epidemiological studies—the ECA program and the more recent NCS.

These two epidemiological studies used slightly different diagnostic criteria. The ECA study was conducted from 1980 to 1983 and thus depended on DSM-III criteria in use at that time, as determined by the Diagnostic Interview Schedule (DIS; Robins et al. 1985). The NCS, conducted from 1990 to 1992, used the more recently developed DSM-III-R criteria, as diagnosed by the Composite International Diagnostic Interview (CIDI; Wittchen et al. 1991). The NCS was a nationwide survey based on a probability sample of the continental United States. The NCS surveyed men and women between ages 15 and 54; the ECA study interviewed patients 18 and older (Eaton et al. 1994).

The lifetime prevalence of panic attacks in the ECA study, as defined with DSM-III criteria (including four or more psychophysiological symptoms), was 9.7%. The NCS estimate, as defined with similar criteria, was 15.6%; however, when the definition of panic attack was more narrowly defined with DSM-III-R criteria, its prevalence decreased to 7.3%. The ECA study determined that approximately 1.7% of the general population experience panic disorder in their lifetime; the NCS estimated the lifetime prevalence at 3.5%. The 1-month prevalence of panic disorder was 0.5% in the ECA study and 1.5% in the NCS.

Panic disorder is more commonly diagnosed in women than in men; the female-to-male ratio is approximately 3 to 1 in patients with agoraphobia and 2 to 1 in patients without agoraphobia. Although the average age at onset of panic disorder is typically in the third decade, approximately half of the adult patients with panic disorder report experiencing significant difficulties with anxiety during childhood, in the form of overanxious disorder, social phobia, or separation anxiety disorder (Pollack et al. 1996). Although early reports posited a specific link between separation anxiety in childhood and adult panic disorder (Klein 1964), this conceptualization has been broadened to include a more general link between childhood and adult anxiety difficulties (Aronson and Logue 1987; Berg 1976; Berg et al. 1974; Otto et al. 1994). The onset of panic disorder also has been reported (Biederman et al. 1997) to occur spontaneously, but most individuals with panic disorder are able to identify a life stressor occurring within the year prior to onset of panic, which may be associated with its onset (Manfro et al. 1996; Roy-Byrne et al. 1986). It is unclear whether patients with panic disorder actually experience more life stressors than do other individuals or whether they are more sensitive to the aversive effects of life events because of genetic endowment, temperamental predisposition, or conditioning.

Impairment Associated With Panic Disorder

The effects of psychiatric disorders, in general, on both physical and emotional health have received increasing empirical attention. Whereas a large medical outcome study (Wells et al. 1989) documented the deleterious effects of depression on physical and emotional function, finding the effects to be as bad as or worse than that found in other chronic medical conditions, examination of the health and social consequences of panic disorder has yielded more inconsistent results. Results from one epidemiological sample, for instance, reported that rates of physical and social impairment in panic patients were comparable to or worse than those found in patients with major depression and other chronic medical conditions (Markowitz et al. 1989). Panic was associated with high rates of vocational dysfunction and financial dependence as well as increased use of medical services (Klerman et al. 1991). In contrast, a study examining patients with panic disorder from a variety of outpatient settings and in various phases of treatment found relatively few of the expected adverse effects on physical and general health, although it did document significant impairment in social and emotional functioning (Sherbourne et al. 1996). However, detection of the adverse effects of the disorder may have been obscured because of the potential inclusion of patients benefiting from treatment. In another study, examination of quality of life in a group of panic disorder patients evaluated before initiating treatment in a clinical setting documented significant disruption in patients with panic disorder, including significant impairment in physical and mental functioning comparable to and sometimes worse than that in patients with chronic medical conditions and depression (Candilis et al. 1999).

Panic disorder is common in the general medical setting and is associated with increased health care use in affected individuals. In one survey of 250 primary care physicians, anxiety was the most common psychiatric problem seen in their patients (Orleans et al.

1985), with up to 13% of primary care patients having panic disorder alone or in combination with depression (Katon et al. 1986). Like other psychiatric conditions, panic disorder often is unrecognized and untreated in primary care settings; a recent World Health Organization primary care study documented that the diagnosis of panic was overlooked in half of the affected patients in primary care (Lecrubier and Usten 1998; Ormel et al. 1994; Sartorius et al. 1993). Underrecognition may, in part, be attributable to the typical presentation of panic patients with predominantly somatic (i.e., chest pain, dizziness, shortness of breath, irritable bowel) rather than psychological symptoms (Bridges and Goldberg 1985; Katon 1984). Analysis of data from the ECA study indicated that patients with panic disorder were five to eight times more likely than nonaffected individuals to be high users of medical services (Simon and VonKorff 1991). Even the presence of panic attacks not meeting full criteria for panic disorder may be associated with significant impairment in functioning and treatment seeking (Klerman et al. 1991). Recognition and treatment of panic disorder in general medical settings is critical, given the association of the disorder with adverse effects across multiple domains of function and the demonstration that treatment results in symptomatic relief, improvement in role functioning, decreased use of medical resources, and reduction in overall costs (Salvador-Carulla et al. 1995). In addition, men with panic disorder may be at premature risk for death from cardiovascular causes (Coryell et al. 1982; Kawachi et al. 1994). Of interest, one study (Tucker et al. 1997) reported that selective serotonin reuptake inhibitor treatment of panic disorder normalized the decreased heart rate variability that has been hypothesized to contribute to excessive cardiac mortality associated with panic.

Comorbidity

Panic disorder may be complicated by the presence of comorbid conditions, including other anxiety disorders (i.e., social phobia, generalized anxiety disorder, specific phobia, posttraumatic stress disorder, obsessive-compulsive disorder), depression, and alcohol abuse.

Social phobia may occur in up to a third (Stein et al. 1990) of the patients with panic disorder. The differential diagnosis between panic and social phobia sometimes may be difficult, particularly when panic attacks occur in social situations. Focus on the core fears of the patient may help make the diagnosis; in panic disorder, the central fear is of having a panic attack and may manifest in situations outside of social ones. Patients with social phobia, who panic on exposure to social scrutiny, focus primarily on the possibility of humiliation or embarrassment in social situations. For many patients, both types of fears may be present, and the diagnosis of both conditions is warranted.

Generalized anxiety disorder also is frequently comorbid with panic disorder. To receive the diagnosis of generalized anxiety disorder, patients must be excessively worried about life activities or stressors, with the anxiety focused not just on anticipation of recurrent panic attacks. The episodic and crescendo nature of panic attacks as compared with the more persistent, but often less intense, anxiety associated with generalized anxiety disorder is another distinguishing element.

Patients with *specific phobias*, *posttraumatic stress disorder*, and *obsessive-compulsive disorder* also may experience panic attacks, but these are typically cued by exposure to or anticipation of specific phobic situations (e.g., heights or other phobic situations in the case of specific phobias, situations evocative of traumatic events associated with trauma in the case of posttraumatic stress disorder, and contamination in patients with obsessive-compulsive disorder). For individuals affected with these conditions, panic attacks are cued by specific situations and would not be expected to occur spontaneously unless panic disorder also were present.

Among the most common conditions comorbid with panic disorder is *depression*, with up to two-thirds of panic patients experiencing major depression at some point during their lifetime (Ball et al. 1994; Breier et al. 1984; Stein et al. 1990). Depression may either predate or emerge after the onset of panic disorder and reflect a reactive demoralization to the negative effects of panic or the emergence of an independent condition. As is true with other comorbid conditions, the presence of comorbid depression may complicate treatment and increase the overall severity of the patient's distress; the presence of panic attacks in patients with major depression is associated with an increased risk of suicide (Fawcett et al. 1990), and the presence of comorbid depression in individuals with panic disorder appears to confer increased risk for suicide (Cox et al. 1994). Although data from the ECA study suggested an increased risk for suicide associated with panic disorder alone (Weissman et al. 1989), evaluations of this issue in clinical populations have suggested that the risk is elevated predominantly in those panic patients with comorbid depression and/or personality dysfunction (Cox et al. 1994; Friedman et al. 1992).

Alcohol abuse and *dependence* also may be present in up to a quarter of the individuals with panic disorder. Some individuals report that their abuse of alcohol developed in the context of an attempt to self-medicate their anxiety, but the temporal relation between alcohol abuse and panic disorder tends to follow diagnostic values, with the mean age at onset of alcohol abuse in the late teens and early 20s and panic disorder in the late 20s (Otto et al. 1992). Clinically, the presence of alcohol abuse should be considered in all individuals presenting with panic and other anxiety disorders and may represent a relative contraindication to the use of benzodiazepines; patients abusing alcohol or drugs require focused substance abuse treatment, in addition to the treatment directed at the panic disorder, to facilitate comprehensive recovery.

Conclusion

Panic disorder is a common distressing and disabling condition. It is frequently complicated by the presence of agoraphobia and other anxiety disorders, mood disorders, and alcohol and substance abuse. It is often present in the general medical setting and is associated with increased use of medical services, underscoring the need for timely recognition and treatment.

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19

Pathogenesis of Panic Disorder

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In this chapter, we review the neurobiology of panic disorder. Because it would be impossible to cover all aspects of this wide topic, we focus quite specifically on integrating data derived from our primate studies of developmental psychobiology and findings we have obtained in patients with panic disorder within the context of the wider fund of knowledge. The reader is referred to other sources for further information (Goddard and Charney 1997).

We now know that at least three central neurotransmitter systems—noradrenergic, serotonergic, and γ-aminobutyric acid (GABA)ergic—are acutely affected by certain pharmacological compounds that provide therapeutic benefit for patients with panic disorder. The relation of these neurotransmitter systems to classic neuroendocrine stress responses is intimate and requires careful scrutiny. Of primary focus is the purported overactivity of the hypothalamic-pituitary-adrenal (HPA) axis and the attenuation of the hypothalamic-pituitary-somatotropic (HPS) axis, as reflected by the blunted growth hormone response to clonidine. The relation of stress and the aforementioned neurobiological systems to the well-documented aberrations of ventilatory physiology in panic disorder is explored. From a neuroanatomical standpoint, the potential role of an overactive central nucleus of the amygdala, perhaps driven by the excitatory limbic neuropeptide corticotropin-releasing factor (CRF), is cited as an important component in the orchestration of anomalous autonomic function. Finally, based on primate studies, amygdalohippocampal sites and related frontolimbic structures are posited to bear the psychobiological "stamp" of adverse early life events. Such events may serve as a template for the development of certain adult anxiety disorders. Moreover, frontolimbic dysfunction, as a result of either early environment or genetic diathesis, may be modified by therapeutic psychosocial intervention. The description of an inherited, familial form of panic disorder comorbid with inherited connective tissue laxity, aberrant pain perception, mood disorders, and altered immune function is presented. Preliminary evidence for serotonin autoimmunity is described. Clearly, further systematic, controlled studies are required to validate the views put forward.

Clinical Overview

The symptoms of panic disorder have long been recognized under various guises; soldier's heart, DaCosta's syndrome, and cardiac neurosis referred to a symptomatology reminiscent of modern-day panic disorder

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(Demitrack and Abbey 1996). The disorder also presumably has been subsumed under other sundry diagnoses such as hypochondriacal neurosis, hyperventilatory syndrome, and neurocirculatory anesthesia (Block and Szidon 1994). Because physicians frequently order extensive medical tests on patients with panic disorder, which yield negative results, our colleagues traditionally have been mired by the varied presentations of panic disorder and have ironically labeled its etiology as *supratentorial.* The term implicitly invalidates the severity of the patient's symptomatology and the legitimacy of the condition. However, a plausible biological basis for the psychophysiological presentation of panic disorder and the vital recognition of the importance of central nervous system dysfunction in its pathogenesis are only recent developments.

One of the critical factors in spurring the notion that panic disorder may have a "chemical" basis was the discovery by Donald Klein, M.D. D.F. Klein and Fink (1962) noted that the tricyclic antidepressant imipramine effectively blocked the panic attacks often observed in patients with anxiety neurosis. The spontaneous panic attack was viewed as the core pathology of panic disorder, with subsequent development of anticipatory anxiety and phobic avoidance as secondary symptoms (D.F. Klein 1964). Those patients who have anxiety neurosis without panic attacks have been subsequently categorized as having generalized anxiety disorder.

Pharmacotherapy as Evidence of Biological Basis

Further evidence for a biological basis of panic disorder was provided by the observation that a range of psychotropic medications, in addition to imipramine, eliminated or at least significantly ameliorated panic disorder symptoms. Currently accepted medications for panic disorder include the selective serotonin reuptake inhibitors (SSRIs), the tricyclic antidepressants, the high-potency benzodiazepines, and the reversible and irreversible monoamine oxidase inhibitors (MAOIs) (Coplan et al. 1996b).

Rigorously applied nonpharmacological treatments of panic disorder, such as cognitive-behavioral therapy (CBT), have emerged as being equally efficacious to pharmacotherapy on certain measures. CBT may, however, also work by effecting biological changes similar to those effected by pharmacotherapy. Schwartz et al. (1996) reported that CBT-treated obsessive-compulsive disorder patients had reduced metabolic activity in the caudate nucleus and prefrontal cortex in parallel with clinical improvement. Thus, effective CBT may produce measurable biological effects in patients with panic disorder (Abelson et al. 1996).

Biological Theories of Panic

The acute pharmacological effects of psychotropic medications prompted speculation that specific neurotransmitter systems may be directly implicated in the onset, maintenance, and/or progression of the illness. Biological theories therefore include noradrenergic (a component of acute tricyclic antidepressant effects), serotonergic (SSRI and tricyclic antidepressant mechanism of action), and GABAergic (high-potency benzodiazepine mechanism of action) systems. The ultimate common mechanism of action for this group of agents may, in part, be the attenuation of activity of the neuropeptide neurotransmitter CRF—both at the level of the paraventricular nucleus of the hypothalamus, regulating the HPA axis, and at extrahypothalamic sites such as the amygdala, bed nucleus of the stria terminalis, and prefrontal cortex (De Bellis et al. 1993; Reul et al. 1994).

Noradrenergic Theory

Redmond (1981) conducted seminal studies in chair-restrained rhesus monkeys, demonstrating that direct electrical stimulation of the locus coeruleus, a collection of noradrenaline-producing neurons located bilaterally in the pons area, produced fear responses reminiscent of animals being threatened by a predator. Additional evidence was provided for the view that noradrenergic stimulation was implicated in fear and anxiety responses by the observation that administration of the α_2 antagonists yohimbine and piperoxane produced behavioral effects analogous to those of direct electrical stimulation. These important preclinical studies led investigators to study the noradrenergic system in panic disorder.

When considering a single individual noradrenergic neuron, three important synaptic junctions are emphasized. The first concerns the α_2 autoreceptor mechanism, which regulates firing of the neuron by mediating negative feedback inhibition. α_2 Antagonists interrupt this negative feedback, whereas α_2 agonists, such as the centrally acting antihypertensive agent clonidine, en-

hance negative feedback. The latter therefore reduces noradrenergic firing and diminishes anxiety, at least on a temporary basis. The second synaptic junction of importance concerns afferent projections that synapse on noradrenergic neurons. These include inhibitory (serotonergic and GABAergic) and excitatory (glutamatergic) inputs. Thus, the three neurotransmitter systems affected by antipanic drugs intersect at the noradrenergic neuron. The final synaptic junction is between noradrenergic axonal efferents and an extensive range of projection sites ranging from the prefrontal cortex to the spinal cord. For the purpose of this chapter, we focus primarily on the efferent axons that project to the hypothalamus (for review, see Charney and Heninger 1986). In the hypothalamus, norepinephrine terminals synapse onto two important neuroendocrine systems, leading to the release of CRF and growth hormone releasing hormone into the portal circulation. The release of these two peptide releasing factors produces activation of the HPA axis and the HPS axis, respectively.

Several groups of investigators (Abelson et al. 1992; Charney and Heninger 1986; Nutt 1989; Uhde et al. 1992) have conducted pioneering studies of the noradrenergic system in panic disorder. In keeping with the notion that noradrenergic stimulation would increase anxiety, they showed that yohimbine administration produced panic attacks in patients with panic disorder. Studies that used clonidine, which stimulates release of growth hormone releasing factor through α_2 agonism in the hypothalamus, indicated that the growth hormone response to clonidine was blunted in patients with panic disorder The same blunting has been observed in major depressive disorder and generalized anxiety disorder. In panic disorder, the blunting of the growth hormone response to clonidine was thought to reflect downmodulation of postsynaptic α_2 receptors following chronic noradrenergic discharge. In addition, studies indicated that the degree of blood pressure decrease, cortisol secretion, and noradrenergic turnover regularly induced by clonidine administration was exaggerated in panic disorder. Authors speculated that the noradrenergic system may be dysregulated in panic disorder. Dysregulation may be viewed as an ability of the usual homeostatic mechanisms to contain perturbations of a neurotransmitter system from either excessive activation or inhibition (see Coplan et al. 1997b for further details).

To elaborate on the notion of noradrenergic dysregulation in panic disorder and the role of the presynaptic α_2 autoreceptor in this dysregulation, we performed clonidine challenges in patients with panic disorder and healthy volunteers. By applying a formula developed by von Neumann et al. (1941), we were able to assess within-subject volatility of noradrenergic turnover, as reflected by serial plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) measurements, once the noradrenergic system had been inhibited by clonidine (Coplan et al. 1997a, 1997b). Because clonidine is anxiolytic, changes in noradrenergic volatility are not likely the result of acute anxiety induced by laboratory conditions. Patients had markedly elevated within-subject volatility of plasma MHPG level during the clonidine challenge. It should be noted that the overall mean of *all* MHPG values was only marginally higher in patients than in control subjects. Using a post-hoc cutoff, we were able to show a specificity of 100% and a sensitivity of 82.5% for distinguishing a panic disorder patient from a control subject with plasma MHPG volatility as the outcome measure. If replicated, this use of the clonidine test may yield a highly effective technique to distinguish patients with panic disorder from healthy control subjects. Moreover, the notion of noradrenergic dysregulation in panic disorder was reconfirmed (Coplan et al. 1997a).

Under both baseline and stressful conditions, the noradrenergic system and the HPA axis appear to work in synchrony. Elevations of activity within the one system are accompanied by parallel changes in the other system and vice versa. The coordinated interaction between these two systems has been cited by Chrousos and Gold (1992) as crucial for the mammalian organism's stress response. If noradrenergic function is hyperactive, as has been documented in panic disorder, the question is raised as to how the HPA axis responds and whether healthy synchronization of the two systems remains intact. In fact, we have shown that the two systems become "desynchronized" in panic disorder (Coplan et al. 1995b). Nevertheless, there was evidence for moderate HPA axis activation in this study of panic disorder, suggesting that the desynchronization does not completely protect the HPA axis from noradrenergically driven hyperactivity (Coplan et al. 1995b).

Serotonergic System

The serotonergic system is now a major area of focus not only for panic disorder but also for psychiatry as a whole. However, evidence for an etiological role of serotonergic dysfunction in panic disorder remains sparse. The serotonergic system is exceedingly complex (Grove et al. 1997). Several major features are pointed out. First, the rostral nuclei appear most relevant to

psychiatry, with prominent projections to neocortex. A range of more caudal nuclei modulate autonomic responses and have received less attention. The two major rostral nuclei are 1) the dorsal raphe, which provides projections to the cerebral cortex, primarily the prefrontal, and to the basal ganglia and the nucleus locus coeruleus; and 2) the median raphe, which also projects to the cerebral cortex but also projects strongly to limbic structures such as the hippocampus. Administration of methylenedioxymethamphetamine (MDMA, or the street drug dubbed "Ecstasy") to animals will destroy the fragile neuronal terminals of the dorsal raphe but will not affect median raphe fibers.

Although approximately 15 serotonin receptor subtypes have now been discovered, neurotransmission through serotonin type 1A (5-HT_{1A}) receptors located on pyramidal neurons of the hippocampus has been viewed as crucial by Deakin (1996) in engendering a sense of resilience to the organism. If neurotransmission at this site is inadequate, anxiety and avoidant behavior may ensue. Activation of the HPA axis, which occurs phasically in panic disorder (see Coplan et al. 1998a), may contribute to disruption of hippocampal 5-HT_{1A} neurotransmission by uncoupling the 5-HT_{1A} receptor from its intracellular G-protein messenger system (Lesch and Lerer 1991).

Our group and others have been intrigued by the potential role of aberrant noradrenergic/serotonergic function in panic disorder. This area of focus has been directly stimulated by the uniform (and per meta-analytic studies), superior antipanic effects of the SSRIs (Boyer 1995). SSRIs have minimal acute effects on noradrenergic reuptake or benzodiazepine receptors, in comparison to the tricyclic antidepressants and high-potency benzodiazepines. When we rechallenged patients with panic disorder following 12 weeks of treatment with fluoxetine, noradrenergic volatility levels declined to control levels. Noradrenergic volatility levels remained unchanged in healthy volunteers, which suggested that there was no nonspecific visit effect. Moreover, the greater the magnitude of basal MHPG decrease following fluoxetine, the greater the degree of clinical global improvement. Not all studies support such a clear inhibitory or stabilizing role of SSRIs on noradrenergic function. Goddard and colleagues (1993) reported that although fluvoxamine attenuated the anxiogenic effects of yohimbine in patients with panic disorder, it failed to block the yohimbine-induced MHPG increase.

The role of serotonin in ventilatory regulation is directly pertinent to panic disorder. Hyperventilation is one of the cardinal physiological correlates of panic-anxiety. Freud himself noted a strong relation between ventilation and anxiety, and this view has been elaborated on by D.F. Klein (1993) in the form of the "suffocation alarm hypothesis," a pathological sensitivity to accumulation of carbon dioxide. Furthermore, in animal studies, deficient serotonin neurotransmission, through administration of the noncompetitive serotonin antagonist PCPA (parachlorophenylalanine), produced hyperventilation and carbon dioxide sensitivity. Conversely, increasing serotonin neurotransmission in rats with the serotonin precursor 5-hydroxytryptophan depressed ventilation and reduced carbon dioxide sensitivity (Kent et al. 1996).

Little research has examined the relation between serotonin and respiration in the clinical setting. Because SSRIs exert beneficial effects through enhancement of serotonin neurotransmission and normalization of ventilatory overdrive accompanies clinical improvement of panic disorder, we hypothesized that deficient serotonin may contribute to the plethora of ventilatory abnormalities that have been reported in panic disorder. To test the hypothesis, our group (Kent et al. 1996) used the Delgado et al. (1990) method of depleting serotonin In brief, this entails administration of a highly concentrated amino-acid mixture that is free of tryptophan, an essential building block for serotonin synthesis. The amino-acid load stimulates protein synthesis by the liver, and all available tryptophan is rapidly incorporated into protein. The amount of tryptophan that is then available for transport into the brain is greatly curtailed. An acute reduction in serotonin neurotransmission is thus effected. Although our results are in the pilot stage, depletion only had an effect on patients in the expected direction, increasing minute ventilation during room air breathing. Control subjects' ventilatory function remained unaltered despite depletion. Evidence therefore indicates that serotonin does play a role in human ventilation and that patients with panic disorder are particularly sensitive to serotonin depletion. Enhancement of serotonin neurotransmission by SSRIs thus may exert therapeutic effects by normalizing aberrant ventilatory patterns in addition to normalizing noradrenergic dysregulation.

Lactate Infusion Studies

Although lactate infusion remains the most widely reported method of panic induction, the mechanisms for lactate-induced panic are unclear. To shed further light

on lactate-induced panic, we examined its potential determinants. We investigated the role of psychological, acid-base, and biochemical factors during the baseline saline period directly preceding a lactate infusion in determining a panic outcome (Coplan et al. 1998a). The report included all available data acquired during the prelactate period of the lactate infusions performed over the last decade at New York State Psychiatric Institute.

Cortisol levels, indicating HPA axis activation, were elevated only in the group who went on to panic during the lactate infusion phase. Nonpanicking patients were not, however, distinguishable from control subjects. Respiratory alkalosis, indicative of hyperventilation, also was more prominent in the group who would go on to panic. Predictors of lactate-induced panic included self-reported fear levels and the interaction of high cortisol and (hyperventilation-induced) hypocapnia—implying that the combination of high cortisol and hyperventilation was more predictive than either factor alone. Within the panic-prone group, a synchronous relationship was noted among fear, cortisol, and hypocapnia such that all were significantly correlated with one another. In the group of patients who were not lactate sensitive and the healthy volunteer group, no significant correlative relation was found among these variables. Not only activation but also synchronization of ostensibly disparate systems appeared to play a critical role in determining lactate vulnerability. The pattern observed was suggestive of the activation of a common neural substrate with diverse effects. Stimulatory influences include CRF, glutamate, and norepinephrine, whereas inhibitory influences include GABA and serotonin increases (Coplan et al. 1997b).

Neuroanatomy of Fear

Animal studies have indicated that fear and anxiety-like states are mediated by structures that include the amygdala, hippocampus, prefrontal cortex, locus coeruleus, and periaqueductal gray (Graeff 1990). Because of reciprocal connections between the aforementioned structures, the amygdala with prominent prefrontal connections appears poised to integrate fear-related responses most effectively. The central nucleus of the amygdala appears particularly crucial for orchestrating the autonomic response to fear (Davis 1986). It receives sensory input from a host of forebrain structures and then determines the optimal pattern of fear response. Its behavioral influence includes activation of the periaqueductal gray and induction of escape, freeze, and defensive responses; cardiovascular activation mediated through stimulation of the dorsal motor nucleus of vagus; and ventilatory activation mediated through stimulation of the nucleus parabrachialis. The amygdala also can activate the HPA axis through stimulation of the paraventricular nucleus of the hypothalamus and also the locus coeruleus and ventral tegmental area, where dopaminergic neuronal cell bodies are located. Thus, the common neural substrate synchronizing fear, cortisol, and hyperventilation and postulated to be responsible for bestowing vulnerability to lactate-induced panic may well lie in the vicinity of the central nucleus of the amygdala.

One speculative and unproven view is that during the massive expansion of the human prefrontal cortex, there was a parallel development of massive reciprocal connections between the amygdala and the prefrontal cortex. The amygdala, an ancient limbic structure, provides emotional valence for objects that are being processed in the neocortex. One possibility is that the human amygdala has not developed adequately to handle the flood of neocortical input that occurs in our species, especially if that input is excessive and/or stressful. The central nucleus of the amygdala may then respond by excessive discharge. An upset of optimal asymmetry of limbic and prefrontal cortical sites appears to be a common theme in neuroimaging studies and may reflect ipsilateral pathology of limbic and/or prefrontal cortical sites. For instance, in positron-emission tomography scan studies by Reiman and colleagues (1989), an exaggeration of the normal right to left metabolic asymmetry observed in the parahippocampal gyrus predicted lactate-induced panic. This paralimbic structure lies directly adjacent to the amygdala. Thus, the "neural" stage is set for the elaboration of catastrophic cognitions routinely observed in patients with panic disorder. CBT may work by reducing prefrontal cortical overactivity and/or restoring abnormal asymmetry to its healthy state, with a resultant reduction in CRF output.

Corticotropin-Releasing Factor and Related Primate Studies

Extrahypothalamic CRF appears to play a major role in mobilizing the central nucleus of the amygdala into action, perhaps through intimate communication with the closely linked bed nucleus of the stria terminalis.

Moreover, administration of CRF into the ventricular system produces an array of behaviors analogous to human anxiety and affective disorders, including behavioral inhibition, reduced exploratory activity, and increased startle response (Coplan et al. 1995c).

We conducted a series of primate studies investigating the long-term effects of adverse early rearing on anxiouslike behaviors as well as biochemical changes of CRF and related systems that may be of relevance to human studies (Coplan et al. 1996a). We studied grown animals randomly assigned as nursing infants to be raised by their own mothers undergoing different foraging demand paradigms. The low foraging demand group had easy access to food. The high foraging demand group had difficult access to food, but it was constant. The variable foraging demand group had 2 weeks of easy access to food alternating with 2 weeks of difficult access to food. The duration of the study was 12 weeks. The variable foraging demand group had socially inhibited behaviors, reduced affiliative behaviors, and increased susceptibility to despair responses on separation and showed reduced exploratory activity when the mother was present. Note that variable foraging demand primates, when faced with a novel environment, cling to their mothers not unlike human children with separation anxiety. D.F. Klein (1993) viewed separation-induced distress, or separation anxiety, as the developmental precursor most akin to adult panic disorder. Thus, the variable foraging demand model provides an interesting primate phenocopy of a childhood anxiety disorder whose phenotypic expression in all likelihood represents a combination of environmental and genetic influences.

Our initial studies identified an enhanced behavioral response to yohimbine in variable foraging demand subjects (Rosenblum et al. 1994), which, in humans, is observed only in panic disorder and posttraumatic stress disorder (PTSD). In subsequent studies, variable foraging demand subjects had marked elevations of CRF in cisternal cerebrospinal fluid (CSF) samples, whereas low foraging demand and high foraging demand groups were not distinguishable (Coplan et al. 1996a). CSF CRF is believed to be reflective of extrahypothalamic CRF from the amygdala, the closely related bed nucleus of the stria terminalis, and the prefrontal cortex (Plotsky et al. 1995). Thus, a relatively brief period of disturbance of maternal-infant interaction may lead to persistent elevations of CRF, with implications for a long-standing template engendering susceptibility to anxiety and affective-related disturbances. CSF cortisol levels, however, were low. The combination of high CRF and low cortisol is most similar to the findings observed in PTSD rather than panic disorder (Yehuda et al. 1995). Thus, adverse early rearing may lead to a PTSD-like neurobiology. Yehuda and colleagues (2000) recently observed aberrant patterns of cortisol regulation in grown children whose parents were holocaust survivors and had diagnoses of PTSD. Panic attacks are quite frequent in PTSD patients, however, and in patients with borderline personality disorder, who have increased rates of traumatic experiences. Thus, the aberrant neurobiology of the variable foraging demand may bear relevance to an environmentally induced form of separation anxiety with potential relevance to panic disorder in humans

Of interest is that the CRF elevations in the variable foraging demand subjects appeared to occur in synchrony with elevations of several other neurochemicals in comparison to those of non–variable foraging demand subjects (Coplan et al. 1998b). CRF correlated significantly with the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), the dopaminergic metabolite homovanillic acid, and the neuropeptide somatostatin. None of these correlations was significant in the non–variable foraging demand subjects. These data suggest that CRF elevations also may mediate a range of behavioral effects influencing other neurochemical systems involved in affect regulation (Coplan et al. 1998b).

Growth Hormone Response to Clonidine and Early Rearing

Somatostatin, serotonin, and dopamine all can inhibit growth hormone, but we were particularly interested to determine whether the long-standing CRF elevations that had been documented in the variable foraging demand primates would influence the growth hormone response to clonidine. We would therefore be able to show that early environmental factors involving emotional distress in the infant may produce a permanent stamp on the nonhuman (and possibly human) primate through CRF elevations. These elevations then can be detected through testing for the reduced growth hormone response to clonidine. The data supported our hypothesis, with a strong inverse correlation between CSF CRF levels and maximal growth hormone responses to clonidine infusions, despite an interval of between 2 and 3 years (Coplan et al. 2000). "High" CRF animals had reduced growth hormone secretion to clonidine in comparison with "low" CRF animals.

These data raise the possibility that the reduced human growth hormone response to clonidine in humans not only may depend on episodic elevations of noradrenaline activity but also may be an effect of elevated CRF levels following adverse early rearing. Elevations of CRF (in this instance, after disturbance of mother-infant interaction) may inhibit growth hormone response to clonidine and possibly to a range of other growth hormone secretagogues.

Effects of Treatment: Trait Versus State Considerations

In contrast to the effect of fluoxetine antipanic treatment on reducing noradrenergic volatility, fluoxetine did not normalize the growth hormone response to clonidine (Coplan et al. 1995a) or baseline cortisol elevations (Coplan et al. 1995b). The possibility raised is that reduced growth hormone response to clonidine is a trait feature, also reflecting increased activity of the CRF-producing neurons. Antipanic treatment with alprazolam, a high-potency benzodiazepine with direct inhibitory effects on rodent CRF, is associated with normalization of the growth hormone response to clonidine (Brambilla et al. 1995). Thus, divergent pharmacological effects of different antipanic medications may have bearing on which component of abnormal neurobiology is normalized.

Joint Hypermobility Syndrome, Mitral Valve Prolapse, and Serotonin Autoimmunity

In addition to the effect of environmental factors, the heritable nature of panic disorder has been well documented (Perna et al. 1997). The location of chromosomal markers has been difficult despite extensive examination of the genome. Genetic abnormalities may be better identified by studying panic disorder in the context of medical conditions with which it is frequently comorbid. This strategy may facilitate accurate identification of endophenotypes that would otherwise go unrecognized. The joint hypermobility syndrome, an inherited connective tissue condition, has been shown in several different studies by Bulbena and colleagues (Bulbena et al. 1993; Martin-Santos et al. 1998) to occur at a rate of 70% in patients with panic disorder as opposed to 15% in healthy control subjects. In those studies, the connective tissue condition appeared to extend to the mitral valve. Rates of mitral valve prolapse were elevated in the panic disorder patients with joint hypermobility in comparison to nonhypermobile control subjects with anxiety disorder.

In studies related to tissue elasticity and panic disorder, we wanted to determine whether mitral valve prolapse associated with panic disorder, a finding documented by many but not all groups, represented a fixed cardiac abnormality. Alternatively, we wanted to determine whether mitral valve prolapse could represent a state abnormality, reflecting increased end-systolic ventricular pressure secondary to noradrenergic hyperactivity. This would produce excessive cardiac stimulation, thus distending an abnormally elastic mitral valve. The data supported the latter view. Treatment with a variety of antipanic drugs, in some instances combined with CBT, reduced the degree of echocardiographically documented prolapse in patients with panic disorder (Coplan et al. 1992). However, in patients with mitral valve prolapse without a psychiatry history, no statistically detectable change in degree of prolapse was seen between a first and a second echocardiogram. Thus, the mitral valve prolapse in panic disorder appeared partially reversible and may have been created by the combination of lax connective tissue and a noradrenergically driven hyperdynamic circulation.

Other frequent associations with panic disorder (including the joint hypermobility syndrome) include fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, hypothyroidism, asthma, allergic rhinitis, sinusitis and migraine, depression, bipolarity, and antidepressant medication "poop-out" (loss of effectiveness). The possibility is therefore raised that a certain familial form of the disorder exists that shares psychiatric, connective tissue, aberrant pain perception, and autoimmune features. More recently, an exciting and relevant genomic finding emerged from the Barcelona group (Gratacos et al. 2001). This group of investigators identified an interstitial duplication of human chromosome 15q, which is part of several sets of segmental duplications of that chromosome, in 68 of 70 unrelated patients with panic disorder and joint laxity syndrome. Gratacos and colleagues note that the mosaicism in subjects with genetic disorders and the detection of different forms of the duplication within the same family suggest that "we are facing a new non-Mendelian mechanism of disease-causing mutation in humans." The genetic data are consistent with the variable phenotypic expression we have observed in the above-described "syndrome."

A report by R. Klein and colleagues (1992) indicated that patients with fibromyalgias manifested elevated concentrations of serotonin autoantibodies. Because of the documented relation between panic disorder, affective disorders, and fibromyalgia (Hudson et al. 1985), we investigated serotonin autoimmunity in panic disorder. In a reasonably sized sample of panic disorder patients and healthy control subjects, we showed that patients have elevated antibody titers not only to the serotonin transmitter itself but also against the serotonin receptor, referred to as a serotonin anti-idiotypic antibody (Coplan et al. 1999). Thus, a potential model is provided for serotonin dysfunction—interruption of serotonin neurotransmission by serotonin receptor autoantibodies. In this instance, enhancement of SSRIs neurotransmission is effective by stimulating an increased number of postsynaptic receptors.

Conclusion

Understanding of the neurobiology of panic disorder has undergone unprecedented growth since the groundbreaking studies of Klein in the early 1960s. However, many crucial questions remain unanswered. In this chapter, we have focused on the interrelationship among the noradrenergic, GABA, serotonergic, HPA axis, ventilatory, and extrahypothalamic central CRF systems. The focus of this chapter was to examine specific aspects of the neurobiology of panic disorder and should not be regarded as comprehensive. The reader is directed to important work involving the central cholecystokinin system (Bradwejn and Koszycki 1994), studies with carbon dioxide (Papp et al. 1997), and neuroimaging studies (Dager and Swann 1996). The reader also is directed to other sources for more in-depth information on theories involving GABA function in panic disorder.

In conclusion, the following points can be made:

1. Panic disorder has been recognized in various forms for centuries. Explanations of its causation have varied widely, from being viewed as a completely physical condition to a completely psychological one.
2. Various drugs are now widely accepted as effective in panic disorder and provide support for the biological basis of panic disorder, specifically implicating noradrenergic, serotonergic, and GABAergic systems. Effective psychological treatments of panic disorder, such as CBT, do not negate the disorder's biological basis but rather indicate that psychotherapy produces biological effects. All may ultimately work by reducing CRF and HPA axis activity.
3. Noradrenergic dysregulation is well documented in panic disorder, but drugs that augment serotonin neurotransmission reduce noradrenergic volatility, suggesting a stabilizing, and perhaps more primary, role for serotonin.
4. Interruption of serotonin neurotransmission may contribute to the ventilatory abnormalities observed in panic disorder. By increasing serotonin neurotransmission, SSRIs may work in part by normalizing these abnormalities.
5. Vulnerability to sodium lactate infusion appears to involve synchronized activation fear levels, hyperventilation, and HPA axis activation, implicating hyperactivity of the central nucleus of the amygdala and its autonomic efferents in producing anticipatory anxiety and priming the person toward panic.
6. Long-term CRF elevations can be induced in grown nonhuman primates who were raised under stressful conditions as infants. The CRF elevations are associated with other biochemical alterations, including the reduced growth hormone response to clonidine. This primate model also may bear relevance to panic attacks occurring in the context of PTSD and borderline personality disorder.
7. A familial form of panic disorder may entail the combination of psychiatric disorder, inherited connective tissue conditions, abnormalities in panic perception, and propensity to autoimmune activity. The view of autoimmunity in panic disorder is supported by the observation of elevated antiserotonin antibodies and serotonin anti-idiotypic antibodies directed at serotonin receptors. A highly significant gene association with panic disorder in conjunction with joint laxity syndrome has been identified on chromosome 15q (Gratacos et al. 2001). Future developments are anticipated.

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20

Pharmacotherapy for Panic Disorder

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The goal of pharmacological treatment of panic disorder is to reduce the severity and intensity of the panic attacks, avoidance, fearful anticipation, cognitive distortions, and any additional psychiatric disorder. The effectiveness of pharmacotherapy for panic disorder has been unequivocally established in well-controlled scientific studies. Although no unifying hypothesis explains the etiology of panic disorder, basic research findings and clinical studies support theories that neurobiological alterations in brain function are present in individuals who have panic disorder (Coplan and Lydiard 1998). Some alterations in neurotransmitter and/or neurotransmitter receptor system functioning appear to be normalized after effective pharmacological treatment (Johnson and Lydiard 1995).

The doctor-patient information exchange during evaluation of panic disorder is critical. From a clinical perspective, the decision to prescribe medication involves recognition of the patient's wishes, the physician's orientation, and the severity of the panic disorder. At this point, considerable data support the concept that panic disorder is a familial, biomedical disorder. This information can be important in helping the patient understand that the illness is not a matter of his or her inadequate effort to control the symptoms. Because panic disorder is responsive to both medication and cognitive-behavioral treatment, understanding that both a behavioral/psychological and a medication treatment may treat panic effectively can be conceptually difficult for patients. This can be addressed by noting that the different treatments may affect different levels of the panic neural circuit in the brain (Coplan and Lydiard 1998; Gorman et al. 1989, 2000). The treatment of panic disorder with cognitive-behavioral therapy and other behavioral techniques is discussed elsewhere in this volume (see Spiegel and Hofmann, Chapter 21). In this chapter, we focus on the psychopharmacological treatment of panic disorder.

General Principles

As noted earlier, the effectiveness of several different classes of antipanic medication treatments has been firmly established via scientific investigation. Several types of medication treatments are now available, but the clinician suggesting a specific medication treatment for an individual panic disorder patient must consider a variety of factors. Even after considering the relevant clinical variables (Table 20–1), there is no guarantee that a specific medication will be ideal for a given patient, and all medications have some unwanted effects. Therefore, the relative advantages and disadvantages of each of the available treatments should be anticipated for the individual patient, and participation in the initial treatment choice should be negotiated with the patient as an active partner in the process.

In general, any given agent should begin to show effectiveness within the first several weeks of treatment. However, because panic disorder is often a chronic condition, it is important to choose an agent that has shown efficacy and tolerability beyond the first several weeks or months of treatment. Another important aspect of

TABLE 20–1. Summary of key features of panic attacks, panic disorder, and agoraphobia

Panic attacks

A discrete period of intense fear or discomfort in which four (or more) of the following symptoms developed abruptly and reached a peak within 10 minutes:

- Palpitations, pounding heart, or accelerated heart rate
- Sweating, trembling, or shaking
- Sensations of shortness of breath or smothering
- Feeling of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feelings of being dizzy, unsteady, lightheaded, or faint
- Derealization (feelings of unreality) or depersonalization (feeling detached from oneself)
- Fear of losing control or going crazy
- Fear of dying
- Paresthesias (numbness or tingling sensations)
- Chills or hot flushes

Panic disorder

Recurrent unexpected panic attacks in which at least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:

- Persistent concern about having additional attacks
- Worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, "going crazy")
- A significant change in behavior related to the attacks

The panic attacks are not due to the effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).

The panic attacks are not better accounted for by another mental disorder.

Agoraphobia

Anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having an unexpected or situationally predisposed panic attack or paniclike symptoms. Agoraphobic fears typically involve characteristic clusters of situations that include being outside the home; being in a crowd or standing in a line; being on a bridge; and traveling in a bus, train, or automobile.

The situations are avoided (e.g., travel is restricted) or else are endured with marked distress or with anxiety about having a panic attack or paniclike symptoms, or require the presence of a companion.

The anxiety or phobic avoidance is not better accounted for by another mental disorder.

Source. Adapted from American Psychiatric Association 1994.

treatment choice is an assessment of other possible panic-related problems, such as agoraphobia or other coexisting psychiatric disorders (e.g., depression, social phobia, alcoholism, or posttraumatic stress disorder). Assessment of these common coexisting conditions must be included in the initial evaluation, because the presence of one or more of these conditions may affect treatment outcome (Lydiard and Brawman-Mintzer 1997). Medical conditions that may mimic or coexist with panic disorder should be considered. In addition to conditions complicating or mimicking panic disorder, there may be different degrees of response in panic-related symptoms (e.g., phobia, depression, anticipatory anxiety). Table 20–2 provides a "differential diagnosis" checklist for incomplete response in one or more panic-related symptoms.

Is one medication class superior to the others? The vast majority of clinicians treating panic disorder use one of the selective serotonin reuptake inhibitors (SSRIs) as a first-line treatment (Jobson et al. 1995). In fact, this suggestion is included in the American Psychiatric Association practice guidelines for panic disorder (Gorman et al. 1998). The rationale for this choice is that these agents are more tolerable than the traditional tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs) and offer a broader range of efficacy for conditions commonly co-occurring with panic disorder (Figure 20–1).

It is now evident that panic disorder patients experience significant functional disability, including poor quality of life and occupational, social, and physical limitations (Rapaport et al. 1998). Evaluation of the effec-

TABLE 20–2. Differential diagnosis of poor treatment outcome

Problem	Differential diagnosis	Comment
Persistent panic attacks	Inadequate treatment	
	Dosage	Adjust dose (plasma levels may help) Switch or add agent to existing
	Duration	At least 8 weeks
	Situational attacks	CBT/exposure
	Medical condition	Address specific conditions
	Other psychiatric disorder causing attacks	Rule out social phobia, OCD, PTSD
	Agoraphobia: fear/avoidance of situations in which panic attacks might occur	Elimination of agoraphobia severity specifiers (mild, moderate, severe)
Persistent nonpanic anxiety	Medication related:	
	Activation (SSRI or TCA)	Adjust dosage, add benzodiazepine or β-blocker
	Akathisia from SSRI	Adjust dosage, add β-blocker, benzodiazepine
	Generalized anxiety disorder	Benzodiazepine, buspirone
	Substance-related:	
	Interdose rebound from short-acting benzodiazepine	Switch to longer-acting agent
	Benzodiazepine or alcohol withdrawal	Assess and treat as indicated
	Residual anxiety	Add/increase benzodiazepine, add buspirone
Residual phobia	Other etiology	Review for other phobic disorders, depression
	Residual agoraphobia	CBT/exposure, adjust medication treatment
Other disorders	Mood disorder	Antidepressant treatment plus anxiolytic; valproate or gabapentin for bipolar disorder
	OCD	SSRIs, CBT, anxiolytics as indicated
	PTSD	Specific treatment for symptoms present, SSRIs, CBT, others
	Alcohol use disorder	Psychosocial treatment for alcohol-related behavior SSRIs, TCA, avoid benzodiazepines
	Personality disorders	Specific psychotherapy
	Medical disorder	Review and modify treatment as indicated
Environmental event/stressor(s)	Review work, family events, patient perception of stressor	Environmental hygiene as indicated Brief adjustment in treatment plan(s) as needed
	Family/spouse interview and education	
Other	Poor compliance	
	Sexual side effects	Add/switch agents, consider brief drug holiday
	Inadequate understanding of panic disorder/ treatment	Patient/family education Make resource materials available

Note. CBT = cognitive-behavioral therapy; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

tiveness of any medication treatment for panic disorder should therefore be considered in the context of the long-term outcome rather than the acute reduction of severity and intensity of panic attacks. Short-and long-term assessments of the presence of fearful avoidance, anticipatory anxiety, or depression and of whether the illness-related impairment in functional (i.e., occupational, social, and family) activities has been restored to pretreatment levels (Shear and Maser 1994) would provide a more meaningful measure of treatment effectiveness. A recent report of the efficacy of fluoxetine in panic disorder (Michelson et al. 1998) provided empirical support for the superiority of multiple-domain assessment.

A limitation of the studies of panic disorder treatment published to date is that many of them were conducted in relatively uncomplicated patient samples and involved relatively short durations (i.e., 6–12 weeks). Thus, although the literature is somewhat useful in determining the short-term benefits of treatment, it is unfortunately of limited help in discerning the best long-term treatment choice.

In planning treatment with the patient, the clinician must take into account the predicted efficacy and tolerability of the treatment over both the short and the long term. Side effects such as weight gain or sexual dysfunction may accrue over time and may lead to patient non-

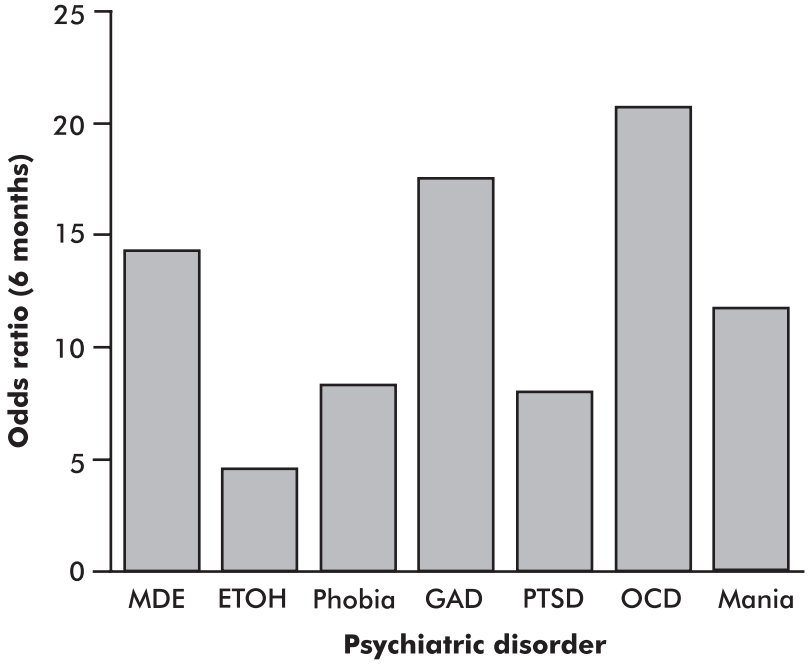

FIGURE 20–1. Relative risk for additional psychiatric disorders in persons with panic disorder (6-month odds ratio).
MDE = major depressive episode; ETOH = ethanol (i.e., alcohol) abuse/dependence; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder; OCD = obsessive-compulsive disorder.
Source. Reprinted from Lydiard RB, Otto MW, Milrod B: "Panic Disorder," in *Treatments of Psychiatric Disorders*, 3rd Edition, Vol. 2. Gabbard GO, Editor-in-Chief. Washington, DC, American Psychiatric Press, 2001, p. 1449. Copyright 2001, American Psychiatric Press, Inc. Used with permission.

compliance and worse treatment outcome. The ideal medication would be associated with the lowest possible rate of relapse after medication discontinuation; studies to date indicate that most patients experience a return of panic-related symptoms within several months of medication discontinuation.

It should be noted here that the wide availability of information via the Internet provides unprecedented opportunities for patients and clinicians to quickly access information relating to mental illness treatment. Because of the increasing use of the Internet for information, it is important that clinicians be familiar with at least a few reliable sources of information for interested patients and families.

Pharmacotherapeutic Treatments for Panic Disorder

Selective Serotonin Reuptake Inhibitors

The SSRIs have become the mainstay of pharmacological treatment for mood and anxiety disorders. SSRIs were considered the first-line treatment by a group of experts in anxiety for years before controlled studies appeared (Jobson et al. 1995), and a meta-analysis of the controlled studies up to 1995 that included clomipramine as an SSRI (Boyer 1995) suggested that the SSRIs may be even more effective than the imipramine or alprazolam. Convincing evidence is now available for the efficacy of each of the available SSRIs, including fluvoxamine (150–300 mg/day) (Black et al. 1993; Hoehn-Saric et al. 1993), paroxetine (40–60 mg/day) (Ballenger et al. 1998; Lydiard et al. 1998; Oehrberg et al. 1995), sertraline (50–200 mg/day) (Londborg et al. 1998; Pohl et al. 1998; Pollack et al. 1998; Rapaport et al. 1998), and citalopram (20–40 mg/day) (Lepola et al. 1998). A recently completed placebo-controlled, fixed-dose study comparing 10 and 20 mg/day of fluoxetine for panic disorder showed that both dosages were superior to placebo on most outcome measures (Michelson et al. 1998, 1999).

For many years, clomipramine, a TCA with potent serotonin uptake inhibition properties, was considered the most potent antipanic TCA (Jefferson 1997). The SSRIs appear to be at least as efficacious as clomipramine and also retain their effectiveness over the longer

term. Clomipramine has been compared with fluvoxamine (den Boer and Westenberg 1987), and paroxetine and citalopram have been compared with clomipramine and placebo (Lecrubier and Judge 1997; Lepola et al. 1998) in long-term studies. The two SSRIs were comparably effective but were significantly better tolerated than clomipramine. In the Lepola et al. (1998) study, panic patients were treated under double-blind conditions with citalopram, clomipramine, or placebo for 1 year. Both active agents were superior to placebo, but fewer patients in the citalopram treatment group than in the clomipramine group dropped out of the study because of adverse side effects. Long-term studies of sertraline (Clayton et al. 1999) and fluoxetine (Michelson et al. 1998) suggest that these agents, like other SSRIs, are also effective over the longer term.

Individuals with panic disorder are particularly sensitive to certain activating side effects of the SSRIs, such as insomnia, restlessness/jitteriness, and agitation. Should these adverse effects occur without prior patient education, early treatment discontinuation (Schneier et al. 1990) may ensue. As with the TCAs, SSRIs should be initiated at low doses (e.g., 5–10 mg for paroxetine, 12.5–25.0 mg for sertraline, 25 mg for fluvoxamine, 2.5–5.0 mg for fluoxetine), with gradual upward titration. Therapeutic advantages of the SSRIs over the older agents are considered by most clinicians to outweigh any additional cost. Less weight gain, few (or no) anticholinergic effects, a benign cardiovascular profile (e.g., no orthostatic dizziness or cardiac conduction effects), and relative safety in overdose are all desirable properties. However, a substantial percentage (20%–30%) of patients taking SSRIs for extended periods develop sexual side effects (Lydiard et al. 2001). Strategies that can be used to reverse these unwanted effects include the addition of buspirone 30–60 mg/day, bupropion 100–200 mg twice daily, amantadine 100 mg twice daily, or sildenafil 50–100 mg daily or prior to anticipated intimacy.

Benzodiazepines

Benzodiazepines were not generally thought to be useful antipanic agents until the late 1980s. The triazolobenzodiazepine alprazolam was demonstrated to be superior to placebo in treating patients with panic disorder (or agoraphobia with panic attacks) (Ballenger et al. 1988). Alprazolam was the first drug approved by the U.S. Food and Drug Administration (FDA) to treat panic disorder (Spiegel 1998). Because of the pharmacokinetic properties of this agent, alprazolam treatment required dosing three to four times a day for many patients. Clinical impressions of rebound interdose anxiety, presumably caused by interdose fluctuations in alprazolam plasma levels during treatment (Herman et al. 1987), prompted exploration of benzodiazepines with longer elimination half-lives. Clonazepam, a nontriazolobenzodiazepine, was subsequently compared with alprazolam and placebo (Tesar et al. 1987). Clonazepam was shown to be as effective (average dosage = 2.5 mg/day; 50% responders) as alprazolam (average dosage = 5.7 mg/day; 46% responders), and both were superior to placebo (14% responders). Furthermore, the long elimination half-life allowed for a dose regimen of once or twice daily for most patients. By extrapolation from the Tesar et al. study, the equivalent clonazepam requirement (mg/day) is probably about half that of alprazolam. Clonazepam has now received FDA approval for treatment of panic (Davidson and Moroz 1998). Substantially less information is available about other benzodiazepines, but lorazepam, diazepam, and others appear effective if given in adequate dosages (Noyes et al. 1996).

Additional efforts have focused on optimal dosing strategies, comparative efficacy (both with other benzodiazepines and with other pharmacological classes), maintenance treatment, and tactics for benzodiazepine discontinuation.

Benzodiazepine Dosage

The study that first demonstrated alprazolam's superiority to placebo for treatment of panic disorder required investigators to attempt to treat all patients with 6 mg/day of alprazolam (average daily dosage = 5.7 mg; range = 1–10 mg/day) (Ballenger et al. 1988). Adverse effects such as ataxia, sedation, and fatigue occurred in a significant proportion of alprazolam-treated patients. A second multinational study comparing alprazolam with the TCA imipramine showed that imipramine was as effective as alprazolam, but with a slower onset of effect and more side effects (Cross-National Collaborative Panic Study 1992; Davidson 1997). This study confirmed that the benzodiazepines were as effective in nondepressed outpatients with panic disorder as was the gold standard tricyclic imipramine. Because the initial alprazolam studies required a dose escalation to 6 mg, which caused significant adverse effects in many subjects, a study was designed to explore a lower dosage (2 mg/day) compared with 6 mg/day and (Lydiard et al. 1992). In that study, a significant percentage of the patients receiving 2 mg/day of alprazolam achieved bene-

fits comparable to those with the higher 6-mg/day dosage with fewer adverse effects.

Benzodiazepine Plasma Levels

The study comparing 2 and 6 mg/day of alprazolam provided some information about the relationships among alprazolam plasma levels, clinical benefits, and adverse effects (Lesser et al. 1992). Plasma levels of approximately 20-40 ng/mL of alprazolam were sufficient for significant reductions in panic attack frequency and moderate improvement overall. Higher concentrations (>70 ng/ml) were associated with greater improvement but also caused more side effects. The only other benzodiazepine for which plasma level has been reported in panic disorder treatment is clonazepam (Beauclair et al. 1994). The limited data on clonazepam plasma levels also may be useful in monitoring compliance with treatment. Measurement of plasma benzodiazepine concentrations is clearly not necessary as a routine procedure but might be helpful in identifying rapid metabolizers. These patients may require above-average oral doses to achieve the expected plasma levels of about 10 ng/mL for each milligram of oral alprazolam per day. Detection of abnormally low levels can allow for dosage adjustment for these poorly responsive patients and can assure the physician that the patient is not abusing the benzodiazepine. Finally, benzodiazepine plasma concentration measurement may help identify medication noncompliance as a cause of treatment failure in the occasional patient who is afraid to take medication.

Anxiety that reappears between doses of medication during chronic treatment with short- to medium-half-life benzodiazepines such as alprazolam or lorazepam has been referred to as interdose rebound anxiety. This recurrent interdose anxiety has been raised as a clinical concern (Herman et al. 1987). As noted earlier in this chapter, clonazepam, with a long elimination half-life (20–50 hours), was clinically equivalent to alprazolam for treating panic disorder (Tesar et al. 1991). Little clinical difference was found between these agents in the short term, but many clinicians who prescribe long-term benzodiazepines prefer to use a longer-acting agent such as clonazepam because of the convenience of less frequent dosing and less frequent rebound anxiety. Agents with longer elimination half-lives also have been suggested to be more user friendly during benzodiazepine tapering. Interestingly, controlled studies (see subsection "Benzodiazepine Discontinuation" below) suggest that the rate of benzodiazepine tapering may be more important than the elimination half-life as a factor in successful discontinuation.

Combining Benzodiazepines With Other Agents

Two studies assessing combined benzodiazepine and antidepressant treatment have been published. The first examined the usefulness of combining a benzodiazepine (alprazolam) with another antipanic agent (imipramine) for the first several weeks of treatment, followed by a taper of the alprazolam (Woods et al. 1990). No particular advantage for this strategy was found. In contrast, Goddard et al. (2001) found that coadministration of clonazepam with sertraline resulted in faster onset of symptom reduction. Clearly, more research on this important question is warranted.

Maintenance Benzodiazepine Treatment

Despite objective evidence to the contrary, concerns related to long-term treatment with benzodiazepines include the development of tolerance, the potential of abuse, and, in particular, the inability to discontinue benzodiazepines when it is clinically indicated. Neither loss of efficacy nor abuse of benzodiazepines has been a significant clinical problem in the population of anxious patients (Uhlenhuth et al. 1988). Nagy and colleagues (1989) initially prescribed alprazolam for patients with panic disorder and followed them up over a range of 1.7 to 4 years. In these alprazolam recipients, the daily alprazolam dose had decreased or remained the same in 60%; 5% were taking a higher dose, and 30% were no longer taking alprazolam. Nagy et al. also reported that about 25% of the patients had experienced an episode of major depression during the follow-up observation period. This suggests that long-term benzodiazepine treatment for panic disorder provides effective anxiolysis, but the possibility of emergence of depressive symptoms in some benzodiazepine-treated patients may represent a relative disadvantage (Lydiard et al. 1987). The phenomenon of delayed emergence of depression also has been reported to occur in 9% of one group of fluvoxamine-treated panic disorder patients who had no history of depression, raising the possibility that emergence of depression may not be unique to the benzodiazepines (Fux et al. 1993). However, this phenomenon appears to occur more frequently in patients receiving only benzodiazepines.

Benzodiazepine Discontinuation

Discontinuation of benzodiazepine treatment has been an area of controversy and a challenge to clinicians treating anxious patients (Ballenger 1992). Many patients are unwilling to take a medication that they be-

lieve will be addicting, and they fear that they will never be able to stop the medication. Some clinicians believe that prescribing benzodiazepines may pose a risk for the development of substance abuse. It is the clinician's responsibility to clearly and fairly present the facts for the patient for whom prescription of a benzodiazepine is being contemplated. Patients should be informed about the proper timing of benzodiazepine tapering and assured that with proper supervision any patient can stop taking a benzodiazepine, even if an alternative treatment is required. Likewise, determination of the benefits of continued use also could be completed rationally via consultation with other clinicians and collateral information from a significant other or family member that the patient has not misused and has benefited from the treatment. This documentation is useful for the clinician who may feel vulnerable to medical authorities overseeing controlled substance prescription and also reassures patients who may be fearful of long-term use but who have received significant benefits from it.

The term *addiction* denotes a destructive pattern of continued and compulsive substance abuse in the face of known negative consequences. This term is sometimes inappropriately used by clinicians and patients to describe what is actually physiological *dependence*—the pharmacodynamic effects of long-term, appropriate medical use of benzodiazepines. The clinician should make the patient aware of the important distinction between addiction and dependence to avoid the pejorative connotations often associated with the term *dependence*. The American Psychiatric Association has endorsed the long-term use of benzodiazepines for some individuals with anxiety disorders, including panic disorder (Salzman 1993). In reality, the rate of benzodiazepine abuse in anxious patients is extremely low (Uhlenhuth et al. 1988). For many patients, continued treatment is required to maintain and extend treatment gains; however, periodic assessment of the continued requirement for medication is prudent. During mutually negotiated periodic attempts to lower and discontinue medication, it can be very difficult to determine whether anxiety symptoms that reappear represent a recurrence of the panic disorder or are related to the tapering. Controlled studies of benzodiazepine taper strategies have been informative. Rickels et al. (1990) conducted a study comparing abrupt versus gradual benzodiazepine tapering in a group of patients who were treated for at least 12 months with either a short- or a long-half-life benzodiazepine. The abruptly tapered patients experienced more bothersome symptoms than did those receiving the more gradual medication taper. Patients receiving chronic short-acting benzodiazepines had an earlier onset of and more severe withdrawal symptoms compared with patients receiving long-acting benzodiazepines. Importantly, the authors noted that with gradual reduction (not more than 25% per week), no substantial differences between the two groups were evident. They concluded that gradual reduction over a period of 2–4 months or more is more likely to be successful than abrupt discontinuation. In addition, they suggested that when the dosage reached is approximately half the original dosage, a reduction in the rate of taper is useful.

More recent research has suggested that adjunctive cognitive-behavioral treatment directed at control of symptoms during benzodiazepine discontinuation has been helpful for some patients (Otto et al. 1993; Spiegel et al. 1994).

Tricyclic Antidepressants

The majority of the information for the efficacy of TCAs in panic disorder is from studies using imipramine and clomipramine (Klein 1964; Lydiard and Ballenger 1987). In almost all of these studies, imipramine and clomipramine have been found to be superior to placebo (Jefferson 1997; Lydiard and Ballenger 1987); one study reported that clomipramine was more effective than imipramine (Modigh et al. 1992). Clomipramine is usually prescribed at dosages of 150–200 mg/day, but it has also been shown to be effective, for at least some patients, at very low doses (10–30 mg/day) (Gloger et al. 1989). The TCAs desipramine (Lydiard et al. 1993; a controlled study) and nortriptyline (Munjack et al. 1988; an uncontrolled study) also were found to be effective in treating panic disorder. However, the TCAs' lack of efficacy in social phobia (Emmanuel et al. 1997) limits their usefulness in 30%–50% of patients with panic disorder.

Unpleasant side effects (activation, anticholinergic and cardiovascular effects, weight gain) significantly limit their usefulness and acceptability in a substantial percentage of patients (Noyes and Perry 1990), especially since more therapeutic options have become available. Toxicity in overdose with TCAs remains an additional disadvantage.

Tricyclic Antidepressant Dosing and Plasma Levels

Imipramine was the mainstay of pharmacotherapy for panic disorder for many years. Some findings from research on the relationship between plasma levels and

clinical outcome may still be useful for the occasional patient who is fails to respond to other treatments. Mavissakalian and colleagues (Mavissakalian and Perel 1989, 1995) conducted a fixed-dose study comparing the effects of 0.5 mg, 1.5 mg, and 3 mg/kg/day imipramine. A significant reduction in panic attacks at the 1.5-mg/kg daily imipramine dose (corresponding to about 100 mg/day orally) was reported. Phobic avoidance effects were seen at the higher dose (3 mg/kg; about 200 mg/day). Predictably, many patients reported adverse effects. Jitteriness and/or activation during the initial phase of TCA treatment (Pohl et al. 1988) can be minimized by starting with a low dose (e.g., 10–25 mg imipramine or the equivalent) and gradually increasing it over time.

Maintenance Tricyclic Antidepressant Treatment Strategies

Mavissakalian and Perel (1992) examined whether a longer duration of maintenance treatment in recovered panic disorder patients would lead to a lower relapse rate. They found that patients who received imipramine for 18 months had a lower relapse rate after imipramine discontinuation than did those who received imipramine for only 6 months. Whether the strategy of longer maintenance will apply to other classes of antipanic agents awaits scientific assessment.

Monoamine Oxidase Inhibitors

The irreversible MAOIs phenelzine and tranylcypromine are as effective as the TCAs (Sheehan et al. 1980); there is some evidence that the MAOIs may even be superior to the TCAs (Lydiard and Ballenger 1987); MAOIs may be more effective than other treatments for patients with coexisting major depression and panic disorder, but this hypothesis has not been tested (Lydiard 1991). There are no data comparing SSRIs and traditional MAOIs. Unfortunately, MAOI-related side effects (weight gain, orthostatic hypotension, and difficulty sleeping) are a significant disadvantage. The need for dietary tyramine restriction and the risk of hypertensive crisis (via dietary indiscretion or by accidental ingestion) further limit the usefulness of these agents as panic disorder treatments. Selective reversible inhibitors of MAO type A (RIMAs) such as brofaromine and moclobemide, represented a potential advance for the MAOIs, but neither of these drugs will be available in the United States. Moclobemide is available in Europe, Canada, South America, and elsewhere. The RIMAs appeared to have a more favorable side-effect profile than the standard MAOIs, and tyramine restriction was unnecessary at clinically effective doses. Although both agents were studied as treatments of panic disorder, there is (to our knowledge) only one published report on the RIMA brofaromine (Garcia-Borreguero et al. 1992).

Other Antidepressants

Two newer antidepressants venlafaxine and nefazodone, each with neuronal uptake inhibition and receptor interaction profiles which are different than the SSRIs, have both shown some promise as treatments for panic disorder (DeMartinis et al. 1996; Uhde et al. 1988). Controlled efficacy studies for nefazodone are now under way. Trazodone, which has been approved for depression, has had mixed results in panic disorder treatment studies (Charney et al. 1986; Mavissakalian et al. 1987). Bupropion (Sheehan et al. 1983), maprotiline (den Boer and Westenberg 1988), and ritanserin (den Boer and Westenberg 1990) do not appear to be effective in the few reported controlled studies.

Antiepileptic Drugs

Valproic acid is a mood-stabilizing antiepileptic drug (AED) that has been reported to have efficacy in panic disorder (Lum et al. 1990; Woodman and Noyes 1994). It has anxiolytic properties that may be useful for selected patient groups, such as individuals with panic disorder coexisting with bipolar disorder and/or alcohol abuse. Gabapentin is another AED with potential anxiolytic and possibly mood-stabilizing effects. This agent is now being investigated as a treatment for panic disorder (and also for bipolar disorder). Carbamazepine is a mood-stabilizing AED that appears to be ineffective for panic disorder (Uhde et al. 1988).

Other Agents

Buspirone, a partial serotonin type 1A (5-HT_{1A}) receptor agonist, does not appear to have a role as a primary treatment for panic (Sheehan et al. 1993). β-Blockers (propranolol, others), which have been widely used as anxiolytics, do not appear to be useful as a first-line treatment of panic disorder but may be useful for controlling symptoms or side effects (tremulousness, tachycardia) (Brawman-Mintzer and Lydiard 1995).

Comparative Efficacy of Antipanic Agents

The overwhelming majority of treatment data (derived from studies of uncomplicated panic disorder) indicates that agents with demonstrated antipanic efficacy (TCAs, SSRIs, benzodiazepines) are generally equally effective in the short term (Bakish et al. 1996; den Boer and Westenberg 1988; Oehrberg et al. 1995) and that RIMAs (Tiller et al. 1999; van Vliet et al. 1996) are also comparable to these agents in efficacy. To our knowledge, there have been no head-to-head comparisons of SSRIs in the treatment of panic disorder.

Two agents that may be superior to the traditional TCA imipramine are clomipramine and phenelzine (Modigh 1992; Sheehan et al. 1980). However, for each of these agents, a major clinical issue is poor tolerability over the longer term. Furthermore, more recent evidence suggests that the SSRI paroxetine and clomipramine were shown to be roughly equivalent in acute treatment of panic disorder (Lecrubier and Judge 1997), and were both superior to placebo over the extension of that study (total observation period was 1 year). There were more dropouts the clomipramine-treated group than in the paroxetine group due to adverse effects. In the future, long-term studies should examine medication tolerability along with other quality-of-life issues in order to more accurately assess overall treatment "effectiveness."

Other Pharmacological Management Strategies

Using More Than One Medication

Clinical efficacy studies of medication treatments for panic disorder necessarily used patient samples with panic disorder unaccompanied by any other significant comorbid psychiatric disorder. As a result, the literature is unfortunately of limited value as a guide for treating patients with two or three coexisting psychiatric disorders, which is more the rule than the exception. Treatment of panic disorder quite regularly requires at least two agents combined with cognitive-behavioral treatment. A recent survey of European psychiatrists' practices indicated that nearly 70% routinely use both an antidepressant (TCA or SSRI) and a benzodiazepine (mostly clonazepam). Some form of behavioral treatment in addition to medication was used by 40% (Ballenger and Lydiard 1997). One case series of patients with panic disorder who were incompletely responsive to either a TCA or fluoxetine reported improvement with a combination of both (Tiffon et al. 1994). It should be stressed that combination treatments should be used very cautiously, with attention to possible TCA-SSRI interactions.

Long-Term Treatment Issues

Among the effective treatments, the response rates range from 50% to 70% (Pollack et al. 1990; Rosenbaum et al. 1996). Long-term observations (1.5–6 years after initial treatment) show that 50%–80% of patients have residual panic-related anxiety, 40% have panic attacks, and 20% remain unimproved and seriously ill (Katschnig et al. 1996). Factors that appear to contribute to persistent symptoms include coexisting depression, other anxiety disorders, concomitant personality disorders, severe agoraphobia at baseline, and frequent and severe panic attacks at baseline (Pollack et al. 1992). Surprisingly little information on treatment of panic disorder with persistent symptomatology has appeared in the literature.

Another important aspect of treatment is relative tolerability. Table 20–3 shows the usual dosage ranges, advantages, and disadvantages of the various antipanic medication treatments. Sexual dysfunction (anorgasmia, reduced libido, and erectile dysfunction) in patients receiving SSRIs is common and may go undetected unless the clinician inquires about it. Unwanted sexual side effects begin after several weeks of treatment. Most antidepressant compounds and the benzodiazepines can cause significant sexual dysfunction. One exception appears to be nefazodone, which may cause fewer sexual side effects than other agents. Sexual side effects cause significant distress, reduce quality of life, and ultimately may lead to noncompliance. Management strategies include patient education regarding the reversibility of these effects, reduction of the dose, and/or addition of a second agent to reduce or reverse sexual side effects (Woodrum and Brown 1998). Finally, switching to another agent may be necessary. Medications with presumably different mechanisms of action that may be of help include bethanechol (10–20 mg before intercourse or 30–100 mg/day), cyproheptadine (4–12 mg/day), and yohimbine (5.4–16.2 mg prior to sexual activity or 5.4 mg three times daily) or sildenafil (50–100 ng/day). Yohimbine must be prescribed with caution in patients with panic disorder because of its

TABLE 20–3. Summary of antipanic agents

Medication class	Advantages	Disadvantages
Selective serotonin reuptake inhibitors (SSRIs)	Antidepressant Favorable side-effect profile Low toxicity	Activation No generics May precipitate mania Sexual side effects Gastrointestinal
Benzodiazepines	Rapid onset Favorable side-effect profile Some generics Plasma levels may be useful (alprazolam)	Physical dependence/withdrawal Emergence of depression? Sexual side effects Interfere with exposure?
Tricyclic antidepressants (TCAs)	Antidepressant Known efficacy Some generics Plasma levels may be useful (e.g., imipramine, desipramine) Single daily dosing	Activation Anticholinergic effects Cardiovascular effects Delayed onset Sexual side effects Weight gain May precipitate mania
Monoamine oxidase inhibitors (MAOIs)	Antidepressant Known efficacy Better antiphobic effects?	Dietary restrictions Hyposomnia Weight gain Orthostatic hypotension Sexual side effects May precipitate mania Multiple daily dosing
Other antidepressants Venlafaxine Nefazodone	Antidepressant Favorable side-effect profile Low toxicity Few sexual side effects Less activation? (nefazodone)	Activation No generics May precipitate mania Sexual side effects Gastrointestinal Twice-daily dosing needed Limited information

potential anxiogenic effects. More popular current strategies include adding bupropion (100–200 mg/day) or buspirone (30–60 mg/day) in divided doses. Switching to an agent such as nefazodone, which causes fewer sexual side effects, may be useful in some patients, but the information about treatment of panic disorder with this agent is minimal at present. Finally, a 1- or 2-day drug holiday has been shown to improve sexual functioning in patients receiving SSRIs such as sertraline and paroxetine for depression (Rothschild 1995). Caution is warranted with this latter strategy because abrupt discontinuation of these shorter-acting SSRIs may precipitate uncomfortable withdrawal effects.

Coexisting Psychiatric Conditions (Comorbidity)

Comorbidity of panic disorder with other psychiatric disorders is common (Kessler et al. 1994) and can have important implications for both acute and long-term outcome in panic disorder. This has been thoroughly reviewed elsewhere (Lydiard and Brawman-Mintzer 1997). If coexisting psychiatric disorders occur in patients with panic disorder, an effective treatment or combination of treatments that addresses all disorders present must be chosen. Undetected comorbid Axis I disorders can contribute to treatment failure if the chosen treatment does not have a broad spectrum of therapeutic activity. Unfortunately, no data are available to guide treatment of comorbid panic disorder and other psychiatric disorders in this large group of patients, in part because agents are individually developed to treat specific disorders. Thus, the ideal strategies for treating panic disorder coexisting with other psychiatric disorders are currently speculative. Recent reviews provide more detail about this clinical problem (Lydiard 1991; Lydiard and Brawman-Mintzer 1997; Rosenbaum 1997). The main strategy for pharmacological treatment is to choose an agent with effectiveness for panic

disorder and the additional condition(s). The SSRIs have proven very useful in this regard, because most conditions that occur in conjunction with panic disorder (e.g., social phobia and major depression) appear to be responsive to these agents. Table 20–2 displays the general range of efficacy for agents used to treat panic disorder for the two disorders most likely to coexist with panic disorder: social phobia and major depression.

Panic Disorder Treatment Considerations in Pregnancy and Lactation

A significant percentage of the individuals who have panic disorder are women of childbearing potential who will face, along with the clinician, the dilemma of whether to continue pharmacological treatment of panic disorder in unplanned or planned pregnancy. Data on the course of panic disorder during pregnancy are inconclusive. There appears to be greater consensus that panic disorder is more likely to worsen in the postpartum period; little empirical evidence has been gathered to support or refute this clinical impression. In our clinical experience, many women experience relative improvement in panic disorder during pregnancy; empirical studies indicate that worsening or no change also is commonly reported. The course of panic disorder over multiple pregnancies in the same individual also may vary from improvement to worsening or no change (Altshuler et al. 1998; Northcott and Stein 1994; Villeponteaux et al. 1992). Antidepressants prescribed when they were thought to be clinically indicated have not been shown to cause serious adverse effects on either the course or the outcome of the pregnancies in women with panic disorder or depression (Cohen et al. 1996). In fact, Schou (1998) concluded in a recent review that both the gestational and the postpartum risks were less than the risk of withholding treatment for depression. Women who are breast-feeding are advised to take the most highly protein-bound antidepressants (paroxetine, fluoxetine, and sertraline) (Baum and Misri 1990); fluvoxamine and venlafaxine are less tightly protein bound.

Although no known serious long-term effects on the postnatal development and behavior of the children exposed in utero or during breast-feeding are directly attributable to psychotropic (antidepressant) use (Wisner et al. 1999), the potential subtle behavioral effects of these agents have only recently received attention from researchers (L.S. Cohen, personal communication, December 1999). At present, these potential risks must be weighed against the potential effects of untreated panic disorder or related disorders on the period of bonding after birth and the ability of the new mother to tolerate the predictable stress of caring for a newborn.

In summary, recommendations for pharmacotherapy for panic disorder during pregnancy are as follows:

- If feasible, all medications should be avoided during the first trimester of planned pregnancies and discontinued, if possible, in unplanned pregnancies.
- Cognitive-behavioral treatment is a good alternative for women planning to become pregnant and for pregnant women who must discontinue medication.
- Daily benzodiazepines may cause physiological dependence and withdrawal in the newborn, so they should be avoided if alternative treatments are available.
- As-needed use of a benzodiazepine after the first trimester is unlikely to cause significant problems but should be avoided if possible.
- Antipanic agents in the SSRI and TCA class appear to be safe and effective.
- Treatment with antidepressants may be reinstituted during the last trimester in women with a history of postpartum depression.

However, the decision to treat, not to treat, or when to treat must be made between the parents and the clinician. The clinician should supply the parents with as much information as possible to facilitate the decision-making process, and the physician managing the pregnancy should be brought in to the decision-making process early. Finally, acknowledging that the balance of risks and benefits may be different from one patient to another and at different times in the same individual requires flexibility and frequent communication of all involved in this difficult decision-making process.

Herbal Medicine Use in Patients With Panic Disorder

Although courses in herbal medicine are now available only as electives in most medical schools, nearly one in four people in the United States has used an herbal medicine on one or more occasions (Wetzel et al. 1998). Individuals with anxiety disorders were among those most likely to seek alternative treatments according to a community survey (N = 16,068). These individuals used alternative health care in addition to rather

than instead of traditional health care. We recently reported that 33% of the subjects who volunteered for clinical studies in anxiety disorders acknowledged using an herbal product in the past year; 56% had used an herbal product in the past 6 months (Emmanuel et al., in press).

Many claims for the therapeutic benefits of herbal products for a variety of conditions are made, and some clinical reports support their usefulness (Yager et al. 1999). Unfortunately, no scientific data have confirmed the effectiveness of herbal products for anxiety disorders. Moreover, other unexpected adverse effects from adding herbal preparations to ongoing pharmacotherapy have been reported (Yager et al. 1999).

It seems prudent for clinicians treating panic disorder to become acquainted with the basic uses of herbal products for emotional symptoms. If the clinician can offer information and asks to be included in decisions about using herbal products during ongoing pharmacotherapy for panic disorder, the likelihood of staying informed will increase. Conversely, claiming ignorance or not asking about herbal use appears to increase the likelihood of not being included in such decisions as the patient makes them.

Conclusion

Medication treatment is clearly a major therapeutic tool for panic disorder. The available psychopharmacological tools that have accrued over the past 30 years represent real progress, but none are effective or tolerable for every patient. More research to extend our knowledge of optimizing current treatments and to develop novel effective treatments is still needed. Interaction with primary care physicians in the use of the effective antipanic agents would be a great benefit to the many patients with panic disorder who never see a psychiatrist. Other areas that require more attention include the comparison of cognitive-behavioral therapy with medication treatments (Shear and Maser 1994) and also other psychotherapeutic and pharmacological strategies alone and in combination.

Finally, an issue of paramount importance is the establishment of the long-term effectiveness of various panic disorder treatments, which must take into account quality of life, productivity, and resource use. As was noted earlier in this chapter, the treatment approach to coexisting psychiatric disorders is currently guided predominantly by clinical intuition. Further research efforts will provide safer, more effective treatments for the millions of individuals with panic disorder.

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21

Psychotherapy for Panic Disorder

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In recent years, there has been a proliferation of treatments for panic disorder and agoraphobia, including new pharmacological, physiological, cognitive, behavioral, psychodynamic, and interpersonal therapies. Indeed, there may be more treatments for panic disorder with some proven efficacy than for any other psychiatric condition. Panic disorder treatments generally are regarded as successful, based on completer analyses of acute treatment trials. However, data from intention-to-treat samples and longitudinal studies present a somewhat more sobering picture, showing that many patients either drop out of treatment or continue to have symptomatic courses despite treatment. For that reason, it has become popular in clinical practice to use a combination of treatment modalities for panic disorder, in the hope that the combination might have greater or broader effects than those attainable with single treatments. In this chapter, we review several types of psychosocial treatment for which there is empirical evidence of efficacy in panic disorder, agoraphobia, or panic disorder with agoraphobia. In addition, we present some data from clinical trials of combinations of psychosocial treatment interventions with each other and with pharmacotherapy. Pharmacological treatments are discussed in Lydiard and Ballenger, Chapter 20, in this volume.

Exposure Therapies

Before panic disorder was identified as a distinct type of anxiety in DSM-III (American Psychiatric Association 1980), psychosocial therapies tended to focus primarily on the behavioral pattern of situational avoidance that frequently occurs in patients with panic attacks. During the 1960s and 1970s, systematic desensitization consisting of imaginal exposure to feared situations paired with muscle relaxation was the principal form of treatment. That approach was used in preference to in vivo exposure because it was thought that the latter might engender too much anxiety for patients to manage.

However, studies evaluating systematic desensitization for agoraphobia found that it was largely ineffective (Gelder and Marks 1966; Marks 1971), and it was gradually replaced by in vivo exposure. As currently administered, exposure therapy for agoraphobia typically begins with the construction of a hierarchy of feared situations that the patient is encouraged to enter repeatedly, starting with easier ones and continuing until anxiety diminishes. Sometimes the therapist or a companion accompanies the patient initially, but ultimately the patient is expected to do the task alone. Reviews and meta-analyses of treatment studies in which in vivo situational exposure was used found that 60%–75% of the treatment completers experienced clinical improvement (Barlow 1988; Jacobson et al. 1988; Jansson and Öst 1982; Munby and Johnson 1980; Trull et al. 1988), and follow-up studies have found maintenance of gains in most cases (Burns et al. 1986; Fava et al. 1995; Jansson et al. 1986; Munby and Johnson 1980). Unfortunately, many patients refuse or drop out of treatment. Although studies vary, a reasonable estimate is that ap-

proximately one in four patients who initiates treatment drops out (Clum 1989; Fava et al. 1995; Marks 1978).

One of the most positive, although uncontrolled, studies of exposure therapy was that by Fava et al. (1995) on a cohort of 110 patients with a primary diagnosis of panic disorder with agoraphobia who received 12 biweekly 30-minute sessions of in vivo exposure therapy emphasizing self-directed practice. In that study, 81 subjects achieved remission, defined as being panic-free for the past month and "much better" on a global rating of improvement. Survival analyses estimated the likelihood of staying in remission at 2, 5, and 7 years posttreatment to be 96%, 77%, and 67%, respectively. For the intention-to-treat sample of 110 patients who entered therapy, those numbers translate into projected remission rates of 71% at 2 years, 57% at 5 years, and 49% at 7 years. Of note, in the Fava et al. study, the intention-to-treat sample was a consecutive series of patients meeting DSM-III-R (American Psychiatric Association 1987) criteria for panic disorder with agoraphobia, which included all levels of agoraphobic avoidance. Many patients, although improved sufficiently to be classified as responders at the posttreatment assessment, continued to have some degree of agoraphobic fear and avoidance which, when present, is a poor prognosis sign. Among the 81 patients who responded to treatment, two-thirds of those who had residual agoraphobia posttreatment relapsed within 5 years. Also of note, benzodiazepine use was permitted during the study, and a sizable proportion of the patients (one-fourth at the conclusion of treatment) were taking benzodiazepines.

Massed Exposure

Whether an optimal intensity for exposure therapy exists is not clear. A few studies have compared massed with spaced exposure sessions. In general, massed exposure has not been better than more gradual procedures (Chambless 1990), and some investigators (e.g., Hafner and Marks 1976; Jansson and Öst 1982) have found higher treatment dropout rates with massed exposure. However, investigators at the Christoph Dornier Foundation (Braunschweig, Germany) reported excellent results with a highly intensive protocol (Ehlers et al. 1995; Fiegenbaum 1988; Schroeder et al. 1996). In that treatment, agoraphobic patients underwent 8–10 days of intensive, therapist-accompanied, ungraded exposure in which tasks were selected based on convenience of grouping rather than their positions on a fear hierarchy. The program began with a 2- to 4-hour session in which the treatment rationale was explained, after which patients were given a week to decide whether they were prepared to commit to treatment. In a preliminary study, Fiegenbaum (1988) compared that approach with graded, massed exposure in which patients gradually worked up a hierarchy of feared situations. The two treatments were equally effective at posttreatment and at 8-month follow-up, but ungraded exposure was superior to graded exposure at 5-year follow-up. Subsequently, Ehlers et al. (1995) reported on a sample of 150 patients treated with ungraded exposure. Attrition was surprisingly low: 7% dropped out after the treatment rationale had been explained, and only 2% dropped out during treatment. Among those who completed the treatment, 85% described themselves as much or very much improved at posttreatment, and 77% did so at 1-year follow-up. The average therapist time per patient was 28 hours.

As impressive as those results are, they do not necessarily indicate a superiority of Fiegenbaum's approach over other, more gradual forms of exposure therapy. Among the intention-to-treat subjects, the response rate for Fiegenbaum's treatment in the Ehlers et al. (1995) trial was approximately 77% at posttreatment and 70% at 1-year follow-up, comparable to the 2-year remission rate of 71% reported by Fava et al. (1995). Like the latter study, the Ehlers et al. trial enrolled patients with all levels of agoraphobic avoidance. We do not know how many subjects had residual agoraphobia posttreatment and whether, as in the Fava et al. study, residual agoraphobia was associated with a poorer long-term outcome. Furthermore, more recent data suggest that the dropout rate reported by Ehlers et al. may have been lower than that which usually occurs with Fiegenbaum's approach. A review of 253 patients at the Christoph Dornier Foundation, of whom 222 had agoraphobia treated with ungraded, massed exposure, found an overall dropout rate of 27% (8% after pretreatment assessment, 15% after explanation of the treatment, and 4% during exposure; Schroeder et al. 1996). In reviewing the existing literature on the efficacy of exposure therapy, Michelson et al. (1996) concluded:

> Contemporary findings, culled from diverse studies, indicate that exposure appears to be a beneficial yet insufficient treatment for PDA [panic disorder with agoraphobia]. Reviews… converge in their critiques that a significant proportion (50%–65%) of PDA clients treated with exposure therapy are left with moderate-severe residual PDA and panic attacks. (p. 299)

Cognitive and Cognitive-Behavioral Treatments

During the 1980s, in parallel with the increasing recognition of the importance of fear of panic attacks as a factor in the development and progression of panic disorder, investigators began to experiment with treatments aimed more specifically at patients' experiences of anxiety related to panic and somatic sensations rather than at avoidance behavior. These treatments are called either cognitive therapies or cognitive-behavioral therapies, depending on the theoretical orientation of the clinician or the emphasis placed on the treatment components, although in practice there is considerable overlap between them.

Panic Control Treatment

The most well studied of the cognitive-behavioral therapies is a form known as panic control treatment (PCT; Barlow and Craske 1994). PCT consists of the following components: education about the nature of anxiety and panic, identification and correction of maladaptive thoughts about anxiety and its consequences, training in arousal reduction techniques such as slow breathing, and graded exposure to bodily sensations that resemble those experienced during anxiety and panic (interoceptive exposure). Treatment usually is delivered in 11 or 12 sessions over a period of 3–4 months.

The efficacy of PCT has been reported in numerous studies. In one (Barlow et al. 1989), an early form of PCT (consisting of cognitive restructuring and interoceptive exposure) was compared with applied relaxation therapy (Öst 1987; discussed later in this chapter in "Relaxation Treatments"), a combination of PCT and applied relaxation therapy, and a wait-list control. All three active treatments were superior to the wait-list control on a variety of measures at posttreatment. Approximately 86% of the patients in the PCT alone and PCT plus applied relaxation therapy groups and 60% in the applied relaxation therapy alone group were panic-free by the end of treatment. At follow-up 2 years later, 81% of the patients in the PCT group were panic-free compared with only 43% and 36% in the other two groups, respectively (Craske et al. 1991).

In a later study, Klosko et al. (1990, 1995) compared PCT with alprazolam, a drug placebo, and a wait-list control. Again, 87% of the patients in the PCT group were panic-free by the end of treatment, compared with 50% in the alprazolam group, 36% in the placebo group, and 33% on the wait list. PCT was superior to all three other conditions. Subsequently, Telch and colleagues (1993) found that PCT was effective when administered in an 8-week group format. At posttreatment, 85% of the PCT patients were panic-free, compared with 30% in a wait-list control condition. When a more stringent outcome measure was used (including measures of panic frequency, general anxiety, and agoraphobic avoidance), 63% of the PCT patients and only 9% of the wait-list subjects were classified as improved.

Most recently, PCT was compared with imipramine, a pill placebo, and combinations of PCT with imipramine or a pill placebo in a large, multicenter trial (Barlow et al. 2000). PCT alone was comparable to imipramine alone on nearly all measures during acute and continuation treatment, with better maintenance of gains after treatment discontinuation. We discuss this study further later in this chapter (see section "Combinations of Psychosocial Treatments With Pharmacotherapy").

Cognitive Therapy

Similar good results have been reported with treatments that focus more exclusively on cognitive restructuring (e.g., Beck et al. 1992; Clark 1989). These therapies involve approximately the same amount of therapist time as PCT does and appear to be comparably efficacious, although they have not been compared directly with PCT. For example, Clark et al. (1994) compared cognitive therapy, applied relaxation therapy, imipramine, and a wait-list control. At posttreatment, 75% of the cognitive therapy patients were panic-free, compared with 70% in the imipramine condition, 40% in the applied relaxation therapy condition, and 7% in the wait-list condition. Cognitive therapy was superior to the wait-list control on all panic and anxiety measures, whereas imipramine and applied relaxation therapy were better than the wait-list control on approximately half of the measures. At 9-month follow-up, after imipramine had been discontinued, the panic-free rates were 85% for cognitive therapy, 60% for imipramine, and 47% for applied relaxation therapy.

Active Ingredients

It is not known at present which components of cognitive-behavioral therapy (CBT) are most important for treatment efficacy or, indeed, whether they all contribute uniquely to efficacy. Good results have been reported for treatments that differ considerably in their emphasis on specific CBT interventions (Clark et al.

1985, 1994; Margraf et al. 1993). Unfortunately, except for the use of a relaxation control condition in some studies, direct comparisons of the various interventions are lacking. Some indirect comparative data are available from a meta-analysis by Gould and colleagues (1995). In that analysis, among studies involving psychosocial treatments for panic disorder, therapies incorporating both cognitive restructuring and interoceptive exposure had the highest overall mean effect size (0.88, $N=7$ studies). Only three studies involved cognitive therapy alone as treatment, and the results were markedly varied (effect size range=−0.95 to +1.10). The authors concluded that "the effectiveness of cognitive therapy alone appears to be highly variable and may depend on the specific interventions used" (Gould et al. 1995, p. 832).

Abbreviated, Computer-Assisted, and Self-Directed Cognitive-Behavioral Therapy

A few studies have investigated the efficacy of abbreviated or self-directed forms of CBT for panic disorder. In one such study, Côté et al. (1994) found that 10 hours of in-person and telephone therapy were as effective as 20 hours of standard face-to-face CBT administered over the same period. More recently, Craske et al. (1995) found that a four-session CBT protocol was more effective than an equivalent amount of nondirective supportive therapy. The short treatment was not compared with alternative effective therapy.

In a recent study, Clark et al. (1999) compared 12 sessions of standard cognitive therapy to a 5-session version of the same treatment combined with self-study modules, and a wait list control ($N = 14$ per condition). The two active treatments, which were administered over a 3-month period, were superior to the wait list on all measures and did not differ significantly from each other. As in previous CBT studies, the great majority (78%) of the patients in the Clark et al. study had no more than mild agoraphobia, however 22% had moderate agoraphobia. The paper does not say whether the degree of agoraphobia predicted outcome. However the authors do mention an investigation reported by Clark, Wells, and Gelder at the 1997 annual meeting of the British Association of Behavioural and Cognitive Psychotherapies, in which a group of PDA patients with severe agoraphobic avoidance was treated with 4 sessions of cognitive therapy administered over a 10-day period. The 4-session treatment "produced substantial reductions in panic, general anxiety, and avoidance and was more effective than an equivalent number of sessions of traditional exposure therapy" (Clark et al. 1999, p. 588).

Promising results also have been reported with self-help treatments involving minimal (e.g., 3 hours) therapist contact (Gould and Clum 1995; Gould et al. 1993; Hecker et al. 1996; Lidren et al. 1994). In most of these trials, the self-directed treatments were not compared with clinician-administered therapies. An exception is the Hecker et al. (1996) study, which compared a 12-week self-help program that used the PCT patient workbook *Mastery of Your Anxiety and Panic* (Barlow and Craske 1989) with 12 weekly sessions of therapist-conducted PCT that covered the same material (eight subjects per condition). Patients in the self-help condition met with a therapist three times during the 12-week period to assign readings and answer questions. Although three patients in the self-help group (38%) dropped out, those who completed treatment in both conditions improved significantly and maintained their gains at 6-month follow-up, with no differences between groups.

The data are somewhat more mixed regarding self-help treatments for moderate to severe agoraphobia. In a small early study, Holden and colleagues (1983) found that a self-help manual incorporating cognitive restructuring and graded in vivo exposure was ineffective for patients with severe agoraphobia. However, subjects in that study were described as experiencing "motivational difficulties" (p. 545) in that they did not comply with the in vivo practice instructions. In contrast, Ghosh and Marks (1987) found that exposure therapy administered by either a self-help book or a computer program based on the book was as effective for agoraphobia as therapist-administered treatment. Since the Gosh and Marks (1987) report, there has been increasing interest in the use of computer technologies, including interactive voice response and virtual reality systems, in the treatment of mental health problems (for an excellent review, see Marks et al. 1998). These technologies offer the promises of greater consistency, cost-effectiveness, convenience, and accessibility of treatment.

An example of an application to panic disorder is a self-help computer program developed by Shaw and Marks (1996). In two small pilot tests, 6 of 15 patients with chronic agoraphobia/claustrophobia and panic who received up to 12 sessions of computer self-help at the Institute of Psychiatry in London, and 3 of 4 patients similarly treated in a rural general practice in Wales, improved moderately or markedly on clinical impressions scores (Shaw et al. 1999). The authors suggested that outcomes could be improved by giving pa-

tients access to brief human help if they have problems with computer treatment. In another application, Newman and colleagues (1996, 1997) used a hand-held computer to ask patients about panic and anxiety symptoms and provide coping and exposure instructions. In a small trial (N=18), the computer plus 4 sessions of CBT did as well as 11 sessions of CBT alone. Clearly, this is an area in which much growth will occur in the future.

Relaxation Treatments

Relaxation therapies, such as progressive muscle relaxation (PMR), in which patients learn to discriminate tense from relaxed muscles and systematically relax specific muscle groups, have long been used in the treatment of generalized anxiety and tension. However, as traditionally administered, these therapies generally have been regarded as weak treatments for panic disorder and agoraphobia. PMR, for example, often has been chosen as a nonspecific or placebo psychological control in clinical trials of panic disorder treatments (Marks et al. 1993). Furthermore, relaxation procedures have been reported to precipitate panic attacks in some individuals with panic disorder (e.g., Barlow 1988). Nevertheless, some evidence indicates that certain modifications of relaxation techniques may be beneficial for panic disorder (e.g., Barlow et al. 1989; Beck et al. 1994; Öst 1988).

Of particular note is a treatment developed by Öst (1987) known as applied relaxation therapy. Applied relaxation therapy begins with training in traditional PMR, after which patients are taught to relax rapidly and selectively during normal activities whenever they experience early signs of panic. Öst (1988) found that applied relaxation therapy was superior to standard PMR in a group of panic disorder patients without significant agoraphobia. All patients in the applied relaxation group were panic-free at both posttreatment and follow-up, compared with 71% at posttreatment and 57% at follow-up in the PMR group. Subsequently, Öst et al. (1993) found that applied relaxation therapy was as effective as standard in vivo exposure therapy or cognitive therapy in patients with panic disorder with agoraphobia, although the investigators suggested that the lack of differences among the treatments may have been the result of self-directed exposure by patients in the applied relaxation and cognitive therapy groups.

Other studies have found more mixed results with applied relaxation therapy. An example is the Barlow et al. (1989) study mentioned earlier in this chapter, comparing an early version of PCT with applied relaxation therapy, a combination of those two treatments, and a wait-list control condition. In that study, all three active treatments were superior to the wait-list condition on a variety of measures at posttreatment. Applied relaxation therapy tended to have a greater effect than PCT on generalized anxiety related to panic attacks, but a smaller proportion of the participants in the applied relaxation condition were panic-free at posttreatment (60% vs. 85% and 87% in the other two treatments), and attrition was higher in the applied relaxation group (33% vs. 6% in the CBT group and 17% in the combined treatment group). The 2-year follow-up of participants in the Barlow et al. (1989) trial found that those who had received applied relaxation therapy, either alone or in combination with PCT, were doing less well than those who had received PCT alone (Craske et al. 1991). Whereas 81% of the patients in the latter group were panic-free at follow-up, only 43% and 36%, respectively, of those in the combined treatment and applied relaxation only groups were. The implications are unclear. On the surface, it appears that the addition of applied relaxation therapy to PCT had a detrimental effect on the long-term outcome of PCT. However, it seems more likely that it simply took time away from PCT, with the result that subjects in the combined treatment condition received less instruction and practice in PCT skills than those in the PCT alone condition.

Finally, the Clark et al. (1994) study compared cognitive therapy, applied relaxation therapy, and imipramine in sample of patients with panic disorder with up to moderate agoraphobic avoidance. All three treatments were more effective than a wait-list control at posttreatment, but cognitive therapy was superior to applied relaxation therapy and imipramine on most measures at 3-month follow-up, and both cognitive therapy and imipramine were superior to applied relaxation therapy at 6-month follow-up.

Breathing Retraining

Relaxation techniques for the treatment of panic disorder often include instruction in slow, diaphragmatic breathing. It has been suggested that panic attacks are closely related to hyperventilation in some panic patients (e.g., Ley 1993). In fact, some uncontrolled studies have found that respiratory control strategies along with education about hyperventilatory sensations led to a significant reduction in panic attack frequency (Bonn et al. 1984; Clark et al. 1985; Salkovskis et al. 1986). How-

ever, other studies found that supplementing in vivo exposure with respiratory control strategies or CBT did not improve overall treatment effectiveness (deRuiter et al. 1989; Rijken et al. 1992). Breathing retraining is rarely used as a single treatment modality for panic disorder.

Psychodynamic Psychotherapies

Although little empirical research has shown the efficacy of psychodynamic therapies for panic disorder (Côté and Barlow 1993), such interventions frequently are used for panic disorder (Goisman et al. 1994). Like cognitive theories of panic disorder, psychodynamic theories hypothesize that anxiety is generated when danger situations are activated. However, unlike cognitive theories, most dynamic theories propose that these danger situations are unconscious and include the threatened emergence of prohibited instinctual urges or the impending disruption of self or object representations (Shear 1991). Accordingly, psychodynamic treatments for panic disorder typically focus on the elucidation of unconscious sources of anxiety and associated, characterologically based maladaptive behaviors. The presumed curative components of treatment typically involve the establishment of a transference relationship and the demonstration and acknowledgment of troublesome or angry feelings held by the patient that are associated with panic attacks (Milrod and Shear 1991b). Through recognition and expression of those feelings, and of intense affects in general, patients can relieve anxiety that would otherwise emerge as panic.

Preliminary studies and case reports indicate that psychodynamic psychotherapies can be efficacious for the treatment of panic disorder (Fewtrell 1984; Malan 1976; Milrod 1995; Milrod and Shear 1991a; Milrod et al. 2000; Sifneos 1972; Silber 1984; see also Milrod et al., Chapter 7, in this volume), and one study investigated the effect of adding psychodynamic psychotherapy to a pharmacological intervention (Wilborg and Dahl 1996). In the latter study, patients received either 9 months of clomipramine therapy (up to 150 mg/day) or the same medication treatment plus 15 weekly sessions of psychodynamic therapy. The psychotherapy included all the main components of dynamic psychotherapy, including clarification, confrontation, and interpretation of resistance, defensive styles, and associated isolated affects. At posttreatment, all patients who had received the combined therapy were panic-free, compared with 75% of those who had received only the medication. More important, at follow-up, 18 patients who had received clomipramine alone had relapsed, compared with only 20% of those who had received the combined treatment. Moreover, patients from the combined condition showed greater global improvement on outcome measures than did patients who received clomipramine alone. Although these results are promising, their interpretation is limited by the lack of a psychotherapy control condition in the study.

Emotion-Focused Psychotherapy

A treatment related to psychodynamic psychotherapy for panic disorder is emotion-focused therapy (EFT), which was developed by Shear and colleagues (Shear and Weiner 1997; Shear et al. 1995). EFT specifically targets emotion regulation as it relates to interpersonal control and to fears of being abandoned or trapped. EFT differs from traditional psychodynamic therapy in that it does not emphasize the interpretation of unconscious material or focus on linking early experiences with present symptoms. Instead, the treatment strategies used during EFT target fear and avoidance of negative affect and their triggers. Several case reports and studies comparing nondirective and empathetic supportive therapy with CBT have offered some early support for this approach (Borkovec and Mathews 1988; Klein et al. 1983; Shear et al. 1994; Sifneos 1972). However, in a recent randomized comparison, EFT was not better than—and a pill placebo and was less effective than—both CBT and imipramine (Shear 2000).

Limitations of Existing Studies

Several limitations of existing studies of panic disorder treatments warrant caution in interpreting and comparing published efficacy data. First, studies of exposure therapy typically have involved more highly agoraphobic patient samples than have studies of cognitive therapy or CBT. When the latter therapies initially were developed, panic disorder was defined by the presence of a certain number of panic attacks within a specified period of time (DSM-III, DSM-III-R). The psychosocial treatments prevailing at the time (e.g., relaxation therapies and situational exposure) tended to focus on general arousal or behavioral avoidance. As noted earlier, CBT differed in that it focused directly on patients' experiences of panic attacks and associated anxiety.

Accordingly, clinical trials of CBT were conducted with patients for whom panic attacks were the primary problem, that is, patients with little or no agoraphobic avoidance. In contrast, exposure therapy trials enrolled subjects with moderate or severe avoidance. Furthermore, until recently, the measures used to assess treatment efficacy with the two approaches also have differed. CBT (and pharmacotherapy) studies typically have used response criteria based on panic attack frequency (e.g., panic-free status), whereas exposure therapy trials have emphasized measures of agoraphobic avoidance. Panic frequency and agoraphobic avoidance have been found to vary relatively independently of each other (Basoglu et al. 1994; Craske and Barlow 1988). In general, the question of how to best assess treatment efficacy for panic disorder is far from settled. It is clear that traditional measures of panic attacks are insufficient; generally, these bear little relation to other dimensions of the disorder, even in samples with little or no agoraphobia (Spiegel 1998). Because of that, some studies have used global or composite measures (e.g., high end-state functioning) to evaluate treatment response (Barlow et al. 1989; Brown and Barlow 1995; Bruce et al. 1999; Clark et al. 1994; Mavissakalian and Perel 1992). However, those measures have been idiosyncratically defined and have varied from study to study. In response to this problem, in 1992, the National Institute of Mental Health convened an expert panel to recommend standardized measures for panic disorder research (Shear and Maser 1994). The panel recommended assessment of a range of symptom and performance measures but stopped short of proposing a measure of overall treatment efficacy. Finally, long-term efficacy data in nearly all studies (psychosocial and pharmacological) have been based on cross-sectional assessments of improvement. As Brown and Barlow (1995) pointed out, such assessments fail to consider the course of symptoms over time. In the few instances when individual panic disorder patients have been followed up longitudinally after treatment, many have shown fluctuating courses, with periods of symptom recrudescence. For example, Brown and Barlow (1995) followed up 63 patients treated with variations of CBT and found that although 40% met criteria for high end-state functioning at 3 months posttreatment and 57% at 24 months posttreatment, only 27% met the criteria at both 3 and 24 months. Fluctuating courses also have been observed in patients treated with exposure therapy (Burns et al. 1986). Moreover, very little is known about effective maintenance treatment strategies for panic disorder and agoraphobia (Öst 1989).

Combined Treatments

Given the variety of available treatments for panic disorder and the multidimensional nature of the disorder, it is logical that clinicians would seek to improve treatment outcome by combining different therapeutic modalities. Two common approaches have involved the coadministration of psychosocial treatments and pharmacotherapy and the combination of various elements of CBT with situational exposure therapy for agoraphobia.

Combined Psychosocial Treatments and Pharmacotherapy

In 1994, Wolfe and Maser observed that the modal clinical treatment for panic disorder was a combination of psychosocial therapy and medication, "although the psychosocial treatment most often co-administered with medication is not the empirically tested cognitive-behavior therapies" (p. 12). The high prevalence of combined treatment approaches reflects a prevailing belief by both physicians and patients that those regimens are superior to drugs or psychotherapy alone. Rapaport et al. (1996) and Waikar et al. (1994/1995) found that approximately three-fourths of patients seeking specialist treatment for anxiety disorders held that view. Similarly, a recent survey of world experts on the pharmacological treatment of anxiety found that most favored combined treatment for panic disorder (Uhlenhuth 1998). In contrast to those opinions, clinical studies of combined treatments have not consistently found significant advantages over single treatments. Considering the added cost and risks of combination therapies, it would seem important to show a benefit.

One of the earliest rationales for combining psychosocial treatments and pharmacotherapy for panic disorder was Klein's (1980) suggestion that drugs might work preferentially to suppress panic attacks, while exposure therapy more specifically addressed agoraphobic avoidance. In accordance with that suggestion, several studies have been conducted comparing the effects of combined drug and exposure treatments with those of one or both treatments alone (for reviews, see Mavissakalian 1993; Telch and Lucas 1994). Most of those studies involved tricyclic antidepressants (de Beurs et al. 1995; Marks et al. 1983; Mavissakalian and Michelson 1986a, 1986b; Mavissakalian and Perel 1985; Mavissakalian et al. 1983; Telch et al. 1985; Zitrin et al. 1980, 1983), but combined treatment studies also have been done with monoamine oxidase inhibitors (Solyom et al.

1981) and benzodiazepines (Hafner and Marks 1976; Marks et al. 1993; Wardle et al. 1994).

Overall, these studies showed modest, short-term advantages across assessment domains for the combination of an antidepressant drug and exposure therapy over either treatment alone. The limited available data on combinations of a benzodiazepine and exposure therapy were less positive. In the Hafner and Marks (1976) and Wardle et al. (1994) studies, the administration of low-dose diazepam prior to exposure sessions or on a daily basis throughout exposure therapy had no significant effect, either positive or negative, on treatment outcome, although patients were somewhat less anxious during treatment. In the Marks et al. (1993) study, high-dose alprazolam plus exposure was marginally better than exposure plus a pill placebo during acute treatment, but relapse was substantially greater in the former cell when treatment was discontinued.

Few studies of combinations of pharmacotherapy with CBT have been published. A recent review of the literature on benzodiazepines and CBT found little evidence that the combination is superior to CBT alone for most patients (Spiegel and Bruce 1997), and some studies have found poorer long-term outcomes for the combination than for CBT alone (Brown and Barlow 1995; Otto et al. 1996). This potential detrimental effect of benzodiazepines on the outcome of CBT appears to be minimized if the drugs are discontinued before the conclusion of CBT (Bruce et al. 1999; Otto et al. 1993; Spiegel et al. 1994). Cottraux et al. (1995) compared the combination of buspirone and CBT with a pill placebo plus CBT in a sample of panic disorder patients with agoraphobia. The combined treatment was superior to CBT plus placebo at posttreatment (16 weeks) on measures of generalized anxiety and agoraphobic avoidance, but the differences disappeared by 1-year follow-up. Almost the only data relating to the combination of antidepressants with full CBT for panic disorder come from the recently concluded multicenter study referred to earlier in this chapter (Barlow 1998; Gorman 1998; Shear 1998; Woods 1998). In that study, the combination of CBT (specifically, PCT) plus imipramine was compared with each treatment alone, with a pill placebo, and with the combination of CBT and a pill placebo. After 3 months of treatment, CBT plus imipramine was marginally better than CBT alone but did not differ from imipramine alone or CBT plus placebo. After 9 months of treatment, the combination was better than both single treatments and CBT plus placebo; however, these advantages were lost when all treatments were discontinued. At follow-up 6 months after treatment discontinuation, only CBT alone and CBT plus placebo continued to be better than placebo.

On the basis of these studies, it would appear that the routine administration of pharmacotherapy with CBT is not warranted in most instances. Whether there are some patients for whom such an approach would be indicated is not known at present. For now, the strongest support for combining treatments is for the addition of in vivo exposure therapy to pharmacotherapy for patients with moderate to severe agoraphobia and for the administration of CBT to patients being discontinued from antipanic medications.

Combined Cognitive-Behavioral Therapy Components With Exposure Therapy

Several investigators have combined exposure therapy with other psychosocial treatment interventions, including relaxation therapy (Michelson et al. 1988, 1996; Öst et al. 1984, 1989), cognitive therapy (de Beurs et al. 1995; Emmelkamp and Mersch 1982; Emmelkamp et al. 1986; Michelson et al. 1988; Öst et al. 1989; van den Hout et al. 1994; Williams and Rappaport 1983), and breathing retraining (Bonn et al. 1984; deRuiter et al. 1989). In most instances in which comparisons were made, the combined therapies were not significantly better than exposure alone. A notable exception to this rule was the study reported by Michelson et al. (1996), which compared graded in vivo situational exposure alone with the same procedure with the addition of cognitive therapy or relaxation training in patients with moderate to severe panic disorder with agoraphobia. Of the three treatments, exposure plus cognitive therapy was the most effective. At posttreatment, 44% of the subjects who had received that treatment achieved high end-state functioning, compared with 22% in the exposure plus relaxation condition and 22% who received exposure alone. Those differences were maintained at 1-year follow-up, when the corresponding numbers were 71%, 33%, and 38%, respectively. Analyses showed that catastrophic cognitions related to anxiety and panic were important factors affecting the short- and long-term outcomes.

More recently, Telch and colleagues (Telch 1996; Telch et al. 1994, 1995) compared the singular and combined effects of CBT and in vivo exposure therapy instructions for panic disorder with agoraphobia. In that study, all treatments were administered in a group format in twelve 90-minute sessions over an 8-week period. Results reportedly showed little evidence of treatment specificity; however, on a composite index of

treatment response, patients who had received the combined treatment showed the greatest improvement at posttreatment and 6-month follow-up. The advantage appears to have been lost by 12-month follow-up because of delayed improvement in subjects who had received the single treatments. In a series of small studies done at our center, we examined the effect of adding a situational exposure component (programmed practice instructions) to standard group PCT for patients with moderate to severe agoraphobia (Turovsky et al. 1994). Contrary to our expectations, the experimental treatment was not significantly better than standard PCT alone on measures of agoraphobic avoidance, panic attack frequency or severity, or level of general anxiety. However, there also was no difference in the amount of exposure subjects in the two treatment conditions reported doing, which was minimal in both. Apparently, simply instructing subjects to do exposure was not a strong enough intervention to produce the desired behavior.

Currently, we are experimenting with combinations of PCT and brief (2 or 3 days), massed exposure adapted from the method reported by Fiegenbaum and colleagues (Ehlers et al. 1995; Fiegenbaum 1988; Schroeder et al. 1996). In one trial, we combined 2 days of individually administered ungraded massed exposure with 6 sessions of group CBT plus a self-study workbook in 29 patients with moderate to severe agoraphobia (Heinrichs et al. 2000). Patients exhibited marked improvements on measures of agoraphobia, social anxiety, fear of anxiety sensations, general anxiety, depression, and disability. More recently, we have been treating patients with moderate to severe agoraphobia using an intensive, 8-day program that combines an abbreviated, largely self-study version of CBT with brief, therapist-assisted, ungraded massed situational and interoceptive exposure (Heinrichs et al., in press). The treatment requires approximately 20 hours of therapist time over 6 days; patients work alone the other 2 days. Results from the first 23 patients have been very positive, suggesting that the treatment may be a useful option for individuals who do not have access to CBT locally, have failed to respond to other treatment modalities, or require more urgent intervention than standard treatments (Spiegel and Barlow 2000).

Conclusion

Naturalistic studies indicate that despite the availability of proven treatments, many patients with panic disorder or panic disorder with agoraphobia do not receive effective treatment in the community. For example, the Harvard/Brown Anxiety Research Program assessed recovery and relapse in 323 panic disorder patients with agoraphobia and 73 without agoraphobia who were treated naturalistically (Keller et al. 1994). In the first 22 months after onset of an episode, only 43% of the patients without agoraphobia and 18% of those with agoraphobia had recovered. Moreover, among recovered patients, 40% of those without agoraphobia and 60% of those with agoraphobia relapsed within 18 months. High relapse rates also were found in a naturalistic study at the Massachusetts General Hospital (Pollack et al. 1990). Consistent with those dismal statistics, surveys have shown that only a small number of patients treated in clinical settings receive an empirically validated psychosocial treatment (Breier et al. 1986; Goisman et al. 1993; Taylor et al. 1989). As Barlow and Hofmann (1997) noted, that situation is caused by, at least in part, a lack of availability, especially in primary care settings, of clinicians who have been trained in those therapies. Lack of information about the efficacy of psychosocial treatments and a misguided belief that pharmacotherapy is less expensive also may be factors. Clearly, if the outlook for patients is to improve, greater efforts must be made to educate health care practitioners and managers about the effectiveness and favorable cost of psychological treatments for panic disorder and to ensure that such treatments are accessible to patients.

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VI

Social Phobia

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22

Phenomenology of Social Phobia

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DSM Social Phobia: Past to Present

The history of social phobia as a diagnostic category is relatively brief. Although the term *social phobia* was coined in the early 1900s to describe individuals with performance-related anxieties (Janet 1903), it was not included in the first two versions of the DSM nomenclature (American Psychiatric Press 1952, 1968). Instead, symptoms resembling social phobia were subsumed under the rubric of phobic disorders. It was not until the advent of DSM-III (American Psychiatric Press 1980) and findings suggesting that certain phobias were qualitatively distinct (Marks and Gelder 1966) that social phobia was given its own diagnostic category.

In its first appearance in DSM-III, social phobia was defined as an excessive fear of observation or scrutiny in performance-related situations (e.g., public speaking, eating in front or others, writing in front of others). Exposure to these situations typically resulted in paniclike symptoms (e.g., heart palpitations, tremors, blushing, and sweating) leading many to avoid these social situations or to endure them with a great deal of distress. DSM-III also required that individuals recognize their fears as unreasonable or excessive. If multiple social situations were avoided, an Axis II diagnosis of avoidant personality disorder was to supersede a social phobia diagnosis. As a result, many individuals received a diagnosis of avoidant personality disorder rather than social phobia. Although the diagnostic criteria for these two disorders overlapped considerably, avoidant personality disorder was to be differentiated by its pervasiveness, intense feelings of inferiority, and earlier age of onset.

The differential diagnosis between social phobia and avoidant personality disorder was not without its consequences and inadequacies. Most importantly, it had profound treatment implications; for example, an individual with a personality disorder was less likely to receive pharmacological therapy than an individual with social phobia (Liebowitz et al. 1985). In fact, it is probable that the assignment of an Axis II diagnosis may have reduced the chances that any form of therapy would have been applied, perhaps resulting in a neglected patient population.

DSM-III-R (American Psychiatric Press 1987) attempted to improve the classification criteria by expanding the social phobia category to include individuals who feared many social situations. With this revision, avoidant personality disorder was dropped as an exclusionary criterion. Such inclusiveness resulted in a very heterogeneous diagnostic group; for example, an individual who feared only public speaking situations was given the same diagnosis as one who feared most social interactions. Consequently, DSM-III-R created a generalized subtype for persons who feared "most" social situations, including both performance (e.g., giving speeches, speaking at a meeting) and interactional situations (e.g., talking to strangers, interacting at a party). Those who did not fit this subtype were informally termed "nongeneralized"; however, labels such as "circumscribed," "discrete," "limited," and "specific" were also applied.

Despite these revisions, DSM-III-R did not escape criticisms. Heckelman and Schneier (1995) noted three main criticisms. First, there was ambiguity surrounding what constituted "most" social situations, a methodological issue that has profound research implications. Second, it was unclear whether the subtypes were quantitatively or qualitatively distinct entities. Third, an inherent flaw seemed to be the absence of an intermediate subtype that could be used to describe persons with the fear of several—but less than most—interpersonal situations. Another issue that quickly became apparent was how to adequately distinguish the generalized social phobia subtype from avoidant personality disorder (Herbert et al. 1992; Holt et al. 1992; Turner et al. 1992).

To address these issues, the American Psychiatric Task Force on DSM-IV (1991) examined the reliability and validity of alternative subtyping systems. A proposed alternative classification was a tripartite system consisting of 1) individuals who had circumscribed social fears (e.g., public speaking anxiety, writing in front of others, etc.), 2) individuals who had "limited" interactional fears (i.e., fear of "some" but not "most" social situations), and 3) individuals who feared "most" social situations (Heimberg et al. 1993). Although this subtyping system appeared to have clinical validity, empirical studies were unable to support the presence of qualitative distinctions between the limited interactional and the circumscribed subtype. It was decided that more research was necessary before changes to the current subtyping system were applied.

Overall, the DSM-IV (American Psychiatric Association 1994; Table 22–1) diagnostic criteria for social phobia remained largely consistent with those put forth in DSM-III-R. With regard to the subtyping system, the generalized subtype was once again included to distinguish those with fears of "most" social situations from those with specific fears. DSM-IV also advised its users to consider the comorbid diagnosis of avoidant personality disorder when diagnosing social phobia. Perhaps the area of greatest revision involved the modification of the social phobia criteria to include children. Previously, children who had symptoms resembling social phobia were given diagnoses of avoidant disorder of childhood or overanxious disorder. Empirical data, however, suggested that these disorders were fairly indistinguishable from social phobia (Beidel 1991; Francis et al. 1992). This diagnostic challenge was furthered by the proposition that such comorbidity would inevitably obscure an accurate understanding of the lifetime course of social phobia (Heckelman and Schneier 1995). As a result, avoidant and overanxious disorder diagnoses in children were deleted from the DSM, and the criteria for social phobia were expanded to apply to children. Specifically, DSM-IV advised that anxiety might be expressed differently in children than in adults (i.e., by children's crying, tantrums, freezing, or withdrawal). It was also noted that children, unlike adults, might not perceive their reactions to social situations as being unreasonable or excessive.

Diagnostic Issues

Distinctions Between Social Phobia Subtypes

Any discussion of clear-cut distinctions between social phobia subtypes is muddled by the fact that subtypes are not consistently defined in the literature. Despite varying definitions, most findings suggest that the generalized subtype is more severe and causes greater impairment than the nongeneralized or circumscribed subtype (e.g., public speaking phobia). More specifically, empirical findings suggest that individuals with generalized social phobia report greater anxiety and depression, avoidance, concern with negative evaluation, and negative self-statements about social interactions than do individuals with circumscribed social phobia (Boone et al. 1999; Heimberg et al. 1990; Holt et al. 1992; Turner et al. 1992).

In addition to differences in level of severity and impairment (i.e., quantitative distinctions), there are also qualitative distinctions—based on pathophysiology, etiology, and treatment responsiveness—across social phobia subtypes. During individualized behavioral challenges (e.g., giving a speech or interacting with a confederate), patients with circumscribed public speaking phobia exhibited greater cardiac reactivity than those with generalized social phobia (Heimberg et al. 1990), a finding that has been replicated in other studies (Boone et al. 1999; Hofmann et al. 1995; Levin et al. 1993). Using an information-processing paradigm (i.e., the Stroop task), McNeil et al. (1995) also found subtype differences: Individuals with circumscribed social phobia had longer latencies of response to public speaking stimuli than did individuals with generalized social phobia. With regard to etiological variables, Stemberger et al. (1995) found that generalized social phobia was more frequently associated with a history of childhood shyness, whereas "specific" social phobia was more commonly associated with traumatic conditioning experiences, suggesting that the former may have a larger heritable component. Finally, some treatment

TABLE 22–1. DSM-IV-TR diagnostic criteria for social phobia

A. A marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing. **Note:** In children, there must be evidence of the capacity for age-appropriate social relationships with familiar people and the anxiety must occur in peer settings, not just in interactions with adults.
B. Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic attack. **Note:** In children, the anxiety may be expressed by crying, tantrums, freezing, or shrinking from social situations with unfamiliar people.
C. The person recognizes that the fear is excessive or unreasonable. **Note:** In children, this feature may be absent.
D. The feared social or performance situations are avoided or else are endured with intense anxiety or distress.
E. The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the person's normal routine, occupational (academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.
F. In individuals under age 18 years, the duration is at least 6 months.
G. The fear or avoidance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition and is not better accounted for by another mental disorder (e.g., panic disorder with or without agoraphobia, separation anxiety disorder, body dysmorphic disorder, a pervasive developmental disorder, or schizoid personality disorder).
H. If a general medical condition or another mental disorder is present, the fear in criterion A is unrelated to it, e.g., the fear is not of stuttering, trembling in Parkinson's disease, or exhibiting abnormal eating behavior in anorexia nervosa or bulimia nervosa.

Specify if:

Generalized: if the fears include most social situations (also consider the additional diagnosis of avoidant personality disorder)

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findings suggest that patients with nongeneralized social phobia may respond better to typical cognitive therapies than do patients with generalized social phobia (Brown et al. 1995; Heimberg 1986; Heimberg et al. 1985; Turner et al. 1994).

Epidemiological findings also support the presence of social phobia subgroups; however, many of these findings suggest more of a quantitative relationship. Latent class analyses of social phobia diagnostic data from the National Comorbidity Survey (NCS; Magee et al. 1996) revealed three groups (Kessler et al. 1998). The largest group (74%) had no social fears. The next-largest group (19%) had significant fear and disability related to *speaking* to large or small groups, and the smallest group (8%) had *other social fears*, either with or without concomitant speaking fears. Individuals with more generalized *other social fears* reported greater impairment in their daily functioning than did people with *speaking-only* social phobia (34% and 14%, respectively); they were also more likely to have seen a mental health professional (16% and 5%, respectively) and to have taken medication (10% and 1%, respectively). In addition, the subtype characterized by more generalized social fears not only was more severe (in that more domains were impaired) than speaking-only social phobia, but also longer-lasting, in many cases appearing to be a lifetime disease. These findings parallel those seen in another study of the longitudinal course of social phobia (Chartier et al. 1998), in which the generalized form of the disorder was found to be more chronic than the circumscribed forms.

In a recent community survey study, which included 188 persons with social phobia, hierarchical cluster analysis was applied to ratings of social distress, functional impairment, number of social fears, and number of avoidant personality disorder criteria met (Furmark et al. 2000). Three clusters emerged: high (generalized subtype), intermediate (nongeneralized subtype), and low (discrete subtype). Point prevalence rates were 2.0%, 5.9%, and 7.7%, respectively. The authors concluded that although categorical distinctions may be used, the data better supported a continuum model based on severity. A similar conclusion was reached by Stein et al. (2000), who found that the number or type of social fears could not be used to establish a defensible subtyping system. Rather, social phobia in the community was found to exist along a continuum of severity (Stein et al. 2000).

Thus far, the validity of subtyping systems is far from conclusive. Although there appears to be some support for qualitative distinctions between generalized social phobia and circumscribed or discrete phobias (e.g., public speaking), the difference between the more vaguely defined "nongeneralized" category and other subtypes is unclear. At this point, social phobia subtypes may have some clinical utility; however, their validity as separate and qualitatively distinct subgroups requires further research.

Comorbidity of Social Phobia With Avoidant Personality Disorder

Considerable overlap exists between generalized social phobia and avoidant personality disorder; in fact, comorbidity rates range from 22% to 89% (Fahlen 1995; Herbert et al. 1992; Holt et al. 1992; Schneier et al. 1991). Whereas both qualitative and quantitative differences have been found between social phobia subtypes, most studies suggest that avoidant personality disorder is not distinct from generalized social phobia but rather is more likely a more severe variant of the disorder. Study designs comparing generalized social phobia subjects with and without avoidant personality disorder have found that the presence of avoidant personality disorder was associated with greater social anxiety, trait anxiety, and functional impairment (Herbert et al. 1992). The presence of avoidant personality disorder, however, was not associated with differences in subjective reports of distress, heart rate, speech length, negative thoughts recounted during the behavioral tasks, or performance of an impromptu speech (Herbert et al. 1992; Holt et al. 1992; Turner et al. 1992). In addition, McNeil et al. (1995) found that generalized social phobia patients with and without avoidant personality disorder performed similarly on various cognitive interference tasks that incorporated social stimuli. Further supporting the hypothesis that the two conditions may be variations of the same construct, Stein et al. (1998) found similar rates of these two disorders in first-degree relatives of generalized social phobia probands (i.e., 25% of relatives had generalized social phobia and 20% had avoidant personality disorder); no cases of avoidant personality disorder were seen in first-degree relatives of comparison probands. With regard to treatment, research findings do not support the hypothesis that a comorbid avoidant personality disorder diagnosis is a significant predictor of treatment outcome among individuals with generalized social phobia (Brown et al. 1995).

Worthy of note is a study by Tran and Chambless (1995), who found a trend for social skills deficits to be associated with avoidant personality disorder. In addition, van Velzen et al. (2000) reported increased depressive symptoms and introversion among social phobia patients with avoidant personality disorder compared with patients without avoidant personality disorder. Although further investigation of other qualitative markers is warranted, current findings suggest that generalized social phobia and avoidant personality disorder are quantitatively related; that is, the latter may be seen as a severe variant of the former.

Epidemiological Findings

In the United States, epidemiological and community-based studies have reported lifetime prevalence rates of social phobia ranging from 2.4% to 13.0% (Kessler et al. 1994; Magee et al. 1996; Schneier et al. 1992), making it the third most common psychiatric disorder (after major depressive disorder and alcohol dependence). Variations in diagnostic rates can be attributed both to changes in diagnostic criteria and to differing methodologies. For example, structured interviews, such as the Diagnostic Interview Schedule (DIS; Robins et al. 1981), query three types of social fears, whereas other interview schedules, such as the Composite International Diagnostic Interview (CIDI; World Health Organization 1990), assess six types of social fears. Use of the DIS has elicited lifetime prevalence rates of social phobia ranging from 0.5% to 3.0%. With the CIDI and other interview schedules that probe more social fears, higher lifetime prevalence rates (7% to 16%) have been found (Furmark et al. 1999; Magee et al. 1996; Stein et al. 2000; Wacker et al. 1992) (Table 22–2).

Cross-National and Cultural Findings

As also shown in Table 22–2, whereas relatively similar rates of social phobia are found among Western cultures (e.g., United States, Canada, New Zealand), lower rates are reported in East Asian countries, such as Taiwan and Korea. These lower prevalence rates are perplexing in light of research that has documented the presence of an East Asian pattern of social anxiety called *taijin-kyofu-sho* (TKS) in countries such as Japan and Korea (Aune and Aune 1996; Murphy 1982). Unlike social phobia, which involves the fear of humiliating oneself, TKS involves the fear of offending others by embarrassing them or by making them uncomfort-

TABLE 22–2. Social phobia lifetime prevalence rates based on the Diagnostic Interview Schedule (DIS) and alternative structured interviews, such as the Composite International Diagnostic Interview

		Lifetime prevalence rates (%)	
Location	**Reference**	**DIS**	**Other interviews**
United States	Schneier et al. 1992	2.4	
	Magee et al. 1996		13.3
	Stein et al. 2000		7.2
Canada	Bland et al. 1988	1.7	
	Stein et al. 1994		7.1
New Zealand	J.E. Wells et al. 1989	3.0	
	Feehan et al. 1994		11.1
Puerto Rico	Canino et al. 1987	1.6	
Taiwan	Hwu et al. 1989	0.6	
Korea	Lee et al. 1990	0.5	
Switzerland	Wacker et al. 1992		16.0
Sweden	Furmark et al. 1999		15.6

able through a personal flaw or shortcoming (e.g., blushing in front of others, emitting an unpleasant body odor, or exposing an unsightly body part). According to Chang (1997), TKS is a cultural pattern of social anxiety because it reflects the "other-oriented" nature of some East Asian societies, just as social phobia reflects the "self-oriented" nature of Western societies. Overall, however, there appears to be significant overlap between TKS and both social phobia and avoidant personality disorder (Kleinknecht et al. 1997; Ono et al. 1996).

Epidemiological findings presenting prevalence rates of social phobia across ethnic groups within the United States are scant. According to the National Comorbidity Survey, comparable rates of social phobia are present among Caucasians, African Americans, and Hispanics (Magee et al. 1996). In addition, rates in Puerto Rico are similar to those found in the five Epidemiologic Catchment Area (ECA) sites (Canino et al. 1987). Differences between ethnic groups were found in a college student sample that included Asian Americans: Asian Americans scored higher than Caucasians on measures of social anxiety and depression (Okazaki 1997). Findings from this study also revealed that self-construal variables were important predictors of social anxiety; that is, interdependent self-construals (e.g., emphasis on self as being part of a group) were better predictors of social anxiety than independent self-construals (e.g., emphasis on self as being autonomous). Furthermore, less acculturated Asian Americans reported higher avoidance and distress in social situations. Additional research is necessary to understand the variables (e.g., language, social ideals, child-rearing practices, social affiliation) that may mediate the expression of social anxiety.

When attempting to explain the presence or absence of cross-cultural differences, methodological factors also should be considered. For example, translation of interview schedules developed in English into other languages may affect the sensitivity of the instruments. In addition, instruments that have a Western psychiatric focus may not be sensitive to patterns of symptomatology found in non-Western countries (Chapman et al. 1995; Guarnaccia et al. 1989). Finally, it may be that members of some cultures are less willing to disclose information in the structured interviews used by research studies.

Demographic Characteristics

Epidemiological studies have also found that individuals with social phobia are more likely to be female, to be single, and to have lower income and education compared with those without the disorder (Schneier et al. 1992; Wells et al. 1994). In patient samples, however, social phobia seems to be equally distributed among males and females (Boyd et al. 1990; Degonda and Angst 1993). Overall, social phobia and simple phobias typically have an earlier age at onset than other anxiety disorders (Scheibe and Albus 1992). Epidemiological and patient sample studies suggest that the mean age at onset of social phobia is the mid-teens to the early 20s and that onsets after age 25 are relatively uncommon (Magee et al. 1996; Schneier et al. 1992).

Comorbidity

Numerous studies suggest that most individuals with social phobia have one or more comorbid conditions (Lepine and Pelissolo 1996; Merikangas and Angst 1995; Schneier et al. 1992). Particularly noteworthy is that the presence of psychiatric comorbidity is associated with a poorer prognosis (Davidson et al. 1993). Axis I disorders that are most frequently comorbid with social phobia are major depression (Reich et al. 1993; Stein et al. 1999; Van Ameringen et al. 1991), panic disorder (Angst 1993; Stein et al. 1989), agoraphobia (Goisman et al. 1995), generalized anxiety disorder (Borkovec et al. 1995; Mennin et al. 2000; Turner et al.

1991), substance use disorders (Dilsaver et al. 1992; Page and Andrews 1996), and eating disorders (Bulik et al. 1997; Schwalberg et al. 1992).

Studies that have investigated the longitudinal course of comorbid conditions have found that social phobia generally precedes mood, substance use, and eating disorders (Alpert et al. 1994; Brewerton et al. 1993; Kessler et al. 1999). Furthermore, in a prospective, longitudinal epidemiological study of adolescents and young adults, the presence of social anxiety in nondepressed persons was associated with an increased likelihood of subsequent depressive disorder (Stein et al. 2001).

Impairment

Even in the absence of comorbidity, social phobia has been associated with significant distress, including increased suicidal thoughts, financial problems, reduced work and school performance, impaired social support systems, increased use of psychotropic medication, and more help seeking from medical and mental health professionals (Davidson et al. 1993; Schneier et al. 1992). Although increased suicidal thoughts have been reported, actual suicide attempts were associated with increased comorbidity (Cox et al. 1994; Schneier et al. 1992). Patients with social phobia also report reduced quality of life (QOL) compared with community norms (Safren et al. 1996–1997; Stein and Kean 2000). On a construct closely related to QOL—Illness Intrusiveness, the extent to which an illness interferes with everyday functioning—patients with social phobia appeared as impaired as persons with chronic medical conditions such as end-stage renal disease or multiple sclerosis (Antony et al. 1998). In addition, the course of social phobia is relatively chronic, enabling it to significantly affect an individual's QOL; however, this relationship seems to apply more to individuals with generalized social phobia than to those with more circumscribed fears (Chartier et al. 1998).

Social Phobia In Primary Care Settings

Several studies have shown that anxiety disorders are highly prevalent among general medical clinic attendees (Fifer et al. 1994; Schonfeld et al. 1997; Sherbourne et al. 1996). Although social phobia was not a primary focus of these studies, one of the studies noted that social phobia was associated with meaningfully reduced role functioning and sense of well-being (Schonfeld et al. 1997). In studies of social phobia in the general medical health care system, investigators have tended to find current prevalence rates at least as high as those in the general population (i.e., in the range of 5%–10%), but poor recognition on the part of treating practitioners (Stein et al. 1999; Weiller et al. 1996). Thus, although prevalent, social phobia remains underrecognized and undertreated in the primary care setting.

Genetic Factors

Familial Associations in Social Phobia

Findings from family studies (Chapman et al. 1995; Fyer et al. 1993; Reich and Yates 1988) and twin studies (Kendler et al. 1992; Warren et al. 1999) suggest that social phobia has a heritable component. Specifically, family studies have found that relatives of social phobia probands have an increased risk for social phobia compared with rates for relatives of control subjects (16% vs. 5%, respectively). Similarly, studies of offspring of adults with social phobia have found increased rates of social phobia, overanxious disorder, and separation anxiety disorder when compared with control subjects (Mancini et al. 1996).

Although a familial component appears to be present in social phobia, few studies have investigated this relationship in social phobia subtypes. Stein et al. (1998) investigated this question by conducting modified structured clinical interviews with first-degree relatives of patients with generalized social phobia. The first-degree relatives of a group of people who did not have social phobia (other Axis I psychiatric disorders were not excluded) also were traced and interviewed to form a control group. In all, 111 relatives of people with generalized social phobia (74% of the living relatives) and 74 relatives of the control subjects (79% of the living relatives) were interviewed. The percentage of first-degree relatives who had nongeneralized social phobia did not differ significantly between the people with generalized social phobia and the control subjects. However, the incidence of generalized social phobia was far higher among the relatives of people with generalized social phobia (25%) than among the relatives of control subjects without social phobia (less than 5%). Moreover, avoidant personality disorder was found in about 20% of the relatives of people with generalized social phobia, but was absent from the control group.

These findings indicate that generalized social phobia is highly familial. Such findings are consistent with those of Mannuzza et al. (1995), who found that the rate of social phobia was elevated only in the relatives of subjects with generalized social phobia. In addition, the

findings of Stein et al. (1998) provide support for the hypothesis that avoidant personality disorder may represent one extreme of the spectrum of social phobia.

Temperament and Social Phobia

A possibly heritable dimension of personality that shares some clinical features with social anxiety is behavioral inhibition. Behavioral inhibition has been described as a tendency to react aversively to the presence of unfamiliar situations and novel stimuli and has been observed in children as young as 21 months (Garcia-Coll et al. 1984; Kagan et al. 1988). Behaviorally, these children are more likely to withdraw, cry, freeze, or cling to their attachment figure in unfamiliar situations. Biological measures suggest that children with an inhibited temperament have higher levels of cortisol in their saliva and higher heart rates in stressful situations (Garcia-Coll et al. 1984). Some have postulated that the threshold of responsivity in limbic and hypothalamic structures to unfamiliarity and challenge is lower for inhibited than for uninhibited children (Kagan et al. 1987; Kagan et al. 1993). Consequently, inhibited children show increases in muscle tension, heightened cardiac arousal, pupillary dilation, and/or increased cortisol in response to minimally unfamiliar or challenging events. Follow-up studies have found that approximately 75% of inhibited children retain this classification through age 7½ years (Kagan 1989; Kagan et al. 1988).

Studies using the Kagan et al. (1988) longitudinal cohort found that inhibited children were at elevated risk for anxiety disorders such as avoidant disorder, which is very similar to social phobia (Biederman et al. 1990). Inhibited children also had parents with significantly greater risks for more than two anxiety disorders, anxiety disorders from childhood continuing into adulthood, social phobia, and childhood avoidant and overanxious disorders (Rosenbaum et al. 1991). In addition, Rosenbaum et al. (1992) found that the prevalence of social phobia in the parents of children with behavioral inhibition (10%) was higher than in the parents of children without behavioral inhibition (0%).

More recently, studies have found that retrospective reports of childhood behavioral inhibition are associated with an increased odds of receiving a social phobia diagnosis during adolescence and young adulthood when compared with an absence of such reports (Wittchen et al. 1999). In a longitudinal study, Hayward et al. (1998) found that adolescents who were elevated on two facets of behavioral inhibition had a risk of developing social phobia that was four times greater than that of subjects who were not elevated on these facets. Also, in a follow-up study of children who had been classified at age 2 as inhibited or uninhibited (Kagan et al. 1988), 61% of adolescents originally classified as inhibited had current social anxiety, compared with 27% of those originally classified as uninhibited (Schwartz et al. 1999). When threshold criteria were used that required significant impairment, 44% of the female adolescents originally classified as inhibited had current generalized social anxiety, compared with 6% of those originally classified as uninhibited. In male adolescents, 22% of those originally classified as inhibited had current generalized social anxiety, compared with 13% of those originally classified as uninhibited—a nonsignificant difference.

Findings also suggest that behavioral inhibition may be differentially related to social anxiety. In the study by Schwartz and colleagues (1999), no association was observed between inhibition in childhood and specific fears, separation anxiety, or performance anxiety in adolescence. In addition, Mick and Telch (1998) found higher levels of retrospectively reported childhood behavioral inhibition in college students with symptoms of social phobia (assessed with self-report questionnaires) than in participants with symptoms of generalized anxiety disorder or subjects in the control group. Behavioral inhibition scores of students who had both generalized anxiety and social phobia symptoms were not higher than those of students who had only social phobia symptoms.

Social Phobia as a Spectrum Disorder

Social Phobia and Shyness

Reviews of the literature have found that social phobia and shyness have many symptoms in common (Henderson and Zimbardo 2001; Turner et al. 1990). Individuals who are shy cannot be differentiated from individuals with social phobia on the basis of physical symptoms (e.g., somatic arousal and heart rate activity) (Amies et al. 1983; Kagan et al. 1988; Ludwig and Lazarus 1983). In addition, cognitions reflecting fear of negative evaluation are common to both constructs. According to Turner et al. (1990), areas that may differentiate the two symptom patterns include severity of avoidance, degree of impairment, and course. Compared with shyness, social phobia is associated with more avoidance and greater functional impairment, and it is seen as more chronic.

According to epidemiological studies, rates of social phobia range from 3% to 16% (Furmark et al. 1999; Kessler et al. 1994; Wacker et al. 1992). Although analogous epidemiological data are not available for shyness, self-reported rates of shyness from college samples range from 40% to 50% (Carducci and Zimbardo 1995; Zimbardo 1977). Based on these findings, one can deduce that shyness and social phobia are not identical constructs, for it would be hard to imagine that any particular disease besets 40% of young adults. Nonetheless, at present the relationship between shyness and social phobia remains unclear.

According to Johnson et al. (1996), only a portion of individuals who describe themselves as shy actually exhibit clinical or subclinical social phobia. Surprisingly, however, few data are available to support this hypothesis. At present, only two studies have assessed the distribution of social phobia among highly shy individuals. St. Lorant et al. (2000) retrospectively reviewed charts of 114 patients presenting for treatment at a shyness clinic and reported that 97% of the sample had a generalized social phobia diagnosis. In a different study that used a nonclinical (college student) sample, 49% of those who were highly shy (i.e., in the upper 10th percentile of the distribution of shyness) received a diagnosis of social phobia, while only 18% of those who were normatively shy (i.e., in the 40th to 60th percentile) received that diagnosis (Chavira et al., in press). When subtypes were examined, approximately 36% of highly shy young adults met DSM-IV criteria for the generalized type of social phobia, compared with only 4% of normatively shy young adults; equal rates were found for nongeneralized social phobia. There were also more individuals who met criteria for avoidant personality disorder in the highly shy group than in the comparison group.

Based on these findings, it may be that shyness is a trait that, at its extreme, becomes impairing and thereupon assumes the characteristics of a disorder, namely social phobia. Furthermore, extreme shyness seems to be more related to the interactional fears that characterize generalized social phobia than to the performance-oriented fears that frequently typify nongeneralized social phobia and more circumscribed social phobias (e.g., public speaking phobias). This relationship is further demonstrated by the disproportionately higher rates of avoidant personality disorder in the highly shy group. Overall, such findings partially support a spectrum model in which higher shyness levels are indicative of more problematic degrees of social anxiety, merging at the upper extreme into clinical disorders such as generalized social phobia and avoidant personality disorder. Additional research is necessary to further evaluate this relationship and to more fully understand the variables that distinguish extreme shyness from social phobia.

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23

Pathogenesis of Social Phobia

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As with other psychiatric syndromes, the etiopathophysiology of social phobia is not known. Over the past decade, however, there has been an explosion in the number of research publications devoted to delineating the pathophysiology of social anxiety, social fears, and social phobia. Unfortunately, the research has been quite scattered, and few, if any, replication studies or studies that are thematically linked have been done. Accordingly, data are insufficient for integrating the available literature. For that reason, in this chapter, we summarize available research reports and conclude with a focused proposal for further study.

Part of the difficulty in understanding the etiopathophysiology of social phobia is the heterogeneity of the populations studied. Many studies have been conducted in analog populations, often undergraduate psychology students, who score above or below the median split on a given psychometric instrument. Other studies have involved community samples that rarely have received treatment for an anxiety problem. The third study population has been treatment-seeking individuals who probably differ in important ways from the community sample individuals. In addition to the heterogeneity of the populations studied, multiple pathways probably lead to the clinical manifestation of social phobia. Accordingly, it is unlikely that a single gene, experience, or environmental condition will explain all cases. More likely, although more difficult to investigate, social phobia is the result of complex interactions between genetic vulnerability, home environment, temperament, and personal experiences.

The relation between social fears, social anxiety, and social phobia remains to be precisely defined and complicates review and integration of extant studies. For example, "social anxiety" is a widely used psychological construct and is the focus of many reports in the literature. Often, these reports are on undergraduates who score high or low on a median split of a particular rating scale. Does research on social anxiety generalize to individuals seeking treatment for social phobia? "Shyness" is another psychological construct. Many subjects with social phobia describe themselves as shy, but others do not. How, therefore, should research on shyness be integrated into our understanding of social phobia? What is the relevance of such research in understanding the pathophysiology of treatment-seeking samples? In this chapter, the term *social phobia* is used to refer to individuals meeting DSM-IV-TR (American Psychiatric Association 2000) criteria. The terms *social fears*, *social anxiety*, and *shy* are used to describe nonclinical, subclinical, or analog populations or studies.

Psychological or Developmental Theories

Several psychological or developmental models have been proposed for the development of social phobia. Models based on conditioning, ethological, personality, behavioral inhibition, and cognitive theories have been proposed. These have been previously described, and

the reader is urged to consult these references for details (Barlow 1988; Bruch and Cheek 1995; Mineka and Zinbarg 1995). In this chapter, the models are briefly described, and some of the limitations of the models are highlighted. Although these models have heuristic value, they are quite difficult to test empirically, especially with regard to the development or onset of the disorder. For example, once the anxiety has developed, it is easy to see how conditioning, cognitive, or learning theories could maintain the anxiety; what is not clear from the models is how the problem developed.

Conditioning Model

The conditioning model is based on the theory that a conditioned aversive situation can lead to the development of phobias (Barlow 1988). The available empirical data are not consistent; some reports support such a model (Stemberger et al. 1995) but others do not (Hofmann et al. 1995). Some patients do report that a traumatic incident led to the development of the phobia, but most patients do not recall such an incident. It is important to note that there is often a delay of greater than 10 years between the onset of symptoms and seeking help for the symptoms, and many traumatic events may have been forgotten. On the contrary, a patient may have identified a traumatic event well into the course of the disorder as the causative trauma. Only prospective, longitudinal evaluation of youths at risk for social phobia will help address the role, if any, of conditioning in the development of social phobia.

Ethological Model

The ethological model was initially formulated by Ohman (1986) and more completely articulated by Mineka and Zinbarg (1995) and D.J. Stein and Bouwer (1997). The ethological model posits an evolutionary wariness of being stared at, which in some individuals leads to arousal and alarm. Possibly, this sensitivity to eye contact or scrutiny is a trait that is inherited in a familial fashion.

Personality Model

Shyness is a personality trait that begins early in life in most people (Buss 1980). Shyness has a genetic component; monozygotic twins are more closely concordant in shyness than are dizygotic twins. Bruch and Cheek (1995) described two types of shyness: a "fearful" shyness, which develops at a very early age, and a "self-conscious" shyness, which develops at around the time of adolescence. The notion is that shyness leads to discomfort in particular social situations, which can lead to worry about such situations and arousal or avoidance of them. Although many individuals with social phobia describe themselves as shy, this is not a universal finding. Conversely, many shy individuals do not meet the criteria for social phobia.

Behavioral Inhibition Model

Behavioral inhibition, a psychological construct developed by Kagan et al. (1988), refers to a stable temperament, recognizable in early childhood. Operationally, it defines a subset of children who behave in a timid, fearful manner when exposed to a novel test environment. Compared with noninhibited children, the behaviorally inhibited children have increased latency to speak, decreased exploratory behavior, increased heart rate, and elevated cortisol and catecholamine levels. Kagan and colleagues followed up several cohorts of children for up to 10 years and found that the behavioral traits were stable in most of the children over time. Behavioral inhibition can lead to decreased social interaction and/or uncomfortable social interactions, which may lead to social fears and social anxiety, which, in turn, may lead, theoretically, to social phobia.

Biederman and colleagues (1990) reported that children of adults with agoraphobia or panic disorder have markedly increased rates of behavioral inhibition compared with children of depressed parents. Unfortunately, the prevalence of behavioral inhibition in the children of parents with social phobia has not been determined. Mancini and colleagues (1996) evaluated the children of parents with social phobia and reported high rates of overanxious disorder and social phobia in the offspring. These investigators did not include a comparison group, so it is not clear if the observed rates of social phobia or overanxious disorder were specific to the children of parents with social phobia.

Cognitive Model

Clark and Wells (1995) presented a cognitive model of social phobia that explains how the phobia can be maintained. Two assumptions made by an individual with social phobia are that 1) he or she will behave or perform in an inept, incompetent, or humiliating fashion; and 2) as a result of the behavior or performance, there will be a disastrous or catastrophic consequence. Such a cognitive model is consistent with psychometric data on rating scales (Shea Gelernter et al. 1991).

In summary, various models have been proposed to explain the development and persistence of social phobia. For the most part, the models are not mutually exclusive, and data supporting one do not negatively affect the rest. The models should be tested in a group of youths at high risk for the development of social phobia who are followed up in a longitudinal fashion.

Family Studies

Direct Interview

Two large direct interview family studies have been reported with social phobic probands. Fyer and associates (1993) compared the rates of social phobia in 83 first-degree relatives of 30 probands with social phobia and no other lifetime anxiety disorder diagnosis with rates of social phobia in 231 first-degree relatives of 77 probands with no lifetime mental disorder diagnosis. They reported that 16% of the relatives of the probands with social phobia met diagnostic criteria for social phobia, compared with 5% of the relatives of the control probands (relative risk=3.12, $P<0.005$). More recently, Stein et al. (1998) reported on a direct interview family study. There were two important methodological differences between the studies. First, the Stein et al. (1998) probands with social phobia had to have the generalized subtype of social phobia. Second, the Stein et al. (1998) study allowed for comorbid anxiety disorder in the probands with social phobia and allowed for lifetime mental illness diagnosis, with the exception of social phobia in the control probands. The investigators compared 106 first-degree relatives of 23 probands with social phobia with 74 relatives of 24 probands without social phobia. Generalized social phobia was found in 26.4% of the relatives of the probands with social phobia, compared with 2.7% of the relatives of the probands without social phobia (relative risk=9.7, 95% confidence interval=2.5–38.1). Interestingly, the rate of performance-only social phobia was similar in the relatives of the probands with generalized social phobia and in the relatives of the probands without social phobia (14.2% vs. 14.9%). This suggests that generalized, but not discrete, social phobia runs in families.

Although these family studies provide important data about the familial nature of the generalized subtype of social phobia, such studies cannot parse out the genetic from the environmental contributions. Twin studies or adoption studies are needed (none are available) to identify the nature of the familial contribution.

Twin Studies

Two twin studies that have examined the heritability of DSM-III-R anxiety disorders (American Psychiatric Association 1987) have been reported. The two studies had different conclusions regarding the heritability of social phobia. Kendler et al. (1992) examined data from 2,163 directly interviewed female twins. They reported that 30%–40% of the development of social phobia is genetic, and the remainder is caused by nonspecific environmental experiences. Skre et al. (1993), however, reported minimal genetic contribution to social phobia and no difference between concordance rates in monozygotic and dizygotic twin pairs. The differences may be the result of sample size and the use of hospitalization to identify probands—as noted earlier in this chapter, most patients with social phobia never get psychiatric help, much less psychiatric hospitalization.

Genetics

No genetic linkage studies have been published, and no candidate gene has been identified in social phobia.

Neurobiology

A wide range of neurobiological measures have been examined in patients with social phobia. To date, only a handful of the studies have reported differences between patients with social phobia and the comparison group. Brain systems that have been implicated in patients with social phobia include the noradrenergic system (M.B. Stein et al. 1992; Tancer et al. 1993, but see Tancer et al. 1994/1995a), dopaminergic system (Liebowitz et al. 1987, but see Tancer et al. 1994/1995a), and serotonergic system (Tancer et al. 1994/1995a). Specifically, Tancer et al. (1994/1995a) reported an exaggerated prolactin response following *d,l*-fenfluramine challenge (60 mg orally) in 21 patients with generalized social phobia compared with 22 healthy volunteers. There was a trend for increased cortisol response as well. This was interpreted as evidence for serotonin supersensitivity in patients with social phobia. This study has yet to be replicated.

Studies that have attempted to replicate the findings have not been able to replicate the positive findings. For the sake of clarity, the "Neurobiology" section is subdivided into sections based on type of research procedure used. Neurobiology of social phobia has previously been reviewed (Miner and Davidson 1995; Tancer et al. 1995). In this section, we focus on the studies

reported since those reviews and only briefly mention the earlier studies.

Brain Imaging

Potts and associates (1994) conducted a volumetric magnetic resonance imaging study in 22 patients with social phobia compared with 22 age- and sex-matched volunteers. No differences in caudate, putamen, thalamus, or cerebral volumes were found between the groups. The investigators did report an age-dependent reduction in putamen volumes only in the patients with social phobia; the volume change was not correlated with illness severity. There have been no replications of this study.

M.B. Stein and Leslie (1996) evaluated regional blood flow patterns with technetium 99m hexamethylpropyleneamine oxime (HMPAO) single photon emission computed tomography (SPECT) in 11 patients with social phobia and 11 psychiatrically healthy volunteers and reported no group differences. Van der Linden and colleagues (2000) recently examined regional blood flow in 15 patients with social phobia using HMPAO SPECT before and after treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram. Treatment led to blood flow reductions (from baseline) in the anterior and lateral parts of the left temporal cortex; the anterior, lateral, and posterior parts of the left midfrontal cortex; and the left cingulum. There was no healthy comparison group, so the findings of Stein and Leslie (1996) have not been replicated.

Tiihonen and associates (1997) measured striatal dopamine reuptake site density with ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)tropane (^{123}I-β-CIT), a SPECT cocaine analogue, in 11 patients with social phobia and age- and gender-matched volunteers (taken from a larger sample of volunteers). The authors reported that patients with social phobia had markedly lower dopamine reuptake site densities in the striatum compared with the volunteers and concluded that social phobia may be associated with dopamine dysfunction.

Neither of these SPECT findings has been replicated. Schneier and associates (2000) recently used ^{123}I-iodobenzamide (^{123}I-IBZM) SPECT to examine dopamine D_2 receptor binding potential in patients with social phobia. They reported that the 10 unmedicated patients with social phobia had lower striatal D_2 binding potential than the age- and gender-matched healthy volunteers. Although not a replication, the findings of two studies are consistent with the proposal by Liebowitz et al. (1987) of a dopaminergic dysfunction in patients with social phobia but are inconsistent with a negative levodopa challenge study conducted by Tancer et al. (1994/1995a).

To date, only one positron-emission tomography (PET) study of patients with social phobia has been published. In this study, Nutt and colleagues (1998) measured blood flow using the oxygen 15-H_2O PET method. They found that social anxiety induced by exposure in imagination to autobiographical data resulted in increased blood flow in the left superior anterior cingulate, medial frontal cortex, and parietal cortex and decreased blood flow in the temporal-occipital cortex, temporal pole, pons, and left amygdala. This methodological approach is quite exciting, and several research groups are in the process of conducting similar experiments.

Tupler et al. (1997) used proton magnetic resonance spectroscopy to measure concentrations of putative neuronal markers *N*-acetylaspartate (NAA), creatine, choline, and *myo*-inositol. At baseline, 19 patients with social phobia had significantly lower NAA-to-choline and higher choline-to-creatine and *myo*-inositol–to–creatine ratios in cortical gray matter compared with 10 control subjects. White matter regions of interest did not differ between groups. Following 8 weeks of clinically effective treatment with clonazepam, the ratios did not change. This exciting finding has yet to be replicated.

In summary, several differences between patients with social phobia and healthy volunteers have been reported with brain imaging studies. The differences in the type of studies conducted to date and the absence of replications make it impossible to make any conclusions about these studies. Several ongoing studies should help clarify the situation.

Chemical Challenge Paradigms

A variety of chemical challenge studies recently have been conducted in patients with social phobia. The earliest studies found that epinephrine was unable to replicate social phobia symptoms (Papp et al. 1988), that lactate was unable to induce panic attacks in individuals with social phobia (Liebowitz et al. 1985), and that caffeine was able to cause panic attacks in approximately 25% of the patients with social phobia, but the anxiety was quite different from their spontaneous social anxiety (Tancer et al. 1994/1995b).

McCann et al. (1997) combined an intravenous pentagastrin challenge with a social interaction task in patients with social phobia, patients with panic disor-

der, and healthy volunteers. Pentagastrin, an analogue of cholecystokinin tetrapeptide, has been found to provoke panic attacks in patients with panic disorder and in patients without panic disorder in a dose-dependent fashion (Abelson and Nesse 1994; Van Megen et al. 1994). McCann and associates found that the social interaction test plus placebo infusion was anxiogenic in both anxiety groups and in the volunteers, whereas the social interaction test plus intravenous pentagastrin (0.6 mg/kg over 60 seconds) caused panic attacks in 47% (8 of 17) of the patients with social phobia, 64% (7 of 11) of the patients with panic disorder, and 11% (2 of 19) of the healthy control subjects. Interestingly, in the context of a social interaction test, neither the patients with social phobia nor the patients with panic disorder described the panic attacks as similar to their naturally occurring symptoms. The authors concluded that the ability of pentagastrin to induce panic attacks in both patients with social phobia and patients with panic disorder at rates greater than in healthy volunteers is evidence of a "shared neurobiological substrate" between the two anxiety disorders.

A second pentagastrin challenge study was reported by van Vliet et al. (1997) in seven patients meeting DSM-IV criteria for social phobia and seven control subjects. In this study, subjects underwent two infusions under double-blind conditions. Unlike in the McCann et al. (1997) study, no social interaction test was given. van Vliet and associates (1997) also administered pentagastrin (0.6 mg/kg) over 10 seconds instead of over 60 seconds. Five of the seven (71%) patients with social phobia compared with two of the seven (29%) control subjects met strict criteria for a panic attack following pentagastrin administration. No subject had a panic attack following the placebo administration. As in the McCann et al. (1997) report, patients with social phobia described the panic attacks caused by pentagastrin as different from their typical phobic anxiety. These two studies represent the only concordant replication studies in social phobia, but the fact that the induced panic was different from the patients' typical anxiety symptoms suggests that pentagastrin fails a required component of an ideal chemical challenge (symptom convergence, specificity, clinical validation, and replicability) (Gorman et al. 1987; Guttmacher et al. 1983; Uhde and Tancer 1989).

Inhalation of various concentrations of carbon dioxide (CO_2) has been used to induce anxiety (Gorman et al. 1990; Holt and Andrews 1989b). Gorman et al. (1990) reported that 35% CO_2 administered as a "double-breath" induced panic attacks in patients with social phobia at a rate greater than room air inhalation. In contrast, healthy volunteers had no increased rate of panic following CO_2 administration compared with room air inhalation. Caldirola et al. (1997) conducted a study in which patients with social phobia, patients with panic disorder, and healthy volunteers inhaled one vital capacity of 35% CO_2 and 65% O_2 or compressed air. Both patients with social phobia and patients with panic disorder had greater anxiogenic responses to CO_2 than to compressed air, and both reported greater distress than did the volunteers.

Room air hyperventilation also has been used as a mechanism to induce symptoms of anxiety (Holt and Andrews 1989a; Maddock and Carter 1991; Spinhoven et al. 1992). Holt and Andrews (1989a) reported that patients with panic disorder and/or agoraphobia had higher symptom ratings following room air hyperventilation than did patients with social phobia or generalized anxiety disorder, who had ratings greater than those of the volunteers. Interestingly, the patient groups did not differ in end-expiratory pCO_2 levels. Finally, Asmundson and Stein (1994) examined the physiological and anxiogenic effects of respiratory manipulations in 15 patients with social phobia compared with 15 patients with panic disorder and 15 healthy control subjects. As in the study by Holt and Andrews (1989a), there were no group differences in the physiological response to hypoventilation, normoventilation, or hyperventilation. Two of the 15 (13%) patients with social phobia, 2 of the 15 (13%) patients with panic disorder, and none of the volunteers experienced a panic attack during hyperventilation.

In summary, a variety of anxiogenic stimuli have been used in patients with social phobia. To date, none of the symptoms provoked are similar to the individual's typical phobic symptomatology. The fact that patients with social phobia appear to be more sensitive than healthy volunteers to the anxiogenic effects of pentagastrin, CO_2 inhalation, or hyperventilation may be a function of basal arousal rather than a specific clue to the etiopathophysiology of social phobia.

Peripheral Markers

Another commonly used research procedure involves measuring basal plasma neurotransmitter or hormone levels, which may provide indirect evidence of central abnormalities. Alternatively, receptor density and/or affinities on platelets and/or lymphocytes have been used as surrogate markers of central neurotransmitter activity. Murray Stein and his collaborators examined a variety of peripheral markers and found no evidence of

peripheral abnormalities in patients with generalized social phobia. Specifically, M.B. Stein et al. (1993a) reported no differences in lymphocyte β-receptor density or binding affinity in 17 patients with generalized social phobia compared with 17 age- and sex-matched healthy volunteers when iodinated pindolol was used as the ligand. M.B. Stein et al. (1995) examined platelet serotonin transporter capacity by using [^{3}H]paroxetine binding in 18 patients with generalized social phobia compared with 15 patients with panic disorder and 23 healthy volunteers. The patient groups were medication-free. The density and binding affinity of the serotonin transporter did not differ between groups.

Johnson et al. (1998) recently examined the density of peripheral benzodiazepine receptors in the platelets of patients with generalized social phobia. Low peripheral benzodiazepine receptor densities have been reported previously in patients with panic disorder, posttraumatic stress disorder, and generalized anxiety disorder but not in patients with obsessive-compulsive disorder or major depressive disorder. Fifty-three patients with generalized social phobia were compared with 53 healthy volunteers. The mean receptor density in the generalized social phobia group was 2,744 ± 1,242 fmol/mg protein compared with 4,327 ± 1,850 fmol/mg protein in the control subjects.

Possible abnormalities in signal transduction and/or second messenger systems have been examined by quantifying G-protein subunit levels from platelets and leukocytes in 10 untreated patients with social phobia, 13 untreated patients with panic disorder, and 12 healthy subjects (M.B. Stein et al. 1996). None of the G-protein subunit levels examined differed across the three groups.

Following-up on reports of psychoneuroimmunological abnormalities in depression and schizophrenia, Rapaport and Stein (1994) examined serum levels of interleukin-2, an immune modulator, and soluble interleukin-2 receptor levels, a marker of T-cell activation, in 15 patients with generalized social phobia and 15 healthy volunteers. The groups had similar mean interleukin-2 and soluble interleukin-2 receptor levels.

In summary, of the peripheral markers evaluated to date, only the peripheral benzodiazepine receptor density markers have differentiated patients with social phobia from healthy volunteers.

Sleep

Two studies have reported measures of sleep in patients with social phobia. M.B. Stein et al. (1993b) used a sleep questionnaire, and patients with social phobia reported complaints of decreased sleep quality and increased sleep latency. Brown et al. (1994) conducted a polysomnographic study in 17 patients with social phobia and 16 healthy volunteers and found normal sleep parameters in the patients with social phobia.

Autonomic Reactivity

The palpitations, sweating, and flushing symptoms that are so characteristic in patients with social phobia have led to a variety of studies of autonomic function in patients with social phobia. One of the first studies examined the heart rate and blood pressure response to a public speaking task (Levin et al. 1993). Levin and colleagues found increased heart rate and blood pressure in the patients with social phobia during the public speaking, but the increase was similar to that seen in the healthy volunteers. Interestingly, patients with the discrete or specific subtype of social phobia had a greater heart rate increase before and during the phobic challenge. This was initially observed by Heimberg et al. (1990). Naftolowitz et al. (1994) also reported no differences in physiological parameters between volunteers and patients with social phobia. They also found no differences between groups in plasma cortisol or norepinephrine elevations.

M.B. Stein et al. (1992) reported increased norepinephrine responses to postural challenge in a sample of patients with mixed social phobia. M.B. Stein et al. (1994) failed to replicate this finding in a larger (15 vs. 10) sample of patients with generalized social phobia. They did note an exaggerated blood pressure elevation following Valsalva's maneuver, suggestive of increased vagal withdrawal.

In summary, most of the autonomic studies in social phobia have been normal, with a suggestion of differential responses between patents with generalized versus specific subtypes of social phobia.

Conclusion

Social phobia is a common anxiety disorder with prominent physiological and subjective symptoms. To date, neurobiological studies have not shed valuable information about the etiopathophysiology of social phobia. We believe that the pathophysiology of social phobia has a biological component and that more sophisticated multimodal research methods (combining neuropharmacological and functional imaging studies) will begin to provide clues as to the nature of social phobia. Spe-

cifically, we suggest that PET studies or functional magnetic resonance imaging studies be used during the induction of phobic symptoms to try to localize brain regions associated with the phobic symptomatology. Replication of the dopamine transporter SPECT study with PET should be a high priority for groups with access to the requisite technology. At least in the patients with discrete social phobia, there may be abnormalities in autonomic function, and these should be examined with more sensitive instruments and under more physiologically relevant conditions.

The family studies that have been conducted should be extended in size to allow a large enough sample for some genomic studies. In addition, prospective and longitudinal studies of high-risk children (children of adults with social phobia) will provide invaluable information for understanding the etiopathophysiology of social phobia.

Fortunately, while this research continues, safe and effective treatments for social phobia are already available.

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Pharmacotherapy for Social Phobia

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Until recently, the symptoms of social phobia often were overlooked or dismissed as normal personality traits equivalent to shyness. It is now clear, however, that social phobia is an impairing and painful, yet treatable, disorder. Recent research findings indicate that social phobia is quite responsive to psychopharmacological treatment. Furthermore, although nonpharmacological treatments also are effective in social phobia, some data suggest that pharmacological treatment may have an earlier onset of action and more potent short-term effects, even though the effects of cognitive-behavioral treatment may persist longer. In this chapter, we present a review of the research literature on pharmacotherapy for social phobia and offer some practical guidelines for its implementation.

Medications

Irreversible, Nonselective Monoamine Oxidase Inhibitors

The suggestion that monoamine oxidase inhibitors (MAOIs) might have efficacy in the treatment of social phobia first came from two different sources. One line of evidence consisted of four placebo-controlled studies of phenelzine on mixed phobic populations. Although those studies had important methodological problems, such as lack of operationalized diagnostic criteria, small sample sizes, and use of low doses of medication, all of them reported a significant improvement in symptom measures related to social phobia. The second line of evidence came from studies of the use of phenelzine in atypical depression. Two studies in the early 1980s found that phenelzine ameliorated interpersonal sensitivity. Because interpersonal sensitivity may be common to both social phobia and atypical depression, the findings suggested that MAOIs may be useful in the treatment of social phobia.

At present, phenelzine is the best established and possibly most efficacious treatment of social phobia. Four double-blind, placebo-controlled trials have studied the efficacy of phenelzine in social phobia. Liebowitz et al. (1992) randomized 85 patients to 8-week treatment with phenelzine, atenolol, or placebo. Mean doses of medication used were as follows: phenelzine, 75.7 mg/day (SD = 16; range = 45–90 mg/day); and atenolol, 97.6 mg/day (SD = 10.9; range = 50–100 mg/day). Only patients who completed at least 4 weeks of treatment, with 2 weeks at therapeutic dose (phenelzine, 45 mg/day, or atenolol, 50 mg/day), were included in the statistical analysis ($N = 74$). A Clinical Global Impressions (CGI) Scale change rating of 1–2 was used to define "responders," and the response rates were as follows: phenelzine, 64%; atenolol, 30%; and placebo, 23%. Both social and performance anxiety were reduced, and social and work function improved. Improvements were greater as assessed by the clinician's scales than by self-ratings. Responders were enrolled for an additional

8 weeks to study the durability of the improvement and the possibility of further gains, but no change in clinical status was detected overall. Finally, 16 patients who had completed the maintenance phase entered a discontinuation phase of another 8 weeks. Of the 11 taking phenelzine, 6 were tapered off and switched to placebo, and 2 of those patients relapsed. Among the 5 who continued taking phenelzine, 1 dropped out, and the other 4 remained well. Given those small sample sizes of the discontinuation phase, little can be said beyond the recognition that some patients do maintain gains after phenelzine discontinuation.

In the second study, Gelernter and colleagues (1991) randomly assigned 65 patients to one of four groups: 1) group cognitive-behavioral therapy (CBT), 2) phenelzine, 3) alprazolam, or 4) placebo. All pharmacotherapy patients also were given exposure instructions. Duration of the trial was 12 weeks for all treatments. Clinician raters were blind to particular medication groups but not to medication versus group therapy.

Medication dosages were increased until all social phobic symptoms had disappeared, until side effects precluded further increases, or until the maximum medication dosage was reached (i.e., phenelzine, 90 mg/day, and alprazolam, 6.3 mg/day). Actual mean doses were phenelzine, 55 mg/day (SD = 16; range = 30–90 mg/day), and alprazolam, 4.2 mg/day (SD = 1.3; range = 2.1–6.3 mg/day). At 12 weeks, phenelzine and alprazolam were both superior to placebo on the physician-rated Work and Disability Scale. CBT patients were not rated on this scale. Phenelzine also was superior to all the other treatment groups on the State-Trait Anxiety Inventory (STAI; Spielberger 1983). At 2-month follow-up, those gains were maintained. Patients were considered responders if their final Fear Questionnaire (FQ; Marks and Matthews 1979) social phobia subscale scores were equal to or below those of normative samples. According to that criterion, 69% of the patients taking phenelzine were responders, compared with 38% of those taking alprazolam, 24% of those receiving CBT, and 20% of those taking placebo.

The third study, conducted by Versiani and colleagues (1992), was a comparison of phenelzine, moclobemide, and placebo. It included 78 patients and consisted of three 8-week phases. In the acute phase, patients given phenelzine were titrated up to 90 mg/day or the highest tolerated dose, whereas patients given moclobemide were titrated up to 600 mg/day or the highest tolerated dose. The actual mean dose of phenelzine was 67.5 mg/day (SD=15.0), and the actual mean dose of moclobemide was 570.7 mg/day (SD=55.6). At week 8, phenelzine was superior to placebo on all global and social phobia measures. Additionally, phenelzine was superior to moclobemide on the social avoidance subscale of the Liebowitz Social Anxiety Scale (LSAS; Liebowitz 1987). Responders were defined as those patients with 1 or 2 on the CGI change scale, as well as at least a 70% decline on the LSAS. Of the patients taking phenelzine who completed 16 weeks of treatment, 91% were classified as responders. Those patients in the active treatment group who were switched to placebo in the third phase of the study had an increase in the mean scores of all parameters at week 24, indicating that some patients relapse when treatment is discontinued. Although 59% of the patients had met criteria for avoidant personality disorder at baseline, at week 8 only 3 of the patients taking active drugs compared with 14 of 16 in the placebo group continued to meet those criteria.

In the most recent study, Heimberg et al. (1998) recruited 133 patients for a study comparing phenelzine, placebo, an educational supportive group, or group CBT for 12 weeks. Phenelzine and CBT were superior to the other groups, and phenelzine also was superior to CBT on some measures. Patients with generalized phobia were more impaired at initiation of the study and remained more impaired at the end of the trial than patients with nongeneralized social phobia, but there were no differences in the degree of change in both groups.

In a small uncontrolled study, Oberlander et al. (1994) treated eight patients who met criteria for social phobia, except the for the exclusion criterion of presence of physical illness as a focus of social concern. Phenelzine at doses of 45–105 mg/day decreased the intensity of the phobic symptoms, as assessed by the clinical impression of the treating clinician. Six of those patients had been randomly assigned to atenolol or placebo in a previous study (Liebowitz et al. 1992), without improvement.

Tranylcypromine, another MAOI, has been studied in only two published open trials. In the first one (Versiani et al. 1988), 32 patients with social phobia were followed up for 1 year. Three dropped out in the first month of treatment, did not achieve a minimum of 40 mg/day for 2 weeks, and were not included in the analyses. Sixty-two percent of the remaining 29 patients showed marked improvement, 17% showed moderate improvement, and 21% showed no improvement. In all responders, improvement was maintained throughout the year. In some instances, initial improvement waned temporarily but was restored by increasing the dose.

When tranylcypromine was discontinued, 62% of the patients relapsed to baseline within 3 months, and an additional 22% had a partial return of their symptoms.

In a second study, an 8-week open trial including 81 patients, Versiani et al. (1989) found statistically significant reductions in both CGI Scale severity and LSAS scores. CGI Scale severity scores went from 5.2 (SD = 0.9) to 1.5 (SD = 1.0). LSAS scores changed from 90.4 (SD = 18.7) to 28.2 (SD = 17.9).

In summary, substantial evidence shows that phenelzine is highly effective in the treatment of many patients with social phobia. Its main disadvantage, as with the other nonreversible MAOIs, is its side-effect profile, particularly the risk of hypertensive crisis if a low-tyramine diet and related precautions are not strictly followed. Although it has never been compared directly with a selective serotonin reuptake inhibitor (SSRI) in the treatment of social phobia, phenelzine is frequently considered the reference medication in treatment efficacy for social phobia; however, it is not necessarily the treatment of choice for most patients because of its adverse-effect profile. The evidence also suggests that patients respond to phenelzine regardless of the severity of their symptoms. Although tranylcypromine has no data from controlled trials, open trials and clinical experience indicate that it is also helpful.

Reversible Inhibitors of Monoamine Oxidase–A

The use of standard nonreversible MAOIs is limited by their side effects, especially the risk of hypertensive crisis if dietary restrictions are not followed. This led to the development of the reversible inhibitors of MAO-A (RIMAs), which have a significantly lower ability to potentiate the pressor effect of tyramine. This allows for relaxation or total elimination of dietary restrictions. Other MAOIs side effects such as fatigue and hypotension also seem to be much less common. Unfortunately, RIMA efficacy appears inferior to that of phenelzine.

Moclobemide

Four double-blind, placebo-controlled of studies of moclobemide have been published, with mixed results. In the aforementioned study by Versiani and coworkers (1992), moclobemide was superior to placebo on the LSAS, CGI Scale, Social Avoidance and Distress Scale (Watson and Friend 1969), and Willoughby Personality Inventory (Willoughby 1932), an index of social anxiety, at the end of week 8. Moclobemide was as effective as phenelzine on all measures, except on the social avoidance subscale of the LSAS. Five of 26 (19%) patients were not included in the continuation phase because of lack of response in the acute phase, and 4 more dropped out during the continuation phase because of other reasons. Of the 21 patients who entered this phase, 14 (67%) were classified as responders at the end (week 16). Moclobemide was much better tolerated than phenelzine, with rates of side effects similar to those of placebo, especially in the second phase of the study.

A larger multicenter study (Katschnig et al. 1997) compared two doses of moclobemide (300 and 600 mg) with placebo in a double-blind design over a 12-week period. The 600-mg dose was superior to placebo on all measures of social phobia, general anxiety, and disability. The 300-mg dose was superior to placebo on the LSAS and Patient Impression of Change–Social Phobia scale. However, the magnitude of drug-placebo differences on both doses was smaller than those seen in the Versiani study or studies of other active compounds such as phenelzine, clonazepam, or the SSRIs.

Noyes et al. (1997) compared five doses of moclobemide (75, 150, 300, 600, and 900 mg/day) with placebo in a 12-week double-blind study. Those assigned to 75 and 150 mg received the full dose from the time of randomization, and those assigned to 300, 600, and 900 mg received 150 mg initially followed by increments of 150 mg every 4 days until the full dose was achieved. None of the doses of moclobemide was superior to placebo. At 12 weeks, 35% of the subjects who received 900 mg and 33% of the subjects who received placebo were at least much improved on the CGI Scale.

Schneier et al. (1998) administered moclobemide or placebo to 77 patients with social phobia in a double-blind, flexible-dose design. Moclobemide was initiated at 100 mg twice a day and increased over 2 weeks to a maximum of 400 mg twice a day, adjusted as clinically indicated. Mean dose was 728 mg in the moclobemide group. At the eighth week, 7 of the 40 (18%) moclobemide patients and 5 of the 37 (14%) placebo patients were rated as much or very much improved (responders). Moclobemide was superior to placebo on only 2 of the 10 primary outcome measures. Patients who were rated by an independent evaluator to be at least minimally improved on the CGI Scale after the 8 weeks were offered 8 additional weeks of the same treatment (n=21). Among the 9 moclobemide and 7 placebo patients who agreed to continue, some further improvement occurred on the CGI Scale in the moclobemide group, but neither group showed significant changes on any continuous measures.

In summary, of the four published double-blind, placebo-controlled studies of moclobemide, one showed

strong efficacy, another showed weak efficacy, and two showed no clinically significant efficacy. Thus, moclobemide is probably better tolerated but less efficacious than phenelzine in the treatment of social phobia.

Brofaromine

van Vliet et al. (1992) studied brofaromine in a 12-week placebo-controlled study of 30 patients. The dose of brofaromine was gradually increased from 50 to 150 mg/day (75 mg twice daily) over 3 weeks and then maintained at 150 mg/day for the rest of the treatment. Brofaromine was superior to placebo on the LSAS, general (or anticipatory) anxiety, interpersonal sensitivity, obsessive-compulsive, and phobic avoidance scales. Eighty percent of the patients taking brofaromine and 14% of those taking placebo judged themselves responders, although criteria for response were not provided. Based on a final Hamilton Anxiety Scale score of less than 10 as a criterion for response, 73% of the patients taking brofaromine were classified as responders, compared with 0% of the placebo group. The group taking brofaromine had an increase in plasma serotonin and melatonin and a decrease in 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG), suggesting that the drug was active. However, no correlation between clinical and biochemical measures was provided. Twelve patients entered a follow-up phase of 12 additional weeks. Eleven patients (10 taking brofaromine and 1 taking placebo) completed that phase. In the patients taking brofaromine and the patient taking placebo, improvement in general anxiety and on the avoidance subscale, but not the anxiety subscale, of the LSAS was noted. Four months after discontinuing brofaromine, 3 patients relapsed.

In a second double-blind trial, Fahlen et al. (1995) randomized 77 patients to brofaromine (n=37) or placebo (n=40) for 12 weeks. Patients were given a fixed dosage of 150 mg/day or a matching placebo after a 2-week titration phase. A much or very much improved outcome on the CGI Scale was used as a criterion for response; 78% of the patients taking brofaromine and 23% of those in the placebo group were classified as responders. Changes in LSAS scores also were significantly greater in the brofaromine group than in the placebo group. LSAS scores for the brofaromine and placebo group were 67.2 and 65.3 at baseline, respectively. The corresponding end-point mean scores were 34.4 and 53.3. The clinical effects were not correlated with blood levels of brofaromine. Further improvement was achieved by the brofaromine group during a 9-month follow-up period, whereas 60% of the placebo responders who continued long-term treatment relapsed.

Recently, Lott et al. (1997) treated patients with brofaromine (n=52) or placebo (n=50) for 10 weeks. Brofaromine was started at 50 mg and titrated up to 150 mg/day depending on tolerance and treatment response. Actual mean dosage for brofaromine patients was 107.2 mg/day (SD=27.9). Patients taking brofaromine had a significantly greater change from baseline on the LSAS than did patients taking placebo. A significantly greater percentage of the brofaromine patients (50%) than the placebo patients (19%) were rated much or very much improved at end point on the CGI Scale. Mean LSAS scores decreased from 81.8 at baseline to 62.6 at end point for brofaromine and from 79.8 to 70.7 for placebo. Despite the superiority of brofaromine over placebo, its treatment efficacy in this trial may be characterized as modest because the end-point LSAS score of 62.6 is still in the clinical range.

RIMAs were initially seen as promising alternatives to phenelzine and tranylcypromine. They seem to be safer and better tolerated than nonreversible MAOIs because they allow for the dietary restrictions to be greatly relaxed or even eliminated. However, the evidence at hand suggests that RIMAs are also less effective. Moclobemide is not marketed in the United States, and brofaromine development was stopped by the manufacturer during the treatment trials for reasons unrelated to the efficacy or safety of the drug in social phobia, and it is not currently marketed.

Selegiline

Simpson et al. (1998b) conducted an open trial of selegiline, a selective MAO-B inhibitor, in 16 patients with social phobia. The dose of selegiline was fixed at 5 mg twice a day. Nine patients completed the trial. Two patients dropped out because of side effects, and one had to stop selegiline because of the need to take medications that could cause toxic interactions with selegiline. Four patients were lost to follow-up. Only three patients were considered responders, with an average improvement of 33% in the LSAS score, suggesting only moderate efficacy for low-dose selegiline. Further research is needed to establish whether selegiline is more efficacious at higher, nonselective doses.

Selective Serotonin Reuptake Inhibitors

The success of SSRIs in the treatment of depression and their favorable side-effect profile have stimulated

clinicians to find new applications for these medications. The usefulness of the MAOI class of antidepressants in the treatment of social phobia and the improvement in social functioning in patients whose major depression was successfully treated with SSRIs encouraged researchers to systematically study the use of SSRIs in social phobia. Paroxetine is currently the only drug approved by the U.S. Food and Drug Administration for the treatment of social phobia.

Paroxetine

Stein et al. (1996) conducted an 11-week open-label study of paroxetine in the treatment of generalized social phobia in 36 patients. The target dosage was 50 mg/day, and patients were withdrawn from the study if they were unable to tolerate a minimum of 20 mg/day. At a mean dosage of 47.9 mg/day (SD=6.2), 23 of the 30 patients who completed the study were considered responders on the basis of a clinician rating of much or very much improved on the CGI Scale. LSAS scores decreased from 75.1 (SD=25.4) at baseline to 37.2 (SD=32.5) at the end of the open phase. Sixteen responders were randomized to an additional 12 weeks of paroxetine (with no dose change) or placebo (after a 1-week taper period on 20 mg/day) on a double-blind basis. One of the eight patients taking paroxetine relapsed, compared with five of the eight taking placebo.

This study was followed by a 12-week randomized clinical trial of 187 patients with generalized social phobia (Stein et al. 1996). The initial dose of paroxetine was 20 mg/day, with weekly increases of 10 mg permitted after the second week of treatment, up to a maximum of 50 mg/day. Response was defined as a score of 1 or 2 on the CGI Scale. Fifty-five percent of the patients receiving paroxetine and 24% of those receiving placebo were classified as responders. Patients taking paroxetine (n=94) had greater mean improvement from baseline than did those taking placebo (n=93) on the LSAS (30.6 vs. 14.4) and the Sheehan Disability Inventory social life (2.7 vs. 1.4) and work subscales (1.4 vs. 0.7).

These findings recently have been confirmed by another large multicenter 12-week trial (N=323). In a double-blind, placebo-controlled study, Baldwin et al. (1999) found a response rate of 66% in the paroxetine group and 32% in the placebo group.

In a third study conducted in Sweden by Allgulander and colleagues (1999), 92 patients were randomized to paroxetine or placebo for 3 months. Patients were started at 20 mg/day of paroxetine or placebo, and the dosage was increased by 10 mg/day every week. At the end of the study, 70% of the patients on paroxetine and 8% of the patients on placebo had a CGI Scale score of much or very much improved and were considered responders.

Fluoxetine

There have been several reports of open treatment of social phobia with fluoxetine, but no placebo-controlled studies have been published to date. Sternbach (1990) reported on the use of fluoxetine in two patients. The first of these had recently discontinued lorazepam and amitriptyline because of alcohol abuse. The second patient had failed 2 years of psychodynamic and behavior therapy. Both patients responded quickly to fluoxetine.

Schneier and colleagues (1992) reported on 12 patients with social phobia (10 with generalized type and 2 with nongeneralized type) treated with fluoxetine at a starting dose of 5–20 mg/day. Fifty-eight percent of the patients (5 with generalized type and the 2 with nongeneralized type) improved much or very much on the CGI Scale. In 3 patients, treatment with fluoxetine appeared as effective as phenelzine had been in the past but with fewer side effects. In several fluoxetine responders, prior treatment with benzodiazepines, buspirone, or β-blockers had been ineffective.

Black et al. (1992) studied the response of 14 patients with generalized social phobia to fluoxetine. The mean daily dose was 41.4 mg/day (range=10–100 mg/day). Ten patients (71%) showed moderate or marked improvement. Tolerance was good in general, although 2 patients needed slow titration, and 2 other patients were unable to tolerate more than 10 mg/day of fluoxetine Three patients who had been taking phenelzine previously preferred the fluoxetine treatment because of similar efficacy and much better tolerated side effects.

Van Ameringen et al. (1993) treated 16 patients with generalized social phobia with fluoxetine, 20–60 mg/day. Most patients also had a comorbid diagnosis of another anxiety or affective disorder. Three patients dropped out because of side effects. Of the remaining 13, the authors classified 10 as responders and 3 as nonresponders. Two were greatly improved, 6 experienced large improvement, and 2 showed moderate improvement.

Fluvoxamine

van Vliet et al. (1994) conducted a 12-week placebo-controlled study of fluvoxamine in 30 patients with social phobia. Fluvoxamine was started at 50 mg/day and

gradually increased to 150 mg/day, depending on tolerance to side effects. Efficacy was measured with the LSAS, Symptom Checklist–90 (SCL-90), Hamilton Anxiety Scale, and STAI. One patient taking fluvoxamine dropped out because of nausea, and 1 patient taking placebo dropped out because of lack of efficacy. At the end of the study, patients taking fluvoxamine showed statistically significant improvement on all scales, compared with the placebo group. A 50% reduction in the LSAS score was used as a criterion; 7 of the 15 patients (47%) taking fluvoxamine and 1 of the 15 (7%) taking placebo were classified as responders to treatment. Fourteen of the 15 patients (93%) taking fluvoxamine chose to enter an additional 12-week continuation phase. Further improvement was seen in general anxiety and in both subscales of the LSAS.

Fluvoxamine (mean dose=202 mg) also was superior to placebo in the treatment of social phobia in a multicenter randomized trial (N=92) (Stein et al. 1999). Significantly more patients responded to fluvoxamine (43%) than to placebo (23%).

Sertraline

Katzelnick et al. (1995) conducted a placebo-controlled crossover trial of 12 patients. The patients were randomly assigned to receive either sertraline (n=6) (50–200 mg/day, flexible dosing) or placebo (n=6) for 10 weeks, followed by taper and no treatment for 2 weeks. The patients were subsequently crossed over to the other treatment for another 10 weeks. Sertraline was started at 50 mg and increased 50 mg/day every 2 weeks if no treatment response was seen, unless the patient was unable to tolerate it. The mean daily dose at the end of sertraline treatment was 133.5 mg/day (SD = 68.5, range=50–200 mg/day). The main outcome measure was the LSAS. A statistically significant improvement on the LSAS was found with sertraline but not with placebo. The mean change in total score with sertraline was 22.0 (SD=17.3), compared with 5.5 (SD = 15.8) for placebo. Four patients were rated markedly improved and 2 patients were rated moderately improved while taking sertraline, compared with 1 patient rated markedly improved while taking placebo. One patient dropped out while taking sertraline because of side effects (anxiety and insomnia), and another dropped out 1 week after crossover to placebo for lack of efficacy. Patients who received sertraline first did not return to their high baseline level of symptoms when crossed over to placebo. Additionally, 3 responders who stopped taking sertraline after treatment completion relapsed within the following 6 weeks. Although no carryover effects were detected in the statistical analyses, this may have been caused by the lower statistical power associated with such a small sample size.

In a larger, controlled trial, Van Ameringen et al. (2001) randomized 204 patients to sertraline or placebo for a period of 20 weeks. The maximum allowed dosage was 200 mg/day. Sertraline was superior to placebo, with response rates of 53% versus 29% in the intent-to-treat (ITT) sample at the end of 20 weeks.

In summary, because of their favorable side-effect profile, SSRIs can be considered a possible first-line treatment for social phobia. Although no direct comparisons of SSRIs and MAOIs have been done, SSRIs may be as efficacious as, but better tolerated than, MAOIs in the treatment of social phobia. Most patients can tolerate regular starting doses without experiencing the hyperstimulation common in panic disorder. We believe it is reasonable to raise the dose as tolerated over a 6- to 8-week trial before considering alternatives.

Benzodiazepines

Since the development of chlordiazepoxide, benzodiazepines are known to have anxiolytic properties. Benzodiazepines had been shown useful in the treatment of generalized anxiety disorder and panic disorder. A logical extension was to assess their usefulness in social phobia. However, the first reports of the efficacy of benzodiazepines for social phobia only appeared in the literature in the late 1980s (Deltito and Stam 1989; Lydiard et al. 1988). Even though clinical experience suggests that benzodiazepines may be effective when used on an as-needed basis for discrete social fears, systematic studies (i.e., clinical trials) have been conducted only for standing-dose treatment.

The most studied benzodiazepines are clonazepam and alprazolam. Several open trials with clonazepam have obtained positive results. Versiani et al. (1989) treated 40 patients with social phobia over 8 weeks. Statistically significant decreases in the CGI Scale severity and LSAS scores were noted between baseline and posttreatment assessment. Munjack and colleagues (1990) compared 10 patients treated with clonazepam with 10 who received no treatment, matching them for baseline severity. Of the clonazepam patients, 3 were very much improved, 3 were much improved, 3 were minimally improved, and 1 was unchanged. In the no-treatment group, 1 was markedly improved, and 1 was mildly improved. The clonazepam group also was superior to the no-treatment group on the LSAS and self-ratings of social anxiety. However, scores of social disability did not change.

Ontiveros and Fontaine (1990) treated five patients with clonazepam at an average dosage of 3 mg/day; all patients improved. Reiter et al. (1990) treated 11 patients with clonazepam. Six were very much improved, 1 was much improved, and 2 were minimally improved.

Following those results, clonazepam showed efficacy in a 10-week placebo-controlled study of 75 patients (Davidson et al. 1993). The mean dose of clonazepam at end point was 2.4 mg/day (range = 0.5–3 mg/day). At the end of the treatment, 78% of the patients taking clonazepam were classified as responders according to the CGI Scale, compared with 20% taking placebo. Drug effects were evident on performance and generalized social anxiety, on fear and phobic avoidance, on interpersonal sensitivity, on fears of negative evaluation, and on disability measures. Prior to this double-blind study, Davidson had conducted an open trial with 26 patients treated for an average of 11.3 months (range = 1–20 months). At the end of the trial, 42% of the patients were very much improved, 42% were much improved, and 15% were minimally or not improved.

Two open trials and one double-blind study of alprazolam in social phobia have been done. In the first open trial, Lydiard and colleagues (1988) administered alprazolam, in dosages ranging from 3 to 8 mg/day, to four patients. All four patients had moderate to marked reduction of their symptoms. One of the patients who had an initial partial response had a full response when phenelzine was added. The duration of the treatment was not reported. Reich and Yates (1988) treated 14 patients over 8 weeks. The mean dosage of alprazolam was 2.9 mg/day (range=1–7 mg/day). Ten patients were very much improved and four much improved on the CGI Scale. One week after drug discontinuation, however, symptoms returned to baseline. It was unclear whether that was due, at least in part, to withdrawal symptoms from alprazolam. In the only double-blind study of alprazolam, Gelernter et al. (1991) compared phenelzine, alprazolam, placebo, and CBT. The mean alprazolam dose was 4.2 mg/day (SD=1.3). Response was defined as a posttreatment FQ score equal to or below those of normative samples. Only 38% of the patients taking alprazolam were considered responders at 12 weeks. Patients were reassessed 2 months after discontinuation of alprazolam. In most cases, symptoms had returned, suggesting the low durability of already limited gains. Given the time lapsed since the discontinuation of the drug, it is unlikely that those symptoms represented benzodiazepine withdrawal.

Use of bromazepam has been reported in only one study. Versiani et al. (1989) treated 10 patients in an 8-week open trial. The mean dose was 26.4 mg/day (SD=4.9). CGI Scale severity scores decreased from a baseline 5.0 (SD=0.8) to 1.3 (SD=0.5) at the end of treatment. The LSAS score improved from a baseline 69.3 (SD=20.5) to 15.8 (SD=9.1) at week 8.

In summary, eight open and two placebo-controlled trials have studied the efficacy of benzodiazepines in social phobia. All open trials suggested that benzodiazepines may be useful in the treatment of social phobia, but the results of the double-blind trials were mixed, with clonazepam, but not alprazolam, being superior to placebo. Whether those differences are due to true differential efficacy or are related to study design and sampling requires further examination. Both studies showed high rates of relapse after discontinuation, but this may be reduced by a slow taper. Benzodiazepines also may be helpful on an as-needed basis for performance anxiety. The benefit of decreased anxiety must be balanced with the risk of sedation interfering with the quality of performance.

β-Adrenergic Blockers

β-Adrenergic blockers came into use initially as a treatment for cardiac conditions and subsequently showed efficacy in the treatment of essential tremor. Later studies showed a connection between anxiety, signs and symptoms of peripheral arousal, and increased plasma levels of norepinephrine. This led to β-blocker trials in nonclinical samples of performers with high levels of anxiety (it is likely that those individuals currently would receive diagnoses of social phobia, nongeneralized subtype). The results of those trials seemed to indicate that β-blockers were successful in decreasing the autonomic manifestations of anxiety. β-Blockers are currently used on an as-needed basis for nongeneralized social phobia, based on anecdotal evidence from performers with social phobia. The controlled trials of β-blockers for social phobia have used standing doses and combined patients with generalized and nongeneralized social phobia. Although the results suggested that β-blockers are not effective in the treatment of the generalized type, the subsamples of patients with nongeneralized subtype have been too small to perform meaningful analysis.

Falloon et al. (1981) conducted a study of social skills training (SST) combined with either propranolol or placebo for patients with generalized social phobia. No differences were found between the groups. However, results were difficult to interpret because of small sample size and lack of a drug-only group.

Gorman et al. (1985) conducted an open trial of atenolol in 10 patients with social phobia. The number of patients with nongeneralized or generalized social phobia was not reported. Five patients had a marked reduction in social phobia symptoms, and 4 reported moderate reduction, as assessed by clinicians and patients. Medication generally was well tolerated.

However, in the aforementioned double-blind study of phenelzine (Liebowitz et al. 1992), 30% of the patients taking atenolol responded, compared with 23% taking placebo, a nonsignificant difference. The mean dosage of atenolol was 97.6 mg/day (SD = 10.9). Some further improvement occurred in the 8-week continuation phase but still was not significantly different from placebo. The nongeneralized social phobia subgroup was too small to perform meaningful separate analysis.

Similarly, Turner at al. (1994) included 72 patients in a 12-week study of atenolol (25–100 mg/day) versus flooding versus placebo. Twenty-five were given atenolol, 26 were assigned to flooding, and 21 were given placebo. Patients who received behavior therapy were seen for 90 minutes twice a week for the first 2 months and once a week for the last month, for a total of 20 sessions. Flooding was superior to atenolol, which was not superior to placebo. On a composite index of improvement, 89% of the patients who received flooding improved, compared with 47% of the group that received atenolol and 44% of the placebo group. Six months posttreatment, 9 of the 25 atenolol patients and 6 of the 26 flooding patients were lost to follow-up. However, those who were assessed had maintained most of the gains.

β-Blockers have not been proven superior to placebo in controlled clinical trials. However, anecdotal experience suggests that they are effective for specific and circumscribed performance anxiety, especially for patients with prominent symptoms of sympathetic hyperarousal such as palpitations and tremor. β-Blockers have the advantage over benzodiazepines of rarely impairing concentration or coordination. Nonselective β-blockers (affecting both β_1 receptors in the heart and β_2 receptors that mediate tremor), such as propranolol or nadolol, may in theory be more effective than those selective for the β_1 receptor, such as atenolol or metoprolol, although this remains to be empirically tested (Schneier 1995). Patients may be instructed to try a test dose at home, to ensure that the degree of β-blockade is sufficient and that untoward side effects will not develop during the performance. Most healthy individuals tolerate propranolol quite well, especially because the sympathetic arousal of anxiety will partly compensate for the hypotensive effects. Propranolol (10–40 mg) taken 45–60 minutes before the performance is sufficient for most patients.

Other Medications

Buspirone

Some studies have shown that the anxiolytic effects of buspirone can be as effective as those of benzodiazepines in the treatment of generalized anxiety disorder, with less addiction liability. Buspirone is an azaspirone that acts as a full agonist on the serotonin type 1A ($5\text{-}HT_{1A}$) autoreceptor and as a partial agonist on the postsynaptic $5\text{-}HT_{1A}$ receptor. Positive results of the trials with SSRIs for social phobia stimulated further research with drugs that have a serotonergic effect.

Munjack et al. (1991) conducted a 12-week open trial of buspirone in 17 patients with generalized social phobia. Eleven patients completed the trial, receiving an average of 48 mg/day. Of those who completed the trial, 4 (36%) reported marked improvement, 5 (45%) reported moderate improvement, and 2 (18%) reported minimal improvement. The overall response rate (defined as marked or moderate improvement) was 53% of the original sample.

Schneier et al. (1993) conducted another 12-week open trial with 21 patients. Seventeen completed at least 2 weeks of treatment and were included in the analysis. The response rate in this study (47%) was similar to that in Munjack and colleagues' study. Interestingly, responders received a higher average dose of buspirone than did nonresponders (56.9 vs. 38.3 mg/day).

Clark and Agras (1991) treated 34 musicians with social phobia with buspirone and placebo plus CBT in a 2×2 design. The average dose of buspirone was 32 mg. Buspirone was not superior to placebo, but CBT was superior to either buspirone or placebo without psychotherapy.

van Vliet et al. (1997) investigated the efficacy of buspirone in a 12-week placebo-controlled study. Thirty patients with social phobia were treated with fixed-dose buspirone (30 mg/day) or placebo. Efficacy was measured with the LSAS and Hamilton Anxiety Scale. Response was defined as 50% or more reduction in LSAS scores. Only one patient receiving buspirone and another taking placebo were classified as responders. A subjective and clinically relevant improvement was reported by four patients taking buspirone and two taking placebo. There were no statistically significant differences between the two treatment groups on any of the outcome measures. Of note, the fixed dose of buspirone

was lower than the mean dose taken by nonresponders in Schneier and associates' open trial. No correlations were found between baseline MHPG and any of the outcome measures.

Neither of the two controlled trials of buspirone was able to show the efficacy of buspirone as monotherapy for social phobia, in contrast with the promising results of the open trials. Additionally, the dosage of buspirone needed seems to be in the upper range (60 mg/day), which may limit its usefulness on the basis of side effects, such as nausea or headache. It may, however, augment partial responses to SSRIs.

Venlafaxine

An open trial reported on 10 patients with social phobia treated with venlafaxine in doses ranging from 75 to 300 mg/day (Emmanuel et al. 1995). Two patients were not entered in the analysis because of incomplete data. Of the remaining 8 patients, 4 improved much or very much on the CGI Scale. Patients experienced a high prevalence of side effects, including nausea, decreased libido, erectile dysfunction, and urinary difficulty. Although further research is warranted on venlafaxine as a treatment for social phobia, these pilot data seem to indicate that venlafaxine may not be as useful as phenelzine or SSRIs in the treatment of this disorder.

Tricyclic Antidepressants

Based on its efficacy in the treatment of panic disorder, imipramine has been studied in social phobia. The results of the trials indicated that imipramine is ineffective in the treatment of social phobia. Zitrin et al. (1983) found no improvement in patients with social phobia treated with imipramine. Benca et al. (1986) reported on two patients with social phobia who showed a rapid resolution of symptoms after treatment with imipramine (250 mg/day). Both patients had panic attacks and mitral valve prolapse, rendering them rather atypical. A recent open trial by Simpson et al. (1998a) also found that imipramine was ineffective in social phobia. The authors treated 15 patients with imipramine at a mean dose of 176.4 mg/day. Nine patients completed the study; 6 dropped out because of side effects. The mean change in the LSAS score was 15%. The response rate, defined as much or very much improved on the CGI Scale, was 20%.

In two studies, clomipramine was used in the treatment of social phobia. Beaumont (1977) treated a mixed population of patients with social phobia and agoraphobia, but only modest improvement was seen. The heterogeneity of the sample and the use of non-DSM-III (American Psychiatric Association 1980) criteria made the interpretation of the data difficult. In a later study, Pecknold et al. (1982) combined clomipramine with L-tryptophan and compared it with clomipramine plus placebo. No additional benefit was found from the addition of L-tryptophan.

Clonidine

In only one report, a patient with severe blushing who had not responded to propranolol, alprazolam, or phenelzine responded rapidly to clonidine (Goldstein 1987).

Bupropion

Emmanuel et al. (1991) successfully treated one patient with bupropion (300 mg/day). The mechanism of action of bupropion seems to be a combination of noradrenergic and dopaminergic effects. Assessment of this case was complicated by the presence of comorbid depression in the patient. Others have reported negative results in a limited number of patients (Potts and Davidson 1995).

Medication Selection

Until 1985, little was known about psychopharmacotherapy for social phobia. At present, evidence indicates that several drugs may be useful in the treatment of that disorder. Twenty double-blind, placebo-controlled studies have been published to date, evaluating 10 drugs (phenelzine = 4, brofaromine = 3, moclobemide = 4, clonazepam = 1, alprazolam = 1, atenolol=2, fluvoxamine = 2, sertraline = 2, buspirone = 2, paroxetine = 2; some studies included more than one drug in their design) (Table 24–1). The drugs appeared superior to placebo in all studies except for atenolol (in both trials), buspirone (in both trials), moclobemide (not superior to placebo in two of the four double-blind trials), and alprazolam (not clearly superior to placebo in the only published double-blind trial).

Although the demarcation of "normal" shyness and social phobia may be unclear, clinically it seems reasonable to offer treatment, including pharmacotherapy, when significant distress or impairment is present, as is required for a DSM-IV-TR (American Psychiatric Association 2000) diagnosis of social phobia. Some patients may be surprised by the idea of taking medication for a problem that they see as a long-standing personality

TABLE 24–1. Summary of placebo-controlled studies of pharmacotherapy in social phobia

Drug	Number of studies	Efficacy	Main side effects	Observations
Phenelzine	4	+++	Sleep disturbances, hypotension, risk of hypotension	Risk of hypertension
RIMAs	7	++	Insomnia, daytime sedation, dry mouth, light-headedness	Not marketed in United States
SSRIs	5	+++	Sexual dysfunction, nausea, restlessness	
Benzodiazepines	2	+++	Sedation, impaired coordination, memory impairment	Slow taper maintains gains more than fast taper
Atenolol	2	– –	Bradycardia and hypotension (rare)	Probably useful in performance anxiety
Buspirone	2	– –	Nausea, dizziness, insomnia	Can be used with SSRIs

Note. –– = not efficacious; ++ = moderately efficacious; +++ = very efficacious. RIMAs=reversible inhibitors of monoamine oxidase–A; SSRIs=selective serotonin reuptake inhibitors.

trait. Several complementary lines of reasoning can be used to support the use of pharmacotherapy in the treatment of social phobia (Liebowitz and Marshall 1995):

1. The research literature has clearly confirmed the efficacy of several drug classes in the treatment of social phobia.
2. Physical symptoms of anxiety can interfere with optimal performance and ultimately encourage avoidance of feared situations; thus, medications that can directly decrease anxiety may help improve performance in social or professional situations.
3. Concerns about social comparisons and shyness are likely to be strongly biologically based, given the evolution of humans as a group-living species and evidence of a significant genetic contribution from twin and family studies.

The choice of a pharmacological agent for a specific patient depends on the diagnostic subtype of social phobia, presence of comorbidity, and preference of the patient. Cases of nongeneralized social phobia, in which feared performance situations arise only occasionally and predictably (e.g., musicians, professional presentations), can be treated initially with β-blockers used on an as-needed basis. If β-blockers are ineffective or are contraindicated, an alternative is the use of a benzodiazepine. Unfortunately, the doses needed to control anxiety may cause sedation and sometimes interfere with performance.

In cases of nongeneralized social phobia with frequent unexpected performance situations or generalized social phobia, irreversible MAOIs or SSRIs may be useful. Irreversible MAOIs and SSRIs may be equally effective, but SSRIs generally are better tolerated. Options include recommending a trial of SSRIs and switching to an irreversible MAOI in case of failure after an appropriate washout period, or choosing an MAOI as a first option if its side effects and limitations do not appear too onerous to the patient. High-potency benzodiazepines, such as clonazepam, are another option. At present, no systematic information is available on how to treat nonresponders or even to decide when a patient should be classified as such. However, it seems reasonable to allow 6–8 weeks for a trial with a drug. If no improvement is seen, other options should be considered, but partial improvement may continue to build over several months. Clinical experience suggests that benzodiazepines and β-blockers on an as-needed basis can augment response to an MAOI or SSRI, and many patients are treated with combination medication regimens (Liebowitz and Marshall 1995). It is important to keep in mind the risk of increased hypotension when combining MAOIs and β-blockers. MAOIs and SSRIs should never be combined because of the risk of serotonergic syndrome. Buspirone also seems to be a useful augmentation strategy for SSRIs.

Although the integration of pharmacotherapy and psychosocial treatment has been insufficiently studied, it seems to benefit many patients. To assess the real benefit of any treatment, it may be necessary to encourage patients to enter previously feared situations to test progress and monitor improvement (Liebowitz and Marshall 1995). The addition of CBT to pharmacotherapy may augment improvement and result in more enduring benefits. The addition of pharmacotherapy to CBT may hasten and increase treatment response and facilitate exposure to feared situations. However, further research is needed to determine which patients are candidates for combined treatment.

It is helpful to help set reasonable expectations for response. In the short term, we expect to see symptomatic relief and improved social relatedness and performance. Over the long term, we hope to see increased vocational or educational functioning and improved capacity for more intimate relationships of all kinds. Although some patients have a complete remission of symptoms, more commonly seen is a substantial reduction without altering the typical patient's self-perception as someone who tends to be shy.

Treatment in Children

Although social phobia often begins in childhood, no studies have specifically addressed pharmacotherapy for social phobia in children. Fairbanks et al. (1997) treated mixed anxiety disorders that had not responded to psychotherapy in a group of children. Treatment with fluoxetine was started at 5 mg/day and increased weekly by 5–10 mg/day for 6–9 weeks until improvement occurred or to a maximum of 40 mg (children younger than 12 years) or 80 mg (adolescents). Of the 10 children with social phobia, 8 were much improved as assessed by the CGI Scale. Simeon and Ferguson (1987) treated avoidant and overanxious disorders with open-label alprazolam in a group of children. Both child- and parent-rated anxiety symptoms decreased for both diagnostic groups, and cognitive functioning also improved with treatment. Subsequently, Simeon et al. (1992) conducted a placebo-controlled study of alprazolam compared with placebo in 30 children with avoidant and overanxious disorders but failed to find significant differences.

There are also reports of medication treatment of selective mutism, a condition that recently has been shown to greatly overlap with social phobia. In the first study, a 12-year-old girl who had failed two trials of psychotherapy was successfully treated with fluoxetine (20 mg) (Black et al. 1992). In the other report, a 7-year-old girl who had failed to respond to previous trials of behavior therapy and amantadine (200 mg/day) responded to phenelzine (52.5 mg/day). Medication was tapered and withdrawn by week 24, with gains maintained at 5-month follow-up. More recently, Black and Uhde (1994) conducted a double-blind, placebo-controlled study of fluoxetine for the treatment of selective mutism. Six patients were assigned to the fluoxetine group and nine to the placebo group. Patients in the treatment group were significantly more improved than placebo-treated patients on parent's ratings of mutism change and global change. Clinician and teacher ratings did not show significant differences between treatment groups. Medication was well tolerated. Dummit et al. (1996) treated selective mutism in 21 children in a 9-week open trial of fluoxetine. The mean dose was 28.1 mg (range = 10–60 mg). After fluoxetine treatment, 76% were improved. Side effects were similar to those generally experienced by adults taking SSRIs.

Early treatment of social phobia in children holds theoretical promise for reduction of long-term morbidity. At present, however, the place of pharmacotherapy for treatment of social phobia remains unclear.

Future Directions

As our knowledge about social phobia and its treatment expands, new questions arise that open new areas of research. Frequently, patients are interested in knowing how long they should be taking medication. The current data seem to indicate that taper of the medication carries an increased risk of relapse. Whether longer treatment periods may decrease the danger of relapse is unknown and remains a topic of research for the future.

Another important area of current and future research is the integration of basic and clinical research. Until now, the introduction of new drugs in the treatment of social phobia generally has been based on symptom overlap with other disorders. Improved animal models of shyness and submissiveness and increased understanding of the brain chemistry and circuitry may help develop more specific drugs.

A third area of potential research is that of treatment selection. Which patients will benefit from psychotherapy and which patients are more suitable for pharmacotherapy? What are the predictors of response for those modalities? If medication is chosen, what are the best ways to match the drug to the patient?

A related but scarcely researched area is the use of combined treatment. Only two studies have examined that issue (Clark and Agras 1991; Falloon et al. 1981). As noted earlier in this chapter, there are some indications that MAOIs tend to work faster than psychotherapy. However, the therapeutic effects of cognitive-behavioral group therapy seem to last longer than those of phenelzine after treatment discontinuation. Further work on this area is warranted. More refined taper strategies or combinations of pharmacotherapy and psychotherapy may allow for rapid-onset and long-term therapeutic effects.

As already noted, the literature on the treatment of social phobia in children is limited. There is a need and an opportunity for child pharmacologists to delineate what are the appropriate treatment strategies for children with social phobia and potentially related disorders.

Finally, the relation between childhood anxiety and development of adult psychopathology also deserves further study. Children with behavioral inhibition and social avoidance frequently develop social phobia as they reach adolescence or early adulthood. Could early pharmacological treatment of those symptoms prevent the development of social phobia in adulthood?

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Psychotherapy for Social Phobia

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Before social phobia was introduced into DSM-III (American Psychiatric Association 1980), few studies had investigated the effectiveness of psychosocial approaches to the treatment of debilitating social anxiety. Since that time, the number of studies that have examined the efficacy of psychological treatments for social phobia has increased dramatically. The treatment literature has become increasingly sophisticated and has been extended to special populations such as children and adolescents. Furthermore, factors contributing to successful outcomes are being explored. A growing body of evidence suggests that treatments, including exposure and cognitive restructuring, are effective and that gains made with these treatments are durable.

Cognitive-Behavioral Approaches

Exposure Treatments

Exposure has long been recognized as an essential ingredient in the most effective treatments for specific phobias, agoraphobia, and obsessive-compulsive disorder (Barlow and Wolfe 1981). Behavioral models of social anxiety assert that exposure provides the opportunity for habituation to the feared stimulus and increases contact with reinforcers for nonphobic behavior (McNeil et al. 2001). Cognitive models of social anxiety propose that exposure provides the opportunity for the collection of powerful corrective information, which facilitates the modification of dysfunctional beliefs and the alteration of information-processing biases, thereby decreasing anxiety (e.g., D.M. Clark and Wells 1995; Rapee and Heimberg 1997). In fact, abundant research shows that exposure effectively reduces social anxiety (e.g., Fava et al. 1989), although there is some question as to the durability of gains when exposure is administered alone (Heimberg and Juster 1995). In comparative studies, exposure has proven superior to progressive relaxation training (Al-Kubaisy et al. 1992; Alström et al. 1984), pill placebo (Turner et al. 1994b), waiting-list control (Butler et al. 1984; Newman et al. 1994), and a control therapy consisting of education, self-exposure instructions, and unspecified anxiolytic medication (Alström et al. 1984).

Most often, treatments for social phobia have combined exposure with cognitive techniques, and the efficacy of this approach is discussed in the next section. A potentially important exception, however, is social effectiveness training, a multicomponent treatment package that combines exposure with social skills training and education in a mixture of group and individual formats (Turner et al. 1994a). Results of a pilot study with 17 patients with generalized social phobia (13 who completed treatment) indicated significant improvements in self-reported and clinician-rated social anxiety as well as anxiety experienced during behavior tests. At posttreatment, 84% of those who completed the study

were classified as having achieved either moderate or high end-state functioning. Eight of the 13 patients completing this study participated in a 2-year follow-up (Turner et al. 1995). Self-report and clinician ratings indicated maintenance of treatment gains or additional improvement during the follow-up interval, although 3 of the 8 patients had received additional treatment. These initial studies of social effectiveness training are promising, but controlled treatment trials are necessary to evaluate its efficacy and to determine whether social skills training adds any benefit beyond that of exposure alone.

Combined Cognitive Therapy and Exposure

The core feature of social phobia is fear of negative evaluation. It has been observed that many patients with social phobia regularly expose themselves to feared social situations but do not experience anxiety reduction (Butler 1985). This may occur because simple exposure to feared social situations provides little information about the potential or reality of negative evaluation, given that social feedback often may be indirect or ambiguous. Simple self-exposure may not provide patients with exposure either to the disapproval they fear or, more important, to the information that other people are seldom as critical as they expect (Butler 1985). Contemporary cognitive models of social phobia propose that anxiety is largely maintained by dysfunctional beliefs and biased information-processing strategies; therefore, successful treatment will be associated with modification of these cognitive problems (e.g., D.M. Clark and Wells 1995; Rapee and Heimberg 1997).

With few exceptions, most cognitive therapies for social phobia include systematic exposure to feared social situations and behavioral experiments (Juster and Heimberg 1998). Thus, these treatments are not "purely" cognitive. A growing body of research supports the efficacy of treatments incorporating both cognitive techniques and exposure. In comparative studies, these treatments have been shown to be superior to waiting-list control groups (Butler et al. 1984; DiGiuseppe et al. 1990; Hope et al. 1995a; Kanter and Goldfried 1979), an educational-supportive control therapy (Heimberg et al. 1990, 1993, 1998; Lucas and Telch 1993), and pill placebo (Heimberg et al. 1998).

One cognitive approach is rational-emotive therapy (RET). According to Ellis (1962), individuals develop certain irrational beliefs through experiences with the family and other societal institutions. These beliefs then cause and sustain negative emotional states. A particularly common irrational belief is that one should be completely competent, adequate, and achieving in order to be viewed as a worthwhile person. Individuals with social phobia may easily be conceptualized as clinging to this irrational belief, along with others discussed by Ellis (1962). The goal of RET is to confront and modify these irrational beliefs through discussion and persuasion to change the patient's fundamental ideology. RET and modified versions of RET have been shown to result in significant treatment gains among individuals with social phobia in several studies (e.g., DiGiuseppe et al. 1990; Emmelkamp et al. 1985; Mattick and Peters 1988; Mattick et al. 1989; Mersch et al. 1989). Treatment gains appear to be durable, with patients maintaining their improvements at follow-ups as long as 18 months (Scholing and Emmelkamp 1996a, 1996b).

In contrast to RET, Beck's theoretical approach asserts that negative emotions are produced by cognitive-processing errors such that patients label, interpret, and evaluate their experiences in a biased, highly personalized, overly arbitrary, or extreme manner (Beck 1976). Beck's cognitive therapy attempts to correct these errors through logic, Socratic discussion, and empirical testing of negative cognitions. The goal of therapy is to remold the patient's rigid, maladaptive rules to be more accurate, realistic, and flexible. Beck's cognitive therapy was influential in the development of cognitive-behavioral group therapy (CBGT) for social phobia (the CBGT literature is reviewed below). For the treatment of social phobia, Beck's cognitive therapy has been shown to produce treatment gains similar to those produced by RET and superior to those produced by a waiting-list control (DiGiuseppe et al. 1990).

Self-instructional training is a modified version of Meichenbaum's (1985) stress inoculation training. In self-instructional training, patients observe and record the negative thoughts and feelings they experience in problematic situations to facilitate the development of more adaptive appraisals. They then work collaboratively with their therapist to develop coping thoughts and skills relevant to anticipating the problematic situation, engaging the situation, and thinking about the situation after it has concluded. Patients practice these coping thoughts and skills in imaginal rehearsal, role-plays, and real-life situations. In three studies, self-instructional training produced significant improvements among individuals with social phobia (DiGiuseppe et al. 1990; Emmelkamp et al. 1985; Jerremalm et al. 1986).

CBGT, a treatment protocol developed specifically for social phobia (Heimberg and Becker, in press), has been the object of several studies. The first 2 sessions of CBGT are devoted to teaching patients a cognitive-behavioral model of social phobia, providing a treatment rationale, and introducing cognitive restructuring concepts. The remaining 10 sessions integrate cognitive restructuring and exposure in a manner that allows patients to examine and challenge their negative thoughts before, during, and after engaging in role-plays of feared social situations within a group setting. These integrated exposures serve as behavioral experiments that allow patients to test the veracity of their negative thoughts. Exposures outside of group are an integral part of homework assignments, and patients are taught to use the cognitive restructuring procedures practiced in group in conjunction with these exposures.

Heimberg et al. (1985) investigated the efficacy of an early version of CBGT, which differed from the current version primarily in that it included imaginal exposures and placed less emphasis on cognitive restructuring prior to exposures. Seven patients with DSM-III social phobia participated in this study, which used a multiple baseline design. After treatment, patients reported less social anxiety, decreased fear of negative evaluation, and greater satisfaction with their performance in a behavior test. These gains were maintained over 3- and 6-month follow-up periods for six of the seven patients.

A later version of CBGT was compared with educational-supportive group therapy, a psychosocial treatment consisting of lectures, discussions, and support (Heimberg et al. 1990). Educational-supportive group therapy was designed to control for therapist attention, treatment credibility, and patient expectancies. Forty-nine patients meeting criteria for DSM-III social phobia were treated. Patient ratings confirmed that treatment credibility and outcome expectations were similar for CBGT and educational-supportive group therapy. Following treatment, clinical assessors assigned 75% of the CBGT patients, but only 40% of the educational-supportive group therapy patients, phobic severity ratings below the level defined as clinically impaired. After treatment, CBGT patients also reported less anxiety before and during an individualized behavior test than did educational-supportive group therapy patients. Both groups showed similar improvement on self-report measures after treatment, but 6-month follow-up assessments showed an attenuation of these gains for educational-supportive group therapy patients. In contrast, CBGT patients maintained their gains on self-report measures at 6-month follow-up and remained more improved than educational-supportive group therapy patients on both assessor and behavior test anxiety ratings.

Nineteen of these patients participated in a long-term follow-up study in which the follow-up interval ranged from 4.5 to 6.25 years (Heimberg et al. 1993). Unfortunately, follow-up participants were less impaired before and after treatment than were nonparticipants. However, no pretreatment differences were found between CBGT and educational-supportive group therapy follow-up participants. At long-term follow-up, 89% of the CBGT patients were given phobic severity ratings below the clinical threshold by independent assessors, compared with 44% of the educational-supportive group therapy patients. Assessor ratings indicated that the CBGT patients had a level of social anxiety not much greater than that in the general population. Furthermore, CBGT patients were rated as less anxious and more socially skilled during an individualized behavior test than were educational-supportive group therapy patients.

Lucas and Telch (1993) compared the effectiveness of CBGT, educational-supportive group therapy, and an individual version of the CBGT protocol in the treatment of DSM-III-R (American Psychiatric Association 1987) social phobia in 66 patients. This study replicated Heimberg and colleagues' (1990) finding that patients who received CBGT were more improved than patients who received educational-supportive group therapy. CBGT and individual cognitive-behavioral therapy (CBT) resulted in similar treatment gains, both superior to educational-supportive group therapy. However, the group protocol was more cost-effective.

Heimberg et al. (1998) recently completed a two-site study in which 133 patients were randomized to CBGT, the monoamine oxidase inhibitor phenelzine, educational-supportive group therapy, or pill placebo conditions. All treatments were delivered at each site, one known for cognitive-behavioral treatment and the other for pharmacological treatment of anxiety disorders. At the week 6 (midtreatment) assessment, independent assessors rated phenelzine patients as more improved and less anxious than patients in all other conditions. At the 12-week (posttreatment) assessment, the independent assessors rated 75% of the CBGT patients, 77% of the phenelzine patients, 35% of the educational-supportive group therapy patients, and 41% of the placebo patients as treatment responders (either moderately or markedly improved). Thus, after 12 weeks of treatment, CBGT and phenelzine produced similar proportions of treatment responders, and both

active treatments had higher proportions of responders than did placebo or educational-supportive group therapy conditions. After 12 weeks, however, phenelzine patients were significantly more improved than CBGT patients on some measures. It is encouraging that there was no significant site by treatment interaction, suggesting that these treatments can be efficacious at facilities with differing theoretical orientations.

After the 12 weeks of acute treatment described above (Heimberg et al. 1998), patients who had a positive response to either CBGT or phenelzine received monthly maintenance treatment for 6 months, which was followed by a 6-month treatment-free follow-up (Liebowitz et al. 1999). Over the course of maintenance and follow-up, patients who had received CBGT were less likely to relapse than were patients who had received phenelzine, and this was especially the case among patients with generalized social phobia. Thus, phenelzine may provide somewhat more immediate relief, but CBGT may provide greater protection against relapse. Our research group is currently examining whether the combination of phenelzine and CBGT produces outcomes more favorable than either treatment alone.

Do Cognitive Techniques Enhance Treatment Gains Beyond Those Attained With Exposure Alone?

Both exposure alone and the combination of cognitive interventions and exposure appear to be effective approaches to the treatment of social phobia. In recent years, research has increasingly attempted to address the question of whether cognitive interventions increase treatment gains above and beyond those produced by exposure alone.

In an early study addressing this issue, Butler et al. (1984) randomly assigned 45 patients meeting DSM-III criteria for social phobia to either exposure plus anxiety management training (Suinn and Richardson 1971), exposure plus an attention control therapy, or a waiting list. Anxiety management training is composed of relaxation, distraction, and rational self-talk. Before treatment, both exposure conditions received similar credibility ratings, but at the fourth treatment session, exposure plus control therapy received lower credibility ratings than exposure plus anxiety management. After treatment, both exposure conditions were superior to a wait-list group, as reflected by reductions in phobic severity, anxiety during a behavior test, general anxiety, and depression. Patients receiving exposure plus anxiety management training achieved lower scores than did patients receiving exposure plus control therapy on two measures of social anxiety at posttreatment and four measures of social anxiety at 6-month follow-up. In the 12 months after treatment, 40% of the patients receiving exposure plus control therapy sought additional treatment, whereas none of the patients receiving exposure plus anxiety management training did so. Although anxiety management training is a multicomponent intervention, post hoc analyses suggested that rational self-talk was the most frequently used coping technique.

Although the Butler et al. (1984) study suggested that the efficacy of exposure may be enhanced by the addition of cognitive restructuring, it had several limitations. First, because the exposure plus control therapy condition was rated as less credible than the exposure plus anxiety management condition, patient expectancies might have contributed to the observed differences. Second, cognitive restructuring was only one component of anxiety management training, making it difficult to assess whether it was actually the cognitive elements of that treatment that provided the added benefits. Third, exposure exercises may have been more effective if the therapists had accompanied patients into feared situations rather than simply advising patients how to conduct exposures between sessions (Mattick and Peters 1988).

To address these issues, Mattick and Peters (1988) randomly assigned 51 patients with DSM-III social phobia to therapist-assisted exposure with or without cognitive restructuring. In contrast to the study by Butler et al. (1984), no control intervention was added to the exposure alone condition. Both treatments were conducted in groups, and therapists accompanied patients to locations that allowed them to become engaged in fear-eliciting social interactions (e.g., eating at a cafe). In the combined exposure and cognitive restructuring condition, patients developed rational and adaptive thoughts about their phobic situations and were encouraged to actively use their cognitive restructuring skills when entering feared situations. Patients in both conditions gave similarly high ratings for treatment credibility and reported spending a similar amount of time engaging in exposure exercises. Both treatment conditions yielded posttreatment improvement, including reductions in avoidance, phobic severity, and depression. At 3-month follow-up, patients in the combined treatment group completed a greater percentage of tasks during a behavior test, reported less avoidance, and had higher scores on composite measures of improvement and end-state functioning.

In another study by the same research group, Mattick et al. (1989) randomly assigned 43 patients with DSM-III social phobia to either exposure alone, cognitive restructuring alone, combined exposure and cognitive restructuring, or waiting-list control. The three active treatment conditions resulted in more improvement than the waiting list, as assessed by percentage of tasks completed during a behavior test and self-reported phobic severity and avoidance. Patients in the active treatments gave similarly high ratings of treatment credibility. At posttreatment, patients in the exposure alone condition and the combined condition were able to complete more tasks during a behavior test than were patients in the cognitive restructuring alone condition. However, at 3-month follow-up, patients in the cognitive restructuring alone and combined conditions showed continued improvement, as measured by the behavior test. In contrast, patients in the exposure alone condition deteriorated slightly. Few differences were found among active treatments on self-report measures, and no differences were found among the three conditions on composite measures of improvement and end-state functioning.

In a similar study, Hope et al. (1995a) compared the efficacy of standard CBGT (including exposure and cognitive restructuring), exposure alone, and a waiting-list control in the treatment of 43 patients with DSM-III-R social phobia. Exposure alone was conducted in the same format as CBGT, but material relevant to a habituation model replaced the cognitive restructuring components of the treatment. CBGT and exposure alone produced equivalent credibility and group cohesion ratings. At posttreatment, CBGT and exposure alone patients were more improved than waiting-list participants, according to independent assessor ratings, social anxiety questionnaires, cognitive measures, self-rated quality of performance during a behavior test, and behavior test performance ratings assigned by independent judges. Furthermore, although not statistically significant, only 36% of the CBGT patients were classified as treatment responders by an independent assessor, compared with 70% of the exposure alone patients. Therefore, CBGT appears to have been less effective than in the other CBGT studies reviewed earlier in this chapter. Although attrition rates were not significantly different among the conditions, five patients who received CBGT dropped out, compared with only one patient who received exposure alone. Hope et al. (1995a) speculated that the reduced efficacy of CBGT might have been the result of disruption of group process caused by attrition, which was generally unrelated to therapy.

Recently, Taylor et al. (1997) randomly assigned 65 patients with DSM-III-R social phobia to either eight individual sessions of cognitive restructuring or eight sessions of the control therapy used by Butler et al. (1984). These two conditions constituted the first phase of treatment. No formal exposures were conducted as part of either of these therapy conditions. The control therapy involved free associating thoughts and memories of recent and past social encounters and was meant to control for the informal exposure inherent in cognitive restructuring. The treatments did not differ in credibility. After these initial eight therapy sessions, cognitive restructuring was superior to the control therapy, as reflected by greater reductions in social phobia severity, decreased social avoidance, and fewer negative and more positive thoughts during a behavior test. These results suggest that cognitive restructuring is not simply effective as a result of the exposure or other nonspecific aspects of therapy inherent in the procedure. Thereafter, both groups received additional sessions of exposure to determine whether cognitive restructuring would enhance the effects of subsequent exposure, as predicted by Beck et al.'s (1985) cognitive model. After this second phase of treatment, both the cognitive restructuring and the control therapy groups showed additional improvement in social phobia severity and social avoidance. After exposure, no differences were found between patients initially receiving cognitive restructuring and initially receiving the control therapy. Exposure with and without prior cognitive restructuring produced similar improvement. Thus, cognitive restructuring prior to exposure did not appear to facilitate its effectiveness.

Three recent studies used meta-analytic techniques to examine whether cognitive restructuring amplifies the effectiveness of exposure in patients with social phobia. Feske and Chambless (1995) included 12 conditions of cognitive restructuring plus exposure and 9 conditions of exposure alone. Both treatments resulted in similar attrition and yielded similar effect sizes at posttreatment and follow-up on self-report measures of social anxiety, cognitive symptoms, and depression or anxiety. Gould et al. (1997) included only studies with a control group and replicated the finding that cognitive restructuring plus exposure and exposure alone yield similar attrition rates and effect sizes. Finally, Taylor (1996) conducted a meta-analysis that compared six conditions: waiting-list control, placebo, exposure, cognitive restructuring without exposure, cognitive restructuring with exposure, and social skills training. Attrition was comparable across conditions.

The four active therapies and placebo produced greater effect sizes than did the waiting-list control; however, only cognitive restructuring combined with exposure had a significantly larger effect size than placebo.

Whether cognitive interventions significantly increase treatment gains above and beyond those produced by exposure alone remains open to debate. The results of the studies conducted to date are contradictory, and the disagreements among the studies are not easily reconciled. Several studies produced equivalent outcomes for exposure alone and exposure plus cognitive restructuring. Other studies found combined treatments to be superior on several posttreatment outcome measures and to result in greater protection against relapse or to provide additional gains during the follow-up period.

Various explanations for the disagreements among studies have been suggested. One possibility is that cognitive procedures improve the efficacy of exposure but that the effect size is moderate and therefore inconsistently detected in a literature characterized by power that is typically inadequate to detect even large effect sizes (Taylor et al. 1997). Alternatively, the inconsistencies across studies, and even across measures within studies, may reflect the possibility that some of the positive findings for the incremental benefit of cognitive restructuring may be the result of chance (Scholing and Emmelkamp 1993b). Difficulties in detecting differential changes in cognition in particular also may be an artifactual result of the measures used. Because of the relatively high correlation between questionnaire measures commonly used to assess cognition and measures of social phobia symptoms, change on measures of cognition may reflect changes in cognition, anxiety, or both (Heimberg 1994). Thus, commonly used measures of cognition may be rather nonspecific to cognitive change and, therefore, may not be specifically sensitive to changes produced by cognitive techniques. It is also possible that some patients benefit adequately from exposure alone but that for others, cognitive restructuring is necessary to produce optimal clinical outcomes, although we do not yet know what variables differentiate these two groups of patients (Scholing and Emmelkamp 1996b).

Exposure only treatments may not be as easily differentiated from combined treatments as these studies imply. That is, in their actual implementation, exposure only and combined treatments may overlap to a significant degree, making similar treatment outcomes a virtual certainty. For example, in exposure only treatment, feedback regarding patient skill, visibility of anxiety symptoms, ability to cope with anxiety, and so forth are likely aspects of therapy, although these interventions may not be labeled as cognitive by noncognitive therapists (Newman et al. 1994; Turk et al. 1999). Furthermore, whether cognitive restructuring enhances exposure may be influenced by whether it is presented as a separate module in treatment or integrated with exposure procedures (Heimberg and Juster 1995).

Scholing and Emmelkamp (1993a, 1993b) conducted two studies that examined whether cognitive therapy is more beneficial when integrated with exposure or administered as a module separate from exposure. In the Scholing and Emmelkamp (1993a) study, 30 patients with DSM-III-R social phobia who reported fear of showing anxiety symptoms were randomly assigned to exposure followed by cognitive therapy, cognitive therapy followed by exposure, or integrated cognitive-behavioral treatment. In each condition, patients completed a 4-week block of individual treatment, followed by a 4-week no-treatment phase, followed by another 4-week block of treatment. For the exposure and integrated blocks of treatment, in vivo exposures were planned and discussed but not practiced during the therapy session. Thus, integrated sessions focused on changing irrational beliefs related to home-based exposure exercises. All treatment conditions resulted in similar improvements on self-reported avoidance, negative cognitions, and somatic symptoms. Gains were maintained at 18-month follow-up, with no significant differences among treatments (Scholing and Emmelkamp 1996a). Nineteen percent of the sample received additional treatment, with no differences across conditions.

In the Scholing and Emmelkamp (1993b) study, 73 patients with generalized social phobia were randomly assigned to exposure alone, cognitive therapy followed by exposure, or integrated cognitive-behavioral treatment. Treatments were provided in blocks (as described in the previous paragraph) in either individual or group modalities. For individual therapy patients, the exposure and integrated blocks of treatment included exposures as homework but not during sessions. For group therapy patients, the exposure and integrated treatments incorporated exposures during sessions. However, discussion of maladaptive cognitions was the primary emphasis in the integrated group treatment. After the first 4-week block, integrated treatment patients had more somatic complaints than did patients in the other two conditions, but no differences were noted for avoidance or negative cognitions. The three treatment conditions resulted in similar levels of improvement af-

ter the second block of treatment and at the 3-month follow-up. The treatment modality produced minimal effect on outcome. Improvements generally were maintained for the 59 patients who participated in an 18-month follow-up (Scholing and Emmelkamp 1996b). However, this finding is qualified by the fact that, during the interim, 47% of the participants receiving exposure alone had sought additional treatment, compared with 28% of the participants receiving cognitive therapy followed by exposure and only 6% of the participants receiving integrated treatment.

These two studies generally do not support the hypothesis that cognitive restructuring is most beneficial when integrated with exposure procedures. However, an important caveat should be considered. The integrated individual treatments in both of these studies did not provide patients with the opportunity to practice their cognitive restructuring skills while confronting fear-provoking social situations in the presence of a therapist. That is, exposures were conducted by the patients alone, outside of therapy sessions, and patients essentially were asked to integrate cognitive restructuring and exposure on their own (Scholing and Emmelkamp 1993a, 1993b). Similarly, in the group modality, therapist supervision of integrated exposures within session appears to have been minimal (Scholing and Emmelkamp 1993b). In our clinical experience, many patients fail to apply cognitive restructuring skills in the heat of anxiety-provoking social interactions unless they have had considerable coaching and practice. Indeed, studies providing integrated treatment with therapist guidance have produced results superior to that of exposure alone (e.g., Mattick and Peters 1988; Mattick et al. 1989), although this finding is not without exception (e.g., Hope et al. 1995a).

Regardless of how it is produced, cognitive change may be central to optimal outcomes. Exposure alone may provide sufficient disconfirmatory information to alter dysfunctional beliefs for some patients, and cognitive change has been reported in the exposure only condition in several studies (e.g., Hope et al. 1995a; Mattick and Peters 1988; Newman et al. 1994). That is, both cognitive and behavioral procedures may be different means of achieving cognitive change. Importantly, change in fear of negative evaluation is a potent predictor of end-state functioning (Mattick and Peters 1988; Mattick et al. 1989). Finally, some studies have found treatments that incorporate a cognitive restructuring component to produce superior outcomes on cognitive indices of improvement (e.g., Butler et al. 1984; Emmelkamp et al. 1985; Jerremalm et al. 1986).

Social Skills Training

The use of social skills training in the treatment of social phobia is predicated on the assumption that socially anxious patients often have behavioral deficiencies (e.g., poor eye contact, difficulty maintaining a conversation). Presumably, these behavioral deficiencies elicit negative reactions from others, causing social interactions to be punishing and anxiety provoking for the patient (Lucock and Salkovskis 1988). The literature examining the social skills of socially anxious individuals has produced mixed results, with some studies suggesting behavioral deficiencies (Halford and Foddy 1982; Stopa and Clark 1993) and others not (J.V. Clark and Arkowitz 1975; Glasgow and Arkowitz 1975; Rapee and Lim 1992). Furthermore, even when behavioral deficits are observed, it is unclear whether they are a function of a lack of social knowledge or skill, of behavioral inhibition or avoidance produced by anxiety, or a combination of these and other factors. In our clinic, it is not uncommon for patients to complain that they do not know how to behave in various situations. However, observation of their performance during exposures often indicates that their behavior is within acceptable limits. This observation is consistent with research suggesting that individuals with social phobia often underestimate the adequacy of their social performance (e.g., Rapee and Lim 1992).

Techniques commonly used in social skills training include therapist modeling, behavioral rehearsal, corrective feedback, social reinforcement, and homework assignments. Notably, if these techniques effectively reduce anxiety for some individuals with social phobia, it is not necessarily because deficiencies in the patient's repertoire of social skills have been remediated. Social skills training may provide benefits because of the training aspects (e.g., repeated practice of feared social behaviors), the exposure aspects (e.g., confrontation of feared situations), or the cognitive elements (e.g., corrective feedback about the adequacy of one's social behavior) inherent in the procedures.

In the only controlled study of social skills training, 15 weeks of training failed to produce improvements in social anxiety, social skills, and overall clinical adjustment superior to those shown by a wait-list control group (Marzillier et al. 1976). In several other studies, social skills training resulted in significant improvements in various aspects of social phobia such as reductions in self-reported anxiety, depression, and difficulty in social situations (Falloon et al. 1981; Lucock and Salkovskis 1988; Stravynski et al. 1982; Trower et al. 1978; Wlazlo

et al. 1990). However, none of these studies included adequate control conditions. Therefore, it is not possible to state with confidence that these treatments were responsible for successful outcomes or that social skills training per se was what led to the observed outcomes.

Relaxation Strategies

The rationale for the application of relaxation strategies to the treatment of social phobia is that excessive physiological arousal prevents optimal social performance and that relaxation can help the individual to overcome the adverse effects of anxiety. Progressive muscle relaxation alone has been shown to have a minimal effect on social phobia in two studies (Al-Kubaisy et al. 1992; Alström et al. 1984). Self-control desensitization, in which patients use progressive muscle relaxation in response to anxiety experienced while visualizing increasingly more anxiety-evoking scenes, was superior to a waiting-list control condition on only 3 of 19 measures in a study of the treatment of social anxiety in volunteers (Kanter and Goldfried 1979). Systematic desensitization, another technique that combines progressive muscle relaxation and the presentation of scenes of gradually increasing anxiety-evoking potential to imagination, resulted in improvement on many measures, but this improvement was superior to a waiting-list condition on only one variable (Marzillier et al. 1976). Trower et al. (1978) reported treatment gains for patients with social phobia in response to systematic desensitization, but the lack of a waiting-list condition in this study makes these findings inconclusive.

Progressive muscle relaxation alone or combined with fear-evoking imagery may not effectively help an individual overcome social phobia. However, when individuals are specifically trained to apply relaxation skills in feared social situations, the results are more promising (Jerremalm et al. 1986; Öst et al. 1981). In applied relaxation, patients learn to increase their awareness of the earliest signs of anxiety, to practice relaxation techniques until they are able to achieve a moderately relaxed state quickly, and then to apply their relaxation skills during anxiety-provoking situations (Öst 1987). Thus, applied relaxation combines relaxation with exposure techniques, with relaxation skills being used as a means of coping with anxiety. Research suggests that applied relaxation is superior to a waiting-list condition (Jerremalm et al. 1986) and may match the efficacy of social skills training (Öst et al. 1981). However, applied relaxation appeared to be less effective than cognitive treatment in one study (Jerremalm et al. 1986).

Other Psychosocial Approaches

Cognitive-behavioral treatments are by far the most extensively researched psychosocial approaches for social phobia. However, in clinical practice, other theoretical approaches are used in the treatment of social phobia, although little research has examined their efficacy.

Interpersonal Psychotherapy

Interpersonal psychotherapy (IPT) is based on the assumption that psychiatric disorders occur and are maintained within a psychosocial and interpersonal context. The main goal of IPT is to improve the patient's interpersonal functioning as a means of achieving symptomatic recovery. IPT is a time-limited (12- to 16-week) therapy that has been shown to be efficacious in the treatment of acute depression (Elkin et al. 1989; Sloane et al. 1985; Weissman et al. 1979), dysthymic disorder (Markowitz 1994), and other disorders with an interpersonal component such as bulimia nervosa (Wilfley et al. 1993). Lipsitz and colleagues (1999) recently modified IPT for social phobia. In this treatment, core interpersonal problem areas are identified and then examined through multiple techniques (e.g., exploration of feelings and thoughts related to the problem area, encouragement of affective expression, clarification of feelings, communication and decision analysis, and role-playing).

An initial uncontrolled study of IPT with nine individuals with social phobia provided promising results (Lipsitz et al. 1999). Following treatment, 78% of the patients were classified as responders by independent evaluators. Ratings of improvement also were significant on a clinician-administered measure of social anxiety, and self-ratings of global symptom severity and social distress also decreased following treatment. This preliminary trial of IPT is promising, but future controlled trials with larger samples are needed.

Psychodynamic Perspectives

Psychodynamic theorists rarely have addressed social phobia and have made few contributions to theory or treatment. One model of social phobia that includes a psychodynamic component is that of Trower and Gilbert (1989). Trower and Gilbert's model combines psychobiological and psychodynamic components with those of ethological and cognitive theories. They proposed two systems of interaction among members of the same species: the agonic system and the hedonic system. In the *agonic system*, individuals are constantly

on guard for possible threats and act in a defensive manner. In the *hedonic system*, the goals of dominance are no longer central. Instead, cooperation is emphasized. Trower and Gilbert proposed that individuals with social phobia overuse their agonic (i.e., defense) system and underuse their hedonic (i.e., safety) system.

Two recent studies addressed the validity of the Trower and Gilbert model of social phobia. Hope et al. (1998) found that socially anxious undergraduates rated themselves higher in competitiveness, submissiveness, and reassurance seeking than their nonanxious counterparts. In the second study (Walters and Hope 1998), individuals with social phobia were shown to be less cooperative and less dominant than nonphobic control subjects, although this finding was not consistent across all measures.

In their modification of Trower and Gilbert's model, Cloitre and Shear (1995) argued that defense and safety systems are both necessary components of proper social functioning. Further, Cloitre and Shear integrated aspects of attachment theory into the model and proposed that attachment exists independently of, and is not derived from, the safety system. They proposed that during development, a lack of safety signals from parents may cause children to be insecurely attached. These children will come to fear abandonment and may attempt to please their parents in exchange for parental attention and closeness. This pattern of underuse of the safety system may be replicated in later relationships and maintain anxiety in social situations. Based on this revised model, Cloitre and Shear recommended working with patients to recognize the normality of interpersonal competition, identifying interpersonal realms in which the patient may dominate, and accepting the inevitability of submission in other interpersonal arenas.

In another psychodynamic account, Gabbard (1992) proposed three models for understanding the symptoms of social phobia: 1) shame experiences regarding unconscious wishes to be the center of attention, 2) guilt concerning wishes to eliminate competitors while doubting one's ability to actually do so, and 3) separation anxiety concerning attempts for autonomy leading to long-term loss of a caregiver's love. He proposed that parents' actions interact with biological predispositions to either exacerbate or lessen social anxiety. Gabbard suggested that specific treatment recommendations are mediated by patient characteristics. However, he proposed that when patients are cooperative, therapists may wish to use an eclectic approach, including dynamic exploration, medication, and exposure.

An individual case of social phobia conceptualized from a psychodynamic perspective was presented by Zerbe (1995). Like Gabbard, Zerbe (1995) proposed that shame is an important underlying dynamic in social phobia. Zerbe presented the case of a woman with fears of performance situations (e.g., public speaking) and interaction situations (e.g., dating) based on the belief that she could never "measure up" to the demands of other people. Zerbe attributed the development of social phobia in this patient to a lack of nurturance and support from her parents during childhood. Zerbe (1995) asserted that "one can safely assume that the early traumatogenic environment of this patient played a substantial role in the etiology of her social phobia" (p. 10). Although case conceptualization and descriptions have advocated the use of psychodynamic therapy for the treatment of social anxiety, controlled trials are needed.

Morita Therapy

Morita therapy is a Japanese therapy for anxiety that emphasizes behavior change and personal growth (Reynolds 1980). It encourages patients to relinquish control of emotions and redirect their attention toward more active and constructive pursuits. The experience of ego transcendence (i.e., forgetting oneself and one's symptoms) through immersion in activities is believed to play an integral role in patients' reformulation of themselves and their behavioral capacities. Although Morita therapy does contain some unique aspects (e.g., not explicitly attempting to reduce or eliminate anxious symptoms), it shares other components with Western therapies (e.g., use of reattribution, attentional refocusing, modifying dysfunctional beliefs, positive reinterpretation). Morita therapy emphasizes that anxiety is not an abnormal experience or trait, that anxiety can be accepted as it is, and that attempts to manipulate or explicitly reduce anxiety often paradoxically result in increased preoccupation with symptoms. In feared situations, patients are instructed to persevere through anxious moments by focusing on the task at hand, to recognize that they have a choice of action and not emotion, and to consider that the intensity of emotion is a reflection of the importance of the task.

A small but growing body of literature has addressed the application of Morita therapy to shyness and social anxiety (Alden 1988; Ishiyama 1987). Ishiyama (1987) posited three fundamental philosophical premises in Morita therapy regarding social anxiety: 1) social anxiety is a normal human emotion, 2) social anxiety has a

self-actualizing meaning, and 3) social anxiety can be used as a motivator-facilitator of constructive action. Case studies have shown Morita therapy to be successful in helping patients to accept their anxiety and redirect their attention away from it (Alfonso 1992; Ishiyama 1986). In a study of five socially anxious college students, Ishiyama (1991) found that Morita therapy was successful in reducing patients' target complaints, increasing coping effectiveness, and reducing social anxiety and avoidance. Although controlled trials are needed, preliminary studies suggest that Morita therapy for social anxiety warrants further attention.

Conclusions

A review of noncognitive behavioral treatments for social phobia suggests a variety of alternatives for the conceptualization and treatment of the disorder. However, controlled trials are needed to assess the efficacy of these approaches to treatment before they can be widely recommended. Case studies and open trials suggest the promise of some of these approaches, but their true efficacy needs to be assessed with more rigorous methods.

Special Populations

Children and Adolescents

Researchers have begun to focus on the treatment of childhood and adolescent social phobia, and much more work is needed in this area. Early studies focused on extremely shy adolescents and examined only single cases or very small samples (Christoff et al. 1985; Franco et al. 1983). Later studies included children and adolescents with social phobia or avoidant disorder of childhood or adolescence. However, these studies typically combined socially anxious children and children with other anxiety disorders without considering possible diagnosis effects. For example, Kendall (1994) and Kendall et al. (1997) investigated the efficacy of a 16-session cognitive-behavioral treatment program for anxiety disorders in children (ages 9–13 years). Both studies included samples of adolescents with overanxious disorder, separation anxiety disorder, and avoidant disorder (social phobia). Kendall (1994) showed that cognitive-behavioral treatment was superior to a wait-list condition, and improvements in the cognitive-behavioral group were maintained at 1-year follow-up. Kendall et al. (1997) replicated these findings, showing significant symptom reductions following treatment. More than 50% of the treated children no longer met criteria for their primary anxiety disorder.

Family interactions have been proposed to exacerbate social anxiety in children and adolescents. For example, compared with nonanxious children, clinically anxious children are more likely to interpret ambiguous situations in a threatening manner and to choose avoidant solutions. Importantly, after discussing the ambiguous situations with their parents, anxious children's avoidant responses increase (Barrett et al. 1996b). To address the potential importance of family factors in the maintenance of anxiety, family anxiety management (FAM; P.M. Barrett, M.R. Dadds, and R.M. Rapee, "Coping Koala Workbook" [unpublished manuscript], Nathan, Australia, Griffith University, School of Applied Psychology, 1991) was designed as an adjunct to individual CBT for anxious children. FAM involves the training of parents: 1) to reward courageous behavior and extinguish anxious behavior, 2) to better cope with their own anxiety, and 3) to use communication and problem-solving skills. Barrett et al. (1996a) compared CBT alone, CBT plus FAM training, and a wait-list condition. Their sample included 30 children with overanxious disorder, 30 children with separation anxiety disorder, and 19 children with social phobia. Their results again supported the effectiveness of CBT in comparison to the waiting-list condition and extended the literature by showing that the effectiveness of CBT for anxious children was enhanced with adjunctive FAM training. Although most of the analyses conducted by Barrett et al. (1996a) combined the three anxious samples, the authors did address (but did not find) differential rates of response based on diagnosis. The percentage of patients who no longer met diagnostic criteria after treatment was 68.2% for overanxious disorder, 77.8% for separation anxiety disorder, and 61.5% for social phobia.

Two cognitive-behavioral treatment protocols have been developed specifically for social phobia in children and adolescents. Social effectiveness training for children (D.C. Beidel, S.M. Turner, and T.L. Morris, "Social Effectiveness Training for Children: A Treatment Manual" [unpublished manuscript], Charleston, SC, Medical University of Charleston, 1996) targets children ages 8–12 years. CBGT for adolescents (Albano et al. 1995a, 1995b) targets children ages 13–17 years.

Social effectiveness training for children is a 12-week modified version of the adult social effectiveness training protocol. In a preliminary study of the efficacy of social effectiveness training for children, Beidel and Turner (1998) showed a significant decrease in self-

reported social anxiety among 16 children with social phobia. Changes in self-report measures were accompanied by positive changes in parent ratings, with parents reporting that their children had fewer internalizing behaviors following treatment. Furthermore, the children showed significant improvement in social interaction skills and oral reading skills during behavior tests, along with reductions in self-reported anxiety.

CBGT for adolescents is a downward extension of the CBGT protocol with the addition of parental involvement. CBGT for adolescents involves 16 sessions over 3 months, and parents attend 4 key sessions. The program includes education, skill building, cognitive restructuring, behavioral exposures, and homework assignments. Albano et al. (1995b) showed preliminary support for the efficacy of CBGT for adolescents in a clinical trial of five adolescents with social phobia. After treatment, patients' weekly self-rated anxiety and depression improved. Three months after treatment, four of the five patients no longer met criteria for social phobia. Anxiety during two behavioral tasks decreased, and these gains were maintained at a 12-month follow-up.

Minorities

The importance of proper assessment and treatment of social phobia (as well as other psychological disorders) in minority populations is becoming increasingly evident because of the shifting composition of the United States population (Vargas and Willis 1994). It is predicted that in the near future, 40% of all mental health services will be delivered to ethnic minority persons (Cross et al. 1989). One recent study examined the prevalence of DSM-III-R disorders among Mexican Americans in California (Vega et al. 1998). Mexican Americans who had been in the United States less than 13 years had lifetime rates of social phobia half that of Mexican Americans who have lived in the United States for more than 13 years (and the national population of the United States). More research is needed to address possible differences in the prevalence of social phobia among individuals of different ethnic backgrounds and possible effects of acculturation. Further studies are also needed to assess possible differences in response to treatment interventions for individuals of varying ethnic backgrounds. To date, no controlled studies have specifically examined the efficacy of psychosocial treatments for social phobia among minority populations or whether specific modifications of validated procedures are necessary for treating individuals from different minority groups.

Fink et al.'s (1996) treatment of a 39-year-old African American woman illustrates the importance of cultural factors in the treatment of social phobia. The patient presented in this case study initially reported fear of interacting with colleagues in the medical field. When her fears were further examined, it became evident that she was particularly fearful of interactions with Caucasian individuals, including settings in which she interacted with male Caucasian physicians and classroom settings in which she was the only African American student among many Caucasian students. Inclusion of these culturally relevant factors in the patient's imaginal flooding scenes and in vivo homework assignments (e.g., imagining or interacting with Caucasian doctors or students) enhanced the social-evaluative, fear-provoking nature of the scene or event and enhanced the efficacy of the flooding exercise. Fink et al. (1996) argued that it is unlikely that the long-term success realized by their patient would have been observed if her core concerns about cultural factors had not been addressed.

Treadwell et al. (1995) addressed the role of cultural factors in an examination of 178 clinic-referred children (ages 9–13 years). Among 81 clinically anxious youth, prevalence, content, and intensity of fears did not differ as a function of either sex or ethnicity. Furthermore, cognitive-behavioral treatment was equally effective across ethnic minority groups. However, this study did not specifically address social phobia and highlights the need for further research into the relation of cultural issues in the treatment of social phobia.

Conclusions

Positive steps have been taken, but further efforts are needed to address the efficacy of psychological treatments for social phobia in special populations. As stated earlier in this chapter, proper identification and treatment of children and adolescents with social phobia during the earlier years of the disorder have potential positive implications for both immediate and long-term functioning. Furthermore, as the composition of the United States quickly comes to include a larger percentage of minority persons, it is essential that cultural issues in the development, maintenance, and treatment of social phobia be addressed. Controlled research with other population groups (e.g., elderly samples, gay and lesbian samples) is nonexistent. Researchers and clinicians who have begun to address issues in the treatment of social phobia in special populations are to be commended. Their continued efforts will enable us to better alleviate social anxiety in all individuals.

Factors Affecting Treatment Outcome

Although effective treatments for social phobia have been devised, not all patients complete treatment or show adequate response. Previous studies (e.g., Heimberg et al. 1998) have shown that 75% of the patients who completed a 12-week trial of CBGT were rated as responders, but many had residual symptoms. Several studies have attempted to identify predictors of response to CBT (Brown et al. 1995; Chambless et al. 1997; Holt et al. 1990; Hope et al. 1995b; Juster et al. 1993; Turner et al. 1996).

Demographic Characteristics

Demographic characteristics have added little to the prediction of outcome of CBT for social phobia. Holt et al. (1990) showed that younger patients were more likely to improve with CBGT, but there were no differences in improvement due to sex. Juster et al. (1993) did not find a relation between demographic factors (sex, age, marital status, employment status, and educational level) and response to CBGT.

Clinical Characteristics

Investigations of the relation of clinical characteristics to treatment outcome have produced mixed results. Holt et al. (1990) found that patients with less severe symptoms, later onset, and shorter duration of symptoms were more likely to improve with CBGT. However, Juster et al. (1993) found no relation between locus of control, social anxiety, general anxiety, depression, and response to CBT.

Subtype of Social Phobia and Comorbid Avoidant Personality Disorder

Other studies have examined the subtype of social phobia and comorbid avoidant personality disorder as potential predictors of treatment outcome. Turner et al. (1996) found that when controlling for pretreatment differences, patients with generalized social phobia and patients with specific social phobia responded similarly to flooding. However, when examining posttreatment scores in an absolute sense, patients with specific social phobia were less impaired than patients with generalized social phobia. Two studies examining the relation of social phobia subtype and the outcome of CBGT found that patients with generalized social phobia improved with treatment as much as patients with nongeneralized social phobia (Brown et al. 1995; Hope et al. 1995b). However, because patients with generalized social phobia began with greater impairment than patients with nongeneralized social phobia, patients with generalized social phobia remained relatively more impaired after treatment. Patients with generalized social phobia were less likely to achieve high levels of end-state functioning than were patients with nongeneralized social phobia. These results suggest that to reach optimum levels of end-state functioning, patients with generalized social phobia may require more prolonged or intensive treatment than do those with nongeneralized social phobia.

The effects of avoidant personality disorder on treatment of social phobia have been shown to be smaller than anticipated. Patients with and without a comorbid diagnosis of avoidant personality disorder often have been shown to make similar treatment gains (Brown et al. 1995; Hofmann et al. 1995; Hope et al. 1995b), although two studies (Chambless et al. 1997; Feske et al. 1996) showed poorer treatment response among patients with comorbid avoidant personality disorder. However, the weight of the evidence suggests that although the presence of comorbid avoidant personality disorder before treatment predicts lower end-state functioning after treatment, as for social phobia subtype, this outcome appears to be primarily related to pretreatment severity. In fact, comorbid avoidant personality disorder is most common in individuals with generalized social phobia, and generalized social phobia patients with and without comorbid avoidant personality disorder have been shown to respond similarly to cognitive-behavioral treatment (Brown et al. 1995).

Expectancies

The effects of patient expectancies on treatment outcome also have been examined. Two studies found expectancy to be a unique predictor of outcome, even when other important variables such as pretreatment severity were controlled (Chambless et al. 1997; Safren et al. 1997). Chambless et al. (1997) found that patients who had low expectancy for positive outcomes reported significantly smaller reductions in anxious apprehension by posttreatment. Patients who had higher expectancies for positive outcomes reported significantly more improvement in anxious apprehension and speech skills at follow-up, even after controlling for the effects of depression. Similarly, Safren et al. (1997) reported that expectancy significantly predicted improvement on various self-report and interviewer measures.

They suggested that the modification of negative expectancies should be a priority early in treatment because of their association with poorer outcomes. However, as noted by Chambless et al. (1997), the mechanism by which expectancies are associated with outcome is unknown and not necessarily causal.

Homework Compliance

Homework (e.g., practice of cognitive coping skills and exposure to real-life social situations) is as an integral component of CBT for social phobia. Likelihood of homework compliance does not appear to be related to pretreatment levels of social anxiety (Edelman and Chambless 1995; Leung and Heimberg 1996) or to pretreatment perceptions of control over outcomes (Leung and Heimberg 1996). However, homework compliance has been shown to be associated with positive outcomes at posttreatment (Leung and Heimberg 1996) and 6-month follow-up (Edelman and Chambless 1995).

Specifically, in the study by Edelman and Chambless (1995), patients who adhered better to instructions for homework assignments between sessions reported less fear of negative evaluation after treatment. Six months later, patients who had completed a larger number of homework assignments achieved higher levels of end-state functioning (rated themselves as more skillful and less anxious during simulated speeches and also were rated as more skillful by observers). Greater homework compliance during the earlier and later portions of CBGT was related to better treatment outcomes in the study by Leung and Heimberg (1996), suggesting that adherence may be particularly important in the initial and final portions of CBGT. Although Leung and Heimberg (1996) did not examine follow-up outcomes, the findings of Edelman and Chambless (1995) suggest that the benefits of homework compliance may continue to be evident well after treatment has ended.

Conclusions

The studies reviewed here have identified numerous variables that predict treatment outcome. Attempts to manipulate these predictors may serve to improve already effective treatments. For example, techniques for modifying negative expectancies or increasing homework compliance may lead to better outcomes. These studies also have provided us with information about patients who may require additional or more intensive treatment, such as patients with generalized social phobia.

Summary and Future Directions

In this chapter, we reviewed the principal psychosocial approaches to the treatment of social phobia. Clearly, cognitive-behavioral approaches have been the most widely researched, and the evidence suggests that exposure is a component of successful treatment. Because cognitive factors have been hypothesized to play a central role in the maintenance of social phobia, many studies have examined the effectiveness of the combination of cognitive techniques and exposure. These studies have shown that cognitive restructuring plus exposure is an effective combination, resulting in significant within-group gains and outperforming attention control conditions. However, the question of whether cognitive interventions significantly increase treatment gains above and beyond those produced by exposure alone remains unresolved.

The research examining social skills training and relaxation techniques is less abundant and less sophisticated. Lack of well-controlled trials limits our ability to make strong statements about the efficacy of these approaches. An urgent need exists to examine the effectiveness of non-cognitive-behavioral approaches to the treatment of social phobia.

A dearth of research also exists regarding the treatment of social phobia among special populations. The greatest strides have been made in applying cognitive-behavioral techniques to the treatment of children and adolescents with social phobia, and studies in this area are currently under way at several research centers. Greater efforts are needed to examine how diversity relates to the development, maintenance, and treatment of social phobia. Additional research is needed to continue to identify predictors of treatment response.

In conclusion, we are much better equipped to treat patients with social phobia than we were when social phobia was first introduced in DSM-III. However, this progress is satisfying but not sufficient. Review of the treatment literature suggests directions for future research that will allow us to improve the quality of treatments for individuals with the disruptive effects of social phobia.

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VII

Specific Phobia

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26

Specific Phobia

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Specific phobia is a relatively common psychiatric disorder across the population. As suggested by its name, it is characterized by a marked fear of and a desire to avoid a specific situation or object. Typically, the objects that become the target of a phobia are those that cause distress and distaste in the general population. However, people with specific phobia overestimate the consequences of enduring exposure to the feared stimulus (Beck et al. 1985).

Relatively few individuals with specific phobia actually seek treatment (Magee et al. 1996; Merckelbach et al. 1996). This is perhaps because many people with specific phobia view the fear as a "normal" part of their personality. In addition, many phobic stimuli can be avoided in daily life with relatively little difficulty. For example, it usually provides relatively little interference in life for a person with dog phobia to select routes where there are no dogs. When not confronted with the phobic stimulus, people with specific phobia are generally symptom free (Butler 1989). Nonetheless, for many individuals, a phobia can be a life-interfering problem that requires treatment. In at least one case reported in the literature, specific phobia was even implicated in suicide (Pegeron and Thyer 1986). Consequently, clinicians and researchers must be aware of the current issues relating to the nature, theory, and treatment of specific phobia. In addition, specific phobia represents a diagnosis that was of interest to the very earliest cognitive-behavioral therapists and researchers. In accord, a review of specific phobia represents an interesting historical foray into the development of psychological theory and treatments.

Classification and Symptomatology

The early classification of phobias used a vast number of Greek words to describe the feared object. More recent classification systems have distinguished between types of phobias based on statistical analysis of data collected from a large cohort of phobic individuals. For example, Beck and colleagues (1985) distinguished between three classes of phobias: 1) those that are related to social rejection, 2) those that are agoraphobic in nature, and 3) those that are related to blood and injury. A factor analysis reported by Fredrikson et al. (1996) supported the classification of phobias into three slightly different categories: 1) situational phobias, 2) animal phobias, and 3) mutilation phobias. In a third attempt to organize phobic types, DSM-IV (American Psychiatric Association 1994) distinguished between four subtypes of phobia: 1) animal, 2) natural environment (e.g., storms, water), 3) blood-injection-injury, and 4) situational type (e.g., flying, enclosed spaces). However, a recent study found that specific phobias may not be particularly specific in that 68% of the individuals receiving a diagnosis of specific phobia also reported fears from other specific phobia subtypes (Hofmann et al. 1997). This finding may question the validity of subtyping phobias. However, given that these were people presenting to a specialist clinic for treatment of their phobia, one may question the representativeness of the sample.

In terms of blood-injury phobia, Page (1994) differentiated two subtypes of patients: those who manifest the sympathetic nervous system activation characteris-

tic of most other specific phobias and those who are characterized by fainting, a response specific to blood-injury phobias. The fainting is caused by the steep drop in blood pressure following an initial rise when the individual is initially exposed to blood- or injury-related stimuli. Another factor that has been found to differentiate individuals with blood-injury phobia from many other phobic groups is disgust. Specifically, patients with blood-injury phobia were more likely to describe disgust on exposure to blood or injury, whereas individuals with many other phobias were predominantly characterized by fear (Tolin et al. 1997). Extending this line of thinking, Davey and colleagues (e.g., Ware et al. 1994) suggested that types of phobias can be distinguished in terms of the principal emotion they elicit-disgust or fear.

Apart from the patients with blood-injury phobia who faint, all phobic individuals show two broad sets of symptoms (Mavissakalian and Barlow 1981). The first is the anxiety or sympathetic nervous system activation that occurs on anticipation of, or confrontation with, the phobic stimulus. The anxiety reaction typically includes any combination of the following symptoms: unsteadiness, feelings of unreality, perception of impending doom, dryness of the mouth, pounding heart, nausea, fear of dying, fear of going crazy, sweating, shortness of breath, feelings of choking or being smothered, chest pain, chest discomfort, faintness, and trembling (American Psychiatric Association 1980). The second set of symptoms is the desired or attempted avoidance that individuals with specific phobias engage in. That is, phobic individuals show a behavioral preference to minimize contact with the feared event. When the event cannot be avoided, it will be endured with a high level of anxiety, and the phobic individual will escape as soon as possible. Often, this tendency toward avoidance renders the individual quite restricted in his or her activities. However, the level of impairment experienced will depend on the extent to which the target of the phobia can be readily avoided (Sturgis and Scott 1984). A third characteristic of specific phobia added by Beck and colleagues (1985) is the insight the individual usually has into the overly exaggerated nature of the phobia.

Turning now to formal diagnostic systems, the three aspects of specific phobia highlighted form the basis of the DSM-IV diagnostic criteria. Specifically, DSM-IV stipulates that the fear must be "marked and persistent" (criterion A) and that on exposure, the phobic individual must have an immediate increase in anxiety, which may take the form of a panic attack (criterion B). The individual must recognize this response as excessive (criterion C), and the symptoms cause significant interference with the person's social or occupational functioning (criterion E). Finally, criterion D reflects the avoidance aspect of the diagnosis (see Table 26–1 for the full criteria).

Differential Diagnosis and Comorbidity

As can be seen in Table 26–1, DSM-IV states that the avoidance and anxiety manifested by a phobic individual should not be better accounted for by another mental disorder. To accurately diagnose specific phobia, a key differentiating factor is that the individual with specific phobia does not present as generally anxious. Instead, the anxiety typically is limited to the anticipation of exposure to or actual confrontation with the phobic stimulus.

In terms of differentiating specific phobia from other anxiety disorders, several points should be considered. First, like specific phobia, the fear in posttraumatic stress disorder (PTSD) is mostly specific, but the fears have been triggered by an external traumatic event. Furthermore, PTSD is characterized by intrusions and nightmares that are not typical of specific phobia. Similarly, the hallmark symptoms of obsessive-compulsive disorder are obsessions and compulsions that are not a feature of specific phobia.

The key factor in the differential diagnosis of psychosis and specific phobia is the insight the individual with specific phobia has as to the irrationality of the phobia and the resistance to the alteration of the fear being delusional in intensity in psychotic individuals (Andrews et al. 1994). Social phobia can be distinguished from specific phobia by its focus on fear of negative evaluation in social situations.

Perhaps the more difficult differential diagnosis is between individuals with specific phobia who experience panic attacks and individuals who meet diagnostic criteria for panic disorder. The key differentiating factor between specific phobia and panic disorder is that in the latter, the fear is specifically focused on having a panic attack. A study illustrating this point was reported by McNally and Louro (1992). These authors compared a group of individuals who reported a fear of flying. Half were given diagnoses of panic disorder with agoraphobia, and half met criteria for specific phobia. The comparison showed that individuals in the specific

TABLE 26–1. DSM-IV-TR diagnostic criteria for specific phobia

A. Marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood).
B. Exposure to the phobic stimulus almost invariably provokes an immediate anxiety response, which may take the form of a situationally bound or situationally predisposed panic attack. **Note:** In children, the anxiety may be expressed by crying, tantrums, freezing, or clinging.
C. The person recognizes that the fear is excessive or unreasonable. **Note:** In children, this feature may be absent.
D. The phobic situation(s) is avoided or else is endured with intense anxiety or distress.
E. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational (or academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.
F. In individuals under age 18 years, the duration is at least 6 months.
G. The anxiety, panic attacks, or phobic avoidance associated with the specific object or situation are not better accounted for by another mental disorder, such as obsessive-compulsive disorder (e.g., fear of dirt in someone with an obsession about contamination), posttraumatic stress disorder (e.g., avoidance of stimuli associated with a severe stressor), separation anxiety disorder (e.g., avoidance of school), social phobia (e.g., avoidance of social situations because of fear of embarrassment), panic disorder with agoraphobia, or agoraphobia without history of panic disorder.

Specify type:

Animal type
Natural environment type (e.g., heights, storms, water)
Blood-injection-injury type
Situational type (e.g., airplanes, elevators, enclosed places)
Other type (e.g., fear of choking, vomiting, or contracting an illness; in children, fear of loud sounds or costumed characters)

Source. Reprinted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000, pp. 449–450. Used with permission.

phobia group avoided flying because they feared crashing, whereas those in the agoraphobic group feared experiencing a panic attack. Given that the distinction can be difficult (Ehlers et al. 1994), requiring some clinical judgment, DSM-IV recommends that information about 1) the situations that elicit the fear, 2) the type and number of panic attacks, 3) the range of situations that the individual avoids, and 4) the level of anxiety between episodes of fear on exposure to the situation be gathered and considered when making the diagnostic decision.

In terms of comorbidity, an individual with one anxiety disorder commonly also has one or more other anxiety disorders. This tendency for comorbidity among the anxiety disorders applies less to specific phobia compared with the other anxiety disorders (Kendler et al. 1992; Sanderson et al. 1990). Nevertheless, in a national comorbidity survey (Magee et al. 1996), most individuals with specific phobia reported at least one additional lifetime disorder. The odds ratios indicated that specific phobias are strongly comorbid with other phobias (agoraphobia and social phobia), other anxiety disorders, and the affective disorders.

Epidemiology

Age at Onset

The mean age at onset for specific phobia is reported to be between ages 13 and 16 years (Thyer et al. 1985). However, collapsing across different specific phobias may mask interesting differences. Several studies have analyzed the age at onset of phobia subtypes and found that they are quite variable (Sturgis and Scott 1984). Specifically, persons with situational phobia have a later age at onset relative to patients with other types of phobias (Himle et al. 1989). In contrast, animal and blood-injection-injury types of phobias tend, on average, to begin in childhood (Mavissakalian and Barlow 1981; Öst 1987). Öst (1987) found that the mean age at onset for claustrophobia was 20, whereas the mean age at onset for animal and blood phobias was 7 and 9 years, respectively. In one interesting longitudinal study, Agras and colleagues (1972) found that 100% of the patients with specific phobia younger than 20 years were improved at follow-up, but only 43% of the adults with specific phobia were improved. Similarly, 40% of the participants younger than 20 were asymptomatic at fol-

low-up, but no adults were asymptomatic. Based on these data, it could be suggested that many specific fears in youth are relatively transient, but those that extend into adulthood are more severe and persistent.

Prevalence and Sex Ratio

Overall, the lifetime prevalence of specific phobia has been found to be between 8.8% and 12.5% (Kessler et al. 1994; Magee et al. 1996; Reiger et al. 1988). The variation in diagnostic rates may at least partly be attributable to the different thresholds used to judge the level of impairment.

Fredrikson et al. (1996) dissected the prevalence rates according to sex ratio and reported that women (21.2%) were more likely than men (10.9%) to meet criteria for any single specific phobia. Women also reported higher rates of multiple phobias than did men (women, 5.4%; men, 1.5%). Similar rates were reported by Kessler et al. (1994), who found a lifetime prevalence rate for males of 6.7% and for females of 15.7%. Most of the different types of specific phobias are characterized by a considerably higher proportion of females; the exception is blood-injection-injury type phobia. Several researchers have found relatively equal proportions of males and females with blood-injection-injury fears (Agras et al. 1969; Fredrikson et al. 1996; Himle et al. 1989).

Pathogenesis

Conditioning

Several early researchers conceptualized the etiology of phobias within a classical conditioning framework. In the famous "Little Albert" study, Watson and Raynor (1920) reported that the pairing of a white rat (considered to be the neutral stimulus) with a loud noise (considered to be the aversive stimulus) produced a conditioned fear response when the participant was exposed to the rat on future occasions. Mowrer (1960) extended this classical conditioning model by proposing that conditioning is mediated by motivations such as the desire to reduce the fear. Thus, the model was extended to account for avoidance behavior, a strategy that is reinforced by the reduction in fear response. Although the conditioning model is still influential in the field of phobias, it is now recognized to have some shortcomings (for review, see Rachman 1976, 1977, 1978, 1991). The most salient difficulties include 1) the distinct categories of fears noted in epidemiological studies, which is contrary to the proposal made by conditioning theorists that all stimuli can become feared stimuli (equipotentiality premise); 2) the fact that many people experience aversive conditioning but do not develop a phobia (Ehlers et al. 1994; Hofmann et al. 1995); 3) the fact that a traumatic etiology is not reported by all, or even most, individuals (Menzies and Clarke 1995b; Öst 1987); 4) the limited success of studies that have endeavored to condition stable fears in humans in an experimental setting (Bancroft 1969; Marks and Gelder 1967); and 5) the evidence attesting to the indirect and vicarious modes of onset for fears (Rachman 1978).

Preparedness

To attempt to account for some of the limitations of the traditional Pavlovian account of phobias, Seligman (1971) developed the preparedness theory of fear acquisition. Seligman noted that the common feature of stimuli that become the target of a phobic reaction is that they are biologically threatening. He postulated that as a consequence of natural selection, human beings are biologically prepared to develop fears to stimuli that threaten personal safety. That is, phobias were conceptualized to be a result of prepared learning. Seligman defined four features of "prepared" phobias: 1) they are often acquired through one trial conditioning (note that Seligman's account is still an associative theory because he hypothesized that phobias are still acquired via conditioning, albeit in a single trial), 2) they are noncognitive in that they persist despite insight into the irrationality of the fear, 3) the object will involve a threat relevant to humankind of the past and remain as a result of natural selection, and 4) they are not easily extinguished.

Taking the findings relating to ease of acquisition first, McNally (1987) reviewed 17 studies that measured the acquisition stage of conditioning of fear-relevant and fear-irrelevant stimuli and found little evidence for the first prediction. Specifically, several studies have shown that, in the laboratory, nonprepared stimuli can acquire aversive associations just as quickly as prepared stimuli (McNally 1987). The second hypothesis of preparedness theory, that fears are not cognitive and thus will be held despite the knowledge that the phobic object will not cause harm, has received mixed support. For example, Öhman et al. (1975) showed subjects pictures of phobic stimuli and pictures of neutral stimuli and administered shock to half of the subjects when the phobic stimuli were presented and to the other half when the neutral stimuli were presented.

Both groups acquired the conditioned fear, as measured by skin conductance responses. However, instructing subjects that no more shocks would be administered was not effective in extinguishing the fear to the snake pictures. However, McNally (1981) found the opposite result with a different methodology. Taken together, no clear conclusion about the second assumption of preparedness theory can be drawn (McNally 1987). The third and perhaps most basic assumption of preparedness theory, that there will be differential associativity for stimuli that are biologically prepared, has again failed to gather clear support. However, methodological problems have rendered this hypothesis difficult to unequivocally test (McNally 1987). The final hypothesis, that phobias will be difficult to extinguish, has received the most empirical support of the four predictions (e.g., Öhman and Dimberg 1978). However, some studies were not able to replicate these findings (McNally 1986; McNally and Foa 1986). Furthermore, McNally (1987) outlined several alternative explanations for the studies that showed support for the notion of resistance to extinction in an attempt to reconcile the contradictory findings. Taken together, the evidence suggests that three of the predictions of preparedness theory have not been supported empirically, and although some evidence has been gathered for the fourth prediction, alternative explanations are possible (McNally 1987). There is little doubt that the central premise of Seligman's theory—that certain stimuli are "evolutionarily prepared" to support phobic responding—is well supported. However, the details of the theory, that phobic responding is acquired in a single, associative experience, have not met with a great deal of support.

Multiple Pathways

In accord with the mixed support that has accumulated for the preparedness theory and with the observation that direct conditioning accounts have difficulty explaining vicarious conditioning, Rachman (1991) suggested that there may be several alternative pathways to the acquisition of phobic fears. Specifically, he proposed that conditioning, vicarious transmission, and verbal acquisition all could be modes by which a phobia could be acquired.

Evidence for vicarious conditioning has been indicated via numerous sources but is difficult to adequately test. First, laboratory experiments with humans have found learning by way of observation. For example, Bandura and Rosenthal (1966) arranged for participants to view a confederate feigning a pain reaction to an electric shock. After a few trials, the buzzer that preceded the shock resulted in an increase in physiological responding, even though the participants had not had contact with the electric shock apparatus. Second, a similar pattern of results has been found with animals. Cook and Mineka (1989) reported two experiments in which rhesus monkeys watched videotapes of monkeys behaving fearfully to stimuli that were either fear relevant (snakes, crocodiles) or fear irrelevant (flowers, rabbit). Monkeys who observed the videotapes acquired a fear of the fear-relevant stimuli but not of the fear-irrelevant stimuli. This demonstration of a preparedness aspect to vicarious learning has been replicated across several studies (e.g., Cook et al. 1985; Mineka et al. 1984). Third, several studies that have asked individuals to self-report on the perceived mode of onset for their phobia have consistently identified a small subgroup of subjects who nominate vicarious pathways (Fazio 1972; McNally and Steketee 1985; Menzies and Clarke 1993a, 1993b; Öst 1987; Rimm et al. 1977).

Evidence for the acquisition of phobias via verbal information can be seen in the epidemics of *koro* reported in Singapore and Thailand. Individuals with *koro* perceive that their genitals are shrinking, and they report an intense fear of dying. The epidemics were thought to have been caused by verbal transmission via the media (Rachman 1991; Tseng et al. 1988). Furthermore, many studies have reported increases in skin conductance to a target stimulus after informing the participant that the stimulus would be followed by a shock (Cook and Harris 1937).

Nonassociative Theory

The potential methods of fear acquisition described above are based on an associative theory of phobias. That is, the central mechanism in the development of phobias is believed to be the formation of an association between the feared stimulus (which was previously neutral) and a potentially threatening outcome. Recently, some authors have questioned such associative accounts of phobia acquisition. The nonassociative theory emerged as a result of evidence from various sources that converged on the proposal that phobias may be acquired without previous direct or indirect associative learning (Menzies and Clarke 1995b).

The first source of evidence is that many phobic individuals report no direct or indirect contact with a conditioning event. For example, Menzies and Clarke

(1993a) interviewed the parents of children with a water phobia. They found that only 1 parent out of 50 could recall a classical conditioning episode, and 58% of the parents reported that the fear had always been present. The second source of evidence is Walk and Gibson's (1960) demonstration of the response of human infants to the "visual cliff" apparatus (Menzies and Clarke 1995b). Specifically, in the original study by Walk and Gibson, all 27 (100%) infants called by their mother crawled onto the shallow "safe" side at least once, and only 3 (11%) infants crawled onto the deep "unsafe" side on occasion. Importantly, this effect appears to be innate and is manifested at the time an infant is able to move independently (Bertenthal et al. 1984). Therefore, it is argued that natural selection has prepared humans with the ability to avoid, without prior experience, situations that could lead to significant harm. In this context, it has been proposed that fear is innate or acquired in accord with a particular stage of development (Menzies and Clarke 1995b). Further support for this position can be drawn from the research finding fear of strangers in both humans (Dennis 1940) and rhesus monkeys (Sackett 1966). These findings are particularly compelling in the latter study in which the monkeys were reared alone, and thus the fear manifested to pictures of threatening monkeys obviously developed in the absence of a direct or an indirect conditioning episode. Finally, separation anxiety in human infants (Smith 1979) and several other mammals (Mineka 1982) has been found to be unrelated to past aversive experiences of separation (Bowlby 1975; Clarke and Jackson 1983).

Based on these data, Menzies and Clarke (1995b) argued that learning experiences (either verbal, vicarious, or direct) are not necessary for the development of phobias. Instead, these normal childhood concerns are hypothesized to continue and become phobias in adult life in some individuals via two means. First, some adults may have learned as children to successfully avoid an object in the domain of physical harm because their parents used avoidant coping styles or verbally reinforced the fears. In this way, the fear is maintained and in adulthood takes on phobic proportions (Menzies and Clarke 1995b). Second, during particularly stressful periods, a dishabituation of previous childhood fears may occur (Clarke and Jackson 1983). For example, 16% of the students who feared heights reported that their fear developed during a stressful period (Menzies and Clarke 1993b). Taken together, the case for the occurrence of nonassociative factors as a fourth mode of the onset of specific phobia appears to be convincing.

Biological Factors

Some evidence also has suggested that genetic variation may play a role in the etiology of phobias. For example, Fyer and colleagues (1990) reported a significantly higher risk for specific phobias among first-degree relatives of probands with specific phobia compared with the first-degree relatives of control subjects who had never received a diagnosis of a psychiatric disorder. Although these results suggest that specific phobia is a highly familial disorder, such data do not distinguish between genetic and shared environmental factors. However, a more recent study was able to comment on the role of genetic factors because a large cohort of female twins of differing zygosity were interviewed (Kendler et al. 1992). The investigators concluded that genetic factors play a significant role in the etiology of specific phobia but that the environment is also an important etiological factor. However, some evidence indicates a more specific genetic contribution for blood phobia (Fyer et al. 1990; Marks 1988). In summary, the evidence suggests that the mode of onset for specific phobia may be at least partially mediated by genetic transmission, and for one phobia subtype, blood-injection-injury phobia, heritability appears to be elevated.

Research on the neurobiology of specific phobia is currently sparse; most attention is being given to other anxiety disorders such as social phobia (Tancer 1993) and obsessive-compulsive disorder (Rauch et al. 1994). One study that used positron-emission tomography in individuals with diagnoses of simple phobia found an association between the paralimbic structures and the anxiety state experienced during phobia symptom provocation (Rauch et al. 1995). However, another study showed no differences in cerebral blood flow under provoked and resting conditions (Mountz et al. 1989). Further work is required to delineate the role of the brain both functionally and structurally in specific phobia.

Cognitive Factors

The development of a cognitive approach to specific phobia is a relatively recent phenomenon because phobias generally have been conceived to be caused by behavioral factors. Although some theorists suggest that acquisition of phobias may be mediated by cognitive appraisal (Rachman 1991), most attention has focused on the role of cognitions in the maintenance of phobias (Thorpe and Salkovskis 1995). Specifically, it is proposed that the focus of attention for an individual with social phobia is on 1) interpretation of the physiological

changes that accompany the anxiety, 2) anticipatory plans to avoid the feared stimulus, and 3) thoughts relating to escape from the stimulus (Last 1987). The cognitive approach argues that such cognitions increase arousal and anxiety and increase the likelihood that the phobic individual will attempt to avoid or escape the feared situation, an option that precludes habituation to the feared object (Last 1987). Empirically, several studies have supported this view.

Last and Blanchard (1982) found that when an individual with a specific phobia diagnosis is exposed to a feared situation, negative self-statements are triggered, which then heighten physiological activity. Similarly, Thorpe and Salkovskis (1995) found that most people with specific phobia reported at least one unrealistic belief about the harm that could befall them if exposed to the feared object or situation. Furthermore, the review of studies with phobic individuals (May 1977a, 1977b; Rimm et al. 1977; Wade et al. 1977) led Last (1987) to conclude that "maladaptive cognitions may be an important phenomenon in the genesis and maintenance of fear in clinically significant phobias" (p. 179).

Biases in information processing also have been implicated in the maintenance of phobias (Davey 1995). Specifically, the findings from several methodologies converge on the conclusion that phobic subjects have an attentional bias toward phobia-related threats. For example, Burgess et al. (1981) asked phobic and control participants to complete a dichotic listening task. Participants were asked to speak out loud the information presented in one ear and indicate when either neutral or phobia-related words were presented in the other ear. Phobic subjects readily detected phobia-related words presented in the unattended ear, but control subjects did not.

The Stroop paradigm is another methodology used to investigate the influence of cognitive processes in the maintenance of specific phobia. The Stroop Test requires participants to rapidly name the color in which words are presented while ignoring the word content. Longer response latencies are assumed to reflect interference in the processing of the color of the word. Watts et al. (1986) found that phobia-related words were named more slowly than were neutral words and that this bias was reduced following exposure treatment. Öhman and Soares (1994) took this experiment a step further by including masked trials to assess whether the lower threshold for the detection of threat occurs below the level of conscious awareness. These authors found that masked phobia-related objects (in which subjects could not intentionally name the object) can elicit a physiological reaction in individuals with a phobia but not in control participants. Recently, van den Hout et al. (1997) added to the strength of these findings by reporting that the intensity of phobic symptomatology was associated with a processing bias on both conscious (unmasked) and preconscious (masked) trials in individuals with a specific phobia. Furthermore, consistent with the results reported by Watts et al. (1986), the interference caused by phobic stimuli on masked and unmasked presentations was reduced with treatment. Öhman (1996) accounted for the preattentive bias toward threat by postulating that automatic, preattentive attentional systems operate to maintain and detect threat in the environment. When threat is detected by these efficient, involuntary systems, controlled or effortful attentional processes switch into operation to further ascertain the level and nature of the threat. If the stimuli are deemed to be threatening, the arousal system is activated.

Some authors have attempted to examine cognitive biases associated with specific phobias. A controversy in the literature on the cognitive mediation in specific phobias has focused on two factors of potential importance. On the one hand, Williams and colleagues (Williams and Watson 1985; Williams et al. 1985) argued that phobic avoidance and fear are principally mediated by low perceptions of self-efficacy. In contrast, Menzies and Clark (1995a) argued that phobic reactions are primarily mediated by exaggerated perceptions of danger and not by perceptions of self-efficacy. A recent study by Rapee (1997), however, implicated both self-efficacy and exaggerated perception of danger as additional cognitive factors that are likely to mediate phobic reactions.

Summary

Taken together, this section shows the possible utility of considering various theoretical approaches to understanding the causation of specific phobia. Consistent with this conclusion, Wilhelm and Roth (1997) summarized five pathways to the development of phobias: 1) direct conditioning, 2) vicarious conditioning, 3) verbal acquisition (Rachman 1991), 4) nonassociative means (Menzies and Clarke 1995b), and 5) mediation by cognitive factors (Butler 1989; Last 1987; Wilhelm and Roth 1997). Whether each of these pathways in fact provides an alternative possible means to the acquisition of phobic avoidance or whether some will prove to be empirically unsupported awaits further investigation.

Treatment

Exposure Therapy

The earliest treatments for specific phobia were developed based on conditioning theory and, thus, were exposure based (Wolpe 1958). Consistent with the predictions of conditioning theory, systematic desensitization was found to be more effective than insight-oriented group or individual psychotherapy for specific phobia (Gelder et al. 1967). Today, the most compelling evidence for successful treatment remains with exposure-based treatments. The basic principle of exposure is that the prevention of escape or avoidance will result in learning that the feared outcome will not occur (Butler 1989). Specifically, flooding (Sherry and Levine 1980), in vivo exposure (Hecker 1990), modeling (Denney et al. 1977), and systematic desensitization (Curtis et al. 1976; Wolpe 1958) all have been found to provide successful treatment for specific phobia. Flooding involves the patient being exposed to the phobic stimulus in its most threatening form, with exposure continuing until the anxiety has dissipated. The extreme discomfort implicit in this method tends to discourage its wide use given the success of alternative methods of exposure. In vivo exposure involves live exposure to the phobic object and usually is conducted in a graded fashion, beginning with situations that elicit a small amount of anxiety and moving up the hierarchy of fears as the anxiety habituates and confidence increases. Modeling involves the therapist encouraging the patient to have contact with the phobic stimulus by providing demonstrations of approaching and contacting the phobic stimulus. Systematic desensitization (Wolpe 1958) relies on progressive muscle relaxation to manage the anxiety elicited during imaginal exposure to the phobic stimulus. That is, the patient is first trained in relaxation and is then asked to imagine a series of anxiety-provoking images while maintaining the incongruent relaxed state.

Although exposure techniques have proven efficacy in the treatment of specific phobia, research has delineated some considerations that should guide the specific treatment procedures. First, several studies (Barlow et al. 1969; Crowe et al. 1972; Emmelkamp and Wessels 1975; Gelder et al. 1973) have indicated that in vivo exposure is preferred to imaginal exposure (Barlow 1988; Marks 1978). Furthermore, recent research indicated that in vivo exposure combined with modeling yielded significantly better results in the treatment of spider phobia compared with direct observation (watching another patient being treated) and indirect observation (watching a videotape of a treatment session) (Öst et al. 1997). These recommendations make intuitive sense because the transfer of learning from imaginal experiences and watching others with the feared object to real-life situations could be difficult.

Second, longer exposure to the phobic stimulus has been recommended. It is theorized that moving away from the feared object prior to anxiety reduction will result in fear sensitization because it will cause escape and anxiety reduction to be paired (Öst 1989). Interestingly, however, empirical support for this intuitively appealing suggestion has been mixed (Rachman et al. 1986).

Finally, it has been proposed that exposure should be based on a graded hierarchy of fears (Barlow 1988). That is, the phobic patient should be asked to identify all the stimuli he or she is avoiding and order them from those that elicit the least fear to those that elicit the most fear (see Butler 1989 for guidelines). Following the construction of the hierarchy, patients should be assisted to establish experiments that involve exposure to each feared object or situation. Working to move up the hierarchy as the patient's anxiety habituates to each step will increase the patient's comfort and compliance with treatment and between-session exposure tasks. In terms of the duration of treatment, a recent body of work has begun to show some exciting findings. Specifically, evidence has accumulated to suggest that one single intensive session of exposure-based treatment (2–3 hours) produces results comparable to those obtained over several sessions (Arntz and Lavy 1993; Hellström and Öst 1995; Öst 1989, 1996; Öst et al. 1991b).

As described by Öst (1989), the session for an individual with spider phobia begins with a detailed rationale for exposure that emphasizes the importance of staying in the exposure situation until the anxiety decreases. The individual is then exposed to four or five spiders of increasing sizes in turn. Each step is modeled by the therapist, and then the patient attempts the same task. The first step involves teaching the patient to catch the spider with a glass and a piece of paper and then to simulate throwing it out of the house. As the anxiety habituates, the amount of contact with the spider increases in the tasks. Throughout the session, the patient will be exposed to having a spider walking on his or her hand and even to having the spider on the patient's back or hair. This latter task exposes the patient to situations in which he or she has no control over the spider. The end goal of the session is that the individual will be able to handle contact with a spider in everyday situations with little anxiety. Furthermore, recent evi-

dence has indicated that the intensive single session is as successful with a group of patients as when individualized therapy is conducted (Öst et al. 1997).

Eye Movement Desensitization and Reprocessing

A recent study tested the efficacy of eye movement desensitization and reprocessing (EMDR) in the treatment of spider phobia in children (Muris et al. 1997). Shapiro (1995) described EMDR as a revolutionary treatment for psychological disorders that involve phobias and avoidance. The procedure involves many of the components of imaginal exposure therapy already outlined except that during the desensitization, a set of horizontal eye movements is elicited from the patient via hand movements by the therapist. The study by Muris et al. (1997) compared one session of EMDR with one session of in vivo exposure. Both treatments resulted in better performance on the self-report measures, but in vivo exposure was superior in reducing avoidance. It was concluded that there is no basis for suspecting that EMDR should replace in vivo exposure in the treatment of specific phobia.

Hypnotherapy

Several case studies have reported on the success of hypnosis in the treatment of specific phobia (Bird 1997; Ginsberg 1993). In terms of group studies, some either have not included a comparison group (Peretz et al. 1996) or have had many dropouts from treatment, markedly reducing statistical power (Hammarstrand et al. 1995). Randomized controlled trials of the efficacy of hypnosis in the treatment of specific phobia are still required. Particular attention to the differentiation of hypnosis from imaginal exposure methodologically (perhaps they are identical procedures) and in terms of outcome is necessary.

Psychopharmacology

Few studies have, to date, tested the efficacy of psychopharmacology in the treatment of specific phobia. Bernadt et al. (1980) found positive initial results with diazepam and β-blockers, but the improvements did not generalize. Similarly, use of benzodiazepines showed no evidence of longer-term reduction in anxiety and avoidance (Campos et al. 1984; Whitehead et al. 1978). Based on these preliminary studies, it has been concluded that psychopharmacology is not the treatment of choice for specific phobia (Andrews et al. 1994; Barlow 1988; Fyer 1987). However, the utility of recent advances in psychopharmacology and the possibility of combining pharmacological and psychological treatments remain to be explored.

Treatment of Blood-Injection-Injury Phobia

Treatment of blood-injection-injury phobia often becomes a priority when life-threatening illnesses can be averted by way of medical procedures that involve the feared object (e.g., injections, regular blood transfusions). As in the other types of phobias, exposure has been found to be a central component in the successful treatment of blood-injection-injury type phobia (Curtis and Thyer 1983; Lloyd and Deakin 1975). Furthermore, initial evidence based on a single case report indicates that cognitive therapy may provide added assistance in the treatment of blood-injection-injury phobia (Wardle and Jarvis 1981).

Note that the treatment of blood-injection-injury phobia can be complicated by fainting. Two treatment interventions have been highlighted by Page (1994) to protect the patient from fainting. The first technique, termed *applied tension*, involves instructing the patient to rapidly and frequently tense various muscle groups in his or her body during exposure, an activity that creates a physiological state that is incompatible with fainting. Indeed, Kozak and Montgomery (1981) successfully used exposure therapy in a group of individuals with blood-injection-injury phobia, with applied tension used as an adjunct. In a more recent study, Öst and associates (1991a) compared three groups of patients with blood-injection-injury phobia: 1) those who were given exposure alone, 2) those who were given applied tension alone, and 3) those who were given applied tension plus exposure. The two applied tension groups had a better outcome than the exposure alone group. This study raised the possibility that for blood-injection-injury phobia, the skill of applied tension is more important than the exposure component of treatment. In a case study, a second strategy was a successful adjunct to the treatment of blood-injection-injury phobia. This strategy involved eliciting the emotional state of anger from a patient during exposure to elicit a physiological change that is incompatible with fainting (Cohn et al. 1976). The patient was instructed to identify and, during exposure, recreate in his mind four personal situations in which he felt particularly angry. If the patient does faint during exposure, the fainting response prob-

ably will subside over a few sessions if exposure continues as consciousness returns (Marks 1988).

Conclusion

In conclusion, in this chapter, we have outlined the symptomatology, epidemiology, pathogenesis, and treatment of specific phobia. The empirical evidence supports the proposal that there are multiple pathways to the onset of specific phobia. The most recent theoretical development has been in the domain of the nonassociative accounts of specific phobia, which argue that phobias may occur outside of direct or indirect contact with the feared object. Furthermore, the consensus in the literature is that exposure therapy is the basis of a successful intervention for specific phobia. An exciting recent development in the treatment of specific phobia has been the one-session group treatment developed by the Swedish research group led by Öst. This represents a cost-effective alternative to the four to six sessions traditionally required for the treatment of specific phobia. Many individuals with blood-injection-injury phobia represent a distinct category of patients with specific phobia because of the fainting that may occur on exposure to the feared object; a feature that requires the teaching of specialized strategies.

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Part

VIII

Posttraumatic Stress Disorder and Acute Stress Disorder

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27

Phenomenology of Posttraumatic Stress Disorder

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Background Issues

The last two decades have been a period of intense interest in psychological trauma, leading to a very fruitful period of research and changes in clinical practice that have had a significant effect on psychiatry in general. Nevertheless, a similar period of focused attention occurred at the end of the nineteenth century. For example, Seguin, in summarizing the field in 1890, highlighted the broad interest in the question about psychological trauma on both sides of the Atlantic. Based on the collective evidence, he suggested that the term *traumatic neurosis* should replace the range of other terms that were used, such as *railway spine*, *hysteria*, and *compensation neurosis*. It took 90 years for this recommendation to come to fruition in the form of DSM-III (American Psychiatric Association 1980).

Understanding the two dimensions of the human response to traumatic events can clarify polarity of reactions to psychological trauma as a medical, legal, and social issue. On the one hand, both individuals and societies tend to try to avoid or even develop amnesia for the fear, suffering, and helplessness that these experiences cause. On the other hand, individuals are often intensely preoccupied by intrusive and distressing traumatic memories of experiences long gone. This is perhaps most recognized in war veterans, in whom combat became an organizing experience even for those who survived relatively unscathed psychologically. These patterns of reaction characterize not only individuals' responses to trauma but also legal and psychiatric knowledge about trauma.

Perhaps the starkest exemplar of a period of amnesia is in the area of childhood sexual abuse. The absence of a developed paradigm for understanding the effects of traumatic stress and psychiatry's acceptance of the psychoanalytic notion of neurosis as being caused by conflict over childhood sexual fantasies allowed one of the most respected textbooks in psychiatry to publish in 1975 that the prevalence of incest was 1 per 1,000,000 (Henderson 1975). This is a remarkable underestimate by any objective evidence; even the most conservative of estimates would set the prevalence of sexual abuse in children to at least 5%.

However, some unsophisticated clinicians believe without question any claims of alien abduction and satanic ritual abuse and often seem to have given up reasonable suspicion and the need to consider the capacity for the creation of myth to explain horror and misfortune. Other advocates conceptualize the mishaps of day-to-day life as toxic stressors and explain their effects as being similar to traumatic stressors, which is a misuse of the concept. Also, some doctors are trapped by their ongoing relationships with patients and will use diagnoses to resolve industrial disputes when they are framed as worker's compensation claims. The propensity to polarize these issues emphasizes the importance of using empirical information that has been collected in a systematic and reliable manner to inform a debate.

Despite the experience of two world wars, a systematic investigation of the effects of traumatic stress could not be sustained. The failure to learn from these calamities is an issue of historical and social importance. One reason for this failure was the military's inability to recognize the difference between the acute stress reactions of soldiers to battle and cowardice. There is a difference between being exposed to a life-threatening event and experiencing horror, fear, and disgust and having posttraumatic stress disorder (PTSD). This has long been a source of fundamental confusion.

The Nature of Trauma

Traumatic events inflict both an external and an internal reality that attacks ideals and beliefs about safety, control, and freedom from pain. The external reality is of danger because these events have the capacity to kill, maim, brutalize, and destroy. Examples of such events are disasters, wars, rape, assault, motor vehicle accidents, and predatory violence. These events bring an internal reality of fear, horror, and lack of control because the victim is powerless to change the course of the events as they unfold. Often, the individual is left trapped more by the memory of their own perceptions and feelings of helplessness than by the experience of what has occurred. This leads to a sense of fragmentation as well as a constant retraumatization by the memories triggered by often subtle reminders of the event. Previous life knowledge does little to equip people for these events.

Traumatic events have a range of practical effects. For some, these experiences leave only the scars of the shattered assumptions of safety and personal invulnerability. However, they also may inflict personal injuries that disable, which means that the experience is colored with physical pain and suffering. If a relative is killed or a house destroyed, grief will further complicate the experience because while the victim tries to avoid disturbing memories of the experience, he or she also may wish to retain memories of the lost person or home. With certain traumas such as domestic violence and rape, the intentional cruelty of the perpetrator can radically disturb the victim's sense of trust. Relationships become a constant reminder of the danger and risk. The loss of personal autonomy in war, both in military service and during the experience of occupation, can reframe an individual's sense of self-effectiveness. Societies have a range of traditions and institutions to attempt to protect against these events or create philosophies to deal with the aftermath. The reaction to these experiences is a social issue as well as one of individual psychology.

Definition of the Stressor Criterion

One of the central issues for this field has been defining and observing a *traumatic event*. DSM-III adopted the definition of a traumatic event as "a stressor that would be markedly distressing to almost anyone" (American Psychiatric Association 1980, p. 247). The qualifier states that "the essential feature…is the development of characteristic symptoms following a psychologically distressing event that is outside the range of usual human experience" (American Psychiatric Association 1980, p. 247). The stressors described include combat, natural disasters, accidental man-made disasters, or deliberate man-made disasters. Also, some stressors frequently may produce the disorder (e.g., torture), whereas others produce it only occasionally (e.g., car accidents).

This definition was further clarified in DSM-III-R: "The most common traumata involve either a serious threat to one's life or physical integrity; a serious threat or harm to one's children, spouse, or other close relatives and friends; sudden destruction of one's home or community; or seeing another person who has recently been or is being seriously injured or killed as the result of an accident or physical violence" (American Psychiatric Association 1987, pp. 247–248).

ICD-10 (World Health Organization 1992a) further elaborates with the current definition:

> PTSD arises from a delayed and/or protracted response to a stressful event or situation (either short lived or long lasting) of an exceptionally threatening or catastrophic nature which is likely to cause pervasive distress in almost everybody (e.g., natural or man-made disasters, combat, serious accidents, witnessing the violent death of others or being a victim or torture, terrorist, rape or other crime). Predisposing factors such as personality traits (e.g., compulsive asthenic) or previous history of neurotic illness may lower the threshold for the development of the syndrome or aggravate its course but is neither necessary nor sufficient to explain its occurrence. (p. 147)

DSM-IV (American Psychiatric Association 1994) introduced a further dimension in defining the stressor criterion:

1. "The person experienced, witnessed, or was confronted with an event or events that involved actual

or threatened death or serious injury, or a threat to the physical integrity of self or others" (p. 427)
2. "The person's response involved intense fear, helplessness, or horror. **Note:** in children, this may be expressed instead by disorganized or agitated behavior" (p. 428)

This definition acknowledges the possibility of a personal subjective response to a significantly greater degree. This was included in an attempt to account for the role of dissociative reactions, which are presumed to be one determinant of the outcome. A significant disparity frequently exists between the perceived threat in a situation and the actual threat to the individual, which poses a clinical dilemma. This is perhaps most apparent in considering cases of PTSD following rear-end motor vehicle collisions. The lack of opportunity for an individual to anticipate or prepare himself or herself for the accident in this situation may be one of the reasons that such events are so readily perceived as being threatening.

Prevalence of Trauma

Careful definition of the stressor criterion has provided a benchmark for conducting epidemiological research. Population-based research has identified a surprising frequency of the type of events qualifying as traumatic. The National Comorbidity Survey in the United States (Kessler et al. 1995) and the Australian Bureau of Statistics Epidemiology Study in Australia (Australian Bureau of Statistics 1998) reported that more than 50% of the adult community have been exposed to such traumatic experiences (Kessler et al. 1995; Norris 1992). This finding challenges the original notion that these are events outside the range of usual human experience. The interesting question emerges as to why these experiences are not described more fully or directly reported in the absence of such research. For example, in a United States study, 25% of the male population and 14% of the female population reported having been exposed to life-threatening accidents. Hence, any discussion about an epidemic of PTSD claims is not justified by the empirical data. PTSD was found to be the most common anxiety disorder among females (Kessler et al. 1995).

There is little doubt that many people experience the threat and distress of these events without being disabled or developing long-term psychological symptoms. Kessler et al. (1995) found that the most common causes of PTSD in men are engaging in combat and witnessing death or severe injury, whereas the most common causes of PTSD in women are being raped and sexually molested. Among the men in this representative sample, 60.7% had experienced a qualifying trauma, and a further 17% had been exposed to a trauma that produced intrusive recollections but was not covered by the stressor criterion. In contrast, 51.2% of the women had experienced a traumatic stressor. Significant sex differences were found in the types of events experienced. For example, 25.0% of the men had had an accident, in contrast to 13.8% of the women, whereas 9.2% of the women had been raped, in contrast to 0.7% of the men. The capacity of these events to produce PTSD varied significantly, ranging from 48.4% of the female rape victims to 10.7% of the men witnessing death or serious injury.

In a study of 1,000 adults in the southern United States, Norris (1992) found that 69.0% of the sample had experienced a traumatic stressor in their lives, including 21% in the past year alone. The most common trauma was tragic death, with sexual assault again leading to the highest rates of PTSD and motor vehicle accidents presenting the most adverse combination of frequency and effect. Both Norris (1992) and Kessler et al. (1995) found important age, racial, and sex effects on exposure to trauma, although Norris did not recruit a strictly random sample. For example, Norris (1992) observed that black men had the lowest rates of exposure to trauma and that young people had the highest rates of PTSD. Kessler et al. (1995) found that women had twice the risk of developing PTSD following a trauma compared with men and that no age effect was seen in women because PTSD in early age has increased in recent cohorts of women.

Contrary to the perception of some, most traumatized people are reluctant to speak of their experience or distress. The issues individual victims face in declaring their predicament are complex, and many victims are highly ambivalent about describing their experience for good reason. For example, the rape victim has to face not being believed, hurting her parents and partner, and confronting the pain and shame of self-disclosure. Women often have denied the existence of domestic violence because of the importance of the social illusion of harmony and the desire to avoid an acknowledgment of their powerlessness. There can be not only a conspiracy of silence but also a conspiracy of false accusation.

Phenomenology of the Traumatic Stress Response

DSM-IV-TR (American Psychiatric Association 2000) describes three main criteria (Table 27–1):

1. Reexperiencing of the traumatic event via intrusive remembrances, dreams, and flashbacks
2. Physical or emotional avoidance of stimuli associated with the trauma or a numbing of responsiveness (including symptoms such as restricted range of affect, feeling of detachment from others, and inability to recall important aspects of the trauma)
3. Persistence of symptoms of increased arousal, such as poor sleep, difficulty concentrating, and exaggerated startle response

The evidence has shown that the same pattern of symptoms emerges following a variety of traumatic events, such as natural disasters (McFarlane 1988), accidents (Schottenfeld and Cullen 1986), and wartime experiences (Foy et al. 1987; Keane and Fairbank 1983). This suggests that the underlying process of symptom formation is determined more by a shared response diathesis than by a trauma-specific pattern of distress. The critical dimension of PTSD that separates it from other psychiatric disorders is the recognition that extremely traumatic events are able to produce a disorder with a specific pattern of symptomatology in which the exposure plays a central organizing etiological role.

Two differing diagnostic systems—DSM-IV-TR and ICD-10 (World Health Organization 1992a)—are currently in use. Although many criticisms have been made of the diagnostic criteria of DSM-III, DSM-III-R, DSM-IV, and ICD-10, the provision of precise definitions has allowed a great deal of research to be conducted. Epidemiological and phenomenological research has made a central contribution and has allowed these definitions and the boundaries to be tested. By providing a benchmark, the definition of PTSD was an important step forward, particularly because it has allowed the exploration of the nature of the reactions to these types of events.

The uniqueness of PTSD lies within DSM-IV-TR criterion B. Essentially, as van der Kolk and van der Hart (1991) emphasized, PTSD is a disorder of memory, in which the traumatic experience is not normally integrated. This is evident in the memory's dominance of the patient's consciousness. Thus, the reexperiencing symptoms reflect the primary characteristic of the disorder. The definition in ICD-10 emphasizes this feature and does not require avoidance to be present all the time. The existence of the ICD-10 and DSM-IV-TR definitions with their differences in the stressor criterion definition and the extent of avoidance creates the possibility of these systems being used alternatively, with the clear potential for conflict in medicolegal settings. Similarly, important differences exist in the ICD-10 and DSM-IV-TR definitions of acute stress reaction, with the ICD-10 definition focusing on the polymorphic nature of acute reactions and the DSM-IV definition highlighting the dissociative aspect of the disorder.

Intrusive memories. Repeated involuntary memories may recur spontaneously or can be triggered by a variety of real and symbolic stimuli. These may involve intense sensory and visual memories of the event, which may or may not be accompanied by extreme physiological and psychological distress. They also may occur with a dissociative quality characteristic of flashbacks and also in dreams.

Avoidance of stimuli and numbing. A second pattern of response that sometimes dominates the clinical picture is characterized by avoidance and numbing. Here, the individual enters a state of detachment, emotional blunting, and relative unresponsiveness to his or her surroundings. This is associated with an inability to gain the same sense of pleasure out of activities and an avoidance of situations that were reminiscent of the trauma.

Symptoms of increased arousal. Finally, the individual shows a pattern of increased arousal, which is indicated by sleep disturbance, difficulties with memory and concentration, hypervigilance, irritability, and an exaggerated startle response. In the more chronic forms of the disorder, this pattern of hyperarousal and the avoidance tend to be the more predominant clinical features.

The manifestations of PTSD can best be understood as being driven by several simultaneous processes. First, the repetition of traumatic memories is a well-demonstrated fact of traumatic experiences. This probably occurs in part because of the way in which these memories are laid down and the continued difficulties the individual has in processing them and forming a complete representation. The triggering of these memories is also a consequence of primitive conditioning mechanisms, which are critical to many aspects of human learning.

TABLE 27–1. DSM-IV-TR diagnostic criteria for posttraumatic stress disorder

A. The person has been exposed to a traumatic event in which both of the following were present:

(1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
(2) the person's response involved intense fear, helplessness, or horror. **Note:** In children, this may be expressed instead by disorganized or agitated behavior

B. The traumatic event is persistently reexperienced in one (or more) of the following ways:

(1) recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. **Note:** In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.
(2) recurrent distressing dreams of the event. **Note:** In children, there may be frightening dreams without recognizable content.
(3) acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). **Note:** In young children, trauma-specific reenactment may occur.
(4) intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
(5) physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:

(1) efforts to avoid thoughts, feelings, or conversations associated with the trauma
(2) efforts to avoid activities, places, or people that arouse recollections of the trauma
(3) inability to recall an important aspect of the trauma
(4) markedly diminished interest or participation in significant activities
(5) feeling of detachment or estrangement from others
(6) restricted range of affect (e.g., unable to have loving feelings)
(7) sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:

(1) difficulty falling or staying asleep
(2) irritability or outbursts of anger
(3) difficulty concentrating
(4) hypervigilance
(5) exaggerated startle response

E. Duration of the disturbance (symptoms in criteria B, C, and D) is more than 1 month.
F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

Acute: if duration of symptoms is less than 3 months
Chronic: if duration of symptoms is 3 months or more

Specify if:

With Delayed Onset: if onset of symptoms is at least 6 months after the stressor

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These serve to sustain and kindle the increased arousal. The avoidance and numbing represent homeostatic mechanisms, whereby the individual attempts to modulate and shut down his or her hyperresponsiveness. The disorder arises because some individuals are unable to progressively quench or shut off the acute stress response, which is ubiquitous at times of exposure to such events.

Individuals with PTSD remain trapped by intense past experience to an unusual degree. This significantly interferes with their capacity to maintain involvement in current life activities and relationships. This happens for two reasons. First, their pattern of numbing and decreased general responsiveness makes it difficult for them to gain the normal rewards from ongoing interactions with their environment. Second, their hyperarousal means that they readily become distressed by unexpected stimuli, which further encourages their withdrawal. Apart from their detachment, their propensity to experience triggered memories of the past highlights how their internal perceptual organization becomes excessively centered on the involuntary seeking out of the similarities between the present and the traumatic past. As a consequence, many neutral experiences become reinterpreted as having traumatic associations.

A third mechanism is that of dissociation. For an individual to integrate an experience, a coherent internal representation must be developed. Traumatic experiences have the capacity to disrupt this information-processing capacity of the brain. As a consequence, traumatic memories tend to be laid down as primary sensory memories with only partial cognitive representation. The distress associated with the symptomatology further tends to encourage this pattern of dissociation. One consequence of dissociation is that it significantly decreases the individual's pattern of hyperarousal. However, as this psychological process becomes progressively more involuntary, it can lead to a significant disorganization of the individual's behavior because of his or her inability to deal with the present in an organized and integrated fashion.

Comorbidity and Posttraumatic Stress Disorder

The existence of any psychiatric disorder without the co-occurrence of other disorders in a clinical setting is the exception rather than the rule. Large epidemiological studies indicate that a range of other disorders, particularly affective disorders, panic disorder, and alcohol and substance abuse, frequently emerge in conjunction with PTSD in the significant majority and that this is not isolated to treatment-seeking populations. Patients with comorbid disorders are likely to have a worse long-term outcome than those without comorbidities and may require chronic maintenance therapy. Studies also have broadened attention as to the range of psychiatric disorders that may arise as a consequence of traumatic exposure.

The complexity of people's responses to trauma, and the comparative simplicity of the PTSD conceptualization, is illustrated by the recent rediscovery of the intimate association between trauma, dissociation, and somatization (van der Kolk et al. 1996). Trauma can affect individuals on every level of functioning: biological, psychological, social, and spiritual. Merely focusing on the existence of PTSD symptoms does little justice to presenting an adequate description of the complexity of what is experienced and the extent of a victim's suffering. Excessive attention to the intrusion, numbing, and arousal phenomena in PTSD may severely limit accurate observations of how people react to trauma and may interfere with appropriate treatment. The recognition of the profound personality changes that can follow childhood trauma or prolonged exposure to trauma in adults has been an important development because those changes are major sources of distress and disability. This issue is beginning to be recognized, as demonstrated by the inclusion of complex adaptations to trauma (in the form of disturbed affect regulation, aggression against self and others, attention and dissociative problems, somatization, and altered relationships with self and others) in the "Associated Features and Disorders" subsection of the "Posttraumatic Stress Disorder" section of DSM-IV-TR.

Dissociation and Personality Functioning

The contribution of trauma to the development of borderline personality disorder and multiple personality disorder is generally accepted (Herman 1992). Childhood trauma, particularly sexual and physical abuse, can lead to a range of changes in an individual's ability to modulate and tolerate affect, propensity to dissociative behavior, and capacity for relationships (Saxe et al. 1993). ICD-10 has recognized that enduring personality change can occur after catastrophic experiences, such as being in a concentration camp or being tortured. These changes are characterized by a hostile or mistrustful attitude to the world, social withdrawal, feelings of emptiness, a sense of constant threat, and estrangement. The relationship between such personality changes and PTSD has been investigated; findings suggest that it is uncommon for the personality changes to exist in the absence of PTSD (Herman 1992). Similarly, such changes are much more likely to occur as a re-

sponse to childhood trauma than as a response to traumatic experiences in late adolescence and adulthood. Thus, the developmental stage of an individual can be an important determinant of the nature and duration of the consequences of a traumatic experience. DSM-IV-TR also incorporates several other specific diagnostic issues related to PTSD.

First, acute stress reactions are specifically differentiated from PTSD because current diagnostic definitions imply that PTSD is established only after the symptoms have been present for a month. Although the concept of acute stress reaction was embodied relatively recently in DSM-IV and ICD-10, in military settings, combat stress reactions have long been recognized as a specific pattern of reaction that requires particular treatment. This raises the question as to whether PTSD arises from the normal distress response or whether the immediate response of someone who develops PTSD is different from that of the individual who does not appear to have any specific adverse consequences of the trauma. The definition of acute stress reaction and the recent change in the DSM-IV stressor criterion reflect the current view that the presence of dissociative phenomena in close proximity to the traumatic event is critical to an adverse outcome (Spiegel and Cardena 1991).

Somatic Symptoms

The question arises as to whether a specific pattern of associated physical symptoms occurs as part of the traumatic stress response. Historically, PTSD was described by a series of names that focused on the physical accompaniments of the response, such as "soldiers' heart" in the American Civil War (Trimble 1985). The controversy about the effects of herbicides on the physical health of Vietnam War veterans similarly highlights how even in more recent times, the physical symptoms associated with PTSD can be the primary concern of traumatized populations and their search for compensation (Hall 1986). The Gulf War syndrome has again incited this controversy. This is an important issue in traumatized individuals, who may or may not have been injured. In the injured patient, the significance of somatic distress is particularly likely to be missed or incorrectly attributed to the ongoing sequelae of the physical injury.

Several studies have noted an increased reporting of physical symptoms in individuals with PTSD (Lipton and Schaffer 1988; Litz et al. 1992; Shalev et al. 1990; Solomon and Mikulincer 1987; White and Faustman 1989). Most of the studies that have examined the relationship between physical symptoms and trauma have been with war veterans. For example, Shalev and colleagues (1990) compared Lebanese war veterans who had chronic PTSD with matched combat veterans who did not have PTSD. Veterans in the PTSD group self-reported statistically significantly higher rates of cardiovascular, neurological, gastrointestinal, audiological, and pain symptoms in comparison with those in the non-PTSD group. A detailed medical examination, including chest X ray, electrocardiogram, spirometric tests, blood counts, and urinalysis, however, detected few differences between the two groups. Thus, either the physical symptoms are related to a psychological process or patients with PTSD generally report symptoms in a different way than do patients without PTSD.

The integral nature of somatic symptoms to the phenomenology of PTSD may be accounted for by the existence of several psychological mechanisms. Some authors (Spiegel 1988) see dissociation as a central part of the psychological mechanisms influencing symptom formation in PTSD that may therefore predispose the expression of distress in somatic forms. Growing evidence indicates that information processing is disordered in PTSD, and this may contribute to the presentation of somatic symptoms in PTSD (Galletly et al., in press). An impaired ability to process and differentiate relevant from irrelevant information may be at the root of the disturbed concentration and memory found in PTSD. This problem with defining the salience of information may contribute to a focus on and misinterpretation of somatic sensations.

Longitudinal Course and the Effect on Symptoms

Blank (1993) highlighted the fact that the longitudinal course of PTSD has multiple variations and suggested that these need to be discriminated from the acute, delayed, chronic, intermittent, residual, and reactivated patterns. Also, he suggested that the available data indicate a need for the establishment of a posttraumatic stress syndrome when full diagnostic criteria for PTSD are not met.

The series of alterations of the DSM diagnostic criteria across editions reflects the way in which the perceived symptoms of the disorder have changed over time. The original criteria were substantially based on the observations made by Kardiner (1941) of World

War I veterans with chronic morbidity. These suggested that the disorder had much in common with schizophrenia, particularly the constriction of affect and withdrawal.

The changes in DSM-IV were largely to accommodate the findings of studies conducted in the interim. As a consequence, these criteria place greater emphasis on the role of acute traumatic memories and dissociation. The utility of the criteria therefore may vary significantly with the duration of the disorder. The National Comorbidity Survey data (Kessler et al. 1995) suggested that PTSD will resolve in the first 6 years in 60% of those who develop the disorder. For the remainder, the disorder has a chronic course, which poses a serious public health problem. Longitudinal studies have provided valuable information about how the sensitivity and specificity of symptoms change with time. For example, Solomon et al. (1987) found that the prominence of intrusive symptoms in Israeli servicemen decreased over a 2-year period, whereas symptoms of avoidance increased (Blank 1993).

The relation between the acute symptoms and the emergence of PTSD is also an issue of considerable theoretical and clinical importance. It appears that the timing of the point of maximal intensity and the kindling of the traumatic response are critical to the emergence of chronicity (Weisaeth 1989). Foa (1997) noted that a poor response to treatment is predicted by delayed timing of the maximal traumatic response. She concluded that engagement with the traumatic memory is a critical dimension to the processing of these experiences. The lack of or delayed engagement means that the affect and intensity of the memory have been distanced. Anger and dissociation are two mechanisms that interfere with this process.

A study of motor vehicle accident victims showed very few differences within the first 24 hours of the trauma between individuals who develop PTSD or major depressive disorder and the majority who have no long-term psychological sequelae (Atchison and McFarlane 1997). Those who develop PTSD have a progressive kindling of their reactions, which can be detected by the tenth day after the accident, but the severity of their intrusions further increases over the next 6 months. This suggests that a progressive recruitment of dysregulation occurs in the immediate posttrauma period. The avoidance emerges as a secondary attempt at downregulating this distress. Investigation of these relationships has considerable relevance to the development of interventions targeted at acutely distressed populations.

Epidemiology of Posttraumatic Stress Disorder

A variety of different settings and methodologies are available for investigating the prevalence of PTSD. The studies that have had the greatest effect have examined large representative population samples.

General Population

Seven studies have assessed the prevalence of PTSD in the general population, independent of the exposure to specific stressful events. The most important of these was the National Comorbidity Survey mentioned earlier in this chapter (Kessler et al. 1995). This study was replicated recently in Australia (Australian Bureau of Statistics 1998). The latter examined some of the effects of comparing the use of ICD-10 and DSM-IV criteria. In general, the two systems appear to be reasonably similar.

Andrews et al. (1999) compared the equivalence of the two sets of criteria in an epidemiological data set in Australia. A significant disparity in PTSD was found in the pilot data set for the Australian Bureau of Statistics (1998) study, in which there was only a 35% concordance between the two diagnostic systems. Similar discordance existed for substance abuse. In this study, the 12-month prevalence of PTSD based on ICD-10 criteria was 7%, compared with 3% based on DSM-IV criteria. The discordance appears to emerge because of the avoidance and numbing symptoms (DSM-IV criterion C). Although numbing is noted as a general feature in the "Clinical Descriptions and Diagnostic Guidelines" section of ICD-10, this was not given the same prominence in a "diagnostic criteria for research" version of ICD-10 (World Health Organization 1992b). Some other important differences also were seen, such as a reference in the ICD-10 to the timing of the onset as being important, whereas the DSM-IV criterion E refers to the *duration* of the disturbance as being of great importance. Similarly, ICD-10 does not refer to the impairment in the diagnosis, but this was included in DSM-IV. Peters et al. (1999) reported that the differences in qualifying for criterion C accounted for those who met DSM-IV but not ICD-10 criteria. When subjects with a positive diagnosis based on ICD-10 but not DSM-IV criteria were examined similarly, it again appeared to be criteria D and F, which focus on the degree of distress and impairment, that accounted for the differences. In patients who had a negative diagnosis based

on DSM-IV but a positive one based on ICD-10, the major difference emerged on the qualifying degree of distress and impairment.

Three studies have been carried out in the framework of the Epidemiological Catchment Area (ECA) study (Robins and Regier 1991). These studies provide information about the total number of patients in different communities, which reflects both the prevalence of various traumas that may have affected the members of the community in question and the potency of the individual traumatic events to trigger PTSD.

In the first study, carried out in a sample of 2,493 people living in St. Louis, Missouri, a lifetime PTSD rate of 0.5% among men and 1.3% among women was found; however, the number of those who experienced some symptoms after a trauma was substantially higher (15% among men and 16% among women), with an average of 2.4 symptoms per person among those affected (Helzer et al. 1987). The rates found in the subgroups such as veterans were less than would be expected from previous studies, such as the National Vietnam Veterans' Readjustment Study (Kulka et al. 1990), that specifically examined at-risk populations. This raises questions about the sensitivity of case detection in this and other general population samples.

At the St. Louis site, additional data were collected as part of the second wave of the same survey (Cottler et al. 1992). The overall rate of PTSD was very similar to that found in the first wave (1.4%). One of the main aims of this study was to assess the association between PTSD and substance use: cocaine or opiate users were more than three times more likely than control subjects to report a traumatic event. At the North Carolina site of the ECA, the lifetime and 6-month prevalence rates of PTSD in 2,985 subjects were 1.3% and 0.4%, respectively (Davidson et al. 1991). In comparison with subjects without any history of PTSD, those with PTSD reported significantly more job instability, family history of psychiatric illness, parental poverty, experiences of child abuse, and separation or divorce of parents before age 10.

A fourth survey was carried out in a random sample of 1,007 young adults (aged 21–30 years) from a large health maintenance organization in Detroit, Michigan (Breslau et al. 1991), who subsequently were followed up longitudinally (Chilcoat and Breslau 1998). The lifetime exposure to traumatic events was 39.1% among the sample surveyed. The rate of PTSD in those who were exposed was 23.6%, yielding an overall lifetime prevalence rate in the total sample of 9.2% and placing this diagnosis among the most common psychiatric disorders for this age-specific population group, preceded only by phobia, major depression, and alcohol and drug dependence. Among those who were exposed to a traumatic event, a significant sex difference in the rate of the disorder was seen; 30.7% of the women met PTSD criteria as compared with 14.0% of the exposed men. Risk factors for PTSD following exposure included early separation from parents, neuroticism, preexisting anxiety or depression, and a family history of anxiety. It is unclear why the rates in this study were higher than in the ECA samples, given that the population was not markedly atypical of the general population of similar age.

Finally, Lindal and Stefansson (1993) reported the lifetime prevalence rates of anxiety disorders, including PTSD, assessed through the administration of the Diagnostic Interview Schedule, in a cohort consisting of half of those born in 1931 (N=862) and living in Iceland. The overall prevalence of anxiety disorders was 44.2%, and the lifetime prevalence of PTSD was 0.6%; however, the disorder was found in only females (1.2%) and had a mean age at onset of 39 years. Women with a diagnosis of PTSD had, on average, 3.2 additional diagnoses.

War Veterans

Nearly 50 studies have been done in war samples, with Vietnam War veterans being the most commonly studied. Sample size and composition, study setting, assessment methods, prevalence period (point, period, or lifetime), and inclusion of a comparison group remarkably differ among various studies. These differences are reflected in a marked variation in prevalence rates, ranging from a low of 2% (current prevalence) in the Centers for Disease Control (1988) Vietnam Experience study to more than 70%, found in 5 studies.

The National Vietnam Veterans' Readjustment Study was probably the most in-depth investigation of the overall psychological and psychosocial consequences of the Vietnam War among veterans (Kulka et al. 1990). It included an overall sample of 3,016 subjects whose symptoms were assessed with a variety of standardized instruments. This study reported that 15% of all male veterans who were involved in active war operations currently had PTSD, and an additional 11% had partial PTSD. These rates must be compared with a PTSD rate of 3% among Vietnam War era veterans who did not serve in Southeast Asia and of 1% among civilian control subjects who were matched on age, sex, race/ethnicity, and occupation. Among the females who served in Vietnam, the PTSD prevalence estimate was

9%. The same study found few differences in the rate of other psychiatric disorders among the three groups (Jordan et al. 1991).

Another study evaluated the influence of military service during the Vietnam War era on the occurrence of PTSD among a sample of more than 2,000 male-male monozygotic veteran twin pairs (Goldberg et al. 1990). A PTSD prevalence rate of almost 17% was found in twins who served in Southeast Asia compared with 5% in co-twins who did not. A ninefold increase in the rate of PTSD was seen among twins who experienced high levels of combat compared with those who did not serve in Vietnam.

Most studies found an association between severity and duration of combat exposure on the one hand and prevalence and persistence of PTSD on the other (Solomon et al. 1987). Having been wounded or involved in certain highly traumatic experiences (e.g., handling dead bodies, witnessing mutilation or atrocities) was generally strongly associated with PTSD. High comorbidity rates also have been found, showing that PTSD is only one of the possible psychopathological outcomes following exposure to combat and highly stressful situations.

Other Populations

More than 20 studies have assessed the prevalence of PTSD among victims of natural and technological disasters. These studies showed that symptoms are similar in a variety of these events. Former prisoners of war and other types of prisoners, generally imprisoned for political reasons (e.g., Basoglu et al. 1994; Bauer et al. 1993), also have been extensively examined. In all of these studies, the PTSD rate was quite substantial; the prevalence rate in 6 studies was equal to or higher than 50%, and 3 studies showed prevalence rates of 70% or more. This prevalence probably indicates the severity of the effects of torture on many of the victims. In almost all of these studies, patients had PTSD symptoms for the first time decades after the end of their imprisonment; many others were still experiencing symptoms decades after the end of detention and the first appearance of the disorder.

The other form of political violence that has been investigated is terrorist attacks (Abenhaim et al. 1992; Bell et al. 1988; Curran et al. 1990; Shalev 1992; Weisaeth 1993). The rate of PTSD has been substantial, exceeding 20% of the subjects studied and in two studies being higher than 40% (Curran et al. 1990; Weisaeth 1993).

The PTSD rate also has been determined in samples of resettled refugees, mostly Southeast Asians (e.g., Carlson and Rosser-Hogan 1991; Hauff and Vaglum 1993). Six of these studies found a PTSD rate equal to or higher than 50%. Refugees who have faced very difficult circumstances (including torture, starvation, and witnessing killings) represent a highly traumatized population and have a substantial rate of PTSD and other psychiatric disorders.

Several studies have assessed the prevalence of PTSD among victims of different types of violence, including victims of crime, subjects exposed to multiple homicides, police officers involved in shooting experiences, children and adults exposed to sniper attacks, battered women, and victims of rape or other sexual violence. The latter topic has been investigated in six studies (Bownes et al. 1991; Burge 1988; Dahl 1989; Lopez et al. 1992; Riggs et al. 1992; Rothbaum et al. 1992), and in four studies, the rate of PTSD was more than 70%. The rate of PTSD was substantial in most investigations: only in three studies was the PTSD prevalence rate lower than 25%.

Many other populations, including medical patients hospitalized or treated for different reasons (e.g., patients hospitalized because of major burns or accidental injuries, including motor vehicle accidents; or patients receiving treatment for pain) (Aghabeigi et al. 1992; Benedikt and Kolb 1986), psychiatric patients with other baseline diagnoses (Davidson and Smith 1990; Hryvniak and Rosse 1989; McGorry et al. 1991), and rescuers of disaster victims (Durham et al. 1985; Ersland et al. 1989), have been examined. Across these studies, the rates of PTSD vary, depending on factors related to the type, severity, length, and consequences of the stressor and on the psychiatric status of the subjects before the traumatic event. In particular, a substantial rate of PTSD has been found among psychiatric patients specifically evaluated on measures of PTSD symptomatology and among burn patients.

Impairment

The epidemiological data indicate that PTSD is not only highly prevalent but also associated with substantial morbidity. Also, a growing literature details the negative effect of PTSD in terms of distress and dysfunction. For example, a comparison of PTSD patients and patients with other anxiety disorders showed that the PTSD patients had a worse outcome on a range of dimensions of functioning (Warshaw et al. 1993). In

this longitudinal study in a clinical setting, PTSD had severe effects on quality of life in virtually all domains, including high levels of depression, suicide attempts and gestures, and alcohol abuse. These kinds of data reinforce the important role of psychological trauma in psychopathology and its sequelae.

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Pathogenesis of Posttraumatic Stress Disorder and Acute Stress Disorder

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Posttraumatic stress disorder (PTSD) was originally defined in 1980 to describe long-lasting symptoms that occur in response to trauma. The diagnosis revived psychiatry's long-standing interest in how stress can result in behavioral and biological changes that ultimately lead to disorder. At the time the formal diagnosis of PTSD was being conceptualized, the field was heavily focused on describing what happened to combat Vietnam veterans and other people who had chronic symptoms following exposure to events that typically had occurred years or even decades earlier. It was widely assumed that the symptoms that persisted in these survivors were extensions of those that were present in the earlier aftermath of a trauma (Yehuda and McFarlane 1995). Indeed, some data from recently traumatized burn victims supported the idea that symptoms such as intrusive thoughts were present in the early aftermath of a trauma (Andreasen 1980). However, at the time the diagnosis was established, no longitudinal data—either retrospective or prospective—formally established the relation between acute and chronic posttraumatic symptoms. Thus, the idea that PTSD represented a failure of restitution to normal (Horowitz 1986) was an assumption.

When the diagnosis of PTSD was first established, the intent was to describe symptoms associated with a prolonged response to a traumatic event. Thus, chronic PTSD was not considered qualitatively different from the more acute response but rather was considered to reflect a chronicity of the stress response. Research in the last decade has now questioned the idea that PTSD is simply an extension of a more acute and short-term response to trauma. Rather, PTSD is a condition that occurs in some individuals who are exposed to trauma. Indeed, PTSD is only one of several types of responses to traumatic exposure. Prospective longitudinal studies have found that depression and other anxiety disorders can occur after a traumatic event (McFarlane 1988; Rothbaum and Foa 1993; Shalev et al. 1998a). The question that remains is about the relation between the various types of acute stress responses and more chronic ones. Specifically, it is of interest to determine

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whether the development of PTSD can be predicted from the short-term response to trauma. As we review below, individuals who develop acute stress disorder are more likely to subsequently meet criteria for PTSD. This raises the question of whether PTSD is an extension of acute stress disorder or whether the two conditions represent distinct, albeit overlapping, conditions.

In this chapter, we review the prevalence, course, comorbidity, and biological underpinnings of what is currently known about PTSD and acute stress disorder that may suggest pathogenetic factors in the development of these disorders.

Description of Posttraumatic Stress Disorder and Acute Stress Disorder

Both PTSD and acute stress disorder require exposure to a traumatic event; this is purposely defined as identical for both disorders because what is distinct about the disorders is rather the point in time following the event at which the symptoms occur. In acute stress disorder, symptoms must last for at least 2 days up to 4 weeks (Table 28–1). In PTSD, the symptoms last for a period of at least a month following the traumatic event(s) and can either be acute (symptom duration of less than 3 months) or chronic (symptom duration of 3 months or more).

Acute stress disorder first appeared as a diagnosis in DSM-IV (American Psychiatric Association 1994). Because many clinicians have begun emphasizing early posttrauma intervention such as debriefing, it was convenient to have a diagnosis to describe the condition that was being treated. As such, acute stress disorder arose out of the need for justification for acute intervention in the hopes of preventing more chronic disability. Indeed, people most likely to benefit from acute debriefing were thought to be those with acute stress disorder (Z. Solomon 1993). Although the category of adjustment disorder has been present since 1980 and might have provided an adequate description of early symptoms following a stressful event, the proponents of acute stress disorder were interested in emphasizing that unlike adjustment disorders, which were expected to resolve even without treatment, acute stress disorder was expected to develop into PTSD. Furthermore, acute stress disorder focused on a different set of symptoms, such as dissociation, that were precursors of PTSD. In particular, the symptom of dissociation is a prominent difference between acute stress disorder and adjustment disorder. Interestingly, dissociation per se is not a symptom of PTSD. However, there is much support for the idea that peritraumatic dissociation is a risk factor for the development of PTSD.

Most studies of peritraumatic dissociation and development of PTSD have been retrospective; in some studies, the dissociation was assessed 25 years after the traumatic experiences (Bremner et al. 1992; Marmar et al. 1994) (Table 28–2). However, more recent studies have been prospective. Shalev et al. (1996) reported that peritraumatic dissociation was the best predictor of PTSD 6 months after the trauma in a group of mixed civilian trauma, explaining 30% of the variance in PTSD symptoms. Another study (S. Freedman, T. Peri, D. Brandes, A. Y. Shalev, unpublished data, August 1997) assessed the occurrence of PTSD at 4 months and 1 year following trauma in a subsample of a prior study (Shalev et al. 1997a). This study showed that dissociation was better at predicting PTSD at 4 months than at 1 year. The occurrence of PTSD at 1 year was better predicted by the early occurrence of depressive symptoms. This would perhaps support the idea of including dissociation as a criterion for acute stress disorder given its predictive value.

Interestingly, dissociation has been conceptualized as a positive defense mechanism—that is, "protective" in the acute phases following exposure to trauma (Griffin et al. 1997). A study of debriefing obtained within 72 hours of combat events in Israeli combat veterans who reported peritraumatic dissociation showed a better appraisal of one's own performance and one's military unit's performance during combat (Shalev et al. 1998). Marmar et al. (1994) described "good" and "bad" dissociation, which is really a way of rethinking the idea that there may be both positive and negative ways to cope with a traumatic event. Regardless of whether it is good or bad, the presence of dissociation may place an individual at risk for the development of a more chronic condition, such as PTSD.

Most people with acute stress disorder do develop PTSD. However, there is overlap in that some people with acute stress disorder do not develop PTSD, and some people with PTSD do not develop acute stress disorder (i.e., this is often the case in delayed-onset PTSD). Like acute stress disorder, PTSD is characterized by development of intrusive, avoidant, and hyperarousal symptomatology following a traumatic event. Although dissociation per se is not a symptom of PTSD, it certainly can be present and compatible with the other symptoms of PTSD, such as flashbacks and psychogenic amnesia. The conceptualization of acute stress disorder continues to evolve, and the question still arises as to whether acute stress disorder as it stands today is really

TABLE 28–1. DSM-IV-TR diagnostic criteria for acute stress disorder

A. The person has been exposed to a traumatic event in which both of the following were present:
   (1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
   (2) the person's response involved intense fear, helplessness, or horror.

B. Either while experiencing or after experiencing the distressing event, the individual has three (or more) of the following dissociative symptoms:
   (1) a subjective sense of numbing, detachment, or absence of emotional responsiveness
   (2) a reduction in awareness of his or her surroundings (e.g., "being in a daze")
   (3) derealization
   (4) depersonalization
   (5) dissociative amnesia (i.e., inability to recall an important aspect of the trauma)

C. The traumatic event is persistently reexperienced in at least one of the following ways: recurrent images, thoughts, dreams, illusions, flashback episodes, or a sense of reliving the experience; or distress on exposure to reminders of the traumatic event.

D. Marked avoidance of stimuli that arouse recollections of the trauma (e.g., thoughts, feelings, conversations, activities, places, people).

E. Marked symptoms of anxiety or increased arousal (e.g., difficulty sleeping, irritability, poor concentration, hypervigilance, exaggerated startle response, motor restlessness).

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

G. The disturbance lasts for a minimum of 2 days and a maximum of 4 weeks and occurs within 4 weeks of the traumatic event.

G. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition, is not better accounted for by brief psychotic disorder, and is not merely an exacerbation of a preexisting Axis I or Axis II disorder.

Source. Reprinted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000, p. 471. Used with permission.

a "disorder." If acute stress disorder were a good predictor of PTSD, it may be that this syndrome captures elements of a maladaptive response. It is important to perform longitudinal studies to try and understand the factors that lead to resolution of acute stress disorder compared with prolongation into PTSD. It is clear that each disorder must be better characterized to more fully describe each as a distinct diagnostic entity.

Epidemiology

In considering the prevalence rate of PTSD and acute stress disorder, the main observation is that neither PTSD nor acute stress disorder is an inevitable response to stress.

The range of prevalence rates of PTSD in trauma survivors in DSM-IV is broad (see McFarlane, Chapter 27, in this volume). This great variation is thought to reflect mostly a difference in the type and quality of the trauma experienced. However, it also may reflect how and when studies were performed. Kessler et al. (1995) found that the rates of PTSD differed depending on the type of trauma experienced. For example, 65% of the men and 46% of the women with PTSD reported rape as their most upsetting trauma. On the whole, PTSD is estimated to occur on average in 25% of the individuals who have been exposed to traumatic events (Green 1994), with rates considerably higher for life-threatening events than for those with lower impact (Kessler et al. 1995). Lifetime prevalence of exposure to at least one traumatic event also was found to range from 40% to 55% in various studies. The National Comorbidity Survey (NCS; Kessler et al. 1995) found that about 8% of the population was exposed to four or more types of trauma, some of which involved multiple occurrences. The lifetime prevalence of PTSD has consistently been twice as high in women as in men regardless of the overall prevalence rate of the disorder found in each study sample.

Fewer data have been collected on the prevalence of acute stress disorder. Prevalence rates of various types of trauma, including traumatic brain injury, disasters, and shootings, range from 7% to 33% (Bryant and Harvey 1998; Classen et al. 1998; Eriksson and Lundin

TABLE 28–2. Peritraumatic dissociation as a risk factor for the development of posttraumatic stress disorder

Study	Population
McFarlane 1986	Ash Wednesday bushfire victims
Feinstein 1989	Physical trauma victims
Z. Solomon et al. 1989	Israeli soldiers
Carlson and Rosser-Hogan 1991	Cambodian refugees
Bremner et al. 1993	Childhood abuse and combat veterans
Cardena and Spiegel 1993	San Francisco Bay Area earthquake victims
Holen 1993	North Sea oil rig disaster
Frienkel et al. 1994	Media eyewitnesses to an execution
Koopman et al. 1994	Oakland/Berkeley firestorm victims
Marmar et al. 1994	Vietnam War veterans
Shalev et al. 1996	Injured trauma survivors presenting to emergency room
Eriksson and Lundin 1996	*M/S Estonia* victims

1996; Harvey and Bryant 1998; Staab et al. 1996), which interestingly are about the same as those for PTSD. These studies have found that acute stress disorder is a predictor for the subsequent development of PTSD. Bryant and Harvey (1998) found that 6 months after the trauma in patients with mild traumatic brain injury, PTSD was diagnosed in 82% of the patients who had been given diagnoses of acute stress disorder and in 11% of those who had not been given diagnoses of acute stress disorder. However, the real test of the utility of this concept is whether acute stress disorder predicts very chronic long-term PTSD (e.g., decades later). According to Kessler et al. (1995), about 40% of individuals who develop PTSD fail to show remission, whereas 60% do remit. If acute stress disorder is generally not always predictive of PTSD and is not associated with more chronic forms of PTSD, then perhaps the time frame of acute stress disorder should be lengthened to several months or years rather than weeks, and chronic PTSD should be reserved for those who either fail to return to pretraumatic function or who have relapses.

Risk Factors

Risk factors for PTSD include female gender (Breslau et al. 1997a, 1997b; Kessler et al. 1995); severity of trauma (Foy et al. 1984; March 1993; Yehuda et al. 1998); history of stress, abuse, or trauma (Bremner et al. 1997; Zaidi and Foy 1994); history of behavior or psychological problems (Helzer et al. 1987); preexisting psychiatric disorders (McFarlane 1989); family history of psychopathology (Davidson et al. 1985); genetic factors (True et al. 1993); subsequent exposure to reactivating environmental factors (March 1993; Kluznick et al. 1986; McFarlane 1989; Schnurr et al. 1993; S.D. Solomon and Smith 1995); initial psychological reaction to trauma such as emotional numbing (Epstein et al. 1998; Feinstein and Dolan 1991; Mayou et al. 1993; Shalev et al. 1996); early separation (Breslau et al. 1991; McFarlane 1988); preexisting anxiety and depressive disorders (Anderson et al. 1995; Breslau et al. 1997a, 1997b; Burke et al. 1990; Kessler et al. 1995); and depression at the time of trauma (Shalev et al. 1998a). Parental PTSD also has been found to be a risk factor for the development of PTSD (Yehuda et al. 1995c).

Risk factors for the development of acute stress disorder include female gender, high scores on the Beck Depression Inventory, avoidant coping style, and acute stress severity (Harvey and Bryant 1998). Risk factors predicting exposure to trauma but not to onset of PTSD, controlling for type of trauma, were a history of affective or anxiety disorder and parental mental disorder (Bromet et al. 1998). The apparently higher number of risk factors for PTSD compared with acute stress disorder may be related to the relative newness of the diagnosis and lack of studies rather than to a lack of risk factors per se. Further studies that assess vulnerability to both PTSD and acute stress disorder are needed to clarify further the different and overlapping risk factors for these entities.

Comorbid Disorders

PTSD rarely occurs in the absence of other conditions. Approximately 50%–90% of the individuals with chronic PTSD have a comorbid psychiatric disorder (Freedy et al. 1992; Kulka et al. 1990; see also Chapter 27). This reinforces the idea that PTSD is not randomly distributed throughout the population; rather, subgroups of people are more vulnerable to the development of PTSD and other psychiatric disorders. This also raises the question of whether PTSD develops as a separate disorder from the other psychiatric comorbidities seen in association with it or whether people who have these constellations of disorders are more likely to develop PTSD (Friedman and Yehuda 1995).

Symptoms of depression are frequently observed in trauma survivors with PTSD (Southwick et al. 1991; Yehuda et al. 1994a). Significant correlation between early PTSD symptoms and the occurrence of depression seems to predict chronicity of PTSD (Breslau et al. 1991; McFarlane 1988). The sequence in which PTSD and major depressive disorder occur following trauma is of particular interest. Some studies proposed that depression is secondary to PTSD because its onset followed that of PTSD. In the NCS (Kessler et al. 1995), 78.4% of the patients with comorbid PTSD and major depressive disorder reported that the onset of the mood disorder followed that of PTSD. Vietnam veterans also reported that the onset of their phobias, major depressive disorder, and panic disorder followed that of PTSD (Bremner et al. 1996; Mellman et al. 1992). Retrospective studies were flawed in that patients may not have accurately recalled which symptom came first after being symptomatic for decades. In contrast, 65% of the Israeli combat veterans reported simultaneous onset of PTSD and major depressive disorder, and 16% reported that the major depressive disorder preceded the PTSD (Bleich et al. 1997).

In a groundbreaking prospective longitudinal study, Shalev et al. (1998a) showed that the presence of depression in the early aftermath of a trauma was associated with the development of subsequent PTSD. These data contradict the notion that comorbid conditions in PTSD reflect secondary consequences of the PTSD symptoms and suggest instead that other psychiatric symptoms influence the presence of PTSD symptoms. Indeed, a history of psychiatric symptoms is a predictor of PTSD, but Shalev et al.'s study also indicated that posttraumatic symptoms may be strong predictors.

Hypothalamic-Pituitary-Adrenal Axis Dysregulation in Posttraumatic Stress Disorder

One way to explore differences between PTSD and acute stress disorder is to capitalize on some the distinct findings in the neuroendocrine and psychophysiological areas between the two disorders. Most studies have been done in populations with chronic PTSD and not acute stress disorder. Many aspects of the neuroendocrine responses observed in PTSD do not appear to resemble response patterns observed in acute stress studies in animals. However, some of this may be due to the time evaluated since the onset of the stressor.

Studies have yielded important data with regard to neuroendocrine alterations in PTSD; the hypothalamic-pituitary-adrenal (HPA) axis is hypersensitive to stress, which is manifested by a decreased cortisol release and an increased negative feedback inhibition (Yehuda et al. 1995a, 1998) (Table 28–3). Hypersecretion of corticotropin-releasing factor (CRF) also has been described in PTSD (Bremner et al. 1993), as has blunting of the adrenocorticotropic hormone (ACTH) response to CRF (Smith et al. 1989). Other studies have found lower 24-hour urinary cortisol excretion levels in PTSD patients compared with other psychiatric groups and nonpsychiatric control subjects (Mason et al. 1986; Yehuda et al. 1990, 1993a). PTSD subjects also have been shown to have lower plasma cortisol levels in the morning (Boscarino 1996) and at several points throughout the circadian cycle (Yehuda et al. 1994b) and to have a greater circadian signal-to-noise ratio compared with control subjects without PTSD (Yehuda et al. 1996b). In contrast, Pitman and Orr (1990) found elevated cortisol levels in combat veterans with PTSD compared with combat veterans who did not have PTSD.

In addition, PTSD subjects were found to have an increased number of lymphocyte glucocorticoid receptors (which are needed for cortisol to exert its effects) compared with psychiatric and nonpsychiatric control groups (Yehuda et al. 1992a, 1993a, 1995d) and may have enhanced suppression of cortisol in response to dexamethasone (Dinan et al. 1990; Halbreich et al. 1989; Kosten et al. 1990; Kudler et al. 1987; Olivera and Fero 1990; Yehuda et al. 1993c, 1995a). This response is distinctly different from that found in depression and other psychiatric disorders. In addition, administration of metyrapone, which blocks conversion of 11-deoxycortisol to cortisol and thereby attenuates the negative feedback effects of cortisol at the anterior pituitary, increased ACTH release (Yehuda et al. 1996a). These observations support the hypothesis of enhanced negative feedback regulation of cortisol as an important feature of PTSD (Yehuda et al. 1993b, 1995c).

Similar findings also have been obtained in nonveteran groups. Women with PTSD who had a history of physical or sexual abuse also have been found to have increased lymphocyte glucocorticoid receptors, as in male veterans with PTSD (Stein et al. 1997). In addition, female adult PTSD patients with a history of sexual abuse have patterns of enhanced dexamethasone suppression of plasma cortisol similar to those of male combat veterans with PTSD (Heim et al. 1997; Stein et al. 1997). Holocaust survivors with PTSD have been

TABLE 28–3. Hypothalamic-pituitary-adrenal axis dysregulation in posttraumatic stress disorder

Study	Population	Findings
Mason et al. 1986	Combat veterans	↓ Cortisol
Kudler et al. 1987	Combat veterans	↑ Suppression to DST
Halbreich et al. 1989	Combat veterans	↑ Suppression to DST
Smith et al. 1989	Combat veterans	↓ ACTH to CRH
Dinan et al. 1990	Combat veterans	↑ Suppression to DST
Kosten et al. 1990	Combat veterans	↑ Suppression to DST
Olivera and Fero 1990	Combat veterans	↑ Suppression to DST
Pitman and Orr 1990	Combat veterans	↑ Cortisol
Yehuda et al. 1990	Combat veterans	↓ Cortisol
Yehuda et al. 1993a	Combat veterans	↓ Cortisol/↑ LGR
Yehuda et al. 1993c	Combat veterans	↑ Suppression to DST
Yehuda et al. 1994b	Combat veterans	↓ Cortisol
Yehuda et al. 1995c	Combat veterans	↑ LGR/↑ Suppression to DST
Boscarino 1996	Combat veterans	↓ Cortisol
Grossman et al. 1996	Combat veterans	↑ Suppression to DST
Yehuda et al. 1996b	Combat veterans	↓ Cortisol
Yehuda et al. 1995d	Combat veterans	↑ LGR
Yehuda et al. 1996a	Combat veterans	↑ ACTH with metyrapone
Bremner et al. 1997	Combat veterans	↑ CRF
Jensen et al. 1997	Combat veterans	↓ Cortisol
Kellner et al. 1997	Combat veterans	↓ Cortisol
Lemieux and Coe 1995	Childhood abuse	↑ Cortisol
Resnick et al. 1995	Rape victims	↓ Cortisol
Heim et al. 1997	Sexual abuse	↑ Suppression to DST
Stein et al. 1997	Sexual/physical abuse	↑ LGR/↑ Suppression to DST
Bauer et al. 1994	East German refugees	↓ Cortisol
Yehuda et al. 1995b	Holocaust survivors	↓ Cortisol
Goenjian et al. 1996	Earthquake survivors	↓ Cortisol/↑ Suppression to DST

Note. DST=dexamethasone suppression test; ACTH=adrenocorticotropic hormone; CRH=corticotropin-releasing hormone; LGR=lymphocyte glucocorticoid receptor; CRF=corticotropin-releasing factor.

found to have lower 24-hour urinary cortisol excretion, as in male combat veterans with PTSD (Yehuda et al. 1995b). Adolescent Armenian earthquake victims with PTSD from two towns were evaluated; each town had a different trauma severity associated with it, depending on distance from the epicenter. Adolescents who were exposed to greater trauma and had higher symptom severity had lower morning baseline cortisol levels and greater cortisol suppression by dexamethasone, which is consistent with most of the findings in adult PTSD patients (Goenjian et al. 1996). A subset of 84 refugees from East Germany studied had a diagnosis of PTSD (N=12), and these PTSD patients had lower cortisol levels compared with healthy control subjects (Bauer et al. 1994). In contrast, however, female patients with PTSD related to childhood abuse compared with female patients without PTSD but abused in childhood had increased daily levels of cortisol and norepinephrine (Lemieux and Coe 1995).

Cortisol Responses Acutely Following a Trauma

Few formal studies of the biology of acute stress disorder have been performed. Resnick et al. (1995) studied women rape victims during an emergency room visit hours after the event had occurred. They found that women with a history of rape or assault had significantly lower cortisol levels compared with those who did not. They also found that a history of rape or assault was a potent predictor of the development of PTSD. McFarlane et al. (1997) studied blood cortisol levels in a subset of motor vehicle accident victims and found that those who had lower cortisol levels after the event were more likely to develop PTSD. These studies suggest that the cortisol response is lower in trauma survivors who subsequently develop PTSD compared with either those who develop depression or those who do not develop any psychiatric disorder. Eventually, it may

be possible to identify patients at high risk for acute stress disorder through biological means.

Catecholamine Alterations in Posttraumatic Stress Disorder

The catecholamine system was the first biological system to be linked with trauma exposure. World War I veterans with shell shock had increased heart and respiratory rates in response to gunfire and increased levels of anxiety and blood pressure in response to epinephrine injections (Meakins and Wilson 1918). World War II veterans with this same clinical reaction received diagnoses of *physioneurosis* (Kardiner 1941). These observations prompted many subsequent studies of psychophysiology. Some of these studies noted differences at baseline between combat veterans with PTSD and control subjects not exposed to any trauma (Blanchard et al. 1986; Brende 1982; Dobbs and Wilson 1960; Kardiner 1941; Malloy et al. 1983; Pitman et al. 1990).

Baseline catecholamine studies have yielded mixed results, however (Table 28–4). Some studies noted increased baseline urinary catecholamines in patients with PTSD compared with control subjects (Kosten et al. 1987; Yehuda et al. 1992b). Other studies have not found differences between the two groups (Mellman et al. 1995; Perry et al. 1990), and one study found decreased catecholamine levels in PTSD subjects compared with non-PTSD subjects (Pitman et al., submitted). Studies of baseline plasma catecholamines and their metabolites also have been mixed. No differences between PTSD and control groups were found in some studies (Blanchard et al. 1991; McFall et al. 1990), another study found higher levels in PTSD patients (Yehuda et al. 1998), and yet another showed lower levels in PTSD patients (Murburg et al. 1995).

Plasma catecholamine and metabolite levels have been found to be higher after neuroendocrine provocation (Southwick et al. 1993) or stress testing (Blanchard et al. 1991; McFall et al. 1990) in male combat veterans with PTSD compared with nonpsychiatric control subjects, demonstrating hyperresponsiveness of the catecholamine system, paralleling that of the HPA axis. Fewer α_2-adrenergic receptors also have been found in PTSD subjects (Perry et al. 1987, 1990), perhaps in response to chronic elevations of circulating catecholamines. Epinephrine caused a faster degradation of α_2 receptors in PTSD patients compared with control subjects, indicating that receptors of PTSD patients are more sensitive (Perry et al. 1990). All of the above studies were done in male combat veterans.

TABLE 28–4. Catecholamine alterations in posttraumatic stress disorder

Study	Population	Findings
Meakins and Wilson 1918	Combat veterans	↑ BP with EPI
Kardiner 1941	Combat veterans	↑ BP with EPI
Kosten et al. 1987	Combat veterans	↑ Baseline catecholamines
Perry et al. 1987	Combat veterans	↓ α_2R
McFall et al. 1990	Combat veterans	No difference in baseline catecholamines; ↑ EPI to challenge
Perry et al. 1990	Combat veterans	No difference in baseline catecholamines
Blanchard et al. 1991	Combat veterans	No difference in baseline catecholamines; ↑ HR and NE to challenge
Yehuda et al. 1992b	Combat veterans	↑ Baseline catecholamines
Southwick et al. 1993	Combat veterans	↑ Baseline catecholamines after challenge
Mellman et al. 1995	Combat veterans	No difference in baseline catecholamines
Murburg et al. 1995	Combat veterans	↓ Baseline catecholamines
Yehuda et al. 1998	Combat veterans	↑ Baseline catecholamines
Pitman et al., submitted	Combat veterans	↓ Baseline catecholamines
Lemieux and Coe 1995	Sexual abuse victims	↑ Baseline catecholamines
Orr 1997	Sexual abuse victims	↑ Physiological response to challenge
Perry 1994	Noncombat trauma victims	↓ α_2R
Goenjin et al. 1996	Earthquake survivors	↑ Baseline catecholamines

Note. BP=blood pressure; EPI=epinephrine; α2R=alpha-2 adrenergic receptor; HR= heart rate; NE=norepinephrine.

Among survivors of noncombat trauma with PTSD, the results also have been mixed. Women with PTSD who were sexually abused as children were found to have higher baseline catecholamine levels (Lemieux and Coe 1995), as were sexually abused girls who were not evaluated for the presence of PTSD (De Bellis et al. 1994b) and had increased physiological responses to traumatic imagery (Orr 1997). Armenian children with PTSD who had survived an earthquake showed increased baseline catecholamine metabolite levels (Goenjian et al. 1996). In contrast, Holocaust survivors with PTSD had lower baseline catecholamine levels (Yehuda 1999). Traumatized children had fewer α_2-adrenergic receptors, as was the case in combat veterans (Perry 1994).

Resnick and colleagues' (1995) study of rape victims with PTSD found that 3-methoxy-4-hydroxyphenylglycol (MHPG) was measured in the acute aftermath of the rape. Interestingly, MHPG appeared to be related to subjective stress and intensity of the stressor but not to prior exposure to trauma. The authors concluded that cortisol and catecholamines may reflect different aspects of the experience and consequences of traumatization. This may explain why the two systems do not always appear to be linked in PTSD.

Psychophysiological Response in Posttraumatic Stress Disorder

Most studies conducted with PTSD populations have shown increased physiological response, such as increased heart rate and skin conductance, to challenge stimuli such as imagery or auditory stimuli. Most of the startle response studies in adults showed increased startle to acoustic tones (Table 28–5). The one study conducted in children, however, showed the opposite result of decreased eye blink to loud tones (Ornitz and Pynoos 1989).

Physiological parameters of the initial response to trauma also have been studied as predictors of PTSD. Shalev et al. (1998b) studied trauma victims presenting to an emergency room who had physiological parameters taken on admission to the emergency room at 1 week, 1 month, and 4 months posttrauma. They found that initial heart rate in the emergency room was higher in patients who eventually developed PTSD at 4-month follow-up but did not predict depression or development of acute PTSD at 1 month.

Biological Response to Stress

The neuroendocrine response to stress involves a cascade of secretory events initiated by corticotropin-releasing hormone (CRH) and arginine-vasopression, produced by the hypothalamus, and ultimately results in the release of glucocorticoids from the adrenal gland. The circulating glucocorticoids then regulate the HPA axis through feedback effects on the synthesis and secretion of hypothalamic and pituitary hormones, thereby controlling the basal activity level. The corticosteroid receptors in the hippocampus are very sensitive to this negative feedback system.

The notions of allostasis (the ability to achieve stability through change) (Sterling and Eyer 1988) and allostatic load (the long-term effect of the physiological response to stress) (McEwen and Stellar 1993) have been applied to the stress response by McEwen. Allostatic systems enable us to respond to physical states and respond to a stressful challenge. The most common allostatic responses involve the sympathetic nervous system and the HPA axis (McEwen 1998). Activation of these systems by stress results in the release of catecholamines, corticotropin, and ultimately cortisol. Inactivation of these systems returns cortisol and catecholamine levels to baseline. However, with an inefficient inactivation system, the organisms are overexposed to stress hormones, thereby increasing the allostatic load over time, resulting in pathophysiological consequences (McEwen 1998).

The failure to turn off the HPA axis and sympathetic systems efficiently after stress has been found to be age related in animal studies (McCarty 1985; McEwen 1992; Sapolsky 1992). The return to baseline levels of stress-induced cortisol has been shown to be slowed (Seeman and Robbins 1994) and the negative-feedback effects of cortisol are reduced in elderly human subjects (Wilkinson et al. 1997). It has been speculated that the allostatic systems have become exhausted with increasing allostatic loads. One could postulate that with enormous allostatic loads, as in the case of chronic PTSD, a similar pattern also might emerge (McEwen 1998).

Conclusion

The diagnostic category acute stress disorder may have been established several years after PTSD because the heterogeneity in both short-term and long-term responses to trauma was recognized. To date, it is useful to conceptualize acute stress disorder and PTSD as two dis-

TABLE 28–5. Physiological and startle responses in posttraumatic stress disorder

Study	Population	Finding
Dobbs and Wilson 1960	Combat veterans	↑ Physiological response to challenge
Brende 1982	Combat veterans	↑ Physiological response to challenge
Malloy et al. 1983	Combat veterans	↑ Physiological response to challenge
Blanchard et al. 1986	Combat veterans	↑ Physiological response to challenge
Ornitz and Pynoos 1989	Children trauma victims	↓ EB to auditory startle
Pitman et al. 1990	Combat veterans	↑ Physiological response to challenge
Butler et al. 1990	Combat veterans	↑ EB to auditory startle
Morgan et al. 1991	Vietnam combat veterans	No difference in EB
Shalev et al. 1992b	Israeli patients with PTSD	↑ SC, HR, EMG to imagery
Shalev et al. 1992a	Israeli patients with PTSD	↑ EB, SC, HR, EMG to loud tones
Orr et al. 1993	World War II and Korean War veterans	↑ SC, HR, EMG to imagery
Orr et al. 1995	Vietnam combat veterans	↑ EB to auditory startle in PTSD
Morgan et al. 1996	Gulf War veterans	↑ SC, HR, EMG to imagery
Orr et al. 1997	Yom Kippur War veterans	↑ HR and SC to auditory startle
Morgan et al. 1997	Female sexual assault victims with PTSD	↑ EB to acoustic startle
Shalev et al. 1997a	Israeli civilians in Gulf War	↑ SC and EMG response
Shalev et al. 1997b	Trauma survivors in emergency room	↑ EB and SC to auditory startle
Shalev et al. 1998b	Trauma survivors in emergency room	↑ HR in ER and 1 week posttrauma

Note. EB=eye blink; SC=skin conductance; HR=heart rate; EMG=electromyography.

tinct conditions that are very much related. Acute stress disorder often, but not always, leads to the development of PTSD. It is unclear whether acute stress disorder predicts more chronic, treatment-refractory PTSD. Acute stress disorder and PTSD seem to share similar symptoms, prevalence, risk factors, and neurobiological basis. It will be interesting to know whether and to what extent the two conditions respond to similar treatments. Further research will likely be aimed at identifying subgroups of patients with acute stress disorder who are most likely to develop PTSD or recover from trauma.

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Pharmacotherapy for Posttraumatic Stress Disorder

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Posttraumatic stress disorder (PTSD) is a heterogeneous and complex disorder that may require a multifaceted treatment approach. With the advent of newer pharmacological agents, the role of psychopharmacology in PTSD is emerging. Furthermore, increasing evidence now indicates that severe trauma can produce neurobiological changes (Charney et al. 1993; Davidson and van der Kolk 1996; Kolb et al. 1984), providing a framework for a rational psychopharmacological treatment of PTSD. Nevertheless, the psychopharmacology of PTSD is in its infancy. Thus, only a few controlled medication studies have been done. A critical review of outcome research in PTSD by Solomon et al. (1992) noted about 255 published articles on PTSD treatments—about 11 controlled studies, with 6 in psychotherapy and 5 in pharmacology.

Various agents have been used over time to treat traumatic stress. Casualties from the American Civil War were observed more than 100 years ago by Weir Mitchell. He commented on the use of bromides, opium, chloral, and brandy (Davidson 1997b). The issue of self-medication arose even then and continues to the present with abuse of narcotics, alcohol, and illicit drugs. Wagner Jauregg tried electric therapy for PTSD in Austrian soldiers. World War II brought more consideration of treatments for acute and chronic PTSD. These included barbiturates, insulin, stimulants, and ether. Sargant and Slater (1972) administered carbon dioxide in the 1960s for chronic PTSD and later suggested that antidepressant drugs might be applicable to chronic PTSD. Following combat stress reported after the Vietnam War, phenelzine was evaluated for efficacy in PTSD (Hogben and Cornfield 1981). Phenelzine, a monoamine oxidase inhibitor (MAOI), could enhance psychotherapy by promoting an abreaction. Thus, pharmacotherapy emerged as having either a primary therapeutic effect or an enhancing effect on psychotherapy.

Goals of Pharmacological Therapy for Posttraumatic Stress Disorder

The symptoms of PTSD represent both psychological and biological responses to a definable stressor, an environmental event. Two main categories of PTSD symptoms respond to medication: core symptoms and secondary symptoms (Davidson 1997a). The core symptoms include the basic symptom cluster, as defined by DSM-IV-TR (American Psychiatric Association 2000): 1) intrusive reexperiencing of the original trauma (e.g., nightmares and flashbacks); 2) avoidance of stimuli associated with the trauma; 3) numbing, estrangement, and anhedonia; and 4) hyperarousal. The

secondary symptoms include impaired function, poor resilience to stress, and comorbid conditions.

Medication theoretically may have different roles in treatment: one is to seal over the distress and allow resumption of normal life activities, and the other is to be part of a treatment plan designed to uncover the distress and allow for resolution of the traumatic experience. In the latter role, medication could serve as an adjunct to psychotherapy in working through the distress and trauma. Medication used with the intent of sealing over the pain was an early concept of treatment in the work of Sargant and Slater (1972). They found that when fears were repressed, patients improved; they also found that MAOIs and tricyclic antidepressants (TCAs) were more valuable than abreaction. In later years, the concept of medications that enhanced psychotherapy and abreaction gained recognition. Hogben and Cornfield (1981) noted that phenelzine enhanced psychotherapy in five combat veterans. The end point of pharmacological therapy for PTSD is the same regardless of the conceptual model: to reduce symptom distress, strengthen resilience, and then restore function.

Medication might be helpful if the focus is on symptoms of insomnia or generalized anxiety with a goal to minimize distress while the patient processes the traumatic exposure. Pharmacotherapy also may be needed for exacerbation or relapse of preexisting conditions (e.g., panic), if indicated. If symptoms of anxiety and hyperarousal are prominent, sparing use of anxiolytics may provide short-term relief, but risks of dependence must be considered because substance abuse is relatively common after trauma (North et al. 1994). If symptoms of autonomic arousal are most prominent, noradrenergic blockade with drugs such as clonidine (α-adrenergic agonist) or propranolol (β-blocker) might be effective. Antidepressants also can be effective in this regard. Antipsychotics may be indicated for acute psychosis. Of course, it is important to differentiate psychosis from severe dissociation because the latter does not respond well to antipsychotics (Spiegel 1997).

Additional clinical issues that may influence medication treatments involve comorbidity, such as depression, substance abuse, and borderline personality disorder. Selective serotonin reuptake inhibitors (SSRIs) may be helpful for depression and, possibly, alcohol abuse related to PTSD, but it is unknown how helpful they would be for borderline personality disorder, although the body of literature in this area is increasing. Pharmacotherapy might be indicated for specific symptoms of depression, generalized anxiety, aggression, and impulse-control disorder or other comorbid disorders.

Interpreting the Pharmacotherapy Literature in Posttraumatic Stress Disorder

The diverse presentation of symptoms in PTSD and the number of neurobiological systems that may be affected present a challenge in the search for effective pharmacological agents in treatment. Very few controlled clinical studies in pharmacotherapy exist, although several medications have shown promise in both open trials and case reports. Table 29–1 lists the 15 controlled studies that have been completed to date. Table 29–2 lists open studies and case reports in the current literature.

A key issue in evaluating the controlled studies is the effect-size analysis. This was addressed by Penava et al. (1996/1997); effect size was defined as the difference between the mean of the experimental group at posttreatment and the mean of the control group at posttreatment, divided by the standard deviation of the control group at posttreatment. Thus, standardized scores allow for cross-study comparisons of outcome. Exposure to traumatic stress produces changes in many of the neurotransmitter systems affecting arousal, including the noradrenergic and serotonergic systems. The efficacy of an antidepressant in the treatment of PTSD is related to its potency of serotonin over norepinephrine reuptake blockade. Again, the lack of many controlled studies for a specific medications limits the value of effect-size analysis, which suggests greater efficacy of serotonergic drugs in comparison with noradrenergic drugs.

Possible mechanisms of action of pharmacotherapy must be considered. Drug research findings are conventionally based on proposed mechanisms of action, such as reuptake blockade of various neurotransmitters or specific binding to neuroreceptors. This may be a simplistic approach because interconnections exist within the neurotransmitter systems. Clinical benefits may not be explained solely by receptor binding sites alone. Also simplistic is the concept that a single neurotransmitter system can account for clinical phenomenon, such as a drug response. When drugs are first administered, they could exert their clinical effects through many different pathways. For example, both the dopaminergic and the noradrenergic systems seem implicated in PTSD. Yet, often the serotonergic drugs are clinically beneficial. Currently, it seems necessary to rely on empirical findings from clinical trials; this can be the clinical guide rather than a reliance on what is limited knowledge of pathophysiology (Marshall et al. 1998a).

TABLE 29–1. Controlled drug studies in posttraumatic stress disorder (PTSD)

Study	*N*	Drug, daily dosage	Treatment length	Results
TCAs				
Davidson et al. 1993	62	Amitriptyline, 50–300 mg Placebo	8 weeks	Lower anxiety, depression, and IES scores with active drug
Kosten et al. 1991	62	Imipramine, 50–300 mg Phenelzine, 15–75 mg Placebo	8 weeks	Both active drugs superior to placebo
Reist et al. 1989	18	Desipramine, 100–200 mg Placebo	4 weeks	No change in PTSD, but benefit on depression with active drug
MAOIs/RIMAs				
Katz et al. 1995	45	Brofaromine, 50–150 mg Placebo	14 weeks	Brofaromine significantly reduced PTSD
Shestatzky et al. (1988)	13	Phenelzine, 45–75 mg Placebo	5 weeks	No difference
Baker et al. 1996	118	Brofaromine, titrated to 150 mg Placebo	12 weeks	No difference in CAPS scores, but brofaromine superior on CGI rating
SSRIs				
van der Kolk et al. 1994	64	Fluoxetine, 20–60 mg Placebo	5 weeks	Active drug effective for PTSD, explainable by inclusion of civilian subjects
Nagy et al. 1996	15	Fluoxetine, 20–60 mg Placebo	10 weeks	No significant effect on CAPS-2, CGI, or Ham-D
Connor et al. 1999	53	Fluoxetine, 20–60 mg Placebo	12 weeks	Fluoxetine superior to placebo
Hertzberg et al. 2000	12	Fluoxetine, 10–60 mg Placebo	12 weeks	No response over placebo
Brady et al. 2000	187	Sertraline, 50–200 mg Placebo	12 weeks	Sertraline superior to placebo
Antipsychotics				
Butterfield et al. 2001	15	Olanzapine, 5–20 mg Placebo	10 weeks	No difference
Hamner et al. 2001	40	Risperidone, 1–6 mg Placebo	5 weeks	Significant decrease in PANSS score and reexperiencing
Other				
Braun et al. 1990	16	Alprazolam, 2.5–6 mg Placebo	5 weeks	No change in PTSD
Kaplan et al. 1996	13	Inositol, 12 g Placebo	4 weeks	No effect of inositol on PTSD

Note. TCAs = tricyclic antidepressants; MAOIs/RIMAs = monoamine oxidase inhibitors/reversible inhibitors of monoamine oxidase–A; SSRIs = selective serotonin reuptake inhibitors; IES = Impact of Event Scale; CAPS = Clinician Administered PTSD Scale; CGI = Clinical Global Impression; Ham-D = Hamilton Rating Scale for Depression; PANSS = Positive and Negative Syndrome Scale for Schizophrenia.

TABLE 29–2. Open studies in posttraumatic stress disorder (PTSD)

Study	Subjects	Drug, daily dosage	Treatment length/design	Results
TCAs				
Kinzie and Leung 1989	*N*=9 Dual diagnosis: PTSD-MDD	Imipramine, 50–150 mg Clonidine, 0.2–0.6 mg	12–19 months/ prospective	Promising benefits in depression and severe trauma
SSRI				
Brady et al. 1995	*N*=9 Dual diagnosis: PTSD–alcohol dependence	Sertraline, 50–200 mg	12 weeks	May be effective in PTSD with alcohol dependence
Davidson et al. 1991	*N*=5 Civilian trauma	Fluoxetine, 20–80 mg	8–32 weeks	Marked improvement in intrusive/avoidant symptoms
Davidson et al. 1998a	*N*=15 Civilian trauma	Fluvoxamine, 50–200 mg	8 weeks	Effective with 40%–50% reduction in PTSD scores
Davidson et al. 1998b	*N*=17 Civilian trauma	Nefazodone, 50–600 mg	12 weeks	Effective in treatment completers (60% response rate)
Hertzberg et al. 1998	*N*=10 Combat trauma	Nefazodone, 100–600 mg	12 weeks	Effective for all three PTSD clusters, including sleep disorder symptoms
Marmar et al. 1996	*N*=10 Combat trauma	Fluvoxamine, 100–250 mg	10 weeks	Effective for core PTSD symptoms
Nagy et al. 1993	*N*=27 Combat trauma	Fluoxetine, 20–80 mg	10 weeks	May be effective for reexperiencing and hyperarousal
Marshall et al. 1998b	*N*=13 Noncombat trauma	Paroxetine, 10–60 mg	12 weeks	Effective for all three symptom clusters of PTSD; dissociative symptom reduction
Rothbaum et al. 1996	*N*=5 Female rape trauma	Sertraline, 75–150 mg	12 weeks	CAPS scores decreased by 53%
Anticonvulsants				
Fesler 1991	*N*=16 Combat trauma	Valproate, 250–2,000 mg Various psychotropics	2–16 months	Global improvement in hyperarousal
Wolf et al. 1988	*N*=10 Combat trauma Substance abuse	Carbamazepine, 800–1,200 mg	Unspecified	Improvement in impulse control by observation
Lipper et al. 1986	*N*=70 Combat trauma Substance abuse	Carbamazepine, 400–1,000 mg	5 weeks	Benefits on intrusive symptoms, nightmares, flashbacks

TABLE 29–2. Open studies in posttraumatic stress disorder (PTSD) *(continued)*

Study	Subjects	Drug, daily dosage	Treatment length/design	Results
Antipsychotics				
DeFaria et al. 2001	*N*=12 Psychosis and agitation	Adjunctive risperidone, 1–3 mg	12 weeks	Beneficial effects on reexperiencing and psychotic features
Hamner et al. 2001	*N*=20 Combat trauma	Adjunctive quetiapine, 25–300 mg	6 weeks	Significant improvement in PANSS score, depression, and reexperiencing
Other				
Dow and Kline 1997	*N*=72 Dual diagnosis: PTSD-MDD	12 antidepressants (2 SSRIs, 6 TCAs, 1 MAOI, trazodone, bupropion, lithium)	6 months	Superiority of serotonergic antidepressants over noradrenergic antidepressants
Duffy and Malloy 1994	*N*=8 Combat trauma	Buspirone, 5–30 mg	4 weeks	May be effective
Fichtner and Crayton 1994	*N*=10 Veterans Some alcohol abuse	Buspirone, 10–60 mg Various psychotropics	1 year	40% showed good response
Hargrave 1993	*N*=1 PTSD Dementia Disruptive behavior	Trazodone, 400 mg Buspirone, 45 mg	8 weeks/case report	Effective in both PTSD and multi-infarct disruptive behavior
Horrigan and Barnhill 1996	*N*=1 Sexual trauma	Guanfacine, 1–2 mg	6 weeks/case report	Suppression of nightmares in PTSD
Famularo et al. 1988	*N*=11 Children Acute trauma	Propranolol, 0.8–2.5 mg/kg/day	2 weeks/open off–on–off	Significant improvement in PTSD symptom inventory

Note. TCAs = tricyclic antidepressants; MDD = major depressive disorder; SSR1 = selective serotonin reuptake inhibitor; CAPS = Clinician Administered PTSD Scale; MAOI = monoamine oxidase inhibitor; PANSS = Positive and Negative Syndrome Scale for Schizophrenia.

Review of Pharmacotherapy Literature in Posttraumatic Stress Disorder

Tricyclic Antidepressants

Three placebo-controlled trials of TCAs in chronic PTSD have been published, all among male war veterans (Davidson et al. 1993; Kosten et al. 1991; Reist et al. 1989). The three drugs studied were desipramine, imipramine, and amitriptyline. The outcomes may reflect, in part, differences among these drugs and other factors such as length of trials, dosages, or symptom profiles. Desipramine was studied in 18 war veterans in a 4-week crossover trial (Reist et al. 1989). The results indicated no efficacy for the active drug. One limitation of the study was the brief trial period. Subsequent trials with TCAs did not find placebo differences until after the fourth week of treatment. An additional limitation was the dose, which was relatively low (i.e., in the 100–200 mg/day range).

In a study by Kosten et al. (1991), 61 veterans were studied over 8 weeks with a comparison of imipramine, phenelzine, and placebo. This study is discussed in the "Monoamine Oxidase Inhibitors" section later in this chapter.

Amitriptyline (in doses ranging from 50 to 300 mg/day) was studied in 46 subjects for 8 weeks and compared with placebo (Davidson et al. 1990). Results indicated a significant benefit (50% vs. 17%) compared with placebo on overall PTSD symptoms and also depressive and anxiety symptoms. Residual symptoms remained in many subjects, some of whom continued to meet criteria for PTSD at treatment end (45% of the subjects taking active drug compared with 74% taking placebo). In a subsequent study of the same sample, extended with 16 additional subjects, predictors of drug response were studied. Predictor analysis showed a greater response with amitriptyline in the less severely symptomatic veterans. The poorer responses were related to higher baseline levels of combat intensity, depression, neuroticism, anxious mood, impaired concentration, somatic symptoms, and feelings of guilt (Davidson et al. 1993).

In a retrospective report, desipramine and nortriptyline were studied along with sertraline, fluoxetine, and phenelzine in 72 combat veterans with PTSD and comorbid major depression (Dow and Kline 1997). Treatment outcome was based on clinical global improvement. Antidepressant medications affecting predominantly serotonin reuptake (sertraline and fluoxetine) were associated with better outcomes than were antidepressants affecting predominantly norepinephrine reuptake (nortriptyline and desipramine).

In summary, only three double-blind trials of TCAs for chronic PTSD are available. All of these studies involved veteran populations. Common to all studies was a lack of placebo response in war veterans with chronic PTSD. Two studies showed some improvement in PTSD; amitriptyline may have a preferential effect on avoidant symptoms, and imipramine may affect intrusive symptoms. The one open study compared several antidepressant categories and found treatment advantage with serotonergic reuptake inhibitors, although the nature of this survey limits the confidence that we may have in the results.

Serotonin Reuptake Inhibitors

The SSRIs are now widely used in anxiety disorders, including PTSD. There are underlying reasons for the relevance of serotonin to PTSD. In some animal models, evidence suggests that serotonin type 2 ($5\text{-}HT_2$) receptor pathways are mediators of conditioned avoidance as well as resilience to stress and learned helplessness (Krystal 1990). Clinically, certain symptoms, such as poor impulse control, sleep disturbances, and repetitive responses to intrusive recollections, seem compatible with postulated abnormalities in 5-hydroxytryptophan. Challenge studies with *m*-chlorophenylpiperazine (m-CPP) can produce aggravation of PTSD symptoms in a portion of subjects. The SSRIs, the most used drugs in PTSD, have been studied in open-label and double-blind trials.

Fluoxetine

Seven reports of fluoxetine for PTSD have been published—four controlled studies with both combat and civilian populations, two open studies with mixed trauma populations, and a study of paroxetine binding to blood platelets.

In an open study, fluoxetine was given to five nonveteran patients (Davidson et al. 1991). The dosage ranges were 20–80 mg/day over an 8- to 32-week period. Fluoxetine improved both intrusive and avoidant symptoms. This report is helpful in terms of its focus on nonveteran subjects with PTSD.

An open, prospective trial of fluoxetine was reported by Nagy et al. (1993). The 10-week trial involved an ascending dose in 19 patients with combat-related PTSD. Fluoxetine doses ranged from 20 to 80 mg/day until response was optimal or side effects prohibited the dose

increase. The trial allowed for two important considerations of the drug: the long half-life of fluoxetine and a longer trial period. This study included comorbid depression and panic. Fluoxetine was effective in reducing many key symptoms of PTSD, and efficacy was not limited to depression and panic. Reexperiencing and avoidant or numbing symptoms improved on both the Clinician Administered PTSD Scale (CAPS-2) and the Impact of Event Scale (IOE) (Horowitz et al. 1979). One significant question in this study was whether the higher doses or longer duration accounted for the efficacy. In a subsequent double-blind study, Nagy et al. (1996) administered fluoxetine to a veteran population with PTSD. Fifteen subjects received fluoxetine (20–80 mg/day) or placebo over 5–10 weeks. No significant improvement was seen in CAPS-2 total score, symptom clusters, and Clinical Global Impression Scale or Hamilton Rating Scale for Depression scores. The implication was that veterans may represent a more treatment-refractory group.

van der Kolk and colleagues (1994) conducted a 5-week randomized, double-blind trial comparing fluoxetine and placebo in a diverse population of 22 women and 42 men, of whom 31 were veterans and 33 were nonveterans. Dropout rates for patients receiving fluoxetine were higher than those for patients receiving placebo, and no intent-to-treat analysis was performed. Results indicated that by week 5, the active drug significantly reduced the overall PTSD symptoms, as assessed by the CAPS score, most notably in arousal and numbing. Nonveteran patients did better than the veteran patients, who had a higher level of symptomatology; depression improved more in the veterans taking fluoxetine than in those taking placebo.

Connor and colleagues (1999) compared fluoxetine (up to 60 mg/day) and placebo in 53 civilians with PTSD in a 12-week double-blind study. Fluoxetine was more effective than placebo on most measures of PTSD severity at 12 weeks. In a double-blind evaluation of fluoxetine and placebo in 12 male veterans (Hertzberg et al. 2000), fluoxetine failed to show efficacy.

In another study of fluoxetine, platelet paroxetine binding was studied in 10 Vietnam combat veterans (Fichtner et al. 1993). The study found that pretreatment platelet paroxetine binding measures were lower with the maximal response group. The preliminary findings suggest that platelet paroxetine binding in PTSD patients might serve as a potential predictor of SSRI treatment response.

Finally, interactions of comorbidity with treatment need to be considered. This was reported in a letter by Marshall et al. (1995), in which a cohort of civilian patients with PTSD and comorbid panic disorder had adverse effects with fluoxetine treatment. This group had a heightened rate of anxiety and hyperarousal.

Sertraline

Three open-label studies of sertraline in patients with PTSD have been done; these studies involved patients with dual diagnoses, including depression or alcohol dependence. In a study of 19 combat veterans with major depression (Kline et al. 1994), sertraline treatment resulted in global improvement in PTSD symptoms. The symptoms of reexperiencing, hyperarousal, explosiveness, and depression were reduced.

An open trial of sertraline in comorbid PTSD and alcohol dependence was reported (Brady et al. 1995). This particular study is very important because it is unique in its inclusion of PTSD and comorbid alcohol abuse; this issue is clinically important because these patients usually are excluded from clinical trials. Nine subjects (six women and three men) received sertraline in doses of 50–200 mg/day over 12 weeks. Similar decreases in all three symptom clusters were reported, with a 61% decrease in patients who completed treatment ($n = 6$), as well as significant improvement in substance abuse. However, the findings are limited by concurrent psychosocial treatment of substance abuse and other psychotherapy.

Brady et al. (2000) studied 187 patients with PTSD in a 12-week multicenter, double-blind, placebo-controlled trial with sertraline (50–200 mg). Sertraline was more effective than placebo across a spectrum of outcome measures.

In the retrospective report discussed earlier in this chapter (Dow and Kline 1997), sertraline and fluoxetine were associated with better outcomes than were drugs with noradrenergic reuptake effects (nortriptyline and desipramine). This study population included patients with chronic PTSD and comorbid major depression.

Sertraline was approved in December 1999 by the U.S. Food and Drug Administration as a treatment of PTSD.

Paroxetine

Only one study of paroxetine in patients with PTSD exists in the literature. A 12-week open trial of paroxetine in patients with non-combat-related PTSD, chronic type, was conducted by Marshall et al. (1998b). Seventeen subjects had a significant improvement in all three

symptom clusters, as well as in associated anxiety, depressive, and dissociative features; 11 of the 17 (65%) were rated as much or very much improved. The mean dosage of paroxetine was 42.5 mg/day. The prominence of anxiety symptoms in PTSD, with the effectiveness of paroxetine in studies of depression with anxiety, would suggest its effectiveness in PTSD. Paroxetine produced rapid relief from hyperarousal symptoms in responders within 4 weeks. Avoidance symptoms also improved significantly over 12 weeks. Preliminary analysis showed that childhood trauma correlated inversely with pharmacotherapy response.

Fluvoxamine

Three open studies with fluvoxamine have been done in both combat and civilian populations with PTSD. An open trial of fluvoxamine in 24 Dutch World War II veterans found minimal improvement in intrusive and hyperarousal symptoms (DeBoer et al. 1992). This was a moderately symptomatic group, and the poor findings may have been related to the low motivation of subjects for treatment or high rates of side effects. A 10-week open trial of fluvoxamine was conducted in 10 male Vietnam veterans (Marmar et al. 1996). Fluvoxamine was well tolerated and effective for core intrusion, avoidance, and arousal symptoms of PTSD. The treatment effects were evident by weeks 4–6 and maintained at week 10. Fluvoxamine was studied in 15 civilian subjects in a private practice setting (Davidson et al. 1998a). The dosage range was 50–200 mg/day over 8 weeks. A statistically significant reduction in all PTSD symptom clusters occurred.

Serotonin Antagonist Reuptake Inhibitors

Nefazodone

Six open studies with nefazodone have been conducted in both combat veteran and civilian subjects with PTSD. Two of these studies were published (Davidson et al. 1998b; Hertzberg et al. 1998), and the other four were presented at meetings (Davis et al. 1998; Mellman et al. 1997; Tucker et al. 1998; Zisook et al. 1998). An open trial of nefazodone in 10 combat veterans showed that PTSD symptoms were reduced by 32% (Hertzberg et al. 1998). A 6-week trial of nefazodone in 12 veterans and 2 Holocaust survivors reported that 8 of the 10 subjects completing the study were improved, with significant benefit in hyperarousal (Mellman et al. 1997). In an open-label study of 17 civilian patients, nefazodone was given at dosages of up to 600 mg/day over 12 weeks (Davidson et al. 1998b). A statistically significant reduction in symptom severity over the entire PTSD symptom cluster was observed. Improvement in avoidance was especially noted. The authors postulated that nefazodone may have 5-HT_2 antagonist properties that contribute to a direct antiphobic effect. The response rate of nefazodone in PTSD was characterized by evaluating the pooled data of six open-label studies of both civilians and combat veterans (Hidalgo et al. 1999). The response criterion used was a 50% drop in severity on the primary scale at endpoint relative to baseline. The criteria included effects on each PTSD cluster and on individual symptoms. Nefazodone showed a broad spectrum of action on PTSD symptoms.

In summary, many SSRIs seem promising in PTSD; however, open-label studies have limitations regarding their generalization. Further double-blind studies are needed in this newer pharmacological class. Serotonergic abnormalities are suspected in many anxiety disorders. The possible differences in efficacy among the SSRIs further necessitate comparative double-blind studies. Factors such as the heterogeneity of symptom presentation and the involvement of several theorized neurobiological systems may contribute to these differences in efficacy.

Monoamine Oxidase Inhibitors

Phenelzine

Three studies of phenelzine—two double-blind and one open—have been done in patients with PTSD. In an open trial of phenelzine in Israeli combat veterans with PTSD by Lerer et al. (1987), the 23 patients who completed the study received phenelzine at dosages ranging from 30 mg/day to 90 mg/day over 4–18 weeks. A predetermined therapy endpoint was not stipulated. Thirteen subjects had one of the following diagnoses in addition to PTSD: dysthymia, panic disorder, generalized anxiety disorder, or major depression. The measurements used were a PTSD scale (consisting of 12 DSM-III criteria items with severity rated from 0 [absent] to 4 [incapacitating]), the Hamilton Anxiety Scale, and the Hamilton Rating Scale for Depression. All subjects continued to fulfill criteria for DSM-III (American Psychiatric Association 1980) PTSD at the end point.

The largest study was as 8-week randomized trial comparing two active pharmacotherapies—imipramine and phenelzine—with placebo in 60 veterans with PTSD (Kosten et al. 1991). Both active drugs produced global improvement: 68% with phenelzine and 65% with imipramine compared with 28% in the placebo group. The Impact of Event Scale showed the greatest

reduction in symptoms for phenelzine (45%) compared with imipramine (25%) and placebo (5%). Both phenelzine and imipramine were preferentially beneficial for intrusive over avoidant symptoms; phenelzine showed a 56% improvement over imipramine on the intrusion subscale, and imipramine showed a 27% improvement. Thus, both active drugs produced global improvement, but phenelzine had greater efficacy in several measures. Drug effects were not a result of the reduction in depression because the study did not include major depressive disorders.

In a study by Shestatzky et al. (1988) of 13 patients with PTSD and mixed trauma histories, subjects received phenelzine or placebo over 5 weeks; phenelzine was given in the range of 45–75 mg/day. No difference between medication and placebo was seen; the overall improvement could not be attributed to the active drug. The limitations of this study were the brief trial and small sample. The dropout rate was high (3 of the 10 patients receiving active drug), and the crossover design itself had some shortcomings.

Brofaromine

A multicenter, controlled trial of brofaromine, a combined MAO-A and serotonin transport inhibitor, was conducted in 64 patients with primarily noncombat PTSD (Katz et al. 1995). Subjects received up to 150 mg/day of brofaromine. No difference between active drug and placebo was seen. In a subgroup with more chronic PTSD with symptom duration of at least 1 year, active drug significantly reduced PTSD symptoms.

In a second study in the United States, brofaromine was administered to 146 patients with PTSD, mostly arising from combat trauma (Baker et al. 1996). This study was a 12-week randomized, double-blind, flexible-dose, comparative design with two parallel groups. The primary outcome measure was change in the CAPS score (Blake et al. 1990). Both brofaromine and placebo groups showed significant reductions in the CAPS scores, but no difference between drug and placebo was found. Although brofaromine was somewhat promising in civilians with PTSD, the difference was modest, and the role of reversible inhibitors of MAO-A in PTSD is still very unclear.

Unfortunately, brofaromine has never been commercially available.

Anxiolytics

The anxiolytics initially might seem to be beneficial as a class in PTSD because the hyperarousal symptoms of PTSD resemble general anxiety symptoms that are helped by benzodiazepines.

Benzodiazepines

Three open trials of both alprazolam and clonazepam in PTSD have been done (Dunner et al. 1985; Gelpin et al. 1996; Lowenstein et al. 1988). The only randomized, double-blind study reported with this class of drugs was a 5-week crossover trial with a 2-week interim phase, which compared alprazolam with placebo in a group of 10 Israeli patients with both combat- and civilian-related stress. Minimal efficacy was reported with maximal doses of 4.25 mg/day of alprazolam (Braun et al. 1990). Although anxiety was slightly reduced, no effect on the core symptoms of PTSD was seen.

Lowenstein et al. (1988) reported on an open-label study of clonazepam in subjects with PTSD and multiple personality disorder. Clonazepam is a long-acting benzodiazepine with both antikindling properties, as used in epilepsy, and possibly serotonin effects. In the five subjects described, doses ranging from 1 to 6 mg/day over 6–21 months resulted in improvement in nightmares, insomnia, intrusive recollections, flashbacks, and panic. A shortcoming of this report was that many other subjects had received clonazepam but failed to respond, yet they were not well described.

In general office practice, a benzodiazepine often is used in combination with other drugs. One disadvantage is the withdrawal symptom profile of this medication class and its effects on mood. Even in gradual reductions of alprazolam, severe rage reactions have been noted (Risse et al. 1990). These agents should be used cautiously in PTSD patients who have poor impulse control or proneness to severe depression.

Serotonin Agonists and Antagonists

Buspirone, a partial 5-HT_{1A} agonist, has been reported to be effective in PTSD. In an open trial of eight patients with PTSD, buspirone, in daily doses ranging from 5 to 30 mg, was effective for PTSD symptoms (Duffy and Malloy 1994). Five of the eight subjects showed benefit in dysphoria, a common symptom in PTSD. In a case report of management of both dementia and PTSD in a veteran with a cerebrovascular accident, a combination of trazodone and buspirone was of benefit (Hargrave 1993). Trazodone is a serotonin reuptake inhibitor, and there may have been an augmentation of serotonergic transmission.

In an open trial of 10 combat veterans, which included 4 patients with comorbid alcohol abuse, buspi-

rone was given in doses of 10–60 mg daily for up to a year, along with various other psychotropic drugs (Fichtner and Crayton 1994). The overall response was poor to incomplete. These findings were corroborated by the reports of LaPorta and Ware (1992) and Wells et al. (1991) in similar populations of veterans (LaPorta 1994).

Cyproheptadine, a 5-HT_2 serotonin antagonist, was reported to relieve insomnia and nightmares in two veterans who received doses of 4–28 mg/day (Brophy 1991; Harsch 1986).

Mood Stabilizers

The rationale for the use of mood stabilizers is based on two premises: 1) patients with PTSD have affective instability, and 2) the mechanism of kindling may contribute to exaggerated reaction to stressors, or less stress might be needed to induce a major pathological response. The kindling model suggests that antikindling drugs might be efficacious in PTSD (Friedman 1991).

Lithium

Three open trials or reports of lithium have been conducted in a total of seven veterans with PTSD (Forster et al. 1995; Kitchner and Greenstein 1985; van der Kolk 1987). Kitchner and Greenstein (1985) administered lithium to five Vietnam War veterans with moderate to severe PTSD. These patients were considered treatment resistant, had marked irritability and anxiety, and had used analgesics for pain control. Lithium was given at low dosages (300–600 mg/day) with lithium levels of 0.2–0.4 μg/mL, and follow-up continued over several weeks. Lithium had benefits on degree of rage and potentiation of analgesic and anxiolytic agents, which were concurrently administered. van der Kolk (1987) found that 14 of 22 PTSD patients given a trial of lithium reported markedly diminished autonomic hyperarousal, a decreased tendency to react to stress as if to a recurrence of trauma, and a marked reduction in alcohol intake. Finally, Forster et al. (1995) reported that lithium in dosages of 1,200–1,800 mg/day produced a reduction in violent outbursts in two veterans with PTSD.

Carbamazepine

Three studies of carbamazepine in PTSD have been done—two in veterans and one in children. In two open trials of carbamazepine, veterans with PTSD and irritability, accompanied by comorbid substance abuse, showed improvement (Lipper et al. 1986; Wolf et al. 1988). Lipper and colleagues reported on 10 patients in a 5-week open trial of carbamazepine in dosages of up to 1,000 mg/day and serum levels of 8.4–9.7 μg/mL. Benefit was reported in intrusive symptoms, nightmares, and flashbacks. All patients had some history of substance abuse.

In another study (Wolf et al. 1988), 18 patients with PTSD, behavioral dyscontrol, and head trauma histories but normal electroencephalogram findings had reduced agitation and symptom relief, but no standardized rating scales were reported. Carbamazepine was given in dosages of 800–1,200 mg/day (serum levels not reported).

In a large series of 28 children, ages 8–17 years, with severe PTSD secondary to sexual abuse and comorbid depression, oppositional defiant disorder, and substance abuse, carbamazepine was used in an inpatient setting (Looff et al. 1995). In blood level ranges of 10–11.5 μg/mL, 22 of the 28 patients became asymptomatic. Other therapies used were milieu therapy and other combinations of medicines for comorbidity.

Valproic Acid

Two open studies or reports of valproic acid have been conducted in patients with a primary diagnosis of PTSD with the exclusion of depression. One study by Fesler (1991) reported on 16 veterans who received valproic acid in dosages ranging from 250 to 2,000 mg/day, with serum levels of 44–103 μg/mL. Of the 14 patients who completed the study, the benefits were noted primarily in hyperarousal. However, the rating scales used were global and not standardized. Other psychotropics were concurrently administered. In another report by Szymanski and Olympia (1991), two patients with PTSD and intermittent explosive disorder were treated with valproic acid in the dosage range of 1,000–1,500 mg/day (serum levels not reported). Concurrent TCAs were used. Benefit was reported based on self-reports, but there were no observer-based ratings.

Lamotrigine

Hertzberg et al. (1999) conducted a small placebo-controlled study of lamotrigine in combat veteran and civilian patients with PTSD. Compared with subjects receiving placebo, those receiving lamotrigine showed improvement on symptoms of reexperiencing and avoidance/numbing. This sodium channel–blocking, antiglutamatergic drug shows some promise and deserves future study.

Summary

In summary, controlled studies of mood stabilizers would contribute to understanding how to approach patients with PTSD with marked irritability, aggression, and explosive behavior. The data would be helpful in patients in whom affective disorder is a comorbid diagnosis and in whom augmentation of antidepressants could be evaluated.

Noradrenergic Suppressors

Autonomic arousal symptoms, such as anxiety, restlessness, insomnia, hypervigilance, exaggerated startle response, and irritability, are the core symptoms of PTSD. The locus coeruleus, a norepinephrine-rich area of the brain, is integrally involved in the moderation of adaptive and maladaptive responses to stress, suggesting that noradrenergic suppression may have a possible benefit. Clonidine is an α_2-adrenergic agonist that reduces the rate of firing and inhibits activity of the adrenergic system. In this respect, clonidine has been used in treatment of opioid withdrawal reactions. Marked similarities between opiate withdrawal and hyperactivity in PTSD also have been noted (van der Kolk et al. 1994).

Four studies of noradrenergic suppressors, including propranolol, clonidine, and guanfacine, have been done. In one open study, one of two drugs (propranolol, 120–160 mg/day, or clonidine, 0.2–0.4 mg/day) was given to a total of 21 veterans over a 6-month period (Kolb et al. 1984). A significant improvement was noted in hyperarousal and intrusive symptoms.

In an open study by Kinzie and Leung (1989), nine Cambodian refugees with PTSD and comorbid major depression were given a combination of clonidine (0.2–0.6 mg/day) and TCAs (imipramine, 50–150 mg/day). Improvement was noted in six patients, with specific reduction in, but not necessarily elimination of, hyperarousal symptoms, intrusive thoughts, nightmares, and startle reactions. The avoidance symptoms were minimally affected. Clonidine alone did not reduce the depression symptoms. However, the imipramine-clonidine combination showed promise for severe depression coupled with PTSD.

In an open study of acute PTSD in children, 11 subjects with physical and sexual trauma were treated with an off-on-off medication design with propranolol in doses of 0.8–2.5 mg/kg/day over 2 weeks (Famularo et al. 1988). Subjects improved while taking medication and worsened while off medication, as measured by a PTSD symptom inventory.

The α_2 agonist guanfacine was used for management of recurrent nightmares in PTSD (Horrigan and Barnhill 1996). The subject was reported as improved with doses of 1–2 mg of the drug. The prolonged half-life of 18–22 hours could contribute to the effect on sleep symptoms.

Antipsychotics

The newer atypical antipsychotics show promise both in their effects on mood and anxiety and in their effects on psychosis. Psychotic features may be related to the core PTSD symptoms as part of the reexperiencing phenomenon or may be secondary to comorbid disorders such as major depression or substance abuse (Hamner 1997).

Two open-label studies of atypical antipsychotics in PTSD have been published. A pilot study of adjunctive quetiapine in combat veterans with or without psychotic features indicated significant improvement in PTSD, positive and negative symptoms, and depressive symptoms (Hamner et al. 2001). In another pilot study, risperidone was added in flexible doses to antidepressants, mood stabilizers, or anxiolytic drugs (DeFaria et al. 2001). The study group consisted of combat veterans with or without psychotic symptoms who were only partially responsive to psychotropic drugs. Preliminary results suggest an effect on specific target symptoms such as reexperiencing and sleep disturbance as well as improvement in associated psychotic symptoms.

Two randomized, controlled trials of atypical antipsychotics in chronic PTSD have been conducted. In a pilot study of 15 patients, olanzapine in dosages of 5–20 mg/day was not superior to placebo (Butterfield et al. 2001). A trial of risperidone as adjunctive therapy in 40 patients with chronic PTSD and chronic psychosis found a significant reduction in Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) scores. The trial also showed a significant effect in the CAPS subscale of reexperiencing (Hamner et al. 2000). In a single case report, a Vietnam veteran with PTSD and comorbid paranoia, hallucinations, and thought disorder improved with clozapine (Hamner 1996).

Other Categories of Drug Therapy

Opioid Antagonists

Analgesia may be mediated internally by endogenous opiates. This may occur in stressful conditions as a way to mediate anxiety and fearful response to a stressor. A chronic overproduction of such endogenous opiates

may be involved in the emotional numbing of PTSD, as proposed by Glover (1992). Various drugs may provide pharmacological blockade of opiate effects and relieve numbing to facilitate recovery. In a study of 18 veterans, a long-acting opiate antagonist, nalmefene, produced improvement in eight veterans with PTSD (Glover 1993). Another drug, naltrexone, produced relief of flashbacks in two patients with PTSD (Bills and Kreisler 1993).

Inositol

Inositol, a second-messenger precursor, can affect the function of several neurotransmitters, including serotonin (Rahman and Neuman 1995). It has been shown to be effective in controlled double-blind studies of depression (Levine et al. 1993) and panic disorder (Benjamin et al. 1995). A double-blind study was conducted in 13 patients with PTSD (Kaplan et al. 1996). This was a crossover design with a washout period of 2 weeks, following which patients received either 12 g of inositol or placebo for 4 weeks. No significant difference was found between inositol and placebo in the improvement of core symptoms of PTSD, but treatment may have been administered for too short a time.

Summary

The literature suggests that TCAs and MAOIs are beneficial in combat veterans with PTSD, and SSRIs are of benefit in civilians with PTSD. Overall, phenelzine may have the greatest therapeutic effect (Kosten et al. 1991), although its side effects and risks will always limit its use. SSRIs are of greatest utility at present, and nefazodone shows some promise, especially on sleep parameters.

The current status of pharmacotherapy for PTSD is limited by the number and types of trials and the lack of controlled studies. The effect-size analysis carried out by Penava et al. (1996/1997) enabled cross-study comparison of outcomes in the current controlled studies of pharmacotherapy for PTSD. Their findings, which were based on very few trials, suggest a relative advantage for more serotonergic agents in pharmacotherapy for PTSD.

In a study of response characteristics to antidepressants and placebo in PTSD, Davidson et al. (1997) found that antidepressants were superior to placebo in seven of eight comparisons that used the Clinical Global Impression Scale. However, specific effects on PTSD scales were more variable. Drug response rates were similar for combat and civilian trauma samples, but placebo rates may be higher in the latter. The effect size suggests a moderate to good effect for drug therapy with the following drugs: brofaromine, fluoxetine, imipramine, and phenelzine.

Issues for the Future of Pharmacotherapy for Posttraumatic Stress Disorder

The heterogeneity of PTSD lends itself to consideration of many variables that may affect outcome in the investigations of pharmacotherapy.

Comorbidity

According to the National Comorbidity Survey (Kessler et al. 1995), 79%–88% of the individuals with PTSD met criteria for at least one other disorder. It is important to factor this into our understanding of treatment response. In one study (Davidson and March 1995), the effect of amitriptyline was somewhat less in the face of multiple comorbidities, but we do not yet know if this is a general finding in PTSD. Comorbid alcohol abuse, as mentioned earlier in this chapter, may respond to an SSRI.

Gender Issues

Most published studies of pharmacotherapy for PTSD involved male combat subjects, yet evidence is increasing that women are more likely to have PTSD (Breslau et al. 1997). Do men and women with PTSD respond in similar ways to specific drugs? Are the sex differences in central serotonin synthesis of importance? The question of treatment and safety of medication in childbearing women is also an important issue. A review of the literature by Baum and Misri (1996) on the use of SSRIs in pregnancy and the lactation period points to the recommendation of conservative use with avoidance in the first trimester and during breast-feeding. In severe or decompensating PTSD during pregnancy, whether psychosocial treatment is adequate as a nonpharmacological alternative must be addressed.

Cultural Issues

There is a paucity of data on the effect of cultural factors on either the diagnosis or the treatment of PTSD. Generally, studies have been conducted in the United States, Israel, or a few European countries, although it

has not yet been possible to compare a given treatment across cultures or across ethnocultural groups within a country. There may be important differences in dosage, metabolism, and diet, as well as a lack of validation with respect to rating scales, in a particular culture.

Trauma Severity

There has been less focus on civilian trauma than on combat trauma in the literature. Often, the veteran population has treatment refractoriness, making generalization hazardous. Preliminary findings suggest that adults with PTSD arising from childhood trauma may not respond as well to paroxetine as do other types of patients with PTSD (Marshall et al. 1998a), although this finding requires further substantiation. Trauma severity also may be related inversely to the response to amitriptyline (Davidson et al. 1993).

Conclusion

Overall, antidepressants appear to provide effective pharmacotherapy for PTSD, but there is some disagreement about the magnitude of their efficacy, which also may be influenced by the rating techniques used.

The relation between symptom relief and improvement of functioning or disability has not been studied. For example, pharmacotherapy may aid in coping skills or enhancement of resiliency, but this has been poorly assessed. Factors such as differential responses of civilian and combat populations, female and male patients, severity or type of trauma, length of time before entry into treatment, and other possible vulnerabilities such as comorbid mood disorders or family history of PTSD all may possibly affect outcome of pharmacotherapy. Other unanswered questions include the necessary or ideal treatment period, comparative efficacies of pharmacotherapy versus psychotherapy versus combined pharmacotherapy and psychotherapy, the role of drug combinations, and the relative costs and benefits of effective pharmacotherapy. A further important area of research is that of studying predictors of response to pharmacotherapy for PTSD.

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Psychotherapy for Posttraumatic Stress Disorder and Other Trauma-Related Disorders

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Since posttraumatic stress disorder (PTSD) was first introduced in DSM-III (American Psychiatric Association 1980), an enormous amount has been learned about the complexity of human adaptations to trauma and about the treatment of posttraumatic states. PTSD has turned out to be among the most common of psychiatric disorders, affecting about 8% of the United States population in its lifetime (Yehuda and Wong, Chapter 28, in this volume). The human and economic cost of trauma is enormous. As shown in this chapter, PTSD may affect people's physical heath and immune systems; behaviorally, it tends to be associated with problems with self-regulation and impulse control. Patients with PTSD often have difficulty concentrating, learning from experience, and taking care of their offspring. In short, it sets people up to continue to lead traumatized and traumatizing lives (van der Kolk and McFarlane 1996). What is obviously needed now are studies that determine the expense to society of not treating traumatized individuals versus the cost of effective intervention. For example, somatization is just one costly consequence of exposure to trauma at an early age: people with histories of early trauma have patterns of health care use that are at least three times as high as those of the general population (e.g., Saxe et al. 1994).

People's adaptation to trauma goes well beyond the simple intrusion, numbing, and hyperarousal paradigm that forms the formal diagnosis of PTSD. In diagnostic terms, every epidemiological study has found a high degree of comorbidity of PTSD with other Axis I disorders (see Chapter 28). Most people who respond to a trauma with persistent intrusive and avoidant symptoms also develop a complex set of other interrelated problems. In particular, an intimate association exists between the diagnoses of PTSD, dissociation, somatization disorder, and a variety of problems with affect regulation, including difficulties modulating anger and sexual involvement, as well as aggression against self and others. The severity of this symptom cluster of trauma-related diagnoses is, at least in part, a function of the age at which the trauma occurred and the nature of the traumatic experience (van der Kolk et al. 1996a).

Research has shown that PTSD and the dissociative disorders are inextricably linked. Many investigators believe that scientific justification is lacking for the existence of these disorders as separate in DSM-IV-TR (American Psychiatric Association 2000; Spiegel et al.

1993). Aside from the range of the formal psychiatric diagnoses that are recognized in DSM-IV-TR as related to psychological trauma—PTSD, dissociative disorders, and somatization disorder (van der Kolk et al. 1996a)—unresolved trauma also may profoundly affect people's sense of themselves and their sense of being effective, lovable, and worthy individuals. Attention to the effects of trauma on people's self-concepts and relations to their surroundings can easily be obscured when clinicians are merely asked to decrease people's PTSD symptoms, as rated on one of the numerous scales for PTSD that are now available.

Although most clinicians who treat PTSD have an eclectic approach to treatment (Blake 1993), the systematic treatment outcome studies, which require strict adherence to a prescribed protocol with a preselected population, generally have used circumscribed interventions, such as cognitive-behavioral therapy (Foa et al. 1989), eye movement desensitization and reprocessing (EMDR; e.g., Vaughan et al. 1994a, 1994b; S.A. Wilson et al. 1995), and pharmacotherapy (e.g., van der Kolk et al. 1994). Only two controlled studies have examined the efficacy of psychodynamic therapies: one of accident victims (Brom and Kleber 1989) and one of traumatized police officers (Gersons and Carlier 1994). Both reported significant improvements in their subjects.

Principles of Treatment

People who develop PTSD become "stuck" on the trauma: they keep reliving it in thoughts, feelings, actions, or images. Once this occurs, they begin organizing their lives around avoiding having these feelings or sensations. Avoidance may take many different forms: keeping away from situations, people, or emotions that remind them of the traumatic event; ingesting drugs or alcohol that numb awareness of distressing emotional states; or using dissociation to keep unpleasant experiences from conscious awareness. A chronic sense of helplessness, physiological hyperarousal, and other trauma-related changes may permanently change how a person deals with stress, alter his or her self-concept, and interfere with the view of the world as a manageable place.

Effective planning for goal-directed action requires a sense of relative calm and control. Freud (1911/1958) called the capacity to define one's needs, and to entertain a range of options on how to meet them without resorting to premature action, "thought as experimental action." Traumatized people have trouble tolerating intense emotions and entertaining potentially upsetting cognitions without feeling overwhelmed (van der Kolk and Ducey 1989). They tend to experience their internal world as a danger zone that is filled with trauma-related thoughts and feelings. They often seem to spend their energy on *not* thinking about the trauma instead of on attending to the present and planning for their future. This avoidance of emotional triggers interferes with their capacity to learn from current experience and thus, paradoxically, increases their attachment to the past.

Dissociation

In recent years, the issue of dissociation has received renewed attention as being at the core of the development of PTSD. Many traumatized individuals may contain their traumatic memories in an "ego state," of which they ordinarily have no awareness (Spiegel et al. 1988). Certain emotional states or sensory triggers may precipitate a regression to feelings and behaviors that make them feel or behave as if they were traumatized all over again. However, when they feel or behave that way, they may be quite unaware of the relation between how they currently feel and their histories of trauma. Our research and that of numerous predecessors who have studied the effects of trauma on memory found that trauma often is organized in memory on a perceptual level. "Memories" of the trauma tend to, at least initially, be experienced as fragments of the sensory components of the event: as visual images; olfactory, auditory, or kinesthetic sensations; or intense waves of feelings that patients usually claim to be representations of elements of the original traumatic event (van der Kolk and Fisler 1995). This dissociation of the traumatic experience generally is accompanied by peritraumatic derealization and depersonalization as well as posttraumatic flashbacks, amnesias, and identity disturbances (van der Kolk et al. 1996b). In extreme cases, this dissociation of the trauma may be contained by entirely separate personality fragments, such as occurs in dissociative identity disorder (Spiegel and Scheflin 1994).

Assessment and Diagnosis

How a person copes with the recollections of the trauma depends on a host of preexisting talents and vulnerabilities, as well as the actions taken or not taken at the time of the trauma. Habitual coping style; exposure to prior traumatic experiences; social support; prior psychiatric, medical, social, family, and occupational history; and cultural and religious explanatory beliefs

all play a role in the eventual organization of the traumatic experience. All these factors must be taken into account during treatment planning. Health care providers need to constantly reevaluate whether their treatments are working and assess what particular interventions are most effective for which trauma-related problems. Even though clinical work can almost never be held up to the rigorous standards of research studies, it is important for clinicians to try to find an objective measure to assess whether the treatment is working. In this process, clinicians may need to pay attention to a range of relatively independent posttraumatic problems: 1) intrusions and hyperarousal; 2) dissociative problems, which manifest themselves as "spacing out" and engaging in behaviors for which the patient has no memory; 3) somatization, which may produce tremendously expensive medical interventions without obvious benefit; and 4) affect regulation difficulties, which may manifest themselves as injurious behaviors against self and others, such as self-mutilation, drug abuse, and physical assaults on others. Self-administered computerized assessment instruments are now available to measure degrees of exposure to trauma at different developmental levels and to track the course of response to therapy.

Transference and Countertransference

Legacies of interpersonal trauma tend to become an integral part of the therapeutic relationship: the patient tends to experience mistrust, betrayal, helplessness, longing, and hate in relation to the therapist. Working *with* these transference feelings, instead of treating them as a resistance to the therapist's good intentions, generally makes the critical difference between treatment success and failure. Understanding transference and countertransference feelings may be the most powerful therapeutic tool available to therapists. If not constantly kept in mind, the feelings stirred up by the confrontation with horror, cruelty, and betrayal will evoke intense emotions in the therapist that may interfere with effective treatment or, if properly handled, enhance the effectiveness of therapy (Pearlman and Saakvitne 1995; J.P. Wilson and Lindy 1994).

Phase-Oriented Treatment of Posttraumatic Stress Disorder

To move from being dominated by intrusive reminders of their traumatic past and stop interpreting upsetting events as a return of their trauma, patients need to regain control over their emotional responses and place the trauma in the larger perspective of their lives as something that happened but that can be expected to not recur if the individual is able to take charge of his or her life. Psychotherapy must address three fundamental aspects of PTSD: 1) establish a sense of safety and control from which the patient can approach the memories related to the trauma, 2) decondition the fear and anxiety related to the traumatic memories themselves, and 3) reestablish a feeling of personal integrity and control by addressing the way trauma victims make sense out of their lives. Thus, therapists must use of a variety of techniques to reestablish a personal sense of control, to decondition anxiety, and to maintain meaningful relationships with others. Most clinicians working with traumatized individuals recommend a phase-oriented treatment approach, in which exposure to traumatic reminders is constantly balanced by careful attention to issues of stabilization and mastery.

Different Approaches During Different Phases of the Disorder

Treatments that may be effective at some phases may not be effective at others. For example, initial management with drugs that decrease autonomic arousal will decrease nightmares and flashbacks, will promote sleep, and may prevent limbic kindling, which is thought to underlie the long-term establishment of PTSD symptomatology. Once the disorder PTSD has taken root, and people start interpreting a host of sensory stimuli as threats, these same drugs have only a palliative function, and serotonin reuptake blockers, which seem to have little immediate benefit, may start to allow patients to be less overwhelmed by their emotions and focus less on their fear. On a psychotherapeutic level, safety and soothing are the primary concerns following acute trauma; exposure and desensitization are most helpful when patients have seemingly alien intrusive memories of the trauma. As the disorder unfolds and when avoidance dominates the clinical picture, symptoms of helplessness, suspicion, anger, interpersonal problems, and substance abuse may dominate. When that is the case, primary attention needs to be paid to the establishment of safety, control, and commitment to life itself.

Phase 1: Acknowledgment and Psychoeducation

Before psychotherapy can begin, numerous practical concerns deserve consideration: victims of natural di-

sasters need to secure their possessions and find shelter, battered women need to find a safe place, and sexually and physically abused children need a safe home. Even if the trauma has been inflicted by outside agents, it is critical to establish who the patient can rely on for practical and emotional help; to spell out his or her habitual coping mechanisms; to determine the degree to which he or she relies on alcohol, drugs, or other potentially dangerous self-soothing mechanisms; and to ascertain his or her capacity to tolerate intense emotions.

Traumatized patients are often confused by their intrusive recollections, short tempers, inability to sleep, and trouble concentrating and fear that they may be going "crazy." In the face of their intense grief, anger, and isolation, family members and friends may be equally confused about what to do and give up on trying to help them. The initial encounter with a therapist often provides the first opportunity to make a conscious link between trauma-related thoughts and feelings; explaining to trauma victims what the symptoms of the disorder are often helps them gain some emotional distance from the experience and may be the first step toward putting the event into a larger context. Later, it may be useful to identify which triggers provoke memories of the trauma and find ways to deal with them (Brom et al. 1989; McFarlane 1994).

Because interpersonal trauma tends to occur in contexts in which the rules are unclear, under circumstances that are secret, and in conditions in which issues of responsibility are often murky, the rules, purpose, structure, and methods of treatment, including boundaries, contracts, and mutual responsibilities, must be clearly specified and adhered to (Herman 1992; Kluft 1990). It often is useful to clarify how trauma may cause people to distrust authority figures, including therapists, and how traumatic events may lead to shameful impulses and behaviors, to a fragmented sense of self, and to dissociative episodes. If these issues are ignored, then reenactment of the trauma will be promoted within the therapeutic relationship.

Phase 2: Mastery and Stabilization

Treatment consists of learning to master and "own" one's experiences. This means that patients need to find ways of reestablishing a sense of safety in their bodies and come to trust their own perceptions and feelings. The process of disentangling current reactions to stressful events from reexperiencing a trauma often is complicated, particularly in victims of chronic interpersonal trauma. During this phase, the patient needs to learn to identify and label emotions; identify and use social supports; plan for action; and identify ways of feeling safe, ways of going through the motions of normal functioning, and ways of regaining control over an expanding circle of aspects of daily living (Foa et al. 1991; Linehan 1993; van der Hart et al. 1993). Patients with high levels of dissociation need to learn to control this symptom under stress before they can actively address the memories of their traumatic experiences. A history of exposure to family violence is likely to interfere with the capacity to talk honestly about oneself and one's needs, goals, and plans.

Having PTSD means not only that one's body is likely to react to reminders as if one is being traumatized again but also that one is likely to have a generalized hyperarousal. Chronic hyperarousal interferes with mastery, makes patients feel ashamed and unable to trust themselves, and is likely to keep one's friends and relatives at bay. Although various effective pharmacological interventions have been proposed for this hyperarousal (Davidson and van der Kolk 1996), many patients turn to body-oriented therapies as ways of reestablishing a sense of inner calm. Medications are widely used for the treatment of PTSD, but it is important to remember that very few studies have been done on this subject. Most studies have been on male combat veterans with chronic PTSD that they first developed as adults. A study by van der Kolk et al. (1994) showed a marked difference in responsiveness to fluoxetine between a combat veteran population and a sample of nonveterans with PTSD. In general, the serotonin reuptake blockers can be remarkably useful in helping patients to gain a sense of distance from their intense emotions and to pay attention to a larger array of options. Despite the paucity of systematic studies, it is critical to assist patients in controlling their excessive physiological reactions (including sleep disturbances), which keep them mired in their past and unable to gain perspective on the present.

Most patients themselves are afraid to reexperience their traumas, even in a therapeutic setting, and may primarily seek help to control their traumatic memories rather than to explore them. Clinical wisdom continues to be the determinant about when to help patients stabilize and when to explore the traumatic memories. Psychotherapeutically, during this phase, clinicians should help patients find domains of safety and competence as areas to retreat to when they feel that their emotions are getting out of control. In addition, patients must learn to identify what they are feeling and which emotions are related to their traumas and which

are related to other life experiences, thereby gradually isolating trauma-related perceptions and emotions. Therapists need to assist their patients in learning how to tolerate intense emotions (e.g., anger, fear, sadness, arousal) and (re)learn to use emotional states as guides for action. Linehan (1993) and Foa et al. (1991) have written very useful guides for the practice of stress inoculation training and dialectical behavior therapy that can be immensely helpful during this phase of the treatment.

Phase 3: Deconditioning of Traumatic Responses: Overcoming the Fear of the Memories

When patients have gained a certain degree of stability, control, and perspective, treatment sometimes can be terminated. Past trauma does not always need to be dredged up. Therapy needs to involve controlled exposure to the traumatic memories only if involuntary emotional, perceptual, or behavioral intrusions related to the trauma continue to interfere with functioning. Repeating the trauma, without having perspective on what is being repeated, does not lead to mastery but only disrupts people's lives further (van der Kolk 1989); merely reexperiencing fragments of the trauma (e.g., in nightmares and flashbacks) cannot lead to resolution because the incomplete reliving of perceptual or affective elements of the trauma prevents the construction of an integrated memory, one that no longer serves as a trigger for conditioned responses (van der Hart and Op den Velde 1991).

Many therapists have difficulty exposing their patients to memories that they know will be upsetting to the patients. This exposure should be attempted only when the therapist understands that being able to tolerate the memories of the trauma can free people to live in the present. Note that the safety of the therapeutic relationship makes it possible for patients to revisit the memories and the emotions related to the trauma from a different perspective from the time that the trauma actually occurred. The nature of a traumatic experience makes people feel lost and forsaken; sharing the hurt with a trusted individual is a critical element for the transformation of the timeless memories of the trauma into a historic event.

To be able to fully attend to his or her current experience, an individual must know what happened to him or her in the past and accept the role that he or she played in it. Unless victims complete their memories and are aware of the triggers of trauma, they will likely continue to react with self-blame for failure to prevent the trauma. Without representation in words and symbols, the trauma remains dissociated, leading to conditioned autonomic arousal, psychosomatic reactions, and fight-or-flight reactions. In recent years, several well-controlled treatment outcome studies of PTSD have been done. Edna Foa and her colleagues (1991) believe that the lasting effects of prolonged exposure are significant changes in memory representations of the trauma itself, which are translated into long-term symptom relief.

The clinical usefulness of actively addressing traumatic memories in combat veterans with PTSD has been supported by several studies that used imaginal flooding. Cooper and Clum (1989) found that in comparison with "conventional" PTSD treatment, imaginal flooding resulted in improved sleep and anxiety symptoms, but not depression, 3 months after treatment ended. Keane and his colleagues (1989) found that implosion therapy assessed at 6 months caused a reduction in depression, anxiety, and intrusive symptoms but not in emotional numbing or avoidance. Boudewyns et al. (1990) showed that flooding, but not counseling, led to significant improvement, which was maintained at 3-month follow-up. Other studies, such as a 2-year follow-up of eight veterans who received biofeedback-assisted systematic desensitization, confirmed that the effects of implosion therapy persist over time (Peniston 1986). It is important to emphasize that implosion therapy may lead to serious complications. In a study of 10 subjects with PTSD, Vaughan et al. 1994b) reported that it was useful in 7 subjects; however, 2 were not helped, and 1 experienced an increase in both intrusion and avoidance symptoms. Pitman and colleagues (1991) stopped a flooding study with Vietnam War veterans because a few subjects developed serious adverse reactions.

The particular technique used to help patients confront their traumatic memories is probably *not* the critical variable. For example, Frank and colleagues (1988) found that both cognitive therapy and systematic desensitization significantly reduced anxiety, depression, and fear in rape victims. Resick and Schnicke (1992) used a combination of education, exposure, and cognitive reprocessing and had very similar results to those of Foa and her colleagues (1991), who used implosion therapy and stress inoculation training. In another study that included psychodynamic treatment, hypnotherapy, and desensitization, Brom and Kleber (1989) found that significant improvement occurred in all treatment modalities, except in the wait-list control group.

Eye Movement Desensitization and Reprocessing

A new exposure treatment for PTSD, in which rapid, rhythmic eye movements are used, was first proposed by Francine Shapiro (1989). The patient is encouraged to maintain an image of the original traumatic experience and is asked to simultaneously evoke the event and associated feelings. In the past few years, a steady output of successful case reports has encouraged further investigation (Chemtob et al. 2000). Although some reports (Metter and Michelson 1993; Pitman et al. 1996), which mainly included patients with chronic PTSD, found little to commend this method, other studies have been encouraging and indicate that this new form of treatment appears capable of producing powerful therapeutic effects in some patients with PTSD (Vaughan et al. 1994a, 1994b; S.A. Wilson et al. 1995). In a study in our laboratory, three sessions of EMDR decreased the Clinician Administered PTSD Scale (CAPS) score from 84 to 37 in 12 patients. We did a symptom provocation study with neuroimaging as an outcome measure. Preliminary data analysis indicated that effective treatment is accompanied by increased activity in the left prefrontal cortex and in the anterior cingulate gyrus, bilaterally, indicating that people seem to become more capable of judging whether trauma-related sensory information is an actual recurrence of the trauma or merely a reminder (Levin et al. 1999).

None of the exposure therapies are harmless treatment techniques; evoking traumatic memories is generally intensely upsetting, which increases the risk of sensitizing and aggravating PTSD symptomatology. Excessive arousal may worsen the PTSD by interfering with the acquisition of new information. Hence, the critical issue in treatment is to expose the patient to an experience that contains elements that are sufficiently similar to an existing traumatic memory to activate it, while introducing aspects that are incompatible enough to change it. The most important element that allows patients to confront their traumatic memories is their relationship with a trusted therapist in a safe environment (van der Hart and Spiegel 1993). Behavioral therapists tend to meticulously outline their exposure procedures in treatment manuals but tend to neglect to write about a critical element in the success of effective treatment: the intensely personal element in all psychotherapeutic procedures. Their results are most likely influenced in a major way by their personal investment in the well-being of their patients, which is communicated and translated into a subjective sense of safety.

Phase 4: Restructuring of Trauma-Related Cognitive Schemes: Group Psychotherapy for Posttraumatic Stress Disorder

In many patients with PTSD, trauma-related conceptions of themselves and the world come to dominate their everyday existence. When dissociation is a central element of coping with the trauma, there may be a split: some existing mental schemas are maintained and come to coexist with trauma-related schemes that are activated only when the individual is exposed to a stressful situation. Exposure to later stresses tends to reactivate not only traumatic memories but also trauma-based schemas about self and others. Effective psychotherapy needs to specifically address how the trauma has affected people's sense of self-efficacy, their capacity for trust and intimacy, their ability to negotiate their personal needs, and their ability to feel empathy for other people (Herman 1992; McCann and Pearlman 1990). This is often best accomplished in a group psychotherapy setting.

Emotional attachment is a potent protection against being traumatized. Contemporary research (Raphael 1986; Ursano et al. 1994) has shown that people whose social support network remains intact are relatively well protected against even catastrophic stresses. For young children, the family usually is a very effective source of protection against traumatization, and most children remain resilient as long as they have a caregiver who is emotionally and physically available (McFarlane 1988). Mature people also rely on their families, colleagues, and friends to provide such a trauma membrane. In recognition of this need for affiliation as a protection against trauma, it has become widely accepted that the central issue in acute crisis intervention is the provision and restoration of social support (Lystad 1988; Raphael 1986).

Some form of group therapy is often considered a treatment of choice for both acutely and chronically traumatized individuals. The task of group therapy and community interventions is to help victims regain a sense of safety, connection, and mastery. After an acute trauma, fellow victims often provide the most effective short-term bond because the shared history of trauma can form the nucleus of retrieving a sense of communality. For chronically traumatized individuals, group psychotherapy may provide a sense of mutuality and a forum to explore concerns about safety and trust that have been affected by earlier interpersonal trauma.

Regardless of the nature of the trauma or the structure of the group, the aim of group therapy is to help

people actively attend to the requirements of the moment, without undue intrusions from past perceptions and experiences. The effectiveness of group psychotherapy has been documented following interpersonal violence (Mitchell 1983), natural disasters (Lystad 1988; Raphael 1986), childhood sexual abuse (Ganzarian and Buchele 1987; Herman and Shatzgow 1987), rape (Yassen and Glass 1984), spouse battering (Rounsaville et al. 1979), concentration camps (Laub and Auerhahn 1993), and war trauma (Parson 1985). In a group of people who have gone through similar experiences, most traumatized people eventually are able to find the appropriate words to express what has happened to them. As was observed more than 50 years ago: "by working out their problems in a small group they should be able to face the larger group, i.e., their world, in an easier manner" (Grinker and Spiegel 1946).

Trauma-related group psychotherapies have many levels, with different degrees of emphasis on stabilization, memory retrieval, bonding, negotiation of interpersonal differences, and support. However, to varying degrees, the purpose of all trauma-related groups is to 1) stabilize psychological and physiological reactions to the trauma, 2) explore and validate perceptions and emotions, 3) retrieve memories, 4) understand the effects of past experience on current affects and behaviors, and 5) learn new ways of coping with interpersonal stress.

Phase 5: Exposure to Restitutive Experiences

Patients with PTSD who are primarily preoccupied with reliving or avoiding their traumatic memories have little room for new, gratifying experiences that would help them repair their past injuries. Patients need to be given the courage to actively expose themselves to experiences that provide them with feelings of mastery and pleasure. Engagement in physical activities, such as sports or wilderness ventures; gratifying physical experiences, such as massages; or artistic accomplishments may be experiences that patients build up that are not contaminated by the trauma and that may serve as a core of new, gratifying experiences.

Failure to approach trauma-related material gradually likely will intensify posttraumatic symptomatology, leading to increased somatic, visual, or behavioral reexperiences. Being able to share one's reactions with others can make a great deal of difference in one's eventual adaptation. The trauma can possibly best be worked through if an empathic bond is negotiated with another person, with whom the effects of the trauma on the sense of self and trust in others can be tested with negotiations about safety, trust, disappointment, and commitment.

Talking about the trauma is not enough; trauma survivors need to take some action that symbolizes triumph over helplessness and despair. People who have been traumatized need to both take action to restore a sense of agency in their lives and actively create symbols to mourn what has been lost and to establish the historical and cultural meaning of the traumatic events. These symbols are necessary to remind survivors of the ongoing potential for communality and sharing. This may take the form of writing a book, taking political action, helping other victims, or applying any of the myriad of creative solutions that human beings can find to defy even the most desperate plight.

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Part
IX

Anxiety Disorders in Special Populations

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31

Anxiety Disorders in Children and Adolescents

John S. March, M.D., M.P.H.
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Presumably because they are associated with significant suffering and disruption in normal psychosocial and academic development and family functioning, disorders characterized by excessive fear are among the more common causes of referral to children's mental health care (March 1995). Even more striking, as many as 3%–5% of all children and adolescents have clinically diagnosable anxiety disorders, not including obsessive-compulsive disorder, which affects another 0.5%–1.0% of children (Costello and Angold 1995b). More than 50% of affected young persons will experience a major depressive episode as part of their anxiety syndrome (Costello and Angold 1995b), with consequent increases in morbidity and perhaps mortality (Curry and Murphy 1995).

Echoing many of the findings in this book on adult anxiety disorders, this chapter provides an overview of the anxiety disorders that have a specific onset during childhood or adolescence: generalized anxiety disorder, separation anxiety disorder, social phobia, and specific phobia. Readers interested in etiopathogenesis (Marks and Nesse 1994), assessment (March and Albano 1996, 1998), epidemiology (Costello and Angold 1995b), psychosocial treatments (Eisen and Kearney 1995; Francis and Beidel 1995; Hibbs and Jensen 1996; Silverman and Kurtines 1996), family treatment (Barrett et al. 1996; Wells 1995), medication management (Allen et al. 1995; Kutcher et al. 1995; Popper 1993), or combined treatment (Bernstein et al. 1996) may wish to pursue more in-depth treatments of these and other topics (March 1995). Readers interested in a further exploration of the diagnosis and treatment of posttraumatic stress disorder (PTSD) and obsessive-compulsive disorder also may wish to pursue March (1999a) and March et al. (1997a, 1998) and March and Leonard (1996), March and Mulle (1998), and March et al. (1995), respectively.

Overview of Anxiety in Children and Adolescents

Because most fears occurring during childhood are developmentally appropriate to the context in which they occur, anxiety in contrast to worry usually refers to developmentally inappropriate fears or to developmentally appropriate fears that produce excessive distress or dysfunction (Silverman 1987). Phobias are fears that are attached to specific objects and that usually provoke avoidance, such as the fear of snakes or heights. Anxiety

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is typically more diffuse than either normative fear or specific phobias, so that it is attached to many different situations and events. Thus, one distinguishing feature of anxiety—as in separation or generalized anxiety disorders—in contrast to phobias is that the latter are more sharply circumscribed. Nonetheless, the distinction is to some extent academic. For example, social phobia is both generally (fear of rejection in a variety of social situations) and narrowly defined (public speaking anxiety). Similarly, traumatic specific phobias grade into PTSD insofar as anxiety is diffuse and phobias tend to generalize into an ever-widening circle of life circumstances.

Anxiety disorders in youths are composed of sets of clinically relevant fears selected from among common, but normative, fears that are present at one time or another in many, if not most, children and adolescents. From a diagnostic point of view, such fears and worries are ubiquitous, so that clinicians and researchers interested in childhood anxiety disorders face the daunting task of differentiating pathological anxiety from fears occurring as a part of normal developmental processes (Costello and Angold 1995b).

One approach to this taxonomic problem has been the development of rating scales that inventory common fears in children and adolescents (March and Albano 1996). The Multidimensional Anxiety Scale for Children (MASC; March 1998; March et al. 1997c) nicely illustrates the general approach. The MASC was developed to sample key anxiety symptoms from the universe of anxiety symptoms that have concerned clinicians and researchers working with anxious children and adolescents. Only the most important symptoms and symptom clusters survived the scale development process, so that the MASC can be seen as representing the population factor structure of anxiety in both children and adolescents. As summarized in Table 31–1, the MASC contains four main factors, three of which can be divided into subfactors. To a large extent, the empirically derived factor structure of the MASC matches the DSM-IV-TR (American Psychiatric Association 2000) diagnostic clusters of social phobia, separation anxiety disorder, panic, and, averaged across all four factors, generalized anxiety disorder. In addition, the hypothesized division of harm avoidance into perfectionism and anxious coping also received empirical support, which along with sex and age norms allows empirical quantification of distress and impairment, which is essential to establishing clinical severity and, thus, diagnoses.

In contrast to scalar approaches, DSM-III-R (American Psychiatric Association 1987) took the tack of introducing a categorically defined subclass of anxiety disorders of childhood and adolescence; DSM-IV (American Psychiatric Association 1994) both refined these constructs and established a greater degree of continuity—developmental and nosological—with the adult anxiety disorders. The DSM taxonomy in essence reflects an expert consensus regarding the actual clustering of anxiety in pediatric samples (Shaffer et al. 1989), but empirical support in some cases is questionable (Beidel 1991). More specifically, several DSM-III-R anxiety disorders of childhood (overanxious and avoidant disorders, in particular) were collapsed in DSM-IV into the adult categories (generalized anxiety disorders and social phobia, respectively). However, the DSM-IV criteria sets themselves do not in general reflect a developmental perspective (Angold and Costello 1995; Cantwell and Baker 1988), and therefore the clinician must translate the DSM-IV criteria into terms that are relevant for the age, sex, and cultural background of the child.

When considering how best to inventory anxiety symptoms, the severity and prevalence of fears must be considered. For example, certain specific phobias, such as nighttime fears, are age dependent in that they are much more common in preschool- and early-elementary-school-aged children (King et al. 1992). In older children, however, the presence of such fears may more reliably be seen as indicating pathological anxiety. Similarly, separation anxiety seems more prominent in younger children, in whom it is developmentally appropriate, and becomes increasingly less appropriate as the child moves through middle childhood into adolescence (Black 1992). Other fears, such as fears about self-presentation and consequently social phobia, become more common as children mature into adolescence (Costello and Angold 1995a).

TABLE 31–1. Multidimensional Anxiety Scale for Children (MASC) factors

Physical symptoms
Tense
Somatic
Harm avoidance
Perfectionism
Anxious coping
Social anxiety
Humiliation fears
Performance fears
Separation/panic anxiety

In the DSM taxonomy, children with generalized anxiety disorder typically are characterized as perfectionistic "worriers" who are constantly asking for reassurance (Silverman and Ginsburg 1995). Children with social phobia show an exaggerated concern with self-presentation. They constantly fear saying or doing something foolish or embarrassing, are exquisitely sensitive to rejection and humiliation, and often feel socially scrutinized, which they usually handle by avoiding social interchange, particularly when it involves public speaking (Beidel and Morris 1995). Selective mutism can be conceptualized as an age-appropriate variant of specific (public speaking) or generalized social phobia, dependent on the extent of other areas of social inhibition, in which usually younger children will not talk (despite normal language) to anyone other than "safe" friends and adults (Black and Uhde 1995; Leonard and Dow 1995). Separation anxiety disorder is characterized by an intense fear of harm surrounding important attachment figures. Although separation anxiety disorder typically has been seen as a relational disturbance, recent evidence suggests that separation anxiety disorder may represent an age-appropriate presentation of panic disorder in younger children (Black 1995). As with panic disorder, separation anxiety disorder typically begins with somatic or autonomic complaints, with symptoms then escalating to full panic and, understandably, to activation of important attachment mechanisms as a means of coping with panic. Thus, the fear of not being able to escape to a safe place in panic disorder is not unlike the need to have a parent immediately available in separation anxiety disorder; both involve acute proximity seeking as a means of reducing arousal and fear (Black 1995; Ollendick et al. 1994).

Finally, comorbidity among the anxiety disorders, and between the anxiety disorders and other internalizing and externalizing disorders, complicates both diagnosis and treatment (Albano et al. 1995; Curry and Murphy 1995). For example, a wide variety of specific phobias commonly accompany the anxiety disorders, including fear of the dark, monsters, kidnappers, bugs, small animals, heights, and open or enclosed spaces. Nighttime fears, resistance to going to bed, difficulty falling asleep alone or sleeping through the night alone, and nightmares involving separation themes are not uncommon. These specific phobic symptoms are common triggers for panic or separation anxiety and are responsible for many of the avoidance and ritualized anxiety-reducing behavior (Black 1995). Anxious children also show high rates of comorbid depression (Curry and Murphy 1995). In younger children, separation anxiety disorder precedes depression in approximately two-thirds of the patients and may form the nidus for recurrent affective illness and panic disorder if left untreated (Kovacs et al. 1984). Children and adolescents with both anxiety and depression have a significantly worse long-term prognosis (Pine et al. 1998), with a higher-than-expected risk for suicide (Lewinsohn et al. 1995).

Assessment

As noted earlier in this chapter, a wide variety of normal fears and worries are omnipresent among youth; pathological anxieties are less common but not rare (Costello and Angold 1995b; Ollendick et al. 1985). However, in part because of a lack of acceptable measurement tools (March and Albano 1996), the population prevalence of childhood-onset fears and, even more, the factor structure of anxiety symptoms in community samples has, until now, remained unclear, as has the relative importance of specific anxiety dimensions within sex, racial/ethnic, or cultural groupings across time (Costello and Angold 1995b; Last et al. 1992). To address these issues, instruments designed specifically to assess anxiety in children and adolescents are necessary for several reasons. First, children appear to undergo a developmentally sanctioned progression in anxiety symptoms (Keller et al. 1992; Last et al. 1987). Second, their day-to-day environments differ from those most typically experienced by adults, so that the presentation of anxiety also differs, as in "school phobia." Third, sex, racial/ethnic, and age norms are necessary to differentiate normal from pathological anxiety. Finally, some childhood fears may be viewed as adaptive or protective (Silverman et al. 1995); only when anxiety is excessive or the context developmentally inappropriate does anxiety becomes clinically significant (Marks 1987). Other fears, such as those seen in obsessive-compulsive disorder, are developmentally inappropriate in many, if not all, circumstances (Leonard et al. 1990).

Additional information about assessment of pediatric anxiety disorders is available in Albano 1991; Conners et al. 1995; Hooper and March 1995; Kearney and Silverman 1990; March and Albano 1996; McNally 1991; Rutter et al. 1988; Silverman 1991, 1994; Stallings and March 1995; Thyer 1991; Weiss et al. 1991; Wolff and Wolff 1991.

Self-Report Measures

Some anxiety symptoms, such as refusing to attend school in the patient with panic disorder and agoraphobia, are readily observable; other symptoms are open only to child introspection and thus to child self-report. For this and other reasons, self-report measures of anxiety, which provide an opportunity for the child to reveal his internal or "hidden" experience, have found wide application in both clinical and research settings (March and Albano 1996). Typically, self-report measures use a Likert scale format in which a child is asked to rate each questionnaire item in an ordinal format anchored to frequency or distress/impairment or a combination of the two. For example, a child might be asked to rate "I feel tense" on a four-point frequency dimension that ranges from almost never to often. Self-report measures are easy to administer, require a minimum of clinician time, and economically capture a wide range of important anxiety dimensions from the child's point of view. Taken together, these features make self-report measures ideally suited to gathering data before the initial evaluation because self-report measures used in this fashion increase clinician efficiency by facilitating accurate assessment of the prior probability that a particular child will or will not have symptoms within a specific symptom domain.

Currently published rating scales generally represent age-downward extensions of adult measures (March and Albano 1996). The Fear Survey Schedule for Children—Revised (Ollendick 1983) focuses primarily on phobic symptoms, including fear of failure and criticism, fear of the unknown, fear of injury and small animals, fear of danger and death, and medical fears. Another widely used scale, the Revised Children's Manifest Anxiety Scale (RCMAS; Reynolds and Paget 1981), assesses three factors: 1) physiological manifestations of anxiety, 2) worry and oversensitivity, and 3) fear/concentration. However, the presence of mood, attentional, impulsivity, and peer interaction items on the RCMAS clearly confounds other diagnoses, such as attention-deficit/hyperactivity disorder and major depression (Perrin and Last 1992). Another widely used measure, the State-Trait Anxiety Inventory for Children (STAI-C; Spielberger et al. 1976), consists of two independent 20-item inventories that assess anxiety symptoms from a variety of domains but that do not by any means exhaustively cover the symptom constellations represented in DSM-IV-TR. The state scale purports to assess present-state and situation-linked anxiety; the trait scale addresses temporally stable anxiety across situations. Numerous authors have questioned the validity of the state-trait distinction (Kendall et al. 1976) and the nature of item selection for the STAIC (Finch et al. 1976; Perrin and Last 1992), and clinicians and researchers generally agree (see, for example, (Jensen et al. 1993; March and Albano 1996) that new instruments, such as the MASC (described earlier) and the Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al. 1997), are necessary if the field of pediatric anxiety disorders is to progress scientifically. Differences between the MASC and these other scales are summarized in Table 31–2.

Diagnostic Interviews

Dimensional measures, such as the MASC, can point clinicians toward clinically relevant symptoms and, precisely because of their dimensionality, are more able to gauge severity of symptoms. Conversely, establishing a DSM-IV-TR diagnosis generally requires an interview-based approach. Thus, it is not surprising that investigators have long called for an increased use of valid and standardized diagnostic procedures to compare data across settings (e.g., Albano et al. 1995). The clinical interview has become one such method of standardizing data collection, while minimizing confounds to the reliability and validity of the diagnostic process (Eisen and Kearney 1995). Structured and semistructured interviews allow the quantification of clinical data, reduce the potential for interviewer bias, and enhance diagnostic reliability (Silverman 1987). Virtually all such interviews used with clinically anxious children cover the same general age range (7–17 years), providing evaluation of both children and adolescents. Clinically, semistructured interviews have an advantage over structured interviews because they present diagnostic criteria and related clinical inquiries in a standardized format, while allowing the clinician a limited range of flexibility for elaboration and probing. Thus, a clinician may adapt the wording of a particular question to meet the cognitive developmental level of the child.

Although unified interviews (e.g., parent and child together) are being explored in research settings (J. March, personal communication, June 2001), most diagnostic interviews require that both parent and child be interviewed with complementary versions of the instrument, which makes these instruments cumbersome for clinical practice. Conversely, use of both parent and child interviews permits evaluators to assign diagnoses based on DSM-IV-TR criteria as seen from multiple perspectives. For example, the Anxiety Disorders Inter-

TABLE 31–2. Anxiety rating scales

Domain of comparison	MASC	SCARED	RCMAS	FSSC-R	STAI-C
Broad conceptualization	Yes	Yes	Yes	No	Yes
Specific dimensions	Yes	Yes	Partial	Phobias	No
Validity index	Yes	No	Yes	No	No
Matches DSM-IV	Yes	Yes	No	No	No
Includes harm avoidance	Yes	No	No	No	No
Norms	Yes	No	Yes	Yes	Yes
Reliable	Yes	Yes	Yes	Yes	Trait scale
Convergent validity	Yes	Yes	Yes	Yes	Yes
Divergent validity	Yes	Yes	No	No	No

Note. MASC=Multidimensional Anxiety Scale for Children; SCARED=Screen for Child Anxiety Related Emotional Disorders; RCMAS=Revised Children's Manifest Anxiety Scale; FSSC-R=Fear Survey Schedule for Children—Revised; STAI-C=State-Trait Anxiety Inventory for Children.

view Schedule for DSM-IV (ADIS), Child and Parent Versions (Silverman and Albano 1996), which was developed specifically to facilitate clinical research with anxious children and adolescents but is now widely used in clinical settings as well, is a semistructured clinical interview that assesses the range of anxiety disorders, mood disorders, and related behavioral disturbances in children and adolescents. The ADIS is appropriate for administration to children ages 7 to 17, with developmentally appropriate wording and descriptors incorporated within the interview. The ADIS usually is administered by one evaluator and generally takes up to 3 hours in total to administer. Parents are interviewed separately from the child, with the general rule that data gained from one source not be used in or divulged to the second source. For each diagnosis, an initial inquiry section provides questions that probe for the presence of specific diagnostic criteria for each individual disorder, with skip outs strategically placed if threshold criteria are not met. An interference section provides an assessment of the child's and parent's subjective report of the degree of distress and impairment resulting from each diagnosis. If the clinician is interested in obtaining only diagnostic status, then just these two sections are required to assign a DSM-IV-TR diagnosis. Additional questions are provided to more fully examine the phenomenology of the disorders, to determine the degree of impairment in specific areas of functioning, and to explore relevant research questions pertaining to these disorders in youth. In addition, the ADIS provides an efficient mechanism for tracking overall treatment progress and patterns of symptom remission through follow-up assessments. In particular, the clinician is able to access information about the child's beliefs and interpretation of the problem; rate the child's physiological reactivity and assess for panic symptomatology; and gain an understanding of the behavioral mechanisms involved in escape, avoidance, or other methods of coping with the anxiety, each of which helps considerably with treatment planning and implementation.

Clinical Application

To further anticipate the relevance of a careful diagnostic assessment to treatment, it cannot be overemphasized that the cornerstone of both pharmacological and psychosocial management of pediatric anxiety disorders is a careful functional analysis of problem behaviors. In terms of the disease management model, modern psychiatric treatment requires clear specification of the behavioral or emotional syndrome (e.g., depression); and within syndrome, problems (e.g., oppositional behavior); and within problems, symptoms (e.g., will not go to bed) targeted for intervention. Consequently, a thorough diagnostic assessment, including both a clinical interview and a multimethod, multiinformant, multidomain scalar evaluation, is thought to be essential to generating a cognitive-behavioral treatment plan (March et al. 1995b). The overall assessment goal is to move from the presenting complaint through a DSM-IV-TR diagnosis based on Axes I through V to a tailored treatment plan based on an ideographic portrayal of the problems besetting the child or adolescent. Such an evaluation might begin with review of demographics and developmental, treatment, and psychiatric or medical history; review of findings from normed rating scale data, school records, and previous mental

health treatment records; a clinical interview of the child and his or her parents covering Axes I through V of DSM-IV-TR; a formal mental status examination; and, in some cases, a specialized neuropsychological evaluation. Ideally, a structured interview, such as the ADIS for Children (Silverman and Albano 1996), also should be part of every diagnostic assessment.

Treatment

Overview

With the emergence of a rich psychopathology literature covering all the important domains of child and adolescent symptomatology, pediatric psychiatry and psychology have moved away from nonspecific interventions toward problem-focused treatments keyed to specific DSM-IV-TR diagnoses (Kazdin 1997; Kendall and Panichelli-Mindel 1995). In particular, the past 40 years have seen the emergence of diverse, sophisticated, empirically supported cognitive-behavioral therapies for a range of childhood-onset mental disorders (Hibbs and Jensen 1996). Although psychodynamic psychotherapy (Keith 1995) has considerable clinical support (and, almost certainly, some utility) as a treatment of anxiety in children, individual (e.g., Kendall 1994) and family-centered (e.g., Barrett et al. 1996) cognitive-behavioral therapy (CBT) is the only treatment that has to date received solid empirical support. As a result, many now believe that CBT administered within an evidence-based disease management model is the psychotherapeutic treatment of choice for many, if not all, pediatric mental anxiety disorders (see, for example, March et al. 1997b).

Cognitive-Behavioral Therapy

Historically, behavior therapy evolved within the theoretical framework of classical and operant conditioning, with cognitive interventions assuming a more prominent role with the increasing recognition that person–environment interactions are powerfully mediated by cognitive processes (Van Hasselt and Hersen 1993). Viewed in the context of situational and/or cognitive processes, behavior therapy is sometimes referred to as *nonmediational* (emphasizing the direct influence of situations on behavior) and cognitive therapy as *mediational* (emphasizing that thoughts and feelings underlie behavior). Behavioral psychotherapists work with patients to change behaviors and thereby to reduce distressing thoughts and feelings. Cognitive therapists work to first change thoughts and feelings, with improvements in functional behavior following in turn. Despite their seeming differences, virtually all cognitive-behavioral interventions (including those for disruptive behaviors and depression) share four qualities: 1) an emphasis on psychoeducation, 2) a detailed behavioral analysis of the problem and the factors that maintain or extinguish it, 3) problem-specific treatment interventions designed to ameliorate the symptoms of concern, and 4) relapse prevention and generalization training at the end of treatment. CBT thus fits nicely into the current medical practice environment that appropriately values empirically supported brief, problem-focused treatments. The major techniques used in CBT for pediatric anxiety disorders are summarized in Table 31–3.

Historically, the behavioral treatment of fear and anxiety in children dates back to the classic work of Jones (1924a, 1924b) and the elimination of the fear of rabbits in a small boy referred to as "Peter." Treatment consisted of progressive exposure of Peter to the rabbit while he was engaged in a pleasurable response (eating) incompatible with fear. Following treatment, Peter's fear dissipated to the rabbit and to other similar stimuli to which the fear had generalized. Building on Jones's early work, Wolpe (1958) developed a "graduated deconditioning" technique he called *systematic desensitization* (SD). The rationale for SD is that anxiety is a set of classically conditioned responses that can be unlearned or counterconditioned through associative pairing with anxiety-incompatible stimuli and responses. In SD, anxiety-arousing stimuli are systematically and gradually paired (imaginally or in vivo) with competing stimuli such as food, praise, imagery, or cues generated from muscular relaxation. SD with children consists of three basic steps: 1) training in progressive muscle relaxation, 2) rank ordering of fearful situations from lowest to highest, and 3) hierarchically presenting fear stimuli via imagery while the child is in a relaxed state (Eisen and Kearney 1995). SD appears to work well with older children and adolescents. Younger children, however, often have difficulty with both obtaining vivid imagery and acquiring the incompatible muscular relaxation. Strategies such as use of developmentally appropriate imagery and adjunctive use of workbooks may increase the effectiveness of these procedures with younger children.

Typically, anxious children and adolescents do not remain in the presence of anxiety-arousing stimuli for a sufficient length of time to allow extinction to occur in the natural environment. Following the adult treatment

TABLE 31–3. Techniques used in cognitive-behavioral therapy for pediatric anxiety disorders

Term	Definition	Examples
Cognitive restructuring	Active altering of maladaptive thought patterns; replacing these negative thoughts with more constructive adaptive cognitions and beliefs	Challenging aberrant risk appraisal in the patient with panic disorder or helplessness in the patient with depression
Contrived exposure	Exposure in which the patient seeks out and confronts anxiety-provoking situations or triggers	Intentionally going back to school in the child with separation anxiety
Differential reinforcement of appropriate behavior	Attending to and positively rewarding appropriate behavior, especially when incompatible with inappropriate behavior	Praising (and maybe paying) the child with social phobia for answering the office or home telephone when a responsible adult is not present
Exposure	Prolonged contact with the phobic stimulus in the absence of real threat to decrease anxiety; may be contrived (sought out contact with feared stimuli) or not contrived (unavoidable contact with feared stimuli)	A patient with fear of heights goes up a ladder: the first time, it is scary; the tenth time, it is boring.
Extinction	Conventionally defined as the elimination of problem behaviors through removal of parental positive reinforcement; technically defined as removing the negative reinforcement effect of the problem behavior so that it no longer persists	Refusal to reassure the anxious patient; refusal by the mother to cave in to the anxious oppositional child's tantrums by withdrawing a command
Generalization training	Moving the methods and success of problem-focused interventions to targets not specifically addressed in treatment	Exposure and response prevention in imagination for developmentally appropriate fears, even if not particularly bothersome or not specifically addressed in treatment
Negative reinforcement	Self-reinforcing purposeful removal of an aversive stimulus; stated differently, the termination of an aversive stimulus, which when stopped, increases or stamps in the behavior that removed the aversive stimulus	Obtaining reassurance from a parent provides short-term relief of anxiety in a child. Eliminating reassurance, which at the same time blocks the negative reinforcement for answering by the parent when the child's distress and thus difficult behavior decreases, is a prime goal of treatment.
Positive reinforcement	Imposing a pleasurable stimulus to increase a desirable behavior	Praising the selectively mute youngster who talks to the teacher
Prompting, guiding, and shaping	External commands and suggestions that increasingly direct the child toward more adaptive behavior that is then reinforced; typically, shaping procedures rapidly fade in preference to generalization training.	Gradually encouraging and helping the youngster with social phobia to talk in class and with other children
Punishment	Imposing an aversive stimulus to decrease an undesirable behavior	"Time-out" because of unacceptable behavior or overcorrection (as in extra chores to make restitution for aggressive behavior); typically, punishment worsens anxiety disorders.
Relapse prevention	Interventions designed to anticipate triggers for reemergence of symptoms; practicing skillful coping in advance	Imaginal exposure to a possible new fear followed by use of cognitive therapy and response prevention to successfully resist the incursion of anxiety-driven operant reinforcers
Response cost	Removal of positive reinforcer as a consequence of undesirable behavior	Loss of points in a token economy
Response prevention	Adequate exposure is only possible in the absence of rituals or compulsions.	Typically used with obsessive-compulsive disorder, in which response prevention means not performing rituals, the principle also applies in other situations, such as eliminating an avoidance or escape withdrawal behavior in the socially anxious or agoraphobic patient
Restructure the environment	Changes in setting or stimuli that decrease problem behaviors and/or facilitate adaptive behavior	Intervening to protect the anxious child from punishment by the teacher or teasing by peers
Stimulus hierarchy	A list of phobic stimuli ranked from least to most difficult to resist with fear thermometer rating scores	Unique list of exposure targets ranked by fear thermometer score; an individual patient may have one or more hierarchies, depending on the complexity of symptoms (e.g., a particular patient may have separate hierarchies for social fears and for separation anxiety).

literature (Barlow and Craske 1989), this led to the development of exposure-based interventions for a wide range of pediatric anxiety disorders (March 1995). Because escape and avoidance behaviors are negatively reinforced by cessation of anxiety, exposure-based procedures require extended presentation of fear stimuli with concurrent prevention of escape and avoidance behaviors for the extinction of the conditioned responses to occur. Unlike SD, stimulus presentation is not accompanied by progressive muscle relaxation. Rather, graduated imaginal or in vivo exposure to hierarchically presented fear stimuli is used to attenuate anxiety to phobic stimuli. Gradual exposure, with the consent of the child, is generally considered to produce less stress for the patient (and therapist) and thus is often preferred over the use of more prescriptive techniques, especially flooding.

Cognitive interventions, usually combined with exposure, also play a prominent role in CBT for anxious children and adolescents. For example, Kendall and colleagues (1992) developed a comprehensive cognitive-behavioral protocol for anxious youth, which focused on transmitting coping skills to children in need. Based on the premise that anxious children view the world through a "template" of threat, automatic questioning (e.g., "What if…"), and behavioral avoidance, treatment is focused on providing educational experiences to build a new "coping template" for the child. Therapists help the children to reconceptualize anxiety-provoking situations as problems to be solved, situations to be coped with. Various cognitive-behavioral components assist the therapist and child in building the coping template: relaxation training, imagery, correction of maladaptive self-talk, problem-solving skills, and management of reinforcers. Therapists use coping modeling, role-play rehearsals, in vivo exposure, and a collaborative therapeutic relationship with the child to facilitate the treatment progress. Parents are actively involved in all facets of treatment as collaborators in the change process. Moreover, this demonstrably effective treatment program (Kendall and Southam-Gerow 1996; Kendall et al. 1997) incorporates an innovative relapse prevention component, during which the child assumes the role of an expert and produces a video- or audiotaped "commercial" for the management of anxiety and fear.

Clinically, when significant others are trapped in the child's anxiety symptoms, it is crucial to help the child encourage his or her parents to stop, for example, participating in the avoidance strategies or rituals. To test the hypothesis that adding a family anxiety management (FAM) component would boost treatment effectiveness, Barrett and colleagues (1996) developed a parallel family program to Kendall's "Coping Cat" based on behavioral family intervention strategies found effective for the treatment of externalizing disorders in youth. Following the completion of each child session with the therapist, the child and parents would participate in an FAM session with the therapist. The point of the program is to empower parents and children by forming an "expert team" to overcome and master anxiety. Parents are trained in reinforcement strategies, with emphasis on differential reinforcement and systematic ignoring of excessive complaining and anxious behavior. Contingency management strategies are the main methods for reducing conflict and increasing cooperation and communication in the family. Moreover, parents receive training in communication and problem-solving skills so that they will be better able to function as a team in solving future problems. Preliminary results suggest that combined treatment is more effective and reduces relapse rates compared with individual treatment.

In much the same vein, several investigators have confirmed the wisdom of tailored family involvement in the treatment of obsessive-compulsive disorder in children and adolescents (Knox et al. 1996; March and Mulle 1998; Piacentini et al. 1994). Here, March (1998) suggested that unilateral extinction strategies, such as when a parent returns a child with school phobia to school by force, have significant disadvantages: 1) parents often have no workable strategy for managing the child's distress, 2) the treatment relationship is disrupted, 3) symptoms that are not seen by parents and teachers cannot be targeted, and 4) most important, these approaches do not help the child internalize a more skillful strategy for coping with current and potential future anxiety symptomatology.

Pharmacotherapy

With advances in the identification of child- and adolescent-onset anxiety (March and Albano 1996) has come a concomitant increase in the application of pharmacological treatments borrowed in part from successful strategies applied in adult populations with similar disorders (Allen et al. 1995). Conversely, although psychopharmacological interventions are increasingly recognized as an essential part of the treatment armamentarium for anxious youths (Bernstein et al. 1996), the exact place of medication strategies alone and in combination with psychosocial interventions is as yet un-

clear (American Academy of Child and Adolescent Psychiatry 1997; Popper 1993). Outside of obsessive-compulsive disorder (March et al. 1995a), few empirical studies of the efficacy, much less the safety, of specific medications have been conducted (Klein and Slomkowski 1993), with the use of many compounds in the pediatric population supported solely by clinical lore (Kutcher et al. 1995). In particular, most of the reported investigations either have been open trials or have been conducted in patient populations that are not well characterized (Jensen et al. 1994; Kazdin 1997), making it difficult to determine whether these medications would be effective in typical clinical populations (Conners et al. 1994; March and Albano 1998).

In lieu of a detailed review of psychopharmacology for pediatric anxiety disorders, which is beyond the scope of this chapter (for reviews, see Allen et al. 1995; Kratochvil et al. 1999; Kutcher et al. 1995), Table 31–4 summarizes the general approach to prescribing medication for anxious youth, and Table 31–5 inventories the drugs most commonly used for this purpose. Given the absence of solid empirical data to guide the ordering of treatments, most clinicians treating anxiety in children and adolescents will (or at least should) begin with CBT, which has considerably more empirical support (Albano and Chorpita 1995), and advance to a pharmacological intervention only if the patient does not rapidly respond to CBT. Factors leading to early medication intervention might include unavailability of CBT, patient preference, and severe or multiple comorbidity or suicidality. For many patients with moderately severe to severe symptoms, the combination of CBT and medication may be most likely to lead to durable symptom remission, although empirical evidence for this assertion is largely lacking (March et al. 1997b).

Other complexities are present when using psychotropic medication in pediatric patients that are not present with most adults. For example, children less commonly seek treatment themselves. Alternatively, parents are sometimes "cornered into treatment" by pressure from school or social service agencies. Children commonly fear being labeled a "mental patient" by peers or extended family, so exploring the meaning of the medication to the child is important. Parenthetically, however, prescribing medication in a medical context, namely for an illness that is bothering the child and from which he or she wants relief, increases compliance. The form and taste of medication as well as route of administration influence compliance, especially in younger children. If the cost of the drug is prohibitive, or it is not available locally, treatment may be interrupted. Although many methods are available to assess compliance, such as direct monitoring, questionnaires, pill counts, and measuring levels in body fluids, none is completely reliable. A good therapeutic alliance, a careful explanation of benefits and risks coupled with written informed consent, a combination of medication with targeted psychosocial therapies, and thoughtful monitoring are the factors most likely to result in a positive outcome. Friendly and collegial communication with pediatricians, family doctors, and other professionals involved in the child's care also enhances compliance. Similarly, patients and their families must be informed that not all medicines help everybody and that a period of medication trial and error may be necessary to find the medication that is most helpful.

When patients' symptoms do not respond or only partially respond to initial pharmacotherapy, the clinician must reassess whether treatment targets have been appropriately identified and whether treatments have been appropriately implemented. Conversely, increasing the intensity of the treatment—for example, by adding behavioral family therapy, increasing the dose of medication, or changing medication—may be necessary (March et al. 1997b). Rarely, patients will benefit from combination medication regimens (Wilens et al. 1995) (e.g., a serotonin reuptake inhibitor with an antipsychotic such as

TABLE 31–4. Approach to prescribing psychotropic medication

Conduct a comprehensive baseline evaluation, including rating scales and, if indicated, laboratory measures.
Carefully consider the question of differential therapeutics to identify potential targets for medication treatment as distinct from psychosocial treatments when possible.
Establish risk-benefit ratios for each treatment, and obtain informed consent.
In general, begin with least complicated and risky drug strategies.
Define indicators for each important outcome domain to better track potential benefits and side effects.
Insofar as possible, use only one medication at a time to minimize confusion with respect to tracking outcome.
When adjusting medications, be sure to consider both dose-response (intensity) and time-response (temporal) characteristics of the chosen medication in relation to the patient's psychiatric disorder.
Use an evidence-based stages of treatment model, and establish a defined end point at which a decision can be made about whether the expected benefit has occurred and whether additional treatment(s) can or should be implemented.

TABLE 31–5. Commonly used medications

Psychotropic class	Drug	Brand name	Therapeutic applications	Comments
Serotonin reuptake inhibitors (SRIs)	Citalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	Cilexia Prozac Luvox Paxil Zoloft	SRIs may be useful in all anxiety disorders except specific phobia.	SRIs are first-line compounds, with broad-spectrum activity in many mood and anxiety disorders and unique activity in OCD; well tolerated compared with TCAs.
Tricyclic antidepressants (TCAs)	Imipramine Nortriptyline Desipramine	Tofranil Pamelor Norpramin	All anxiety disorders except OCD and specific phobia	Second-line drugs after the SRIs; require ECG and laboratory monitoring; probably not effective in depression.
	Clomipramine	Anafranil	Only TCA used for OCD	Use after two to three failed SRI trials.
Benzodiazepines	Alprazolam Clonazepam Lorazepam	Xanax Klonopin Ativan	Situation and anticipatory anxiety across all anxiety disorders	Best for short-term use while waiting for an SRI to "kick in." Disinhibition and physiological dependence may be problematic.
Other drugs	Buspirone Propranolol	BuSpar Inderal	Generalized anxiety disorder Specific social phobia	Buspirone is broadly anxiolytic; it is not effective in panic disorder with agoraphobia or OCD; may be useful in place of a benzodiazepine when substance abuse is an issue. Propranolol and other β-blockers are useful primarily in acute performance anxiety.

Note. OCD = obsessive-compulsive disorder; ECG = electrocardiogram.

risperidone) when comorbid schizotypal personality disorder or a tic spectrum disorder is present in the patient with a primary diagnosis of obsessive-compulsive disorder (March et al. 1995a). In many cases, partial improvement is all that can be expected; distinguishing between improvement and residual impairment in the context of the natural history of the disorder is an important part of differential therapeutics and of the psychoeducational process.

To date, the available data suggest that high-potency benzodiazepines may be appropriate short-term treatments for a broad range of anticipatory and situation-related anxiety symptoms. Although empirical data are more limited outside of obsessive-compulsive disorder, for which they are robust, the selective serotonin reuptake inhibitors are probably the agents of choice when long-term treatment is anticipated. Buspirone is a potentially useful agent in generalized anxiety disorder, and its relatively benign side-effect profile and low abuse potential make it an attractive choice, particularly in an adolescent population at risk for substance abuse. Targeted propranolol may be useful to treat performance anxiety in patients with nongeneralized social phobia. Tricyclic antidepressants and antipsychotics should be avoided when possible because of their lack of demonstrated efficacy and high potential for serious side effects. Other agents have a smaller role, if any, to play; combinations of various compounds may be useful in treatment-resistant patients. In every patient, careful attention to dose-response relationships (the intensity dimension) and time-action effects (the temporal dimension) is critical to maximize benefit and minimize side effects.

Conclusion

Despite limitations in the research literature with regard to long-term outcome of treated compared with untreated patients; how best to combine cognitive-behavioral and pharmacological treatments; effectiveness across divergent cultural, age, and racial/ethnic groupings; and optimal assessment procedures, the empirical literature nonetheless is generally positive regarding the benefits of short-term cognitive-behavioral psychotherapy and, to a much lesser extent, pharmaco-

therapy for anxiety disorders in children and adolescents. However, the short-term benefits of treatment do not necessarily translate into long-term benefit across all domains of outcome. Thus, at this stage of our understanding, it is likely that a combination of targeted psychosocial therapies, alone or in combination with psychotropic medication, skillfully applied across time affords the most plausible basis for sustained benefit in anxious children and adolescents.

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Anxiety Disorders in the Elderly

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Despite a growing literature on anxiety disorders, relatively little attention has been devoted to the study of anxiety in the elderly. However, recent research suggests that a significant proportion of the elderly have anxiety disorders and that such symptoms can be extremely distressing and disabling and are often misdiagnosed and inappropriately treated. The relatively complex nature of geriatric anxiety has impeded a comprehensive understanding of the prevalence, etiology, assessment, and treatment of anxiety in this population. In this chapter, we review current knowledge of anxiety disorders in the elderly and highlight some of the central issues that challenge clinicians and researchers in this area.

Epidemiology

The prevalence rates of anxiety disorders in younger adults have been well documented, but the epidemiology of this class of disorder in the elderly population has seldom been comprehensively researched. Traditionally, surveys among this population have explored "neurotic" disorders in general rather than anxiety disorders in particular (Lindesay 1991a), and the consensus in the literature has often been that anxiety disorders are uncommon in the aged (Fuentes and Cox 1997).

Indeed, the accurate establishment of the epidemiology of geriatric anxiety is fraught with several difficulties. First, it has been suggested that elderly persons are relatively reluctant to admit to symptoms of emotional distress, tending to focus on physical signs and symptoms instead (Small 1997; Turnbull 1989). Anxiety disorders are thus often hidden and unacknowledged among the aged or misinterpreted as signs of physical illness. Second, anxiety symptoms characterize other psychiatric disorders common in old age, such as depression, late-onset psychosis, and dementia, resulting in frequent misdiagnosis (Spar and La Rue 1997). Accurate diagnosis is further complicated by the tendency of many physical illnesses common in the elderly (such as cardiac or pulmonary conditions) to mimic the symptoms of anxiety (such as heart palpitations or shortness of breath) (Banazak 1997; Lindesay 1991a). Finally, the instruments and criteria used to assess anxiety in the elderly may not be valid for this population, giving rise to results that significantly underestimate the true prevalence of anxiety disorders among elderly patients (Fuentes and Cox 1997). Therefore, the prevalence of

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anxiety disorders in the elderly may be higher than is indicated in existing epidemiological studies and may warrant greater attention than it is currently afforded by clinicians and researchers.

Methodological differences across existing epidemiological surveys (e.g., the use of different inclusion thresholds and diagnostic hierarchies) have produced a wide variance in both general prevalence rates and rates of specific anxiety disorders (Beekman et al. 1998; Krasucki et al. 1998) (see Table 32–1). This variance, together with the issues outlined above, suggests that the prevalence rates reported below should be regarded somewhat cautiously.

General Prevalence Rates

In general, survey results indicate that anxiety is less prevalent in the geriatric population than among younger adults. Possible explanations for this variance and apparent decline, some of which have been noted above, include nonresponse to surveys, anxiety-related mortality, reluctance to report anxiety symptoms or a tendency to interpret such symptoms as signs of physical illness, diagnostic tendency toward depression or dementia, and age-related neurobiological or cognitive changes (Krasucki et al. 1998).

Although anxiety disorders are less common in the elderly than in the younger adult population, such disorders nonetheless affect a significant portion of the elderly population. An early study by Regier et al. (1988) reported a 1-month prevalence rate of anxiety disorders in adults of all ages of 7.3%, whereas the rate among adults older than 65 years was 5.5%. However, the diagnoses of generalized anxiety disorder (GAD) and posttraumatic stress disorder (PTSD) were not included in this DSM-III–based (American Psychiatric Association 1980) study. A later survey by Blazer et al. (1991), which included GAD but not PTSD, found a 6-month prevalence of 19.7% and a lifetime prevalence of 34.1% among an elderly community sample.

Flint (1994) synthesized eight surveys of community-dwelling elderly populations and found prevalence rates of anxiety disorders ranging between 0.7% and 18.6%. Prevalence rates appear to be higher in elderly patients with medical disorders: Hocking and Koenig's (1995) survey reported that between 10% and 20% of chronically medically ill elderly patients had clinically significant anxiety symptoms. Consistent with the sex pattern reported for younger adults, anxiety disorders are more common among elderly women than among elderly men (Schneider 1996).

Although anxiety disorders tend to begin in younger adulthood and have a chronic course, evidence suggests that the onset of anxiety disorders can occur in old age in the absence of any psychiatric history. Clow and Allen (1951) found that more than one-third of all elderly patients in a hospital sample who had diagnoses of neuroses had no psychiatric history before age 60. Bergmann (1971) reported that in a community sample, about half of the anxiety disorders had an onset after age 60. Certain anxiety disorders, such as agoraphobia, may be particularly likely to have their onset after age 60 (see "Phobic Disorders" subsection later in this chapter).

Obsessive-Compulsive Disorder

The onset of obsessive-compulsive disorder (OCD) in old age is rare. Most cases of OCD in the elderly have their onset in earlier adulthood and persist into old age (Schneider 1996). The lifetime prevalence rate of OCD is between 2% and 3% (Weissman et al. 1994); among adults older than 65 years, the prevalence rate decreases. A current prevalence of between 0.8% (Regier et al. 1988) and 1.5% (Bland et al. 1988) and a lifetime prevalence of between 1.2% (Regier et al. 1988) and 2.5% (Bland et al. 1988) have been reported for persons older than 65 years. Flint's (1994) review of these and other studies found prevalence rates of OCD in elderly community samples that ranged from 0.1% to 0.6%, whereas Beekman et al.'s (1998) more recent review reported a range of 0.2%–1.5%. Although OCD is less common among elderly adults than among younger adults, a significant percentage of OCD patients are elderly. Jenike (1994) found that 12% of all OCD outpatients in the clinics studied were older than 50, and 4% were older than 60.

In the geriatric population, there appear to be sex differences in the prevalence of OCD. The prevalence rate of OCD decreases among men older than 65 (to between 0.1% and 0.7%), but the rate increases in women in this age group (to between 0.7% and 0.9%) (Kasckow and Fudala 1997). Therefore, when the onset of OCD does occur in old age, it is perhaps more likely to occur among women than among men.

Phobic Disorders

Phobic disorders are the most common type of anxiety disorder among the elderly, with reported prevalence rates ranging from 0.7% to 12.0% (Krasucki et al. 1998). In the Epidemiological Catchment Area (ECA) surveys in the United States, phobic disorders among adults older than 65 were the most common psychiatric

TABLE 32–1. Prevalence of anxiety disorders in the elderly (age 65 years and older)

	All anxiety disorders	Phobic disorder	Panic disorder	Generalized anxiety disorder	Obsessive-compulsive disorder	Posttraumatic stress disorder
National Survey of Psychotherapeutic Drug Use 1979 (Uhlenhuth et al. 1983)[a]	10.2	1.4[b]	1.7	7.1	—	—
U.S.–U.K. Cross-National Diagnostic Project—Liverpool (Copeland et al. 1987b)[c]	1.9	0.7	—	1.1	0.1	—
National Institute of Mental Health Epidemiological Catchment Area survey (Regier et al. 1988)[c]	5.5	4.8	0.1	—	0.8	—
Edmonton (Bland et al. 1988)[d]	3.5	3.0	0.3	—	1.5	—
Guy's/Age Concern Survey (Lindesay et al. 1989)[c]	—	10.0	0.0	3.7	—	—

[a]One-year prevalence.
[b]Includes agoraphobia and panic.
[c]One-month prevalence.
[d]Six-month prevalence.

disorder in women (with a 1-month prevalence of 6.1%) and the second most common (after cognitive disorders) in men (2.9%), with a prevalence rate for both sexes of 4.8% (Regier et al. 1988). Bland et al. (1988) reported a 6-month prevalence of 3.0% and a lifetime prevalence of 8.9% among adults older than 65 in a Canadian sample. A longitudinal study in the United Kingdom (Copeland et al. 1987b) found a 0.0% male, 1.2% female, and 0.7% total 1-month prevalence for phobic disorders, whereas Lindesay et al. (1989) reported a total prevalence rate of 10% in a United Kingdom elderly community sample. Lindesay (1991b) further reported that 30% of all cases of phobia in an elderly community sample had an onset after 65 years. Agoraphobia is the most common phobia found in elderly patients, with many reported cases of the onset of agoraphobia in old age (Eaton et al. 1989; Lindesay 1991b).

Panic Disorder

Panic disorder has been reported to be extremely rare in the geriatric population and to very seldom arise for the first time in old age (Flint et al. 1996). Regier et al. (1988) reported a 1-month prevalence of only 0.1% among adults older than 65 years, whereas Bland et al. (1988) found a 6-month and lifetime prevalence of 0.3%. Lindesay et al. (1989) found no cases of panic disorder in their sample. In a recent review of several surveys, Beekman et al. (1998) found that the reported prevalence of panic disorder in elderly samples ranged from 0.04% to 0.3%. Among elderly patients with panic disorder, most are women (Regier et al. 1988). However, a clinical study of elderly patients presenting with chest pain and no evidence of coronary heart disease suggested that late-onset panic disorder may be common in this group (Beitman et al. 1991). Indeed, a range of medical problems (particularly cardiovascular, gastrointestinal, and pulmonary diseases) and depression have been found to commonly occur comorbidly with panic disorder among elderly patients (Hassan and Pollard 1994; Raj et al. 1993).

Posttraumatic Stress Disorder

PTSD in the elderly has seldom been researched, and prevalence rates have not been established. Existing studies have focused on PTSD in Holocaust survivors (Kuch and Cox 1992) and war veterans (Speed et al. 1989), for whom PTSD had persisted into old age in up to 70% of subjects (Flint 1997). However, Goenjian et al. (1994) documented the onset of PTSD in old age among a group of Armenian elders after an earthquake. In this study, the incidence of PTSD in the elderly was found to match that in younger adults. Livingston et al. (1994) also reported on the presence of PTSD in a small group of elders after the Lockerbie air disaster, of whom 21% still met the criteria for the disorder 3 years later. These findings suggest that a significant proportion of elderly persons may be at risk for developing PTSD after trauma and that the lack of data on prevalence rates of PTSD in this population should be urgently addressed.

Generalized Anxiety Disorder

Although prevalence rates for GAD have not been reliably established, this disorder is likely more common than any other anxiety disorder among the elderly (Schneider 1996). Reported prevalence rates range from 0.7% to 7.1% (Flint 1994). In an early study, Uhlenhuth et al. (1983) reported a 1-year prevalence rate of "generalized anxiety syndrome" of 7.1% in elderly adults in a general population sample. Blazer et al. (1991) found a 6-month prevalence rate of 1.9% in adults older than 65, although onset was after age 65 in only 3% of the patients. Lindesay et al. (1989) found a 1-month prevalence of 3.7%.

Comorbid depression in elderly patients with GAD is common, occurring in up to 70% of patients (Manela et al. 1996; Parmelee et al. 1993), and is particularly likely when the onset of GAD occurs in old age (Parmelee et al. 1993). Most new cases of GAD in late life are associated with depression (Larkin et al. 1992; Parmelee et al. 1993). Similarly, 20%–40% of elderly patients with major depression also have GAD (Ben-Arie et al. 1987; Blanchard et al. 1994; Copeland et al. 1987a), and up to three-fourths of older depressed patients report clinically significant subsyndromal anxiety symptoms (Blanchard et al. 1994; Copeland et al. 1987a). Thus, anxious or agitated depression is the most common presentation of anxiety among the elderly attending psychiatric services and primary care facilities (Kay 1988).

Etiology

Although much has been written on the etiology of anxiety throughout the life span, relatively little literature exists on the specific causes of anxiety in the elderly. A major etiological role has been ascribed to the life changes associated with old age, many of which involve some form of loss. This includes loss of, or decline in, both mental and physical abilities and competence, together with the approaching reality of death; loss of a spouse (particularly for men); loss of health; loss of independence; loss of income; and loss of self-esteem on retiring (Banazak 1997; O'Brien-Counihan 1997; Spar and La Rue 1997).

Anxiety disorders in the elderly are also frequently associated with traumatic events. Lindesay (1991b) reported that the onset of agoraphobia in old age frequently occurs after a traumatic event such as acute physical illness, falls, or muggings. The documented presence of anxiety disorders such as PTSD (Sembi et al. 1998), agoraphobia (Burvill et al. 1995), and GAD (Castillo et al. 1993) after a stroke suggests that the trauma of this medical event and/or specific neurobiological changes may play an important role in the onset of anxiety disorders in old age. The relation between the neurobiology of aging and the late onset of anxiety disorders deserves further study.

Although the above factors may serve as precipitants, it is rather less clear whether there are specific predictors for the onset of anxiety in old age. The etiological role of developmental experiences has been suggested: Lindesay's (1991a) study of phobic disorders in the elderly found that subjects reported higher rates than control subjects of parental loss before age 18. A study of the relation between state anxiety and early parenting patterns (Stevens and Andersson 1996) found that anxiety was most common among those elderly patients whose parents had been overprotective but without affection (affectionless control). These developmental factors may play a role in the etiology of phobias in the elderly and bear further exploration.

Assessment and Diagnosis

Phenomenology

The subjective experience of anxiety for younger persons includes uneasiness, worry, fear, and general apprehension, whereas subjective feelings of agitation and a fear or dread of impending doom may be more characteristic of anxiety in the elderly (O'Brien-Counihan 1997). However, perhaps because of the stigma attached to mental distress, complaints of subjective anxiety are relatively rare. Instead, the elderly are more likely to present with physical signs and symptoms of anxiety (Spar and La Rue 1997). Such physical features include sweating, restlessness, muscle tension, pacing, tachycardia, poor concentration, fatigue, dizziness, paresthesia, dry mouth, gastrointestinal disturbances, facial grimacing and flushing, palpitations, tremor, and body aches and pains (Banazak 1997; O'Brien-Counihan 1997; Small 1997).

Although comprehensive, systematic studies are lacking, some evidence suggests that the phenomenology of specific anxiety disorders in the elderly may differ in some respects from their presentation in younger patients.

Sheikh (1993) reported that the late onset of panic disorder in old age, albeit rare, may be characterized by

fewer panic symptoms, less avoidance, and less somatization compared with early-onset panic disorder in the elderly. In a study of the features of OCD among elderly patients, Kohn et al. (1997) reported that elderly patients have fewer concerns about counting rituals, needing to know, and symmetry than do younger patients. For elderly patients with social phobia, eating or writing in public are more common sources of anxiety than is public speaking because of the presence of dentures and tremors, respectively (Sheikh 1996).

Lindesay's (1991b) study of an urban elderly community sample reported that multiple phobias were common in this population. The most common situational fears were of public transport, crowds, and enclosed spaces, and the most common specific fears were of animals and heights. Agoraphobic main fears were typically of late onset, precipitated by an episode of physical illness or other trauma, and associated with modest to severe social impairment, whereas specific main fears tended to be of early onset and associated with minimal social impairment.

Studies with war veterans and Holocaust survivors have found that PTSD is a chronic disorder that can persist for many decades but may remain hidden as a result of cultural expectations of conformity (Kuch and Cox 1992; Snell and Padin-Rivera 1997). The phenomenology of PTSD in the elderly may have unique aspects. Goenjian et al. (1994) reported that the first-time development of PTSD in elderly survivors of an earthquake in Armenia in 1988 was characterized by less reexperiencing and more hyperarousal than was seen in younger survivors. However, they highlighted the need for further studies to accurately establish age-related profiles for PTSD. Cwikel and Rozovski (1998) reported that PTSD symptoms after exposure to the Chernobyl nuclear disaster improved at a slower pace for subjects older than 55 compared with younger subjects, suggesting that elderly patients with PTSD may require a longer period of treatment than do younger adults.

Differential Diagnosis

Transitory Anxiety

Spar and La Rue (1997) noted that elderly persons may experience situational anxiety in much the same way as do younger adults (e.g., on visiting the doctor or driving an unfamiliar car). Although elderly patients may request treatment for situational anxiety, by definition, such anxiety does not interfere with the person's functioning to the same extent that, for example, a specific phobia does. In response to complaints of situational anxiety, the clinician should therefore attempt to clearly establish the patient's level of clinical distress and functioning.

For elderly persons, a period of adjustment anxiety may be precipitated by a change such as moving to a new room in their retirement home or moving to a new apartment, developing a new medical illness (even if it is not life threatening), and having financial difficulties (Spar and La Rue 1997). Adjustment anxiety is transitory and can be precipitated by a stressor that may not be recognized as particularly anxiety provoking by the assessing clinician. The clinician therefore should evaluate carefully and sensitively for any recent experience of change.

Cohort Effects

It has been suggested that the present generation of elderly people has a particular attitude toward mental distress that may not be echoed in future elderly generations. The current generation grew up in a period when mental illness was stigmatized and when psychiatric interventions were viewed with suspicion (Small 1997). During the psychiatric assessment, they may be reluctant to reveal symptoms of emotional distress or to admit the emotional roots of their physical anxiety symptoms. In the absence of a medical illness, physical signs and symptoms of anxiety should alert the clinician to the possible presence of an anxiety disorder, and the elderly patient's subjective experience of anxiety should then be carefully and sensitively probed.

Medical Conditions

The differentiation of psychological and medical causes of anxiety in the elderly is complex and requires careful and thorough assessment. First, a range of chronic medical illnesses is found in the elderly, and many of these manifest symptoms that mimic the somatic features of anxiety, often in the absence of any other physical symptoms. Second, as discussed earlier in this chapter, many elderly patients express anxiety through somatic symptoms that resemble medical illnesses. Third, the presence of a medical illness can result in anxiety and worry for the elderly person about the meaning and effect of the illness (Small 1997). Finally, several medications commonly used by elderly patients can cause anxiety-like symptoms. The clinician should have a high index of suspicion for a medical cause when the elderly anxious patient has 1) anxiety symptoms with a temporal relation to medical illness or drugs

known to cause anxiety symptoms; 2) atypical features of anxiety, such as late-onset panic attacks or loss of consciousness; and 3) resistance to treatment with conventional antianxiety drugs (Vita 1997). Appropriate medical treatment for a medical condition or alteration of the patient's medication should lead to a reversal of the anxiety when medical conditions or drug effects play a role. A comprehensive evaluation, taking into account all these factors, will allow the clinician to accurately diagnose a functional anxiety disorder, a substance-induced anxiety disorder, or an anxiety disorder due to a general medical condition.

Cognitive Disorders

Anxiety has been found to be more common among patients with dementia than among nondemented control subjects (Wands et al. 1990), although in this patient population, anxiety may be associated with the comorbid presence of depression rather than directly with the dementia (Flint 1994). Although not reflected in the epidemiological data, clinical experience indicates that anxiety symptoms often are associated with Alzheimer's and vascular dementias, among others (Lindesay 1991a). Misdiagnosis is more likely in the early stages of dementia, when cognitive deficits may not yet be readily observable. Lindesay (1991a) also noted that delirium-induced hallucinations may trigger a panic-like response in some patients but that an assessment for other features of delirium will allow the diagnosis to be confirmed. Once an organic basis has been established, the underlying condition should be diagnosed and treated.

Depression

Anxiety and depression share many features, and their differentiation requires a careful evaluation of the duration and pattern of the patient's mood characteristics. This is equally true for the evaluation of elderly and younger patients. However, Spar and La Rue (1997) suggested that many elderly patients are not accustomed to introspection and lack the appropriate psychological language to describe accurately their subjective mood and anxiety experiences.

Epidemiological data indicate that anxiety and depression often present comorbidly, although the relation between the two disorders is complex (Flint 1994). It may be difficult to establish whether the two disorders developed concurrently or whether one is primary and the other secondary. To this end, careful tracking of the order of development of symptoms may be helpful.

Substance Abuse

Substance abuse, particularly alcohol abuse and, to a lesser extent, benzodiazepine abuse, is a common, but often hidden, occurrence among elderly populations (O'Brien-Counihan 1997). Withdrawal can result in anxiety symptoms. A sensitive probing of the elderly patient's substance use is therefore an important part of the assessment process and can be supplemented with laboratory testing.

Assessment

The clinician's first task is to establish whether the patient's current level of functioning or impairment warrants a clinical diagnosis of anxiety. Thereafter, a thorough psychological and medical history should form the cornerstone of any clinical evaluation of anxiety in the elderly, including clarifying when the symptoms began, the order in which symptoms developed, and whether the symptoms recurred; obtaining a family medical and psychiatric history; and evaluating comprehensively medication and alcohol use (Banazak 1997). A mental status examination of cognitive and perceptual abilities and a complete physical examination are also vital.

It has been argued that the application of DSM-IV (American Psychiatric Association 1994) criteria for anxiety disorders, developed based on studies of younger adults, to the geriatric population may be inappropriate (Palmer et al. 1997). These criteria do not take into account atypical symptom presentations, comorbid psychiatric and medical conditions common in geriatric patients, and the influence of age-related psychosocial changes. This may contribute to the underdiagnosis of anxiety in the elderly. The clinical evaluation therefore needs to extend beyond the bounds of DSM criteria and to comprehensively and sensitively explore the age manifestations of anxiety and anxiety-related impairment in elderly patients.

The clinical evaluation can be supplemented by the use of anxiety rating scales. The Hamilton Anxiety Scale (Hamilton 1959) is a commonly used observer-rated scale with 14 items that measure 89 psychological and somatic symptoms of anxiety. However, Sheikh (1996) cautioned that this scale may be too long and cumbersome for many elderly patients and that such patients tend to overendorse the somatic items. Self-rated anxiety scales, such as the State-Trait Anxiety Inventory (Spielberger et al. 1970) and the Beck Anxiety Inventory (Beck et al. 1988), also are commonly used.

Laboratory investigations can assist differential diagnosis by screening out many of the medical causes of anxiety. A full blood count, an electrocardiogram, vitamin B_{12} and folate levels, thyroid function tests, blood glucose levels, and a drug and alcohol screening should be considered (Sheikh 1996).

Treatment

Currently, the treatment of anxiety disorders in the elderly is primarily pharmacotherapeutic (Lindesay 1991a). However, although controlled studies are lacking, some evidence indicates that the augmentation of medication with psychotherapeutic interventions may result in greater improvement than with the use of either alone (Foa and Kozak 1992; O'Sullivan et al. 1991). In addition, psychotherapy can provide a useful alternative to pharmacotherapy for those elderly patients who have concurrent medical conditions and prescriptions that increase the risk of side effects and drug interactions or for those who fail to comply with medication regimens (Sheikh 1996). Epidemiological evidence of the common comorbidity of anxiety and depression further suggests that both pharmacotherapy and psychotherapy often need to target a broad range of symptoms.

Pharmacotherapy

Although there is a paucity of literature on controlled clinical trials of pharmacotherapy for anxiety disorders in the elderly, data extrapolated from studies in younger adults suggest that drug treatments used for the anxiety disorders may be safe and effective in this age group (Fernandez et al. 1995; Small 1997; Sheikh and Cassidy 2000).

Special Considerations

Pharmacokinetic and pharmacodynamic changes in the elderly affect drug absorption, drug actions, and drug interactions. Elderly patients are more difficult to treat safely and effectively. With aging, gastric acid secretion decreases, renal and hepatic blood flow diminish, total body water and oxidative metabolism are lower, and the fat content of both body and brain increases (Leonard 1992). Benzodiazepines and antidepressants are primarily lipophilic and protein bound; thus, they have less of an initial effect as they are taken up for storage into lipid-rich sites, but once administered, their duration of action is prolonged. Alteration in central nervous system receptor site sensitivity heightens sensitivity to given plasma levels of drugs. "Starting low and going slow" is therefore a general principle of pharmacotherapy in this population. In addition, the clinician should remember that many elderly patients take several medications concurrently; thus, drug-drug interactions and a worsening of adverse effects may result.

Benzodiazepines

Although all benzodiazepines are thought to be equally effective in treating anxiety, the compounds with short elimination half-lives that undergo single-step conjugation in the liver and have no active metabolites are generally preferable in the elderly. Longer-acting benzodiazepines, such as diazepam and chlordiazepoxide, are strongly lipophilic and lead to higher accumulation in the tissues, as compared with the shorter-acting and less lipophilic drugs, such as oxazepam and lorazepam (Moran et al. 1988). Shorter-acting benzodiazepines are, however, more likely to cause withdrawal symptoms if discontinued abruptly.

Benzodiazepines are perhaps particularly useful when anxiety symptoms are of sudden onset and must be controlled rapidly. The dose of benzodiazepines should be approximately two-thirds the recommended adult dose. Given their significant disadvantages, benzodiazepines should be prescribed for as short a time as possible in the elderly. Troublesome side effects include drowsiness, short-term memory impairment, disinhibition, psychomotor slowing, and dependency and withdrawal (Weiss 1994). The risk of hip fracture, for example, in elderly people taking benzodiazepines may be significantly elevated (Ray et al. 1987).

Nonbenzodiazepine Anxiolytics

Buspirone. Buspirone, a serotonin type 1A (5-HT_{1A}) receptor agonist, has been shown to be an effective anxiolytic in the elderly with some advantages over the benzodiazepines (Markovitz 1993; Weiss 1994). Despite a slower onset of action, buspirone is nonsedating, does not interact with alcohol, does not cause cognitive or motor impairment, and does not have the propensity for dependency or withdrawal. It is therefore a useful first-line agent in GAD in the elderly (Bohm et al. 1990). It also may be useful for agitated patients and anxious demented patients (Small 1997). The recommended dosage in elderly patients is 30–40 mg/day, although higher dosages (60 mg/day) may be required in some patients. Side effects in elderly patients include nausea, headache, dizziness, and fatigue. These effects

can be countered by titrating slowly, lowering the dose if necessary, and recommending that the patient take medication with meals (Salzman 1992, 1995).

β-Blockers. β-Blockers, such as propranolol, may be useful in treating the sympathetic hyperarousal that accompanies performance anxiety. Such data may be extrapolated to older patients, although lower doses may be needed. β-Blockers should be avoided in asthma and congestive cardiac failure (Markovitz 1993).

Antihistamines. Antihistamines are used occasionally to treat anxiety and insomnia in the elderly. Their anticholinergic effects and their potential for cognitive impairment and confusion are, however, undesirable in this population. Antihistamines appear less effective than benzodiazepines for generalized anxiety in the elderly (Salzman 1992).

Antidepressants. Antidepressants are promising first-line agents in the treatment of anxiety disorders, especially in patients who have comorbid depression. The older tricyclic antidepressants are effective in generalized anxiety but have troublesome anticholinergic, hypotensive, and cardiotoxic effects. The selective serotonin reuptake inhibitors have been shown to be effective in the treatment of OCD, panic disorder, social phobia, and PTSD in adult populations (Small 1997) and, more recently, in the treatment of GAD, OCD, and panic disorder in elderly patients (Wylie et al. 2000). They are relatively well tolerated overall, and side effects for most elderly patients are mild (Finkel 1996). Newer antidepressants such as nefazodone, a serotonin antagonist and reuptake inhibitor, also appear effective in depressed elderly patients with comorbid anxiety.

Generalized Anxiety Disorder

Although benzodiazepines have long been considered the treatment of choice for GAD, buspirone is arguably a safer and better-tolerated treatment in the elderly (Steinberg 1994). Buspirone also is a preferred treatment for GAD when medical comorbidity is an issue (e.g., in an elderly patient with chronic bronchitis) (Steinberg 1994). Although relatively little work on the antidepressants has been done in elderly patients with GAD, the tolerability of the newer agents makes these an increasingly reasonable choice, particularly when comorbid depression is present.

Obsessive-Compulsive Disorder

Selective serotonin reuptake inhibitors are the preferred first-line treatment of OCD. They are better tolerated and are relatively free of the anticholinergic, cardiac, and hypotensive effects of clomipramine. Citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline all have shown efficacy in adult OCD (Calamari et al. 1994; Jackson 1995).

Panic Disorder

Both tricyclics (e.g., imipramine) and monoamine oxidase inhibitors (e.g., phenelzine) are effective in adult panic disorder, but the selective serotonin reuptake inhibitors tend to be particularly favored in the elderly because of their better tolerability (Sheikh 1996). The starting dose should be half the adult starting dose. For very anxious patients, high-potency benzodiazepines may provide rapid symptom relief and may be prescribed for short periods (Ballenger 1997; Ballenger et al. 1998).

Social Phobia

There is increasing evidence for the value of the selective serotonin reuptake inhibitors in social phobia, and these might be argued to be a first-line choice in the elderly. Moclobemide (reversible inhibitor of monoamine oxidase–A) is preferable as a first-line choice to the older monoamine oxidase inhibitors because of its lack of tyramine pressor effect and freedom from anticholinergic and cardiovascular effects.

Posttraumatic Stress Disorder

Placebo-controlled studies have shown efficacy of the tricyclic antidepressants, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors in adult PTSD (Vargas and Davidson 1993). However, the database for the selective serotonin reuptake inhibitors is the largest. Furthermore, in an open trial of fluvoxamine in World War II veterans, substantial symptom reduction occurred in 45% of the patients (De Boer et al. 1992), indicating that these agents can be useful in an elderly population.

Medication Compliance

Failure to comply with drug treatment may be a serious problem in the elderly. Patients with acute anxiety may take more than their prescribed dose of medication in the mistaken belief that more of the drug will speed recovery (Salzman 1995). Overuse of medication may result in adverse effects and usually occurs unintentionally because of forgetfulness. Deliberate overuse is not a common occurrence in the elderly. Forgetting to take

medication may result in gross underuse and is likely when many drugs are being taken simultaneously. To improve compliance, the clinician can simplify multidrug regimens and dosage schedules and minimize polypharmacy (Salzman 1995).

Psychotherapy

Psychotherapeutic intervention is seldom offered to the elderly, even when such intervention is widely regarded as the treatment of choice for particular disorders (Flint 1997; Lindesay 1991a). Consequently, there is a lack of systematic, controlled studies of the efficacy of psychotherapy among elderly patients with anxiety disorders (Small 1997; Spar and La Rue 1997). However, no evidence suggests that the elderly are unable to benefit from psychotherapeutic interventions. In fact, persuasive case evidence supports the efficacy of psychotherapy with this population.

The focused and time-limited cognitive-behavioral therapies are favored among practitioners providing psychotherapy to elderly patients with anxiety disorders (Spar and La Rue 1997). Such therapies typically include graded exposure and response prevention, progressive relaxation techniques, and cognitive restructuring. In cases of more pervasive and generalized anxiety, the use of hypnosis, meditation, and guided imagery may be helpful (Spar and La Rue 1997). Cognitive-behavioral treatment should be tailored to individual patient needs and include regular follow-up of anxiety symptoms (Banazak 1997), and the involvement of family members or other caregivers may be an important component during therapy and in the long-term maintenance of recovery (Rasmussen et al. 1993; Wilkinson 1997). Elderly patients receiving cognitive-behavioral therapy may require highly structured sessions, simple devices such as notebooks and tape-recorded sessions, and concrete examples to identify cognitive distortions (Wilkinson 1997).

Case reports, case-controlled studies, and anecdotal evidence suggest that the cognitive-behavioral therapies are an effective form of intervention for some anxiety disorders among geriatric patients. Preliminary data indicate that cognitive techniques can be effective in the treatment of panic disorder in elderly patients (Swales and Sheikh 1993) and are particularly useful in panic disorder with agoraphobia (Clark 1986). King and Barrowclough (1991) provided data on the efficacy of cognitive therapy in the treatment of panic disorder, GAD, and agoraphobia in elderly patients. It also has been reported that the level of improvement among elderly OCD patients after cognitive-behavioral therapy is comparable to that of younger adults (Carmin et al. 1998).

With regard to specific cognitive-behavioral techniques, Woods and Britton (1985) described a case study of the successful treatment of agoraphobia in a 64-year-old woman with graded in vivo exposure. Exposure therapy also has been reported to be successful in alleviating rituals in the elderly (Calamari et al. 1994; Jenike 1994). Hussian (1981) reported on the successful use of imaginal exposure with phobic elderly patients. For social phobia, individual or group cognitive-behavioral therapy over 8–12 sessions may be very effective (den Boer 1997). Favorable results also have been reported for the use of progressive muscle relaxation (Holland et al. 1991), cognitive restructuring (Clark 1989), and token economies (Mishara 1978) to treat anxiety in elderly patients.

Evidence indicates that psychodynamic group therapy can be effective in the treatment of depression in elderly patients (Steuer et al. 1984), but the effectiveness of group psychodynamic therapy with elderly anxious patients has not yet been established. However, a more eclectic group treatment approach has been reported to be effective in the treatment of PTSD in veterans (Snell and Padin-Riviera 1997). This approach combines psychoeducation, stress and anger management techniques, the working through of grief and loss issues, the facilitation of forgiveness, and the bolstering of social support networks.

Thus, although little attention traditionally has been granted to the value of psychotherapy for anxiety disorders in elderly patients, growing anecdotal evidence suggests that such interventions, particularly cognitive-behavioral techniques, are an important component of treatment. However, rigorously designed controlled studies are needed to better understand and evaluate such treatment effects.

Conclusion

Anxiety disorders among the elderly generally have been neglected by clinicians and researchers. However, recent research indicates that anxiety disorders reduce the quality of life of a substantial proportion of the elderly and thus warrant more attention. This is particularly pressing given that the elderly population will increase substantially during the next century. Accurate establishment of the epidemiology of anxiety disorders in the elderly requires more standardized research de-

signs and more relevant assessment instruments, and evaluation of psychopharmacological and psychotherapeutic treatment modalities necessitates more controlled studies.

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33

Anxiety in the Context of Substance Use

Leonard Handelsman, M.D.

Complaints about anxiety are so common among persons who abuse substances that substance abuse has sometimes been characterized as a misguided attempt to self-medicate these symptoms (Khantzian 1985). Anxiety disorders, as defined by DSM-IV-TR (American Psychiatric Association 2000), occur in only a minority of persons who abuse substances. In contrast to depression, the etiology, pathogenesis, and treatment of anxiety disorders in persons who abuse substances have received relatively little attention. Until recently, much of the literature focused on the problem of the false-positive diagnosis of an anxiety disorder in persons who abuse substances (Hasin et al. 1993; Kranzler 1996) and the danger of benzodiazepine dependence (Griffiths and Weertz 1997). The advances in the nosology, neurobiology, and treatment of anxiety disorders that are described in other chapters of this book have had little effect on the thinking about these disorders in the context of substance abuse and even less on treatment or prevention. The purpose of this chapter is to summarize our knowledge about the diagnosis, pathogenesis, and treatment of anxiety disorders that occur in individuals with current or lifetime histories of substance-related disorders and to pose questions for future research.

Anxiety States in Persons Who Abuse Substances

Anxiety disorders do not account for most of the complaints about anxious feelings among persons who abuse substances. A large portion of these complaints are related to intoxication or withdrawal states per se. Substances as diverse as cocaine, marijuana, caffeine, and alcohol may induce anxious feelings, physical signs of anxiety, or even frank panic. Withdrawal after the chronic exposure to virtually any addictive substance provokes anxiety. In withdrawal syndromes from some psychoactive substances, such as opioids, alcohol, or benzodiazepines, the anxiety symptoms are part of a cluster of dysphoric symptoms and physical signs of arousal. However, for other drugs such as marijuana or cocaine, the anxiety symptoms may be more subtle. When anxiety symptoms during intoxication or withdrawal take on the pattern of an anxiety disorder and go beyond the normal bounds of intoxication or withdrawal, they are classified as a substance-induced anxiety disorder and further labeled by the specific substance.

Studies of the neurobiology of anxiety disorders and withdrawal syndromes show some interesting convergences. Several brain regions, such as the amygdala, paraventricular nucleus, locus coeruleus, and mesoprefrontal cortex, have been implicated in anxiety states as well as withdrawal syndromes and drug craving states (Charney and Deutch 1996; Grant et al. 1996; Grove et al. 1997; Herman et al. 1996; Horger and Roth 1996; Koob 2000; Menzaghi et al. 1994). In humans, the infusion of serotonergic agonists may provoke anxiety in panic patients and cravings in alcoholic persons (Charney and Deutch 1996; Krystal et al. 1996). The infusion of yohimbine may provoke anxiety and flashbacks in pa-

tients with posttraumatic stress disorder (Bremner et al. 1997; Southwick et al. 1997) and anxiety in very recently abstinent persons who were addicted to cocaine (McDougle et al. 1994). Withdrawal states, substance craving, and anxiety states therefore resemble one another phenomenologically and neurobiologically.

Even after the period of early withdrawal, treatment-seeking persons who abuse substances continue to have high levels of anxious feelings in conjunction with other negative feelings such as depression, tension, hostility, and shame (Sutherland 1997). Sutherland (1997) recently showed that these "traits," generally labeled *neuroticism* by personality theorists, persist at high levels for several months after treatment but decline somewhat after approximately 6 months of abstinence. This finding corresponds with the clinical observations of specialists in addiction medicine (Kranzler 1996). No evidence shows that psychopharmacological treatment of anxious feelings that occur outside the parameters of a definable anxiety disorder enhances the retention or outcome in treatment for substance use disorders. When persons who abuse substances require intensive medical treatment, however, the short-term use of anxiolytic agents may facilitate adherence to treatment and can be justified on that basis.

Reliability and Validity of Psychiatric Diagnoses Comorbid With Substance Use Disorder

To consider the coexistence of substance use disorders and anxiety disorders, it is particularly important to define the reliability and validity of the anxiety disorder diagnoses in the presence of high levels of substance use. Because most structured psychiatric diagnostic instruments provided little guidance in distinguishing "substance-induced" from "independent" psychiatric disorders, Hasin et al. (1996) added structured probes to a standard diagnostic instrument to improve the reliability of diagnostic decision. When Hasin's modifications were applied in a clinical substance abuse setting, reliability was improved for several psychiatric disorders. However, the test-retest reliability for anxiety disorders still remained in the low to acceptable range, which was lower than the ranges for major depression and bipolar I disorder. Kranzler et al. (1997) attempted to measure the concurrent and predictive validity of anxiety disorders in a clinical substance abuse setting with a "longitudinal, expert, all data" procedure but found no support for the concurrent validity and only marginal support for the predictive validity of anxiety disorders. Dividing anxiety disorders into those that occurred first and those that occurred after the onset of substance use disorders did not improve the indices of validity (Kadden et al. 1995). Response to treatment also may be used as a validating criterion for a diagnostic category. At present, no studies of treatment outcome for any comorbid anxiety disorder were designed to address the issue of the validity of the diagnoses of comorbid anxiety disorders in the presence of a lifetime or current history of substance use disorder.

Epidemiological surveys of psychiatric and addictive disorders indicate high levels of comorbidity of anxiety disorders and substance use disorders (Kessler et al. 1994) as well as high levels of familial aggregation of these disorders (Kendler et al. 1997). The Epidemiological Catchment Area study indicated that several types of anxiety disorders occurred more frequently in individuals with lifetime alcohol dependence than in the general population (Anthony and Helzer 1991; Helzer et al. 1991). However, the prevalence ratios for this excess prevalence were modest, the highest being for panic disorder. All of the comorbid anxiety disorder prevalence ratios were lower than those ratios for antisocial personality disorder, mania, and schizophrenia.

In their seminal review of the comorbidity of alcoholism and anxiety disorders, Schuckit and Hesselbrock (1994) concluded that the prevalence of anxiety disorders among persons with alcoholism was equal to or only slightly higher than that in the general population. Although less studied, this appears to be the case for persons who abuse drugs as well (Brooner et al. 1997; Milby et al. 1996; Rounsaville et al. 1991). In contrast, Merikangas and Avenevoli (2000), in their review of clinic- and community-based epidemiological studies of social phobia, concluded that alcohol and drug dependence was overrepresented in patients with social phobia and vice versa. Kendler et al. (1992) showed excess levels of comorbidity between phobic disorders and alcoholism among female twins from a population-based registry. The discrepancy between the review of Schuckit and Hesselbrock (1994) and those of Merikangas and Avenevoli (2000) and Kendler et al. (1992) could be a result of the degree to which females were included in the epidemiological studies.

The effect of gender on the comorbidity of anxiety and substance use disorders was noted in the Epidemiological Catchment Area study (Anthony and Helzer 1991). Women with alcoholism were more likely than men to have another diagnosis. This may be because of

the higher prevalence of many of the anxiety and depressive disorders among women (Muntaner et al. 1998) or the greater deviance of alcoholism when it occurs in women, implying that other psychiatric disorders be present to increase the likelihood that a woman would be given a diagnosis of alcohol dependence. Adding a further level of complexity, Magura et al. (1998) recently described distinct patterns of multiple comorbid psychiatric disorders in men and women addicted to heroin.

There are many important gaps in our knowledge about comorbid anxiety disorders and substance use disorders. The most glaring is the absence of systematic information about the effect of multiple psychiatric diagnoses (multiple anxiety diagnoses or anxiety diagnoses with other types of disorders) on substance use (Brown and Barlow 1992). We also do not have information on how various sociodemographic risk factors affect the prevalence or natural history of comorbid anxiety and substance use disorders. These variables have significant effects on the prevalence of substance use disorders (Anthony and Helzer 1991; Helzer et al. 1991), panic disorder, and phobic disorders (Muntaner et al. 1998) and even on the likelihood of exposure to trauma (Breslau et al. 1995). How these variables operate on comorbid anxiety and substance use disorders also requires further study.

Pathogenesis of Comorbid Anxiety and Substance Use Disorders

If the distinction of primary and secondary anxiety disorder carries with it little significance other than to screen out obvious cases of anxiety disorder that will remit spontaneously after relatively brief periods of abstinence, how can we understand the etiology and pathogenesis of comorbid anxiety and substance use disorders? Whereas a limited number of familial and genetic studies suggest that anxiety disorders and depression share a common genetic loading (cf., Kendler et al. 1986; Merikangas and Avenevoli 2000; Roy et al. 1995), no evidence supports a common genetic loading between anxiety disorders and substance use disorders.

An anxiety disorder might unmask the vulnerability to develop a substance use disorder, or contribute to the progression and severity of that disorder, or alter the response to treatment, and vice versa. However, these possibilities have not been examined systematically. How substance use unmasks anxiety disorder may be specific for different anxiety disorders. Kendler et al. (1986) studied a population of female twins and showed that phobic disorders differed in how much of the concordance between twins was explained by common and specific genetic and environmental factors. Exposure to substances, therefore, could have differential effects on the emergence of specific anxiety disorders. Recent studies by Breslau et al. (1995, 1997a, 1997b) attempted to identify the precursors and sequelae of traumatic events and posttraumatic stress disorder for men and women. Breslau et al. (1997b) found that in women, posttraumatic stress disorder predisposed to the development of an alcohol use disorder; however, even when more circumscribed analytical designs were used, it was difficult to determine whether the posttraumatic stress disorder caused the alcohol use disorder or whether the traumatic event exposed underlying vulnerabilities. To complicate matters, socioeconomic factors, ethnicity, and the predisposition to neuroticism appear to influence the likelihood of exposure to traumatic events (Breslau et al. 1995).

Cravings to abuse substances followed by substance use often have been compared to obsessive-compulsive behavior. In the Epidemiological Catchment Area study, obsessive-compulsive disorder (OCD) was more prevalent in alcoholic patients than in the general community at a level intermediate between phobic disorders and panic (Anthony and Helzer 1991), and disorders theorized to be part of an OCD spectrum, such as pathological gambling, also have been linked to increased levels of substance use disorder (Feigelman et al. 1998; Rupcich et al. 1997). London et al. (2000) proposed that persons who abuse substances and individuals with OCD may be unable to terminate inappropriate responses even when they know better. Based on the finding that OCD is associated with an abnormality of orbitofrontal cortex function, Grant et al. (2000) hypothesized that persons who abuse substances may share a similar abnormality. It is also possible that persons who abuse substances and who have comorbid OCD or OCD spectrum disorders represent a subgroup who may respond preferentially to agents used to treat OCD in the same way that persons who abuse substances with attention-deficit/hyperactivity disorder may respond preferentially to psychostimulants.

Neurobiological studies of addiction and of anxiety disorders support the plausibility that each type of disorder could either cause the other or expose a vulnerability to the other. The sensitization of the amygdala through substance use may predispose to panic or elements of posttraumatic stress disorder. Neural adaptation to substance exposure could restrict normal cog-

nitive processes, resulting in more severe substance problems, pathological memory in posttraumatic states, and a restricted cognitive focus in generalized anxiety or phobias. The pro- or asocial effects of addictive substances could influence the avoidant features of anxiety disorders. Conversely, it is plausible that anxiety disorders sensitize the brain to the reinforcing effects of psychoactive substances or lower an individual's resistance to use these substances.

Treatment of Comorbid Anxiety and Substance Use Disorders

The treatment of anxiety disorders in persons who abuse substances has been the subject of three reviews (Dupont 1995; Kranzler 1996; Nunes et al. 1995) that agree in their basic approach. The first principle of treatment is to carefully diagnose the anxiety disorder and all comorbid conditions. The second principle is to avoid common pitfalls such as mistaking a substance-induced disorder that will remit spontaneously for a bona fide anxiety disorder (O'Leary et al. 2000) or failing to detect a pattern of tranquilizer use as part of a pattern of polysubstance abuse. The third principle is to treat the anxiety disorder in the context of treatment of a coexisting substance use disorder.

The principles and algorithms for the psychopharmacological management of anxiety disorders in individuals with substance abuse are largely the same as for other individuals. It is uncommon for any treatment of anxiety to work without either cessation or serious reduction of psychoactive substance use (with the exception of opioid substitution treatment). Most clinicians avoid the use of monoamine oxidase inhibitors because they believe that persons who abuse substances will not adhere to dietary and medication restrictions. Similarly, most clinicians avoid benzodiazepines as a first-line treatment of anxiety disorders based on the belief that benzodiazepine use will result in dependence or impaired performance or interact with abused sedatives or alcohol. Mueller et al. (1996) showed, however, that individuals with a history of alcoholism in remission did not encounter greater difficulty in using benzodiazepines for the treatment of an anxiety disorder than did other individuals. Kosten et al. (2000) found that benzodiazepine treatment among posttraumatic stress disorder patients with substance abuse was not linked to adverse effects on clinical outcomes. Furthermore, Posternak and Mueller (2001), in a manual and MEDLINE review of the literature, found little evidence to indicate that a history of substance abuse is a major risk factor for future benzodiazepine abuse or dependence. Therefore, the restriction on using benzodiazepines for the treatment of anxiety in persons who abuse substances must be seen as qualified rather than absolute and should be based on a patient-by-patient cost-benefit analysis. Benzodiazepine treatment of comorbid anxiety may become particularly problematic in the context of unrecognized bipolar disorder. Even subtle levels of hypomania may heighten the reinforcing effects of benzodiazepines, resulting in problematic drug-seeking behavior. Subtle forms of bipolar spectrum disorder may go unrecognized in about 20% of the patients in substance abuse programs.

The effect of race or ethnicity on the association of psychiatric comorbidity and addiction has received little systematic attention. However, Roberts (2000), in reviewing the literature on this subject, noted that African American opioid and cocaine addicts report lower levels of anxiety and mood disorders than do whites. Apart from a study by Kranzler et al. (1994) demonstrating anxiolytic efficacy for buspirone treatment of anxiety in recovering alcoholics, no definitive studies have tested the effectiveness of pharmacological agents for the treatment of anxiety among persons who abuse substances. At present, there is no reason to believe that primary anxiety disorders respond to psychopharmacological agents differently than do secondary disorders. The introduction of novel, non-habit-forming anxiolytic agents will enhance the treatment of anxiety disorders among persons who abuse substances. Note, however, that at present, many non-habit-forming anxiolytics are underused in substance abuse programs.

Psychological treatments have also been used to treat anxiety disorders. To date, there are few studies to demonstrate efficacy for these treatments in the context of substance abuse. One exception is the emerging evidence that brief conjoint cognitive-behavioral therapy for the treatment of substance abuse and posttraumatic stress disorder in female addicts reduces symptoms of both disorders (Triffleman et al. 1999). Virtually all substance abuse treatment strategies incorporate cognitive, behavioral, and psychoeducational strategies to address anxiety symptoms and to improve coping skills. Although many of these strategies overlap with standard approaches to the treatment of anxiety disorders, they may ascribe the anxiety symptoms to substance use or to an "addictive personality" rather than to an anxiety disorder. There is little evidence regarding the effect of anxiety disorders on the outcome of treatment for substance dependencies. Franken et al. (2001) re-

ported that substance abusers with comorbid anxiety acquire coping skills poorly in comparison with nonanxious substance abusers. Analyzing the results of a longitudinal survey of 1,920 substance abusers followed for almost 15 years, Bovasso (2001) showed that individuals who had anxiety or depression symptoms at baseline generally experienced increased distress at follow-up but that those who received mental health treatment experienced decreased distress at follow-up. In the absence of systematic outcome studies, we do not know whether combined substance use and anxiety disorder treatment would be superior to substance abuse treatment alone. For individuals with social phobia, the reduction of exposure to group modalities may enhance retention in substance abuse treatment.

The treatment of anxiety disorders in persons who abuse substances is frequently complicated by medical conditions that are more prevalent among some persons who abuse substances. Problems arise from liver or renal insufficiency, interactions among medications, or side effects of necessary medications. In conditions of grave illness, it is important to evaluate the need for comfort and to not withhold the potential palliation of anxiolytic agents.

Prevention

Of the anxiety disorders, social phobia usually occurs before the onset of substance use problems. It is not certain whether adolescents with social phobia go on to develop substance use disorders at a higher level than do individuals without psychiatric illness. Because substance use disorders can be prevented by restricting or postponing exposure to psychoactive substances, it might be prudent to identify adolescents with social phobia and tailor substance use prevention (perhaps including treatment for social phobia) to them. A special case of this applies to young gay men with social phobia who may rely on alcohol or party drugs to overcome their shyness and thereby diminish their adherence to safer-sex practices.

Suggestions for Different Treatment Scenarios

When individuals with moderate to severe dependence are in the early phases of abstinence, the main focus of treatment is learning to tolerate abstinence, to make plans to stay in treatment, and to avoid relapse. This early phase of treatment may be complicated and undermined by a heavy burden of anxiety symptoms such as panic attacks, intrusive posttraumatic memories, obsessions or compulsions, generalized worry and tension, or extreme fear of judgment in social interaction. In this situation, psychotherapy focused on anxiety is unlikely to help simply because of the need to focus on addiction. However, medications that would be expected to treat anxiety symptoms in nonaddicted persons may reduce the burden of symptoms and thus help the recovering individual to focus on recovery. During this phase, we generally opt for agents that have no abuse liability, but in some cases the anxiety symptoms are so severe that benzodiazepines should be considered. Secondary effects of anxiety such as fear of perceived criticism in group treatment, severe avoidance, or the need to exert unrealistic levels of control often jeopardize substance abuse treatment. Early identification of these problems is essential.

Once the individual has gained some stability in abstinence, has affiliated with long-term treatment, and has learned to implement relapse prevention and coping skills, it is time to address the role of anxiety in the individual's life and to understand how symptoms of anxiety interplay with addiction.

Individuals with anxiety disorders who perceive that alcohol, sedative, or marijuana use relieves anxiety may not be willing to consider that such use could constitute abuse or dependence and may consider the abused substance to have fewer problems than do standard anxiolytic treatments. Sometimes, they are willing to consider anxiolytic treatment but are not willing to give up the abused substance. In these cases, education about anxiety, patience, and flexibility usually carries the day, so the initial focus should be on retention in treatment.

Recovered patients with long-term abstinence who develop anxiety disorders often are concerned about the possibility of relapse or misuse of medication. Physicians generally avoid agents that have known abuse liability, but when these agents are necessary, careful monitoring of appropriate medication use is helpful.

Conclusion

Anxiety disorders and substance use disorders are both common; therefore, many individuals have both disorders. The diagnosis and treatment of anxiety disorders in persons who abuse substances are confounded by the ubiquitous nature of anxiety symptoms among persons who abuse substances, by the poor validity and modest

reliability of the diagnosis of anxiety disorders in the presence of substance abuse, and by the absence of well-designed clinical trials on the treatment of comorbid anxiety disorders. No clear evidence indicates that anxiety disorders and substance use disorders share a common genetic etiology, but a good deal of evidence suggests that the two types of disorders are related to each other pathogenetically in a complex rather than simple way, as suggested by the "self-medication" hypothesis. Special psychopharmacological or psychological treatment of anxiety symptoms in persons who abuse substances does not seem warranted. Psychopharmacological and focused psychological treatments of comorbid anxiety disorder seem prudent, but we do not have a reliable evidence base to guide such treatment. Algorithms for psychopharmacological management of anxiety disorders in persons who abuse substances are by and large similar to those in persons who do not abuse substances, with the exception that benzodiazepines and monoamine oxidase inhibitors generally are avoided. Whether specific types of anxiety disorder are also markers for meaningful subgroups of persons who abuse substances is an intriguing question.

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Anxiety and Anxiety Disorders in Medical Settings

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Health concerns rank with financial issues as major sources of anxiety for individuals (Warr 1978; Wisocki 1988). Both disease states and medical settings foster such fears. Wells and colleagues (1988) noted that 6-month and lifetime prevalence rates of anxiety disorders in patients with chronic medical conditions were 15.3% and 21.3%, respectively. These rates were significantly higher than those found in the general population (6-month prevalence of 6.6% and lifetime prevalence of 12.9%). Therefore, before a particular patient is even admitted to the general hospital, the astute clinician should be prepared to include in his or her initial differential diagnosis a primary anxiety disorder regardless of what the medical illness may be. In outpatient medical settings, 4%–8% of patients have anxiety disorders, whereas in hospitalized patients, the prevalence can rise to 23% (Carroll et al. 1993; Levenson et al. 1986–1987). Although anxiety is often comorbid with depression, the two affects are different. Anxiety is a dysphoric affect, and dread of a future event is an essential feature. In contradistinction, depression is anguish over a loss and is directed toward the past and present. Although anxiety has been partitioned from fear in respect to conscious versus unconscious elements, the phenomenological nature of both appear to be similar.

A Framework of Perspectives

McHugh and Slavney (1983) argued that psychiatry should be viewed from multiple perspectives. Each perspective has a specific logic or internal grammar of its own, with both strengths and weaknesses (McHugh and Slavney 1983; M.A. Schwartz and Wiggins 1988). This approach is useful for the clinician working in the medical setting. The four perspectives are 1) the disease approach, 2) the life history perspective, 3) intersubject differences, and 4) motivated behavior.

Disease Approach

The *disease approach* is based on the medical model, in which a syndromic category is defined based on signs and symptoms that allow categorical designation to be developed and investigated for pathophysiological causes (McHugh and Slavney 1982). The validation process of a diagnosis involves designation of demographic and clinical factors, laboratory studies, syndromal demarcation from other disorders, follow-up studies to ascertain the course of the disorder, investigation of genetic and environmental factors, and documentation of response to various treatments. This is the essence of DSM-IV-TR and ICD-10 (American Psychi-

atric Association 2000; World Health Organization 1992). The strength of the disease model is the fact that rational treatment can be developed if organic etiologies are found. Its limitation is that it formally objectifies the entity by designating "what" the patient has but not "who" he or she is. DSM-IV-TR catalogues a variety of syndromes in which anxiety is the main symptom. When considering anxiety states in the medically ill, clinicians often underdiagnose such syndromes because they rationalize that it is normal to be anxious within such a situation. DSM iterations have partitioned anxiety into a variety of separate categories, such as panic disorder with or without agoraphobia, generalized anxiety disorder, social phobia, specific phobia, posttraumatic stress disorder, obsessive-compulsive disorder, adjustment disorder with anxiety, and acute stress disorder. Goldenberg et al. (1996) showed that "pure culture" of these diagnoses is rare because comorbidity among them is common and concurrent affective disorders or substance abuse frequently exists.

The disease perspective should remind the clinician that the role of organic anxiety must be considered in that a variety of medical conditions, such as congestive heart failure, hyperthyroid disease, and metabolic disorders, may foster anxiety (see Table 34–1) (Hall 1980). Furthermore, various drugs, such as caffeine or steroids, have the potential to cause anxiety in some patients. The clinician must assess both the nature and the degree of anxiety in any categorical diagnosis to best manage the situation. The following are common categorical disorders in DSM-IV-TR that may apply to medical settings (Cassem 1990).

Panic disorder denotes the acute onset of intense fear and physiological arousal with a variety of physiological symptoms, including palpitations, dyspnea, sweating, trembling, a sense of choking, chest pain, nausea or abdominal distress, and numbness and tingling sensations, which all may be interpreted as the onset of a serious illness. Patients with panic disorder use an excess amount of medical care because of misinterpretation of their symptomatology (Katon 1996). The clinician must accurately diagnose this disorder and institute the proper psychopharmacological and psychotherapeutic treatment. A critical step is to educate the patient that his or her symptoms are part of a panic disorder rather than another serious illness (Colon et al. 1995). Patients with pulmonary disease and postpartum women have an increased incidence of panic disorder (Karajgi et al. 1990; Yellowlees et al. 1987).

Adjustment disorder with anxiety is one of the most common psychiatric entities in medically ill patients (Wilson-Barnett 1992). This diagnosis is complicated because it is made in the context of a clearly defined stressor such as a physical illness, but the diagnosis requires that the individual have marked distress that is in excess of what would be expected from exposure to the stressor. Often, it is not clear what is an appropriate and an inappropriate response. The presence of occupational or social impairment due to the anxiety should allow the clinician to be more confident in making the diagnosis.

Acute stress disorder also may be seen in the medical setting and is characterized by a dissociation and detachment from painful affects. The presence of frightening images and dreams about the traumatic event and avoidance of stimuli differentiate this disorder from adjustment disorder. The exact incidence of acute stress disorder within medical settings is not known. That entity as well as posttraumatic stress disorder, however, may be found in both patients with serious illnesses and caregivers who have worked in disaster settings.

Finally, those individuals with generalized anxiety disorders who have a chronic anxiety state with both psychological and physical symptomatology also may use medical care to a greater degree than do those without such disorders. Such individuals may demand both medical evaluations and pharmacological intervention.

Life History Perspective

In the *life history perspective* (Slavney and McHugh 1984), each patient's developmental vicissitudes will create a personal biography with a variety of specialized meanings (Engel 1997). The goal of understanding such meaningful connections is the essence of dynamic psychiatry. In individuals who are medically ill, it is essential to understand how they perceive their illness and what personalized meaning and expectations they attach to the situation in which they find themselves. Such data will begin to define "who" the patient is. This is best done by understanding the individual's life history. Health anxieties may be caused by the presence of illness in the patient's parents, family members, or friends. The life history perspective also is essential in understanding how a patient will react to a specific diagnosis. The patient's knowledge of a disease, as well as fears and fantasies that he or she has gleaned from family or friends, may distort his or her understanding about his or her condition. Such information may lead to catastrophic thinking when a diagnosis is given and foster both anxiety and depression. Unrealistic fears about medications also are common and may have their origins in the patient's experience with others. The cli-

TABLE 34–1. Common medical conditions that may cause anxiety

Cardiovascular
- Anemia
- Arrhythmia
- Congestive heart failure
- Coronary artery disease
- Hypovolemic states
- Mitral valve prolapse

Respiratory
- Asthma and chronic obstructive pulmonary disease
- Hyperventilation
- Hypoxia
- Oat cell carcinoma
- Pneumonia
- Pneumothorax
- Pulmonary embolism

Endocrinological
- Adrenal gland dysfunction
- Hypoglycemia
- Menopause and ovarian dysfunction
- Parathyroid disease
- Pheochromocytoma
- Pituitary disorders
- Premenstrual syndrome
- Thyroid dysfunction

Metabolic
- Acidosis
- Hyperthermia
- Hypocalcemia
- Hypokalemia
- Hypophosphatemia
- Acute intermittent porphyria
- Vitamin B_{12} deficiency

Substance intoxication
- Alcohol
- Amphetamines
- Caffeine
- Cannabis
- Cocaine
- Hallucinogens
- Inhalants
- Phencyclidine

Substance withdrawal
- Medications
- Anxiolytics
- Clonidine
- Hypnotics and sedatives
- Selective serotonin reuptake inhibitors and tricyclic antidepressants
- Other substances
- Alcohol
- Cocaine
- Nicotine
- Opiates

Neurological
- Cerebral anoxia
- Cerebral vascular disease
- Encephalopathy (i.e., delirium)
- Huntington's chorea
- Multiple sclerosis
- Myasthenia gravis
- Mass lesion of the brain (especially third ventricle)
- Pain
- Parkinson's disease
- Polyneuritis
- Postconcussion syndrome
- Postencephalitic disorders
- Posterolateral sclerosis
- Simple or complex partial seizure
- Vestibular dysfunction–related vertigo

Toxicological
- Carbon dioxide
- Carbon monoxide
- Gasoline
- Heavy metals
- Insecticides and organophosphates
- Paint

nician should use his or her own empathic abilities to better understand how the patient is reacting uniquely to his or her condition.

Intersubject Differences

In the *intersubject differences perspective*, individuals differ along a variety of dimensions such as height, weight, intelligence, and personality traits. In conceptualizing anxiety within medically ill populations, it may be useful to consider that beliefs about health exist along a dimension. Health worries that are normally found in populations include fears about health and development of illness, as well as other common anxieties such as finances and fears about the family. Health worries appear to increase as one gets older (Hocking and Koenig 1995). When fears about illness become paramount, such a condition may be labeled *health anxiety*. Health anxiety would be considered pathological if it leads to sufficient distress to promote dysfunction in either caring for one's personal sense of well-being or completing the daily tasks at work or home. Health anxiety could then clearly evolve into the disease perspective category of

hypochondriasis if such distress without a medical basis leads to frequent medical use and dysfunction. Those individuals with panic disorder may well have sufficient autonomic arousal to precipitate hypochondriacal symptoms, which ultimately lead them to medical facilities. Such individuals often misinterpret these physiological events as the onset of a serious illness. Both psychiatric disorders could coexist because Barsky et al. (1992) documented high levels of comorbidity with anxiety disorders in hypochondriacal patients. Finally, the diagnosis of obsessive-compulsive disorder should be considered in patients with obsessive hypochondriacal concerns that cause dysfunction and personal distress.

Like health anxiety, personality traits also can be viewed from a *dimensional* perspective. The tendency to worry, the need to be around others, agreeableness, conscientiousness, and openness to new or different ideas are all descriptions of personality traits that are measured along a dimension. Characteristic personality patterns predispose an individual to predictable reactions given a provocation such as illness or the stress of a hospital setting. One method of describing such personality domains is that of the five-factor model, which divides personality into five basic domains: neuroticism, extroversion, openness, agreeableness, and conscientiousness (Costa and McCrae 1988). Neuroticism is the predisposition to experience anxiety, depression, self-conscientiousness, vulnerability, and hostility (Costa and McCrae 1990). It is not surprising that individuals with high neuroticism have augmented health worries. Russo et al. (1994, 1997) found that elevated neuroticism levels predicted excess medical use. Individuals who are introverted might find the public setting of hospitals with unfamiliar roommates extremely stressful. Individuals with high conscientiousness, who like order, planning, and purpose, may find schedules not kept exactly within the hospital routine, such as waiting for tests or meals, exceedingly difficult. Those individuals who score low on the agreeableness dimension may express hostility to health care providers and provoke negative reactions among doctors, nurses, and other staff members. Understanding these basic personality traits can better allow the clinician to understand untoward responses.

Motivated Behavior

A *motivated behavior* is a goal-directed activity that lowers anxiety or craving. For example, a patient who is very anxious may constantly call a nurse for reassurance. Anxiety will certainly augment such "cravings" unless treated. It is useful to analyze the components of a behavior so that a rational intervention can be used. In the case of a patient frequently calling a nurse, behavioral assessment may show that whenever catastrophic thoughts about the symptom of pain occur, anxiety escalates, and the patient pushes the call button. The proper intervention would be cognitive reframing that the pain does not indicate a dire situation. Many goal-directed activities lead to a specific behavior that lowers anxiety. Thus, a patient who is quite disruptive within a medical setting because of repeated demands on the nursing staff may be initially evaluated by examining the various components that lead to this disruptive behavior.

Medical Environment

For individuals in hospital settings, anxiety may be caused by the nature of the environment. The hospital setting is often a strange and frightening place (Imboden and Wise 1984). Patients enter an unfamiliar world when they set foot in either the medical clinic or the hospital setting. One's unique self is depersonalized when the "ticket to admission" to any medical setting is proof that one has third-party insurance. The search and review by an unfamiliar clerk for insurance information sets up a journey through the medical system that can indeed provoke anxiety and enhance such cognitive fears. Separated from familiar surroundings and social supports, the hospitalized patient is often placed in a room with a complete stranger. Unfamiliar health care professionals ask a series of personal questions and perform physical examinations that include uncomfortable and embarrassing probing of orifices. Simple issues such as cold rooms can enhance anxiety.

The actual medical evaluation may well be a variety of tests. Whether drawing blood in an individual with needle phobia or imaging studies that cause anxiety reactions, phobic reactions and anxiety are quite common during a medical workup. Many patients are not in fact adequately prepared for imaging studies. The confined nature of such studies may provoke claustrophobia. The loud noises caused by the magnet during imaging will foster such fear. It is not surprising, in this setting, that as many as 20% of patients are unable to finish imaging studies because of such anxieties (Lukins et al. 1997; Murphy and Brunberg 1997).

After a medical evaluation is completed, a diagnosis is made, which may or may not precipitate anxiety. If no serious disorder is found, the patient often may be relieved. If he or she continues to experience discomfort,

however, anxiety may persist. If a disease is identified, it is almost always perceived as a threat (Imboden and Wise 1984). The patient usually views serious illness as a potential loss. The most basic fear is loss of life, but the patient also will fear disability and dysfunction. Furthermore, disease states may deprive the patient of his or her characteristic behavior or lifestyle that has been important to preserve self-esteem and happiness (Wise 1974). An individual with a myocardial infarction may find his or her career hopes dashed as a result of the stigma of disease. A young mother with breast cancer may fear that she will never live to see her children fully grown. Financial burdens of illness also will stress the individual and his or her family.

The coronary care unit (CCU) is a specific medical environment where anxiety can predominate and be a burden to patient recovery. Hackett et al. (1968) reported that at least one-half of the CCU patients in their sample were clinically anxious or depressed, whereas others have observed up to two-thirds of subjects with anxiety disorders (Cay et al. 1972). In a more formal study of CCU patients, in which the Clinical Interview Schedule was used, at least 35 of 100 patients had either an anxiety or a depressive disorder (Lloyd and Cawley 1982).

Following a myocardial infarction, the typical pattern of reactions begins with initial fear and anxiety, which is replaced by a feeling that symptoms were a false alarm (denial); eventually, the patient realizes what happened during days 3 through 7, which leads to demoralization and depression. For the clinician, not only the CCU setting and the phenomenology of anxiety but also the day of admission to the CCU offer helpful clues to suspect underlying anxiety (Cassem and Hackett 1971). The consequences of not being alert to the presence of such anxiety can be grave, if not life threatening, for the cardiac patient. Moser and Dracup (1996) measured anxiety symptoms in 56 patients with confirmed myocardial infarctions in the 48-hour period following the infarctions and found more complications in patients with higher levels of anxiety than in patients with lower levels of anxiety (19.6% vs. 6%). These complications consisted of reinfarction, new-onset ischemia, ventricular fibrillation, sustained ventricular tachycardia, and in-hospital death. Even after controlling for clinical and sociodemographic factors that could influence these complications, Moser and Dracup discovered that anxiety level was independently predictive of these complications. Given these findings, it could be argued that anxiety early after myocardial infarction onset should be considered among the conventional risk factors for in-hospital acute myocardial infarction complications.

This relation of anxiety to medical complications is not just specific to the CCU setting. An earlier study conducted by Levenson et al. (1992) reported on the relation between general psychopathology and resource use in medical inpatients. They identified 22% of their sample of 1,020 inpatients as very anxious and found that this subcategory of patients had longer stays and higher costs during the index hospitalization. This association was determined to be independent of the severity of medical illness.

The surgical ward also has been reported to be associated with significant anxiety states. Strain (1985) estimated that up to 5% of general surgical patients have preoperative panic. Preexisting anxiety and new-onset anxiety in the context of serious medical illness were both thought to contribute to this frequency. Such preoperative anxiety was believed to predict postoperative states, but the literature has not been consistent on confirming this relation (Mathews and Ridgeway 1981).

However, several studies clearly indicate that anxiety does occur in the postsurgical period and that this anxiety usually consists of posttraumatic stress disorder or its associated symptoms. Patients who remember the actual surgery because of inadequate anesthesia are at greater risk for developing posttraumatic stress disorder complications (Blacher 1975; Mcleod and Maycock 1992). Memory for events during any part of the anesthesia has been well documented in controlled trials, and postoperative anxiety has been reported to predict such recall in a series of patients who underwent cardiopulmonary bypass surgery (Bennett et al. 1985; Goldmann et al. 1987).

Anxiety can predominate and be disabling in two patient populations besides CCU and surgical patients. In renal dialysis patients, anxiety is as common as depression, and the presence of any psychiatric disorder is associated with poor outcome (Farmer et al. 1979). Patients on ventilators also have been reported to be significantly anxious, wherein anxiety can affect the weaning process because it can transiently increase metabolic demands and cardiac work (Bergbom-Engberg and Haljamae 1989; Cassem and Hackett 1991; Parker et al. 1984).

Cardiac Disease and Anxiety

Anxiety and its relation to the heart deserve special consideration given the extensive literature addressing the

nature and extent of this relation. Osler's descriptions of early-onset angina may represent the first attempt at defining what we have come to know as type A behavior (Friedman and Rosenman 1974). Another early observer of the heart's connection to anxiety was Jacob Mendes DaCosta, who reported on cardiac symptoms of Civil War soldiers for which he could not identify objective cardiac findings. "DaCosta's syndrome" was further elaborated by Sir William Lewis (1918) during World War I when he coined the term *effort syndrome*. These functional syndromes may represent the early attempts of medical practitioners to define panic attacks and the functional cardiac symptoms that accompanied them. Modern researchers also have observed that patients with cardiac symptoms such as chest pain who have no objective cardiac findings on angiography have a high prevalence (between 43% and 61%) of panic disorder (Beitman et al. 1987; Katon et al. 1988; Zinbarg et al. 1994).

Because of these early reports, modern research data have emerged that have been organized around the scientific delineation of anxiety and its psychobiological relation to cardiovascular disease. Researchers who used animal models showed that myriad cardiac abnormalities were produced when animals were exposed to some form of laboratory stress. Human studies also have generated compelling evidence for a psychophysiological relation between anxiety and the heart. In susceptible patients, cognitive stressors such as mental arithmetic can induce arrhythmias much more reliably than do physical maneuvers designed to affect the cardiovascular system. Type A behaviors may correlate with coronary artery disease, although the research is inconsistent. Along with arrhythmias and coronary artery disease, human studies have found that myocardial necrosis and hypertension are attributable to stress. In this animal and human research, the sympathoadrenal system is thought to be the final common pathway that explains the psychophysiological connection between stress and the heart (Henry and Stephens 1977). The activation of this system alters a variety of cardiovascular parameters (heart rate, platelet aggregation, myocardial contractility, arterial tone), which can be adaptive but also can potentially cause deleterious cardiac effects in susceptible individuals, such as those with cardiomyopathy (Kahn et al. 1987; Markovitz and Matthews 1991; Pauletto et al. 1991).

Psychiatric research designed to define and measure anxiety more rigorously has produced data in some studies that are not inconsistent with the data derived from the above-mentioned animal and human studies of the effects of stress on the heart. In a retrospective study, for example, Coryell et al. (1982) examined mortality rates of 113 inpatients with panic disorder to find that panic disorder in males was associated with significantly increased mortality from circulatory disease. In two prospective studies, Kawachi and colleagues (1994a, 1995) reported that anxiety symptoms in two male cohorts, as measured by the Crown-Crisp Index and the Cornell Medical Index, also were associated with an increased risk of mortality from sudden cardiac death.

Because patients with panic disorder and other anxiety symptoms have been found to have significantly decreased heart rate variability and because decreased heart rate variability has been associated with sudden cardiac death, it has been hypothesized that patients with pathological anxiety are vulnerable to developing cardiac arrhythmias that may be fatal (Kawachi et al. 1994b, 1995; Klein et al. 1995; Yeragani et al. 1993). Further research is required in this area because other researchers have found no association between anxiety (panic disorder or social phobia) and decreased heart rate variability (Asmundson and Stein 1994).

Other psychophysiological theories have revolved around the issue of panic disorder and mitral valve prolapse. Originally, it was thought that because these two diseases share similar clinical symptoms, demographic features, and prevalence within the general population, the two may be subsumed within a single classification of mitral valve prolapse syndrome (Pariser et al. 1978; Savage et al. 1983a; Wooley 1976). And because mitral valve prolapse can be associated with potentially life-threatening cardiac illness (arrhythmias, sudden cardiac death, endocarditis, progressive mitral valve regurgitation), patients with panic disorder, mediated by mitral valve prolapse, were considered to be at possible increased risk for sudden cardiac death. These theoretical points, however, have not been borne out in the literature. Although patients with panic disorder may be at increased risk for mitral valve prolapse, these patients are thought to have the more benign form of this cardiac condition (Dager et al. 1986). Also, mitral valve prolapse within the general population has not been shown to be significantly correlated with increased cardiac abnormalities (Savage et al. 1983b). Alpert and colleagues (1991) offer a good review on this matter.

Taken as a whole, then, it is clear that the relation between anxiety and the heart has been carefully explored and delineated since the time of DeCosta and Osler. In fact, the literature generated from the question of this relation may serve as a useful template to more broadly understand the complex interface between anxiety and a variety of other medical illnesses.

Management of Anxiety

Physician-Patient Relationship

The physician must establish a working therapeutic alliance with any patient (Wise 1990). In the crisis of cancer, heart disease, or surgery, the physician is viewed as the individual who can literally save one's life and has a unique task. This demands supportive and empathic care in both imparting information and offering hope regardless of how serious the situation is. A study that found that placebo was as effective as alprazolam in reducing anxiety in cancer patients reinforces the role of the empathic supportive physician (Wald et al. 1993). Such responsibilities also fall on the hospital staff. In fact, strategies to convey critical information and to clarify opinions that seem confusing or conflicted in making treatment choices are often thrust on staff. Clearly, it is inappropriate for staff members to make treatment choices for patients, but offering information and letting the patient know that it is his or her choice and that it will be an appropriate one or that he or she can talk with various physicians and family members can ease the patient's burden.

Supportive Psychotherapy

Listening to a patient's fears may be a uniquely supportive phenomenon. Viederman and Perry (1980) outlined assessment of the individual's life trajectory in which the consultant attempts to understand where the patient was in his or her life and how the disease has modified hopes and dreams. Understanding the patient's marital relationship and how the spouse is coping with the crisis of a serious disease will further elucidate the social system in which the patient resides (Spiegel 1997). It is also essential for the consultant to pay attention to the patient's wider support system, such as friends and employers. The role of group support has been promising. Studies have shown that supportive group therapy is associated with longer survival in breast cancer patients (Spiegel and Kato 1996). Cognitive-behavioral and supportive therapies have improved the prognosis in melanoma patients (F.I. Fawzy 1995; N.W. Fawzy 1995).

Behavioral Medicine in Medically Ill Patients

The field of behavioral medicine has expanded beyond its original scope and has become an integral part of understanding and treating anxiety in medically ill patients (G.E. Schwartz and Weiss 1978). Although fundamentally based on principles of classical and operant learning theories, behavioral medicine has broadened its concept of psychological life to include not only behaviors but also cognitions, emotions, and psychosocial environments. Along with this conceptual shift, many behavioral techniques have been developed, ranging from relaxation, hypnosis, and biofeedback training to environmental modification, cognitive-behavioral psychotherapy, and group education. These techniques have been applied to a variety of medically ill populations to successfully reduce anxiety and its effect on the outcome of disease processes. Several studies have documented the success of such behavioral treatments.

A significant of amount of research in this area has been done on patients with cardiac illness. Anxiety states are one of the most common problems associated with this illness; most effective treatments have resulted in decreases in anxiety levels and changes in cardiac outcome. For example, stress reduction diminishes the risk of cardiac mortality and reinfarction (Frasure-Smith 1991). Indeed, for post–myocardial infarction patients, behavior therapies are superior to all methods of treatment in reducing risk of nonfatal myocardial infarction and cardiac death, except for the use of aspirin in patients with unstable angina and bypass surgery in patients who were classified as "high risk" (Ketterer 1993). Behavioral treatments also have been effective in treating the anxiety that accompanies other medical illnesses. For example, relaxation training helped to reduce preoperative anxiety in ambulatory surgery patients (Domar et al. 1987). Progressive relaxation and biofeedback have been particularly useful in chronic obstructive pulmonary disease and asthma because these techniques do not have the respiratory depressant side effects of various anxiolytic medications (Davis et al. 1973; Hock et al. 1978).

Interestingly, though, not all patients respond to these behavior therapies. As in any other form of psychotherapeutic treatment, contraindications have been found (e.g., psychoanalysis with the schizophrenic patient). These include biofeedback for some extroverted patients and relaxation for patients with panic disorder and possibly patients with generalized anxiety disorder (Adler et al. 1987; Braith et al. 1988; Heide and Borkovec 1983; Leboeuf 1977; Ley 1988). In these studies, relaxation-induced anxiety correlated with measures indicating high internal locus of control and high fear of losing control.

Psychotropic Medications

In situations in which anxiety cannot be quickly relieved via psychotherapy or behavior therapies, the use

of medication is indicated. Medications commonly used in physically healthy patients can be adopted with special considerations for the nature of the medical illness and concurrent medications being taken (Gorman 1987).

Benzodiazepines

Three common issues that complicate benzodiazepine administration in medically ill patients are impaired pulmonary function, liver disease and diminished cognitive capacity, and pregnancy (Stoudemire et al. 1993). Central respiratory suppression should be closely monitored, especially in patients with compromised pulmonary function (Crawen and Sutherland 1991; Thompson and Thompson 1993). In patients with liver impairment, lorazepam and oxazepam should be considered because they do not undergo hepatic oxidation but are excreted via the kidney after glucuronidation (Epstein et al. 1993). In pregnancy, fetal congenital anomalies are associated with first-trimester benzodiazepine exposure. Studies have focused mostly on diazepam and alprazolam. In patients exposed to any benzodiazepines during the first trimester, the rate of oral cleft can be as high as 0.7%, which is 10 times higher than in the general population (Cohen and Rosenbaum 1998). Weinstock and colleagues (2001) studied 27 female subjects exposed to clonazepam, however, and found no evidence of congenital anomalies or fetal withdrawal syndromes and high Apgar scores in all the neonates. Nevertheless, clonazepam use may have its risks because there are early reports of both floppy baby syndrome and withdrawal syndromes in the infants whose mothers were taking this longer-acting benzodiazepine (Fisher et al. 1985).

The effects of benzodiazepines on the central nervous system are also important in the elderly or cognitively compromised patient. Impaired memory can affect recall, especially in elderly patients, or cause anterograde amnesia. In delirious or demented patients, such drugs may foster confusion or disinhibition. Although benzodiazepines can cause amnesia, they can be used to exploit this side effect (Wolkowitz et al. 1987). Intravenous use or oral intake of high-potency short-half-life benzodiazepines such as lorazepam can be useful in the settings of painful and frightening procedures.

Benzodiazepines also can be useful in managing anticipatory anxiety. When patients are preparing for chemotherapy, benzodiazepines—either alone or with dexamethasone and ondansetron—decrease nausea and vomiting (Greenberg 1991). In medical settings, patients often have multiple-drug regimens; thus, drug interactions should be considered (Nemeroff et al. 1996; Preskorn 1996). Benzodiazepines may increase phenytoin and digoxin levels (Ochs et al. 1985).

Nonbenzodiazepine Anxiolytics

Antipsychotics. Low-dose antipsychotics can be useful in treating severe and persistent anxiety when benzodiazepine treatment fails (Colon et al. 1995). For steroid-induced anxiety and anxiety secondary to organic causes, especially delirium, low-dose antipsychotics are very effective (Hall 1980). This population has been reported to be more prone to neuropsychiatric side effects when given antipsychotics, so low doses should be initiated (Edelstein and Knight 1987). Extrapyramidal side effects and the possibility of neuroleptic malignant syndrome should be carefully monitored.

β-Blockers. By directly blocking β-adrenergic stimulation, β-blockers can be effective in treating anxiety symptoms secondary to hyperadrenergic states, such as hyperthyroidism. In such cases, they can improve both somatic and affective symptoms of anxiety (Granville-Grossman and Turner 1966; Kathol et al. 1980; Tyrer and Lader 1974). Nevertheless, depression and some parasomnias, such as hypnagogic hallucinations, have been reported (Fraser and Carr 1976; Gershon et al. 1979). β-Blockers may decrease maximum exercise tolerance as a result of limitations of sympathomimetic response during exercise. Finally, patients with asthma, chronic obstructive pulmonary disease, diabetes, or bradycardia should avoid β-blockers.

Antidepressants. The side effects of tricyclic antidepressants make them more difficult to use in medically ill patients. The newer generation of antidepressants, such as serotonin reuptake inhibitors and nefazodone, are safely used in the medically ill. At low doses, such as 50–100 mg, trazodone can ameliorate anxiety and sleep difficulties in anxious patients. As with benzodiazepines, drug-drug interactions must be considered when a patient is taking other medications in addition to the antidepressant (Nemeroff et al. 1996).

Buspirone. Buspirone is an effective agent for generalized anxiety disorder but not panic. It is well tolerated in the elderly and medically ill. Although buspirone has a lag time of 3–4 weeks before full effect becomes apparent, it has the advantage of not causing sedation or respiratory depression and might improve pulmonary ventilation (Garner et al. 1989; Rapaport and Mendelson 1989). It is thus useful for patients on mechanical

ventilators or with poor respiratory drive (Crawen and Sutherland 1991; Mendelson et al. 1991).

Antihistamines. If respiratory function is a major concern or benzodiazepine abuse is present, antihistamines can be used to treat anxiety because they have minimal pulmonary depression (Bluestine and Lesko 1994). Because of its mild anxiolytic, sedative, and analgesic effects, hydroxyzine is especially useful in treating terminally ill patients with pain (Breitbart and Jacobsen 1996). Antihistamines are not as potent as benzodiazepines and can potentially lower the seizure threshold as well as increase anticholinergic effects (Derogatis and Wise 1989).

Others. Intravenous anesthetics not only control pain but also help make the experience of pain be forgotten. In dying patients, methotrimeprazine has been recognized as a unique treatment for their anxiety as well as pain (Bruera et al. 1987). Child patients who need bone marrow biopsy and aspiration can be benefit from fentanyl or ketamine. However, ketamine causes visual hallucinations in adult patients and therefore should be avoided (Bluestine and Lesko 1994).

Conclusion

Anxiety is common in a wide variety of medical settings. Whether the environment is a physician's office, a medical laboratory, a radiology suite, or a hospital floor, the patient may be frightened because of the meaning of the illness that is being evaluated or treated and because of the realistic pain, disability, and potential mortality inherent in serious disease states. The clinician should approach the patient from a variety of perspectives. First, the clinician must ascertain "what" the patient has. The physician may use the disease model to differentiate psychiatric from medical and medication-related causes of anxiety or determine that both factors are present. Second, the clinician must understand "who" the patient is based on past and present experiences, fears, and fantasies. Third, the clinician should understand the patient's general beliefs about health and his or her personality to allow understanding of reactions to the provocation of a medical disorder or setting. Finally, the clinician should understand a patient's behaviors because they can reflect the patient's motivation to reduce anxiety. By systematically assessing each of these perspectives, the physician can offer the anxious medical patient a rational treatment that uses both biological and psychological interventions.

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Social Aspects of Anxiety Disorders

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Cultural and Social Aspects of Anxiety Disorders

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Recent expanding interest in the anxiety disorders has been driven by advances in our understanding of their psychobiological mediators and interventions. At the same time, however, advances in cross-cultural and social psychiatry may have fundamental implications for a comprehensive understanding of these conditions. The work of Kleinman and his colleagues (Good and Good 1982; Kleinman 1988), for example, has played a major role in the development of a "new cross-cultural psychiatry" (Kleinman 1977; Littlewood 1990). This field focuses not only on psychopathology in non-Western cultures but also on the potentially significant contribution of anthropological theories and methods to the Western clinical setting.

In this chapter, we focus on cultural and social aspects of the anxiety disorders. We begin by considering different ways of approaching the intersection between culture and the anxiety disorders. We then consider each of the anxiety disorders in turn from the perspective of a "clinical anthropological" position. We propose that some anxiety disorders do in fact occur universally but also consider ways in which their experience and expression may differ in crucial ways. In addition, we note that socioeconomic factors may play an important role in mediating the pathogenesis of some anxiety disorders.

Culture and Psychiatry

Several different approaches to the intersection of culture and medicine have been outlined (Hahn and Kleinman 1983). One way of classifying these approaches is to distinguish between a clinical position, an anthropological position, and a clinical anthropological position. These positions reflect different stances on key debates within philosophy of science and medicine. This section draws extensively on a previous discussion of the strengths and weaknesses of these positions (Stein 1993). It should be emphasized that this division is intended to be a heuristic one and may not reflect the work of any single clinician or anthropologist.

Clinical Position

The clinical position is occupied by clinicians and anthropologists who are primarily interested in using Western medical and psychiatric nosologies, in post-hoc fashion, for diverse populations. The DSM-IV-TR (American Psychiatric Association 2000) categories and criteria, for example, constructed in a particular (Western) setting, are used to classify psychiatric data obtained in another (non-Western) context. Cross-

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cultural psychiatrists such as Prince and Tcheng-Larouche (1987), for example, argued that relatively minor alterations in the DSM system would result in a truly international classification of diseases.

This position has a long tradition in medical and psychiatric nosology. For example, Kraepelin, the father of contemporary psychiatric nosology, applied his system of classifying psychoses in German patients to data collected in Java, Indonesia. Kraepelin's nosology was predicated on a biological hypothesis—that the major psychoses each had a distinctive underlying neuropathogenesis, which accounted for their particular symptomatology and course. Thus, psychotic symptomatology had universal forms, which were biologically determined, but diverse contents, which were colored by cultural factors (Littlewood 1990).

Similarly, proponents of a clinical position might argue that anxiety disorders are simply biomedical disorders, and culture can influence only their content rather than their form. For example, the form of obsessive-compulsive disorder (OCD) necessarily comprises obsessions or compulsions, but the content may vary from obsessions about syphilis in one culture to obsessions about acquired immunodeficiency syndrome (AIDS) in a second culture. Proponents of such a position would argue that OCD has a specific neurobiological basis and that cross-cultural differences in the disorder are therefore likely to be only superficial.

The strength of the clinical approach lies in its willingness to extend a particular theoretical framework to diverse settings. The position highlights the scientific process of constructing nosologies. Indeed, international employment of the DSM system has allowed the work of different clinicians to converge and has contributed to increased knowledge of psychiatric disorders. Furthermore, advances in our understanding of the neurobiology of psychiatric disorders, including the anxiety disorders, would seem to strengthen the arguments of proponents of this position.

Nevertheless, this position has been criticized for committing a "category fallacy"—of reifying the categories and criteria of one ethnocentric classification as universal and natural. Indeed, routinized application of one theoretical framework of disease may prevent the nosologist from recognizing the existence, or appreciating the character, of unfamiliar categories and symptoms. The DSM system, particularly prior to DSM-IV (American Psychiatric Association 1994), gives short shrift to the so-called culture-bound syndromes and pays little attention to the differences in psychopathology among different cultures. Conversely, this approach downplays the possible contribution that cross-cultural theories and methods make in helping us recognize the particular sociocultural influences on our own nosology.

Anthropological Position

The anthropological approach states that the form and content of medical disorders are crucially determined by culture; our nosologies are themselves cultural artifacts. Such disorders are inevitably culture-bound (Yap 1951, 1962); they are expressed and experienced in terms of a particular sociocultural context. Thus, clinicians and anthropologists who support this position are interested, for example, in exploring the relation between the construction of DSM-IV and its forerunners and their particular sociocultural setting.

This position also has a long history. Boas, a pioneering figure in American anthropology, wrote that, "If it is our serious purpose to understand the thoughts of a people the whole analysis of experience must be based on their concepts not ours" (Boas 1943, p. 314). Furthermore, Boas (1943) increasingly came to believe that an appreciation of the historical and environmental factors that shaped a culture was required to understand these psychological forms. These ideas also have been applied in medical and psychiatric anthropology, and an extensive literature devoted to the cultural meanings of disease and to the social construction of disease has emerged (Conrad and Schneider 1980; Wright and Treacher 1982).

Critics of the DSM classification of anxiety disorder might, for example, emphasize that this system is itself a social construction. In their review of the anxiety disorders, for example, Good and Kleinman (1985) noted that 1) cross-cultural comparisons that use Western scales of anxiety (Spielberger and Diaz-Guerrero 1990) have several crucial methodological problems; 2) the experience and expression of symptoms of anxiety, as well as the experienced source of anxiety, vary greatly across societies; and 3) anxiety disorders are not only the result of culturally influenced interpretations of an underlying disease but also disorders of the interpretive process. Similarly, Young (1980) emphasized the extent to which the concept of stress and diagnoses such as posttraumatic stress disorder (PTSD) are embedded within our particular Western sociocultural context. In particular, he argued that the focus of DSM on the individual and his or her biology reflects the individualistic, technological aspects of Western society. Conversely, *koro*, or anxiety about penile shrinkage, is not

simply a biomedical entity but rather a disorder constructed within certain non-Western cultures.

The anthropological approach has several strengths. It emphasizes the relation between psychiatric nosology and the social forms in which it is produced. It therefore points to the importance of considering the ways in which cultural factors determine the experience and perception of mental disorder (rather than simply influencing its form). Kleinman (1980), for example, suggested that the emphasis in DSM on the psychological rather than the somatic symptoms of depressive-spectrum disorders makes sense only within Western culture and is not universally applicable. Furthermore, this position points to the importance of thinking through the relation between our nosology and our particular sociocultural setting in a self-reflexive process.

Nevertheless, the anthropological position also falls prey to several criticisms. A view of mental disorder as merely a social construction undermines the existence of mental disorders in DSM as real phenomena that are generated by underlying biopsychological mechanisms. A view of nosology as simply a cultural product undermines the importance of scientific explanation as a component of clinical work. Indeed, important strengths of DSM are its inclusion of advances in contemporary psychiatric science (e.g., recognizing panic disorder as a separate entity with a specific phenomenology and pathophysiology) and its explicit attitude that future editions of DSM will need to change to incorporate new findings. Thus, the anthropological position tends to neglect the reality of the entities and processes of mental disorder and the validity of our explanations of their mechanisms. It tends to downplay commonalities in underlying psychobiology across different cultures.

Clinical Anthropological Position

A synthetic or clinical anthropological position attempts to reach a compromise between the clinical and the anthropological position. This position conceptualizes biomedical disorders as reflecting the operation of real psychobiological mechanisms but acknowledges that disorders are necessarily expressed and experienced within sociocultural contexts. Classifications such as DSM, which are based on scientific knowledge, may be argued to have both intransitive dimensions (they do allow a knowledge of real entities) and transitive dimensions (they are always produced in social forms) (Bhaskar 1978).

An early Greek classification of infectious diseases, for example, divided these diseases into those that resolve after the "krisis" and those that deteriorate after this turning point. At this point, little was known about the underlying mechanisms of infection, and the classification was primarily informed by a wide-ranging theory, which also pertained to other aspects of social life. As knowledge of infectious entities progressed, classifications incorporated discoveries about different bacteria, viruses, and, more recently, prions. Knowledge about infectious disease continues to be produced in social forms and may, for example, reflect a Western focus on individual susceptibility to infection rather than on social responsibility for disease prevention (Young 1980). Nevertheless, the structure of classifications of infectious diseases is based on knowledge of real entities and processes.

Similarly, certain psychobiological mechanisms may result in the phenomenon of social anxiety; however, in Western culture, body dysmorphic disorder is common, whereas in Eastern cultures, olfactory reference syndrome is seen. Both entities may well involve overlapping serotonergic mechanisms (Stein et al. 1998), but the experience of each disorder also may differ in crucial ways. It is not that the "psychotic" disorders are more biological than the "neurotic" ones (Leff 1990) but rather that all psychiatric disorders are composed of psychopathological phenomena that are generated by underlying neurobiological and psychosocial causal mechanisms.

The strength of the clinical anthropological approach is that it has a place for both scientific knowledge and meaning construction. The reality of disease and its biopsychological underpinnings is emphasized, and the construction of disease within a particular sociocultural context also is incorporated. One way to draw on this approach is by differentiating between disease and illness. We discuss this distinction in the subsequent section.

Disease Versus Illness

A central theoretical distinction in modern medical anthropology is that between *disease* and *illness* (Fabrega 1987; Good and Good 1982; Kleinman 1977, 1980; Westmeyer 1987). The term *disease* refers to biomedical disorders that are present across cultures (e.g., raised blood pressure, depressed mood), whereas *illness* refers to the subjective perception and experience of such disorders. Medical anthropologists have emphasized a point well known to psychiatry—that the per-

ception of a disorder can itself affect its course and outcome (Stein and Rapoport 1996). Furthermore, medical anthropologists have emphasized that to negotiate clinical interventions with the patient, the physician must understand the illness (rather than simply the disease).

For example, the experience of the medical disorder known as depression in Chinese culture is informed by explanatory models that highlight the relevance of somatic symptoms and that expect that management involves the family. In this context, patients in fact have the illness experience known as neurasthenia, in which somatic symptoms are prominent. To achieve compliance with an appropriate treatment, an understanding of the patient's explanatory model is needed; this then allows an understanding of the patient's illness and a negotiation of a shared model of the disorder and its treatment (Kleinman 1988).

In the next sections, we use the distinction between disease and illness to address the intersection between cultural and social studies and the anxiety disorders. From a clinical anthropological perspective, although there do appear to be universal disease processes, cross-cultural factors result in different manifestations of psychopathological phenomena. Thus, although DSM diagnoses are culture-bound, this appears to be characteristic of all psychiatric disorders. To define a particular psychiatric disorder as culture-bound is to lose sight of the psychosocial factors in all such disorders. Furthermore, although psychiatric nosologies should be applied tentatively, with self-reflexive criticism (Kleinman 1988), this should be a feature of all psychological science.

In general, we argue that the anxiety disorders do not in fact represent a category fallacy. From a theoretical perspective, neuroevolutionary approaches to the anxiety disorders suggest that universal psychobiological mechanisms are important in the pathophysiology of these conditions. Empirical epidemiological and neurobiological data provide some support for this argument, and clinical data confirm that patients can experience onset of anxiety disorders in the absence of exposure to cultural narratives about their symptoms.

Nevertheless, culture may exert important influences on the experience and expression of anxiety disorders (Friedman 1997; Good and Kleinman 1985; Guarnaccia and Kirmayer 1997; Neal and Turner 1991). In particular, culture may influence the course and outcome of these conditions (Stein and Rapoport 1996). Certainly, strong evidence indicates that the adversity and stress associated with low social status play a causal role in mood and other psychiatric disorders (Dohrenwend et al. 1992; Yu and Williams 1999). Even after controlling for sociodemographic variables, stress from marginal minority status may affect rates of anxiety disorders (Brown et al. 1990).

Panic Disorder

Panic Disorder as Disease

A range of evidence indicates that panic disorder is a universal biomedical disorder and that this diagnosis does not represent a category fallacy. First, increasing evidence indicates that specific neuroanatomical circuits and neurochemical systems underpin the symptoms of panic disorder. Second, epidemiological studies suggest that the prevalence of the disorder in different settings is similar (although differences between populations do emerge) (Karno et al. 1989). Third, clinical and epidemiological studies have found that variables such as age at onset, sex ratio, and psychiatric sequelae of panic disorder are similar in a range of different contexts.

A neuroevolutionary account of panic disorder would bolster claims that it is a universal biomedical entity. Klein (1993) has made perhaps the most comprehensive attempt to do just that. He proposed that panic attacks occur when a suffocation monitor erroneously signals a lack of oxygen and maladaptively triggers an evolved suffocation alarm system. This hypothesis relies on the argument that the physiological mechanism for detecting potential suffocation depends on increased partial pressure of CO_2 (pCO_2) and brain lactate.

The false suffocation alarm theory seems to account for the prominent symptoms of dyspnea during a panic attack (indicating a specific emergency reaction to suffocation) (Anderson et al. 1984) and for the chronic hyperventilation that predicts lactate-induced panic (indicating an attempt to avoid dyspnea by lowering pCO_2) (Papp et al. 1993). The hypothesis also buttresses the differentiation (that Klein was instrumental in drawing) between episodic spontaneous panic and chronic fear-like anxiety (in which hypothalamic-pituitary-adrenal activation occurs) (Klein 1964). The hypothesis also provides an explanation for the lack of panic in patients with absent suffocation alarms (Ondine's curse) and during pregnancy and delivery (when pCO_2 is lowered) (Pine et al. 1994). Conversely, the hypothesis provides an explanation for increased panic during relaxation and sleep, during the premenstrual period, and in pa-

tients with respiratory insufficiency (in whom pCO_2 is increased) (Klein 1993).

A possible objection to Klein's hypothesis is the observation that panic attacks have similar features to many other kinds of fear responses. Thus, it might be suggested that panic attacks serve as a common adaptation for situations from which fleeing is an appropriate response (Nesse 1987). Various triggers, including separation anxiety, other kinds of loss, and traumatic suffocation, might then be expected to increase the threshold for this more general danger response. Indeed, Klein (1981) earlier put forward a hypothesis that panic attacks could be understood as homologous to an evolved separation anxiety response.

Panic Disorder as Illness

If panic disorder is understood as a biomedical disorder involving a false suffocation alarm, then how is this condition perceived and experienced by different persons and in different cultures? As in the case of many other anxiety disorders, relatively few data are available on this issue.

Nevertheless, panic attacks and panic disorder have been documented in a range of different cultures. Of course, these may manifest in somewhat different ways. Simons (1985), for example, provided an example of an Inuit person whose agoraphobic avoidance manifested not in the usual Western avoidance of driving but rather as a fear of kayaking. Liebowitz et al. (1994) noted that "ataque de nervios" in Hispanic Americans can be used to refer to several different patterns of emotional control, including diagnosable anxiety and mood disorders, such as panic disorder. Indeed, of their subjects who met diagnostic criteria for both ataque de nervios and panic disorder, 80% seemed to use the term *ataque* to label their panic attacks.

Is it possible that the perception of panic symptoms itself influences course and prognosis? Certainly, panic attacks are commonly misdiagnosed as medical disorders in Western settings. Self-diagnosis of panic attacks as *ataque de nervios* in Hispanic Americans might similarly lead to ineffective interventions; for example, Salman et al. (1997) noted that many such patients take medications only on an as-needed basis. However, in certain cultures, responses that invoke current cognitive-behavioral principles, such as exposure, may be more prevalent. Cultural norms regarding gender roles, for example, have been argued to facilitate decreased rates of agoraphobia in men (Starcevic et al. 1998).

Social Phobia

Social Phobia as Disease

Again, some evidence indicates that social phobia is a universal biomedical disorder and that this diagnosis does not represent a category fallacy. Although the neurobiology of social phobia remains in its infancy, some preliminary work has found that serotonergic and dopaminergic mechanisms, as well as particular brain regions, are crucial in mediating the disorder. Second, epidemiological studies indicate that the disorder is highly prevalent in almost all countries studied (Weissman et al. 1996). Third, clinical and epidemiological studies have found that variables such as age at onset, sex ratio, and psychiatric sequelae of social phobia are similar in a range of different countries.

It has been hypothesized that patients with social phobia have a pathological triggering of an appeasement display, often characterized by blushing (Stein and Bouwer 1997). This hypothesis relies on the argument that blushing is a communicative fixed action pattern and that there are similarities between blushing in humans and primate appeasement displays that serve to deflect aggression from conspecifics (Leary and Meadows 1991). Nevertheless, the neurobiology of social phobia, blushing, and appeasement displays is not well understood, so that the false appeasement hypothesis currently lacks empirical support. Nevertheless, a growing literature attempts to understand social phobia in terms of different innate defense systems (Trower and Gilbert 1989).

Social Phobia as Illness

Again, if social phobia is understood as a biomedical disorder involving a particular kind of false alarm, then how is this condition perceived and experienced by different persons and in different cultures? Perhaps the most relevant body of literature here is that on *taijin-kyofu-sho* (TKS) or anthropophobia, a condition that has been described in Japanese and other Eastern cultures (Kirmayer 1991). This disorder is characterized by "the presence of extraordinary intense anxiety and tension in social settings with others, a fear of being looked down upon by others, making others feel unpleasant, and being disliked by others, so that it leads to withdrawal from or avoidance of social relations" (Kasahara 1975, cited in Tseng et al. 1992, p. 380). Typical fears in TKS include blushing, unpleasant body odor, and stuttering.

TKS overlaps with and differs from social phobia in interesting ways. Both disorders involve social anxiety

and fears of embarrassment. However, whereas patients with social phobia typically worry about embarrassing themselves, patients with TKS often worry about offending or embarrassing others (Kleinknecht et al. 1994). This may reflect important cultural differences between West and East, particularly the value given to the group over the individual in traditional Asian thought. Although there has been relatively little work on the neurobiology of TKS, it is interesting to note that its symptoms, like those of social phobia, may respond to treatment with serotonin reuptake inhibitors (Kizu et al. 1994; Matsunaga et al. 2001).

An argument that TKS and social phobia overlap to an important extent is perhaps strengthened by the appearance of cases in the West, where concerns are precisely those that characterize the offensive subtype of TKS (Clarvit et al. 1996) or where symptoms are those of olfactory reference syndrome (Stein et al. 1998). Such patients may respond to standard treatments used for social phobia (Clarvit et al. 1996; Stein et al. 1998). However, note that not all patients who receive a culture-bound diagnosis will meet criteria for the overlapping DSM category. Simons (1985), for example, noted that patients with TKS occasionally may be best diagnosed as having a psychotic disorder.

Obsessive-Compulsive Disorder

Obsessive-Compulsive Disorder as Disease

It seems reasonable to assert that OCD, too, is a biomedical disorder mediated by specific neurobiological mechanisms. Certainly, increasing evidence indicates that specific neuroanatomical circuits and neurochemical systems underpin the symptoms of OCD. Again, epidemiological studies indicate that the prevalence of the disorder in almost all countries so far studied is in the order of 2%–3% of the population (Karno et al. 1988; Weissman et al. 1994). Finally, clinical and epidemiological studies have found that variables such as age at onset, sex ratio, and kinds of obsessions and compulsions are again similar in a range of different countries (Greenberg and Witztum 1994; Weissman et al. 1994).

However, some data indicate that the prevalence and symptomatology of OCD do vary in certain respects from country to country. For example, Okasha et al. (1994) provided data suggesting that religious concerns and contamination issues are more common in Muslim than in Christian patients (in whom orderliness and aggression concerns may be higher). Nevertheless, Greenberg and Witztum (1994) argued that close examination of religious symptoms shows remarkable overlap with the content of symptoms in nonreligious patients. Thus, religious obsessions and compulsions can be reframed in terms of the contamination symptoms seen in other cultures. Similarly, several authors have suggested that OCD is uncommon in Africa, but this is contradicted by growing clinical reports of such cases (Gangdev et al. 1996).

Some authors have suggested that from an evolutionary perspective, OCD may be considered as involving an alarm that erroneously signals the need to groom or to perform other danger-quelling behaviors (Rapoport et al. 1992; Stein et al. 1992; Swedo 1989). This hypothesis relies on the argument that the basal ganglia, which appear to play a significant role in the pathogenesis of OCD, are a repository of species-specific motoric and cognitive procedural strategies (i.e., learned habits, response sets).

A possible objection to this view of OCD emerges from an early ethological literature that focused on displacement behaviors. Ethologists have, for example, described the elicitation of repetitive, incomplete motoric patterns in response to conflicting triggers (e.g., for attack and flight) (Tinbergen 1953). In this account, grooming in animals and OCD in humans might be conceived as a nonspecific response to stress. It has been suggested that a prepotency for rituals exists at ages 5–8 years (Marks 1987), so that a stressful environment at that time may be important in reinforcing such behaviors. However, this view does not seem able to explain the specificity of the phenomenology and neurobiology of OCD.

Obsessive-Compulsive Disorder as Illness

The question of how OCD may be experienced and expressed differently in different countries has been considered by Stein and Rapoport (1996), and this subsection draws closely on this work. In certain non-Western cultures, obsessions may be understood in terms of constructs such as intentional witchcraft or ancestor displeasure. Such an understanding would lead the patient to present to a traditional healer. In the African context, for example, Carothers (1953) noted that anxiety was commonly associated with fear of bewitchment and poisoning or fear of having broken some taboo or neglected a ritual. Similarly, Lambo (1962) noted that morbid fear of bewitchment was the commonest cause of an acute anxiety state in Africa. Therefore, African

patients with symptoms revolving around bewitchment and other culturally syntonic concerns may in fact have had OCD.

More radically, the question that arises is whether certain kinds of disorders represent culture-bound variations of OCD. Are body dysmorphic disorder and anorexia nervosa Western forms of OCD? Is *koro* (concern about penile retraction) an Eastern form of OCD? Overall, there would seem to be too little confirmatory evidence for this. The alternatives are then to classify the cross-cultural category under more than one DSM diagnosis or to consider adding the culture-bound category as a separate diagnosis. Body dysmorphic disorder and *koro*, for example, overlap insofar as a concern with a body defect is present in each (Stein et al. 1991). Nevertheless, *koro* is often accompanied by panic, and the concern with penile retraction is often relatively transient. Perhaps *koro* overlaps with body dysmorphic disorder and/or panic disorder. Alternatively, the constellation of symptoms in *koro* may be sufficiently distinct to warrant a separate diagnosis.

Another question is whether perception of OCD symptoms itself influences course and prognosis. Okasha and colleagues (1994) noted that patients with OCD seen in psychiatric settings in Egypt had high scores on the Yale-Brown Obsessive Compulsive Scale, suggesting that these patients have a high tolerance for symptoms before medical, rather than religious, help is sought. Such explanations also may account for why more men than women with OCD are seen in Egypt. Similarly, in Western cultures, nonmedical belief systems may influence treatment-seeking behavior. Thus, religious patients with scrupulosity are perhaps more likely to seek spiritual advice than medical care. It has been argued that in the United States, certain groups of OCD patients, such as African Americans, do not present as commonly for psychiatric care but are more likely to voice somatic complaints (Hollander and Cohen 1994).

It is noteworthy that empirical investigation of OCD has determined that modification of patients' reactions to obsessions may result in changes in brain activity and in symptom levels (Baxter et al. 1992). Unfortunately, few data are available on the various health-seeking pathways taken by OCD patients in different settings. Further research along these lines is clearly called for, with additional exploration of the beliefs and circumstances that prevent individuals with OCD from seeking medical care. Further work on the course and outcome of OCD in different settings would also be of interest.

Posttraumatic Stress Disorder

Posttraumatic Stress Disorder as Disease

In the last few years, it has become clear that PTSD is characterized not by a normal stress response but rather by pathological sensitization of certain neurochemical systems and changes in functional neuroanatomy (Yehuda and McFarlane 1995). Epidemiological studies in a range of different settings show that PTSD is more likely to occur after more severe traumas but that certain individuals appear to be vulnerable to develop the disorder (Yehuda and McFarlane 1995). Also, a good deal of evidence indicates that PTSD symptoms are similar in different historical eras and in different cultures (Marsella et al. 1996).

A neuroevolutionary approach to PTSD has not been well defined, but presumably this disorder involves a dissociation of classical conditioned responses from their cortical control. Preclinical studies showed that thalamo-amygdala pathways play a crucial role in conditioned responses, and clinical studies of PTSD patients found hyperactivity of the amygdala during symptom provocation. Preclinical studies suggested that slow cortico-amygdala studies can override faster thalamo-amygdala pathways; this allows habituation to previously feared stimuli (LeDoux 1996). In patients with PTSD, however, it might be hypothesized that thalamo-amygdala responses, which ordinarily are brought "on-line" only in emergency situations, are continuously recruited.

Posttraumatic Stress Disorder as Illness

How is PTSD experienced and expressed differently in different societies? One point that may shed light on this is how PTSD is experienced and expressed differently in Western men and women; both similarities and differences have been described between male combat veterans and female survivors of rape and abuse. Similar kinds of differences may be seen across different cultures in the aftermath of trauma. Marsella et al. (1996), for example, suggested that the reexperiencing and hyperarousal symptoms of PTSD are universal, but the avoidant and numbing symptoms are more likely experienced in those ethnocultural settings in which avoiding and numbing behaviors are common expressions of distress. There also may be cross-cultural variation in extent of dissociation and somatization after trauma (Stamm and Friedman, in press). Cultural and social factors may be important determinants of vulnerability to PTSD by shaping concepts of what constitutes a

trauma and by affecting known vulnerability factors such as early childhood experiences, comorbidity (e.g., alcohol abuse), and social resources for responding to trauma.

Once again, however, many of these questions remain open for future rigorous empirical research (Marsella et al. 1996). Nevertheless, a strong theoretical argument can be provided to the effect that particular cultural rituals, performed after exposure to trauma, do play a role in preventing PTSD (Shay 1994). Conversely, it is possible to speculate that repression of trauma narratives in certain cultures exacerbates posttraumatic suffering. An interesting experiment at a national level recently was done in South Africa, where a Truth and Reconciliation Commission encouraged the public acknowledgment of past gross human rights violations (Stein 1998). In the absence of rigorous empirical data, it is not clear whether this exercise had a psychotherapeutic effect; there is, however, a small literature on the therapeutic effect of bearing witness to past human rights violations (Weine et al. 1998).

Given that the psychopathology of PTSD frequently involves not only discrete symptoms but also a broader questioning of the self and of identity, understanding the patient's sociocultural background is particularly important. Several authors have emphasized that inadequate appreciation of the sociocultural context of trauma and of responses to trauma may impede the therapeutic process (Stamm and Friedman, in press). A comprehensive and sensitive assessment of this context may allow appropriate individual and community interventions that promote symptomatic improvement as well as broader healing.

Generalized Anxiety Disorder

Generalized Anxiety Disorder as Disease

The question of whether generalized anxiety disorder (GAD) is a universal category is perhaps not as clear as in the case of other anxiety disorders. Good and Kleinman (1985), in fact, concluded that "generalized anxiety disorders exist in nearly all cultures." Nevertheless, the particular overlaps of anxiety, depression, and somatic symptoms may differ substantially from culture to culture. Even when the DSM characterization of GAD is used, there is significant comorbidity with depression and with somatization symptoms. Furthermore, although there have been advances in the neurobiology of GAD, it is unclear whether the underlying mechanisms are specific to this disorder. Finally, relatively few cross-national data are available on the symptoms and epidemiology of GAD.

What has been investigated are various combinations of anxiety, depression, and somatization symptoms in different cultures. Consider, for example, the entity of neurasthenia, which is included in ICD-10 (World Health Organization 1992). Good and Kleinman (1985) noted that in a study of 100 patients with neurasthenia diagnosed with the Schedule for Affective Disorders and Schizophrenia (SADS), 93 had depression, and 69 had anxiety disorders (including 13 with GAD). Most of the patients had major depression along with anxiety disorder, chronic pain, and somatoform disorders. The majority also had a history of significant stressors. Treatment with tricyclic antidepressants of neurasthenia in patients whose symptoms also met diagnostic criteria for depression led to decreased symptoms (although not necessarily to decreased social impairment). These agents are, of course, useful in both depression and GAD.

It is possible, then, to argue that in a range of different cultures, there is an anxiety-depression-somatization disorder that may respond to treatment with antidepressants. Individual vulnerabilities and various stressors are likely to contribute to the pathogenesis of this syndrome. Certainly, there is growing evidence of an inverse and causal relation between socioeconomic status and mental health (Dohrenwend et al. 1992; Yu and Williams 1999). In the National Comorbidity Survey, for example, an anxiety disorder was 2.82 times as common in those who had not completed high school as in those with a college education or more (16 or more years) and was 2.12 times as common in those with a yearly income of less than $20,000 as in those with a yearly income of more than $70,000 (Kessler et al. 1994).

Generalized Anxiety Disorder as Illness

In predominantly Western cultures, this anxiety-depression-somatization disorder may be described and experienced in primarily psychological terms (e.g., the symptoms of major depression, the worries of GAD). However, in other cultures, somatization may be more central. Certainly, the experience of anxiety and depression in Chinese culture is informed by explanatory models that highlight the relevance of somatic symptoms and that expect management to involve the family. In this context, patients may have the illness experience known as neurasthenia. Different kinds of somatic

symptoms of anxiety may be experienced in different cultures; in Nigeria, for example, a core symptom of anxiety appears to be the sensation of an insect crawling through the head or other parts of the body (Awaritefe 1988; Ebigbo 1986).

There are clear clinical implications of such an argument. First, it is important to determine the explanatory model of patients with mixtures of anxiety, depression, and somatic symptoms (Kleinman 1988). A comprehensive clinical interview should include an inquiry into the patient's own causal model of his or her symptoms; this may be significantly different from that of the clinician. Careful negotiation around these models may allow the clinician to justify his or her treatment choices in a way that the patient experiences as empathic and that improves compliance.

Second, additional research is needed that focuses on whether similar psychobiological mechanisms are responsible for the range of anxiety, mood, and somatic symptoms experienced by these patients. The DSM system has encouraged a focus on studies of patients who meet diagnostic criteria for particular disorders. However, even in the West, such a focus causes difficulties with disorders that have high comorbidity. Furthermore, a strong rationale exists for focusing instead on particular symptoms, such as anhedonia, that cut across diagnostic categories and that may be mediated by specific psychobiological mechanisms in all of these categories (Van Praag et al. 1990).

Conclusion

Important recent advances in the anxiety disorders have included more reliable nosological criteria, increased understanding of neurobiology, and more effective treatments. To some extent, this work has been so successful that it is possible to argue that our concepts of the anxiety disorders are universal and that this work never entails a category fallacy. From this perspective, the importance of sociocultural factors in the anxiety disorders is limited to only a consideration of racial/ethnic and gender differences in pharmacokinetics and pharmacodynamics. Certainly, one of the astonishing things about working in the anxiety disorders field is how media educational campaigns result in an "uncovery" of these conditions; patients often have symptoms for years, with no awareness that others have similar symptoms or that specific medical treatments exist.

However, these important advances also run the risk of failing to address cultural and social contexts. Although DSM-IV-TR has highlighted cultural issues in psychiatric diagnosis, the DSM system arguably remains a Western cultural product that does not entirely come to grips with anxiety entities such as TKS and neurasthenia. Such entities deserve increased phenomenological and neurobiological study. Arguably, a more comprehensive approach to anxiety disorders in different cultures and social groups will ultimately result in a more comprehensive understanding of their pathogenesis and management.

Even for disorders for which we can posit universal underlying mechanisms, it is crucial to consider the effect of culture and society on their diagnosis and treatment, expression, and experience. The literature on misdiagnosis of psychiatric disorders in American minority groups should be extended to the anxiety disorders. Ethnicity and gender affect important aspects of pharmacological management (ranging from patient compliance to pharmacogenetic variation), psychotherapeutic treatment, and broader interventions (such as the national media campaigns to improve the recognition and treatment of anxiety disorders).

Women are at greater risk for developing anxiety disorders than men are; the psychobiological and sociocultural mechanisms underlying this predisposition require much further analysis. Data from the National Comorbidity Survey provide strong evidence for an association between low education or income and the diagnosis of an anxiety disorder; investigation of the possible mechanisms whereby low socioeconomic status may play a role in the pathogenesis of anxiety disorders may ultimately lead to new avenues of prevention and management. It is increasingly recognized that specific psychosocial interventions may lead to particular brain changes; it is therefore not implausible that sociocultural variations result in different courses of anxiety disorder. Social phobia, for example, may be experienced somewhat differently in the West and East. Similarly, different reactions to severe trauma may result in changes in the experience and expression of PTSD. Much additional research in this area is required.

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36

Economic Costs of Anxiety Disorders

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Health economics is one of the most visible issues in the world ("Health care in America—your money or your life" 1998; "Patients or profits? Why the HMO revolution must be sustained" 1998b). People who control health care spending in both the public and the private sectors recognize that health care dollars are scarce, and, therefore, priorities must be established to determine how health care dollars are used. The fundamental health economics questions are: 1) How much does the disease cost? and 2) How many dollars does treating a disease save for each dollar spent? (Ginzberg and Ostow 1997). In this chapter, we focus on the economic costs of the anxiety disorders.

The anxiety disorders were once viewed as close to "normal," with patients thought of as "the worried well." In this view, mental disorders were thought of as one continuum from anxiety through depression to psychosis. The psychoses, especially schizophrenia and bipolar disorder, were the major mental disorders, the disorders most worthy of health care resources. The anxiety disorders and, to a lesser extent, depression were believed to be minor mental illnesses.

Today, the anxiety disorders are known to be discrete biopsychosocial disorders separate from the mood disorders and the psychotic disorders as well as separate from normal anxiety and fear (DuPont 1996; Kaplan and Sadock 1998). Anxiety disorders are not merely early stages of psychotic disorders but, like most other mental disorders, are typically chronic or episodic throughout the lifetimes of most patients. The anxiety disorders are also increasingly seen as producing intense suffering and distress rather than as being medically trivial (DuPont et al. 1998; Ross 1994).

Only since 1980 have the anxiety disorders been clearly defined and separated from one another, as well as from other mental disorders (American Psychiatric Association 1980). When this diagnostic specificity was carried into national community surveys in the early 1980s in the Epidemiologic Catchment Area (ECA) study, many public health experts were surprised that, with a 1-year prevalence of 12.6%, the anxiety disorders were more prevalent than not only the psychotic disorders but also the substance use disorders and the affective disorders, which were the other most prevalent groups of mental disorders (Regier et al. 1990a, 1990b, 1993). The more recent National Comorbidity Survey (NCS), which omitted obsessive-compulsive disorder from the survey protocol, found a 12-month prevalence of 17.2% and a lifetime prevalence of 24.9% for the anxiety disorders, again establishing these disorders as the most prevalent group of mental disorders (Kessler et al. 1994, 1996). The NCS was a national sample of people aged 15–54 conducted between 1990 and 1992 in which DSM-III-R (American Psychiatric Association 1987) diagnostic criteria were used, which were similar to the DSM-IV (American Psychiatric Association 1994) diagnostic criteria for the anxiety disorders.

The NCS confirmed the ECA findings that anxiety disorders were more chronic than affective disorders and substance use disorders, that a small proportion of persons who have mental disorders received mental health treatment (one in five received any treatment in the past year, and one in nine received mental health care), and that anxiety disorders were more prevalent in lower than in upper social classes (Kessler et al. 1996; Regier et al. 1990b).

In 1996, the first study of the economic costs of the anxiety disorders, based on 1990 health economic data, was published (DuPont et al. 1996b). That study was based on a variety of data sources, including the ECA data that used the human capital model, which was relied on by the National Institute on Alcoholism and Alcohol Abuse (NIAAA), the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH) (Rice et al. 1990).

In this chapter, we update the DuPont et al. (1996b) study from 1985 to 1994, the most recent year for which economic data are available. For this study, the same methods were used to report comparative data for the affective disorders and schizophrenia, as well as summary data for all mental disorders.

Calculating the Costs of Anxiety Disorders

Core health costs included the direct costs of treatment of the studied disorders plus indirect costs of the value of lost economic output from lost productivity. These indirect costs include both morbidity and mortality costs for all mental disorders. Direct and indirect non-health-related costs associated with the studied disorders were calculated separately.

Cost data were adjusted to 1994 dollars. Costs were adjusted by applying changes in socioeconomic indicators from 1985 to 1994. For direct costs, the rise in health care expenditures by type of expenditure was used. For indirect costs, changes in wages and salaries were used (DuPont et al. 1996b; Rice et al. 1990).

Core Costs

Direct Costs

Medical expenditures, both inpatient and outpatient, were estimated as the product of volume of services and unit prices or charges from published data. Support costs included federal expenditures for medical and health services research, the training costs of physicians and nurses, and the net costs of private health insurance. For example, the costs of hospital care were calculated by multiplying the costs per patient day by the annual number of days of care for hospitalization for a primary diagnosis of an anxiety disorder and the additional days of care associated with secondary or comorbid diagnoses of anxiety disorders.

Indirect Costs

Morbidity. Morbidity costs are the value of reduced or lost productivity due to anxiety disorders. These costs were based on impairment rates that reflected the lifetime effect of anxiety disorders on an individual's current income considering the timing of the onset and duration of the disorder as reported in the ECA data. Data were used for both institutionalized and noninstitutionalized populations, as described in earlier studies.

Mortality. The value of lost productivity was calculated from the present discounted value of future earnings of people who died prematurely from the disorder. Deaths from anxiety disorders are primarily suicides. Depression and other affective disorders are estimated to account for 40%–70% of suicides; the anxiety disorders are estimated to account for 10% of all suicides (DuPont et al. 1996b).

Other Costs

Direct Costs

The direct non-health-related costs included the costs for criminal justice and social welfare administration programs on the basis of the proportion they represent of similar costs for all mental illnesses.

Indirect Costs

The value of lost productivity was estimated for individuals incarcerated in prisons as a result of convictions related to mental disorders. In addition, the value of time spent by family members in caring for individuals with mental disorders, including anxiety disorders, was estimated.

Total costs of each mental disorder were the sum of direct costs and indirect costs (which together are called core costs) added to other costs.

Putting the Costs in Perspective

The overall cost of mental disorders in the United States in 1994 was estimated at $204.4 billion, as shown in Table 36–1. Total cost of the anxiety disorders amounted to $65 billion. The total cost of the affective

TABLE 36–1. Estimated economic costs of mental disorders, by disorder: 1994 (millions of dollars)

	Mental illness	Anxiety disorders	Schizophrenia	Affective disorders	Other disorders
Total costs	204,391	85,006	44,898	41,775	52,711
Core costs	196,579	64,548	40,493	40,107	51,433
Direct costs	91,737	14,936	23,698	26,306	28,797
Mental health organizations	25,761	2,620	8,806	8,432	8,102
Short-stay hospitals	17,677	512	3,425	6,197	7,542
Office-based physicians	4,733	461	526	1,516	2,230
Other professional services	9,430	922	1,015	2,925	4,569
Nursing homes	23,399	7,753	7,549	6,451	1,648
Drugs	2,875	1,531	521	533	290
Support costs	7,862	1,136	2,058	2,251	2,418
Indirect costs	104,842	49,610	16,794	13,801	24,636
Morbidity costs	88,316	47,825	14,972	3,073	22,448
Noninstitutionalized population	82,583	46,347	12,372	2,178	21,886
Institutionalized population	5,733	1,478	2,600	895	760
Mortality costs	16,526	1,785	1,823	10,728	2,190
Other related costs	7,512	460	4,405	1,668	1,278
Direct costs	2,783	278	727	797	981
Crime	2,157	216	583	617	781
Social welfare administration	626	62	164	180	220
Indirect costs	5,029	182	3,878	871	297
Incarceration	696	70	182	199	244
Family caregiving	4,333	112	3,496	672	53

Note. 1994 costs are based on socioeconomic indexes applied to 1985 cost estimates.
Source. Prepared by Dorothy P. Rice, University of California, San Francisco.

disorders, including major depressive disorder, dysthymia, and bipolar disorder, was $41.8 billion; for schizophrenia, the cost was $44.9 billion; and for other mental disorders, the cost was $52.7 billion.

The core costs of anxiety disorders comprise two major categories: 1) the direct costs—$14.9 billion (16.3% of the direct costs of all mental disorders) and 2) the indirect costs—$49.6 billion (47.3% of all indirect costs). Other related costs for the anxiety disorders, separate from the core costs, were $460 million, or less than 1% of the total economic costs of the anxiety disorders, with most of these costs attributable to the criminal justice system. The anxiety disorders accounted for only 5.9% of other related costs for all mental illnesses, reflecting their relatively sparse contribution to overall mental health costs within the criminal justice system.

Based on the groupings of mental illness, the anxiety disorders stood out from the other major groups of mental disorders in two ways. First, the anxiety disorders were responsible for the largest percentage (31.8%) of the total costs of all mental disorders, clearly belying the common stereotype that these are not serious disorders. This reflected not only the high prevalence of the anxiety disorders but also their large effect on economic productivity, which was the result of both the young age at onset of these disorders and the severity of the economic burdens the anxiety disorders imposed.

Second, the anxiety disorders stood out in terms of the relatively low percentage of total direct costs contributed by anxiety to all disorders. For the anxiety disorders, only 23% of their costs were the result of treatment. For all mental disorders, the direct costs represented 45% of all costs. The equivalent figures for the costs of treatment as a percentage of total costs for the other groups of mental disorders were schizophrenia, 53%; affective disorders, 53%; and other mental disorders, 51%. This disparity between anxiety disorders and the other major groups of mental disorders reflected, in part, the fact that the anxiety disorders were less likely to be treated in more expensive inpatient facilities than were other serious mental disorders. It also reflected the relatively high level of indirect costs from the anxiety disorders.

Examining the components of these two large categories of core costs, Table 36–1 shows that direct costs

of mental disorders are divided into seven subcategories, which differ greatly in the relative contributions of the anxiety disorders to the total costs of all mental disorders. Nearly half of the direct costs of the anxiety disorders were attributed to nursing home costs—$7.8 billion out of total direct costs for anxiety disorders of $14.9 billion. This high cost estimate for nursing home costs of anxiety disorders reflected two facts: 1) many nursing home patients have diagnoses of anxiety disorders, and 2) nursing homes are far more expensive than other health care settings, with the exception of inpatient hospitals, which typically have short stays, especially for people with anxiety disorders (DuPont et al. 1996a). For nursing homes, anxiety disorders contributed 33.1% of all mental health costs. In contrast, the anxiety disorders contributed only 2.9% of short-stay hospital costs of all mental disorders.

The allocation of costs in various health care settings to specific mental disorders reflected the proportion of people in these settings who were given formal diagnoses of each disorder. In other words, the health care costs—the direct costs—did not reflect ECA data, but they did reflect diagnoses given to patients in each setting as reflected in published studies (see Rice et al. 1990). Because anxiety disorders are underdiagnosed in most health care settings—especially non–mental health settings—these direct cost estimates are probably substantially lower than the actual costs of the anxiety disorders.

Within the category of mental health organizations are public long-stay inpatient and outpatient programs, including federal mental health treatment programs plus state and county psychiatric hospital costs. The anxiety disorders contributed a comparatively modest 10.9% of total mental disorder costs in this category. Mental health organizations represent 12.6% of the costs of all mental disorders, whereas mental health organizations represent only 4.3% of the costs of the anxiety disorders.

For office-based physician visits (which were 85% for psychiatrist visits because nonpsychiatrist physicians were far less likely to give mental health diagnoses—including the diagnosis of an anxiety disorder—to their patients), the anxiety disorders contributed only 3.7% of the costs of all mental disorders. Other professional services reflected charges for visits to social workers, psychologists, and other nonphysician mental health professionals. In this category, only 3.7% of the costs were attributed to the anxiety disorders. In contrast to these low contributions from anxiety disorders, the costs of prescription drugs showed a far larger contribution of anxiety disorders: 53.3%. This increased proportion may reflect the wider use in recent years of prescription medicines by patients with anxiety disorders as well as the high prevalence of the anxiety disorders (DuPont 1996; DuPont and DuPont 1998).

The indirect costs—the costs of lost productivity—were divided into two subgroups: morbidity costs and mortality costs. The morbidity costs were further divided into noninstitutionalized and institutionalized populations. The institutionalized population contributed 6.4% to all mental disorders but only 3.1% to the anxiety disorders. Conversely, anxiety disorders represented 58.5% of the indirect costs from noninstitutionalized populations of all mental disorders, the largest percentage contribution of the anxiety disorders to any of the categories of costs in this study.

Readers interested in the details of the data collection for this study are referred to our earlier paper and to the report describing the underlying methodology (DuPont et al. 1996b; Rice et al. 1990). The strikingly large contribution of anxiety disorders to the indirect costs of all mental disorders encourages a closer look at the methodology for this category. A timing model was developed with regression analysis to estimate the impairment rates (percent of income lost compared with people who did not have the index diagnoses but who were otherwise demographically similar). Impairment rates reflected the lifetime effect of anxiety disorders and other mental health diagnoses on individuals' current income, taking into account the timing of onset and the duration as reported in the ECA surveys (Rice et al. 1990, 1991). The dollar value of lost productivity due to mental disorders for those living outside institutions was estimated as the product of United States population size, prevalence rates for the disorders, impairment rates per person with the diagnosis, and the average income (imputing value for housekeeping services) that would have been earned without the disorder. These impairment rates were calculated by age and sex and summed across categories to provide estimates of the total loss of income caused by anxiety and other mental health disorders among noninstitutionalized people aged 18–64 years. ECA data were used for estimates of prevalence of impairments for all mental health diagnoses for people in the country (e.g., the noninstitutionalized population).

Morbidity costs for the institutionalized population were based on the number of persons with specific mental disorder diagnoses residing in state and county mental hospitals and in nursing homes. This number was adjusted by demographically matched labor force

participation rates and multiplied by estimated mean earnings adjusted for wage supplements or fringe benefits for each age and sex group.

This study updates our earlier report, which was the first national estimate of the total economic burden of the anxiety disorders (DuPont et al. 1996b). This same methodology was applied to estimate the costs of obsessive-compulsive disorder at $8.4 billion in 1990 (DuPont et al. 1995).

The finding of extremely high costs from lost productivity in this study of the economic burdens of anxiety disorders is validated by studying the ECA data for employment of men and women, comparing individuals who have no Axis I clinical disorders with patients who have panic disorder, obsessive-compulsive disorder, and phobia (see Table 36–2). For men, the rate of being out of the workforce was 21% for those without an Axis I diagnosis, 60% for those with panic disorder, 45% for those with obsessive-compulsive disorder, and 36% for those with phobia. The effects of the anxiety disorders on the labor force participation rates for women were only slightly less dramatic, with 46% being out of the workforce with no Axis I diagnosis and 69% for panic disorder, 65% for obsessive-compulsive disorder, and 54% for phobia. The ECA data for current financial assistance (not shown in table) for the anxiety disorders were equally striking, with only 5% of the men and 4% of the women with no Axis I diagnosis receiving disability payments, in sharp contrast to 15% of the women with a diagnosis of panic disorder receiving disability payments (Leon et al. 1995). Similar sharp elevations in disability rates were observed for the other anxiety disorders.

In the present study of the economic costs of the anxiety disorders, the estimates of lost productivity were not based on a clinical sample but on the ECA sample. In other words, the sample was a community sample, not a sample of patients in treatment. Individuals with anxiety disorders and other mental health diagnoses were compared with persons from the same ECA community sample who did not have Axis I diagnoses to establish the lost productivity attributed to the various diagnoses studied here. Understanding the source of these data on morbidity costs adds substantially to their credibility and to the generalizability of these findings.

This study did not explore the effect of comorbidity, but the NCS found that patients with anxiety disorders usually have comorbid mental and physical disorders and that those who have multiple diagnoses are more disabled and use more medical services than do people who do not have comorbid multiple disorders (DuPont 1997; Kessler et al. 1996).

Other Studies of the Costs of Affective and Anxiety Disorders

The economic burden of depression has been widely studied, beginning with the landmark study of Stoudemire et al. (1986) that reported the 1980 costs at $16.3 billion. Consistent with later studies of the economic costs of affective disorders, most of the costs were indirect costs ($14.2 billion of the total costs). For affective disorders, in contrast to anxiety disorders, the human capital approach applied to ECA data found a relatively smaller contribution from indirect costs (Rice and Miller 1995). Rice and Miller found that for men with depression and dysthymia and for women with mania, depression, and dysthymia, these disorders had a positive effect on income compared with individuals who did not have an Axis I diagnosis. This counterintuitive finding led to a lively debate as many alternative explanations were considered. Rice and Miller (1995, p. 38) concluded that

> The positive finding does not suggest that having an affective disorder increases one's income; only that the likely negative effect on income is outweighed in the regression by the incomplete measurement of controls and by the joint dependency of income, type of occupation, and prevalence which was not modelled.

A subsequent study of the economic costs of depression moved away from the human capital approach of Rice and Miller to focus on the effects of affective disorders on absenteeism and reductions in productive capacity, concluding that absenteeism from depression cost $11.7 billion annually and that lost productive capacity due to depression cost $12.1 billion annually, for a total annual morbidity cost of $23.8 billion. The indirect costs of depression were 55% of the total costs of depression in 1990 dollars (Greenberg et al. 1993). The Greenberg study estimated proportionate indirect costs of the affective disorders that were more similar to the indirect cost proportions based on the human capital method of other mental disorders, including anxiety disorders. The Greenberg approach did not use a community sample to identify reduced labor force participation and disability rates, but built estimates of lost productivity of affective disorders on the experiences of patients in treatment who had affective disorders.

With respect to the economics of anxiety disorders, one of the most striking findings was made in the original ECA studies, which found a powerful correlation between social class and the prevalence of anxiety dis-

TABLE 36–2. Employment status of the 18- to 64-year-old individuals in the sample (rate per 100)

	Not currently employed		Not employed in the past 5 years	
Diagnosis (past 6 months)	**Men**	**Women**	**Men**	**Women**
Panic disorder	60.00	68.57	25.00	28.57
Panic disorder without major depression	64.71	69.64	29.41	28.57
Panic disorder and major depression	33.33	64.29	0.00	28.57
Panic attacks (subclinical)	29.73	55.67	15.09	28.20
Obsessive-compulsive disorder	44.78	65.25	17.91	28.81
Phobia	35.69	54.05	12.72	28.02
No Axis I diagnosis	21.05	45.92	4.63	23.72

Source. Reprinted from Leon AC, Portera L, Weissman MM: "The Social Costs of Anxiety Disorders." *British Journal of Psychiatry* 166 (Suppl 27):19–22, 1995. Copyright 1995, The Royal College of Psychiatrists. Used with permission.

orders, with the lowest quartile having diagnosable anxiety disorders at twice the rate of the highest quartile (see Table 36–3). The increased prevalence among lower social classes is particularly prominent and progressive between all quartiles for phobias. Both panic and obsessive-compulsive disorder showed dramatic differences by social class only between the lowest quartile and the three higher quartiles. Analysis by ethnic background and race showed higher rates of anxiety disorders for blacks than for nonblacks, non-Hispanic (white), and Hispanic groups.

When the ECA data were reanalyzed controlling for social class, no significant racial or ethnic elevations in the prevalence of anxiety disorders were seen (Regier et al. 1990b). In other words, the correlation found for prevalence of anxiety disorders was for social class, not for ethnic or racial status. This effect on prevalence was noted for all anxiety disorders between the lowest quartile and the three higher quartiles by social class, except for phobias, for which the correlation of prevalence and social class was particularly strong and clearly stepwise from the lowest social class (highest prevalence of phobias) to the highest social class (lowest prevalence of phobias).

The finding that anxiety disorders in this community sample were more prevalent in lower social classes is contrary to the common clinical observation that many people with anxiety disorders are socially and economically successful. This latter view may reflect the sampling distortions from private clinical practices. When the finding of higher rates of anxiety disorders among lower social classes (separate from ethnic and racial factors) is combined with the finding of dramatically lower productivity and higher disability (as well as the high prevalence of anxiety disorders in nursing homes), it becomes clear that anxiety disorders may both cause and result from lower economic status. This finding argues for more systematic efforts in public sector mental health treatment programs and other programs targeting the poor to develop and implement effective treatments of anxiety disorders for the large and clearly needy population of lower social class patients with anxiety disorders.

Longitudinal studies are needed to distinguish between anxiety disorders that result from prior lower class status and lower class status that results from the presence and persistence of anxiety disorders. Effective treatment of anxiety disorders, especially in childhood and early adulthood, could possibly prevent people with anxiety disorders from falling into lower class status.

A particularly useful and comprehensive summary of the economic consequences of anxiety disorders has recently been published (Hofmann and Barlow 1999). The authors concluded that anxiety disorders were prevalent and costly and that "Based on tightly controlled efficacy studies, we now have a number of effective psychosocial interventions for treating a range of anxiety disorders." They also concluded that high priority needs to be given to cost-effectiveness studies, particularly in the era of managed care responding to the growing commitment to clinical interventions that are both low cost and highly effective. Various economic studies have been published focusing on specific aspects of the economic burdens of anxiety disorders, including the high rates of medical use from panic disorder (Katon 1996), as well as the offset effects of treatment in terms of reduced medical costs (Salvador-Carulla et al. 1995). The costs of depressive and anxiety disorders in primary care have been shown to be elevated in the 6 months surrounding the study. For those with anxiety or depressive disorders, the health care costs were $2,390 compared with $1,397 for patients in primary care without these diagnoses (Simon et al. 1995).

TABLE 36–3. Anxiety disorders, 1-month prevalence rates, by socioeconomic status (SES) in Nam quartiles: combined five-site Epidemiologic Catchment Area (ECA) data standardized to adult (age 18 or older) United States population

Disorder	Nam SES quartiles			
	Level 1 (highest) % (SE)	Level 2 % (SE)	Level 3 % (SE)	Level 4 (lowest) % (SE)
Any anxiety disorder	4.6 (0.5)	6.4 (0.4)	8.5 (0.5)	10.5 (0.7)
Phobia	3.6 (0.4)	5.7 (0.4)	7.4 (0.4)	8.6 (0.6)
Panic	0.2 (0.1)	0.5 (0.1)	0.5 (0.1)	1.2 (0.3)
Obsessive-compulsive disorder	1.0 (0.2)	1.0 (0.2)	1.4 (0.2)	2.1 (0.3)

Source. Reprinted from Regier DA, Narrow WE, Rae DS: "The Epidemiology of Anxiety Disorders: The Epidemiologic Catchment Area (ECA) Experience." *Journal of Psychiatric Research* 24 (Suppl 2):3–14, 1990. Copyright 1990, Elsevier Science. Used with permission.

The economic costs of obsessive-compulsive disorder were estimated with clinical techniques similar to those of Greenberg (Greenberg et al. 1993; Hollander et al. 1997). Hollander et al. administered a 410-item questionnaire on psychosocial functioning and economic costs to a sample of members of the Obsessive-Compulsive Foundation (N=701). A variety of direct costs were identified, including ineffective treatments (projected to a total cost of $2.4 billion for all patients with obsessive-compulsive disorder) and hospitalizations. Most of the costs of obsessive-compulsive disorder were identified as indirect costs resulting from lost work, which averaged $46,650 per person over their lifetimes.

A review of the costs and efficacy of the treatments for anxiety disorders found that pharmacological and psychosocial interventions (or cognitive-behavioral treatments) were cost-effective in terms of offset costs and in reducing total direct and indirect costs of the anxiety disorders, although further study is needed to convincingly establish this conclusion (Hofmann and Barlow 1999). In particular, the authors pointed to many studies that established the success of the psychosocial interventions. Nonpharmacological therapies were compared with a variety of pharmacotherapies for panic disorder, including generic imipramine (at $912 per treatment episode, the lowest cost for a pharmacological intervention), and with cognitive-behavioral therapy (at $600, the lowest cost for a nonpharmacological treatment episode). Cognitive-behavioral therapy was superior to pharmacotherapy in terms of a higher rate of retention of patients, with approximately the same overall efficacy as pharmacotherapy (Gould et al. 1995).

Because a large proportion of the treatment of anxiety disorders and other illnesses is paid for today by managed care companies concerned with the direct costs of care, medical economics has taken a new turn in recent years. The non–health care costs of illnesses do not show up in the budgets of managed care companies. Not only is lost productivity not a cost factor for managed care, but also health care costs outside the managed care system are not factors either. "Costs," in a modern managed care context, mean the costs of care that are borne by the managed care company and ultimately borne by the insured population. Findings of high indirect costs from anxiety disorders, and even findings that these costs can be reduced by effective treatments, are not likely to influence managed care decision makers to increase the priority given to the treatment of anxiety disorders. Managed care, with its focus on reducing the costs of care, is a potential obstacle to increasing the levels of care for anxiety disorders, in terms of both the percentages of patients treated and the quality of their care. However, managed care's focus on quality of care offers hope that the cost-effective treatments of anxiety disorders will be recognized and that effective treatments for anxiety disorders will be made available more widely and more systematically under managed care than has been the case in the traditional fee-for-service environment (Hofmann and Barlow 1999; Wilson et al. 1997).

Because most managed care is purchased by employers, they may recognize the high lost productivity of mental disorders, including anxiety disorders. Employers have a clear economic stake in the lost productivity related to mental disorders. However, the needs of people not in the labor market usually are not thought of as employers' responsibilities. This is more the concern of the government, which is becoming a bigger player in the managed care field as Medicare and Medicaid come under managed care. In this new world of managed care

decision making, the most relevant health care question is cost offset, or the cost and the benefits of treatment within the managed care cost environment itself. A new breed of cost studies are beginning to focus on these more narrowly defined offset benefits, which include not only health care costs of mental health care but all the costs of health care (Kashner and Rush 1999). Clinical experience and preliminary cost offset studies show that anxiety disorders are high health care cost generators and that effective treatment of the anxiety disorders is cost-effective in this more limited context (DuPont 1982, 1996; Salvador-Carulla et al. 1995).

Depression has been in the forefront of these new cost offset studies (Gabbard 1998; Lloyd and Jenkins 1995; Rupp 1995; Santiago 1993). Noel Gardner (1998) wrote a particularly useful summary of the economic implications of antidepressant therapy, including using antidepressants in the treatment of anxiety disorders. Gardner separated four key variables in the pharmacoeconomics of antidepressant therapy: 1) *efficacy* (a statistically significant treatment response in a placebo-controlled clinical trial), 2) *effectiveness* (the probability that a medication will produce a desired therapeutic effect in a real-world clinical setting), 3) *cost* (the resources in monetary equivalents that are consumed by a condition, intervention, or process), and 4) *value* (the benefit achieved per unit of cost). Gardner noted that antidepressant therapy has become the first-line treatment of depression because it is less costly than psychotherapy (estimated at $50–$150/month for antidepressant therapy compared with $300–$500/month for psychotherapy) and because it can be provided by primary care physicians.

Conclusion

The anxiety disorders produce a substantial economic burden, estimated in 1994 to be $65 billion, or 31.8% of the total costs of all mental disorders. This estimate of the total costs of the anxiety disorders was composed of both high direct costs (costs of treatment—$14.9 billion) and even higher indirect costs (costs of lost productivity—$49.6 billion). The indirect costs of the anxiety disorders represented 76.3% of total costs of the anxiety disorders and 47.3% of the indirect costs of all mental disorders.

These figures, based on standard health economic methods to calculate costs of illnesses, underline the large economic burden imposed by the anxiety disorders and indicate that most of the costs of anxiety disorders are not the costs of treatment but the result of lost income and disability from the morbidity effects of the anxiety disorders among noninstitutionalized persons, most of whom are receiving no treatment for their anxiety disorders.

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Consumer Considerations

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Nam et ipsa scientia potestas est [Knowledge is power].

Sir Francis Bacon, *Meditationes Sacrae* (1597)
***Bartlett's Familiar Quotations*, 16th Edition, p. 158**

In an address delivered at the University of California, Berkeley, on March 23, 1962, John Fitzgerald Kennedy, the 35th president of the United States said, "In a time of turbulence and change, it is more true than ever that knowledge is power." Truer words could not be uttered today to echo the discrepancy that exists in turbulent health care systems throughout the world; namely, the educated, well-informed consumer has a distinct advantage over his or her uninformed counterpart. As Herzlinger (1997) wrote, "The relationship between education and health seems beyond dispute. People who understand the relationship between their own behavior and their health are better prepared to manage their health."

Education, information, and knowledge appear to be key elements for today's demanding health care consumer. These skills empower individuals to gain mastery over their illnesses and to place realistic demands on the health care marketplace. To paraphrase Sir Francis Bacon, the sixteenth-century English philosopher, and President Kennedy, knowledge is power—especially as it pertains to the health care consumer, supplier, and legislator. In fact, in this chapter, I attempt to educate and inform health care consumers, providers, and legislators about several key facets of anxiety disorders, including their severity, the consequences if they are not treated or inadequately treated, the economic burden such disorders impose on society, and barriers to treatment for the consumer.

During the past decade, a proliferation of newspaper and magazine articles, television and radio talk shows, and books—both academic and self-help—has been tremendously helpful in raising consciousness about the seriousness and the treatability of anxiety disorders. Yet, as evidenced by the many people who contact the Anxiety Disorders Association of America (ADAA), the National Mental Health Foundation, Freedom From Fear, the Obsessive-Compulsive Foundation, and other consumer organizations focused on anxiety disorders, people continue to be unable to find and/or afford effective treatment. Millions of people remain in the dark about their anxiety-related conditions.

The Severity of the Problem

Anxiety disorders are among the most common psychiatric illnesses (Ross 1994). Yet, despite the preva-

lence of anxiety disorders, they are and continue to be grossly underdiagnosed, misdiagnosed, or inadequately treated. Furthermore, the mortality rate is higher in individuals with anxiety disorders, especially for those with panic, than in individuals without anxiety disorders. The data, although controversial, also suggest that premature mortality is increased in persons with anxiety disorders because of an increased suicide rate in both sexes and because of an increased rate of cardiovascular disease in men. The comorbidity with other psychiatric illnesses has been extensively cited and includes comorbid anxiety disorders, major depressive disorder, and personality disorders. The concomitant use of alcohol and illicit street drugs is also a complication for individuals with anxiety disorders. In an attempt to self-medicate the dreaded signs and symptoms of anxiety disorders, particularly panic disorder, individuals will often receive temporary relief with the use of alcohol and street drugs. However, they often experience rebound symptoms, which intensifies their anxiety disorder and sets the groundwork for a concomitant substance abuse problem. In fact, studies show that approximately 10% of the adults with alcoholism meet the criteria for panic disorder.

Millions of persons with anxiety disorders suffer in silence or go from doctor to doctor; many have no idea what is wrong with them (Ross 1994). Simply identifying the correct diagnosis can be a challenge, because the physical symptoms that accompany some anxiety disorders send the patients to medical doctors who often have little or no training in the diagnosis and management of anxiety disorders. This category of mental disorders, therefore, is both underrecognized and underdiagnosed by the medical profession. In response to this problem, the ADAA and other consumer organizations have initiated the following proactive activities:

- Promote the education and training of mental health professionals about effective treatments for anxiety disorders.
- Educate non–mental heath specialists such as medical general practitioners, gynecologists, and cardiologists in the diagnosis and treatment of anxiety disorders. Provide these health care professionals with referral information and literature for patients with anxiety disorders.
- Help consumers, families, and friends recognize anxiety disorders and get help.

Rosalynn Carter, former first lady of the United States, maintains that discrimination against those with mental disorders and stigmatization of them by society and by health care professionals, in particular, are common in America today. She writes,

> We must end discrimination against those with mental disorders. Discrimination has denied those who need care access to appropriate services for far too long, and it continues to limit resources available to pay for care. We must recognize that mental health is an integral part of every person's health. Awareness of mental health problems needs to permeate the health-care system. Primary-care physicians, nurses, physicians' assistants—all must have sufficient knowledge about the interdependency between mind and body to know when intervention is necessary and who is best able to intervene. (Ross 1994, p. xi)

The stigma that comes with mental illness in American society has yet to be dissipated and certainly affects those who have an anxiety disorder. Indeed, many persons with agoraphobia, for instance, cite "fear of going crazy" as one of the symptoms of a panic attack. It also was startling to learn that although anxiety disorders are the most common psychiatric illness in the population, and among the most treatable of psychiatric illnesses, fewer than one-quarter of those who have an anxiety disorder receive treatment (Ross 1994).

Consequences of Untreated Anxiety Disorders

Untreated or inadequately treated anxiety disorders can have significant costs to the patient, his or her family, society, the use of health care services, and the gross domestic product, to name a few. As Mrs. Carter noted,

> When an anxiety disorder is not recognized or appropriately treated, the toll is great, not only to the individual, but to his or her family and the community at large. Many people with panic disorder, for instance, have markedly constrained lifestyles because of fear of traveling any distance from home, which often leaves them unable to fulfill family responsibilities, career functions, and social obligations. Many also have concurrent depression. Treating the underlying disorder will not only decrease a great deal of personal suffering, but will also have a positive effect on families, communities, and the workplace. (Ross 1994, p. x)

The ADAA and similar organizations receive tens of thousands of letters each year. Not everyone who writes

tells his or her whole story—many of them are simply seeking information or want to find help. Many individuals, however, do give the details of their stories, and, in particular, they talk about the consequences of untreated anxiety disorders. Some of the issues that many of these poignant letters have in common include the following:

- Repeated doctor and emergency room visits
- Extensive, expensive, and often unnecessary medical examinations
- Reliance on disability insurance
- Academic underperformance
- Vocational limitations
- Use of alcohol to self-medicate
- Depression
- Suicidal ideation and attempts

These patients write about disrupted personal lives, aborted careers, substance abuse, and a great deal of despair and discouragement. Sometimes, they describe symptoms of outright depression. They discuss suicidal ideation and attempts. They describe what it is like to live on disability because they are unable to work. Clearly, this raises issues about their quality of life, which obviously appears to be diminished. In addition, they experience decreased family involvement, increased family burdens on caregivers, decreased career functioning, and decreased social functioning.

Overall Cost of Anxiety Disorders to Society

The overall costs of an illness include not only the direct and indirect costs but also what may be termed *intangible costs*, including pain and suffering experienced by the patient and his or her family (Andreasen 1991; Martin 1995). DuPont et al. (Chapter 36 in this volume) discuss in detail the economic costs of the anxiety disorders. However, it is especially important for the medical profession to embrace this last concept—the intangible costs of an illness to society, particularly in this era of constrained health care dollars because of increased managed care penetration. The lost potential of those with an anxiety disorder, excluded from the cultural, economic, or social life of the United States through fear and ignorance, cannot be quantified in dollars, and even the most conservative estimates barely scratch the surface.

Barriers to Diagnosis and Treatment

Anxiety disorders cost the nation more than $42 billion per year, much of it attributable to misdiagnosis and undertreatment. More than half the tab is associated with repeated use of health care services, as those with anxiety disorders seek relief from symptoms that mimic physical illnesses. People with an anxiety disorder are 3 to 5 times more likely to go to the doctor and 6 times more likely to be hospitalized than are nonsufferers (Greenberg et al. 1999).

In 1996, the National Institute of Mental Health (NIMH) conducted focus groups among patients with anxiety disorders to determine their level of knowledge about the signs and symptoms of anxiety disorders. In addition, they collected data regarding attitudes, motivations, and barriers to both diagnosis and treatment among individuals with anxiety disorders. Unequivocally, the response given most often as the major common barrier to those persons either seeking or receiving treatment for their anxiety disorders was lack of medical coverage in the United States. Of paramount importance, several focus group participants also cited the receipt of inadequate or poor treatment for their disease, either as a direct result of their uninsured status or because of inadequate coverage by their particular plan.

Other barriers to treatment mentioned in these focus groups included the consumer's concern that medical professionals would not have knowledge about the correct treatment for their particular form of anxiety disorder or that they would not be sympathetic to an individual with an anxiety disorder. Several participants said that they have been reluctant to seek treatment because they did not know what treatment would entail. Furthermore, many participants reported that they saw numerous medical and mental health professionals before they were given the correct diagnosis of an anxiety disorder.

Ignorance about anxiety disorders on the part of both physicians and patients, together with a widespread misunderstanding about the relation of mind and body, has been among the chief barriers to treatment of anxiety disorders for most of those who need it. These barriers are compounded by a tendency on the part of physicians (mostly men) and other professionals to ignore or belittle many complaints that affect primarily women, as most anxiety disorders do. A wall of ignorance—and to some extent injustice—has separated those who have an anxiety disorder from those who could treat it (Ross 1994).

To be fair, much of the knowledge about these disorders has emerged only in the past two decades, and much remains to be discovered—about genetic predisposition and about emotional and environmental factors that precipitate the disorders. Nevertheless, as mentioned earlier in this chapter, the stigma that comes with mental illness in our society has yet to be dissipated.

Other barriers to treatment of anxiety disorders for today's health care consumer include the role of the gatekeeper physician in many managed care plans or health maintenance organizations. As we read on a daily basis in our newspapers and hear repeatedly on television, the demanding health care consumer is annoyed with the gatekeeper physician concept. Consumers want to go to a specialist without having to obtain permission in advance from the gatekeeper; hence, the demand is increasing for those managed care plans that allow for some choice and for point-of-service plans, and if they have to go to a gatekeeper physician, they want him or her to be well informed about the signs and symptoms of anxiety disorders. Many legislators, who are crucial in shaping health care policy in the United States, have a lack of understanding about the widespread prevalence of anxiety disorders, coupled with their severity and treatment profiles. Education and information, such as that provided by consumer organizations, may help inform these key legislators and enable them to make more prudent health care policy choices for their constituents.

A Voice for the Consumer and a Resource for Researchers, Clinicians, and Providers

The ADAA, founded in 1980 as the Phobia Society of America, targets the elimination of ignorance surrounding anxiety disorders as its first priority. This national group is devoted to relieving the trivialization and stigma of anxiety disorders. In addition, the ADAA is dedicated to the early identification, prevention, and treatment of anxiety disorders, as well as to improving the lives of people who have them (Ross 1997).

Other consumer organizations similarly focus on public and professional awareness, on promoting research, on advocacy, and on increasing the availability of cost-effective treatment for the anxiety disorders. Public and professional awareness activities seek to raise awareness, reduce and eliminate stigma, increase understanding about recognition, increase diagnostic skills, and increase knowledge about effective treatments.

Consumer organizations serve as clearinghouses for information related to the anxiety disorders and provide a forum for mental health researchers, clinicians, and consumers. Diverging views about some elements of anxiety disorders are often recognized, debate is encouraged, and input from different disciplines is welcomed.

Such organizations handle tens of thousands of requests for help each year and have become public symbols of reassurance to those with anxiety disorders and their friends and families.

Cooperative efforts with other mental health organizations and government agencies to increase access to treatment and erase the stigma surrounding anxiety disorders are another top priority for many consumer organizations, as is the development of self-help groups. Self-help groups have played an increasingly vital role in providing support to individuals with anxiety disorders, helping patients find treatment, and advocating public policies that help ease the burdens of anxiety disorders.

The news media are also a target of consumer groups because of their ability to hone in on the idea that these disorders can happen to anybody at any time. Information on anxiety disorders has been provided on dozens of national television and radio programs and in several hundred newspapers and magazines. Indeed, extensive strategies of public education and policy advocacy can lower treatment barriers and promote the welfare of individuals with anxiety disorders.

Too often, individuals with anxiety disorders have been victimized by ignorance, misdiagnosis, and misunderstanding. In response to these difficulties, consumer organizations can

- Teach clergy, school counselors, and employee assistance personnel how to recognize anxiety disorders, make referrals, and provide information and guidance.
- Extend information outreach to new constituencies, including hospitals and emergency rooms, university networks, and libraries.
- Alert national and state legislators to the societal costs of anxiety disorders, including the expense to the health care system of unnecessary tests and repeat examinations because of misdiagnoses.
- Persuade government agencies to commit increased funds to anxiety disorders research.

- Inform private industry about the economic waste and lost productivity because of untreated anxiety disorders and help them better understand anxiety disorders in the workplace.
- Work for increased insurance reimbursement for anxiety disorders treatment.
- Conduct joint efforts with other mental health organizations to stimulate more focused attention on anxiety disorders.
- Maintain a position as centers of exchange for new information on anxiety disorders.
- Conduct broad-based fundraising to support high-quality research either directly or through existing organizations.

The mission and activities of many consumer organizations are consistent with the philosophy that knowledge is power. These organizations seek to provide education and information to today's health care consumers, providers, and legislators, in an effort to give the individual who has an anxiety disorder a sense of self-empowerment and mastery over the disorder.

Stories From the Front Lines: Consumer Frustrations

In addition to the thousands of letters that are received annually by consumer organizations, hundreds of telephone calls are received on a daily basis. Most of those who call want reassurance that they have a real and treatable condition, that they are not alone, and that help is available for them. Examples of some of the most common frustrations expressed by these individuals are

- "I feel like a hypochondriac."
- "Everyone thinks I act anxious for attention. They think I should just pull myself together."
- "My health insurance paid thousands of dollars for medical tests, but when I was finally given the diagnosis of an anxiety disorder, I was denied coverage for treatment."
- "My community mental health center said that they could not help me. Isn't an anxiety disorder a mental health problem?

Most of the participants in the focus groups conducted by the NIMH in 1996, discussed earlier in this chapter, reported the following key statements:

- Anxiety disorder symptoms or behaviors were present for years before help was sought.
- The behaviors or anxiety experienced by patients were different from that of other people.
- Before receiving a correct diagnosis, many health professionals were seen.
- The worst thing about undiagnosed anxiety disorders was the inability to do what one wanted in life.
- The best thing about receiving an anxiety disorder diagnosis was knowing that one was not "crazy."
- The disorder was seldom discussed with people other than close friends and family.

Additional frustrations voiced by today's more demanding health care consumers, some of whom are patients with anxiety disorders, include a direct challenge to the current managed care environment. In particular, many consumers seem particularly dissatisfied with 1) the role of the gatekeeper physician, especially if he or she is uniformed about the signs and symptoms of the five types of anxiety disorders; 2) the difficulty in getting an appointment with a specialist (i.e., a psychiatrist, a psychopharmacologist, or a psychologist)—in part because of capitation, in which the goal of the health care provider is to reduce the number of referrals to specialists; and 3) the fact that many insurance plans have "carved out" mental health benefits, making it very difficult for persons with anxiety disorders to obtain adequate and appropriate treatment.

Also, today's educated, well-informed health care consumer is more familiar with the widespread prevalence of anxiety disorders and the ease with which most can be successfully treated. However, many individuals with anxiety disorders feel that their "voices in the government" (i.e., health care policymakers) do not understand the severity of the disease or the ease with which it can be properly treated.

The Human Side: Patient Vignettes

The contents of three letters recently received by the ADAA from people describing what it is like to live with these disorders are illustratively poignant.

36-Year-Old Man From Graham, North Carolina

When I get out of bed each morning, I am faced with fighting…to survive….My body is filled with so much anxiety, many times I actually feel…I am dying. I have gone to all kinds of doctors…even

spent some time in the hospital to try to figure out what the symptoms are or what is causing them. The frustrating part…I am told that it is only my nerves. Even worse…my insurance paid for all the doctors and hospitals when no one could help me, but they won't pay for a psychiatrist.

17-Year-Old Girl From Bakersfield, California

My fears have taken over my life. I can't leave my house. I was a straight A student and now I'm too scared to go to school. I don't know what to do. I would like to be able to do things that normal people do…school…job…ride in a car. It's hard remembering what I used to do…all I have are the memories. I'm at a point where I either get on the right track now or I give up. Your organization is my last hope.

39-Year-Old Woman From
Battle Creek, Michigan

I am becoming a very unpleasant burden to my family. I'm a failure as a human being. People/friends make me feel that I'm like this on purpose. I treat my husband awful because I'm mad at me. I have given suicide a lot of thought.…I'm scared of everything. Please, can you help me and my family? My life depends on it.

These are truly tragic stories; however, they are not extraordinary. They are typical of what we read and hear about every day at consumer organizations.

Medical Agenda

In today's tightly regulated managed care environment, most patients with symptoms consistent with an anxiety disorder are initially evaluated by a primary care physician, more commonly known as a gatekeeper. Because of the myriad signs and symptoms associated with anxiety disorders, the differential diagnosis is obviously lengthy and complicated. Therefore, a full battery of standard medical procedures, including history, physical examination, and basic laboratory data, is indicated when working up a patient with a suspected anxiety disorder. However, because the signs and symptoms consistent with anxiety accompany many medical and psychiatric conditions, the differential diagnosis is not always straightforward.

The successful treatment of anxiety disorders often involves collaboration between medical and nonmedical clinicians. However, this can pose a problem in today's competitive health care provider marketplace because turf battles often arise among the various mental health professionals, including psychiatrists, psychologists, and social workers. If one is able to place the needs of the patient over the economic needs of one's parent organization (i.e., managed care company/health maintenance organization), or private practice, then the medical and nonmedical clinicians should be able to work in harmony.

Time and reimbursement constraints are placed on psychiatrists who practice in a managed care setting; therefore, the psychiatrist's role in psychotherapy for many psychopathological conditions has markedly diminished (Wilson et al. 1997). Teamwork and a collaborative effort between medical and nonmedical providers have become crucial to the successful management of anxiety disorders. The ability of the nonmedical clinician to share problems and issues that arise in the management of a particular patient with their medical colleagues can only strengthen the team's ability to maintain a comprehensive, adequate treatment plan that best serves the needs of that patient.

The primary care physician plays a vital role in today's managed care organization and often is active in the treatment and management of psychiatric disorders, including anxiety disorders. From a health consumer perspective, this may be problematic, especially because many primary care physicians are often not knowledgeable about anxiety disorders and are not always sympathetic to the plight of the afflicted patients. Limited training in primary care residency programs may affect their treatment decision making. For example, the primary care physician may not be willing to prescribe a benzodiazepine when it is the drug of choice for a particular patient's signs and symptoms, or the primary care physician may taper a patient's medication too rapidly, causing an iatrogenic withdrawal syndrome. In addition, the primary care physician may not be familiar with the evidence-based efficacy of nonmedical therapies, which may cause difficulties with referrals to nonmedical behavioral health professionals.

Wilson et al. (1997) suggested a list of questions for the health care consumer to ask his or her primary care physician:

1. What training have you received in the treatment of anxiety disorders?
2. What are your views on medication management of this disorder? On cognitive-behavioral therapy?
3. What are your views regarding the origin of anxiety disorders?

4. How do you evaluate treatment progress and outcome?
5. Describe, in general, your treatment protocols for
   A. Panic disorder
   B. Agoraphobia
   C. Social phobia (e.g., public speaking)
   D. Specific phobia (e.g., fear of flying)
   E. Generalized anxiety disorder
   F. Obsessive-compulsive disorder
   G. Posttraumatic stress disorder

Government's Role

Any comprehensive discussion of the political agenda of health care reform must take into account the fact that even in the United States, currently, 44 million Americans are estimated to be uninsured (Mental Health Liaison Group 2000), and the number continues to rise. Coupled with this fact, it is clear that many legislators who are involved in creating health care policy are not properly informed about the severity and treatment success of anxiety disorders (Ross 1994).

Those of us involved in anxiety disorders research, treatment, and public and professional education are all too familiar with the gaps and frustrations in our health care system: the lack of access for people with anxiety disorders to publicly funded mental health facilities and to adequate health insurance to cover private treatment (Ross 1994).

Key goals of the ADAA and other consumer organizations include promoting research on anxiety disorders and the equal treatment of mental and physical illnesses. In 1990, following the NIMH's Consensus Conference on Panic Disorder, consumer organizations were instrumental in encouraging NIMH to launch a major national education campaign to promote awareness of panic disorder. Following the success of that program, NIMH expanded its efforts to embrace all of the anxiety disorders. In a subsequent partnership in 1995, the ADAA and NIMH conducted a survey that found that Americans misunderstand panic disorder and that the most at-risk group (women aged 18–34) is the least likely to recognize the illness and the most likely to incorrectly believe that the condition is a result of a person's difficulty in handling stress. Consumer organizations look forward to their continued involvement in the government's efforts to educate the public and health professionals about the fact that anxiety disorders are real, serious, and treatable.

Progress has been made and momentum generated in research and treatment of anxiety disorders in the 1990s, dubbed the "Decade of the Brain." Consumer organizations have entered the new millennium with continued determination to provide hope, help, and resources (both governmental and private) for those tormented by anxiety disorders and those dedicated to treating these mental illnesses. The goal is to bring anxiety disorders under control and move them nearer the top of the national health care agenda, with support from an enlightened public, with increased awareness by the health care community, and with firm and steady pressure from those with anxiety disorders (i.e., the consumer) (Ross 1997).

The Good News

Although the NIMH reported that about 19 million Americans have an anxiety disorder, the good news is that anxiety disorders are among the most treatable of all psychiatric disorders. In fact, research data compiled during the "Decade of the Brain" suggest that cognitive-behavioral therapy and new medications have mitigated the disturbing signs and symptoms consistent with anxiety disorders in approximately 60%–90% of the afflicted individuals, allowing them to lead normal lives again.

The pervasive problems posed by anxiety disorders have several solutions, which are being addressed on a national level (i.e., the NIMH) and through mental health advocacy groups. The messages concerning anxiety disorders recommended by the NIMH focus groups are consistent with what have found to be most effective in motivating those with anxiety disorders to reach out for help. The following key messages were identified by the NIMH focus groups:

- Anxiety disorders are common, treatable biochemical or genetic disorders.
- Anxiety disorders have a lengthy duration of symptoms and interfere with day-to-day functioning.
- The tone of anxiety disorder education messages should be positive and comforting, not threatening or scary.
- In addition to including a wide range of behavioral, cognitive, and physical symptoms, the common effects of these symptoms across disorders should be stressed:
  1. Feeling a lack of control over one's life
  2. Not being able to live the life one wants to live

3. Wasting time and energy on nonproductive behaviors

Consumers can advocate for the early recognition and diagnosis of anxiety disorders; access to affordable, effective treatment; and increased funding for research from the government and private sources. The psychiatric community is encouraged to join in efforts to educate health care consumers, other health care providers, and legislators at both the state and the national levels about the severity and treatability of anxiety disorders. It is our responsibility to help those who have anxiety disorders to have access to the care they need and deserve.

Finally, one encouraging letter can be shared to show what can happen when the whole system—the media, physicians, and an advocacy group—works together:

> 44-Year-Old Woman From Tulsa, Oklahoma
>
> It's been a long 10 years—2 years on disability, extensive medical tests, thousands of dollars, a broken marriage, lost friendships.…I had no idea what was wrong with me or that help was available. I could go on, but what I want to tell you is that I have returned to a productive life.…I'm now practicing law again… believe it or not, it was an Ann Landers article on panic disorder that saved my life. I cried for 3 days after reading it, wrote to you to get the name of a psychiatrist in my city who could help me, and within 3 months, this nearly suicidal recluse returned to work and got back in touch with friends.

In educating the health care consumer, the health care provider (i.e., primary care physician), and legislators at both national and local levels, the following messages must be emphasized:

- Patients and physicians should be aware of the most common signs and symptoms of anxiety disorders.
- Physicians and legislators should be aware of the widespread prevalence of anxiety disorders in the community.
- Managed correctly, the treatment of anxiety disorders can be highly successful.
- Appropriate treatment can allow patients with anxiety disorders to lead normal, productive lives.
- Successful treatment often involves both medical and nonmedical interventions.
- Knowledge and skill of the health care provider is a major variable affecting treatment outcome.
- Funding for research on anxiety disorders by the NIMH and from pharmaceutical companies in the private sector has steadily increased.
- Consumer organizations are working on the patient's behalf to improve the lives of people who have anxiety disorders.

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Mental Health Liaison Group: Responding to the Mental Health Needs of America: A Briefing Document for Candidates and Policy Makers. Washington, DC, Mental Health Liaison Group, 2000

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Wilson JO, Ross J, DuPont RL: Anxiety disorders in managed care. Behavioral Health Management 17:33–38, March/April 1997

Appendix

Internet Resources*

American Psychiatric Association
http://www.psych.org

American Psychological Association
http://www.apa.org

Anxiety Disorders Association of America
http://www.adaa.org

National Alliance for the Mentally Ill
http://www.nami.org

National Institute for Mental Health
http://www.nimh.nih.gov
Anxiety Disorders: http://www.nimh.nih.gov/anxiety

National Library of Medicine (literature search)
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi

Obsessive-Compulsive Foundation
http://www.ocfoundation.org

Trichotillomania Learning Center
http://www.trich.org

*These sites are linked to many other useful sites that cannot be listed due to space limitations.

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