4

Anxiety

1. A 40-year-old woman came to the doctor with the following complaint: "I am afraid my heart will burst and that I will drop dead." On examination, mild hypertension and rapid pulse were noted. After thorough workup and study of the patient, the physician concluded that anxiety was probably the most important factor in producing her symptoms.

2. An attractive female college student, 22 years old, told her physician that she felt she needed sex therapy. She had had difficulty achieving orgasm during intercourse for several years and now found herself withdrawing socially because of fear of getting into sexual relationships in which she would feel frustrated. She was successful and a high achiever in all other areas, for example, scholastic activity, and felt that she should achieve orgasm every time she had intercourse. The physician's impression was that her anxiety concerning sexual performance was interfering with her ability to enjoy it fully.

3. A 30-year-old housewife would develop overwhelming panic whenever she went out of the house alone, particularly in crowded places. She refused to leave her house unless her husband would go with her and stay by her side. Her physician diagnosed her condition as agoraphobia and referred her to a psychiatrist.

Some writers have labeled our present times "the age of anxiety." "Anxiety" is one of our most commonly used words, and virtually everyone is familiar with it. Like pain, everyone has experienced it, and all wish to avoid it. At present, antianxiety medications are the most commonly prescribed drugs in this country. Anxiety is important in medical practice because it constitutes one of the most common, but often unrecognized, reasons for seeking medical help. In addition to the familiar and easily recognizable symptoms it may produce, it may also contribute to the

development of a myriad of physical symptoms that patients may not attribute to it.

While a great deal is known about this ubiquitous and highly important phenomenon of anxiety, we still have not achieved a fully and satisfactorily integrated understanding of its nature or of the pathophysiological mechanisms whereby it may both induce and influence as well as arise from physical dysfunction (disease). In this chapter, we will first discuss some relevant theories and various aspects of anxiety—that is, its phenomenology, central neurophysiology and neurochemistry, peripheral physiology, function, and regulation (and dysregulation)—and then turn to its clinical evaluation, diagnosis, and management. To discuss so many aspects of such a complex phenomenon presents a problem similar to that presented in the fable of the blind men and the elephant: the very same thing can seem so different depending on which aspect one apprehends and on the amount and kind of detail that various approaches can elucidate (i.e., on the relative technical and theoretical sophistication of different disciplines). In discussing the various aspects of anxiety in the sections that follow, we have attempted to balance presentation of detail in relation to sketching overall patterns in such a way as to achieve maximum relevance for the physician.

PHENOMENOLOGY OF ANXIETY

As in vignette 1, the most prominent subjective feature of anxiety is identical to what is experienced in the *emotion of fear*—namely, a sense of dread and apprehension. This fearful feeling is usually vague and diffuse, but it may also focus on a specific idea, such as fear of dying, or of cardiac arrest, or of having a dreadful disease such as cancer. When the patient is questioned carefully, one can often determine that the vague feeling of dread came first and was later followed by more specific thoughts and ideas such as those mentioned above. *Physiological changes* are part of anxiety. They are mediated by activation of the central and autonomic nervous systems and of neuroendocrine mechanisms. In a fully developed reaction, all structures influenced by these systems may show functional changes. Thus, the symptoms and signs may include rapid pulse, increased blood pressure, excessive sweating, change in bowel function, changes in appetite, trouble sleeping, and difficulty breathing. In essence, then, *subjective feelings of dread and fear* accompanied by *symptoms* and objective *signs* of appropriate physiological changes indicate the presence of anxiety.

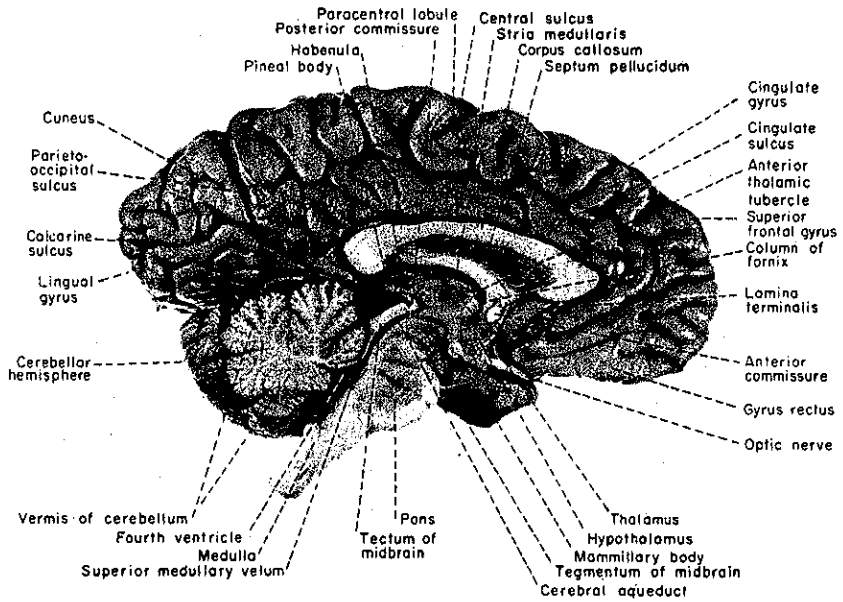

Figure 2. Photograph of the medial surface of the adult brain cut in sagittal section. (From Everett *et al.*, 1971. Copyright 1971 by Lea & Febiger. Reproduced with permission from publisher and the author's estate.)

THEORIES OF ANXIETY AND EMOTIONS

Since anxiety is an emotion, we should first take up some general considerations about emotions. *Emotions*, or *affects* as they are sometimes otherwise called, include three main components: (1) a subjective state of mind or feeling tone (e.g., dysphoria, dread, awe), (2) a neurovegetative motor discharge (e.g., increased heart rate), and (3) perception by the person of the bodily sensations caused by the motor discharge (e.g., palpitation of the heart). Various theories relate these three components to one another in different ways.

The James–Lange theory of emotions, proposed in the late 19th century by the famous psychologist William James and the Danish physician Carl Lange, postulated that bodily changes (motor component) follow directly the perception of an exciting event and that the person's perception of the bodily changes (sensory component) is what we call "emotion" (James and Lange, 1922). According to this theory, changes in the

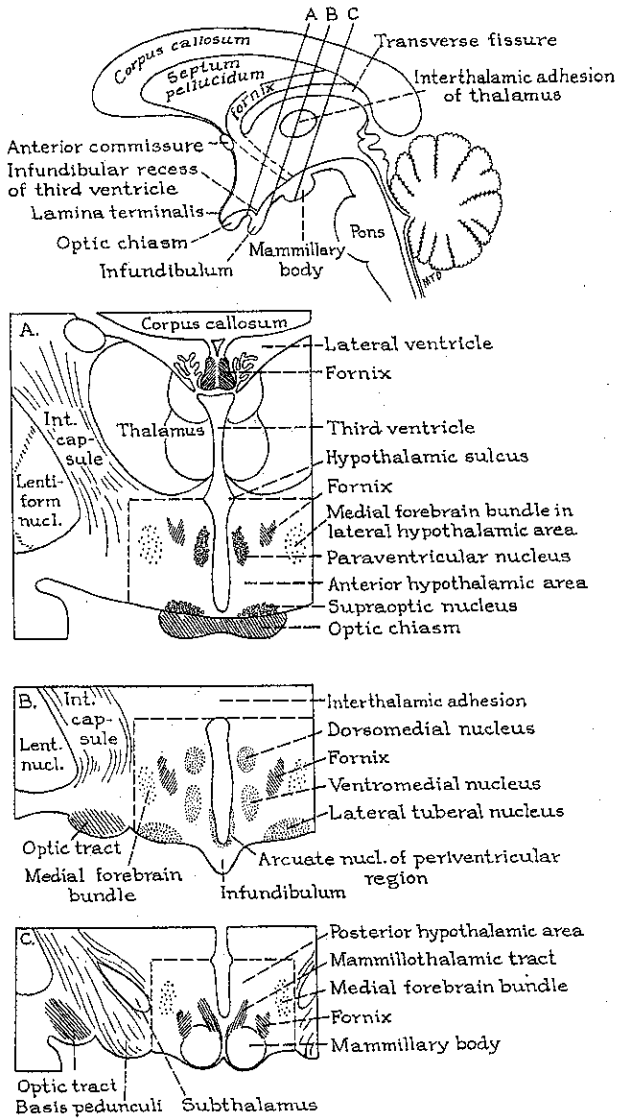

Figure 3. Schematic drawing of a sagittal section of the brain stem showing the relations of the hypothalamus to surrounding brain structures. Lines A, B, and C correspond to the levels at which the three lower drawings were made. Section A is through the supraoptic area, B is through the tuberal area, and C is through the mammillary area of the hypothalamus. (From Everett *et al.*, 1971. Copyright 1971 by Lea & Febiger. Reproduced with permission from the publisher and the author's estate.)

viscera or skeletal muscles or both were thought to be essential for the occurrence of emotions. The subjective component was omitted or assumed to be part of the sensory component. These assumptions were later put to test and disproved by Walter Cannon, the famous American physiologist and also William James's son-in-law. He showed that emotions were felt in persons who had had upper cervical spinal cord transections (thus effectively cutting off all the afferents from the viscera and skeletal muscles) and that in normal persons, the latent periods for the bodily changes were much longer than for the felt emotions (i.e., emotions occurred before bodily changes, not after). This led Cannon to believe that perceptions of noxious stimuli at the level of the *thalamus* (Figures 2 and 3) in the brain led to two distinct pathways of excitation, one upward to the cortex, adding affective quality to the experience through associations with memory traces, etc., and a downward discharge from the thalamus effecting redistribution of blood to viscera and skeletal muscles and changes in metabolism (e.g., rise in blood sugar)—all of such a nature as to prepare the animal for the vigorous muscular work involved in attacking *(fight)* or getting away from *(flight)* the danger. Cannon made extensive investigations into the fight–flight responses, which he felt were related to the basic emotions of displeasure, anger, and fear (anxiety) (Cannon, 1932). Cannon's theory concerning emotions was later modified by Papez (1949) and MacLean (1949), placing more emphasis on the limbic brain structures than on the thalamus (see Figure 4). This *limbic system model* forms the basis of modern neurophysiological theories concerning emotions (see the section on Brain Mechanisms of Anxiety).

The two major theories that address the psychological mechanism (higher cortical function of the brain) by which situations may be *perceived* and *appraised as dangerous,* leading to the generation of anxiety as an emotion, are (1) the *learning-theory or conditioning model* of anxiety based on the studies of Pavlov (1927) and (2) the modern *psychoanalytic theory* of anxiety ("signal theory") first articulated by Freud in 1926 (Freud, 1926/1953).

Learning-Theory Model

When a stimulus is inherently dangerous, such as the sight of a growling tiger, a fear response occurs naturally. A stimulus that is neutral and not inherently dangerous, such as open spaces or elevators, can become associated with a dangerous situation through a process called "conditioning." According to the learning-theory model, then, anxiety is a *conditioned fear response.*

The *conditioning process* by which a neutral stimulus becomes aversive, creating a fear response, may be stated as follows: A neutral stimulus (the sound of a bell) that occurs in close *proximity* to an inherently noxious stimulus (e.g., electric shock) becomes *associated* with the noxious stimulus so that, even in the absence of the noxious stimulus, it acquires the power to *elicit response* in the organism as *though it were the noxious stimulus.*

For example:

1. Electric shock (inherently noxious, and thus called the *unconditioned stimulus,* or US, meaning that no "conditioning process" is necessary to produce the response in question) → fear response (called the *unconditioned response,* or UR, e.g., increase in pulse rate or dilated pupils).
2. Light (usually "neutral" to animals) → no fear response.
3. Light plus electric shock → fear response. In this *pairing* of light and shock, the neutral stimulus is called the *conditioned stimulus,* or CS. If this pairing within a set time interval occurs repeatedly, then . . .
4. Light (CS) alone → fear response. The fear response occurring in response to the CS is called the *conditioned response,* or CR.

Conditioning, of course, occurs to various stimuli, including both pleasant and aversive stimuli. For example, Pavlov's famous experiments involved training dogs to salivate at the sound of a bell using the aforedescribed paradigm with the sight of food used as the *unconditioned stimulus.*

Ordinarily, conditioned responses will disappear *(extinguish)* if the conditioned stimulus is repetitively experienced without any further pairing with the unconditioned stimulus (reinforcement).* This phenomenon is the basis for a form of behavioral therapy (desensitization) that is particularly useful in treating phobias, where an ordinarily neutral stimulus (e.g., elevator) has acquired the capacity to elicit the anxiety response. In phobias, the patient will go to any length to avoid the phobic object or situation in order to avoid experiencing the anxiety reaction. A patient with a phobia for crowds (and open spaces [agoraphobia]) may ultimately become a virtual recluse (vignette 3). This

*If the unconditioned stimulus has been strong enough, the conditioned response may resist extinction permanently (Solomon and Wynne, 1954; Wynne and Solomon, 1955). Sailors who had served during World War II, when a bell was used to signal air attacks ("battle stations"), still showed an increased galvanic skin response to the same gong tone 20 years later (Edwards and Acker, 1962).

illustrates an aspect of anxiety with highly important clinical implications, namely, that human beings have little tolerance for free anxiety and that individuals develop behaviors (coping mechanisms, defense mechanisms) to avert or avoid it. In classical learning theory, this is conceptualized as follows: *Anxiety is so unpleasant that a person will repeat behaviors or seek situations that have been associated with its diminution.* Behaviors that lessen anxiety can be learned through instrumental conditioning; that is, relief from anxiety can be regarded as motivation for behavior (see Chapter 20).

Psychoanalytic Signal Theory of Anxiety

As we will see below, psychoanalytic theory assigns central clinical importance to this noxious aversive quality of anxiety and labels the psychological mechanisms that are developed for averting anxiety "ego defenses" (see Chapter 5).

In making a distinction between fear, in which the danger stimulus is external and recognized (e.g., an escaped grizzly bear), and anxiety, in which the danger stimulus is internal and unrecognized (e.g., an unconscious conflicted impulse such as a murderous wish), psychoanalytic theory turns our attention to a careful and close consideration of "intrapsychic" phenomena. This signal theory of anxiety starts with the idea that every human being is endowed with an inborn capacity for experiencing the combined physiological–psychological reaction that we call anxiety. Freud's theory of anxiety, however, concentrates on the importance and role of anxiety in mental life rather than on providing a fundamental explanation of its nature and basic origin (Brenner, 1955). It assigns to anxiety the central role in the neuroses by asserting that it occurs when there is *conflict* between unconscious wishes for pleasurable gratification and the person's opposing mature goals and moral standards.

The theory further specifies that the form of anxiety with which we are most familiar, that is, the response associated with subjective feelings and motor and conscious sensory components, is but one of two forms of anxiety—a clinical form *(free anxiety).* Free anxiety occurs *when psychological defense mechanisms have failed.* It may vary in intensity from relatively mild apprehension to intense disorganizing panic. The *second* form, which Freud called *signal anxiety,* is conceptualized to be so mild and attenuated as to go unnoticed (or perhaps barely noticed) in consciousness. Nonetheless, it is perceived in the mind and reacted to as a signal of an *impending* danger situation.

The theory specifies a stepwise series of events: (1) when an unconscious wish (that would lead to unacceptable thoughts or behavior or both) is about to attain conscious recognition, an attenuated form of anxiety is generated; (2) this attenuated anxiety reaction then serves as a signal (signal anxiety) indicating that a dangerous situation will develop if the conflictual impulse becomes conscious and gains access to the motor systems that could carry it out in action; (3) in response to the signal anxiety, psychological defense mechanisms come into motion that prevent the dangerous situation from developing by barring access of the threatening impulse to consciousness and the motor systems of the body (see Chapter 5). In other words, the person reacts to the impending emergence into consciousness of a conflictual impulse as to an impending danger and so experiences attenuated anxiety. In response to this attenuated (signal) anxiety, psychological defense mechanisms are mobilized to deal with the offending impulse. In summary, the *attenuated anxiety signals a state of tension within the personality system*—that is, conflict between basic primitive organismic demands *(id)* and demands of the individual's social environment and conscience *(superego)*. It is the function of a part of the personality system called the *ego* to appraise and mediate between these opposing forces and to defend against the forbidden impulses (see Chapter 5).

Success of the personality system, more specifically, the ego, is reflected in satisfactory adaptation without experience of noticeable anxiety; partial success results in experience of somewhat attenuated, but felt, anxiety (clinical anxiety states) or of adaptive states marred by neurotic symptoms or behavior or both. Failure is regarded as resulting in panic states (unattenuated anxiety) and perhaps psychotic experience and behavior.

The psychoanalytic theory of anxiety as summarized has been incorporated into clinical psychiatric theory and is regarded as basic and essential for understanding clinical disorders involving the personality system.

Anxiety is also considered to function as a stimulus to growth and to development of adaptive behaviors. This aspect will be discussed in a later section of this chapter. More detailed aspects of the theory dealing with the ontogenetic developmental aspects and metapsychology of anxiety are more controversial but perhaps of less general importance to those working outside of psychiatry.*

*Recommended readings by Freud, Brenner, and Reiser at the end of this chapter should be consulted for acquaintance with these more specialized features.

While the learning-theory model and the psychoanalytic theory of anxiety are quite different with respect to formulations concerning the nature and origin of anxiety and of danger situations, there are many aspects of both theories that are congruous, even though they may differ in emphasis. For example, both theories recognize that anxiety is associated with potential danger situations. The emphasis in learning theory is on external danger situations and how neutral stimuli might have become deliberately or accidentally associated with them; psychoanalytic theory emphasizes internal danger situations arising from psychological conflicts.

Psychological defense mechanisms are mobilized to reduce the unpleasant affect of anxiety in potentially dangerous situations (including being ill and being in the hospital) that threaten the individual's personality system.

PHYSIOLOGY OF ANXIETY

As already noted, when a stressful event is perceived, the cerebral cortex and its efferent pathways are activated, including those to the limbic system and brain stem nuclei, including the locus ceruleus and the reticular activating system. This increases the arousal level and the motor outflow through the pyramidal and extrapyramidal systems, thereby increasing general muscle tension and causing specific changes in the tone of the facial muscles, giving rise to the tense expression seen in anxiety states. Tension of vocal cords may sometimes seriously interfere with speech. In general, these changes are demonstrable by the use of the electroencephalogram (EEG) and the electromyogram (EMG), the EEG showing fast, low-voltage waves typical of arousal and the EMG showing increased electrical activity of muscles involved in the response.

At the same time, activation of the limbic system (see Figure 4) results in activation of the *hypothalamus* and *autonomic nervous system* (predominantly, but not exclusively, the sympathetic division) and of the hypothalamic nuclei that secrete the *releasing factors* (hypophysiotropic hormones). The hypothalamic releasing (or inhibiting) factors influence the *pituitary gland* and lead to the stimulation or inhibition of the release of various tropic hormones. Autonomic nervous system arousal leads to an increase in circulating *epinephrine* and *norepinephrine* by sympathetic stimulation of the adrenal medulla.

Direct effects of the autonomic arousal in acute anxiety include (1) *circulatory changes*—increase in systolic blood pressure and pulse pressure

(diastolic pressure and peripheral resistance may remain the same or fall); increase in stroke volume, heart rate, and cardiac output; increased blood flow to skeletal muscle, heart, lungs, and brain and decreased blood flow to the splanchnic vascular bed and skin; (2) exocrine *changes in skin*—increased sweating and skin conductance (cold, clammy hands); (3) dilation of the pupils; (4) changes in rate and depth of respiration; (5) changes in gastrointestinal function—secretion, motility, and mucosal vascularity; and (6) some metabolic changes such as increase in levels of sugar, free fatty acids, and lactic acid in the blood. Imbalance of sympathetic and parasympathetic components may contribute to untoward reactions such as development of disturbances in cardiac rate and rhythm and even fainting, as will be discussed in a later section of this chapter.

Indirect effects of anxiety (via effects of released hypothalamic factors on pituitary tropic function) include increase in the secretion of adrenal cortical hormones, which gives rise to profound metabolic changes (in water and electrolyte balance, in suppression of immune mechanisms, and in catabolic carbohydrate and protein metabolism), and other widespread hormonal changes, for example, in secretion of growth hormone, prolactin, and thyrotropic, gonadotropic, and antidiuretic hormones.

Immune mechanisms are profoundly altered in stressful situations causing anxiety (Locke, 1982; Kemeny *et al.*, 1989; Stein, 1986; Stein *et al.*, 1976). Lymphoblast transformation (a measure of lymphocyte responsivity to mitogens) was found to be depressed eight weeks following bereavement of spouse (Bartrop *et al.*, 1977). Interestingly, coping ability as measured by an "ego strength scale" was positively correlated with antibody response to influenza vaccine in normal subjects (Roessler *et al.*, 1979).

An interesting example of stress effects on cellular immune mechanisms is provided by a study of lymphoblast transformation which was conducted on a group of psychiatric residents in Canada preparing for a major qualifying examination, a particularly stressful event (Dorian *et al.*, 1981). The lymphoblast transformation was significantly reduced in the candidates as opposed to an age- and sex-matched control group of physicians. By two weeks after the exam, however, the lymphoblast transformation was higher among the candidates compared to the controls. The level of immune suppression pre-exam was greater in the subjects who expressed high subjective distress as compared to those who expressed low subjective distress. Interestingly, the immunosuppression in the candidates did not seem to be mediated by plasma corticosteroid levels, which were *lower* in the candidates than in the controls.

What might be the mediating mechanisms among stress, anxiety, and immune changes? Certainly hormonal changes, especially corticosteroids, are known to influence immune mechanisms. In addition, the autonomic nervous system may exert influence on the immune system through the adrenergic pathways. In general, substances that increase intracellular cyclic AMP levels, such as histamine and isoproterenol, as well as β-adrenergic agonists, are immunosuppressive, while substances that increase intracellular cyclic GMP levels, such as phenylephrine, acetylcholine, and insulin, as well as (α-adrenergic agonists are immunoenhancing (Locke, 1982). There is evidence that the organs that subserve the immune mechanisms, such as the thymus gland and the spleen, are directly controlled by the CNS through neural influences (Bullock and Moore, 1980; Williams *et al.*, 1981). Receptors for β-endorphin and met-enkephalin have been discovered on lymphocytes (Hazum *et al.*, 1979; Wybran *et al.*, 1979). Thus, the immune mechanism seems to be controlled both directly and indirectly by the CNS through direct neural, autonomic, endorphinergic, and endocrine systems.

In general, the longer-lasting endocrine and immune systems are called into play when response to danger is intense and sustained. Then, more profound metabolic effects are added to the more acute autonomically innervated reactions. Selye's now classic studies of stress call attention to the role of the pituitary–adrenal cortical system and the adrenal cortical hormones in the *adaptation syndrome* and point to their importance as probable contributors to pathogenesis of a variety of clinical disorders of (unknown) multiple-factor etiology such as rheumatoid arthritis and essential hypertension (Selye, 1950).

As the preceding discussion shows, consideration of the psychophysiology of anxiety leads quite naturally to a more general look at the psychophysiology of stress and to contemplation of some clinical implications. For the student of medicine, there are two highly important points to emphasize here. The first concerns the distinction between stress and strain. *Stress* consists of an *external* and/or internal *challenge* to the integrity of an organism requiring adaptation or adjustment, whereas *strain* is a measure of the tension or imbalance endured *within* the responding (stressed) organism. A physical analogy would be that of a heavy truck crossing a bridge, the weight of the truck constituting the stress and the disturbance in molecular alignment of the bridge structure constituting the strain. In psychophysiological systems, the stress might be a psychosocial crisis (e.g., death of a close relative); strain would be measured by the degree to which balance of psychophysiological systems is upset and required to adjust in order to restore a previously steady state.

The second point to emphasize is that there is in the human a complex relationship between the personality and coping styles, psychologi-

cal defense mechanisms, and the degree of physiological activation. In general, when psychological defenses break down and are ineffective, physiological changes are intense; when defenses are highly effective, physiological changes are minimal (reviewed by Mason, 1975). On the other hand, certain personality or coping traits, such as "defensiveness" measured by certain psychological tests* may show the paradoxical combination of low anxiety levels and high physiological reactivity to stress (Jamner and Schwartz, 1986; Jamner *et al.*, 1988; Leigh *et al.*, 1990). Thus, the assessment both of the individual's personality and coping styles as *trait variables*, and effectiveness of psychological defense mechanisms as *state variables* is of crucial importance in assessing the degree of physiological and psychological strain.

Psychosocial stress, then, carries the potential for *inducing* profound and widespread physiological, metabolic, and chemical effects in virtually all systems, organs, and tissues of the body—effects that may influence the balance between health and disease—but the extent and intensity (potential seriousness) of such effects depend on the personality and psychological defenses. The physiological, metabolic, and chemical effects referred to above probably influence the health-disease balance in a nonspecific fashion, that is, by affecting the resistance or receptivity of tissues to pathogenic vectors of any type (e.g., bacteria, viruses, metastatic neoplastic cells, and allergens). These are the mechanisms and relationships that account for the profound effects of life change on morbidity and mortality as well as on illness and help-seeking behavior (see Chapters 1 and 14).

BRAIN MECHANISMS OF ANXIETY

We mentioned earlier that the modern concept of emotion is based on the neuroanatomical model proposed by Papez and MacLean. According to this model, the structures of the limbic system, the inner core of the brain, play a major role in the brain mechanisms of emotions, including anxiety. The word *limbic* refers to a border or a hem. This term was coined by Broca in 1878 to denote the inner brain tissue surrounding the brain stem and lying under the neocortical mantle (Figure 4). The microscopic structures of the limbic brain are presumed to be organized into two layers. The phylogenetically oldest tissue (allocortex)

*Such as the Marlowe Crowne Social Desirability Scale or Minnesota Multiphasic Personality Inventory's lie scale; the term *defensiveness* used in this sense should be differentiated from the psychological defense mechanisms discussed in the next chapter.

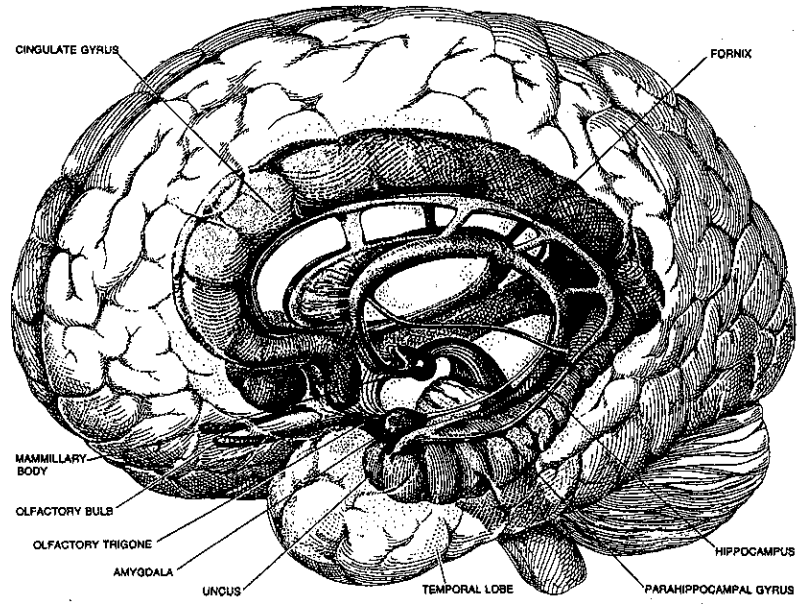

Figure 4. Limbic system (shaded area): a series of evolutionarily primitive regions at the core of the brain that are primarily involved with smelling in lower vertebrates and with the arousal of emotions in humans. (From Synder, 1977. Copyright 1977 by Scientific American, Inc. Reproduced with permission.)

makes up the inner ring, and the outer ring (called the transitional cortex) consists of a peculiar cellular structure, not resembling either the neocortex of the allocortex (Isaacson, 1974). Some portions of the inner aspects of the neocortex and thalamus, although not part of the original "limbic lobe" described by Broca, are often considered as being part of the functional unit, the limbic system. Thus, the structures involved with this system include the *hypothalamus*, the *amygdala*, the *hippocampus*, the *septum*, and the *cingulate gyrus*. These structures are closely related to the *anterior thalamus* and the *reticular activating system*, which runs through the limbic system and the brain stem and extends into the spinal cord (see Figures 2-7).

Various studies, including direct electrical stimulation and surgical ablation of structures of the limbic system, indicate that basic emotions and drives manifested by eating, sexual behavior, drinking, as well as "sham rage" attacks, are controlled by these structures.

In general, pleasurable feelings are produced by stimulation of certain areas of the limbic system and related structures, such as the lateral

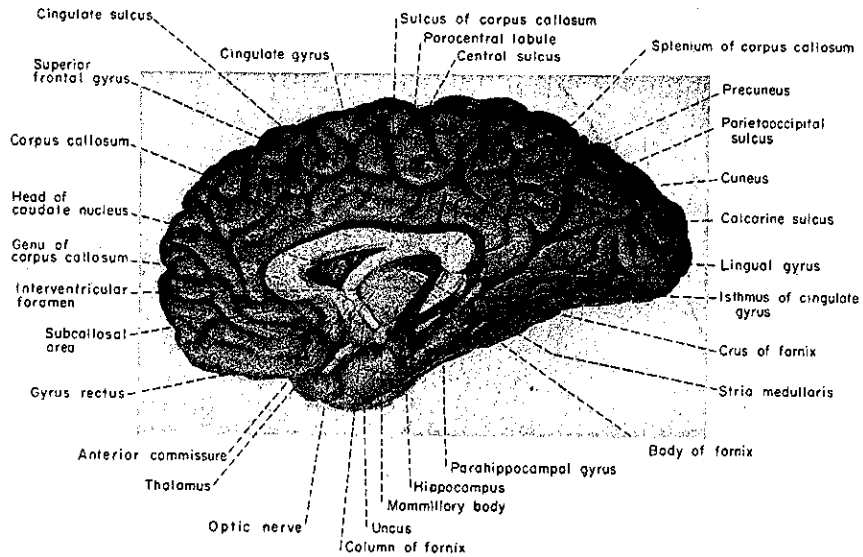

Figure 5. Photograph of the medial surface of the adult brain cut in sagittal section and partially dissected to show the hippocampus and fornix. (From Everett *et al.*, 1971. Copyright 1971 by Lea & Febiger. Reproduced with permission from the publisher and the author's estate.)

hypothalamus and the medial forebrain bundle, a neuron system arising from the noradrenergic, serotonergic, and dopaminergic neurons of the brain stem and distributing widely through the limbic system and to the forebrain (see Figures 3 and 6). Lesions of the medial forebrain bundle produce a drop of 90% or more of the norepinephrine levels in the forebrain, which may be of significance in disorders of mood, such as manic or depressive disorders (see Chapter 6). Stimulation of other areas of the limbic brain, such as the medial hypothalamus or the medial portion of the amygdala, the almond-shaped structure lying at the top of the hippocampus, produces aggressive and angry responses.

If an internal or external stimulus is processed by the neocortex and the stimulus is found to be associated with unpleasant or painful memories, then the signal of anxiety would be generated. That is, the neocortex would play a major role in the processing, evaluation, and integration of perception and the activation of associative pathways. The result of such activation may be stimulation of certain parts of the limbic system concerned with the feeling of anxiety. In fact, there are extensive connecting pathways between many parts of the neocortex, especially between and

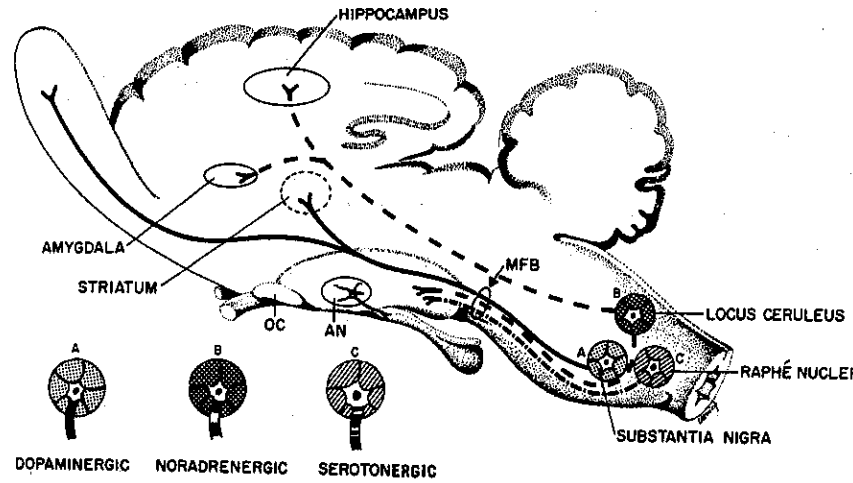

Figure 6. Monoaminergic pathways in mammalian brain. The principal localization of the neurons containing norepinephrine, dopamine, and serotonin is in the mesencephalon and pons. Axons of these cells are distributed to widespread area of the cortex, limbic system, and striatum. The dopaminergic system of the arcuate is an exception to this general scheme of distribution. Abbreviations: MFB, medial forebrain bundle; AN, arcuate nucleus; OC, optic chiasm. (From Martin *et al.*, 1977. Copyright 1977 by F.A. Davis Co. Reproduced with permission from the publisher and authors.)

among the prefrontal cortex (concerned with intention and plans), the temporal cortex (concerned with memory), and the amygdala and hippocampus of the limbic system. The limbic system and the neocortex have extensive connections with the brain stem. Nuclei in the brain stem, especially the noradrenergic locus ceruleus (see Figure 6), may have important functions in anxiety–fear mechanisms, as we will discuss in the next section.

The amygdala, hippocampus, and septum all have modifying influences on the functions of the *hypothalamus*, which is the *final common pathway* of limbic system functions. Different areas of the *amygdala* are concerned with searching, curiosity, and aggressive reactions. Complete ablation of both amygdalae in animals tends to produce placidity and lack of fear. This is a part of the *Klüver–Bucy syndrome*, produced by bitemporal lobectomies. Other features of the Klüver–Bucy syndrome include visual agnosia, a compulsiveness to contact and examine objects, a strong oral tendency, and hypersexuality.

The *hippocampus* is connected to the septum via the fornix, which terminates in the mammillary body of the hypothalamus (Figures 3–5).

Destruction of the hippocampus in animals usually results in a greater willingness to undertake new actions and in decreased fear reactions. The hippocampus, together with the septum, forms an inhibitory system, the excitation of which causes behavioral inhibition. The hippocampus is also intimately involved in the conversion of *recent memory* into long-term memory and in the association of stimulus with painful experience in avoidance conditioning (Gray, 1972; Isaacson, 1974). Parenthetically, *psychomotor epilepsy* (also known as temporal-lobe epilepsy) is often associated with extensive scarring of the hippocampus and neighboring structures and with many behavioral and emotional problems.

The *amygdala* and the *septohippocampal system* are considered by many to act as a push–pull balanced control system with regard to anxiety. The hippocampus is thought to be primarily responsible for recognition of a "mismatch" between the incoming stimulus and an expected stimulus. Together with the amygdala, the septohippocampal system determines the degree of *uncertainty* in a given situation and determines the overall reaction of the organism via the final common pathway of the hypothalamus.

The *hypothalamus* is the final common pathway and effector organ of the limbic system. The hypothalamus may be divided loosely into an *anterior, parasympathetic* part and a *posterior, sympathetic* part. The anterior hypothalamus is considered to be "trophotropic," that is, related to energy conservation and pleasurable states. The posterior hypothalamus is "ergotropic," having to do with the interaction between the organism and the environment. Stimulation of the posterior hypothalamus results in sympathetic nervous system activation and anxiety–fear responses as well as anger. Stimulation of the anterior hypothalamus can result in either relaxation or acute distress.

The hypothalamus is sometimes called the *homeostat* of the body, since it controls most of the homeostatic mechanism through its outflow into the autonomic nervous system and the endocrine system via the pituitary gland. When the outcome of the excitation of the neocortex and the limbic system structures of the amygdaloseptohippocampal system is excitation of the posterior, ergotropic part of the hypothalamus, a *fight–flight* reaction may be elicited with concomitant emotions of anxiety, fear, and anger. If the outcome is stimulation of the anterior, trophotropic part of the hypothalamus, a *relaxation* response might be elicited. Various gradations of simultaneous stimulation also occur, thus eliciting mixtures of ergotropic and trophotropic responses. Also, in situations of acute fear and distress, the stimulation of the trophotropic, parasympathetic system may be considerable, and sometimes predominant

(such as decreased blood pressure, decreased heart rate, and immobilization with depressive or apathetic affect).

In addition to the brain structures described above, the *reticular activating system* plays an important role in anxiety mechanisms (see Figure 7). The diffuse network of nerve cells extending from the neocortex through the limbic system into the spinal cord (called the reticular formation) has both ascending and descending pathways. The major function of this system is the control of the *tone* of the central nervous system *(arousal).* The perception of a potentially dangerous situation results in *activation of the reticular activating system,* thus preparing the brain and the central nervous system for the fight–flight response, and contributes to the emotional experiences of anxiety, fear, and anger.

With the anxiety–fear response, the hypothalamus facilitates the release of certain *"stress" hormones* through its control of the pituitary gland by means of the *hypothalamic releasing and inhibiting factors* (hypophysiotropic hormones).

Once the anxiety–fear response has been elicited by specific activation of the hypothalamus and the pituitary gland, the effect on the brain of the sensory input from the bodily changes due to sympathetic activation, such as increased heart rate and blood pressure, and the direct effect on the brain of the hormones released by the pituitary may form a *secondary component* of the experience of anxiety and fear. This component (the effect on the brain of the bodily changes accompanying the stimulus of emotion) had been equated with emotion itself in the *James–Lange theory of emotions.* Although Cannon disproved the equation, further studies have shown that some bodily changes accompanying emotion, such as levels of epinephrine in the blood, can influence the *readiness of individuals* to experience specific emotions, although this reactivity is modified a great deal by cognitive factors, such as what the subject had been told prior to an intravenous infusion of epinephrine (Schachter and Singer, 1962). For example, intravenous infusion of norepinephrine and epinephrine simulates the bodily changes observable in anxiety–fear or rage reactions, and the subject will experience these emotions at the slightest provocation. However, if the subject has had explained exactly what bodily changes to expect, he will not be as ready to react emotionally.

Studies on the direct effects of "stress hormones" on the brain indicate that adrenocorticotropic hormone (ACTH) increases the anxiety–fear response in animals. For example, ACTH injection increased the latency period for animals to enter a cage where they had been shocked previously. Adrenocortical steroids such as cortisol seem to improve avoidance learning in animals, suggesting increased anxiety–fear response. On

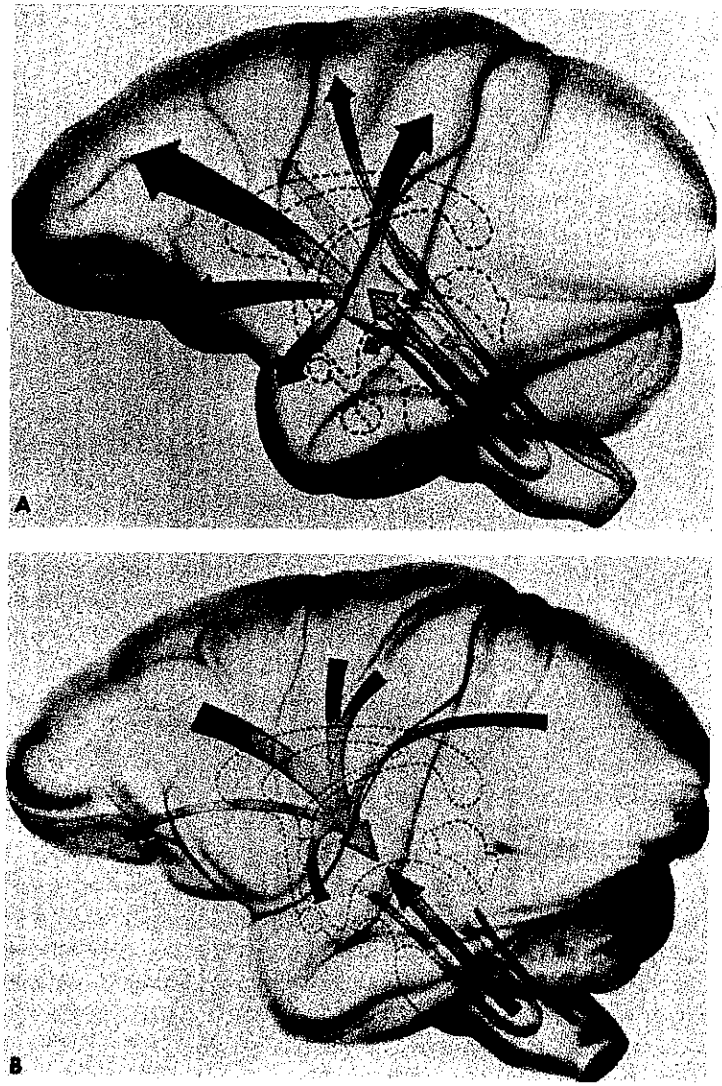

Figure 7. Reticular activating system. A: Ascending reticular activating system schematically projected on a monkey brain. (Originally published in Lindsley: *Reticular Formation of the Brain.* Boston, Little, Brown & Co.) B: Convergence of pathways from the cerebral cortex and from the spinal afferent systems on the reticular activating system. (Originally published in French, Hernandez-Peon and Livingston: *J Neurophysiol* 18:74, 1955.) (From Guyton, 1976. Copyright 1976 by W. B. Saunders Co. Reproduced with permission from the publisher and author.)

the other hand, in humans, exogenous corticosteroids tend to cause euphoria, although anxiety symptoms also occur in some subjects. Some studies indicate that ACTH enhances, while cortisol tends to inhibit, the dorsal area of the hippocampus (see McEwan and Brinton [1987] for detailed discussion of neuroendocrine aspects of adaptation and the possible role of glucocorticoids in the pathogenesis of some brain pathologies such as Cushing's syndrome and Alzheimer's disease).

CENTRAL NEUROTRANSMITTERS IN ANXIETY

At present, data concerning the roles of various neurotransmitter substances in the brain during anxiety states are confusing and often contradictory. Almost all known CNS neurotransmitters seem to be involved in the functioning of the various structures involved. The substances that may be implicated in the anxiety mechanisms include catecholamines (including norepinephrine, epinephrine, and dopamine), the indoleamine serotonin, acetylcholine and γ-aminobutyric acid (GABA), glycine, substance P, and endorphins (enkephalins). The noradrenergic system is involved in the pleasure–reward system as well as in the anxiety–fear system; the serotonergic pathways, in sedation and sleep mechanisms; the cholinergic pathways, in arousal determined by the reticular activating system as well as in the functions of the neocortex and movement. GABA seems to exert a generalized inhibitory effect within the CNS as well as to play a major role in anxiety regulation.

GABA is perhaps the most prevalent neurotransmitter in the brain and seems to exert its inhibitory function by opening chloride channels that are directly linked to the GABA receptors. This increases the influx of chloride ions into the cell, hyperpolarizing it. The antianxiety drugs in the class of *benzodiazepines* (which include diazepam, chlordiazepoxide, lorazepam, etc.) bind to specific receptor sites in the brain, the benzodiazepine receptors (Squires and Braestrup, 1977). Recent evidence suggests that the benzodiazepine receptors are functionally linked to the GABA receptors to form a GABA–benzodiazepine–chloride ionophore complex (Paul *et al.*, 1981). Although most benzodiazepines have both sedative and anxiolytic action, it seems that these effects are not necessarily related. For example, benzodiazepines have been discovered that possess anxiolytic action with minimal sedative action. They seem to bind to a specific subclass of benzodiazepine receptors. The imidazodiazepam Ro 15-1788 is a benzodiazepine-receptor antagonist. Ro 15-1788 blocks the anticonvulsant, depressant, and "antipunishment" effects of

benzodiazepines in animals, but does not possess anxiogenic effects in animals or humans (Hunkeler *et al.*, 1981). The ethyl ester of β-carboline-3-carboxylic acid (β-CCE) is another substance that has a high affinity for benzodiazepine receptors in the brain. In rhesus monkeys, β-CCE infusion produced marked signs of anxiety, including increase in heart rate, blood pressure, and behavioral characteristics, which were reversed by Ro 15-1788 and by diazepam (Ninan *et al.*, 1982). Thus, the GABA–benzodiazepine–chloride ionophore complex seems to be an important mediator in the regulation of anxiety experience.

While the benzodiazepines are effective in most generalized anxiety states, and in anticipatory anxiety to a stressful event, they are ineffective in episodic attacks of panic. It appears that for panic attacks, the norepinephrine system may be more intimately involved.

Stimulation of the *locus ceruleus* in the brain stem (pons) in monkeys results in typical anxiety–fear behaviors, and most antianxiety agents appear to inhibit the locus ceruleus or its synaptic projections (Redmond and Huang, 1979; Redmond *et al.*, 1977). The locus ceruleus consists of noradrenergic cell bodies that provide the principal noradrenergic input into the brain. The cells in the locus ceruleus have receptors for GABA, benzodiazepines, and opiates, as well as for norepinephrine. Clonidine, an α_2-receptor agonist, reduces the activity of the locus ceruleus and is effective in reversing the anxiety–fear behaviors induced by locus ceruleus stimulation. In humans, clonidine is effective in decreasing episodic anxiety attacks, but less effective than other antianxiety agents in reducing generalized nonepisodic anxiety symptoms (Hoehn-Saric, 1982). Antidepressant drugs (tricyclics and monoamine oxidase inhibitors [see Chapter 21]) generally decrease the activity of the locus ceruleus, probably by increasing norepinephrine levels at the autoreceptor sites. They are most effective in reducing panic attacks, but not in generalized or anticipatory anxiety. Thus, it appears that the norepinephrine system is probably involved in some types of anxiety, particularly panic attacks.

The serotonergic system seems also to be involved in anxiety responses and stress. The antidepressant drugs affect not only the noradrenergic system but also the serotonergic system in the brain. In fact, the long-term effects of tricyclic antidepressant treatment seems to be an enhancement of the serotonergic and α-noradrenergic transmission with a down-regulation of the β-adrenergic transmission in the brain (Aghajanian, 1981; Price *et al.*, 1990.) Tricyclic antidepressants with major serotonin-reuptake-blockage effects (clomipramine, fluvoxamine) are effective in panic attacks, phobic anxiety, and obsessive–compulsive disorders. While it seems clear that changes in the serotonergic system are involved in anxiety, their role seems complex. For example, a serotonin-

receptor agonist, metachlorophenylpiperazine (m-CPP), caused panic attacks in patients with panic disorders and increased anxiety ratings in normal subjects (Murphy and Pigott, 1990).

The endorphine system may also be involved in anxiety and stress regulation. The limbic system and the locus ceruleus have numerous opiate receptors, and stress-induced analgesia is mediated by the endorphinergic system (Emrich and Millan, 1982). Naloxone administration, however, does not cause severe signs of anxiety or autonomic arousal in normal volunteers or in chronically anxious persons, although it does cause mild dysphoria (Hoehn-Saric, 1982).

FUNCTION OF ANXIETY

Anxiety is an unpleasant emotion and certainly a major cause of suffering. One might wonder, then, why we have anxiety at all; that is, why was anxiety not discarded eons ago in the evolutionary process? The obvious reason is that anxiety serves highly important *adaptive functions*. We have already seen that anxiety prepares the organism physiologically for fight–flight reactions essential for survival, and we have discussed the role of anxiety in learning; that is, it *facilitates avoidance learning*, thus preventing repeated exposure of the organism to dangerous situations. Another highly important function of anxiety that we have discussed is its signal function and role in initiating the *mobilization of psychological defense mechanisms*.

But beyond these more immediate and obvious survival values, anxiety serves broader and more far-reaching functions—it is an important force in stimulating and supporting *personality development*, particularly maturational processes responsible for acquisition and effective performance of *socially valued skills*. Perhaps the easiest way to open discussion of the productive, constructive, or generative function of anxiety is to look at its immediate or short-term role as an influence on skilled performance. Anyone who has had to face the challenge of, say, an important academic examination, or athletic competition, or public speaking knows very well that there is an optimal level of "tension" or anxiety for realizing the best of one's capabilities. With too little anxiety (and insufficient motivation), performance is likely to be lackluster and below par. We all have our own ways of getting "psyched up" for such challenges. On the other hand, if the level of anxiety becomes too high, performance suffers because of the disorganizing effects on finely tuned cognitive and sensorimotor mechanisms—increased incidence of forgetting and of errors,

loss of fine motor coordination, loss of confidence, feeling "clutched up," panic, and so on. In vignette 2, it seems likely that excessive anxiety in relation to success in sex may have played a disruptive role in the patient's experience of sexual activities and contributed to her eventual aversive response. The *inverted U relationship between level of drive and performance* (Yerkes–Dodson law) in this way can be seen to apply to anxiety, again calling attention to its "drive" or motivational quality.

Many theories of personality development postulate a similar motivational, generative, and facilitating-inhibiting function for anxiety in cognitive and social development. Psychoanalytic theory (particularly developmental ego psychology) details how frustration generates anxiety and motivates development of the requisite cognitive and defensive ego functions and related social skills on which mature adult adaptive behavior depends (Freud, 1926/1953; Hartmann, 1958, 1964).

DYSREGULATION OF ANXIETY

As is the case with other primarily adaptive mechanisms (e.g., immune responses, fever, and inflammation), anxiety is subject to dysregulation. Major disruptions in its regulation not infrequently contribute to clinical morbidity—and sometimes even to fatal reactions (Schwartz, 1977). Walter Cannon, fascinated by the phenomenon of voodoo death, reviewed the world literature on it and wrote a now classic paper on the subject (Cannon, 1942). In Africa, some superstitious primitive tribes believed that certain powerful medicine men or witch doctors had the power to kill through the magical ritual of "bone pointing." There were numerous accounts describing how vigorous, healthy individuals, after having had the bone pointed at them and being convinced they were going to die, would leave the tribe and within a few days be dead—of no apparent or usual natural cause.

Cannon speculated that the mechanism might be excessive sympathetic adrenal stimulation. Richter studied an experimental model of sudden functional death in captured wild Norway rats and demonstrated that (1) the pathogenic mechanism was vagal inhibition of the heart and (2) the phenomenon was influenced by sensory and psychological factors. There are, in fact, quite a number of examples of behaviorally induced or associated sudden death or feigned death in animals (Richter, 1957). Sudden death due to fatal arrhythmia is not an unusual occurrence in humans (400,000 deaths each year are attributed to it in the United States) (DeSilva and Lown, 1976). Most studies of this phenomenon implicate

the effects of abrupt autonomic imbalance on the cardiac rate-setting and impulse-conducting tissues (Lown *et al.*, 1977). This effect is probably most likely to occur in persons with structural damage to these tissues (e.g., due to arteriosclerosis), but it is not really known whether or not the phenomenon can occur in persons with entirely healthy hearts.

Three other common and clinically important examples of anxiety dysregulation are fainting (syncope), hyperventilation, and panic disorder (discussed below, page 66).

Fainting

In the common form of fainting *(vasodepressor syncope)*, the mechanism involves primarily the cardiovascular aspects of the anxiety reaction, specifically as it affects distribution of blood throughout the body. The loss of *consciousness* is caused by inadequate blood supply to the brain even though the anxiety response normally increases cardiac output and redistributes blood so as to increase blood flow to the brain as well as the skeletal muscle, heart, and lungs. In vasodepressor syncope, blood pools in the periphery, particularly in the extensive vasculature of the skeletal muscle of the lower extremities. This results in decreased venous return to the right side of the heart, decreased cardiac filling, and fall in cardiac output—sufficient to result in inadequate blood supply to the brain. Engel (1962) postulates that the circulatory changes of anxiety prepare for fight or flight, both of which require vigorous muscle activity, which in turn keeps the increased blood supply to muscle circulating and literally massages it out of the muscle bed back toward the heart, ensuring adequate cardiac filling and output. If, however, the danger situation is abrupt, overwhelming, and one that the person is powerless to influence, and if the person would be ashamed to flee (retreat) and does not act, that is, does not move, the large amount of blood sent to the muscles stays there instead of being pumped back to the heart by muscle contraction. Epidemics of vasodepressor syncope commonly occur among army recruits when they are lined up for blood tests by venipuncture. If one recruit faints, it is common for several more to follow suit in short order, illustrating another interesting aspect, namely, social contagion. The issue of pride (shame) preventing retreat in this situation is clear. Another aggravating circumstance is that the subjects are standing up, so that gravity aggravates or accentuates the pooling of blood in the legs.*

*For a thorough description and discussion of mechanisms of all forms of syncope, readers are referred to Engel (1962) and medical textbooks.

Hyperventilation Syndrome

The second clinically important acute dysregulation syndrome is the "hyperventilation syndrome." In this condition, an exaggeration of the respiratory aspect of the anxiety response leads to difficulty, that is, excessive increase in rate or depth, or both, of breathing. This is easily observed by the physician, although the patient most often is not aware of it. With the overbreathing, there is excessive loss of carbon dioxide, leading to *respiratory alkalosis* (reduced pCO_2). The increased blood pH leads to decreased ionization of calcium, which may produce clinical signs of tetany (in which painful muscle contractions occur). In addition to the usual symptom of anxiety, the hyperventilating patient experiences light-headedness (altered blood gases), headache, nausea, tingling around the mouth, tingling of the fingers and toes (hypocalcemia), and, if the overbreathing lasts long enough, even cramping or spasm of muscles in the extremities. All this is enough to make the person even more anxious, resulting in a vicious circle. A patient who has such attacks is usually terrified by the experience. Dramatic reassurance can be given by demonstrating that the attacks can be reproduced at will by deliberate overbreathing. Then the symptoms can be reversed by having the patient breathe into a paper bag and rebreathe the exhaled air, which has a higher concentration of carbon dioxide. Confirming the diagnosis through this technique can be dramatic and highly gratifying to both patient and physician. Most doctors remember with great pleasure the first time they had the opportunity to use this treatment for hyperventilation. Further evaluation should then be done to understand the underlying cause of anxiety in the patient that leads to hyperventilation.

Stress-Related Disorders

As noted in the section on the physiology of anxiety, when stress (and strain) is prolonged, anxiety responses merge into states in which additional systems, for example, neuroendocrine systems, are mobilized, and extensive metabolic chemical changes eventuate in the central nervous system and throughout the entire body. These changes, in interaction with other factors (e.g., constitutional, specific tissue vulnerabilities, specific pathogens), may contribute to or aggravate many clinical disorders such as hypertension and peptic duodenal ulcer. Although there is growing experimental literature on stress-related disorders, the mechanism of interaction between stress and disease is far from completely understood. We are only beginning to appreciate the multiple interacting and intervening variables that can influence the response of somatic systems

to psychological-social stress. For example, let us look at just two (somewhat contradictory) experiments in the vast experimental literature on production of gastric ulcers in animals by exposure to stress.

When monkeys were trained to press bars constantly to avoid electric shock in a complex and highly demanding operant conditioning program with many contingencies, they developed bleeding gastric ulcers and died ("executive" monkeys). On the other hand, yoked control monkeys that were shocked the same amount but did not have to press bars to avoid shock did not develop bleeding ulcers (Brady, 1958). In another experiment, rats that were trained to avoid shock by bar-pressing did not develop bleeding ulcers, while yoked control rats that were exposed to inescapable shock developed bleeding ulcers (Weiss, 1968). In the latter experiment, however, the rats trained to press bars to avoid shock had *feedback* in the form of light—that is, the light indicating impending shock was turned off as the bar was pressed—unlike the "executive" monkey situation, in which there was no direct feedback concerning adequate performance.

One might speculate that the "executive" rats had a *sense of control* with performance of bar-pressing, while the monkeys had to perform without this sense of control. In any case, it seems that a sense of control and feedback of success from coping strategies in anxiety states may be one important factor in buffering the physiological strain resulting from the stress and in influencing whether or not a "stress disorder" will result.

Dysregulation of anxiety and stress reactions may occur due to *uncontrollable* and *sustained external or internal anxiety-provoking situations* (e.g., as in battle fatigue or unresolved conflict), or it may occur due to *inherent instability, defect, or malfunction in any of the many structures and systems involved, including the target organs of physiological arousal.*

A somewhat unique side effect of modern medicine is the increase in *iatrogenic dysregulations* of anxiety. This often results when physicians, overlooking the psychosocial origins of the reactions or, in some cases, the adaptive significance of mild to moderate levels of anxiety, prescribe *antianxiety medications at times* and *in dosages* that are *not indicated.* Since antianxiety medications, especially minor tranquilizers such as the benzodiazepines, are habit-forming, a person would have to take increasing doses to maintain anxiety at an imperceptible level. This will be especially marked if the psychological and/or social causes of the anxiety are ignored and allowed to continue operating unabated. As a further complication, the patient will eventually experience exacerbation of the anxiety, due to the effects of withdrawal, when the dose of the medication is lowered. This is *not* to say that antianxiety medications should

not be used—there are many situations in which they are indicated. The physician should have, however, a clear idea as to why, and for how long, the medication is to be prescribed.

Classification of Anxiety Dysregulation Syndromes

While it is not within the scope of this book to discuss all stress disorders, a brief discussion of the classification of anxiety dysregulation syndromes is in order. Essentially, anxiety dysregulation syndromes can be categorized according to whether they involve (1) dysfunction in the experience of anxiety (excessive or insufficient), (2) dysfunction in psychophysiological systems, or (3) dysfunction in behavior.

Disorders in the Experience of Anxiety. The *locus* of the problem in this category is often the *brain* and the *personality system.*

Excessive experience of anxiety. Anxiety disorders (neurosis), anxious personality traits, impulsiveness, tendency to become paralyzed with anxiety in the face of moderately stressful situations, and similar disorders, fall within this category. Drug abuse, including alcoholism, may be secondary to this type of anxiety dysregulation.

Panic disorder is characterized by panic attacks occurring with relatively high frequency (e.g., more than one per week). This condition is often associated with agoraphobia (fear of open spaces and crowds). Activation of the locus ceruleus plays a major role in the pathogenesis of this disorder.

Panic disorders, phobias, generalized anxiety disorders, and obsessive compulsive disorders comprise the major subcategories of anxiety disorders. A panic attack is a discrete period of intense fear or discomfort, often unexpected and overwhelming, accompanied by at least four of the following—dyspnea, dizziness, palpitations, trembling, sweating, choking, nausea, depersonalization, paresthesias, flushes or chills, chest pain or discomfort, fear of dying, or fear of losing control (DSM-III-R, 1987). Phobia is an irrational fear and consequential avoidance of an object or situation. Intense anxiety is experienced if such an object or situation cannot be avoided. Social phobia (fear of public or social situations) and simple phobia (for example, fear of cats—ailurophobia) are common. Agoraphobia is a condition characterized by fear of being in places or situations from which escape might be difficult or embarrassing or in which help might not be available if symptoms were to develop suddenly, such as dizziness, falling, loss of bladder control, etc. Agoraphobia can be quite disabling and is often associated with panic disorders.

Obsessions are persistent and intrusive ideas, thoughts, images, or impulses, such as of violence. Compulsions are repetitive, purposeful, and intentional behaviors that are performed in response to an obsession in a stereotyped fashion (DSM-III-R, 1987). The behavior, which is irrational or clearly excessive, was originally consciously designed to neutralize or to prevent the dreaded event or situation. If the person resists performing the compulsion, there is increasing tension which can be immediately relieved by yielding to the compulsion.

In general, antidepressant drugs such as imipramine, fluoxetine, and phenelzine, rather than antianxiety drugs, are effective, although the antianxiety drug alprazolam is effective in panic disorders.

Obsessive-compulsive disorder is also classified as an anxiety disorder by the *Diagnostic and Statistical Manual* of the American Psychiatric Association (DSM-III-R). In obsessive-compulsive disorder, the patient has repetitive intrusive thoughts (obsessions), and may have to engage in repeated behaviors (compulsions), such as handwashing, in order to ward off overwhelming anxiety. Antidepressant drugs that are especially serotonergic, e.g., clomipramine, fluoxetine, and fluvoxamine, seem to be effective for this condition.*

Insufficient experience of anxiety. Persons who chronically experience little or no anxiety tend to lack motivation and become underachievers. Some persons, on the other hand, tend to seek extremely dangerous situations to experience arousal (excessive risk-seeking behavior). Inability to learn from unpleasant experiences may be one factor contributing to development of antisocial personality disorders.

Psychophysiological Disorders. Stress disorders in the form of tissue damage or organ dysfunction or both may occur following *sustained physiological arousal* in anxiety. The *locus* of the problem may be in the perceptual apparatus, cerebral cortical structures, and the *personality system* (excessive generation of anxiety), in the *neuroendocrine* and *autonomic nervous systems* (instability or excessive excitation), and/or in the *target organs* (vulnerability). Psychophysiological disorders may occur in relatively healthy and disease-resistant persons with intact personality systems and central nervous and endocrine systems if the organism-environmental interaction is such that the physiological component of anxiety is activated for prolonged periods in an uncontrollable way. If disease (such as essential hypertension, peptic ulcer, migraine, the depressive syndrome, or schizophrenia) eventuates, the selection of the affected system probably

*The psychobiology of panic disorder is extremely complex. For more details, see Ballenger, 1986; Barlow, 1988; Charney *et al.*, 1984; Roy-Byrne *et al.*, 1986.

rests on *constitutional* (genetic and developmental) *predisposing* factors related to the organ system involved.

Dysfunction in Behavior. Heterothetic behaviors. As we discussed in Chapter 1, some persons who find themselves in anxiety-provoking situations seek medical help for minor physical symptoms without recognizing that the help-seeking behavior is motivated by anxiety. An example is the woman who, when family problems arose, came to see her physician for varicose veins she had had for 20 years. Prompt recognition of the presence of heterothetic behaviors is important for the physician to prevent "addiction to sick-role behavior" or unnecessary and potentially dangerous medical procedures or both (see Chapters 2 and 18).

Cognition–action dissonance. This occurs when a person takes no action to alleviate an anxiety-generating situation, even when the situation is readily identifiable and the means of avoiding danger is readily available. The *locus* of the problem in this case is obviously in the personality system and, secondarily, in the organism–environment interaction. This syndrome can eventually contribute, of course, to development of any of the disorders discussed above. "Learned helplessness" may be one possible explanation for this disorder (Seligman and Maier, 1967). Animal and human experiments show that repeated prior exposure to situations in which behavior has no effect (learning helplessness) may influence individuals' behavior in future situations. They may tend to "give up" the quest for ways of coping, even in new situations in which their behavior could have an effect. Such learned helplessness is often encountered in depression (see Chapter 6).

EVALUATION OF ANXIETY

The diagnosis of anxiety is based on the signs, symptoms, and behavioral changes discussed in previous sections of this chapter.

Once the presence of anxiety is established, the evaluation should proceed to the contexts of its occurrence, that is, the questions of the meaning and significance of anxiety (What is the danger situation?), the kind of individual (Prone to anxiety? Tending to deny anxiety?), the cultural–social matrix (What is the method of expressing anxiety the patient is accustomed to? Complaining of physical symptoms? Taking medications?), and the reasons the patient is seeking help now (Limit of tolerance? Heterothetic? Occurrence of psychophysiological disorder?). These

questions should be considered in terms of the current, recent, and background contexts of the anxiety.

Contexts of Anxiety

Current Context. Presenting symptoms. What are the immediate circumstances (and accompanying thoughts) under which the anxiety is experienced? Include considerations of patient's antianxiety medications or withdrawal therefrom. How effective are the psychological defenses?

Recent Context. What is the danger situation? Why is the situation seen to be dangerous in the light of the patient's experience? Any cumulative effect of stressful events in the recent past? Has the body been weakened by physical illness (e.g., recovering from an infection, presence of chronic disease)? Are there any physical illnesses or vulnerabilities that may tend to dysregulate anxiety at central nervous system, neuroendocrine, or target organ levels?

Background Context. Is the patient habitually prone to experience anxiety? What psychological defenses does he ordinarily use? How is anxiety handled in the patient's cultural and social class matrix (e.g., by somatization or suppression)? If a physical symptom related to anxiety is present, what is the patient's early experience concerning such symptoms either in himself or in a relative?

A fuller discussion on the systematic evaluation of patients will be presented in Chapter 12.

DIFFERENTIAL DIAGNOSIS OF ANXIETY STATES

Any *disease* of any part of the brain, autonomic nervous system, or neuroendocrine system associated with the anxiety mechanism may mimic anxiety states, as may some diseases of target organs. It is important to *rule out* such diseases. Physical examination and psychiatric evaluation, including mental status examination and appropriate laboratory test, will usually clarify the diagnosis. To establish the psychiatric diagnosis of anxiety disorder (neurosis), it is not sufficient to "rule out organic disease" by negative physical examination and laboratory findings. It is also necessary to adduce, by psychiatric evaluation, evidence for a positive psychiatric diagnosis, such as clarification of the psychosocial context or

the danger situation. Some diseases capable of mimicking anxiety states are thyrotoxicosis, pheochromocytoma, carcinoid syndrome, hypoglycemia, seizure disorders, drug withdrawal states, brain tumors, and Cushing's syndrome. Some major psychiatric disorders such as schizophrenia and affective disorders are often accompanied by anxiety, but in addition, one would find evidence of other psychiatric difficulties such as a thought disorder in patients with schizophrenia and altered neurovegetative function and sleep disorders in patients with the depressive syndrome.

MANAGEMENT OF ANXIETY

Careful evaluation and appraisal of the patient with anxiety should lead naturally to formulation of a rational management plan. The first order of business is to determine whether or not the experienced anxiety is excessive, that is, whether it threatens to paralyze or decrease *coping* and adaptive *abilities* of the patient or to cause other dysregulation syndromes such as psychophysiological disorders. If excessive anxiety is present, then prompt reduction of such anxiety by means of appropriate reassurance and antianxiety medications is indicated. (Sometimes even hospitalization is desirable as a way of getting the patient away from a stressful life situation and providing a supportive setting.) In prescribing antianxiety agents such as diazepam (Valium) or chlordiazepoxide (Librium), the physician, being aware of the habit-forming qualities of the medications, should take care that they are used only *temporarily*, almost as an emergency measure. Antianxiety agents may be used on a long-term basis if the symptoms are due to hyperreactivity of end organs (as in irritable bowel syndrome), or due to an established anxiety disorder such as generalized anxiety disorder. For the treatment of panic disorders and agoraphobia, antidepressant drugs (both tricyclics and monoamine oxidase inhibitors) and the benzodiazepine alprazolam are effective. For obsessive-compulsive disorder, certain serotonergic antidepressants (such as clomipramine, fluoxetine, and fluvoxamine) are effective in the majority of (but not all) patients. The degree of improvement varies. Most of those who respond show appreciable clinical relief of symptoms. In some cases, in anxiety states with predominant symptoms of sympathetic arousal (e.g., palpitations), β-blockers such as propranolol are useful. (A more comprehensive discussion of these and other medications will be found in Chapter 21).

Having determined the severity of anxiety present, and having made a decision as to whether or not to *treat the manifest anxiety* per se, the physician should next attempt to define the *causes* and *contexts* of the anxiety and, having done so, to institute appropriate treatment modalities. A few examples follow.

Careful evaluation of the contexts of anxiety may reveal that the main danger situation is an *intrapsychic* one (intensification of psychological conflicts, for example, between basic drives and learned inhibitions). In this instance, *psychotherapy is* indicated. The danger situation may be an *external* one, such as threats to health or occupation. *Medical treatment* or *counseling* may be necessary in these situations. On occasion, it may be necessary to advise *environmental change* or suggest *new coping strategies* (especially in the presence of action-cognition dissonance). If the anxiety-provoking situation is pervasive and seems to be a result of *faulty learning, behavioral treatment modalities* such as desensitization, cognitive therapy, or learning of relaxation techniques may be helpful.

If a target-organ disorder, such as hypertension, is present, *it should be treated medically in parallel with the management of the psychological and social factors* that might have contributed to it. Excessive anxiety determined predominantly by *intrinsically unstable brain structures* (acute toxic or structural brain damage) may be managed successfully by teaching the patient new coping strategies and relaxation techniques.

SUMMARY

Anxiety, together with pain, is one of the most common major causes of help-seeking behavior. The experience of anxiety involves *subjective* feelings of fear and dread that are usually vague, although on occasion the patient may complain of specific fears such as that of dropping dead. *Physical examination* will usually reveal signs of sympathetic nervous system activation, including rapid pulse rate, elevated blood pressure, and excessive sweating.

Anxiety can be regarded as a *warning response* to impending danger that may be external or intrapsychic. The term "signal anxiety" in psychoanalytic theory refers to the special case in which the person is not aware of the nature of the danger situation (i.e., the impending situation is internal, psychological, and "unconscious"). Anxiety may develop as a conditioned response to previous exposure to unpleasant or dangerous situations. Anxiety serves the adaptive *functions* of preparing the organism for fight or flight, of mobilizing psychological defense mechanisms, and of facilitating performance.

All parts of the *brain* participate in the anxiety mechanism. The most important parts of the brain include the neocortex for processing of information, the limbic system for the emotional reactions leading to the neural and endocrine discharge via the hypothalamus, the brain stem nuclei, especially the locus ceruleus, which may play a major role in the generation and suppression of the anxiety-fear response, and the reticular activating system for the arousal levels of the central nervous system accompanying anxiety.

Many neurotransmitters are involved in anxiety modulation. The GABA-benzodiazepine-chloride ionophore complex plays a particularly important role. In addition, norepinephrine, serotonin, and endorphins probably play major roles in anxiety regulation.

Activation of specific parts of the hypothalamus in anxiety-fear reactions results in specific patterns of excitation of autonomic and endocrine systems. Anxiety is usually associated with excitation of the autonomic nervous system and altered function of neuroendocrine systems.

Although anxiety serves a useful function in moderate levels, it may, so to speak, go out of kilter, resulting in "anxiety dysregulation syndromes." Dysregulation may have multiple causes, and any combination of the following may be involved: the perceptual apparatus, the brain and personality system, the neuroendocrine and autonomic nervous systems, target organs, organism-environment interaction, and iatrogenic factors.

Anxiety dysregulation syndromes may be classified broadly into (1) disorders in the experience of anxiety (excessive or insufficient), (2) psychophysiological disorders, and (3) dysfunction in behavior, including heterothetic behaviors and cognition-action dissonance.

Evaluation of anxiety should include the determination of the presence of the *state* of anxiety by means of indicators including subjective reports and an evaluation of the *contexts* of anxiety, which include current, recent, and background contexts. The recent context includes determination of the possible danger situation generating the anxiety, recent life events, and stresses. The background context includes the cultural factors, early learning factors, and the *trait* of the patient in experiencing anxiety.

The *management* of anxiety should naturally follow from the information obtained in the evaluation phase. Excessive anxiety may be successfully treated by medication, behavioral treatment modalities, and reassurance. The danger situation should be identified and coped with, for which psychotherapy or counseling is often indicated. Target-organ disorders may need specific medical treatment.

In general, antianxiety medications should be used temporarily to alleviate massive and paralyzing anxiety while evaluation and treatment continue to deal with the situational and psychological factors that are generating the anxiety.

IMPLICATIONS

For the Patient

Since anxiety is an unpleasant and vague feeling the cause of which is usually not obvious, some patients may tend to *attribute the cause of dysphoria to a physical illness* or may displace their concern onto physical sensations associated with minor disorders. Thus, the presence of anxiety is one of the most common reasons for help-seeking behavior, *ostensibly for other physical symptoms* (heterothetic, or problems of living presenting as a symptom). In such instances, the fact that physical examination and laboratory tests reveal no serious medical condition will not completely reassure the patient, since the cause of the anxiety was not related to the physical symptoms in the first place. If the situation (usually interpersonal or intrapsychic or both) that is generating the anxiety is not explored by the physician, the patient often interprets continuing high levels of anxiety as evidence that the physician either lacks competence or "does not care."

For the Physician

The physician should be aware that the patient is *suffering* when anxiety is present. Alleviation of this suffering can be achieved only by comprehensive evaluation and management of the patient. Although anxiety often results in heterothetic behaviors, the physician should also be aware that (1) actual physical illness, especially chronic illness, may increase the patient's propensity to experience anxiety and (2) on occasion, some medical illnesses *simulate* anxiety states. Any disease affecting the brain and peripheral structures concerned with anxiety mechanisms may mimic anxiety states. A rational management plan can be formulated only after a thorough evaluation of the patient according to the principles outlined in this chapter. Emphasis should be placed on understanding the recent context or the danger situation to which the patient may be responding with anxiety. To elicit this information, the physician has to ask *specific questions* about recent events, such as the patient's *relationships* with spouse, relatives, and friends, the financial

situation, and the health status of people close to the patient. Questions should be asked about the patient's *demographic data* and early experiences, especially in relation to anyone who had a disease or symptom similar to the one the patient is complaining of now, in order to elicit information concerning the background context. The patient should also be asked whether or not he has a tendency to feel anxious or to get upset easily, whether he has had many physical illnesses and complaints in the past, etc. (the "trait" of the patient). An evaluation of the current context should include the question, "What do you think is causing your present symptoms?" (e.g., palpitations, dizziness, or whatever). Often, the patient may tell you, "I think it's because I have cancer" (or heart disease, or leukemia, etc.). This should be followed by the question, "Why do you think that?" or "Do you know of anyone who had cancer?" (or heart disease, or leukemia, etc.). This will often give information concerning what the *meaning* of the symptom might be for the patient and, sometimes, what the danger situation might be, given the patient's unique experiences and exposures ("priming factors").

For the Community and the Health-Care System

We are often told that we live in an age of anxiety. We have seen that one of the important elements in reducing undesirable effects of anxiety (or perhaps anxiety itself) in animals and humans is a *sense of control or mastery* and *feedback* indicating that the attempt to control or master the situation generating anxiety has been successful. At the level of social systems, it seems imperative to facilitate, as much as possible, the sense of mastery available to the individual members and to provide feedback of such mastery. More responsive decision-making and administrative structures with a minimum of bureaucratic red tape (an excellent device to reduce or delay feedback) at all levels of the social system would be highly desirable. This would apply particularly to the health-care system, including the hospital, the ward, and the treatment team.

Patients with anxiety disorders can become more anxious, frustrated, and sick when their requests for p.r.n. ("when necessary") medications (or bedpan or whatever) remain unanswered or ignored for hours.

Medical curricula should include the evaluation and management of anxiety and anxiety dysregulation disorders. Special emphasis should be placed on the role of anxiety in facilitating heterothetic help-seeking behaviors and in the treatment of target-organ disorders, as well as on the psychopharmacological management of acute anxiety. Drug treatment of anxiety should always be accompanied by an attempt to understand and cope with the danger situation and underlying factors generating the anxiety.

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