Library of Congress Cataloging-in-Publication Data

Advanced abnormal psychology/edited by Michel Hersen and Vincent B. Van Hasselt.—2nd ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-306-46381-4
1. Psychology, Pathological. 2. Mental illness—Treatment. I. Hersen, Michel. II. Van Hasselt, Vincent B.

RC454 .A325 2000
616.89—dc21

00-046624

Photo 0182

ISBN 0-306-46381-4

233 Spring Street, New York, N.Y. 10013

http://www.wkap.nl/

10 9 8 7 6 5 4 3 2 1

A C.I.P. record for this book is available from the Library of Congress

Printed in the United States of America

6

Biological Model

DOIL D. MONTGOMERY AND PAMELA M. PLANTHARA

INTRODUCTION

Within the biological models of behavior, there are various major themes about what determines or underlies both normal and abnormal behavior. The most widely accepted premise is that the nervous system is the center of control for all behavior. Therein lies the content of this chapter. What controls the development of the nervous system, and what elements combine to determine its state and function at any given time? To answer these questions, the following must be considered: (1) genetic determinants of the development of the nervous system, (2) how environmental factors interact with genetics to influence neural development; and (3) the dynamics of change in the developed nervous system.

We now know that the nervous system is a dynamic structure whose anatomy and chemical and electrical states are constantly changing. It is known that these changes are due to an interactive combination of neural activity determining behavior and behavior changing neural activity. This two-way interaction between the nerves initiating behavior and behavior changing neural connections and chemistry determines how the nervous system will perceive and respond to the world. Some of the most well-documented models are discussed in this chapter.

MAJOR MODELS

There are three major biological models postulated to account for dysfunctional behavior: the anatomical model, the neuronal model, and the learned model. The anatomical model postulates that the brain and spinal cord are topographically organized. This means that specific areas of the brain and the spinal cord control or sense certain processes. As examples, the occipital area of the cortex processes visual information, and the motor strip on the cortex controls skeletal muscles. Therefore, when the anatomy is altered by various events, specific behaviors will change.

DOIL D. MONTGOMERY AND PAMELA M. PLANTHARA • Center for Psychological Studies, Nova Southeastern University, Fort Lauderdale, Florida 33314.

Advanced Abnormal Psychology, Second Edition, edited by Hersen and Van Hasselt. Kluwer Academic/Plenum Publishers, New York, 2001.

The next model, the neuronal model, postulates that individual nerve cells function normally within their structural and chemical parameters. When the structure or chemistry is altered outside normal limits, behavior is changed. The last model, the learned model postulates that the anatomy and/or neural functioning is altered by experience. This model assumes that behavior previously learned and adaptive at that time and situation is now no longer appropriate and therefore is dysfunctional. The learning model does not postulate a dysfunctional nervous system but implies that the nervous system is functioning normally and is responding to events based on previous experience, but that the response is not appropriate in the present situation. These three models are not incompatible in that behaviors, once functional but now dysfunctional, may have changed neuronal structure and/or chemistry leading to further dysfunctional behaviors.

Our chapter is organized into the major dysfunctional types of behavior that has been the focus of most of the research into biological explanations of dysfunctional behavior. These areas will be schizophrenia, depression, anxiety, and Alzheimer's disease. There are many other specific disorders such as Parkinson's disease, Huntington's disease, obsessive compulsive disorder, and more global disorders such as obesity, and sexual disorders, which it has been shown, have a biological basis, but due to the limitation of space these and other dysfunctions are not discussed.

SCHIZOPHRENIA

Anatomical and Neurochemical Influences

For many years, this disorder has been the focus of attempts to understand the physiological basis of abnormal behavior. It has a prevalence of approximately 1% in the general population and is equally distributed worldwide (Jablensky et al., 1992). It is a public disorder that manifests itself in easily observed bizarre behavior. Many of the those suffering from it appear on our streets and comprise a large portion of the homeless. There have been several biological markers of this affliction, and although much research has been generated in this area, there are still many unknowns associated with its conditions of onset, manifestations, treatment, and instances of its sudden and unexplained termination. Features of the varied forms of this disorder include disturbance of thought, paranoid and/or grandiose delusions of self and others, extreme lability or flat affect, and auditory and visual hallucinations. The disorder usually has its onset during adolescence and is known to have a genetic propensity, but is certainly influenced by stress and coping styles. The key symptoms are a dissociative thinking style accompanied by hallucinations, delusional interpretations, and unusual affect.

Gross Anatomy

Because symptoms of this disorder are so bizarre and persistent, investigators have looked to structural changes in the brain to account for the behavior. One area of investigation is the gross structure of the brain. Early studies using postmortem evidence were inconclusive. Recent studies using advances in brain imaging techniques such as computerized axial tomograms (CAT) and magnetic resonance imaging (MRI) have revealed structural abnormalities that may be primary to the disorder. Enlarged cerebral ventricles, especially the lateral ventricles have been shown to be associated with schizophrenia (Hyde & Weinberger, 1990;

Torrey, Bowler, Taylor, & Gottesman, 1994). Andreasen (1994) found that enlarged ventricles are a static trait that remain years after the initial breakdown. Based on research by Gooding and Iacono (1995), these structural changes may be related to subgroupings of this disorder. One example of this subgrouping is that those who have larger ventricles have been shown to have a higher degree of cognitive impairment and social maladjustment (Kemali et al., 1985). These types of findings prompted some researchers such as Gottesman (1995) to call for more clearly delineated classifications to better differentiate among outcomes, which seem confusing due to lack of separating results along probable subcategories of this disorder.

The finding of larger ventricles combined with the results of the study by Mednick, Huttunen, and Machon (1994), which noted that the affected discordant, identical twin has a smaller hippocampus and amygdala, suggests that enlarged ventricles may be due to atrophy of neural tissue located near the ventricle. In addition to the smaller hippocampus, there is also histological evidence that nerve cells in this nucleus are not structurally organized in schizophrenics as they are in non-diagnosed individuals (Kovelman & Scheibel, 1984; Conrad, Abebe, Austin, Forsythe, & Scheibel, 1991). Additional evidence from a study by Machon, Mednick, and Huttenen (1994) suggests that this disarray of neural circuits could arise from maternal viral exposure during the second trimester of pregnancy.

Specific Structures

On the basis of postmortem studies, it is apparent that there are structural and neurochemical differences in the frontal cortex and the limbic system in schizophrenics (Benes, 1993; Akbarian et al., 1995; Wible et al., 1995). This is known as the corticolimbic hypothesis of schizophrenia (Benes, 1993). The corticolimbic system is comprised of the cortex, primarily the frontal cortex, the limbic system, and interconnecting fibers. The limbic system is a loosely defined, subcortical, widespread group of nuclei comprised of the septum, fornix, cingulate cortex, thalamus, hippocampus, amygdala, and mammillary bodies. The limbic system is implicated in controlling emotion, learning, and memory (Rosenzweig, Leiman, & Breedlove, 1999). It is further speculated that the structural and neurochemical changes in this part of the brain are likely to be a result of altered neural development of the fetus (Watson, 1996). Both increases and decreases in neurotransmitters, such as aspartate and GABA, have been found in the corticolimbic system nuclei of schizophrenic individuals (Watson, 1996). There is also evidence that schizophrenics have reduced blood flow in the frontal cortex during cognitive demanding tasks (Berman & Weinberger, 1990; Andreason et al., 1992; Weinberger et al., 1994).

Structures in the basal ganglion have also been implicated in schizophrenia because it has been found that nuclei in the basal ganglion of schizophrenics have higher concentrations of dopamine D2 receptors than normals (Seeman, Guan, & Van Tol, 1993). The basal ganglia are another group of subcortical nuclei comprised of the caudate, putamen, and the globus pallidus. The basal ganglia are important in controlling skeletal motor activity (Rosenzweig, Leiman, & Breedlove, 1999).

Neurotransmitters

Another major hypothesis for brain abnormalities in schizophrenics is the dopamine hypothesis. This is due, in part, to the findings that high levels of amphetamines induce conditions that mimic schizophrenia. Amphetamines promote the release of catecholomines, especially dopamine, and prolong the action of the neural transmitter by blocking its re-uptake.

Rapid relief from psychotic symptoms is often observed from the use of a dopamine antagonist. There are numerous well-controlled studies that demonstrate the effectiveness of blocking the psychotic effects in schizophrenics with dopamine blocking agents (see Rosenzweig, Leiman, & Breedlove, 1999). What is still unclear is whether this relationship to dopamine involvement is due to over production of dopamine in certain neural tissue, over sensitivity of post-synaptic membranes, or failure to re-uptake the neural transmitter after release (Davis et al., 1991; Brier et al., 1997; Rosenzweig, Leiman, & Breedlove, 1999). The related discovery that dopamine levels vary in different parts of the brain and that abnormal levels may be specifically related to aspects of the disorder raises intriguing questions about the complications of treatments. By using dopamine-related medications, abnormal levels in specific brain regions may be brought to normal levels while changing other brain site levels to a dysfunctional level (Watson, 1996).

It is becoming increasingly clear that schizophrenia involves both generalized changes in the brain, as well as regionally specific alterations in key components of the corticolimbic system and basal ganglia. Because the onset for most individuals occurs during adolescence or early adulthood, these findings highlight the importance of discovering the relationship to pre- and postnatal development of the brain and the way maturational changes interact with genetic and environmental factors. The challenge now facing the understanding of the biological mechanisms proposed is detailing the genetically determined structural architecture of specific brain regions during both prenatal and perinatal disturbance of the normal ontogeny of neural tissue. Understanding these mechanisms still may not help explain why the manifestation of schizophrenic symptoms typically occurs in late adolescence long after most neural tissue has been structurally formed.

Genetics

The role genetics plays in determining schizophrenia has been an area of interest for some time. The first evidence was provided by noting the familial relationship of schizophrenia in twin studies, where concordance rates for monozygotic twins were higher than those of dizygotic twins, and those adopted by normal parents, but had a schizophrenic biological parent had a higher incidence of the disorder (see Slater & Roth, 1960) than those born to nonschizophrenic parents. Recent studies of families that have the disorder show a mean incidence of 46.1% for monozygous twins and only 13.5% for dizygous twins (Trimble, 1996). In the general population, the incidence rate is 0.9%, for half sibs it is 7.1%, full sibs 14.2%, children of one schizophrenic parent 16.4%, and for children of two schizophrenic parents 39.2% (Trimble, 1996). This ever increasing relationship with increased genetic similarity provides strong support for the idea that a major factor is some genetic determinant. Tsaung (1993) has provided evidence that when specific symptoms are considered, even stronger genetic relationships are found. Even though specific genetic markers have been postulated, to date none has been proven (Cichon et al., 1995). However, Crow (1991) has implicated a possible sex-related relationship on the Y chromosome as a source of the disorder. Some support is provided by evidence of a higher occurrence of child schizophrenia when the mother is schizophrenic than when the father is (Crow et al., 1994). However, environmental factors must play a significant role in that adopted children of schizophrenic mothers have a higher incidence of schizophrenia than those adopted by nonschizophrenic mothers (Kety, 1983; Kety et al., 1994).

In summary, the answer to the way the knowledge of dysfunctional neural tissue translates into schizophrenic behavior is presently explained as follows. Because the frontal cortex

directs behavior based on perceived elements of the situation compared with memory through a complex network of informational pathways, such as the limbic system, the dysfunction of these abnormal pathways may prevent effective conversion of long-term memory into "working" memory to determine appropriate behavior (Goldman-Rabic, 1996).

DEPRESSION

No one is a stranger to feeling down or depressed, especially if the sadness is associated with loss. However, clinical depression is quite different from feeling down at certain times in your life. It is more debilitating and dangerous, and the overwhelming sadness combines with a number of symptoms. The DSM-IV characterizes depression as the following: an unhappy mood; diminished interests; disturbance in sleep and appetite, loss of energy; difficulty in concentration; feelings of worthlessness; restless agitation; and recurrent thoughts of death or suicidal ideation. It is estimated that 13–20% of the population suffers from depression (Cassens et al., 1990). Nemeroff (1996) estimates that 5 to 12% of men and 10 to 20% of women in the United States will suffer from a major depressive episode at some time in their life. Clinical studies of depression also estimate that individuals who have been depressed in the past will become depressed more than once and that up to 10% of these depressed individuals (about 1.0 to 1.5% of Americans) will experience manic phases in addition to depressive ones, a condition known as manic depressive illness or bipolar disorder (Mann & Kupfer, 1993). Individuals who experience bipolar disorder go from the top of the world to an abyss of despair, or vice versa. From not being able to get out of bed or talk to anyone, they become loquacious. This period of euphoria is known as mania. Mania is marked by a decreased need for sleep, hyperverbal or pressured speech, delusions of grandeur, racing thoughts, hyperactivity, and propensity to engage in potentially self-destructive activities (DSM-IV). Examples of some potentially self-destructive activities are promiscuous sex, spending sprees, or reckless driving. Not everyone is at equal risk of developing depression. It appears that those who are more prone to depression are individuals who may have inherited a vulnerability to this disorder. They are especially sensitive to the effects of environmental stress or lack of social support (Selye, 1978).

Genetic Hypothesis

Researchers have found that depression and manic depression frequently run in families (Cardoret & Winokur, 1975). In fact, research on depression in twins reveals a higher concordance rate for monozygotic twins than dizygotic twins (Moldin et al., 1991). These concordance rates are the same whether the twins are reared apart or together. In the same way, adoption studies show higher rates of affective illness in the biological parents than foster parents. These findings suggest that close blood relatives of individuals who have severe depression or bipolar disorder are much more likely to suffer from those conditions than members of the general population. During the past 20 years, genetic research has begun to focus on specific chromosomes implicated in depression. Much of this research has focused on chromosome 11 (Egeland et al., 1987; Baron et al., 1987). More recently, chromosome 18 and a site on chromosome 21 have been the focus of attention. The chromosomes have been implicated by contributing to a vulnerability to bipolar illness, but these findings await replication (Nemeroff, 1996).

Neurotransmitter Hypotheses

Other researchers are concentrating on neurotransmitters. In 1967, Joseph Schildkraut and Seymour Kety presented the monoamine hypothesis of depression. They postulated that depression is associated with a deficit of the monoamine transmitters norepinephrine and serotonin. The evidence for this hypothesis was supported by empirical findings of drug clinical efficacy of two forms: antidepressant drugs and electroconvulsive shock therapy. Antidepressant drugs inhibit monoamine oxidase, the enzyme that inactivates norepinephrine, dopamine, and serotonin, thereby increasing the availability of monoamines. Further support for the hypothesis came from a study using reserpine, an antihypertensive that depleted norepinephrine and serotonin in the brain. Fifteen percent of patients treated with reserpine developed significant depressive symptoms (Schildkraut, 1965; Bunney & Davis, 1965). It is also postulated that norepinephrine, dopamine, serotonin, and histamine are impacted by electroconvulsive shock treatment (ECT). Electroconvulsive treatment apparently increases postsynaptic responsiveness to norepinephrine, serotonin, and particularly dopamine, possibly by increasing receptor sensitivity (Grahame-Smith, Green, & Costain, 1978). Because feeding and locomotion are thought to be regulated by the dopaminergic systems this effect would explain ECT's effectiveness in patients who exhibit psychomotor retardation and weight loss (Ungerstedt, 1979). Another explanation is based on the observation that repeated convulsions in animals result in decreased synthesis and concentration of Gamma-aminobutryic acid (GABA) in certain regions of the brain. Consequently, ECT may act to switch off the inhibitory effects of GABA function (Green, 1978).

The most recent antidepressants are the serotonin re-uptake inhibitors (SSRIs) such as fluoxetine. There is evidence that decreased serotonin (5-HT) activity can either increase vulnerability to or cause depression (Dalack et al., 1995). Serotonin activity has been associated with numerous processes that are dysregulated in depression, including negative mood, sleep disturbance, shortened rapid eye movement (REM) latency, disturbed circadian rhythms, abnormal neuroendocrine functions, and sexual abnormalities. 5-HT and its major metabolite, 5-hydroxyindoleactic acid (5-HIAA), have been found to be depleted in both the brains of suicide victims and in the cerebrospinal fluid of depressed patients (Mann & Stanley, 1986).

Neuroreceptor Regulation Hypothesis

An alternative hypothesis proposed by Siever and Davis (1985) suggests that depression may be the result of diminished functioning of the neuroreceptor on the postsynaptic neuron, rather than depletion of a neurotransmitter. Here, impaired postsynaptic neurons result in down-regulation of neuronal transmitting activities. This suggests that stress and the release of glucocorticoids reduce brain production of neurotrophic factors, specifically brain-derived neurotropic factor (BDNF). Neurotropic factors have been implicated in the survival and growth of neurons (Ockel et al., 1996). A reduction in BDNF leads to neuronal atrophy at certain sites and therefore depression (Duman, 1998). According to this, drugs that increase stimulation of serotonin and norepinephrine lead to an increase in BDNF release. The BDNF then maintains other brain neurons to alleviate depression. Serotonin-producing neurons project from the raphe nuclei in the brain stem to neurons in diverse regions of the central nervous system, including those that secrete or control the release of norepinephrine. Serotonin-producing cells extend into many brain regions thought to participate in depressive

symptoms—including the amygdala (an area involved in emotions), the hypothalamus (involved in appetite, libido, and sleep), and cortical areas that participate in cognition and other higher processes. Failure of this regulating mechanism that governs transmitting operations results in inappropriate response to external and internal stimuli. Because serotonin is depleted, other neurons are affected and depressive symptoms are thought to occur.

Neuroendocrine Hypothesis

Cortisol Abnormalities

Selye (1978) explored the effects of life stress on psychophysiological functioning. The hypothalamic–pituitary–adrenal (HPA) axis is the system that mediates the generalized stress response. Patients who have major depression have been observed to have hyperactivity of the hypothalamus–pituitary adrenal. Hypercortisolemia has long been recognized as an essential part of abnormal adaptation process to stress and, it has been shown, alters mood, cognition, and behavior (Stokes, 1995). This well-studied neuroendocrine abnormality occurs in 30 to 50% of depressed patients (Rubin, 1989). This finding has been elaborated in many studies of depression that have employed the dexamethasone suppression test (DST). Dexamethasone is a potent synthetic corticoid that ordinarily suppresses a rise in adrenocorticotropic hormone (ACTH). When given, dexamethasone seems to "trick" the hypothalamus into believing that there is a high level of circulating corticol. In nondepressed individuals, dexamethasone clearly suppresses cortisol levels, but in depressed individuals it fails to suppress circulating levels of cortisol, possibly due to the hyperactivity of the hypothalamus. As depression is relieved, dexamethasone again suppresses cortisol.

The following structures in the CNS have been implicated in depression. The basal forebrain has been implicated in behavioral arousal, motivated behavior, attention, learning, and memory. The projections of the basal forebrain complex to the amygdala (involved in emotions) and the hippocampus (involved in short-term memory) are important areas of stimulation and negative feedback of the HPA axis, respectively, and to the cortex, where metabolic changes have been noted in depression (Wainer, Steininger, Roback, Burke-Watson, Mufson, & Kordower, 1993). These structures provide a unifying framework for the hypothesis of dysregulated CNS cholinergic transmission influences the HPA axis in major depression (Dilsaver, 1986).

Thyroid Abnormalities

In recent years, studies have demonstrated that "subclinical" hypo- and hyperthyroid conditions can also produce depression. This can occur in patients whose traditional thyroid function tests are considered normal but who demonstrate increases in production of thyroid stimulating hormone (TSH) or an abnormally blunted TSH response to thyrotropin-releasing hormone (TRH) (Loosen, 1985; Loosen & Prange, 1982). This latter finding is the basis of the TRH test, developed with the hope that it would be a specific diagnostic tool for depression. Like the dexamethasone suppression test, the TRH test has proven to be another nonspecific measure of HPA axis dysregulation. In many cases, thyroid supplementation can enhance the responsiveness of patients to antidepressant drugs (Kalin et al., 1987). However, additional studies are needed to determine whether any components of the hypothalamic–pituitary–thyroid axis are sensitive and reliable markers of depression.

Melatonin Abnormalities

Another area of neuroendocrinology of depression focuses on the pineal gland's production of the hormone melatonin. This hormone is of particular interest, because its synthesis is almost exclusively controlled by noradrenergic neurotransmission, and thus it has become a marker for norepinephrine activity. The pineal gland synthesizes melatonin at night, and this nocturnal synthesis has been found diminished in depressed patients (Brown et al., 1985).

Reproductive Endocrinology

Physicians have long been aware of the association between reproductive functions in women and specific depressive syndromes. These include postpartum depression, premenstrual dysphoric disorder, and menopause-related depression. Endocrinological changes are clearly associated with postpartum and menopausally precipitated depression. Average estrogen, progesterone, prolactin, and β-endorphin (opioid peptides) levels have been known to drop after delivery (Smith et al., 1990). As for premenstrual syndrome (PMS), numerous clinical studies have shown that hormonal and endocrine changes cause associated symptoms. However, studies indicate that different endocrine events may be involved at different levels, so that further research is needed.

Sleep Disturbance Hypothesis

Circadian (daily) rhythms are responsible for the normal regulation of sleep-wake cycles, patterns of arousal, and corresponding patterns of hormonal secretions. However, patterns of arousal are constantly changing because an individuals emotional state, vigilance, and attentional processes are constantly changing (Lang, 1995). Interestingly, there is evidence that there is a subset of depressed patients whose disorder may reflect a dysregulation in their circadian rhythm. There is much evidence that (1) emotional disturbances frequently result in changes in sleep regulation; (2) disrupted or insufficient sleep can cause changes in the control of affect and attention; and (3) the neurobiology underlying the regulation of sleep overlaps to a large extent with neurobehavioral systems involved in regulating arousal, attention, and emotions.

It is evident in both clinical and nonclinical populations that there is a close relationship between emotional level and sleep regulation. Cartwright and Wood (1991) and Hall, Dahl, Dew, and Reynolds (1987) found that most people who report emotional distress-trauma, separation, personal loss, anxiety provoking events, etc. experience at least transient disruptions in sleep. Even positive emotions can interfere with sleep. The early stages of an intense romantic relationship or the anticipation of an exciting trip is also often associated with disrupted sleep. This link between emotional regulation and sleep regulation is even more apparent in clinical disorders. Disturbed sleep is characteristic of affective disorders. A similar relationship can be shown in the opposite direction as well. Inadequate sleep results in alterations in affect, attention, mood deterioration, decreased arousal, difficulties with focused attention, and "tiredness." A third line of evidence to link the regulation of sleep, affect, and attention comes from neurobiology. The neurobehavioral systems involved in regulating sleep overlap with, and are closely linked to, neural systems involved in regulating affect and attention.

EEG sleep changes are among the most common psychobiologic correlates of depression that demonstrate abnormalities in 90% of adult subjects who have major depressive disorder

(Reynolds & Kupfer, 1987). Normally, an individual goes through four stages of sleep (stages 1 and 2 are lighter; stages 3 and 4 are deeper) before entering REM. Patients who have major depression have been found to have a reduction in stages 3 and 4 and an increase in 1 and 2. REM sleep is misplaced and extended in the sleep of depressives. Depressed patients describe having less sleep, more disrupted sleep, and more intense frequent dreaming. The brain regions and pathways critical for wakefulness, slow-wave sleep, REM sleep, and cycling between states involve a complex interplay among multiple cortical and subcortical systems. For example, it has been found that human sleep deprivation impairs the prefrontal cortical functioning which results in less executive control. This translates into decreased goal-directed behaviors and diminished cognitive modulation of drives, impulses, and emotions. There is a complex relationship between the control of sleep and affective disorders.

Understanding the psychophysiological aspects of depression is critically important. Exciting trends and core issues have been discussed regarding the biological factors that may underlie depression. However, it is important to remember that interaction does exist between behavior and biology. Understanding normal and abnormal behavior needs to take into account social, cultural, personal, and historical factors. Biology affects behavior, and the environment and behavior have important effects on biology. The challenge lies in integrating both biological and environmental factors to provide optimal understanding and treatment. It seems prudent to propose that the role of biological influences in mental disorder may be best understood in terms of the vulnerabilities or strengths of an organism that directly interact and influence the environment and behavioral factors. However, what is clear is that by distinguishing the biological markers and understanding the integration of environmental influences, health-care providers can improve methods of diagnosing, treating, and preventing depression.

Anxiety

Anxiety is a normal reaction to many of life's stressors, and none of us is completely free from it. In fact, anxiety is undoubtedly useful in causing us to be more alert and to take important things seriously. However, the anxiousness that we may feel from time to time is different from overwhelming feelings of dread, apprehension, uncertainty, nervousness, impatience, irritability, concentration difficulties, and sleep disturbance (DSM-IV, 1994). Among some of the mental symptoms of anxiety, there are many physical symptoms of anxiety which can include increased blood pressure, difficulties in breathing, faintness, dizziness, chest pain, cramps, nausea, constipation, diarrhea, trembling, chills, sweating, frequent urination, muscle aches, and dry mouth. All of these symptoms can range from mild to severe. In the United States, about 13.1 million people suffer from anxiety disorders (Wilson, 1988). There are 14 categories of anxiety disorders listed in the DSM-IV. Each category has it own unique biological underpinnings; however, for the purposes of this chapter the major biological components of anxiety will be elaborated. Evidence from anatomical and physiological research, which include neural pathways, brain structures, and endocrine functions have been identified as being involved in anxiety disorders.

Autonomic Nervous System

Physiological symptoms are central to the assessment process as seen through the DSM-IV for specific anxiety disorders. A subject who is experiencing anxiety is undergoing many

visceral changes such as changes in the heart rate, blood pressure, stomach contractions, dilations or constriction of blood vessels, skin resistance, or sweating of the palm or soles. The autonomic nervous system (ANS) is concerned with regulating these physiological variables. On account of the strong physiological component of anxiety, the debate over the cognitive and noncognitive aspects of anxiety was started as early as the first third of the twentieth century by William James and Walter Cannon. James (1884) proposed that "reflex currents" initiate visceral reactions and overt muscle activity that are interpreted by the cortex as the experience of emotion (Bindra, 1970). Cannon (1920) responded with the observation that activation of the autonomic nervous system and thus the physiological arousal may lead to feeling as if one is anxious. He demonstrated that cats exposed to barking dogs exhibited behavioral and physiological signs of fear that are associated with adrenal release of epinephrine. Other studies have activated the autonomic nervous system with chemical agents. Several different substances such as yohimbine, isoprenaline, adrenaline, lactate, caffeine, beta-carboline, and CO_2 induce anxiety (Ehlers et al., 1986; Barlow, 1988).

In 1970, John and Beatrice Lacey reported a longitudinal study that monitored individual response patterns by provoking the ANS. Under stress conditions, such as immersing hands in cold water, they found that there is an individual profile of response that starts from infancy. For example, some newborns responded with blood pressure changes, others with heart rate changes, and still others with gastric changes. Later, Jerome Kagan and colleagues investigated newborns' behavioral responses to cues such as alcohol-soaked cotton swabs. He measured the newborns' behavioral responses from not reacting very strongly to reacting strongly. Many of the newborns who reacted strongly in Kagan's study (1997) later were described as shy, and a third of them developed phobias by the time they were old enough to go to school. A literature review by Barlow (1988) concludes that anxious patients are hyperaroused and slow to habituate. Such a slower habituation rate correlates with higher anxiety. Therefore, these studies suggest inborn biological differences.

Genetic Studies

Research does indicate that genetic components contribute to the development of anxiety disorder. In fact, according to Slater and Shields (1969), more than 50% of first-degree relatives suffer from the same disorder. Shields (1962) reported that there is a higher concordance rate with anxiety between monozygotic twins than dizygotic twins.

Brain-Imaging Studies

Structural studies using (CT) and (MRI) have found increases in the size of cerebral ventricles in individuals who suffer from anxiety disorders. Functional brain-imaging studies such as positron emission tomography (PET), single photon emission tomography (SPECTS), and electroencephalography (EEG) of anxiety disorder patients have found abnormalities in the frontal cortex, the occipital and temporal areas, and the parahippocampal gyrus (Swedo et al., 1992; Rubin et al., 1995; Schwartz et al., 1996). Other researchers, such as Breiter et al. (1996), found increased activity of the anterior cingulate cortex, the basal ganglia, and the amygdala. Several regions of the prefrontal cortex showed increased activity in a functional MRI.

Neurotransmitters

The three major neurotransmitters associated with anxiety on the basis of animal studies and responses to drug treatment are norepinephrine, γ-amino butyric acid (GABA), and serotonin.

Norepinephrine

The theory of norepinephrine activity and its role in anxiety disorders is that affected patients may have a poorly regulated noradrenergic system that has occasional bursts of activity. The cell bodies of the noradrenergic system are primarily localized in the locus coeruleus (LC) of the rostral pons, and they project their axons to the cerebral cortex, the limbic system, the brain stem, and the spinal cord. The axon terminals contain inhibitory and excitatory amino acids, monamines, and neuropeptides, many of which exert differential physiological effects on LC activity (Van Bockstaele, 1998). Research studies have shown that stimulation of the locus coeruleus produces a fear response in the animal and that ablation of the same area inhibits or completely blocks the ability of the animals to form a fear response (Redmond, 1979). Clinical drug studies have found that clonidine inhibits locus coeruleus activity (Seiver & Uhde, 1984). Other evidence indicates that inhibitory neurochemicals, which arise from extrinsic sources, include γ-aminobutryic acid (GABA) and epinephrine, as well as the neuropeptides, methionine-5-enkephalin, and leucine-5-enkephaline (Van Bockstaele, 1998).

GABA

The implication of (GABA) neurons is that slowed activity increases anxiety by loss of inhibitory action on anxiety-producing brain sites. γ-Aminobutryic acid type A (GABA(A))-receptor agonist decreases anxiety by facilitating the neuronal influx of chloride. GABA is the most common inhibitory transmitter in the brain and blocks anxiety. Yet, the exact locus of anxiolytic action of GABA in the brain is not clearly delineated (Imamura & Prasad, 1998). Nevertheless, clinical drug studies have found that the GABA receptors of some patients with anxiety disorder function abnormally and their GABA receptors fail to release inhibitory transmitters. Benzodiazepenes have a potentiating effect on the GABA neurotransmitter and facilitate its release at the synapses. The ultimate function of the benzodiazepene–GABA receptor complex is to regulate permeability of neural membranes to chloride ions. The neuron is inhibited from firing by chloride ions moving into the nerve cell (Marx, 1985).

Serotonin

Due to the therapeutic effects of serotonergic antidepressants such as buspirone and clomipramine in alleviating symptoms of anxiety, serotonin has received attention in the pathogenesis of anxiety. Most of the serotonergic neuron-cell bodies are located in the raphe nuclei in the rostral brain stem and project to the cerebral cortex, the limbic system, particularly the amygdala and the hippocampus, and the hypothalamus. Clinical studies show that blocking the re-uptake of serotonin improves symptoms of anxiety (Owens & Nemeroff, 1994).

Hypothalamic–Pituitary–Adrenocortical System

The hypothalamic–pituitary–adrenocortical (HPA) system controls a variety of neurohormones that may be implicated in anxiety. Specific hormonal products of HPA such as cortisol, prolactin, and thyroid-stimulating growth hormone increase under stressful conditions (Curtis, Nesse, Buxto, & Lippman, 1979).

By investigating anatomical hypotheses and synaptic communication hypotheses, we achieve a better understanding of the biological components of anxiety. We now know that

there is a strong genetic factor involved in developing anxiety. However, integrating environmental influences with biological markers will be the key to understanding anxiety fully.

Alzheimer's Disease

The loss of cognitive ability from aging, not from injury, has been of interest for some time. One particular type of loss was identified by Alois Alzheimer in publications in 1906, 1907, and 1911 (see Forstl & Levy, 1991). This disorder is now known by his name: Alzheimer's disease (AD). He was the first to identify the neural changes of plaques and neurofibrillary tangles which are the major markers of this disorder. This disorder is found worldwide, and the frequency of occurrence increases exponentially with age (Rocca et al., 1991). The other major markers of this disorder are cerebral atrophy, enlarged sulci and narrow convolutions, reduced white matter, and ventricular enlargement. There is also evidence of reduced subcortical tissue in areas such as the hippocampus. One study by Saeb et al. (1988) found an average reduction of 40% in hippocampal volume compared to nondemented controls. In another study, Golomb (1994) reported evidence from a study of normals 55 to 87 years of age and found that reduction in the size of the hippocampus was more closely correlated with memory loss than was generalized shrinkage of the brain. These two studies emphasize the role of the hippocampus in memory loss of both normals and ADs.

Neurological Features

Neuritic plaques (Sps) are the prominent feature of AD. These plaques consist of an amyloid core surrounded by argyrophilic axonal and dendritic processes (Morris, 1996). The amyloid fibers are composed of residues of amyloid beta-protein. Amyloid is a generic description of a class of tissue protein. This tissue may be deposited throughout the body or may be confined to a particular organ. The amyloid associated with AD is deposited around meningeal and cerebral vessels and in gray matter. However, because it has been determined that amyloid beta-protein is found in several species and in body fluids, the exact role it plays in AD is unclear (Haass et al., 1992; Thinakaran et al., 1998).

Sps are present in various numbers in elderly nondemented individuals, but they are more uniformly distributed in demented patients (Mirra et al., 1991). Although widely distributed in the brain, greater concentrations are often observed in the cerebral cortex, hippocampus, and subcortical areas primarily in those that are part of the limbic system. However, recent studies have shown little or no correlation between the concentration of Sps and cognitive decline (Dickson et al., 1992). What has been correlated with cognitive decline is the neurofibrillary tangles (NFT). NFTs are abnormal helically wound filaments of a microtubule associated with glycoprotein (Goedert et al., 1988). Increased density of NFTs in the cortex and some subcortical areas, again primarily those in the limbic system, has been associated with cognitive and memory decline (Arriagada et al., 1992; Bierer et al., 1995).

Genetics

The two most prominent risk factors for Alzheimer are age and a family history of the disorder (Bird, Lampe, Wijsman, & Schellenberg, 1998). Early linkage between Down's syndrome and AD has implicated chromosome 21 (St. George-Hyslop et al., 1987; St. George-Hyslop, 1993). However, some cases of AD have also linked AD with abnormalities of

chromosome 19. Chromosome 19 has been implicated with the age of onset of AD (Roses, 1994). Lampe, Bird, Nochlin et al. (1994) presented strong, detailed evidence of pathological findings on chromosome 14 and AD. Other chromosomes have also been associated with the onset of AD (Levy-Lahad et al., 1995). Although research on AD and chromosomal abnormalities is still in its infancy, a growing body of evidence points toward a strong linkage between chromosomal abnormalities and the onset of AD.

SUMMARY

The conclusion which may be drawn from the research indicates that certain specific pathologies have underlying biological mechanisms associated with them. What seems to be the most parsimonious explanation is that genetics provides a general template for neural development which is modified by the experiences of the individual. We inherit propensities which place limits on behavior, yet the constraints may be altered by impoverished or enriched environments or by intense or sustained interventions. Recent information about neural development indicates that only approximately half of the neurons produced during embryonic development will survive the development of the nervous system (Oppenheim, 1991). These findings combined with evidence from animal studies indicate that the major determinant as to which nerve cells die and which survive depends on which neurons are activated by experiences. The cells that are activated by experience survive and form connections with other neurons, and those that are not activated die. This provides powerful support for the role early experiences have on neural development and subsequent behavior.

There is also a growing body of evidence that chemical states of neural tissue underlie some pathological behavior. However, what is not clear is the cause and effect relationship between behavior and neural activity. For instance, although unusual dopamine levels are related to schizophrenia, the reason that specific levels are present in certain neural sites is not clear. Whether these unusual levels are a result of atypical experiences combined with genetic propensities or just result from genetic influences alone is unknown. So the reason that these levels are unusual in one or more neural site and not others is still a mystery. Another puzzle is why atypical levels of some neurotransmitters such as dopamine are associated with different disorders such as schizophrenia and depression.

By necessity, research on the biological basis of behavior is reductionistic. This approach is used when research that focuses on specific factors such as the nature of genetic determinants of behavior must look at specific disorders and specific biological factors to observe whether there is a relationship between well-defined aspects of the study. This type of research discovers the absence or presence of relationships in most instances, but it does not rule out the likelihood of other influences upon the relationship. These influences may be dietary, early learning experiences, cultural factors, and trauma, to mention just a few. Therefore, although research has clearly demonstrated that relationships exist among such factors as chromosomal abnormalities, neural tissue disorganization, gross anatomical brain changes, synaptic changes, and pathological behavior, there is no research on humans that unequivocally demonstrates a cause and effect relationship between biological factors and behavior. This does not mean they do not exist, just that it has yet to be demonstrated with present day techniques and technologies. The type of interventions needed to demonstrate such relationships are unethical because they would require manipulations that would change the course of the individual's life experiences. Perhaps with further advancement of techniques such as imaging with devices such as functional MRI, interventions which would provide cause and

effect relationships could be conducted on humans with acceptable risks and outcomes. An example of this could be providing the individual with intense sensory stimuli while observing neural changes in particular areas of the nervous system.

In summary, this is an exciting time for individuals interested in the biological basis of behavior because new information is increasing rapidly. Through new assay techniques of tissue chemistry and new imaging techniques of neural and chromosomal tissue, new discoveries are being reported. There is great promise for better understanding of the biology of behavior which is likely to help direct early optimum experiences and specific interventions at multiple levels to facilitate the individual's development.

REFERENCES

Akbarian, S., Kim, J. J., Potkin, S. G., Hagman, J. O., Tafazzoli, A., Bunney, W. E., Jr., & Jones, E. G. (1995). Gene expression for glutamic acid decarboxylase is reduced without loss of neurons in prefrontal cortex of schizophrenics. *Archives of General Psychiatry, 52*, 267–278.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders*, 4th ed. Washington, DC: Author.

Andreasen, N. C., Rezai, K., Alliger, R., Swayze, V. W., II, Flaum, M., Kirchner, P., Cohen, G., & O'Leary, D. S. (1992). Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. Assessment with xenon 133 single-photon emission computed tomography and the Tower of London. *Archives of General Psychiatry, 49*, 943–958.

Andreason, N. C. (1994). Changing concepts of schizophrenia and the ahistorical fallacy. *American Journal of Psychiatry, 151*, 1405–1407.

Arriagada, P. V., Growdon, J. H., Hedley-Whyte, T., and Human, B. T. (1992). Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology, 42*, 631–639.

Barlow, D. H. (1988). *Anxiety and its disorders: The nature and treatment of anxiety and panic*. New York: Guilford.

Baron, M., Risch, N., Hamburger, R., Mandel, B., Kushner, S., Newman, M., Drumer, D., Belmaker, R. H. (1987). Genetic linkage between X-chromosome markers and bipolar affective illness. *Nature, 326*, 289–292.

Benes, F. M. (1993). The relationship between structural brain imaging and histopathologic findings in schizophrenia research. *Harvard Review of Psychiatry, 1*, 100–109.

Berman, K. F., & Weinberger, D. R. (1990). The prefrontal cortex in schizophrenia and other neuropsychiatric diseases: *In vivo* physiological correlates of cognitive deficits. *Progress in Brain Research, 85*, 521–536.

Bierer, L. M., Hof, P. R., Purohi, D. P., Carlin, L., Schmeider, J., Davis, K. L., Perl, D. P. (1995). Neocortical neurofibrillary tangle correlate with dementia severity in Alzheimer's disease. *Archives of Neurology, 52*, 81–88.

Bindra, D. A. (1970). Emotion and behavior theory: Current research in historical perspective. In P. Black (Ed.), *Physiological correlates of emotion* (pp. 3–20). New York: Academic.

Bird, T. D., Lampe, T. H., Wijsman, E. M., & Schellenberg, G. D. (1998). Familial Alzheimer's disease: genetic studies. In M. F. Folstein (Ed.), *Neurobiology of primary dementia*. Washington, DC: American Psychiatric Press.

Breier, A., Su, T. P., Saunders, R., Carson, R. E., Kolachana, B. S., DeBartolomeis, A., Weinberger, D. R., Weisenfeld, N., Malhotra, A. K., Eckelman, W. C., & Pickar, D. (1997). Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: Evidence from a novel positron emission method. *Proceedings of the National Academy of Sciences USA, 94*, 2569–2574.

Breiter, H. C., Rauch, S. L., Kwong, K. K., Baker, J. R., Weisskoff, R. M., Kennedy, D. N., Kendrick, A. D., Davis, T. L., Jiang, A. P., Cohen, M. S., Stern, C. E., Belliveau, J. W., Baer, L., O'Sullivan, R. L., Savage, C. R., Jenike, M. A., & Rosen, B. R. (1996). Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. *Archives of General Psychiatry, 53*, 595–606.

Brown, R. P., Kocsis, J. H., & Frazer A. (1985). Serum melatonin in affective disorders. *American Journal of Psychiatry, 142*, 811–816.

Bunney, W. E., Jr., & Davis, J. M. (1965). Norepinephrine in depressive reactions: A review. *Archives of General Psychiatry, 13*, 483–494.

Cannon, W. B. (1920). *Bodily changes in pain, fear, and rage*. New York: Appleton.

Cardoret, R. J., & Winokur, G. (1975). X-linkage in manic-depressive illness. *Annual Review of Medicine, 26*, 21–25.

Cartwright, R. D., & Wood, E. (1991). Adjustment disorders of sleep: The sleep effects of a major stressful event and its resolution. *Psychiatry Research, 39*, 199–209.

Cassens, G., Wolfe, L., & Zola, M. (1990). The neuropsychology of depression. *Journal of Neuropsychiatry and Clinical Neurosciences, 2*, 202–213.

Cichon, S., Noethen, N. M., Catalano, M., Di Bella, D., et al. (1995). Identification of two novel polymorphisms and a rare deletion variant in the human dopamine D4 receptor gene. *Psychiatric Genetics, 5*(3), 97–103.

Conrad, A. J., Abebe, T., Austin, R., Forsythe, S., & Scheibel, A. B. (1991). Hippocampal pyramidal cell disarray in schizophrenia as a bilateral phenomenon. *Archives of General Psychiatry, 48*, 413–417.

Crow, T. J. (1991). The search of the psychosis gene. *British Journal of Psychiatry, 158*, 611–614.

Crow, T. J., Delisi, L. E., Lofthouse, R., Poulter, M., Lehner, T., Bass, N., Shah, T., Walsh, C., Boccio-Smith, A., & Shields, G. (1994). An examination of linkage of schizophrenia and schizoaffective disorder to the pseudoautosomal region (Xp22.3). *British Journal of Psychiatry, 164*, 159–164.

Curtis, G. C., Nesse, R., Buxton, M., & Lippman, D. (1979). Plasma growth hormone: Effect of anxiety during flooding in vivo. *American Journal of Psychiatry, 136*(4-A), 410–414.

Curtis, G. C., Nesse, R. M., Buxton, M., & Lippman, D. (1979). Plasma growth hormone: Effect of anxiety during flooding in vivo. *American Journal of Psychiatry, 136*, 410–414.

Dalack, G. W., Glassman, A. H., Rivelli S., Covey, L., & Stetner, F. (1995). Mood, major depression, and fluoxetine response in cigarette smokers. *American Journal of Psychiatry, 152*(3), 398–403.

Davis, K. L., Kahn, R. S., Ko, G., & Davidson, M. (1991). Dopamine in schizophrenia: A review and reconceptualization. *American Journal of Psychiatry, 148*, 1474–1486.

Dickson, D. W., Crystal, H. A., Mattiace, L. A., Masur, D. M., Blau, A. D, Davies, P., Yen, S. H., & Arson, M. K. (1992). Identification of normal and pathological aging in prospectively studied nondemented elderly humans. *Neurobiology of Aging, 13*, 179–189.

Dilsaver, S. C. (1986). Cholinergic mechanisms in depression. *Brain Research Reviews, 11*(3), 285–316.

Duman, R. S. (1998). Novel therapeutic approaches beyond the serotonin receptor. *Biological Psychiatry, 44*(5), 324–335.

Egeland, J. A., Gerhard, D. S., Pauls, D. L., Sussex, J. N., et. al. (1987). Bipolar affective disorder linked to DNA markers on chromosome 11. *Nature, 325*(6107), 783–787.

Ehlers, A., Margraf, J., Roth, W. T., Taylor, C. B., Maddock, R. J., Sheik, J., Kobell, M. L., McClenahan, K. L., Gossard, D., Blowers, G. H., Agras, W. S., & Kopell, B. S. (1986). Lactate infusions and panic attacks: Do patients and controls respond differently? *Psychiatry Research, 17*, 295–308.

Forstl, H., & Levy, R. (1991). Foreword to the translation of "On certain peculiar diseases of old age" (by Alois Alzheimer). *History of Psychiatry, ii*, 71–74.

Goedert, M., Wischik, C. M., Crowther, R. A., Walker, J. E., & Klug, A. (1988). Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer's disease: Identification as the microtubule-associated protein tau. *Proceedings of the National Academy of Sciences USA, 85*, 4051–4055.

Goldman-Rakic, P. S. (1996). Dissolution of cerebral cortical mechanisms in subjects with schizophrenia. In S. J. Watson (Ed.), *Biology of schizophrenia and affective disease* (pp. 113–128). Washington, DC: American Psychiatric Press.

Golomb, J., deLeon, M. J., George, A. E., Kluger, A., Convit, A., Rusinek, H., deSanti, S., Litt, A., Foo, S. H., & Ferris, S. H. (1994). Hippocampal atrophy correlates with severe cognitive impairment in elderly patients with suspected normal pressure hydrocephalus. *Journal of Neurology, Neurosurgery and Psychiatry, 57*, 590–593.

Gooding, D., & Iacono, W. (1995). Schizophrenia through the lens of a developmental psychopathology perspective. In *Developmental psychopathology*, Vol. 2: *Risk, disorder, and adaptation*. Wiley Series on Personality Processes (pp. 535–580). New York: Wiley.

Gottesman, I. L. (1995). *Schizophrenia genes: The origins of madness*. New York: Freeman.

Grahme-Smith, D. G., Green, A. R., & Costain, D. W. (1978). Mechanism of the anti-depressant action of electroconvulsive therapy. *Lancet, 1*, 254–256.

Green, A. R. (1978). ECT—How does it work? *Trends in Neuroscience, 1*, 53–54.

Haass, C., Schlossmacher, M. G., Hung, A. Y., Vigo-Pelfrey, C., Mellon, A., Ostaszewski, B. L., Lieberburg, I., Koo, E. H., Schenk, D., Teplow, D. B., & Selkoe, D. (1992). Amyloid beta peptide is produced by cultured cells during abnormal metabolism. *Nature, 359*, 322–325.

Hall, M. H., Dahl, R. E., Dew, M. A., & Reynolds, C. F. (1995). Sleep patterns following major negative life events. *Directions in Psychiatry, 15*, 1–10.

Hyde, T. M., & Weinberger, D. R. (1990). The brain in schizophrenia. *Seminars in Neurology, 10*, 276–286.

Imamura, M., & Prasad, C. (1998). Increased GABA-gated chloride ion influx in the hypothalamus of low anxiety rats. *Physiological Behavior, 64*(3), 415–417.

Jablensky, A., Sartorius, N., Ernberg, G., Anker, M., Korten, A., Cooper, J. E., Day, R., & Bertelsen, A. (1992). Schizophrenia: Manifestations, incidence, and course in different cultures. *Psychological Medicine, Monograph Supplement, 20.*

James, W. (1884). What is emotion? *Mind, 9*(Series I), 188–204.

Kagan, J. (1997). Temperament and the reactions to unfamiliarity. *Child Development, 68*, 139–143.

Kalin, N. H., Dawson, G., Traiot, P., Shelton, S., Barksdale, C., Weiler, S., & Thienemann, M. (1987). Function of the adrenal cortex in patients with major depression. *Psychiatry Research, 22*, 117–125.

Kemali, D., Galderisi, M. S., Ariano, M. G., Cesarelli, M., Milici, N., Salvati, A., Valente, A., & Volpe, M. (1985). Clinical and neuropsychological correlates of cerebral ventricular enlargement in schizophrenia. *Journal of Psychiatric Research, 19*, 587–596.

Kety, S. S. (1983). Mental illness in the biological and adoptive families of schizophrenic adoptees: Findings relevant to genetic and environmental factors in etiology. *American Journal of Psychiatry, 140*, 720–727.

Kety, S. S., Wender, P. H., Jacobsen, B., Ingraham, L. J., Jansson, L., Faber, B., & Kinney, D. K. (1994). Mental illness in the biological and adoptive relatives of schizophrenic adoptees. Replication of the Copenhagen study in the rest of Denmark. *Archives of General Psychiatry, 51*, 442–455.

Kovelman, J. A., & Scheibel, A. B. (1984). A neurohistological correlate of schizophrenia. *Biological Psychiatry, 19*, 1601.

Lacey, J. I., & Lacey, B. C. (1970). Some autonomic-central nervous system interrelationships. In P. Black (Ed.), *Physiological correlates of emotion*. New York: Academic.

Lampe, T. H., Bird, T. D., Nochlin, D., Nemens, E., Risse, S. C., Sumi, S. M., Koerker, R., Leaird, B., Wier, M., & Raskind, M. A. (1994). Phenotype of chromosome 14-linked familial Alzheimer's disease in a large kindred. *Annals of Neurology, 36*, 368–378.

Lang, P. J. (1995). The emotion probe: Studies of motivation and attention. *American Psychologist, 50*(5), 372–385.

Levy-Lahad, E., Wijsman, E. M., Nemens, E., Anderson, L., Goddard, K. A., Weber, J. L., Bird, T. D., & Schellenberg, G. D. (1995). A familial Alzheimer's disease locus on chromosome 1. *Science, 269*, 970–973.

Loosen, P. T. (1985). The TRH-induced TSH response in psychiatric patients: A possible neuroendocrine marker. *Psychoneuroendocrinology, 10*, 237–260.

Loosen, P. T., & Prange A. J., Jr. (1982). Serum thyrotropin response to thyrotropin-releasing hormone in psychiatric patients: A review. *American Journal of Psychiatry, 139*, 405–416.

Machon, R. A., Mednick, S. A., & Huttunen, M. O. (1997). Adult major affective disorder after prenatal exposure to an influenza epidemic. *Archives of General Psychiatry, 54*, 322–328.

Mann, J. J., & Stanley, M. (Eds.). (1986). Psychobiology of suicidal behavior. *Annals of the New York Academy of Science, 487*, 1–357.

Mann, J. J., & Kupfer, D. J. (Eds.). (1993). Biology of depressive disorders, Part A: A systems perspective. In *The depressive illness* (p. 272). New York: Plenum.

Marx, J. L. (1985). "Anxiety peptide" found in brain. *Science, 227*, 934.

Mednick, S. A., Huttunen, M. O., & Machon, R. A. (1994). Prenatal influenza infections and adult schizophrenia. *Schizophrenia Bulletin, 20*, 263–267.

Mirra, S. S., Heyman, A., McKeel, D., Sumi, S. M., Crain, B. J., Brownlee, L. M., Vogel, F. S., Hughes, J. P., vanBelle, G., & Berg, L. (1991). The consortium to establish a registry for Alzheimer's disease. *Neurology, 41*, 479–486.

Moldin, S. O., Reich, T., & Rice, J. P. (1991). Current perspectives on the genetics of unipolar depression. *Behavior Genetics, 21*, 211–242.

Morris, R. G. (1996). *The cognitive neuropsychology of Alzheimer-type dementia*. Oxford, England: Oxford University Press.

Nemeroff, C. B. (1996). The corticotropin-releasing factor (CRF) hypothesis of depression: New findings and new directions. *Molecular Psychiatry, 1*(4), 336–342.

Ockel, M., Lewin, G. R., & Barde, Y.A. (1996). In vivo effects of neurotrophin-3 during sensory neurogenesis. *Development, 122*(1), 301–307.

Oppenheim, R. W. (1991). Cell death during development of the nervous system. *Annual Review of Neuroscience, 14*, 453–501.

Owens, M. J., & Nemeroff, C. B. (1994). The role of serotonin in the pathophysiology of depression: Focus on the serotonin transporter. *Clinical Chemistry, 40*, 288–295.

Redmond, D. E. (1979). New and old evidence for the involvement of a brain norepinephrine system in anxiety. In W. E. Fann, I. Karacan, & A. Pokorny (Eds.), *Phenomenology and the treatment of anxiety* (pp. 152–203). New York: SP Medical and Scientific Books.

Reynolds, C. F., & Kupfer, D. J. (1987). Sleep research in affective illness: State of the art circa. *Sleep, 10*(3), 199–215.

Rocca, W. A., Hofman, A., Brayne, C., Breteler, M. M., Clarke, M., Copeland, J. R., Dartigues, J. F., Engedal, K.,

Hagnell, O., Heeren, T. J., et al. (1991). The prevalence of vascular dementia in Europe: Facts and fragments from 1980–1990 studies. *Annals of Neurology, 30*, 817–824.

Rosenzweig, M. R., Leiman, A. L., & Breedlove, S. M. (1999). *Biological psychology: An introduction to behavioral, cognitive, and clinical neuroscience*. Sunderland, MA: Sinaur Associates.

Roses, A. D. (1994). Apolipoprotein E affects the rate of Alzheimer disease expression: J-Amyloid burden is a secondary consequence dependent on APOE genotype and duration of disease. *Journal of Neuropathology and Experimental Neurology, 53*, 429–437.

Rubin, R. T. (1989). Pharmacoendocrinology of major depression. *European Archives of Psychiatry and Neurological Sciences, 238*(5–6), 259–267.

Rubin, R. T., Ananth, J., Villanueva-Meyer, J., Trajmar, P. G., & Mena, I. (1995). Regional 133 Xenon cerebral blood flow and cerebral 99m Tc-HM-PAO uptake in patients with obsessive–compulsive disorder before and during treatment. *Biological Psychiatry, 38*, 429–437.

Rubin, R. T., Poland, R. E., Lesser, I. M., & Martin, D. J. (1989). Neuroendocrine aspects of primary endogenous depression: V. Serum prolactin measures in patients and matched control subjects. *Biological Psychiatry, 25*(1), 4–21.

Saeb, J. P., Jagust, W. J., Wong, S. T. S., et al. (1988). Quantitative NMR measurements of hippocampal atrophy in Alzheimer's disease. *Magnetic Resonance Imaging, 8*, 200–208.

Schildkraut, J. J. (1965). The catecholamine hypothesis of affective disorders: A review of supporting evidence. *American Journal of Psychiatry, 139*, 471–475.

Schildkraut, J. J., & Kety, S. S. (1967). Biogenic amines and emotion. *Science, 156*, 21–30.

Schwartz, M. W., Peskind, E., Raskind, M., Boyoko, E. J., & Porte, D. (1996). Cerebrospinal fluid leptin levels: Relationship to plasma levels and to adiposity in humans. *Nature Medicine, 2*, 589–593.

Seeman, P., Guan, H. C., & Van Tol, H. H. (1993). Dopamine D4 receptors elevated in schizophrenia. *Nature, 365*, 441–445.

Selye, H. (1978). *The stress of life*. New York: McGraw-Hill.

Siever, L. J., & Uhde, T. W. (1984). New studies and perspectives on the noradrenergic receptor system in depression: Effects of the alpha-2 adrenergic agonist clonidine. *Biological Psychiatry, 142*, 184–187.

Shields, J. (1962). *Monozygotic twins brought up apart and brought up together*. London: Oxford University Press.

Siever, L. J., & Davis, K. L. (1985). Overview: Toward a dysregulation hypothesis of depression. *American Journal of Psychiatry, 142*(9), 1017–1031.

Slater, B., & Shields, J. (1969). Genetical aspects of anxiety. In *British Journal of Psychiatry Special Publication No. 3: Studies of Anxiety*. Ashford, Kent: Headly Bros.

Slater, E., & Roth, M. (1960). *Clinical Psychiatry*, 1st ed. London: Bailliere, Tindall, and Cassel.

Smith, R., Cubis J., Brinsmead, M., Lewin, T., Singh, B., Ownes, P., Chan, E. C., Hall, C., Adler, R., Lovelock, M., Hurt, D., Rowley, M., & Nolan, M. (1990). Mood changes, obstetric experiences and alterations in plasma cortisol, beta-endorphin and corticotrophin releasing hormone during pregnancy and the puerperium. *Journal of Psychosomatic Research, 34*(1), 53–69.

St. George-Hyslop, P. H. (1993). Recent advances in the molecular genetics of Alzheimer's disease. *Neuroscience, 1*, 171–175.

St. George-Hyslop, P. H., Tanzi, R. E., Polinsky, R. J., Haines, J. L., Nee, L., Watkins, P. C., Meyers, R. H., Feldman, R. G., Pollen, D., Drachman, D., Growdon, J., Bruni, A., Jean-Francois, F., Salmon, D., Frommelt, P., Amaducci, L., Sorbi, S., Piacentini, S., Stewart, G. D., Hobbs, W. J., Conneally, M., & Gusella, J. F. (1987). The genetic defect causing familial Alzheimer's disease maps on chromosome 21. *Science, 235*, 885–890.

Stokes, P. E. (1995). The potential role of excessive cortisol induced by HPA hyperfunction in the pathogenesis of depression. *European Neuropsychopharmacology, 5*(Suppl.), 77–82.

Swedo, S. E., Leonard, H. L., Kraesi, M. J. P., Rettew, D. C., Listwak, S. J., Berrettini, W., Stipetic, M., Hamburger, S., Gold, P. W., Potter, W. Z., & Rapoport, J. L. (1992). CSF neurochemistry in children and adolescents with obsessive–compulsive disorder. *Archives of General Psychiatry, 49*, 29–36.

Thinakaran, G., Regard, J. B., Bouton, C. M., Harris, C. L., Price, D. L., Borchelt, D. R., & Sisodia, S. S. (1998). Stable association of presenilin derivatives and absence of presenilin interactions with APP. *Neurobiology of Disease, 4*, 438–453.

Torrey, E. F., Bowler, A. E., Taylor, E. H., & Gottesman, I. I. (1994). *Schizophrenia and manic depressive disorder*. New York: Basic Books.

Trimble, M. R. (1996). Schizophrenia. In *Biological psychiatry* (pp. 183–225). New York: Wiley.

Tsuang, M. T. (1993). Genotypes, phenotypes, and the brain. *British Journal of Psychiatry, 163*, 299–307.

Ungerstedt, U. (1979). Central dopamine mechanisms and unconditioned behaviour. In A. S. Horn, J. Korf, & B. H. C. Westerink (Eds.), *The neurobiology of dopamine* (pp. 577–596). New York: Academic.

Van Bockstaele, E. J. (1998). Morphological substrates underlying opoiod, epinephrine and gamma-aminobutyric acid inhibitory actions in rat locus coeruleus. *Brain Research Bulletin, 47*, 1–15.

Wainer, B. H., Steininger, T. L., Roback, J. D., Burke-Watson, M. A., Mufson, E. J., & Kordower, J. (1993). Ascending cholinergic pathways: Functional organization and implications for disease models. *Progress in Brain Research, 98*, 9–30.

Watson, S. J. (1996). *Biology of schizophrenia and affective disease*. Washington, D.C.: American Psychiatric Press.

Weinberger, D. R., Aloia, M. S., Goldberg, T. E., & Berman, K. F. (1994). The frontal lobes and schizophrenia. *Journal of Neuropsychiatry and Clinical Neurosciences, 6*, 419–427.

Wible, C. C., Shenton, M. E., Hokama, H., Kikinis, R., Jolesz, F. A., Metcalf, D., & McCarley, R. W. (1995). Prefrontal cortex and schizophrenia. A quantitative magnetic resonance imaging study. *Archives of General Psychiatry, 52*, 279–288.

Wilson, J. (1988). Anxiety disorders: Current treatments and controversies. Paper presented at *Annual Convention of the American Psychological Association*, Atlanta, GA, August, 1988.