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Review Article

Hormones and Cognition: Current Concepts and Issues in Neuropsychology

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This article provides an extensive and comprehensive review of the effects of hormones on cognition. Studies detailing specific neurocognitive functions affected by variation in hormone levels across the life span are presented. Dysregulation of hormone levels is considered from models of both normal and diseased functioning. Patterns of cognitive dysfunction are described for a range of syndromes involving the neuroendocrine system, and evidence of specific neurophysiological mechanisms that can account for these findings is outlined. This review includes discussion of treatment outcomes and the permanency of endocrine-related cognitive dysfunction. The authors present a set of guidelines for clinical neuropsychologists to use for assessment of patients with neuroendocrine system dysfunction. Clinical and methodological issues in research and treatment settings are discussed.

KEY WORDS: Neuropsychology; neuroendocrinology; hormones; cognition; review article.

INTRODUCTION

Human behavior is governed by two interdependent systems: the nervous system and the endocrine system. Clinical neuropsychology and neuropsychological research have been concerned primarily with the former. Nevertheless, neuropsychologists frequently encounter patients with endocrine system dysfunction in conditions ranging from diabetes to Graves' disease. In pediatric, adolescent, and adult patients, research has consistently shown profound effects of hormonal dysregulation on behavior, affect, and cognition. These effects may be due to severe syndromes or even to subclinical endocrine dysfunction. Researchers and clinicians are increasingly studying hormones for their potential in diagnosing and treating cognitive problems associated with a variety of conditions that affect the central nervous system. This review of research is intended to update neuropsychologists in clinical and research settings on the neuropsychology of endocrine functions.

The review is organized as follows: First, the endocrine system functions are briefly delineated. Second, the neuroanatomical features and neurophysiological actions of the principal components of the neuroendocrine system are summarized. Third, neuroendocrine syndromes marked by dysfunction of multiple hormone systems are noted, and principal pathological processes are described. Fourth, the literature demonstrating the discrete effects of hormones on cognition is reviewed. Attention is paid to neuropsychological and neurocognitive features, mechanisms of action, and assessment methods. The review concludes with a set of guidelines for assessment of patients with neuroendocrine dysfunction in clinical and research settings and a rationale for providing interventions, including cognitive remediation.

FUNDAMENTALS OF ENDOCRINE FUNCTION

The endocrine system produces its effects on bodily and mental functions by means of various hormones. A *hormone* is a chemical substance that is secreted by a specific endocrine gland and exerts physiological control on other cells. Unlike neurotransmitters, which act locally, hormones may act on cells located at a distance. In this way, hormones perform a range of functions, such as maintaining metabolism, regulating the rates of chemical

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Table I. Principal Endocrine Glands and Hormones

Anterior pituitary gland
Growth hormone causes growth of most bodily tissues and cells.
Prolactin promotes breast development and milk secretion.
Follicle-stimulating hormone is involved in reproductive and gonadal functioning.
Luteinizing hormone causes ovulation in females and stimulates the gonads in both sexes.
Adrenocorticotropin stimulates the adrenal cortex to secrete adrenocortical hormones.
Thyroid-stimulating hormone causes the release of thyroid hormones by the thyroid gland.
Posterior pituitary gland
Vasopressin causes the kidneys to retain water and regulates blood vessels.
Oxytocin facilitates childbirth and lactation.
Thyroid gland
Thyroxine and triiodothyronine regulate the chemical processes in cells.
Calcitonin causes the deposit of calcium in bones.
Adrenal cortex
Cortisol contributes to the control of proteins, carbohydrates, and fats.
Aldosterone regulates sodium and potassium levels.
Pancreas
Insulin promotes the storage of glucose into cells.
Glucagon promotes the release of glucose into the bloodstream.
Testes
Testosterone causes growth of male sex organs and secondary sex characteristics.
Ovaries
Estrogen causes growth of female sex organs and secondary sex characteristics.
Progesterone nurtures the developing fetus and causes development of milk apparatus.
Pineal gland
Melatonin regulates circadian rhythms and aspects of sexual behavior.
Parathyroid gland
Parathormone controls calcium ion concentrations in extracellular fluid.

reactions in cells, and promoting growth. Through their actions on the central nervous system, hormones influence affect, sexual and social behavior, and cognition. Certain hormones can affect virtually all cells in the body, whereas others have specific receptors on various organs, including the brain. Metabolic control of hormone levels is maintained by feedback loops of associated hormones; these loops are referred to as *axes*. For example, the hypothalamic–pituitary–thyroid axis, or *HPT axis*, comprises TRH (a hypothalamic releasing hormone), TSH (a pituitary trophic hormone), and T_3 and T_4 (thyroid hormones), which provide feedback to the hypothalamus and thus regulate stable thyroid hormone levels.

Hormones are secreted at different rates (a) according to metabolic needs, (b) according to periodic cycles ranging from daily to monthly to seasonally, and (c) in response to intrapsychic and environmental stimuli. In addition, levels of certain hormones vary widely during key growth phases across the life span: in the fetal and perinatal environments, during adolescence, and as a natural consequence of aging.

The body creates more than 50 basic hormones. However, the essential elements of the endocrine system can be summarized as including the major endocrine glands and their respective principal hormones as outlined in Table I.

As noted, individual hormones may perform a number of roles and have a multiplicity of receptors. Not all the hormones included in Table I exert direct or even secondary effects on cognitive processes. As is the case with any chemical substance, a given hormone's effects on behavior are due not only to the identity, dose, and duration of the hormone, but also to the brain substrate upon which it acts. In this way, cognition may be affected as a result of (a) abnormal amounts of hormones acting on a normal brain (e.g., Cushing's syndrome), (b) normal amounts of hormones acting on an abnormal brain substrate (e.g., premenstrual syndrome), or (c) abnormal amounts of hormones acting on an abnormal brain (e.g., congenital adrenal hyperplasia). Following is a review of the literature pertinent to the hormones known to influence cognition.

THE NEUROENDOCRINE SYSTEM: BASIC NEUROANATOMY AND NEUROPHYSIOLOGY

The Hypothalamus and Its Connections

The hypothalamus is well known to neuropsychologists as the principal autonomic center of the brain, acting

on the sympathetic and parasympathetic nervous systems to maintain homeostasis and to prepare the body to deal with emergencies. No less important is the role of the hypothalamus as a component of the limbic system; in this role, it mediates drives for hunger and thirst, sexual activity, and aggression. In addition, the hypothalamus directly regulates the majority of endocrine functions, largely by means of its regulatory effect on the pituitary gland. Behaviorally, all these components may act in concert. For example, an aggressive response will raise a person's heart rate, induce anger, increase glucose concentrations, and elevate serum cortisol levels.

The hypothalamus has been referred to as the *head ganglion of the internal milieu.* It is composed of a single grouping of small nuclei, weighing approximately 4 g and lying ventral to the thalamic nuclei. The inferior surface is exposed to the subarachnoid space and is bounded by the optic chiasm, the optic tracts, and the mamillary bodies. Although complex, the connections of the hypothalamus can be broken down into three principal divisions:

1. Reciprocal pathways connect the hypothalamus to the brain stem and spinal cord, interconnecting various visceral and somatic nuclei, both motor and sensory.
2. Reciprocal pathways connect the hypothalamus with the limbic system, including the septal area, hippocampus, and amygdala. Additional afferents arise in the orbital cortex of the frontal lobes and optic tracts.
3. Efferent pathways connect to the pituitary gland.

These rich interconnections illustrate not only the widespread influence of the hypothalamus, but also how activation can be affected by autonomic processes as well as through psychic and environmental stimuli. They also underscore the interdependence of the discrete systems, shedding light on why, for example, patients with temporal lobe epilepsy may experience thyroid dysfunction or why persons who are diabetic may experience memory problems.

The Pituitary Gland

Immediately juxtaposed to the hypothalamus, within the sella turcica at the base of the brain, the pituitary gland, or *hypophysis*, measures approximately 1 cm in diameter and weighs approximately 1 g. It is connected to the hypothalamus by the pituitary stalk, which contains the hypothalamic–hypophysial portal system. Pituitary hormones are secreted primarily under stimulation by hormones generated in the hypothalamus, and they are modulated by means of feedback loops and various neurotransmitter mechanisms. Known as the *master endocrine gland*, the pituitary affects the body's overall metabolism, the nervous system, and many aspects of behavior both through the direct effect of its hormones and secondarily through its effects on other endocrine glands.

Anatomically, the gland consists of two distinct components, the anterior pituitary (*adenohypophysis*) and the posterior pituitary (*neurohypophysis*), which are connected by a relatively avascular region known as the *pars intermedia*. Stimulation of the anterior pituitary results from the influence of specialized releasing and inhibitory hormones generated within the hypothalamus. The hormones in turn are secreted through small blood vessels in the hypothalamic–hypophysial portal system. The anterior pituitary secretes a number of hormones vital to the body's metabolic function and capacity to deal with stress. Known as *trophic* hormones, these substances act to stimulate their target organs at distances from the pituitary. Chief among these are growth hormone (GH), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), the gonadotropins known as *follicle-stimulating hormone* (FSH) and *luteinizing hormone* (LH), and prolactin.

Stimulation of the posterior pituitary is accomplished by means of nerve tracts that originate in the supraoptic and paraventricular nuclei of the hypothalamus and pass through the pituitary stalk. These nerve signals cause the secretion of the posterior hormones from secretory granules that lie on the surface of the capillaries. Chief among these hormones are vasopressin (VP), also known as *antidiuretic hormone* (ADH), and oxytocin.

COGNITION AND GENERALIZED DYSFUNCTION OF THE NEUROENDOCRINE SYSTEM

Dysfunction of the hypothalamus, whether due to trauma, vascular disease, primary hypothalamic neoplasm, or other etiology, typically manifests a combination of symptoms entailing both autonomic functions and behavioral responses. Symptoms include temperature dysregulation, diabetes insipidus, obesity, aphagia and emaciation, hypersomnia, and sexual dystrophy. Episodic fear and rage reactions may also result. Severe compromise of hypothalamic functions may lead to stupor and coma.

Commonly, hypothalamic dysfunction may result from compression secondary to a pituitary adenoma. Pituitary adenomas are age-linked, increasing in incidence into the eighth decade. Macroadenomas (>10 mm) frequently come to medical attention as a result of their prominent mass effect, producing symptoms such as headache, due to

traction of the meninges, and visual abnormalities, due to extension of the tumor into the suprasellar region, which results in compression of the optic chiasm or optic tract. These problems are accompanied by generalized pituitary dysfunction manifesting as combinations of symptoms such as those noted previously, due both to *hyper*secretion of a hormone as a result of the tumor and to *hypo*secretion of other hormones secondary to the tumor's mass effect on the pituitary gland and hypothalamus. Hormonal declines due to mass effect follow a pattern: Hyposecretion of GH precedes that of LH and FSH, which precedes that of TSH, which precedes that of ACTH. Cognitive deficits including amnesia and executive dysfunction may persist following treatment (Grattan-Smith *et al.*, 1992; Peace *et al.*, 1997). However, the etiologies of such deficits appear to be multifactorial. Possible factors include surgical sequelae, pre- and postsurgical hormonal imbalance, tumor size, secondary hydrocephalus, and radiotherapy (see McCord *et al.*, 1997, regarding long-term outcome and sequelae).

All adults experience age-related changes in multiple hormone systems, including reduced production of GH, thyroid hormones, sex hormones, certain adrenal androgens, and pancreatic hormones (Lamberts *et al.*, 1997). Moreover, adults may experience a generalized hypopituitarism syndrome characterized by chronic pituitary insufficiency. Patients experience a range of symptoms such as decreased energy, loss of libido, depressed mood, and/or increased irritability. Women may experience irregular menses or amenorrhea, and men may experience impotence and fertility problems.

Pituitary microadenomas (<10 mm), as well as vascular lesions, inflammation, trauma, immune system dysfunction, and other etiologies, may also produce discrete hypo- or hypersecretion of individual hormones. For simplicity in compiling evidence regarding the cognitive effects of individual hormones, these syndromes—such as acromegaly and Cushing's disease—are reviewed in the next section with regard to the specific hormone or hormonal axis involved, and not necessarily the gland of origin. That is, the gonadotropic hormones FSH and LH are discussed in the context of the reproductive hormones because of their role in stimulating production of androgens and ovarian hormones by the gonads. The hypothalamic releasing hormones corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH), as well as the pituitary hormones ACTH and TSH, can also affect cognition. They do so, however, primarily through their influence on the production of cortisol by the adrenal glands and of thyroid hormones by the thyroid gland, respectively. Their actions are therefore discussed in the next section with regard to the glands they affect.

DISCRETE EFFECTS OF HORMONES ON COGNITION

Growth Hormone

Growth hormone (GH), also known as *somatotropic hormone* or *somatotropin*, is necessary for promoting growth and plays a role in other aspects of metabolic processes. These include suppressing glucose utilization, increasing the rate of protein synthesis in cells, and increasing the utilization of fatty acids for energy. Normal serum levels are <10 ng/ml for children and <5 ng/ml for adults.[4] It is secreted by the anterior pituitary under stimulation by the hypothalamic growth factor–releasing hormone (GFRH) and itself stimulates production of insulin-like growth factor–I (IGF-I) in the liver.

GH variation in childhood is typically associated with more widespread hypopituitary symptoms resulting in dwarfism and permanent sexual immaturity, although for approximately one-third of this population there is a deficiency in GH alone. Among this latter group, early treatment with GH therapy can completely cure the abnormality. The incidence of GH deficiency is approximately 1:4,000, and there is a higher incidence in boys than in girls by a 2.5:1 ratio. Adults may acquire GH deficiency as part of a generalized pituitary syndrome due either to tumor or to thrombosis of pituitary blood vessels. Symptoms associated with these conditions are due to depressed pituitary, thyroid, adrenal, and/or gonadal functioning and include lethargy, decreased libido, and weight gain.

GH may also be produced in excess as a result of dysfunction or tumor. If this occurs before adolescence, gigantism will occur. When the excess is caused by tumor, the pituitary gland is typically damaged either by mass effect or by local invasion, which results in hyposecretion of other hormones. Hyperglycemia is also common as a result of the effect of GH on the pancreatic beta cells that regulate insulin production. If occurring after adolescence, excessive GH manifests as acromegaly, a condition in which the bones increase in thickness, especially those in the hands and feet, but also the membranous bones of the face, forehead, and jaw. Hypersecretion of GH is also associated with heart failure.

A number of studies have attempted to determine the possible effects of GH on the brain and cognition. In their study of 29 children with idiopathic GH deficiency, Meyer-Bahlburg *et al.* (1978) found average IQ and no difference in IQ between children with GH deficiency treated

[4]Throughout the text, hormone levels noted are approximate. Also, units of measurement vary. For simplicity, levels are supplied in the more commonly used unit formats.

with GH replacement therapy and those not treated. Two additional studies of short-stature children revealed similar findings (M. Gordon *et al.*, 1982; Stabler *et al.*, 1994). One double-blind, placebo-controlled study reported increased attentional functioning in children with GH deficiency who received replacement therapy (M. Q. Smith *et al.*, 1985).

Among adult populations, however, there is evidence associating congenital GH deficiency with memory weaknesses. In a study comparing men with GH deficiency with men with multiple hormone deficiencies (including GH deficiency) and healthy control subjects, Deijen *et al.* (1996) identified significant weaknesses on list-learning (Bouma and Lindeboom, 1988) and paired associates (Emmen *et al.*, 1988) tasks as the factors associated with both patient groups, but not with the normal subjects. Further, two studies demonstrated statistically significant improvement in mnestic functioning, independent of depression and other psychological factors, in adults with GH deficiency who received GH therapy (Clopper, 1990; Deijen *et al.*, 1998).

Although no mechanism has yet been identified to account for these memory weaknesses, Deijen *et al.* (1996) noted the existence of GH receptors in the hippocampus (Lai *et al.*, 1991), as well as the possible effects of GH on dopamine activity at that site. However, GH deficiency in Deijen's subjects was present at least since birth and likely during the early fetal environment as well. It is not clear, therefore, whether the assessed mnestic dysfunction was due to decreased circulating GH, chronic GH deficiency, possible effects of GH deficiency on the developing brain, or some combination of these factors.

Vasopressin

Vasopressin (VP), also known as *antidiuretic hormone* (ADH), is secreted by the posterior pituitary. It causes retention of water by the kidneys to regulate serum osmololality (i.e., the relative concentration of water to electrolytes in blood) and can also elevate blood pressure by the constriction of blood vessels throughout the body. The normal plasma reference range is 2–12 pg/ml if serum osmolality >290 mosm/kg, or <2 pg/ml if serum osmolality is <290 mosm/kg. VP receptors are present in numerous central nervous system locations, including the hippocampi (Van Wimersma Greidanus *et al.*, 1986).

Diabetes insipidus is caused by a lack of VP and is characterized by polyuria (passage of large quantities of dilute urine) and polydipsia (increased water intake), which together may lead to dehydration, causing stupor, coma, and death. Diabetes insipidus may be the result of a pituitary tumor, a head injury, or another disease process, as well as of pituitary surgery, most typically that affecting the hypothalamus or upper pituitary stalk.

Although early animal studies indicated that learning could be facilitated by VP (e.g., De Wied, 1965), attempts to demonstrate this in humans have met with only limited success thus far. Short-term administrations of VP to older subjects showed improvements that could be attributed to modestly enhanced memory or attentional processes (Jennings *et al.*, 1986; Nebes *et al.*, 1984; Weingartner *et al.*, 1981) or to increased cortical arousal (Fehm-Wolfsdorf and Born, 1991). Although one study suggested possible memory benefits for both older subjects and patients with dementia (Legros and Gilot, 1979), two studies found that neither short-term nor long-term VP therapy improved memory and other cognitive deficits in patients with Alzheimer's disease (AD) (Peabody *et al.*, 1985; Wolters *et al.*, 1990).

In a double-blind, placebo-controlled study of older healthy volunteers administered long-term VP therapy, Perras *et al.* (1997) found an increased primacy effect on the Rey Auditory Verbal Learning Test (Rey, 1964; Taylor, 1959) for the subjects receiving VP therapy vs. the controls ($\mu = 42.6 \pm 3.1\%$ vs. $\mu = 37.2 \pm 3.1\%$, $p < .05$). A trend was also noted in the reduction of proactive interference effects on the distractor list. Although no improvement in learning ability was evident, the results were consistent with increased attention and semantic encoding, and possible decreased distractibility. The authors interpreted these results as consistent with enhanced "mnestic preactivation" because of the effect of VP on general arousal.

Introduction to the Reproductive Hormones

Virtually every discipline in the neurosciences, psychology, sociology, and anthropology has conducted extensive investigations regarding the origin and nature of gender differences in humans and other animals. After genetic/chromosomal differences, which determine gender, hormonal differences have long been looked to as a leading factor for explanations of behavioral differences: gender identity, sexual preference, emotional and social behavior, and cognition. Certainly, there is much evidence that hormones play an important role in gender differences. However, regarding cognitive factors, caution is required in attributing gender-based behavioral differences to reproductive hormone levels. Central to this caveat is the following observation: Reproductive hormones are not gender specific. Furthermore, although androgens are present at higher levels in males, as are ovarian hormones in females,

small variations may produce larger effects in the "opposite" sex as a result of the relative size of change from baseline levels. Finally, because of synergistic effects of hormones on the same axis, a rise in one hormone may cause a decrease in another, which makes causal attributions difficult.

As outlined in many of the following discussions of the literature, in studies of group differences, women generally outperform men on certain verbal tasks, and men surpass women on certain visuospatial tasks (Halpern, 1992; Maccoby and Jacklin, 1974). However, the differences are small and there is considerable overlap in the range of performance across groups. Existing evidence suggests a relatively minor role for circulating levels of reproductive hormones in accounting for these differences. Variability in performance due to circulating hormone levels in healthy normal subjects has been identified primarily by utilizing very sensitive tests designed to detect subtle changes in the laboratory setting. For this reason, for a better understanding of the role of hormones in cognition, researchers have largely turned their attention to individuals with developmental abnormalities affecting hormone levels (e.g., congenital adrenal hyperplasia), persons with naturally occurring or surgically induced declines in hormone levels (e.g., menopause), or individuals with changes in hormone levels due to disease processes (e.g., AD).

Gonadotropins: Follicle-Stimulating Hormone and Luteinizing Hormone

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH), referred to jointly as *gonadotropic* hormones, are secreted by the anterior pituitary gland and stimulate the production of gonadal hormones: androgens, estrogens, and progestins. However, their functions within the sexes differ. In the male testes, FSH promotes spermatogenesis and LH promotes testosterone production. Normal adult male serum levels are 2.25–20 IU/L and 3.6–17.1 IU/L, respectively. In the female ovary, FSH causes follicle growth and estrogen production, and LH induces ovulation and promotes androgen production. Normal serum levels in adult premenopausal women are 5–24 IU/L and 4.5–24.3 IU/L, respectively, and are considerably higher during the midcycle peak. Normal FSH and LH levels in postmenopausal females are 50–300 IU/L and 29–189 IU/L, respectively.

The gonadotropins' role in cognition is not clear, in part because receptors have not yet been identified in the brain. Although pituitary adenomas are frequently the source of a syndrome known as amenorrhea/galactorrhea (absence of menses with persistent milk secretion) that is due to excessive prolactin secretion, which inhibits gonadotropin production, no reports of cognitive sequelae unique to this syndrome have yet been described.

Nevertheless, there is evidence that these hormones may influence cognition. There is one study of LH and FSH levels and cognitive functioning in a normal population. H. W. Gordon and colleagues (H. W. Gordon *et al.*, 1986; H. W. Gordon and Lee, 1986) assayed FSH, LH, and gonadal hormones in healthy men and women who were administered a number of visuospatial and verbal/sequential tests from the Cognitive Laterality Battery (H. W. Gordon, 1986). For males, FSH correlated negatively with the visuospatial tests, with high FSH levels associated with poorer performance. In contrast, LH had positive, but weaker, correlations with both the visuospatial and the verbal/sequential tests. For women, FSH was also negatively correlated with the visuospatial tasks, but less strongly and only after the effects of ovarian hormones were partialled out. FSH and LH were both positively correlated with the verbal fluency task. These results suggest that FSH and LH have independent properties that affect cognition. Unfortunately, for populations in which significant variation in gonadotropin levels occurs as a result of genetic and/or developmental abnormalities (e.g., idiopathic hypogonadotropic hypogonadism, Turner's syndrome, Klinefelter's syndrome), it is not possible to parse out the unique effects of the individual gonadotropins from one another or from the effects of variation in gonadal hormones. Also, genetic factors likely play a key role in the cognitive problems associated with these conditions. (For discussions of these conditions, see Collaer and Hines, 1995, and H. W. Gordon *et al.*, 1988).

Androgens

In males, androgens are secreted principally by the testes. By far, the most abundant of these is testosterone. Almost nonexistent during most of childhood, testosterone is nevertheless produced in large quantities in the newborn male in the first few months, as well as following the onset of puberty. Normal levels of total serum testosterone are 300–1,000 ng/dl for males. Women also produce endogenous testosterone, with normal levels of approximately 30–70 ng/dl.

The term *androgen* refers to any steroid hormone with masculinizing effects. Although 95% of these are produced in the testes, androgens are produced at other sites as well, including the adrenal glands. Because of the low rate of production, adrenal androgens do not typically cause significant masculinizing activity. However,

excessive masculinization can occur secondary to overproduction of these androgens due to dysfunction, such as occurs in congenital adrenal hyperplasia (CAH).

The principal functions of the androgens include their role in spermatogenesis and masculinization of the fetus and the development of male secondary sex characteristics. Regulation of production is maintained by a feedback loop, which begins with the production of gonadotropin-releasing hormone (GnRH) by the hypothalamus. This in turn stimulates the secretion of the two anterior pituitary gland gonadotropic hormones: LH, the main stimulus for testosterone production by the testes, and FSH, which principally stimulates spermatogenesis. Gonadotropin secretion can be affected by environmental and intrapsychic stimuli as well, particularly those involving the limbic system. For instance, the amygdalae give large afferent projections that directly modulate the function of the hypothalamic neurosecretory cells. A feedback loop is provided by the action of testosterone on the hypothalamus.

There is reason to believe that the presence of androgens underlies morphological differences between the two genders in the human brain. Differences in the size of the anterior hypothalamic nuclei (Allen *et al.*, 1989; Swaab and Fliers, 1985) and a number of midline structures, such as the splenium of the corpus callosum and the anterior commissure, have been identified (Allen and Gorski, 1986; Holloway and de LaCoste, 1986). Geschwind and colleagues (Geschwind and Behan, 1982; Geschwind and Galaburda, 1985a,b) hypothesized that perinatal exposure to testosterone differentially affects development of the right cerebral hemisphere, citing enhanced spatial ability, increased frequency of left-handedness, and greater incidence of verbal learning disabilities in males. Behaviorally, androgens have been associated with sexual drive and increased aggression in both genders (see Hines and Green, 1991). However, because aggressive encounters alter testosterone levels, no clear cause–effect relationship between the two variables has been established. Males receiving testosterone replacement therapy report enhanced well-being and increased energy. However, testosterone in males is converted, or *aromatized*, into estrogens, which obscures the interpretation of these reports.

Research on a possible role for androgens in cognition has focused on spatial abilities because statistically significant differences favoring males are consistently reported (see Linn and Petersen, 1985). Moreover, these differences become apparent following the onset of puberty (Maccoby and Jacklin, 1974) and have been identified across various groups for many decades, which suggests that differences are not likely due to psychosocial factors (Gladue and Baily, 1995). These capacities are typically measured by means of route-learning tasks and mental rotation tasks, although many neuropsychological studies examine performances on visuospatial tasks such as the Wechsler Adult Intelligence Scale—Revised (WAIS-R: Wechsler, 1981) Block Design subtest or across a range of related tasks, such as those composing the WAIS-R Performance domain subtests.

There is support from the animal literature for enhanced spatial ability in males. In a number of nonhuman species, spatial-navigational ability is sexually differentiated, with males learning to use routes more efficiently (Beatty, 1984). Further, relative to controls, male mice castrated at birth exhibit reduced spatial efficiency in adulthood (Williams *et al.*, 1990).

Congenital Adrenal Hyperplasia

Excessive levels of androgens are associated with congenital adrenal hyperplasia (CAH), an endocrine disorder beginning in the early prenatal environment. The condition is typically detected at birth, and androgen levels are normalized. Although early studies found increases in Full Scale IQ in patients with CAH, these findings were apparently largely due to selection bias (Nass and Baker, 1991a). Nevertheless, because of their high androgen levels in utero, patients with CAH may be expected to show enhanced spatial ability. Researchers have focused largely on females with CAH because identifying enhanced spatial ability in males with CAH may be more difficult. Research by Resnick *et al.* (1986) utilizing a sample of adolescent females with CAH revealed selectively better performances on the Mental Rotations Test (Vandenberg and Kuse, 1978), the Card Rotation Test (Ekstrom *et al.*, 1976), and a hidden figures test, compared with the performance of unaffected siblings. Strengthening the case for a prenatal organizational effect of androgens on the developing brain, Hampson *et al.* (1998) found a similar advantage ($\approx$1 SD) in spatial capacity among preadolescent females with CAH (compared with controls), by utilizing the Spatial Relations Test from the Primary Mental Abilities battery (Thurstone and Thurstone, 1963). Although other researchers have not found strength on certain visuospatial tasks in females with CAH (Baker and Ehrhardt, 1974; McGuire *et al.*, 1975; Perlman, 1973), it is likely that discrepant findings may be attributed to differences in test sensitivity (Collaer and Hines, 1995). In addition, Hampson *et al.* (1998) found that boys with CAH scored significantly lower (>1 SD) than did control boys on the Spatial Relations Test, which suggests that overexposure to androgens may have a "demasculinizing" effect on spatial ability in males.

Significant Verbal IQ–Performance IQ (VIQ-PIQ) discrepancies favoring performance domain abilities have been reported among female patients with CAH, relative to the abilities of unaffected sibling controls (Nass and Baker, 1991b). Similarly, using controls matched for IQ in their study of adult females with CAH, Helladay *et al.* (1994) found greater discrepancies on verbal vs. visuospatial/nonverbal reasoning tasks favoring the latter domain among the patient sample. In this study, however, the observed differences appeared to be due largely to superior logical inductive reasoning scores, not to spatial abilities. The authors postulated that these inconsistent findings could be attributed to the presence of low androgen levels in the CAH group at the time of assessment, and suggested that this finding supported other research indicating that variation in circulating androgen levels may influence spatial abilities in humans.

Androgen Insensitivity

Patients with androgen insensitivity (AI) are genetic males who produce androgens but manifest partial to total insensitivity of androgen receptors. Depending on the degree of insensitivity, they either are born with external female genitalia (and no female reproductive organs)—*total AI*—and are raised as girls, or are born with ambiguous genitalia—*partial AI*—and are raised as either girls or boys (Grumbach and Conte, 1992). Patients with AI typically demonstrate a VIQ-PIQ discrepancy with decreased PIQ (Imperato-McGinley *et al.*, 1991; Masica *et al.*, 1969; Perlman, 1973). In the Imperato-McGinley *et al.* (1991) study, patients with AI were compared with both male and female controls, which suggests that the differences were not due to psychosocial factors. However, it was ambiguous whether the lower PIQ and individual subtest scores were due to visuospatial deficits or attentional factors on speeded tests.

Androgens in Normal Subjects

Studies of androgens in normal populations suggest a possible inverted U-shaped curve regarding the effects of androgens on spatial tasks. Using somatic indices of androgenization such as muscle–fat distribution, genital and breast size, body shape, and amount of pubic hair, Petersen (1976) found that more-masculine women outperformed less-masculine women on spatial tasks. More-masculine men, however, performed worse than less-masculine men on the same tasks. These results have been tentatively supported by studies that directly measured testosterone levels (Gouchie and Kimura, 1991; Shute *et al.*, 1983). Recently, Moffat and Hampson (1996) reported a curvilinear relationship between testosterone and a composite spatial abilities score obtained from the Mental Rotations Test (Vandenberg and Kuse, 1978) and the Paper Folding Test (Ekstrom *et al.*, 1976) that was evident only in right-handed subjects. As in the earlier studies, testosterone was positively correlated with a spatial task for right-handed females but negatively correlated with spatial abilities for right-handed males. Notably, this finding is consistent with the previously described evidence of the masculinizing effects of excessive androgen exposure in girls with CAH and the demasculinizing effects of excessive androgen exposure in boys with CAH (Hampson *et al.*, 1998).

Two additional lines of inquiry further suggest that optimal, not extreme, levels of testosterone may be associated with enhanced spatial ability in normal subjects. Janowsky *et al.* (1994) administered testosterone supplements to men undergoing normal age-associated declines in androgen levels. Subjects' performance on the WAIS-R (Wechsler, 1981) Block Design subtest was significantly ($p < .04$) improved ($\mu = 27.96 \pm 7.56$ to $\mu = 30.17 \pm 6.78$) relative to that of controls ($\mu = 28.72 \pm 8.61$ to $\mu = 27.90 \pm 8.57$). In contrast, performances on the California Verbal Learning Test (CVLT: Delis *et al.*, 1987), Wechsler Memory Scale—Revised (WMS-R: Wechsler, 1987) Visual Reproduction subtest, Grooved Pegboard test (Kløve, 1963), and Trail Making Test (Reitan and Davison, 1974) were unchanged for both experimental and control groups. Additional support for the influence of circulating androgens on visuospatial functions has been found in measures of natural fluctuation in testosterone. Moffat and Hampson's study (1996, discussed previously) also measured subjects at a time interval that allowed assessment according to the diurnal drop in testosterone levels. In keeping with other findings, for men, higher levels of testosterone were associated with more errors on spatial tests, and for women, errors correlated with lower levels.

Finally, studies of transsexuals undergoing cross-sex hormone treatment prior to surgery (Slabbekoorn *et al.*, 1999; Van Goozen, 1994; Van Goozen *et al.*, 1995) support an activating role for testosterone. In these studies, female-to-male patients undergoing testosterone supplementation demonstrated improved spatial performance, and male-to-female patients receiving antiandrogens and estrogen showed declines in spatial ability as measured by the Card Rotation Test (Ekstrom *et al.*, 1976) and the Rotated Figures, Three-Dimensional (Vandenburg and Kuse, 1978). In the most recent of the studies, the effects did not disappear after termination of cross-sex hormone therapy for a period of 5 weeks. Instead, the differences continued to increase slightly.

An alternative hypothesis exists for certain of the preceding findings, because testosterone acts to lower estrogen levels in females. It is therefore possible that estrogen has a negative effect on spatial ability for the tests involving female subjects.

Summary

Despite the evidence outlined associating androgens with visuospatial ability, it is unclear how circulating androgens influence cognition. Evidence exists that pre- and perinatal exposure to androgens may lay the neural substrate for later visuospatial ability. There is also support for a role for testosterone in producing a transient activation of spatial ability (either through a direct effect or through its influence on estrogen levels) according to an inverted U-shaped curve. However, it is unclear to what degree circulating androgen effects may depend on or interact with the neural substrate. The finding of stronger correlations of circulating testosterone levels and visuospatial skills for right-handed subjects suggests a contribution of each of these two factors.

Ovarian Hormones

The female reproductive hormones (estrogens and progestins) are primarily secreted by the ovaries. As in the male, these hormones are secreted in response to the two anterior pituitary gland gonadotropic hormones: LH and FSH. These are in turn regulated by the hypothalamic hormone GnRH. However, the female hormonal system differs markedly from the male hormonal system regarding hormonal function and the regulation of hormonal cycles.

Female reproductive hormones are thought to be largely responsible for the feminization of the brain during fetal stages (Gorski, 1991). With the onset of puberty and lasting until menopause, these hormones are secreted at vastly different rates according to the female menstrual cycle. Approximately every 28 days, LH and FSH cause the growth of new follicles within the ovaries. During the first 2 weeks, estrogen levels rise steadily to a midcycle peak and then dip just after ovulation. Following ovulation, progesterone production begins in the corpus luteum and is maintained at a high level for approximately 2 weeks. In the absence of fertilization, the corpus luteum then ceases progesterone and estrogen production. These declines mark the onset of menstruation and a new ovarian cycle. Beginning when a woman reaches approximately 40 years of age, the ovaries produce decreasing amounts of estradiol, the principal estrogen. Following menopause, occurring on average at age 51, estradiol and progesterone production declines sharply.

Of the estrogens, β-estradiol is far more potent than either estrone or estriol. Their principal functions include stimulating the development of adult female sex organs and secondary sex characteristics. Serum levels range from 20–100 pg/ml in the early follicular phase to 100–350 pg/ml in the preovulatory and luteal phases. In adult males, serum estradiol typically ranges from 20–50 pg/ml. Of the progestins, progesterone is generally considered to be the single most important hormone. In addition to its role in reproductive capacity, progesterone aids in nutrition of the fertilized ovum. Serum levels range in females from 0.3–0.8 ng/ml in the follicular phase to 4–20 ng/ml in the luteal phase. In males, serum levels range from 0.12–0.3 ng/ml.

Affective features associated with normal variation in ovarian hormone levels have been the subject of numerous investigations. Premenstrual syndrome (PMS) is a cyclical disorder with depressive/mood-related and somatic symptoms occurring during the luteal phase of the menstrual cycle and clearing with the onset of menstruation. A recent study by P. J. Schmidt *et al.* (1998) has demonstrated that PMS symptoms are not due to increased levels of reproductive hormones, but to an abnormal response of the brain substrate to normal changes in hormone levels. Menopause has been researched because of its association with depressive disorders. Although there is evidence that major depression is more common in postmenopausal women (Weissman, 1996), estrogen replacement therapy (ERT) alone does not appear to alleviate depressive symptoms (M. A. Schneider *et al.*, 1977). The utility of ERT for the prevention of major depression and as an adjunct to antidepressant therapy is currently under investigation. In contrast to the depressive features associated with declines in estrogen, there is evidence from research on epileptic disorders that progesterone is a potent anxiolytic by means of its role as a γ-aminobutyric acid (GABA) agonist (Herzog, 1991). Indeed, studies have demonstrated that progesterone has significant anticonvulsant effects (Herzog, 1995).

Cognitively, female hormones are thought to account in part for sexually dimorphic characteristics in brain structure and function, particularly with regard to verbal abilities in general (Linn and Petersen, 1985) and verbal memory in particular (Sherwin, 1994). Morphologically, Hines *et al.* (1992) pointed to the relatively larger size of the female corpus callosum as well as greater language lateralization in males as underlying this female verbal advantage. An ongoing role for estrogen in the regulation of verbal abilities is suggested by the emergence of this advantage following the onset of puberty (Maccoby and

Jacklin, 1974). Sherwin (1998) has proposed that the specificity of estrogen's effect (i.e., on verbal memory) suggests that estrogen serves to activate neural pathways established under the influence of this hormone during prenatal life.

Estrogen Levels and Cognition

Evidence of a role for estrogen in accounting for enhanced verbal skills in females comes from research on women during their menstrual cycle. An early study compared preovulatory women (in whom estrogen levels were high) with women taking birth control pills (in whom estrogen levels were low) and with men. The preovulatory women performed better than the control groups on tests of color naming and color reading (Komnenich *et al.*, 1978). More recently, Hampson (1990a,b) found modestly improved performance on speeded tests of verbal articulation (Mateer and Kimura, 1977), color naming (Uhlmann, 1962), and several fine motor tasks during the high-estrogen phase of the menstrual cycle. Keenan *et al.* (1992) replicated earlier findings of improved color naming (Stroop Test: Stroop, 1935) and found greater mental flexibility (Trails B: Reitan and Davison, 1974) as well. Also, Phillips and Sherwin (1992) found an association between the high-estrogen phase of the menstrual cycle and the Paired Associates subtest of the Wechsler Memory Scale (Wechsler, 1974). However, using the Cognitive Laterality Battery (H. W. Gordon, 1986), H. W. Gordon and colleagues (H. W. Gordon *et al.*, 1986; H. W. Gordon and Lee, 1993) twice failed to find relationships between ovarian hormone levels and gender-based verbal/sequential ability according to natural hormonal variations in women. Although the authors described a number of possible confounding factors, their results point to the need for further research in this area.

Another set of investigations has examined the response to ERT in premenopausal women undergoing medical procedures that disrupted estrogen production. In a series of well-controlled studies (Phillips and Sherwin, 1992; Sherwin, 1988; Sherwin and Phillips, 1990), cognitive performances were examined in premenopausal women before and after surgically induced menopause (e.g., hysterectomy) under ERT and placebo conditions. Subjects were also compared with women who had undergone hysterectomy but whose ovaries were not resected. Using an adaptation of the Wechsler Memory Scale with alternate forms (Russell, 1975; Stone *et al.*, 1946; Wechsler, 1945), the investigators found that paragraph-recall capacity was maintained at presurgical levels for all women whose estrogen levels remained constant, whether as a result of natural secretion or of ERT. Moreover, women in the placebo condition demonstrated a significant decline on the verbal paired associates task. Similarly, paragraph recall was found to be significantly decreased ($\approx$1 SD) in a group of premenopausal women with benign uterine neoplasms who were administered an agent causing suppression of estrogen production. This decrement reversed with "add-back" ERT (Sherwin and Tulandi, 1996).

Animal studies support the existence of a role for estrogen in enhanced memory processes during the estrous (i.e., menstrual) cycle. Estrogen promotes the formation of dendritic spines and synapses (Wooley and McEwen, 1993) and enhances long-term potentiation in the rat hippocampal CA1 region (Warren *et al.*, 1995). Ovariectomy has been shown to decrease hippocampal synaptic density, a process that can be reversed with the addition of estradiol (Wooley and McEwen, 1993). Two behavioral learning paradigms utilizing ovariectomized rats have associated a lack of estrogen with deficits on learning tasks and estradiol replacement with the maintenance of learning (O'Neal *et al.*, 1996; Singh *et al.*, 1994). Estrogen is also known to enhance activation of the cholinergic system (Toran-Allerand *et al.*, 1992), which could account in part for the aforementioned findings associated with processing by the basal forebrain and frontal lobes in general (i.e., color naming and mental flexibility).

One study provides direct evidence that the hormonal milieu modulates the prefrontal cortex in humans. Berman *et al.* (1997) found increased cerebral blood flow in pharmacologically controlled conditions in young women by using positron emission tomography (PET) scans obtained during performance of the Wisconsin Card Sorting Test (Berg, 1948; Grant and Berg, 1948). However, although patterns of enhanced activation were found for both estrogen and progesterone, there was no change in task performance parameters.

Postmenopausal Estrogen Replacement Therapy

ERT studies provide another format for consideration of the effects of estrogen on cognition in human females. Following menopause, the ovaries virtually stop producing estradiol, and a weaker hormone produced by the adrenal glands, estrone, becomes the predominant estrogen. ERT has been used for many years because of its vasoactive properties that reduce the risk of stroke (Paganini-Hill *et al.*, 1988), heart disease (Barrett-Connor and Bush, 1991), and vascular dementia (Funk *et al.*, 1991). ERT is also known to prevent osteoporosis (Lindsay *et al.*, 1976). Despite these potential benefits, a controversy exists regarding the utility of ERT for women with a family history of breast cancer (see Colditz *et al.*, 1995; Grady and Ernster, 1991).

Memory problems are a frequent complaint of postmenopausal women (Anderson *et al.*, 1987). Because memory functions that require the encoding of new information are increasingly compromised with age in both genders (Craik, 1984), these memory problems are not likely due entirely to low circulating levels of estrogen. Nevertheless, studies of ERT in both normal and patient populations suggest a role for estrogen in maintenance of cognitive functions, and perhaps verbal memory in particular.

The first such study examined cognitive performances of two groups of 75-year-old females who were administered either estradiol or a placebo for 12 months. Those in the treatment group demonstrated increases in VIQ and memory, whereas those in the placebo group experienced declines in both domains. After discontinuation of estrogen treatment, the cognitive abilities of those in the experimental group declined to below pretreatment levels (Caldwell, 1954; Caldwell and Watson, 1952). However, the possible inclusion of a number of subjects with mild dementia may have confounded these findings.

A number of subsequent studies yielded inconsistent results: Three (Feydor-Freybergh, 1977; Hackman and Galbraith, 1977; R. Schmidt *et al.*, 1996) reported enhanced general cognitive functioning with ERT, and three (Polo-Kantola *et al.*, 1998; Rauramo *et al.*, 1975; Vanhulle and Demol, 1976) reported no effect. Differences among the subject populations, experimental designs, functions assessed, and measures make it difficult to reconcile these disparate findings. However, several of these studies may be reconciled by the hypothesis that short-term ERT is not as effective as long-term ERT in enhancing general cognitive functioning in symptomatic women.

Recently, Kampen and Sherwin (1994) found that women on ERT performed better on the Story Memory test from the Wechsler Memory Scale (Russell, 1975; Stone *et al.*, 1946; Wechsler, 1945) than did woman never on ERT who had been matched for age, education, and socioeconomic status. Similarly, in a community-based epidemiological study of 727 women, D. M. Jacobs *et al.* (1998) found that women who had used estrogen replacement scored higher on measures of verbal memory (Buschke Selective Reminding Test: Buschke and Fuld, 1974), naming (Boston Naming Test: Kaplan *et al.*, 1983), and abstract reasoning (WAIS-R, Similarities: Wechsler, 1981) than did nonusers, regardless of duration of treatment, demographic factors, or Apolipoprotein (APOE) genotype. All tests were significant for $p < .05$, with differences averaging about 0.5 SD. Follow-up data were available for a subset of subjects. Women with histories of ERT showed improved verbal memory relative to their own baseline performances, whereas nonusers' performances declined. Along these lines, in a recent study of older men and women (μ age = 72.1), Carlson and Sherwin (1998) found significantly better performances on Digit Span Total and Digit Span Forward subtests of the WAIS-R for ERT users and men than for nonusers. Women ERT users also had higher Digit Span Backward scores than those of nonusers. Women ERT users scored higher than but did not differ significantly from nonuser and male subjects on the Logical Memory and Paired Associates subtests of the WMS-R (Wechsler, 1987) and on a selective reminding task (Buschke and Fuld, 1974).

In contrast, in a prospective/cross-sectional study of a large population of older, educated women, Barrett-Connor and Kritz-Silverstein (1993) found no verbal memory or other cognitive advantages for women who had undergone ERT for 20 or more years, compared with women who had discontinued ERT or who had never been placed on it. D. M. Jacobs *et al.* (1998) noted numerous demographic and ERT history differences between these two study populations as factors that could account for the discrepant findings. Supportive of the Barrett-Connor and Kritz-Silverstein findings, Yaffe, Sawaya, *et al.* (1998) concluded in their meta-analysis that ERT benefits cognition only in symptomatic, recently menopausal women. Unfortunately, their meta-analysis did not include the studies of D. M. Jacobs *et al.* (1998) and Carlson and Sherwin (1998), which were published at about the same time.

Estrogen and Alzheimer's Disease

A potential role for female reproductive hormones regarding Alzheimer's disease (AD) is suggested by the disease's greater prevalence among women than men, even after differences in life expectancy have been adjusted for (Jorm *et al.*, 1987). Likewise, several studies have found that women with AD perform worse than men with AD on various verbal tasks (Henderson and Buckwalter, 1994; Ripich *et al.*, 1995), despite the women's premorbid advantage on such tasks. A number of other clinical and experimental findings, including body weight, neurophysiological processes, and genetic mechanisms, further support the relevance of estrogen to AD (see Henderson, 1997, for a discussion).

Clinically, ERT has been used to treat women with AD for many years. In a number of studies, ERT has been shown to be useful in improving cognition in general (Fillit *et al.*, 1986; Honjo *et al.*, 1989, 1993; Ohkura *et al.*, 1994a,b). Some limitations noted in these studies include small sample size and the use of general cognitive screening instruments, not norm-referenced neuropsychological tests. Also, certain of these studies were criticized

in part for not parsing out cognitive improvements due to mood enhancement. In a 9-month longitudinal study of nondepressed women with mild AD, Birge (1997) reported improvement in general cognitive functioning in 8 of 10 subjects receiving ERT and either no change or decline in 10 control subjects. Results consistent with these findings were reported for women receiving ERT as part of a large study of the effects of tacrine (Knapp *et al.*, 1994; L. S. Schneider *et al.*, 1996). A recent double-blind, placebo-controlled, parallel group study examined the response to transdermal estrogen therapy in postmenopausal women with AD (Asthana *et al.*, 1999). Patients self-corrected mistakes on the Stroop (Stroop, 1935) interference trial more frequently ($p < .03$) and recalled more words ($p < .02$) on the delayed cued recall condition of the Buschke Selective Reminding Task (Buschke, 1973). Performances declined when ERT was discontinued.

Henderson *et al.* (1996) designed a study to identify specific cognitive functions enhanced by ERT in an AD population. Men and women with similar levels of AD symptoms were matched to women with AD who were receiving ERT. The women in the treatment condition performed significantly better than the women in the control group on the Boston Naming Test (Kaplan *et al.*, 1983; $\mu = 34.8 \pm 13.1$ vs. $\mu = 19.1 \pm 12.2$, $p < .003$), the Digit Span Forward ($\mu = 5.8 \pm 0.7$ vs. $\mu = 4.2 \pm 2.1$, $p < .008$) and Digit Span Backward ($\mu = 3.8 \pm 2.0$ vs. $\mu = 1.9 \pm 1.7$, $p < .01$) subtests of the WAIS-R (Wechsler, 1981), and a modified Clock Drawing task (Henderson *et al.*, 1989, after Goodglass and Kaplan, 1983; $\mu = 11.1 \pm 3.6$ vs. $\mu = 6.4 \pm 5.2$, $p < .01$). Women on ERT also performed better than control group men, but the differences were not statistically significant. The authors interpreted their results as consistent with findings that females with AD may have gender-associated differences that reflect a state of relative acquired estrogen deficiency.

Several retrospective studies of clinical registries have found at least a 45% lower relative risk factor for dementia in women receiving ERT (Birge, 1994; Henderson *et al.*, 1994; Mortel and Meyer, 1995). However, demographic factors and possible treatment variables in clinics make it difficult to generalize these findings to the population at large. Also, a risk reduction for vascular dementia has been linked to ERT, and not all these studies discriminated women with AD from those with vascular dementia. Nevertheless, in a retrospective study that matched patients with AD to controls on variables of age at menarche and age at menopause, Waring *et al.* (1999) reported an odds ratio of 0.42 for ERT of at least 6 months in control subjects vs. those with AD, which remained significant after education was adjusted for. There was a significant trend of decreasing odds ratios with increasing duration of ERT use.

Prospective epidemiological studies also suggest a significant reduction in risk for AD in women receiving ERT. Henderson, Paganini-Hill, and colleagues (Henderson *et al.*, 1994; Paganini-Hill and Henderson, 1994) found an approximatly 30% lower risk for ERT-using females than that for matched controls in their study of dementia at time of death in upper-middle-class women at the Leisure World retirement community. Researchers for the Baltimore Longitudinal Study of Aging (Kawas *et al.*, 1997; Morrison *et al.*, 1996) found a reduced risk of more than 50% for women who had ERT, compared with that for women who never had ERT. Notably, these investigators did not find an effect for duration of ERT. Similarly, Tang *et al.* (1996) found a 60% reduced risk and a later age of AD onset for women with a history of ERT. They found that this was true even for women with other significant AD risk factors such as possession of the APOE $\varepsilon 4$ genotype. Only one study, by Brenner *et al.* (1994), found no reduced risk, and this discrepancy may be partly due to differences in ERT delivery mechanisms (i.e., oral vs. oral plus injection or cream vs. injection or cream only) considered in that study. In their meta-analysis, Yaffe, Sawaya, *et al.* (1998) concluded that there is a 29% reduced risk of AD for estrogen users.

Summary

The data are inconsistent regarding circulating levels of estrogen and cognitive abilities for premenopausal women. The most consistent finding is a strength in color naming, although some researchers have found an effect on mental flexibility, fine motor dexterity, and verbal skills, including verbal memory. The data are also mixed regarding the effect of ERT on verbal memory for healthy post-menopausal women. Although controlled studies of younger women who undergo surgical menopause consistently demonstrate enhanced ability on paragraph-recall tasks, for postmenopausal women, ERT immediate benefits may be limited to symptomatic women in the immediate postmenopausal period. The issues regarding how affective features associated with menopause may interact with attention and memory have not yet been teased apart. Also, distinctions between the effect of ERT on symptomatic vs. asymptomatic postmenopausal women remain to be clarified. Nevertheless, ERT does appear to improve verbal memory and general cognitive functioning in women with AD. Of even greater consequence are several studies that have found that ERT appears to lower women's risk of developing AD, perhaps by as much as 50%.

Thyroid Hormones

The thyroid gland is located just below the larynx and anterior to the trachea, opposite the fifth, sixth, and seventh cervical vertebrae and the first thoracic vertebra. It consists of two oblong, shield-shaped lobes, each approximately 2.5 cm wide by 4.5 cm long and 20 g in weight, connected by a narrow portion termed the *isthmus*. This gland consists of densely packed follicles containing approximately 100 days' average output of thyroglobulin, a protein that contains the thyroid hormones within its molecule. The main function of the thyroid gland is the synthesis of the principal thyroid hormones triiodothyronine and thyroxine—commonly referred to as T_3 and T_4, respectively—which are largely responsible for regulating the metabolic rate of the body. The functions of T_3 and T_4 are the same, but they differ in speed and intensity of action. T_3 is approximately 10 times more potent than T_4 but is present in smaller quantities and persists for shorter periods. The thyroid hormones result from iodine processed in the presence of TSH, a product of the anterior pituitary gland. This in turn is regulated by TRH, which is synthesized in the hypothalamus and is subject to the influence of a number of neurotransmitters as well as exogenous factors such as temperature and stress. Normal serum levels for TSH, total T_3, and total T_4 are 0.4–5.0 μU/ml, 88–160 ng/dl, and 5.0–12.0 μg/dl, respectively.

Although the classic action of thyroid hormones is the stimulation of heat production, their influence on metabolic processes throughout the organs and tissues is significant. Accordingly, variability of thyroid functioning occurs both as a result of primary dysfunction of the thyroid gland and as a secondary result of systemic illnesses. The hormones and their receptors are widely distributed throughout the brain. Their regulatory action on the central nervous system appears to include the effects on adrenergic function, striatal dopaminergic activity, and levels of substance P and serotonin.

Administration of TRH in normal, neurological, and psychiatric populations appears to increase levels of motivation, relaxation, and adaptation in a non-disease-specific manner (Loosen, 1992). Among patients who are depressed, subclinical levels of hypothyroidism may be present. Additionally, administration of tricyclic antidepressants (TCA) appears to be augmented by T_3 and can convert response failure with TCAs to success in up to 66% of patients (Joffe and Singer, 1990). TRH is known to directly affect the central nervous system (Bennett *et al.*, 1989) and has been investigated for use as a potential therapeutic agent in AD (Kelly, 1995). Also, there is evidence that postictal cognitive dysfunction in patients undergoing electroconvulsive therapy may be mitigated by administration of TRH (Khan *et al.*, 1994; Stern *et al.*, 1991).

Hyperthyroidism

In most patients with hyperthyroidism, the thyroid gland undergoes a two- to three-fold increase in size. When associated with diffuse goiter, ophthalmopathy, and dermopathy due to an autoimmune disorder (i.e., the presence of antibodies to TSH receptors), hyperthyroidism is referred to as *Graves' disease*. Notable symptoms include excitability, intolerance to heat, increased sweating, weight loss, muscle weakness, fatigue with dyssomnia, anxiety, and tremor. Increased metabolic rates may be accompanied by abnormal cardiovascular rates, myopathy, and autonomic tremor. These symptoms are mediated by increased serum levels of T_3 and T_4 and their action on the catecholaminergic system. The incidence of this disorder is approximately 0.3:1,000 in the United States. The condition peaks during the third and fourth decades of life and is 7 to 10 times more common in women than in men. The explanation for this gender difference and for the underlying cause of the disease is unknown. However, immune dysfunction is more common in women in general. Among older patients, symptoms of hyperthyroidism may be more subtle and include apathy, limb myopathy, and cardiovascular disease. Also, there is an association between hyperthyroidism and myasthenia gravis (MG): Approximately 5% of patients with MG manifest hyperthyroidism.

Prominent psychiatric symptoms have complicated the differential diagnosis since the earliest descriptions by Parry (1825) and Graves (1835), both of whom attributed elevated thyroid activity to psychogenic etiology. Möbius (1886) was the first to identify these symptoms as secondary to hyperfunction of the thyroid gland. Psychiatric symptoms such as irritability, anxiety, insomnia, weight loss, change in appetite, and hyperkinesis, paired with relatively subtle cognitive problems in aspects of attention and mental control, can continue to lead patients and health professionals to form an initial impression of an anxiety or a mood disorder. Additional diagnostic ambiguity may result from the presentation of typical somatic symptoms of anxiety such as tremor and tachycardia, which are consistent with peripheral sympathetic activation. Enhanced sympathetic tone in hyperthyroidism is not due to increased catecholamine levels, however, but is thought to be due to increased sensitivity of certain receptors to norepinephrine, secondary to increased levels of thyroid hormones. Classic clinical features of hyperthyroidism that may clarify the differential diagnosis include increased heat sensitivity, prominence of the eyes, diplopia, and goiter.

According to a survey by Stern *et al.* (1996), it is likely that many health professionals initially interpret the presenting symptoms of Graves' disease as a primary psychiatric disorder. Patients' psychiatric symptom patterns in Graves' disease vary; many individuals meet criteria for multiple diagnoses including major depression, generalized anxiety disorder, panic disorder, agoraphobia, hypomania, obsessive–compulsive disorder, and obsessive–compulsive personality disorder. Nevertheless, a common symptom across a number of studies appears to be the presence of anxiety, which is common in both frequency and severity of report.

Studies investigating cognitive problems in Graves' disease have focused on identifying the nature of cognitive dysfunction in the hyperthyroid state and on determining the degree of resolution upon the patient's returning to a euthyroid state following treatment (Beckwith and Tucker, 1988). The first such study, by Artunkal and Togrol (1964), compared patients with hyperthyroidism with matched normal controls on tests of motor performance and reaction time on visual and auditory discrimination tasks. The patient group performed significantly worse than the controls did on a number of these measures, which produced a clinical picture of fatigued individuals. When retested in a euthyroid state, the patients showed no significant improvement in visual discrimination, reaction time, or fine motor ability.

Whybrow *et al.* (1969) compared patients with hyperthyroidism and patients with hypothyroidism on a number of psychiatric and neuropsychological measures. Although both subject groups had reduced scores initially, patients in the hyperthyroidal group performed better on the Trail Making (Reitan and Davison, 1974) and Porteus Maze (Porteus, 1959) tests following treatment than did either the treated or the untreated patients with hypothyroidism. Although these findings are suggestive of a readier recovery of cognitive functioning following treatment for hyperthyroidism, without the use of a control group of healthy matched subjects, one does not know whether the results were due in part to differential retest characteristics of the study groups. Another study, comparing women with hyperthyroidism and healthy matched controls on measures of attention (Stroop Test: Stroop, 1935), paired associates learning (Wechsler Memory Scale: Wechsler, 1945), motor speed (Tapping Test: Reitan, 1955), and speed of information processing (The Spokes Test: Reitan, 1955), revealed no statistically significant differences between the groups (MacCrimmon *et al.*, 1979; Wallace *et al.*, 1980). Within the patient group, however, T_4 levels were associated with weaknesses in concentration and memory. This correlation disappeared following treatment, but patients with initial elevated levels of T_4 continued to demonstrate weakness on the paired associates task. Alvarez *et al.* (1983) did not find a correlation between T_4 and attention but did find that patients with hyperthyroidism performed significantly worse on a test of attention (Tolouse-Pieron Concentration Attention Test: Szekely, 1966) than did healthy controls.

In a study comparing 26 patients with hyperthyroidism and a control group with nontoxic goiter, 2 years and 10 years following treatment, Perrild *et al.* (1986) found evidence of ongoing neurocognitive dysfunction due to hyperthyroidism. Fifty-four percent of the treated individuals manifested cognitive dysfunction at 10 years post treatment, and in half of these persons, the dysfunction was described as marked to severe in range. Weaknesses were identified in the areas of attention, concentration, conceptual reasoning, visuospatial processing, and long-term memory. However, 31% of the controls scored in the mildly impaired range on certain of the measures. The authors did not detail psychiatric or other factors that might have accounted for these intra- and intergroup findings.

More recently, Trzepacz, McCue, Klein, Greenhouse, *et al.* (1988) and Trzepacz, McCue, Klein, Levey, *et al.* (1988) examined the performances of 10 subjects with hyperthyroidism on measures of psychiatric symptoms and attention at three stages: baseline (hyperthyroidal) assessment, following treatment with propranolol (an anxiolytic) for 2 weeks, and following 6 months of antithyroid treatment. Although psychiatric symptoms improved following both treatment phases, significant improvement in attention as measured by the Stroop Test *color* ($\mu = 77.2 \pm 8.4$ to $\mu = 85.8 \pm 5.8$, $p < .03$) and *color-word* ($\mu = 39.2 \pm 10.8$ to $\mu = 52.0 \pm 8.9$, $p < .01$) conditions (Stroop, 1935) was observed only following the third stage of treatment with an antithyroid agent. This was in contrast to the earlier studies, which found only subtle differences or no improvement between hyperthyroid and euthyroid states. Also in contrast to earlier studies, the authors found a *positive* correlation between levels of T_4 and tests of attention during the hyperthyroid state. The authors suggested that these findings were consistent with a noradrenergic effect on attention related to dose in an inverted U-shaped curve. Other neuropsychological tests were administered at treatment stages 1 and 3 only. As in earlier studies, reductions in fine motor speed and simple attention did not improve significantly with time. Significant improvements on measures of IQ (WAIS-R: Wechsler, 1981), conceptual reasoning (Category Test: Halstead, 1947; Reitan and Davison, 1974), visual-spatial processing (Tactual Performance Test: Reitan and Davison, 1974), and memory (Wechsler Memory Scale: Wechsler, 1945) were attributed to practice effects and/or a lessening of

psychiatric symptoms, not to structural or neurophysiological changes. Supporting the hypothesis that thyroid hormones may correlate with attention according to an inverted U-shaped curve, Schlote *et al.* (1992) also found reduced psychomotor speed in overt but not subclinical cases.

Despite the inconclusive nature of the aforementioned investigations regarding the relationship of hyperfunction of the thyroid and neurocognitive test performance, these findings are generally consistent with patient reports of initial dysfunction in both psychiatric and cognitive realms followed by a partial return to baseline functioning. Moreover, Bommer *et al.* (1990) found that a less complete neuropsychological recovery was characteristic of patients who relapsed within 2.5 years of initial treatment. In Stern *et al.*'s (1996) survey, 33.1% of respondents reported being prescribed psychotropic medication following diagnosis of Graves' disease, even though only 7.7% of the sample reported such treatments as part of their premorbid history. Furthermore, 24% reported ongoing problems in cognitive functioning, especially slowed mental processing and memory problems. Overall, patients reported significant differences between premorbid and current (euthyroid) levels of functioning in the areas of memory, attention, planning, and productivity, which suggests that cognitive problems persist following stabilization of thyroid functioning. However, no tests for interactions between ongoing psychiatric and cognitive symptoms were reported, so it is unclear whether these problem areas are independent or related.

Hypothyroidism

Children born with congenital hypothyroidism (CH) are typically identified at birth. In the United States, the incidence is 1:5,000 in the White population and 1:32,000 in the Black population. Early intervention prevents the development of severe motor and sensory impairments as well as mental retardation. Nevertheless, meta-analysis demonstrates a relatively small but significant trend toward lower IQ (≈6.3 points) and reduced motor skills in treated children with CH (Derksen-Lubsen, 1996). This finding has been replicated in a study of identical twins, only one of whom was affected by CH, secondary to thyroid dysgenesis. Although the affected twin performed within normal limits at 8 years of age, her IQ was 7 points lower and she consistently performed worse than her sister on tasks of writing, reading, and verbal memory (Bargagna *et al.*, 1997). Absence or delay in treatment leads to severe cognitive problems: In one study, 45% of patients obtained IQ scores below 70 and only 28% scored above 85 (Mendorla *et al.*, 1988). Similarly, rearing in an environment deficient in iodine results in cognitive weaknesses, particularly with respect to the development of psychomotor skills. The severity of the cognitive dysfunction appears to be linked to the extent of the iodine deficiency (Aghini-Lombardi *et al.*, 1995; Fenzi *et al.*, 1990; Sankar *et al.*, 1994; Vitti *et al.*, 1992).

Adult hypothyroidism, typically associated with an autoimmune mechanism, is the result of decreased serum levels of thyroid hormones. The incidence of primary hypothyroidism is approximately one-eighth that of hyperthyroidism, being four to seven times more common in females than in males. Hypothyroidism is also commonly associated with hypothalamic–pituitary disease. The condition can also result from Hashimoto's thyroiditis, a condition roughly comparable to Graves' disease in incidence, in which the thyroid gland at first enlarges and subsequently atrophies. Another important cause is iatrogenic (e.g., after treatment for Graves' disease). The number of older adults at risk for hypothyroidism steadily increases with age (Osterweil *et al.*, 1992).

The clinical symptoms of hypothyroidism reflect the numerous physiological systems subject to thyroid dysfunction: intolerance to cold; puffy face; coarse, dry skin and hair; fatigue and somnolence; muscular sluggishness; decreased heart rate and cardiac output; weight gain; depressed growth of hair; development of a husky voice; and edematous body tissue. Because a lack of thyroid hormone increases levels of serum cholesterol, hypothyroidism is also associated with arteriosclerosis. Psychiatric symptoms include depression, paranoia, and psychotic ideation, and neurological symptoms range from myopathy and ataxia to cognitive confusion and dementia. Diagnostic findings include low circulating T_3 and T_4 levels, elevated TSH, low radioiodine uptake by the thyroid gland, and an increase in cerebrospinal fluid protein.

Cognitively, severe hypothyroidism is considered a "reversible" dementia with treatment by thyroid replacement therapy. However, variables mediating the extent of recovery following treatment are still being investigated. Mennemeier *et al.* (1993) pointed out that although thyroid replacement therapy is associated with remission of psychiatric symptoms, the link with improved cognitive functioning is less well established. Although both patients with hyperthyroidism and those with hypothyroidism report a range of psychiatric symptoms that have a great deal in common, hypothyroidism most typically presents with depression in combination with motor retardation, not anxiety and agitation (Whybrow *et al.*, 1969).

Impairment in cognition has been noted in patients with hypothyroidism since Gull's (1873) initial description of "a cretinous state supervening in adult life in

women" due to hypothyroidism. Similarly, some of the first modern reports noted impairment in intellectual capacities (Crown, 1949; Reitan, 1953). Moreover, of six studies utilizing unselected patient populations—Crown, 1949; Denicoff *et al.*, 1990; Jain, 1972; Reitan, 1953; Schon *et al.*, 1961; and Whybrow *et al.*, 1969—cognitive impairment, not psychiatric disturbance, was noted to be the primary problem in four—Crown, 1949; Denicoff *et al.*, 1990; Reitan, 1953; and Schon *et al.*, 1961. Although several of the six studies attempted to assess response to treatment, results have been inconclusive. Initial reports (Crown, 1949; Schon *et al.*, 1961) indicated improvement in general cognitive functioning following thyroid replacement therapy. However, design and measurement problems may have distorted these findings. Whybrow *et al.* (1969) reported subjective complaints of memory problems, observer reports of poor general cognition, and weaknesses in concentration (Trail Making: Reitan and Davison, 1974) and problem solving (Porteus Maze Test: Porteus, 1959), with no improvement following return to a euthyroid condition. Interpretation of these findings is complicated by use of a comparison group comprising patients with hyperthyroidism, not healthy normal subjects. Denicoff *et al.* (1990), using a mental status exam and the WAIS-R Digit Symbol subtest (Wechsler, 1981), also reported no change in cognitive functioning following therapeutic intervention.

One recent large-scale study by Osterweil *et al.* (1992) examined hypothyroidism and the effect of thyroid replacement among older adults without dementia. Fifty-four men and women with hypothyroidism ranging from minimal to overt and untreated for varying lengths of time were compared with 30 euthyroid controls. Hypothyroidal patients in general performed significantly worse than controls did ($p < .01$) on tests of general cognitive function (Mini-Mental State Exam; $\mu = 26.1$ vs. $\mu = 28.7$), cube drawing, paired associate learning (Inglis, 1959), animal naming, and psychomotor speed (Trail Making A: Reitan and Davison, 1974; Symbol Digit Modalities Test: A. Smith, 1982). However, among the patients with minimal hypothyroidism, no performances were significantly reduced relative to those of controls. Moreover, differences in cognitive functioning were apparent between the minimal and overt hypothyroidal groups on all indices except Digits Forward (Wechsler, 1981) and a set of Yes/No questions and Sequential Commands adapted from the Boston Diagnostic Aphasia Examination (Goodglass and Kaplan, 1983). Also, the control subjects and the patients with overt hypothyroidism whose duration of thyroid dysfunction was brief (10–20 days, secondary to discontinuation of thyroid hormone replacement following thyroidectomy) displayed no statistically significant differences on neuropsychological tests.

A subset of these patients was available for retesting following 5 months of thyroid replacement therapy. Improvement was detected on the Symbol Digit Modalities Test (A. Smith, 1982; $\mu = 33.6$ to $\mu = 37.9$, $p < .016$), Trail Making A (Reitan and Davison, 1974; $\mu = 67.9$ to $\mu = 56.4$, $p < .03$), and Inglis Paired Associates medium association items (Inglis, 1959; $\mu = 0.86$ to $\mu = 0.93\%$ correct, $p < .0006$), which suggests that attention, psychomotor speed, and learning were the principal functions that responded to treatment. A lack of significant improvement on a number of other tests, including animal naming, Digits Forward and Digits Backward (WAIS-R; Wechsler, 1981), and Trail Making B (Reitan and Davison, 1974), suggested that some dysfunction in aspects of effortful attention may persist for certain patients despite treatment. Finally, the authors reported evidence that age may increase vulnerability to the effects of hypothyroidism on cognitive functioning.

Thyroid replacement therapy such as that used in the aforementioned studies typically consists of administration of thyroxine (T_4) alone. A recent study (Bunevicius *et al.*, 1999) compared cognitive improvement in patients with hypothyroidism treated with T_4 alone vs. T_4 plus triiodothyronine (T_3). Each patient received a 5-week treatment of each protocol, and the order was randomized. Subjects receiving the combination therapy performed significantly better on Digits Backward (Wechsler, 1981) and on incidental learning recall of Digit Symbol pairs (Wechsler, 1981). Although the results were statistically significant, their clinical significance is unclear. For Digits Backward, raw score means of 5.5 ± 1.6 and 6.0 ± 1.3 ($p < .04$) were obtained for monotherapy and combination therapy, respectively. Similarly, for Digit Symbol pairs, raw score means of 5.5 ± 2.3 and 6.3 ± 2.1 ($p < .05$) were obtained for monotherapy and combination therapy, respectively. The results of other cognitive measures did not reach significance, including those for Digits Forward, speed indices on Digit Symbol, and a test of visual scanning.

Researchers of minimal and subclinical hypothyroidism have found that a complete return to baseline following treatment may be anticipated. Monzani *et al.* (1993) obtained pretreatment Memory Quotient scores on the WMS-R (Wechsler, 1974) of 89.1 for a group of subclinical patients with hypothyroidism. Following treatment and return to a euthyroid state, patients' scores rose to 99.9. Similarly, Baldini *et al.* (1997) found improved memory performance on the WMS-R in a subclinical hypothyroid population following return to a euthyroidal state.

Nevertheless, recent case studies provide evidence of persistent cognitive deficits despite thyroid replacement therapy in patients with severe hypothyroidism. Leentjens

and Kappers (1995) reported the case of a 43-year-old female administrator who was severely incapacitated by problems with concentration and memory following extensive treatment for hypothyroidism. Reduced performances on a continuous performance test, Digit Span and Digit Symbol subtests of the WAIS-R (Wechsler, 1981), recall of the Rey Complex Figure (Rey, 1941) and Benton Visual Retention Test (Benton, 1974; Sivan, 1992), and the Rivermead Behavioral Memory Test (Wilson *et al.*, 1985) supported the patient's complaints of difficulty reading books and magazines, watching television, following conversations, and driving, despite the absence of depressive symptoms.

In another single case study, with the benefit of multiple control subjects, Mennemeier *et al.* (1993) reported initial impairment on a number of verbal and visual memory indices. Improvement in a range of cognitive and psychiatric symptoms following diagnosis but preceding treatment suggested the influence of nonspecific treatment effects. Repeated measures obtained during 7 months of thyroid replacement therapy revealed significant ongoing memory dysfunction relative to the function of controls, despite modest improvement. Measures included the Wechsler Memory Scale (Wechsler, 1974) and the Buschke Selective Reminding Test (Buschke and Fuld, 1974) with various alternate forms. The authors suggested that although memory may not have been significantly helped by thyroid replacement therapy in this patient, such treatment may have arrested a progressive deterioration of mnestic functioning due to hypothyroidism.

Recent animal studies support the hypothesis of irreversible cognitive dysfunction due to hypothyroidism. Selective cell destruction in the hippocampus was demonstrated in rats that underwent thyroidectomy or were made hypothyroidal by injection with propylthiouracil (Madeira *et al.*, 1992). Return to a euthyroid condition did not correct for the cell loss.

Summary

Despite the high frequency of disorders of thyroid function and the prominence of the associated cognitive symptoms, research on neuropsychological patterns of impairment and recovery is sparse. The preceding findings suggest that neurocognitive dysfunction results from both increased and decreased levels of thyroid hormones. The former is associated with impairment or reduction in fine motor speed, attention, and memory, and the latter with general cognition, attention, learning, and psychomotor speed. Recovery following treatment appears to be more complete for hyperthyroidism and mild hypothyroidism than for severe hypothyroidism, in which thyroid replacement therapy may serve to arrest a progressive process. Moreover, in both hyper- and hypothyroidism, impairment and recovery of cognitive functioning appears to be relatively independent of resolution of psychiatric symptoms.

Adrenal Hormones I: Cortisol

The adrenal glands weigh approximately 4 g each and are located at the superior poles of the kidneys. Each gland is divided into two distinct portions: the adrenal medulla, which secretes the hormones epinephrine and norepinephrine and is functionally related to the sympathetic nervous system, and the adrenal cortex, which secretes the hormones known as *corticosteroids*, of which cortisol is of principal interest in regard to cognitive functions. Another adrenal hormone, dehydroepiandrosterone (DHEA), has recently been studied for its possible effects on mood and memory and is discussed subsequently. The adrenal glands also produce small amounts of certain androgens, which are similar in function to testosterone. These are discussed in the context of CAH in the preceding section on male sex hormones.

The hypothalamic–pituitary–adrenal axis is the endocrine system most integral to the body's reaction to physiological stressors. It prepares the organism to respond to environmental stimuli and maintains homeostasis. Cortisol is integral to these preparations through its role in increasing blood glucose concentrations, which in turn mobilizes available energy stores. The axis is controlled by a feedback loop as follows: Corticotropin-releasing hormone (CRH) is produced by hypothalamic neurons both according to a circadian pattern and in response to physiological stress. CRH regulates the release of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH stimulates the adrenal glands, which in turn produce cortisol. Cortisol completes the feedback loop by its effect on the hypothalamus and other structures. Further modulation of the hypothalamus and pituitary are provided through the amygdala, the hippocampus, and other pathways. The normal plasma ACTH level is 10–52 pg/ml. Normal serum cortisol levels range from 3–20 μg/dl in the morning to 2.5–10.0 μg/dl in the afternoon.

In normal subjects, short- and long-term administration of exogenous corticosteroids has been shown to produce mild dysfunction of verbal mnestic processes, although it is unclear whether this is due to disruption of attentional factors, memory processes, or both (Naber *et al.*, 1996; Wolkowitz, 1994; Wolkowitz *et al.*, 1990). On a verbal learning test, higher rates of intrusion errors were associated with dexamethasone, and poor discrimination

on a recognition paradigm was associated with prednisone (Wolkowitz, 1994). McEwen (1982) has suggested that deficits such as these may be due to impaired filtering of stimuli by the hippocampus. In contrast, Naber *et al.* (1996) reported improved performances on Trails A (Reitan and Davison, 1974) and verbal fluency measures, which they attributed to a hyperactivating effect or "sensory sharpness" due to cortisol.

Elevated cortisol levels are also evident among many patients with major depression, in whom memory and attention problems have been frequently observed (Carroll, 1982). However, there is not evidence that elevations in serum cortisol levels can account for the range of cognitive problems associated with depression. Also, there is evidence that hypersecretion of the hypothalamic–pituitary–adrenal axis releasing hormone CRH, not cortisol, plays the more important role in mediating cognitive problems in patients who are depressed (Muglia *et al.*, 1995).

Hypercortisolism

Cushing's syndrome refers to the clinical manifestation of increased concentrations of cortisol and generalized catabolism: truncal obesity, plethoric (full) facies, hirsutism and baldness, osteoporosis, and generalized muscular weakness. Psychiatric symptoms may include depression, anxiety, and psychosis (i.e., "steroid psychosis"). Cognitive functions may be affected, including disruptions in orientation, concentration, memory, and comprehension (Starkman and Schteingart, 1981; Whelan *et al.*, 1980). The condition may be the result of a pituitary adenoma, a primary adrenal tumor, ectopic production of ACTH by a carcinoma of the lung, or, frequently, the long-term treatment of a variety of diseases with exogenous cortisol such as cortisone or prednisone. Ectopic ACTH syndrome due to a carcinoma is three times more prevalent in men than in women and has its highest incidence between ages 40 and 60.

When due to the secondary effects of a pituitary adenoma, the condition is known as *Cushing's disease.* In this case, a hypothalamic–pituitary defect, most typically a pituitary tumor, causes hypersecretion of ACTH, which leads to increased cortisol secretion. Onset is typically between the ages of 20 and 40, but this disease has been reported in infants and in patients older than 70 as well. Unlike Cushing's syndrome, Cushing's disease develops in females eight times more often than in males. There is some evidence that psychiatric disturbances may be more frequent in cases of pituitary hyperfunction (i.e., Cushing's disease) than in cases of adrenal adenomas (i.e., Cushing's syndrome) because of the higher levels of ACTH associated with the former condition (Starkman *et al.*, 1981). Also, because the tumor may exert a mass effect on other portions of the pituitary gland, other endocrine complications such as diabetes insipidus, hypertension, and amenorrhea or impotence may be comorbid.

Initial studies of neuropsychological function in patients with Cushing's syndrome revealed a pattern of diffuse bilateral frontal dysfunction manifesting as poor concentration, comprehension, and orientation, together with impairments in visual memory, nonverbal reasoning, and spatial/constructional ability (Whelan *et al.*, 1980). In a subsequent study, however, weaknesses in visuospatial functions were found to correlate with affective and vegetative symptoms (Starkman *et al.*, 1986), which suggests that depressive symptoms had confounded the earlier findings. The authors noted, however, that they did not find significant correlations between depressive symptoms and memory problems.

Neuroimaging has suggested that the hippocampus may play a role in mnestic dysfunction of patients with Cushing's disease. Starkman *et al.* (1992) reported significant positive correlations between hippocampal volume and measures of verbal memory, together with significant negative correlations between hippocampal volume and plasma cortisol levels. However, improvement in memory following normalization of cortisol levels indicated that corticosteroids can cause cognitive deficits independent of hippocampal neuron loss. Such a mechanism is suggested by the animal literature, in which corticosterone has been shown to suppress hippocampal excitability and long-term potentiation (Bliss and Lomo, 1973; Gufstafsson and Wigstrom, 1988) in a concentration-dependent manner (M. C. Bennett *et al.*, 1991). However, generalization of these findings is uncertain because corticosterone and cortisol differ in their behavioral effects in humans.

A recent study compared the performance of 25 patients with Cushing's disease without psychosis and/or severe affective symptoms as determined by both clinical interview and objective self-report (Minnesota Multiphasic Personality Inventory [MMPI]; Hathaway and McKinley, 1943) with the performance of a control group on an extensive neuropsychological battery (Mauri *et al.*, 1993). Moderate dysfunction was identified relative to the function of controls on the Logical Memory (I: $\mu = 6.3 \pm 2.2$ vs. $\mu = 8.3 \pm 2.4$, $p < .01$; II: $\mu = 7.1 \pm 3.1$ vs. $\mu = 10.0 \pm 2.5$, $p < .001$) and Visual Reproductions (I: $\mu = 8.8 \pm 3.7$ vs. $\mu = 10.9 \pm 2.2$, $p < .05$; II: $\mu = 6.8 \pm 3.9$ vs. $\mu = 10.0 \pm 2.2$, $p < .001$) subtests of the Wechsler Memory Scale (Wechsler, 1945). In addition, weaknesses on the Digits Backward ($\mu = 3.5 \pm 0.8$ vs. $\mu = 4.1 \pm 0.8$, $p < .01$) and the Digit Symbol ($\mu = 36.8 \pm 14.1$ vs. $\mu = 47.3 \pm 11.2$, $p < .01$) subtests of the WAIS-R (Wechsler, 1981) indicated problems with attention/concentration

and, possibly, visuomotor functioning. No correlations between ACTH/cortisol levels and cognitive performances were found for the patients with Cushing's disease. However, in 8 of these subjects retested 6 months following surgical ablation of the neoplasia, normalization of ACTH and cortisol levels was accompanied by a significant amelioration of memory dysfunction.

Among older persons, increases in cortisol levels with time are predictive of weaknesses in explicit memory and selective attention (Lupien *et al.*, 1994). Significantly, increases in cortisol levels have been associated with hippocampal atrophy in patients with AD, independent of depressive symptoms (Davis *et al.*, 1986; Dodt *et al.*, 1991). Also, hippocampal atrophy has been found in patients with post-traumatic stress disorder, in whom elevated cortisol levels are thought to be associated with a traumatic emotional stressor (Bremner *et al.*, 1995). Further, although corticoid receptors have been shown to be present throughout the brain, a concentration of receptors with a high affinity for corticosterone is present in the hippocampus (Ruel and DeKloet, 1985; Sarrieau *et al.*, 1988). These findings support the hypothesis that increased adrenal activity can account in part for age-related hippocampal pathology and memory dysfunction due to elevations in cortisol, ACTH, and/or CRH. Moreover, there is evidence from the animal literature that the hippocampus plays a major role in the regulation of pituitary–adrenal activity (for a discussion, see Jacobson and Sapolsky, 1991).

Chronic Hypocortisolism

Adrenal cortical insufficiency, a primary disease of the adrenals also known as *Addison's disease*, may result in conditions ranging from mild generalized weakness to sudden-onset vascular collapse. Insufficient production of cortisol is accompanied by increased CRH and ACTH levels due to decreased feedback to the hypothalamus and anterior pituitary. This disease is characterized by pigmentation of the skin and mucous membranes, nausea, vomiting, weight loss, muscle weakness, fatigue, and dizziness. Psychiatric symptoms include depression, confusion, apathy, psychosis, paranoia, schizophrenic behaviors, and self-mutilation (Johnstone *et al.*, 1990). The etiology is typically an autoimmune adrenalitis due to tuberculosis, malignancy, sarcoidosis, or infection but may also result from bilateral adrenal hemorrhage after sepsis, trauma, surgery, or burns (Claussen *et al.*, 1992; Murphy *et al.*, 1993; Szalados and Vukmir, 1994). Secondary adrenal insufficiency may also result from disease of the pituitary or hypothalamic lesions. Primary Addison's disease is rare, with a prevalence of approximately 39 per 1 million. It is more common in females than in males (2.6:1) and is usually diagnosed in the third to fifth decades of life.

Despite reports of depression, apathy, and confusion, investigations of neurocognitive functioning of patients with hypocortisolism are few. One case of primary adrenal insufficiency due to a traumatic brain injury provides some insight into the nature of the condition. In their case study, Webster and Bell (1997) reported confusion and severe problems with short-term memory and attention in a 31-year-old male 6 weeks after severe traumatic brain injury. The patient also manifested obsessive and paranoid thoughts, anxiety, and depressive features. Diagnosed at that point with primary adrenal insufficiency, the patient was treated with adrenal replacement therapy. After 2 weeks, the patient was participating in 3 hours of therapy per day, including a 45-min speech therapy session, which indicated significant improvement in attentional processes. The patient's history of depressed skull fractures, bifrontal epidural hematomas, and frontal contusions indicate that traumatic etiology, not adrenal insufficiency, likely accounted for a significant degree of the cognitive dysfunction observed. However, the patient's positive response to the hormonal intervention underscores the importance of the adrenal system in general metabolic functioning. Notably, the patient was eventually able to return to work, resume driving, and participate in leisure activities.

Summary

In studies of hypercortisolism due to exogenous and endogenous factors, there is a clear association with impaired hippocampal functioning. Although improvement in mnestic capacity may result following normalization of cortisol levels, there is evidence supportive of permanent neurotoxic effects on the hippocampal structures due to hypercortisolism. Age-related increases in cortisol are similarly associated with memory dysfunction, independent of mood. Although little researched, hypocortisolism appears to be associated with attentional and motivational factors as they influence cognition. Finally, the different roles that CRH, ACTH, and cortisol play in cognition and behavior are only beginning to be understood, although there is evidence that they may vary considerably.

Adrenal Hormones II: Dehydroepiandrosterone

The biological roles of dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) have recently been the subject of much investigations because of the decrease of these hormones with normal aging and their correlation

with age-related immune system decline (Thoman and Weigle, 1989). Epidemiological data have demonstrated an association between low circulating DHEA levels and cardiovascular morbidity in males (Barrett-Connor *et al.*, 1986) and breast cancer in females (Helzlsouer *et al.*, 1992). DHEA is also thought to affect behavior and cognition. Although the precise mechanism of action has not yet been identified, DHEA has been found in the brain and may mediate certain interactions with GABA receptors (Robel and Baulieu, 1994). DHEA-S has been identified as a potent GABA antagonist (Deutsch *et al.*, 1992). The reference range for serum DHEA is 160–800 ng/dl for adult males and adult premenopausal females. The Postmenopausal female range is 30–450 ng/dl. For DHEA-S, normal serum levels are 110–690 μg/dl for adult males and 80–340 μg/dl for adult premenopausal females. For males older than 50 years and postmenopausal females, normal serum levels are 40–330 μg/dl and 17–77 μg/dl, respectively.

In healthy subjects, the effects of DHEA appear to be on general well-being. Morales *et al.* (1994) administered replacement doses, sufficient to raise levels comparable to those of 20-year-olds, to a group of men and women aged 40–70. Self-report indices gathered during the 6-month duration of the double-blind, placebo-controlled study indicated an effect of DHEA on a range of variables, including increased energy, deeper sleep, improved mood, greater relaxation, and better stress-handling capacity. However, despite a number of animal studies demonstrating antiamnestic properties (Flood *et al.*, 1988; Frye and Sturgis, 1995; Melchior and Ritzmann, 1996), DHEA administration had no benefit on memory tests for either young subjects receiving a single replacement treatment (Wolf, Koster, *et al.*, 1997) or for older subjects receiving a 2-week DHEA replacement protocol (Wolf, Neumann, *et al.*, 1997).

Specific cognitive benefits were found, however, in pilot studies of patients with major depression receiving DHEA supplements (Wolkowitz *et al.*, 1994, 1997). Using standardized psychiatric rating scales and verbal tasks measuring semantic encoding, free recall, recognition memory, and categorical fluency, the researchers identified significant mood enhancement but no improvement in cognitive performance following 6 months of replacement therapy. For a single subject, however, a 63% improvement in categorical fluency was accompanied by substantial improvement on mood indices. These gains declined to baseline levels when her treatment ended. Mood and cognition were significantly related to plasma levels of DHEA and DHEA-S for this patient.

DHEA-S has also been the subject of study. Yaffe, Ettinger, *et al.* (1998) found that during a 4-year period, DHEA-S levels did not predict cognitive performance or decline in older women on the Trail Making B (Reitan and Davison, 1974) or Digit Symbol subtest (Wechsler, 1981). Elevation in DHEA-S has been identified as a possible cause of neurobehavioral disturbances in certain individuals with anomalous brain substrates. A. R. Jacobs *et al.* (1995) diagnosed adult-onset CAH in a series of 12 patients referred for refractory psychiatric disturbances. A majority of anxiety-related disturbances underscored the action of DHEA-S as a GABA antagonist. Each patient had evidence of an anomalous brain substrate such as neuropsychological deficits and/or EEG abnormalities. Treatment with adrenal suppressive therapy produced amelioration of psychiatric symptoms in all cases in which endocrine correction was obtained.

Pancreatic Hormones and Insulin

Along with its role in digestion, the pancreas secretes a number of hormones that regulate glucose levels in the bloodstream. In the pancreas, the islets of Langerhans contain three principal cell types—alpha, beta, and delta—which secrete glucagon, insulin, and somatostatin, respectively. Together, these hormones are regulated by means of feedback loops as well as through their direct actions on one another within the islets of Langerhans.

Insulin is secreted in response to energy-giving foods, such as carbohydrates and proteins, and causes them to be stored as glycogens in the liver and muscles, and as fats in other tissues, in order to meet future energy needs. It inhibits the release of glucose into the bloodstream and causes enhanced glucose uptake from the blood by the liver. It is important in promoting protein formation and in preventing protein degeneration, thus promoting growth in a synergistic relationship with GH. The normal serum level is 5–25 μU/ml (0.2–1 ng/ml) for fasting adults.

Glucagon is secreted in response to low blood glucose concentrations and thus plays a role diametrically opposed to insulin. That is, glucagon is responsible for breaking down liver glycogens and for gluconeogenesis, the process that releases glucose into the bloodstream. Somatostatin acts directly to inhibit both insulin and glucagon within the islets of Langerhans.

Unlike other body tissues, which in addition to using blood glucose can use fats and proteins for energy, the brain depends on a steady glucose supply. Normal serum glucose levels are $\approx$90 mg/dl, and maintenance above a critical level is necessary for normal functioning. Even mild transient hypoglycemia has been found to affect healthy subjects' performance on psychomotor tasks (Mellman *et al.*, 1994). When glucose concentrations

fall too low, hypoglycemic shock develops, characterized by nervousness, sweating, irritability, and fainting, which leads to clonic seizures and, if untreated, coma. This hypoglycemic reaction may develop as a consequence of excessive administration of insulin by patients with diabetes, causing a syndrome known as *insulin shock*. Prolonged hypoglycemia typically results in permanent damage to the central nervous system secondary to both reduced cerebral oxygen consumption and decreased brain glucose metabolism (McCall, 1992).

Diabetes Mellitus

Diabetes mellitus is a term that applies to a group of disorders that produce chronic elevations in blood glucose levels, or *hyperglycemia*. In the United States, approximately 500,000 persons have been diagnosed with juvenile-onset insulin-dependent diabetes mellitus (IDDM), also known as *Type I diabetes*. The age of onset peaks at 10–14 years (Carter Center, 1985). Although the etiology is unclear, environmental factors are thought to cause an autoimmune reaction in genetically vulnerable individuals that destroys the beta cells within the pancreas, which thus curtails the body's insulin supply. Treatment is by means of intramuscular injection of insulin, with the primary goal of therapy being the maintenance of metabolic control by avoiding both hyperglycemic and hypoglycemic states.

Maturity-onset non-insulin-dependent diabetes (NIDDM), or *Type II diabetes*, is characterized by an insidious onset of symptoms due to hyposecretion of insulin and/or insulin resistance. The prevalence increases with age so that by 65 years, approximately 20% of the population may be affected (Winograd *et al.*, 1990). Estimates that include undiagnosed cases of impaired glucose tolerance more than double that figure (Minaker, 1990). Reports of gender differences vary, with higher rates reported both for women (Carter Center, 1985) and for men (Winograd *et al.*, 1990). Differences in diagnostic criteria likely account for these conflicting data. For many individuals diagnosed with NIDDM, metabolic control is frequently achieved through a combination of diet and/or oral hypoglycemic agents.

Medical complications due to macro- and microvascular damage are common, and patients with diabetes are at increased risk for stroke, heart attack, retinopathy, and end-stage renal disease. Symptoms of peripheral neuropathy may develop, including paresthesias and/or painful sensations in the distal limbs. Autonomic neuropathies may also occur, including impotence and loss of bladder sensation. Cognitively, the increased risk of stroke results in increased rates of vascular dementia in persons with diabetes (McCall, 1992).

Cognitive dysfunction due to diabetes per se has been the subject of a number of investigations. For adolescent patients with Type I diabetes, the age of onset has been shown to be related to cognitive deficits (Rovet *et al.*, 1987; Ryan *et al.*, 1985). Impairments in visuospatial tasks were evident in patients afflicted before the age of 4 years, compared with those diagnosed at later ages and with nondiabetic controls. Ryan (1988) pointed to higher rates of hypoglycemic seizures and greater sensitivity of the pediatric brain to metabolic or physiological insult as possible explanations for these findings. Noting the deleterious effects of hypoglycemia on medial temporal lobe structures, Hershey *et al.* (1997) identified significantly lowered performances on a delayed verbal recall task (Story Recall: Squire *et al.*, 1987) in a group of patients with Type I diabetes who had experienced severe hypoglycemic episodes ($\mu = 3.3$), compared with the performance of patients with Type I diabetes but no history of severe hypoglycemia, and with that of controls. The same subjects performed less well than the other two groups on the delayed recall trial of the CVLT (Delis *et al.*, 1987) and a Word Stem Priming test (Squire *et al.*, 1987), but differed significantly only from the control group. Both IDDM groups manifested significantly reduced performances on a verbal fluency test (Benton, 1968; Milner, 1964) and a picture priming task. No between-group differences were found on tests of attention and visuospatial functioning, or on a serial reaction time test.

There are conflicting findings regarding the relative vulnerability of persons with Type I diabetes according to gender: Although Rovet *et al.* (1987) initially found greater visuospatial skill dysfunction in young females, a recent study found that young males with diabetes may perform more poorly on certain measures (Holmes *et al.*, 1992). Complicating the picture, Ryan and colleagues (Ryan & Williams, 1993; Ryan *et al.*, 1992), found main effects for both group (diabetic vs. nondiabetic) and gender (male vs. female) but no interaction on both the Digit Vigilance (Lewis and Rennick, 1979) and Grooved Pegboard (Kløve, 1963) tests, which illustrated a likely selection problem.

Specific deficits in adults with Type I diabetes appear to be related to the individual's history of metabolic control. Long histories of poorly controlled glucose levels are associated with the vascular complications noted previously, the peripheral neuropathies being most apparent on neuropsychological tests (Ryan *et al.*, 1992; Young *et al.*, 1983). Skenazy and Bigler (1984) found decreased PIQ on

the WAIS-R (Wechsler, 1981) and reduced mental flexibility (Trails B: Reitan and Davison, 1974) and conceptual reasoning (Category Test: Halstead, 1947; Reitan and Wolfson, 1993) in a group of patients with Type I diabetes compared with the performance of nondiabetic controls. When grouped according to history of metabolic control, those with more problematic histories had significantly greater dysfunction on tasks involving a motor component, including Trails B. Franceschi *et al.* (1984) found similar dysfunction in a group of patients with histories of poor control, but also reported lower overall Memory Quotient scores on the WMS-R (Wechsler, 1987). Poor metabolic control has also been associated with decreased learning efficiency (Bale, 1973; Lichty and Klachko, 1985). More recently, however, Ryan and Williams (1993), in a well-controlled study, found no impairment on measures of learning and memory. Significant differences were identified on the WAIS-R PIQ (Wechsler, 1981; $\mu = 99.4$ vs. $\mu = 105.8$, $p < .001$), an embedded figure test, a cancellation task (Lewis and Rennick, 1979), and the Grooved Pegboard test (Kløve, 1963). Greater impairment on a psychomotor speed index was associated with a greater degree of chronic hyperglycemia. Similarly, Ryan *et al.* (1992) reported a strong association between psychomotor slowing and distal symmetrical polyneuropathy and a weaker association of psychomotor slowing with a history of poor glycemic control.

Neurocognitive dysfunction has also been identified in patients with Type II diabetes. Meuter *et al.* (1980) compared patients with Type I and Type II diabetes and found slowed reaction time and weaknesses in learning and memory for patients with Type II. Slowed psychomotor speed and memory dysfunction were subsequently confirmed by a number of investigators (Mooradian *et al.*, 1988; Perlmuter *et al.*, 1984, 1987; Reaven *et al.*, 1990; Tun *et al.*, 1987; U'Ren *et al.*, 1990), with mnestic dysfunction correlating with history of metabolic control. Consistent with these findings, one recent prospective study recruited only patients with Type II diabetics histories of good metabolic control; on a series of cognitive tests (Corsi Blocks: Milner, 1971; Raven Progressive Matrices: Raven, 1938; Rey Auditory Verbal Learning Test: Rey, 1964; Taylor, 1959; Digit Span: Wechsler, 1945), no differences were found between the patients' test results and those of nondiabetic controls (Assisi *et al.*, 1996).

Two studies have examined the effect of improved metabolic control on cognitive functions in patients with Type II diabetes. Gradman *et al.* (1991) reported improved learning (Buschke Cued Recall: Buschke and Fuld, 1974), complex psychomotor speed (visual choice reaction time), and attention following 2 months of treatment. Meneilly *et al.* (1993) measured subjects after 6 months of treatment and found improvements in attention/concentration (Trail Making A: Reitan and Davison, 1974; $\mu = 47.4 \pm 3.4$ to $\mu = 40.4 \pm 3.3$, $p < .05$), reading speed (Stroop, Word Naming: Stroop, 1935; $\mu = 31.9 \pm 2.4$ to $\mu = 28.5 \pm 2.3$, $p < .01$), fine motor speed (Grooved Pegboard: Kløve, 1963; $\mu = 98.6 \pm 5.1$ to $\mu = 91.0 \pm 3.9$, $p < .05$), learning (Buschke Cued Recall: Buschke and Fuld, 1974; $\mu = 31.9 \pm 2.4$ to $\mu = 30.5 \pm 1.5$, $p < .05$), and conceptual thinking (WAIS-R Picture Arrangement: Wechsler, 1981; $\mu = 8.4 \pm 1.0$ to $\mu = 10.1 \pm 1.2$, $p < .05$). After adjusting for Type I errors and possible practice effects, the authors concluded that the improvements in attention/concentration and fine motor speed were statistically significant. These results are consistent with earlier findings that blood glucose levels at the time of testing may have an impact on attention/concentration mechanisms (Holmes *et al.*, 1983).

The differential vulnerability of learning and memory processes in patients with Type II diabetes compared with patients with Type I diabetes has been discussed by Ryan and Williams (1993), who suggested that mnestic functions are not likely due to chronic hyperglycemia alone, because patients with Type I diabetes do not manifest memory dysfunction. These authors also noted that patients with Type I have a more severe form of the disease, marked by longer histories, more medical complications, and less easily controlled glucose levels. An initial investigation also indicates that the mnestic dysfunction of patients with Type II is not likely due to higher rates of cardiovascular disease (Reaven *et al.*, 1990). Instead, Ryan and Williams (1993) hypothesized an Age × Hyperglycemia interaction to account for the findings. The aging brain has been found to be increasingly vulnerable to mnestic dysfunction in other patient groups (e.g., patients addicted to alcohol; Ryan and Butters, 1984). Animal models show evidence of neuronal loss in chronic hyperglycemia (Jakobsen *et al.*, 1987). Neurochemically, hypoglycemia is associated with a partial cerebral energy failure, by means of brain fuel starvation or neuroglycopenia (McCall, 1992). Animal models have demonstrated the sensitivity of the hippocampal neurons to fluctuations in glucose utilization levels (Yashino *et al.*, 1991), which further supports the hypothesis that poorly controlled hyperglycemia could account in part for chronic mnestic dysfunction. (See McCall, 1992, for an extended discussion of the impact of diabetes on the central nervous system.) Other possible factors suggest a complex explanation. In a critical review of 19 published studies, Strachan *et al.* (1997) detailed many of the methodological problems in studying Type II diabetes and discussed nine potential factors associated with cognitive dysfunction in Type II diabetes, including depression, hyperlipidemia, impaired vision, renal failure, and others noted previously.

Summary

Patients with Type I and Type II diabetes face the risk of developing a mild chronic encephalopathy. Poorly controlled glucose levels are associated with psychomotor slowing and possible decreases in concentration and mental flexibility for both groups of patients. Among patients with Type I, an early onset, a history of severe hypoglycemia, or both is associated with greater degrees of dysfunction. Patients with Type II diabetes with histories of poor glucose control also experience mnestic dysfunction, perhaps due to the greater vulnerability of the aging brain in this patient group. Cognitive dysfunction in both patient groups appears to be due to multiple etiologies, including metabolic crisis, vascular disease, course of illness, and neurochemical disturbances. Patients, especially those with Type II, may have no dysfunction if glucose levels are well controlled. Also, cognition may normalize to a large extent with improved metabolic control.

The Pineal Gland and Melatonin

The pineal gland, along with the habenula and associated structures, compose the epithalamus. It is known by many as Descartes' hypothetical "*seat of the soul*" and for its phyloanatomical history as a remnant of a "third eye" in the posterior portion of the head in lower animals. It is located within the cranium, between the third and fourth ventricles, at approximately the level of the midbrain. In addition to its possible role in the seasonal regulation of human sexual behavior, the pineal gland has received scrutiny because of its synthesis of the hormone melatonin.

Melatonin is secreted cyclically under the regulation of the suprachiasmatic nucleus of the hypothalamus (Reiter, 1990). It serves as the "dark" signal to the brain, with low levels associated with daylight and increases peaking toward midnight and then gradually returning to baseline by morning. Exogenous melatonin is currently enjoying popularity as a treatment for jet lag because of its ability to reset the body's circadian rhythms (Lewy *et al.*, 1992) and to induce sleepiness (Lieberman *et al.*, 1984). Its other principal effect is to suppress core body temperature (Deacon *et al.*, 1994). Although the "clock-setting" capacities of melatonin are most likely controlled directly by afferents from the suprachiasmatic nucleus, its temperature-suppression function is governed by more complex hypothalamic thermoregulation factors (Saarela and Reiter, 1994).

Several studies have found significant variation in cognitive functioning, particularly in reaction time tasks, under the influence of both exogenous melatonin—to increase daytime levels (Deacon *et al.*, 1994; Lieberman *et al.*, 1984; Wynn and Arendt, 1988)—and melatonin-suppression treatments—to decrease nighttime levels (Badia *et al.*, 1990; Dollins *et al.*, 1994; Myers and Badia, 1993). In an elegantly designed single-case, double-blind, placebo-controlled study, Slotten and Krekling (1996) found evidence that circulating melatonin has no direct effect on cognitive capacities. Reduced speed and accuracy during peak serum melatonin levels did not differ from the control condition. However, during the temperature trough that occurs approximately 2 hours after peak serum levels, decrements in speed and accuracy on a computerized battery of tests of logical reasoning, sustained attention, visuospatial orientation, and reaction time (Performance Assessment Battery: Thorne *et al.*, 1985) were evident on all tasks. The authors hypothesized that the cognitive weaknesses were due to reduced speed of information processing secondary to melatonin's hypothermic properties.

CONCLUSION

Hormones interact with the brain and can produce profound effects on behavior and cognition. As the previous discussions illustrate, the actions of the neuroendocrine system are complex. Nevertheless, neuropsychologists should acquire a basic working understanding of the principal disorders. It is suggested that clinicians use the preceding review as a reference regarding the specific cognitive and neurobehavioral sequelae of their individual patients' neuroendocrine disorders. Also, Table II summarizes the principal characteristics and cognitive findings relevant to neuropsychological assessment and the neuroendocrine system.

The following guidelines will assist the clinician in conceptualization of neuroendocrine disorders, history taking, and, ultimately, protocol interpretation. Here, clinicians should use these concepts, while referring to the particular characteristics of the hormone involved.

- *Endocrine disorders can be analyzed according to principles familiar to neuropsychologists.* Patient symptoms can be "localized" to discrete neuroendocrine systems according to the pattern of effects on behavior and cognition. Knowledge of the underlying pathophysiology will aid the clinician in providing effective interventions and in formulating recommendations.
- *Cognitive dysfunction may be due to any of three conditions:* (1) Abnormal hormonal levels

Table II. Reference Summary of Neuroendocrine Effects on Behavior and Cognition

Hormone/condition	Primary hormonal axis	Primary axial hormones	Aging effects?	Psychological features	Principal cognitive areas of dysfunction[a]	Permanency of dysfunction?
Growth hormone (congenital dwarfism, gigantism, acromegaly)	Hypothalamic–pituitary–hepatic	GFRH, GH, IGF-I	Decline	NA	Memory	Improvement with replacement therapy
Vasopressin (diabetes insipidus)	NA	VP (ADH)	No	NA	*Attention, cortical arousal,* memory	Improvement with replacement therapy
Luteinizing hormone	Hypothalamic–pituitary–gonadal	GnRH, LH, FSH, T, E_2, progesterone	Decline	NA	Positive correlation with visuospatial/verbal tasks	NA
Follicle stimulating hormone	Hypothalamic–pituitary–gonadal	GnRH, LH, FSH, T, E_2, progesterone	Decline	NA	Negative correlation with visuospatial tasks	NA
Androgens (congenital adrenal hyperplasia, androgen insufficiency)	Hypothalamic–pituitary–gonadal	GnRH, LH, FSH, T, E_2, progesterone	Gradual decline in males	Libido, aggression	*Inverted U-shaped curve with visuospatial tasks*	Improvement with replacement therapy
Ovarian hormones	Hypothalamic–pituitary–gonadal	GnRH, LH, FSH, T, E_2, progesterone	Rapid decline in females	Depression, anxiety	*E_2 with verbal fluency and verbal memory,* attention, visual memory	Improvement with replacement therapy
Hyperthyroidism (Graves' disease)	Hypothalamic–pituitary–thyroid	TRH, TSH, T_3, T_4	Decline	Anxiety, hypomania	*Fine motor, attention,* memory	Improvement with suppression therapy
Hypothyroidism (congenital & adult-onset hypothyroidism)	Hypothalamic–pituitary–thyroid	TRH, TSH, T_3, T_4	Decline	Depressive symptoms	*General cognition, attention, learning, psychomotor speed*	Limited improvement, especially of attention
Hypercortisolism (Cushing's disease/syndrome)	Hypothalamic–pituitary–adrenal	CRH, ACTH, cortisol	Possible increase	Anxiety, psychosis, hypomania	*Memory; attention*	Limited improvement, especially of memory
Hypocortisolism (Addison's disease)	Hypothalamic–pituitary–adrenal	CRH, ACTH, cortisol	Possible increase	Depression, poor motivation	*General attention and motivation*	Improvement with replacement therapy
DHEA	NA	DHEA, DHEA-S	Decline	DHEA: Depression DHEA-S: Anxiety	*General cognition,* memory	Improvement with replacement therapy
Type I diabetes (IDDM)	NA	Insulin, glucagon, somatostatin	Decline in insulin	Anxiety	*Psychomotor speed, Inefficient Processing,* memory	Improvement with replacement therapy
Type II diabetes (NIDDM)	NA	Insulin, glucagon, somatostatin	Decline in insulin	Anxiety	*Psychomotor speed, inefficient processing, memory*	Improvement except for memory
Melatonin	NA	Melatonin	None	NA	Reduced speed of information processing	NA

Note. GFRH = growth factor–releasing hormone; GH = growth hormone; IGF-I = insulin-like growth factor–I; VP = vasopressin; ADH = antidiuretic hormone; GnRH = gonadotropin-realising hormone; LH = luteinizing hormone; FSH = follicle-stimulating hormone; T = testosterone; E_2 = estradiol; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone; T_3 = triiodothyronine; T_4 = thyroxin; CRH = corticotropin-releasing hormone; ACTH = adrenocorticotropic hormone; DHEA = dehydroepiandrosterone; DHEA-S = DHEA sulfate; IDDM = insulin-dependent diabetes mellitus; NIDDM = non-insulin-dependent diabetes mellitus; NA = not applicable.

[a]Normal type indicates inconsistent or unreplicated findings.

present in a normal brain, (2) normal hormonal levels present in an abnormal brain, or (3) abnormal hormonal levels present in an abnormal brain.

- *Pituitary adenomas produce deficit patterns that are due to multiple factors.* These include presurgical hypo- or hypersecretion of one or more hormones, deficits due to mass effect, sequelae of resection, and postsurgical hormone replacement therapy. History taking should carefully track the chronology of symptom onset and development along with the sequence of therapeutic procedures. This will aid in more accurate attribution of symptoms and may be pertinent to referral questions regarding employment and rehabilitation.
- *Histories of metabolic control may be complex.* Psychiatric symptoms frequently mask an insidious onset of symptoms of hormone dysregulation and delay diagnosis. Once such dysregulation is diagnosed, stabilization through hormone replacement therapy may be an ongoing process. Often, treatment of hyperfunction may result in hypofunction of an endocrine gland and, occasionally, vice versa.
- *Special notice should be taken of episodes associated with extreme hormonal imbalance and acute metabolic crises because even isolated events may produce persistent cognitive sequelae.* Examples include significant traumatic experiences such as shock due to Addison's disease, hypoglycemic shock and its associated seizure or coma, and post-traumatic stress disorder.
- *Age of onset is an important factor.* In general, perinatal and early childhood events increase the likelihood of neurocognitive deficits because of the greater vulnerability of the child brain and/or greater chronicity. Also, aging produces lower basal levels of endocrine function, and the aging brain may be more vulnerable to certain types of deficits, particularly those entailing memory. For instance, patients with Type II diabetes appear to experience memory dysfunction more frequently than patients with Type I do.
- *Metabolic control at time of testing may affect neuropsychological test performance.* For instance, glucose levels may directly affect a range of cognitive capacities. Also, anxiety or depressive symptoms due to variation in thyroid or cortisol levels may affect attention in particular and other functions. Clinicians should obtain information regarding current metabolic control and the patient's compliance with his or her medication regimen. Careful attention should be paid to recent treatment adjustments. When feasible, patients should be tested only when under adequate metabolic control. At times, neuropsychological testing may need to be deferred for a number of weeks to allow for accurate assessment.

In the research setting, knowledge of cognitive functions determined by neuropsychologists is increasingly important to scientific endeavors. Recent advances regarding the role of ovarian hormones in AD represent an exciting opportunity to utilize complex knowledge of neuroendocrine functioning to treat a central nervous system disorder. Other hormone-based treatments are currently being investigated to treat cognitive problems associated with aging and disease processes. Most recently, DHEA has generated considerable interest. It is hoped that the previous discussions will serve to facilitate future research efforts by neuropsychologists.

The preceding discussions note many of the methodological problems inherent in studying the effects of hormonal dysfunction on cognition. Indeed, many of the conflicting findings are due to selection problems, measurement difficulties, and confounding factors. Still, a number of the studies reviewed demonstrate that careful planning can mitigate these problems successfully. The following guidelines are suggested:

- *Full neuropsychological batteries should be used whenever feasible.* When this is impractical, specialized investigations into target domains should utilize multiple measures within each domain (e.g., sustained visual attention vs. sustained auditory attention, list learning vs. incidental learning, etc.) to add specificity to the interpretation of findings. This would also allow for more measures to be duplicated between studies, which would enable reconciliation of disparate findings.
- *Robust IQ data are crucial* for interpreting between-group differences on domain measures because relatively small differences will likely be of interest.
- *Mood/symptom inventories are important* in the study of neuroendocrine disorders because of their common comorbidity and potential to affect neuropsychological test performance.
- *A careful history of metabolic control should be obtained for each subject* because individuals with the same disorder may manifest different patterns of neuropsychological weakness based on this factor.

- *Control subjects should be recruited with care.* Several studies have clarified discrepancies in the literature by utilizing siblings or matched controls, or by using subjects as their own control.

Finally, it is worth noting that neuropsychologists do not yet routinely provide cognitive remediation and other treatments to individuals with cognitive dysfunction secondary to hormonal dysregulation. Although the medical condition of these patients frequently improves with hormone replacement therapy, cognitive dysfunction persists in many cases. Cognitive rehabilitation techniques are likely to be useful to patients in developing compensatory resources. Because neuroendocrine disorders appear in many instances to produce cognitive dysfunction independent of neuronal degeneration, application of cognitive remediation techniques may produce outcomes that differ from those of patients with injuries that produce necrosis, such as traumatic brain injury, stroke, and so forth. However, there is no systematic research at present in this area. Also, psychological issues regarding affective symptoms and adjustment to illness are familiar to most neuropsychologists, as are the significant family issues that pertain to dealing with chronic cognitive dysfunction. Given the benefits of a therapy that integrates these diverse areas, neuropsychologists appear extremely well qualified to play a major role in the multidisciplinary treatment of these patients.

REFERENCES

Aghini-Lombardi, F. A., Pinchera, A., Anonangeli, L., *et al.* (1995). Mild iodine deficiency during fetal/neonatal life and neuropsychological impairment in Tuscany. *Journal of Endocrinological Investigation* 18: 57–62.

Allen, L. S., and Gorski, R. A. (1986). Sexual dimorphism of the human anterior commissure. *Anatomical Record* 214: 3A.

Allen, L. S., Hines, M., Shryne, J. E., and Gorski, R. A. (1989). Two sexually dimorphic nuclei in the human brain. *Journal of Neuroscience* 9: 497–506.

Alvarez, M. A., Gomez, A., Alavez, E., and Navarro, D. (1983). Attention disturbance in Graves' disease. *Psychoneuroendocrinology* 8: 451–454.

Anderson, F., Hamburger, S., Liu, J. H., and Rebar, R. W. (1987). Characteristics of menopausal women seeking assistance. *American Journal of Obstetrics and Gynecology* 156: 428–433.

Artunkal, S., and Togrol, B. (1964). Psychological studies in hyperthyroidism. In Cameron, M.R., and O'Connor, M. (eds.), *Brain–Thyroid Relationships*, Little Brown, Boston, pp. 92–113.

Assisi, A., Alimenti, M., Maceli, F., Di Pietro, S., Lalloni, G., and Montera, P. (1996). Diabetes and cognitive function: Preliminary studies. *Archives of Gerontology and Geriatrics* (Suppl. 5): 229–232.

Asthana, S., Craft, S., Baker, L. D., Raskind, M. A., Birnbaum, R. S., Lofgreen, C. P., Veith, R. C., and Plymate, S. R. (1999). Cognitive and neuroendocrine response to transdermal estrogen in postmenopausal women with Alzheimer's disease: Results of a placebo-controlled, double-blind, pilot study. *Psychoneuroendocrinology* 24: 657–677.

Badia, P., Culpepper, J., Myers, B., Boecker, M., and Harsh, J. (1990). Psychophysiological and behavioral effects of bright and dim light. *Sleep Research* 10: 387.

Baker, S. W., and Ehrhardt, A. A. (1974). Prenatal androgen, intelligence and cognitive sex differences. In Friedman, R. C., Richart, R. M., and Vande Wiele, R. L. (eds.), *Sex Differences in Behavior*, Wiley, New York, pp. 53–76.

Baldini, I. M., Wita, A., Mauri, M. C., *et al.* (1997). Psychopathological and cognitive features in subclinical hypothyroidism. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 21: 925–935.

Bale, R. N. (1973). Brain damage in diabetes mellitus. *British Journal of Psychiatry* 122: 22–39.

Bargagna, S., Chiovato, L., Dinetti, D., *et al.* (1997). Neuropsychological development in a child with early-treated congenital hypothyroidism as compared with her unaffected identical twin. *European Journal of Endocrinology* 136: 100–104.

Barrett-Connor, E., and Bush, T. L. (1991). Estrogen and coronary heart disease in women. *Journal of the American Medical Association* 265: 1861–1867.

Barrett-Connor, E., Khaw, K., and Yen, S. S. C. (1986). A prospective study of DS, mortality and cardiovascular disease. *New England Journal of Medicine* 315: 1519–1524.

Barrett-Connor, E., and Kritz-Silverstein, D. (1993). Estrogen replacement therapy and cognitive function in older women. *Journal of the American Medical Association* 269: 2637–2641.

Beatty, W. W. (1984). Hormonal organization of sex differences in play fighting and spatial behavior. *Progress in Brain Research* 61: 315–329.

Beckwith, B. E., and Tucker, D. M. (1988). Thyroid disorders. In Tarter, R. E., van Thiel, D. H., and Edwards, K. L. (eds.), *Medical Neuropsychology: The Impact of Disease on Behavior*, Plenum Press, New York, pp. 197–221.

Bennett, G. W., Marsden, C. A., Fone, K. C. F., Johnson, J. V., and Heal, D. J. (1989). TRH–catecholamine interactions in brain and spinal cord. *Annals of the New York Academy of Sciences* 553: 106–120.

Bennett, M. C., Diamond, D. M., Fleshner, M., and Rose, G. M. (1991). Serum corticosterone level predicts the magnitude of hippocampal primed burst potentiation and depression in urethane-anesthetized rats. *Psychobiology* 19: 301–307.

Benton, A. L. (1968). Differential behavioral effects in frontal lobe disease. *Neuropsychologia* 6: 53–60.

Benton, A. L. (1974). *Revised Visual Retention Test* (4th ed.), The Psychological Corporation, San Antonio, TX.

Berg, E. A. (1948). A simple objective technique for measuring flexibility in thinking. *Journal of General Psychology* 39: 15–22.

Berman, F. B., Schmidt, P. J., Rubinow, D. R., *et al.* (1997). Modulation of cognition-specific cortical activity by gonadal steroids: A positron-emission tomography study in women. *Proceedings of the National Academy of Sciences, USA* 93: 8836–8841.

Birge, S. J. (1994). The role of estrogen deficiency in the aging central nervous system. In Lobo, R. A. (ed.), *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects*, Raven Press, New York, pp. 153–157.

Birge, S. J. (1997). The role of estrogen in the treatment of Alzheimer's disease. *Neurology* 48 (Suppl. 7): S36–S41.

Bliss, T. V. P., and Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *Journal of Physiology (London)* 232: 331–356.

Bommer, M., Eversmann, T., Pickardt, R., Leohnardt, A., and Naber, D. (1990). Psychopathological and neuropsychological symptoms in patients with subclinical and remitted hyperthyroidism. *Klinische Wochenschrift* 68: 552–558.

Bouma, L., and Lindeboom, J. (1988). *Klinisch neuropsychologische Assessment, een Handlekding voor de Praktijk*. Internal report, Vrije Universiteit, Amsterdam.

Bremner, J. D., Randall, P., Scott, T. M., *et al.* (1995). MRI-based measurement of hippocampal volume in patients with combat-related

posttraumatic stress disorder. *American Journal of Psychiatry* 152: 973–981.

Brenner, D. E., Kukull, W. A., Stergachis, A., *et al.* (1994). Postmenopausal estrogen replacement therapy and the risk of Alzheimer's disease: A population-based case-control study. *American Journal of Epidemiology* 140: 262–267.

Bunevicius, R., Kazanavicius, G., Zalinkevicius, R., and Prange, A. J. (1999). Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. *New England Journal of Medicine* 340: 424–429.

Buschke, H. (1973). Selective reminding for analysis of memory and learning. *Journal of Verbal Learning and Verbal Behavior* 12: 543–550.

Buschke, H., and Fuld, P. A. (1974). Evaluation of storage, retention, and retrieval in disordered memory and learning. *Neurology* 11: 1019–1025.

Caldwell, B. M. (1954). An evaluation of psychological effects of sex hormone administration in aged women. *Journal of Gerontology* 9: 168–174.

Caldwell, B. M., and Watson, R. I. (1952). An evaluation of psychologic effects of sex hormone administration in aged women. Results of therapy after six months. *Journal of Gerontology* 7: 228–244.

Carlson, L. E., and Sherwin, B. B. (1998). Steroid hormones, memory and mood in a healthy elderly population. *Psychoneuroendocrinology* 23: 583–603.

Carroll, B. J. (1982). The dexamethasone suppression test for melancholia. *British Journal of Psychiatry* 140: 292–304.

Carter Center. (1985). Closing the gap: The problem of diabetes mellitus in the United States. *Diabetes Care* 8: 391–406.

Claussen, M. S., Landercasper, J., and Cogbill, T. H. (1992). Acute adrenal insufficiency presenting as shock after trauma and surgery: Three cases and review of the literature. *Journal of Trauma* 32: 94–100.

Clopper, R. R. (1990). Assessing the effect of replacement hormone treatment on psychosocial and psychosexual behavior in growth hormone deficient individuals. In Holme, C. S. (ed.), *Psychoneuroendocrinology*, Springer-Verlag, New York, pp. 56–78.

Colditz, G. A., Hankinson, S. E., Hunter, D. J., *et al.* (1995). The use of estrogens, and progestins and the risk of breast cancer in postmenopausal women. *New England Journal of Medicine* 332: 1589–1593.

Collaer, M. L., and Hines, M. (1995). Human behavioral sex differences: A role for gonadal hormones during early development? *Psychological Bulletin* 118: 55–107.

Craik, F. I. M. (1984). Age differences in remembering. In Squire, L. R., and Butters, N. (eds.), *Neuropsychology of Memory*, Guilford Press, New York, pp. 3–12.

Crown, S. (1949). Notes on experimental study of intellectual deterioration. *British Medical Journal* 2: 684–685.

Davis, K. L, Davis, B. M., Greenwald, B. S., *et al.* (1986). Cortisol and Alzheimer's disease. I. Basal studies. *American Journal of Psychiatry* 143: 300–305.

Deacon, S., English, J., and Arendt, J. (1994). Acute phase-shifting effects of melatonin associated with suppression of body core temperature in humans. *Neuroscience Letters* 178: 153–160.

Deijen, J. B., de Boer, H., Blok, G. J., and van der Veen, E. A. (1996). Cognitive impairments and mood disturbances in growth hormone deficient men. *Psychoneuroendocrinology* 21: 313–322.

Deijen, J. B., de Boer, H., and van der Veen, E. A. (1998). Cognitive changes during growth hormone replacement in adult men. *Psychoneuroendocrinology* 23: 45–55.

Delis, D. C., Kramer, H. H., Kaplan, E., and Ober, B. A. (1987). *California Verbal Learning Test: Adult Version*, The Psychological Corporation, San Antonio, TX.

Denicoff, K. D., Joffe, R. T., Lakshmanan, M. C., Robbins, J., and Rubinow, D. R. (1990). Neuropsychiatric manifestations of altered thyroid state. *American Journal of Psychiatry* 147: 94–99.

Derksen-Lubsen, G. (1996). Neuropsychologic development in early treated congenital hypothyroidism: Analysis of literature data. *Pediatric Research* 39: 561–566.

Deutsch, S. I., Mastropaolo, J., and Hitri, A. (1992). GABA-active steroids: Endogenous modulators of GABA-gated chloride ion conductance. *Clinical Neuropharmacology* 15: 352–364.

De Wied, D. (1965). The influence of the posterior and intermediate lobe of the pituitary and pituitary peptides on the maintenance of a conditioned avoidance response in rats. *International Journal of Neuropharmacology* 4: 157–167.

Dodt, C., Dittmann, J., Hruby, J., *et al.* (1991). Different regulation of adrenocorticotropin and cortisol secretion in young, mentally healthy elderly and patients with senile dementia of Alzheimer's type. *Journal of Clinical Endocrinology and Metabolism* 72: 272–276.

Dollins, A. B., Lynch, H. J., Wurtman, R. J., and Deng, M. H. (1994). Effects of illumination on human nocturnal serum melatonin levels and performance. *Physiology and Behavior* 53: 153–160.

Ekstrom, R. B., French, J. W., Harman, H. H., and Derman, D. (1976). *Manual for Referenced Cognitive Tests*, Educational Testing Service, Princeton, NJ.

Emmen, H., Hogendijk, E., Hooisma, J., Orlib eke, J., and Uijtdehaage, S. (1988). *Adaptation of two standardized international test batteries for use in the Netherlands for detection of exposure to neurotoxic compounds.* Internal report, Medisch Biologisch Laboratorium TNO, Rijswijk, The Netherlands.

Fehm-Wolfsdorf, G., and Born, J. (1991). Behavioral effects of neurohypophyseal peptides in healthy volunteers: 10 years of research. *Peptides* 12: 1399–1406.

Fenzi, G. F., Giusti, L. F., Agnini-Lombardi, F., *et al.* (1990). Neuropsychological assessment in schoolchildren from an area of moderate iodine deficiency. *Journal of Endocrinological Investigation* 13: 427–431.

Feydor-Freybergh, P. (1977). The influence of estrogen on the well-being and mental performance in climacteric and postmenopausal women. *Acta Obstetricia et Gynecologica Scandinavica* 64: 5–69.

Fillit, H., Weinreb, H., Cholst, I., *et al.* (1986). Observations in a preliminary open trial of estradiol therapy for senile dementia–Alzheimer's type. *Psychoneuroendocrinology* 11: 337–345.

Flood, J. F., Smith, G. E., and Roberts, E. (1988). Dehydroepiandrosterone and its sulfate enhance memory retention in mice. *Brain Research* 447: 269–278.

Franceschi, M., Ceccetto, R., Minicucci, F., Smizne, S., Baio, G., and Canal, N. (1984). Cognitive processes in insulin-dependent diabetes. *Diabetes Care* 7: 228–231.

Frye, C. A., and Sturgis, J. D. (1995). Neurosteroids affect spatial/reference, working and long-term memory of female rats. *Neurobiology of Learning and Memory* 64: 83–96.

Funk, J. L., Mortel, K. F., and Meyer, J. S. (1991). Effects of estrogen replacement therapy on cerebral perfusion and cognition among postmenopausal women. *Dementia* 2: 268–272.

Geschwind, N., and Behan, P. (1982). Left-handedness: Association with immune disease, migraine, and developmental learning disorder. *Proceedings of the National Academy of Sciences, USA* 79: 5097–5100.

Geschwind, N., and Galaburda, A. M. (1985a). Cerebral lateralization. Part I. *Archives of Neurology* 42: 428–459.

Geschwind, N., and Galaburda, A. M. (1985b). Cerebral lateralization. Part II. *Archives of Neurology* 42: 521–552.

Gladue, B. S., and Baily, J. M. (1995). Spatial ability, handedness, and human sexual orientation. *Psychoneuroendocrinology* 20: 487–497.

Goodglass, J., and Kaplan, E. (1983). *The Assessment of Aphasia and Related Disorders* (2nd ed.), Lea & Febiger, Philadelphia.

Gordon, H. W. (1986). The Cognitive Laterality Battery: Tests of specialized cognitive function. *International Journal of Neuroscience* 29: 223–244.

Gordon, H. W., Corbin, E. D., and Lee, P. A. (1986). Changes in specialized cognitive function following changes in hormone levels. *Cortex* 22: 399–415.

Gordon, H. W., and Lee, P. A. (1986). A relationship between gonadotropins and visuospatial function. *Neuropsychologia* 24: 563–576.

Gordon, H. W., and Lee, P. A. (1993). No differences in cognitive performance between phases of the menstrual cycle. *Psychoneuroendocrinology* 18: 521–531.

Gordon, H. W., Lee, P. A., and Tamres, L. K. (1988). The pituitary axis: Behavioral correlates. In Tarter, R. E., van Thiel, D. H., and Edwards, K. L. (eds.), *Medical Neuropsychology: The Impact of Disease on Behavior*, Plenum Press, New York, pp. 159–196.

Gordon, M., Crouthamel, D., Post, E. M., and Richman, R. A. (1982). Psychosocial aspects of constitutional short stature: Social competence, behavior problems, self esteem, and family functioning. *Journal of Pediatrics* 101: 477–480.

Gorski, R. A. (1991). Sexual differentiation of the endocrine brain and its control. In Motta, M. (ed.), *Brain Endocrinology*, Raven Press, New York, pp. 71–104.

Gouchie, C., and Kimura, D. (1991). The relationship between testosterone levels and cognitive ability patterns. *Psychoneuroendocrinology* 16: 323–334.

Gradman, T., Taus, A., Thompson, L., and Reaven, G. M. (1991). Effects of glycemic control on cognitive function in older subjects with NIDDM. *Clinical Research* 39: 14A.

Grady, D., and Ernster, V. (1991). Does postmenopausal hormone therapy cause breast cancer? *American Journal of Epidemiology* 134: 1396–1400.

Grant, D. A., and Berg, E. A. (1948). A behavioral analysis of degree of impairment and ease of shifting to new responses in a Weigl-type card sorting problem. *Journal of Experimental Psychology* 39: 404–411.

Grattan-Smith, P. J., Morris, J. G. L., Shores, E. A., Bachelor, J., and Sparks, R. S. (1992). Neuropsychological abnormalities in patients with pituitary tumors. *Acta Neurologica Scandinavica* 86: 626–631.

Graves, R. G. (1835). Newly observed affection of the thyroid gland in females. *Medicine and Surgery* 7: 516.

Grumbach, M. M., and Conte, F. A. (1992). Disorders of sex differentiation. In Wilson, J. D., and Foster, D. W. (eds.), *Williams Textbook of Endocrinology*, Saunders, Philadelphia, pp. 853–951.

Gull, W. W. (1874). On a cretinoid state supervening in adult life in women. *Transactions of the Medical Society of London* 21: 298–300.

Gustafsson, B., and Wigstrom, T. (1988). Physiological mechanisms underlying long-term potentiation. *Trends in Neuroscience* 11: 156–162.

Hackman, B. W., and Galbraith, D. (1977). Six month study of oestrogen therapy with piperazine oestronesulphate and its effects on memory. *Current Medical Research and Opinion* 4: 21–27.

Halpern, D. F. (1992). *Sex Differences in Cognitive Abilities* (2nd ed.), Erlbaum, Hillsdale, NJ.

Halstead, W. C. (1947). *Brain and Intelligence*, University of Chicago Press, Chicago.

Hampson, E. (1990a). Estrogen-related variations in human spatial and articulatory-motor skills. *Psychoneuroendocrinology* 15: 97–111.

Hampson, E. (1990b). Variations in sex-related cognitive abilities across the menstrual cycle. *Brain and Cognition* 14: 26–43.

Hampson, E., Rovet, J. F., and Altmann, D. (1998). Spatial reasoning in children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Developmental Neuropsychology* 14: 299–320.

Hathaway, S. R., and McKinley, J. C. (1943). *Booklet for the Minnesota Multiphasic Personality Inventory*, The Psychological Corporation, New York.

Helladay, J., Bartfai, A., Martin Ritzén, E., and Forsman, M. (1994). General intelligence and cognitive profile in women with congenital adrenal hyperplasia (CAH). *Psychoneuroendocrinology* 19: 343–356.

Helzlsouer, K. J., Gordon, G. B., Alberg, A., Bush, T. L., and Comstock, G. W. (1992). Relationship of prediagnostic serum levels of DHEA and DS to the risk of developing premenopausal breast cancer. *Cancer Research* 52: 1–4.

Henderson, V. W. (1997). Epidemiology of estrogen replacement therapy and Alzheimer's disease. *Neurology* 48 (Suppl. 7): S27–S35.

Henderson, V. W., and Buckwalter, J. G. (1994). Cognitive deficits of men and women with Alzheimer's disease. *Neurology* 44: 90–96.

Henderson, V. W., Mack, W., and Williams, B. W. (1989). Spatial disorientation in Alzheimer's disease. *Archives of Neurology* 46: 391–394.

Henderson, V. W., Paganini-Hill, A., Emanuel, C. K., *et al.* (1994). Estrogen replacement therapy in older women: Comparisons between Alzheimer's disease cases and non-demented control subjects. *Archives of Neurology* 51: 896–900.

Henderson, V. W., Watt, L., and Buckwalter, J. G. (1996). Cognitive skills associated with estrogen replacement in women with Alzheimer's disease. *Psychoneuroendocrinology* 21: 421–430.

Hershey, T., Craft, S., Bhargava, N., and White, N. (1997). Memory and insulin dependent diabetes mellitus (IDDM): Effects of childhood onset and severe hypoglycemia. *Journal of the International Neuropsychological Society* 3: 509–520.

Herzog, A. G. (1991). Reproductive endocrine considerations and hormonal therapy for women with epilepsy. *Epilepsia* 21 (Suppl. 6): S27–S33.

Herzog, A. G. (1995). Progesterone therapy in women with complex partial and secondary generalized seizures. *Neurology* 45: 1660–1662.

Hines, M., Chiu, L., McAdams, L. A., Beutler, P. M., and Lipcamon, J. (1992). Cognition and the corpus callosum: Verbal fluency, visuospatial ability, and language lateralization related to midsagittal surface areas of callosal subregions. *Behavioral Neuroscience* 106: 3–14.

Hines, M., and Green, R. (1991). Human hormonal and neural correlates of sex-typed behaviors. *Review of Psychiatry* 10: 536–555.

Holloway, R. L., and de LaCoste, M. C. (1986). Sexual dimorphism in the human corpus callosum: An extension and replication study. *Human Neurobiology* 5: 87–91.

Holmes, C. S., Dunlap, W. P., Chen, R. S., and Cornwell, J. M. (1992). Gender differences in cognitive performance in diabetes. *Journal of Consulting and Clinical Psychology* 60: 698–704.

Holmes, C. S., Hayford, J. T., Gonzalez, J. L., and Weydert, J. A. (1983). A survey of cognitive functioning at different glucose levels in diabetic persons. *Diabetes Care* 6: 180–185.

Honjo, H., Ogino, Y., Naitoh, K., *et al.* (1989). In vivo effects by estrone sulfate on the central nervous system—senile dementia–Alzheimer's type. *Journal of Steroid Biochemistry* 34: 521–525.

Honjo, H., Ogino, Y., Tanaka, K., *et al.* (1993). An effect of conjugated estrogen to cognitive impairment in women with senile dementia–Alzheimer's type: A placebo-controlled double-blind study. *Journal of the Japanese Menopause Society* 1: 167–171.

Imperato-McGinley, J., Pichardo, M., Gautier, T., Voyer, D., and Bryden, M. P. (1991). Cognitive abilities in androgen-insensitive subjects: Comparison with control males and females from the same kindred. *Clinical Endocrinology* 34: 341–347.

Inglis, J. (1959). An experimental study of learning and "memory function" in elderly psychiatric elders. *Journal of Mental Science* 103: 796–803.

Jacobs, A. R., Coleman, A. E., and Herzog, A. G. (1995). *Late onset congenital adrenal hyperplasia: A treatable cause of anxiety and maladaptive behavioral disorders.* Paper presented at the American Neuropsychiatric Association, October, Pittsburgh, PA.

Jacobs, D. M., Tang, M. X., Stern, Y., *et al.* (1998). Cognitive function in nondemented older women who took estrogen after menopause. *Neurology* 50: 368–373.

Jacobson, L., and Sapolsky, R. (1991). The role of the hippocampus in feedback regulation of the hypothalamic–pituitary–adrenocortical axis. *Endocrine Review* 12: 118–134.

Jain, V. K. (1973). A psychiatric study of hypothyroidism. *Psychiatric Clinician* 5: 121–130.

Jakobsen, J., Sidenius, P., Gendersen, H., and Osterby, R. (1987). Quantitative changes of cerebral neocortical structure in insulin-treated

long-term streptozocin-induced diabetes in rats. *Diabetes* 36: 597–601.

Janowsky, J. S., Oviatt, S. K., and Orwoll, E. S. (1994). Testosterone influences spatial cognition in older men. *Behavioral Neuroscience* 108: 325–332.

Jennings, J. R., Nebes, R. D., and Reynolds, C. F., III (1986). Vasopressin peptide (DDAVP) may narrow the focus of attention in normal elderly. *Psychiatry Research* 17: 31–39.

Joffe, R. T., and Singer, W. (1990). A comparison of triiodothyronine and thyroxine in the potentiation of tricyclic antidepressants. *Psychiatry Research* 32: 241–251.

Johnstone, P. A., Randell, J. R., and Esposito, M. (1990). Mental status changes of Addison's disease. *Psychosomatics* 31: 103–107.

Jorm, A. F., Korten, A. E., and Henderson, A. S. (1987). The prevalence of dementia: A quantitative integration of the literature. *Acta Psychiatrica Scandinavica* 76: 475–479.

Kampen, D., and Sherwin, B. B. (1994). Estrogen use and verbal memory in healthy postmenopausal women. *Obstetrics and Gynecology* 83: 979–983.

Kaplan, E., Goodglass, H., and Weintraub, S. (1983). *Boston Naming Test*, Lea & Febiger, Philadelphia.

Kawas, C., Resnick, S., Morrison, A., *et al.* (1997). A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: The Baltimore Longitudinal Study of Aging. *Neurology* 48: 1517–1521.

Keenan, P. A., Stern, R. A., Janowsky, D. S., and Pedersen, C. A. (1992). Psychological aspects of premenstrual syndrome. I: Cognition and memory. *Psychoneuroendocrinology* 17: 179–187.

Kelly, J. A. (1995). Thyrotrophin-releasing hormone: Basis and potential for its therapeutic use. *Essays in Biochemistry* 30: 133–149.

Khan, A., Mirolo, M. H., Claypoole, K., Bhang, J., Cox, G., Horita, A., and Tucker, G. (1994). Effects of low-dose TRH on cognitive deficits in the ECT postictal state. *American Journal of Psychiatry* 151: 1694–1696.

Kløve, H. (1963). Clinical neuropsychology. In Forster, F. M. (ed.), *The Medical Clinics of North America*, Saunders, New York.

Knapp, M. J., Knopman, D. S., Solomon, P. R., *et al.* (1994). A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease: The Tacrine Study Group. *Journal of the American Medical Association* 271: 85–91.

Komnenich, P., Lane, D. M., Dickey, R. P., and Stone, S. C. (1978). Gonadal hormones and cognitive performance. *Physiological Psychology* 6: 115–120.

Lai, Z., Emtner, M., Roos, P., and Nyberg, R. (1991). Characterization of putative growth hormone receptors in human choroid plexus. *Brain Research* 46: 222–226.

Lamberts, S. W. J., van den Beld, A. W., and van der Lely, A. (1997). The endocrinology of aging. *Science* 278: 419–424.

Leentjens, A. F. G., and Kappers, E. J. (1995). Persistent cognitive defects after corrected hypothyroidism. *Psychopathology* 28: 235–237.

Legros, J., and Gilot, P. (1979). Vasopressin and memory in the human. In Krieger, D. T., Brownstein, M. J., and Martin, J. B. (eds.), *Brain Peptides*, Wiley, New York, pp. 347–364.

Lewis, R., and Rennick, P. (1979). *Manual for the Repeatable Cognitive–Perceptual–Motor Battery*, Axon, Grosse Point Park, MI.

Lewy, A. J., Ahmed, S., Latham Jackson, J. M., and Sack, R. (1992). Melatonin shifts circadian rhythms according to a phase-response curve. *Chronobiology International* 9: 380–392.

Lichty, W., and Klachko, D. (1985). Memory in Type I diabetics [Abstract]. *Diabetes* 34 (Suppl. 1): 19.

Lieberman, H. R., Waldhauser, F., Garfield, G., Lynch, H. J., and Wurtman, R. J. (1984). Effects of melatonin on human mood and performance. *Brain Research* 323: 201–207.

Lindsay, R., Hart, D. M., Aitken, J. M., MacDonald, E. B., Anderson, J. B., and Clarke, A. C. (1976). Long-term prevention of postmenopausal osteoporosis by oestrogen: Evidence for an increased bone mass after delayed onset of oestrogen treatment. *Lancet* 1: 1038–1040.

Linn, M. C., and Petersen, A. C. (1985). Emergence and characterization of sex differences in spatial ability: A meta-analysis. *Child Development* 56: 1479–1498.

Loosen, P. T. (1992). Effects of thyroid hormones on central nervous system in aging. *Psychoneuroendocrinology* 17: 355–374.

Lupien, S., Lecours, A. R., Lussier, I., *et al.* (1994). Basal cortisol levels and cognitive deficits in human aging. *Journal of Neuroscience* 14: 2893–2903.

Maccoby, E. E., and Jacklin, C. N. (1974). *The Psychology of Sex Differences*, Stanford University Press, Stanford, CA.

MacCrimmon, D. J., Wallace, J. E., Goldberg, W. M., and Streiner, D. L. (1979). Emotional disturbance and cognitive deficits in hyperthyroidism. *Psychosomatic Medicine* 41: 331.

Madeira, M. D., Sousa, N., Lima-Andrade, M. T., Calheiros, F., Cadete-Leite, A., and Paula-Barbosa, M. M. (1992). Selective vulnerability of the hippocampal pyramidal neurons to hypothyroidism in male and female rats. *Journal of Comparative Neurology* 322: 501–518.

Masica, D. N., Money, J., Ehrhardt, A. A., and Lewis, V. G. (1969). IQ, fetal sex hormones and cognitive patterns: Studies in the testicular feminizing syndrome of androgen insensitivity. *Johns Hopkins Medical Journal* 124: 34–43.

Mateer, C., and Kimura, D. (1977). Impairment of nonverbal oral movements in aphasia. *Brain and Language* 4: 262–276.

Mauri, M., Sinforiani, E., Bono, G., *et al.* (1993). Memory impairment in Cushing's disease. *Acta Neurologica Scandinavica* 87: 52–55.

McCall, A. L. (1992). The impact of diabetes on the CNS. *Diabetes* 41: 557–570.

McCord, M. W., Buatti, J., Fennell, E., *et al.* (1997). Radiotherapy for pituitary adenoma: Long-term outcome and sequelae. *International Journal of Radiation Oncology and Biological Physiology* 39: 437–444.

McEwen, J. W. (1982). Glucocorticoids and hippocampus: Receptors in search of a function. In Ganten, D., and Pfaff, D. (eds.), *Adrenal Actions on Brain*, Springer-Verlag, New York, pp. 1–22.

McGuire, L. S., Ryan, K. O., and Omen, G. S. (1975). Congenital adrenal hyperplasia. II. Cognitive and behavioral studies. *Behavioral Genetics* 5: 175–188.

Melchior, C. L., and Ritzmann, R. F. (1996). Neurosteroids block the memory-impairing effects of ethanol in mice. *Pharmacology, Biochemistry and Behavior* 53: 51–56.

Mellman, M. J., Davis, M. R., Brisman, M., and Shamoon, H. (1994). Effect of antecedent hypoglycemia on cognitive function and on glycemic thresholds for counterregulatory hormone secretion in healthy humans. *Diabetes Care* 17: 183–188.

Mendorla, G., Sava, L., Calaciura, F., Lisi, E., Castorina, S., and Vigneri, R. (1988). Personality traits and mental prognosis in patients with congenital hypothyroidism not treated from early life. *Journal of Endocrinological Investigation* 11: 289–295.

Meneilly, G. S., Cheung, E., Tessier, D., Yakura, C., and Tuokko, H. (1993). The effect of improved glycemic control on cognitive functions in the elderly patient with diabetes. *Journal of Gerontology* 48: M117–M121.

Mennemeier, M., Garner, R. D., and Heilman, K. M. (1993). Memory, mood and measurement in hypothyroidism. *Journal of Clinical and Experimental Neuropsychology* 15: 822–831.

Meuter, F., Thomas, W., Grüneklee, D., Gries, F., and Lohmann, R. (1980). Psychometric evaluation of performance in diabetes mellitus. *Hormone and Metabolic Research (Supplement)* 9: 9–17.

Meyer-Bahlburg, H. F. L., Feinman, J. A., MacGillivray, M. H., and Acetor, T., Jr. (1978). Growth hormone deficiency, brain development, and intelligence. *American Journal of Diseases of Children* 132: 565–572.

Milner, B. (1964). Some effects of frontal lobectomy in man. In Warren, J. M., and Akert, K. (eds.), *The Frontal Granular Cortex and Behavior*, McGraw-Hill, New York, pp. 313–331.

Milner, B. (1971). Interhemispheric differences in the localization of psychological processes in man. *British Medical Bulletin* 27: 272–277.

Minaker, K. L. (1990). What diabetologists should know about elderly patients. *Diabetes Care* 13 (Suppl. 2): 34.

Möbius, P. J. (1886). Cited in Beckwith, B. E., and Tucker, D. M. (1988). Thyroid disorders. In Tarter, R. E., van Thiel, D. H., and Edwards, K. L. (eds.), *Medical Neuropsychology: The Impact of Disease on Behavior*, Plenum Press, New York, pp. 197–221.

Moffat, S. D., and Hampson, E. (1996). A curvilinear relationship between testosterone and spatial cognition in humans: Possible influence of hand preference. *Psychoneuroendocrinology* 21: 323–337.

Monzani, R., Del Guerra, P., Caraccio, N., *et al.* (1993). Subclinical hypothyroidism: Neurobehavioral features and beneficial effect of L-thyroxine treatment. *Clinical Investigator* 71: 367–371.

Mooradian, A., Perryman, K., Fitten, J., Kavonian, G., and Morley, J. (1988). Cortical function in elderly non–insulin dependent diabetic patients. *Archives of Internal Medicine* 148: 2369–2372.

Morales, A. J., Nolan, J. J., Nelson, J. C., and Yen, S. C. C. (1994). Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *Journal of Clinical Endocrinology and Metabolism* 78: 1360–1367.

Morrison, A., Resnick, S., Corrada, M., Zonderman, A., and Kawas, C. (1996). A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease in the Baltimore Longitudinal Study of Aging. *Neurology* 46: A435–A436.

Mortel, K. F., and Meyer, J. S. (1995). Lack of postmenopausal estrogen replacement therapy and the risk of dementia. *Journal of Neuropsychiatry and Clinical Neuroscience* 7: 334–337.

Muglia, L., Jacobson, L., Dikkes, P., and Majzoub, J. A. (1995). Corticotropin-releasing hormone deficiency reveals major fetal but not adult glucocorticoid need. *Nature* 373: 427–432.

Murphy, J. F., Purdue, G. F., and Hunt, J. L. (1993). Acute adrenal insufficiency in the patient with burns. *Journal of Burn Care and Rehabilitation* 14: 155–157.

Myers, B. L., and Badia, P. (1993). Immediate effects of different light intensities on body temperature and alertness. *Physiology and Behavior* 52: 199–202.

Naber, D., Sand, P., and Heigl (1996). Psychopathological and neuropsychological effects of 8-days' corticosteroid treatment. A prospective study. *Psychoneuroendocrinology* 21: 25–31.

Nass, R., and Baker, S. (1991a). Androgen effects on cognition: Congenital adrenal hyperplasia. *Psychoneuroendocrinology* 16: 189–201.

Nass, R., and Baker, S. (1991b). Learning disabilities in children with congenital adrenal hyperplasia. *Journal of Child Neurology* 6: 306–312.

Nebes, R. D., Reynolds, C. F., and Horn, L. C. (1984). The effect of vasopressin on memory in the healthy elderly. *Psychiatry Research* 11: 49–59.

Ohkura, T., Isse, K., Akazawa, K., *et al.* (1994a). Evaluation of estrogen treatment in female patients with dementia of the Alzheimer type. *Endocrine Journal* 41: 361–371.

Ohkura, T., Isse, K., Akazawa, K., *et al.* (1994b). Low-dose estrogen replacement therapy for Alzheimer disease in women. *Menopause* 1: 125–130.

O'Neal, M. F., Means, L. W., Poole, M. C., and Hamm, R. J. (1996). Estrogen affects performance of ovariectomized rats in a two-choice water-escape working memory task. *Psychoneuroendocrinology* 21: 51–65.

Osterweil, D., Syndulko, K., Cohen, S. N., Pettler-Jennings, P. D., Hershman, J. M., Cummings, J. L., Tourtellotte, W. W., and Solomon, D. H. (1992). Cognitive function in non-demented older adults with hypothyroidism. *Journal of the American Geriatric Society* 40: 325–335.

Paganini-Hill, A., and Henderson, V. W. (1994). Estrogen deficiency and risk of Alzheimer's disease in women. *American Journal of Epidemiology* 140: 256–261.

Paganini-Hill, A., Ross, R. K., and Henderson, B. E. (1988). Postmenopausal oestrogen treatment and stroke: A prospective study. *British Medical Journal* 297: 519–522.

Parry, C. H. (1825). Cited in Beckwith, B. E., and Tucker, D. M. (1988). Thyroid disorders. In Tarter, R. E., van Thiel, D. H., and Edwards, K. L. (eds.), *Medical Neuropsychology: The Impact of Disease on Behavior*, Plenum Press, New York, pp. 197–221.

Peabody, C. A., Theimann, S., Pigache, R., Miller, T. P., Berger, P. A., Yesavage, J., and Tinklenberg, J. R. (1985). Desglyciamide-9-arginine-8-vasopressin (DGAVP, Org 5667) in patients with dementia. *Neurobiology of Aging* 6: 95–100.

Peace, K. A., Orme, S. M., Thompson, A. R., Padayatt, S., Ellis, A. W., and Belchetz, P. E. (1997). Cognitive dysfunction in patients treated for pituitary tumours. *Journal of Clinical and Experimental Neuropsychology* 19: 1–6.

Perlman, S. M. (1973). Cognitive abilities of children with hormone abnormalities: Screening by psychoeducational tests. *Journal of Learning Disabilities* 6: 21–29.

Perlmuter, L. C., Hakami, M., Hodgson-Harrington, C., Ginsberg, J., Katz, J., Singer, D. E., and Nathan, D. M. (1984). Decreased cognitive function in aging non-insulin-dependent diabetic patients. *American Journal of Medicine* 77: 1043–1048.

Perlmuter, L. C., Tun, P., Sizer, N., McGlinchey, R. E., and Nathan, D. M. (1987). Age- and diabetes-related changes in verbal fluency. *Experimental Aging Research* 13: 9–14.

Perras, B., Droste, C., Born, J., Fehm, H. L., and Pietrowsky, R. (1997). Verbal memory after three months of intranasal vasopressin in healthy old humans. *Psychoneuroendocrinology* 22: 387–396.

Perrild, H., Hansen, J. M., Arnung, K., Olsen, P. Z., and Danielsen, U. (1986). Intellectual impairment after hyperthyroidism. *Acta Endocrinologica* 112: 185–191.

Petersen, A. C. (1976). Physical androgyny and cognitive functioning in adolescence. *Developmental Psychology* 18: 77–94.

Phillips, S. M., and Sherwin, B. B. (1992). Variations in memory function and sex steroid hormones across the menstrual cycle. *Psychoneuroendocrinology* 17: 497–506.

Polo-Kantola, P., Portin, R., Polo, O., Helenius, H., Irjala, K., and Erkkola, R. (1998). The effect of short-term estrogen replacement therapy on cognition: A randomized, double-blind, cross-over trial in postmenopausal women. *Obstetrics and Gynecology* 91: 459–466.

Porteus, S. D. (1959). *The Maze Test and Clinical Psychology*, Pacific Books, Palo Alto, CA.

Rauramo, L., Lagerspetz, K., Engblom, P., and Punnonen, R. (1975). The effect of castration and peroral estrogen therapy on some psychological functions. *Frontiers of Hormone Research* 3: 94–104.

Raven, L. C. (1938). *Progressive Matrices: A Perceptual Test of Intelligence: Individual Form*, H. K. Lewis, London.

Reaven, G. M., Thompson, W. W., Nahm, D., and Haskins, E. (1990). Relationship between hyperglycemia and cognitive function in older NIDDM patients. *Diabetes Care* 13: 16–21.

Reitan, R. M. (1953). Intellectual function in myxedema. *AMA Archives of Neurology and Psychiatry* 69: 436–449.

Reitan, R. M. (1955). Investigation of the validity of Halstead's measures of biological intelligence. *Archives of Neurological Psychiatry* 73: 28.

Reitan, R. M., and Davison, L. A. (1974). *Clinical Neuropsychology: Current Status and Applications*, Hemisphere, New York.

Reitan, R. M., and Wolfson, D. (1993). *The Halstead–Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation*, Neuropsychology Press, Tucson, AZ.

Reiter, R. J. (1990). Pineal rhythmicity: Neural, behavioral, and endocrine consequences. In Shafii, M., and Shafii, S. L. (eds.), *Biological Rhythms, Mood Disorders, Light Therapy, and the Pineal Gland*, American Psychiatric Press, Washington, DC, pp. 41–66.

Resnick, S. M., Berenbaum, S. A., Gottesman, I. I., and Bouchard, T. J., Jr. (1986). Early hormonal influences on cognitive functioning in congenital adrenal hyperplasia. *Developmental Psychology, 22*, 191–198.

Rey, A. (1941). Psychological examination of traumatic encephalopathy. *Archive de Psychologie* 28: 286–340. (Sections translated by

J. Corwin and F. W. Bylsma, *The Clinical Neuropsychologist*, 1993, 4–9.)

Rey, A. (1964). *L'Examin Clinique en Psychologie*, Presses Universitaires de France, Paris.

Ripich, D. N., Petril, S. A., Whitehouse, P. J., and Ziol, E. W. (1995). Gender differences in language of AD patients: A longitudinal study. *Neurology* 45: 299–302.

Robel, P., and Baulieu, E. E. (1994). Neurosteroids: Biosynthesis and function. *Trends in Endocrinology and Metabolism* 5: 1–8.

Rovet, J. F., Erlich, R. M., and Hoppe, M. G. (1987). Specific intellectual deficits associated with the early onset of insulin-dependent diabetes mellitus in children. *Diabetes Care* 10: 510–515.

Ruel, J. M., and Dekloet, E. R. (1985). Two receptor systems for corticosterone in rat brain: Microdistribution and differential occupation. *Endocrinology* 117: 2505–2511.

Russell, E. W. (1975). A multiple scoring method for the assessment of complex memory functions. *Journal of Consulting and Clinical Psychology* 43: 800–809.

Ryan, C. M. (1988). Neurobehavioral disturbances associated with disorders of the pancreas. In Tarter, R. E., van Thiel, D. H., and Edwards, K. L. (eds.), *Medical Neuropsychology: The Impact of Disease on Behavior*, Plenum Press, New York, pp. 121–158.

Ryan, C. M., and Butters, N. (1984). Learning and memory impairments in young and old alcoholics: Evidence for the premature-aging hypothesis. *Alcoholism: Clinical and Experimental Research* 4: 288–293.

Ryan, C. M., Vega, A., and Drash, A. (1985). Cognitive deficits in adolescents who developed diabetes early in life. *Pediatrics* 75: 921–927.

Ryan, C. M., and Williams, T. M. (1993). Effects of insulin-dependent diabetes on learning and memory in adults. *Journal of Clinical and Experimental Neuropsychology* 15: 685–700.

Ryan, C. M., Williams, T. M., Orchard, T., and Feingold, D. (1992). Psychomotor slowing is associated with distal symmetrical polyneuropathy in adults with diabetes mellitus. *Diabetes* 41: 107–113.

Saarela, S., and Reiter, R. J. (1994). Function of melatonin in thermoregulatory processes. *Life Science* 54: 295–311.

Sankar, R., Rai, B., Pulger, T., *et al.* (1994). Intellectual and motor functions in schoolchildren from severely iodine deficient region in Sikkim. *Indian Journal of Pediatrics* 61: 231–236.

Sarrieau, A., Sharma, S., and Meaney, M. J. (1988). Postnatal development and environmental regulation of hippocampal glucocorticoid and mineralocorticoid receptors in the rat. *Developmental Brain Research* 43: 158–162.

Schlote, B., Nowotny, B., Schaaf, L., *et al.* (1992). Subclinical hyperthyroidism: Physical and mental state of patients. *European Archives of Psychiatry and Clinical Neuroscience* 241: 357–364.

Schmidt, P. J., Nieman, L. K., Danaceau, M. A., Adams, L. F., and Rubinow, D. R. (1998). Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. *New England Journal of Medicine* 338: 209–216.

Schmidt, R., Fazekas, F., Reinart, B., *et al.* (1996). Estrogen replacement therapy in older women: A neuropsychological and brain MRI study. *Journal of the American Geriatrics Society* 44: 1307–1313.

Schneider, L. S., Farlow, M. R., Henderson, V. W., *et al.* (1996). Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. *Neurology* 46: 1580–1584.

Schneider, M. A., Brotherton, P. L., and Hailes, J. (1977). The effect of exogenous oestrogens on depression in menopausal women. *Medical Journal of Australia* 2: 162–163.

Schon, M., Sutherland, A., and Rawson, R. (1961). Hormones and neuroses—the psychological effects of thyroid deficiency. In *Proceedings of the Third World Congress of Psychiatry*, McGill University Press and University of Toronto Press, Montreal, Canada, pp. 835–839.

Sherwin, B. B. (1988). Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. *Psychoneuroendocrinology* 13: 345–357.

Sherwin, B. B. (1994). Estrogenic effects on memory in women. *Annals of the New York Academy of Sciences* 743: 756–762.

Sherwin, B. B. (1998). Estrogen and cognitive functioning in women. *Proceedings of the Society for Experimental Biology and Medicine* 217: 17–22.

Sherwin, B. B., and Phillips, S. (1990). Estrogen and cognitive function in surgically menopausal women. *Annals of the New York Academy of Sciences* 592: 474–475.

Sherwin, B. B., and Tulandi, T. (1996). "Add-back" estrogen reverses cognitive deficits induced by a gonadotropin releasing–hormone agonist in women with leiomyomata uteri. *Journal of Clinical Endocrinology and Metabolism* 81: 2545–2549.

Shute, V. J., Pellegrino, J. W., Hubert, L., and Reynolds, R. W. (1983). The relationship between androgen levels and human spatial abilities. *Bulletin of the Psychonomic Society* 21: 465–468.

Singh, M., Meyer, E. M., Millard, W. J., and Simpkins, J. W. (1994). Ovarian steroid deprivation results in a reversible learning impairment and compromised cholinergic function in female Sprague-Dawley rats. *Brain Research* 644: 305–312.

Sivan, A. B. (1992). *Benton Visual Retention Test* (5th ed.), The Psychological Corporation, San Antonio, TX.

Skenazy, J., and Bigler, E. (1984). Neuropsychological findings in diabetes mellitus. *Journal of Clinical Psychology* 40: 246–258.

Slabbekoorn, D., van Goozen, S. H. M., Megens, J., Gooren, L. J. G., and Cohen-Kettenis, P. T. (1999). Activating effects of cross-sex hormones on cognitive functioning: A study of short-term and long-term hormone effects in transsexuals. *Psychoneuroendocrinology* 24: 423–447.

Slotten, H. A., and Krekling, S. (1996). Does melatonin have an effect on cognitive performance? *Psychoneuroendocrinology* 21: 673–680.

Smith, A. (1982). *Symbol Digit Modalities Test*, Western Psychological Services, Los Angeles.

Smith, M. O., Shaywitz, S. E., Shaywitz, B. A., Gernter, J. M., Raskin, L. A., and Gelwan, E. M. (1985). Exogenous GH levels predict attentional performance: A preliminary report. *Journal of Developmental and Behavioral Pediatrics* 6: 273–278.

Squire, L. R., Shimamura, A. P., and Graf, P. (1987). Strength and duration of priming effects in normal subjects and amnestic patients. *Neuropsychologia* 25: 195–210.

Stabler, B., Clopper, R. R., Siegel, P. T., Stoppani, C., Compton, P. G., and Underwood, L. E. (1994). Academic achievement and psychological adjustment in short children. *Journal of Developmental and Behavioral Pediatrics* 15: 1–6.

Starkman, M. N., Gebarski, S. S., Berent, S., *et al.* (1992). Hippocampal formation volume, memory dysfunction and cortisol levels in patients with Cushing's syndrome. *Biological Psychiatry* 32: 756–765.

Starkman, M. N., and Schteingart, D. E. (1981). Neuropsychiatric manifestations of patients with Cushing's syndrome. *Archives of Internal Medicine* 141: 215–219.

Starkman, M. N., Schteingart, D. E., and Schork, M. A. (1986). Depressed mood and other psychiatric manifestations of Cushing's syndrome: Relationship to hormone levels. *Psychosomatic Medicine* 43: 3–18.

Stern, R. A., Nevels, C. T., Shelhorse, M. E., Prohaska, M. L., Mason, G. A., and Prange, A. J., Jr. (1991). Antidepressant and memory effects of combined thyroid hormone treatment and electroconvulsive therapy: Preliminary findings. *Biological Psychiatry* 30: 623–627.

Stern, R. A., Robinson, B., Thorner, A. R., Arruda, J. E., Prohaska, M. L., and Pranges, A. J., Jr. (1996). A survey of neuropsychiatric complaints in patients with Graves' disease. *Journal of Neuropsychiatry and Clinical Neurosciences* 8: 181–185.

Stone, C. P., Girdner, J., and Albrecht, R. A. (1946). An alternate form of the Wechsler Memory Scale. *Journal of Psychology* 22: 199–206.

Strachan, M., Dear, I., Ewing, M., and Frier, B. (1997). Is Type II diabetes associated with an increased risk of cognitive dysfunction? *Diabetes Care* 20: 438–445.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology* 18: 643–662.

Swaab, D. F., and Fliers, E. (1985). A sexually dimorphic nucleus in the human brain. *Science* 28: 1112–1115.

Szalados, J. E., and Vukmir, R. B. (1994). Acute adrenal insufficiency resulting from adrenal hemorrhage as indicated by post-operative hypotension. *Intensive Care Medicine* 20: 216–218.

Szekely, B. (1966). Tolouse-Pieron Concentration Attention Test. In *Los Test*, Kapelutz, Buenos Aires, Argentina, pp. 703–709.

Tang, M. X., Jacobs, D., Stern, Y., *et al.* (1996). Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* 348: 429–432.

Taylor, E. M. (1959). *Psychological Assessment of Children with Cerebral Deficits*, Harvard University Press, Cambridge, MA.

Thoman, M. L., and Weigle, W. O. (1989). The cellular and subcellular bases of immunosenescence. *Advances in Immunology* 46: 221–261.

Thorne, D. R., Genser, S. G., Sing, H. C., and Hegge, F. W. (1985). The Walter Reed Performance Assessment Battery. *Neurobehavioral Toxicology and Teratology* 7: 415–418.

Thurstone, L. L., and Thurstone, T. G. (1963). *Primary Mental Abilities*, Science Research Associates, Chicago.

Toran-Allerand, C. D., Miranda, R. S., Bentham, W. D., *et al.* (1992). Estrogen receptors colocalize with low-affinity nerve growth factor receptors in cholinergic neurons of the basal forebrain. *Proceedings of the National Academy of Sciences, USA* 89: 4668–4672.

Trzepacz, P. T., McCue, M., Klein, I., Greenhouse, J., and Levey, G. S. (1988). Psychiatric and neuropsychological response to propranolol in Graves' disease. *Biological Psychiatry* 23: 678–688.

Trzepacz, P. T., McCue, M., Klein, I., Levey, G. S., and Greenhouse, J. (1988). A psychiatric and neuropsychological study of patients with untreated Graves' disease. *General Hospital Psychiatry* 10: 49–55.

Tun, P. A., Perlmuter, L. C., Russo, P., and Nathan, D. M. (1987). Memory self-assessment and performance in aged diabetics. *Experimental Aging Research* 13: 151–157.

Uhlmann, R. W. (1962). *Test of Color Recognition, Form De X-27-61*, Detroit Edison, Detroit, MI.

U'Ren, R. C., Riddle, M. C., Lezak, M. D., and Bennigton-Davis, M. (1990). The mental efficiency of the elderly person with Type II diabetes mellitus. *Journal of the American Geriatric Society* 38: 505–510.

Vandenberg, S. G., and Kuse, A. R. (1978). Mental Rotations: A group test of three-dimensional spatial visualization. *Perceptual and Motor Skills* 47: 599–601.

Van Goozen, S. H. (1994). *Male and Female: Effects of Sex Hormones on Aggression, Cognition, and Sexual Motivation*, University of Amsterdam Press, Amsterdam.

Van Goozen, S. H., Cohen-Kettenis, P. T., Gooren, L. J., Frijda, N. H., and Van de Poll, N. E. (1995). Gender differences in behavior: Activating effects of cross-sex hormones. *Psychoneuroendocrinology* 20: 343–363.

Vanhulle, R., and Demol, R. (1976). A double-blind study on the influence of estriol on a number of psychological tests in postmenopausal women. In van Keep, P. A., Greenblatt, R. B., and Albeaux-Fernet, M. (eds.), *Consensus on Menopausal Research*, MTP Press, London, pp. 94–99.

Van Wimersma Greidanus, T. B., Burbach, J. P., and Veldhuis, H. D. (1986). Vasopressin and oxytocin: Their presence in the central nervous system and their functional significance in brain processes related to behavior and memory. *Acta Endocrinologica* 276: 85–94.

Vitti, P., Aghini-Lombardi, F., Antonangeli, L., *et al.* (1992). Mild iodine deficiency in fetal/neonatal life and neuropsychological performances. *Acta Medica Austriaca* 19 (Suppl. 1): 57–59.

Wallace, J. E., MacCrimmon, E. J., and Goldberg, W. M. (1980). Acute hyperthyroidism: Cognitive and emotional correlates. *Journal of Abnormal Psychology* 4: 519–527.

Waring, S. C., Rocca, W. A., Petersen, R. C., O'Brien, P. C., Tangalos, E. G., and Kokmen, E. (1999). Postmenopausal estrogen replacement therapy and risk of AD. *Neurology* 52: 965–970.

Warren, S. G., Humphreys, A. G., Jraska, J. M., and Greenough, W. T. (1995). LTP varies across the estrous cycle: Enhanced synaptic plasticity in proestrus rats. *Brain Research* 703: 26–30.

Webster, J. B., and Bell, K. R. (1997). Primary adrenal insufficiency following traumatic brain injury: A case report and review of the literature. *Archives of Physical Medicine and Rehabilitation* 78: 314–318.

Wechsler, D. (1945). A standardized memory scale for clinical use. *Journal of Psychology* 19: 87–95.

Wechsler, D. (1974). *Wechsler Memory Scale Manual*, The Psychological Corporation, San Antonio, TX.

Wechsler, D. (1981). *WAIS-R Manual*, The Psychological Corporation, New York.

Wechsler, D. (1987). *Wechsler Memory Scale—Revised Manual*, The Psychological Corporation, San Antonio, TX.

Weingartner, H., Kaye, W., Gold, P., Smallberg, S., Peterson, R., Gillin, J. C., and Ebert, E. (1981). Vasopressin treatment of cognitive dysfunction in progressive dementia. *Life Sciences* 29: 2721–2726.

Weissman, M. M. (1996). *Epidemiology of major depression in women.* Paper presented at the American Psychiatric Association Annual Meeting, May, New York City, New York.

Whelan, T. B., Schteingart, M. N., Starkman, M. N., and Smith, A. (1980). Neuropsychological deficits in Cushing's syndrome. *Journal of Nervous and Mental Disease* 168: 753–757.

Whybrow, P. C., Prange, A. J., Jr., and Treadway, C. R. (1969). Mental changes accompanying thyroid gland dysfunction. A reappraisal using objective psychological measurement. *Archives of General Psychiatry* 20: 48–63.

Williams, C. L., Barnett, A. M., and Meck, W. H. (1990). Organizational effects of early gonadal secretions on sexual differentiation in spatial memory. *Behavioral Neuroscience* 104: 84–97.

Wilson, B. A., Cockburn, J., and Baddeley, A. (1985). *The Rivermead Behavioral Memory Test*, Thames Valley Test Co., Reading, England; National Rehabilitation Services, Gaylord, MI.

Winograd, D. L., Sensheima, P., Barrett-Connor, E. L., and McPhillips, T. B. (1990). Community-based study on the prevalence of NIDDM in older adults. *Diabetes Care* 13 (Suppl. 2): 3–8.

Wolf, O. T., Koster, B., Bierings, H. G., *et al.* (1997). A single administration of dehydroepiandrosterone (DHEA) does not enhance memory performance in young healthy adults, but immediately reduces cortisol levels. *Biological Psychiatry* 2: 845–848.

Wolf, O. T., Neumann, O., Hellhammer, D. H., *et al.* (1997). Effects of a two-week physiological dehydroepiandrosterone substitution on cognitive performance and well-being in healthy elderly women and men. *Journal of Clinical Endocrinology and Metabolism* 82: 2363–2367.

Wolkowitz, O. M. (1994). Prospective controlled studies of the behavioral and biological effects of exogenous corticosteroids. *Psychoneuroendocrinology* 19: 233–255.

Wolkowitz, O. M., Reus, V. I., Roberts, E., *et al.* (1994). Antidepressant and cognition-enhancing effects of DHEA in major depression. *Annals of the New York Academy of Sciences* 774: 337–339.

Wolkowitz, O. M., Reus, V. I., Roberts, E., *et al.* (1997). Dehydroepiandrosterone (DHEA) treatment of depression. *Biological Psychiatry* 41: 311–318.

Wolkowitz, O. M., Reus, V. I., Weingartner, H., *et al.* (1990). Cognitive effects of corticosteroids. *American Journal of Psychiatry* 147: 1297–1303.

Wolters, E. C., Riekkinen, P., Lowenthal, A., Van der Plaats, J. J., Zwart, J. M., and Sennef, C. (1990). DGAVP (Org 5667) in early Alzheimer's disease patients: An international double-blind, placebo-controlled, multicenter trial. *Neurology* 40: 1099–1101.

Wooley, C. S., and McEwen, B. S. (1993). Roles of estradiol and progesterone in regulation of hippocampal dendritic spine density during the estrous cycle in the rat. *Journal of Comparative Neurology* 336: 293–306.

Wynn, V. T., and Arendt, J. (1988). Effect of melatonin on the human electrocardiogram and simple reaction time responses. *Journal of Pineal Research* 5: 427–435.

Yaffe, K., Ettinger, B., Pressman, A., *et al.* (1998). Neuropsychiatric function and dehydroepiandrosterone sulfate in elderly women: A prospective study. *Biological Society* 43: 694–700.

Yaffe, K., Sawaya, G., Lieberburg, I., and Grady, D. (1998). Estrogen therapy in postmenopausal women. *Journal of the American Medical Association* 279: 688–695.

Yashino, A., Hovda, D., Kawamato, T., Katayama, Y., and Becker, D. (1991). Dynamic changes in local cerebral glucose utilization following cerebral concussion in rats: Evidence of a hyper- and subsequent hypometabolic state. *Brain Research* 561: 106–119.

Young, R. J., Ewing, D. J., and Clarke, B. F. (1983). Nerve function and metabolic control in teenage diabetics. *Diabetes* 32: 142–147.