Interest in the neurocognitive and sensory impairments resulting from many cancers and their interventions has grown considerably over the past decades as an important aspect of quality of life issues for cancer patients and survivors. The Neuropsychology of Cancer and Oncology features current findings on the neuropsychological effects of these cancers and their treatments along with the most promising neuropsychological and behavioral health interventions available to mitigate these deficits. This edited volume, part of the Contemporary Neuropsychology series, bridges the gap between the knowledge of neuropsychologists, who are grounded in the biological and physiological bases of cognition and behavior but not in pathology, and that of oncologists, who often lack expertise in the neuropsychological aspects of cancer.

This text first addresses the biological components and medical care of these cancers, and issues relating to bioimaging. It then discusses the neurological impact of these cancers as they affect different functions, such as memory, learning, and sensory-motor ability, as well as discusses the effects of childhood cancers on neurological development. State-of-the-art neuropsychological and behavioral health interventions are considered, including neuropsychological/cognitive rehabilitation and habitation, pharmacological interventions, and collaborative medical practices. This text is a unique and timely resource for clinical neuropsychologists, clinical psychologists, neurologists, oncologists, oncology nurses, and neurorehabilitation professionals.

**Key Features:**
- Bridges the gap of knowledge between neuropsychologists and oncologists
- Explores the most current research on the neuropsychological effects of various cancers and their treatments
- Provides state-of-the-art information on promising neuropsychological and behavioral-health interventions for impairments created by cancers and their treatments
- Represents a collaboration between some of the foremost scholars and practitioners in neuropsychology and oncology
The Neuropsychology of Cancer and Oncology
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The Neuropsychology of Cancer and Oncology

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Thomas Tarter, PhD, MD, Gary Johnson, MD, and Rhonda Johnson, PhD
I dedicate this to my uncle, Gail LeCount, who passed away during the preparation of this book, following a long battle with cancer. I also dedicate this book to my grandparents, Walter “Papa” Burress, who passed away due to cancer, and Francis “Mama” Burress who was a survivor of cancer—CAN

To my children with all my heart—RSD
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Preface

Whether due to the effects of the disease process itself or the negative outcomes associated with various treatment methods from the time of diagnosis and even beforehand, cancer patients frequently experience a number of adverse symptoms. Fatigue, sleep disturbances, and emotional problems such as depression and anxiety are often reported. In addition, cognitive deficits are being recognized with increasing frequency as possible negative outcomes related to cancer and its treatment. Cognitive dysfunction occurs in both patients with central nervous system (CNS) tumors and those with non-CNS disease types. In addition, a majority of patients during active treatment will experience cognitive problems. While these deficits are not consistently identified on objective assessment, their impact on a patient’s daily life can be quite significant. Patients may struggle returning to school or work. They may find themselves unable to handle the same amount and type of work as they did before. Normal tasks are more trying and may take more time to complete.

Neuropsychology, a field that represents the study of brain–behavior relationships, is being utilized more frequently within the cancer population to assess cognitive functioning prior to, during, and after treatment. Advances in functional and structural neuroimaging, as well as other biological tests have provided further insight into the pathological roots of cognitive deficits in the cancer population. Still, the majority of practicing neuropsychologists are not well versed in their knowledge of cancer, oncology, and their potential influence on cognitive functioning. At the same time, professionals within oncology and surrounding domains have minimal exposure to neuropsychological practice or the literature on the neuropsychological impact of cancer and antineoplastic care.

The Neuropsychology of Cancer and Oncology is a unique text in that it discusses the integration of neuroscience, neuropsychology, and cancer and oncology to outline how both the disease (i.e., CNS and non-CNS cancers) and its treatment (i.e., surgery, radiation, chemotherapy, hormonal therapies, etc.) may negatively impact cognition. In lieu of simply discussing brain tumors or therapies that specifically target the CNS, we have chosen to cover both these issues while also discussing the means by which non-CNS cancers and their treatments affect cognition. Because deficits may be indirect manifestations of treatment (e.g., poor memory due to fatigue that itself is due to treatment), an understanding of current methods of treatment is important as is an understanding of the disease processes themselves. The chapters included herein discuss many of the different forms of cancer, including current methods of treatment and the potential for neurocognitive deficits related to the disease process and therapies employed. Potential neurocognitive deficits are discussed from a domain perspective as well. Finally, supplementary services and resources are discussed. We hope that this volume will serve professionals in two diverse areas of practice—clinical neuropsychology, clinical psychology, and psychiatry on the one hand, and oncology on the other—in order to provide the highest quality of care to the patients in their care and to ensure a better quality of life for these patients overall.
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A book such as this is only made possible through the contribution of various authors. We want to acknowledge their willingness to volunteer their time and knowledge to this work. As always, we must acknowledge the support of our colleagues and associated institutions; SIU School of Medicine and Ball State University, without whom this project would not be possible. Finally, we would like to express our sincerest gratitude to our publisher and those with whom we have worked with very closely to complete this book, especially Nancy S. Hale and Joseph Stubenrauch.
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The Neuropsychology of Psychopathology
The Neuropsychology of Cancer and Oncology
Neuropsychological Rehabilitation
The Neuropsychology of Cortical Dementias
The Neuropsychology of Pervasive Developmental Disorders
The Neuropsychology of Psychopharmacology
Biological Components, Medical Care, and Special Considerations
Annually, nearly 1.5 million people in the United States are diagnosed with cancer. While in previous decades the 5-year survival rate was far lower, continued advances in early diagnosis and treatment options has led to improved morbidity and mortality rates. In the past, treatment mainly took on an antineoplastic approach, with the intention of treating the disease and increasing quantity of life. Yet, increased survival rates have simultaneously led to an increase in the number of reported long-term complications of the disease and its treatment. Consequently, as the population of cancer survivors has grown, we too have grown in our focus on issues pertaining to and ensuring a quality of life (QOL).

QOL can be described in many ways. We conceptualize it as an individual’s self-appraisal of how their life is currently compared to where they would like it to be. However, this global QOL is merely the by-product of various domain-specific appraisals and qualities of life. As depicted in Figure 1.1, we conceptualize QOL as a multifactorial entity with contributions and influences from various aspects of one’s life. Hyperfocus on one or only a few domains can still lead to poor quality of life, due to the influence of negative self-appraisals within the neglected domains. The classic approach to cancer care is a good example of this approach. Focus was primarily placed on the individual’s health and antineoplastic treatment. However, factors such as emotional well-being, cognitive well-being, and so on, were neglected and, thus, patients could demonstrate a positive response to treatment but still have a poor net QOL. In reality, within the cancer population, from initial diagnosis through treatment and on into survivorship, all of these domains are susceptible to negative influence and, consequently, diminished or poor QOL.

In the past two decades, one area that has received increased attention within this population is cognition. More specifically, cognitive dysfunction associated with cancer and its treatment has grown in interest over the past few decades. Though changes in cognition may not be as noticeable as external features, such as an individual losing his or her hair due to chemotherapy, patients often struggle to cope with and overcome such cognitive deficits. Patients may report things like “I don’t feel like the same person,” “My mind just does not work the same,” “I cannot remember anything anymore,” and “My short-term memory is horrible.” All of these statements have been made to the lead author of this chapter by actual patients, either through clinical encounters or as part of research studies. Such cognitive complaints are significant as they may exert an influence over multiple other domains of one’s

Portions of this chapter were adapted with permission from Noggle & Dean (2011a,b).
Individuals may struggle in returning to school or work. As they perceive difficulties within these settings, individuals may develop strong emotional reactions such as depression or anxiety in response to their self-awareness of these cognitive deficits. This is in addition to the risk of depression and anxiety related to having cancer. Emotionality (e.g., depression or anxiety) may then serve to exacerbate the cognitive deficits, thus creating a cyclical exchange between cognition and emotions.

Though cognitive complaints within the cancer population are discussed more frequently today than 20 years ago, there remains considerable limitation in the knowledge of the subject matter by those in and around the fields of neuropsychology, oncology, and other neuroscience and medical fields. Although previous conceptualizations primarily isolate neurocognitive deficits to cancer or treatment directly affecting the CNS (e.g., primary or metastatic brain tumors, neurosurgical intervention), research has demonstrated this is an inaccurate conclusion. The reality is that neurocognitive dysfunction arises from both direct and indirect influences of the disease and its forms of treatment. Furthermore, these influences are not limited to CNS foci, as systemic disease and systemic treatment have also been related to persistent cognitive complaints within the cancer population. We would argue that neuropsychology as a field is best suited to address these cognitive issues. Oftentimes, when cognitive deficits present, they stem from a mixture of physiological, medical, or psychological factors. Neuropsychologists, through their training within multiple domains, tend to have a great appreciation for the potential influence of these various factors. The robustness of neuropsychological assessments also provides a means for fully appreciating ones individual strengths and weaknesses. Screening measures such as the Mini Mental Status Examination, with its low ceiling, is often insensitive to the effects of cancer and its treatment on cognition. Consequently, a comprehensive, standardized, and objective measure of cognition, as is pursued as part of a neuropsychological assessment, remains the most appropriate way of assessing cognitive deficits related to cancer and its treatment.

In this chapter, we provide a brief overview of the field of neuropsychology, including the field’s historical roots and principles of clinical practice. From there we discuss cognitive deficits as they present in cancer and its treatment. This includes a general introduction to the potential etiologies of these deficits, which will be expanded upon in later chapters through disease specific and domain specific discussions.

HISTORY OF NEUROPSYCHOLOGY

Historically, the field of clinical neuropsychology grew out of a need to localize cerebral lesions and determine the extent of neurological impairment through noninvasive methods. Regarding working with the medical fields and assisting in rehabilitation 30 years
ago, neuropsychologists were primarily responsible for localizing lesions and determining the lateralization of impairment. Early neuropsychologists utilized both direct and indirect observation. Indirect observation included observing visible neurological impairment and extrapolating to observable behaviors (e.g., the case of Phineus Gage) or using neuropsychological test instruments that measure behavior as supposedly correlated to specific processing areas. Direct measurement was not possible until autopsy, such as the case of Paul Broca examining the brain of his famous patient with expressive aphasia after death. Despite the success of neuropsychologists using indirect measurement, it is difficult to argue that direct measurement of functions is the future of the field, as well as the far superior technique. Indirect measurement and estimation of localization of impairment suffers from the fact that neuropsychologists are not really measuring a neurological region, they are measuring behavior that they believe is related to a specific neural processing area based on research or anecdotal evidence.

Humans have long been aware of the brain–behavior relationship, with the search for information and treatment extending back thousands of years. Archeologists have discovered several thousand skulls that show evidence of humans having survived trephination (Zillmer & Spiers, 2001). Trephination is the ancient practice of removing pieces of the skull, designed to relieve swelling of the brain. The ancient Greeks produced the first written records of brain–behavior relationships. They tended to regard cognitive functioning from a divine nature. The first recorded observation that the brain is the center of human reasoning was produced by Pythagoras (580–500 BCE). Pythagoras and other scholars developed the idea of the brain hypothesis, which stipulated that the brain is the source of all behavior (Zillmer & Spiers, 2001).

Hippocrates, largely credited with founding modern medicine, held that the brain was the center of sensations, wisdom, consciousness, emotions, and movement. He also postulated that psychological disorders were caused by brain pathology and head trauma. This was in opposition to the commonly held belief that brain disorders, especially seizures, were the work of gods. In discussing head trauma, he correctly noted that paralysis occurred contralaterally to the hemisphere of the injury. Plato (420–347 BCE) wrote that the soul, responsible for rational thought, was located in the brain and noted that head trauma will result in impairment in reasoning (Robinson, 1970). Aristotle (384–322 BCE), a student of Plato, postulated that the heart is the seat of all mental processes. He argued that as the heart is warm and active, it was the seat of emotions such as love and anger. The brain worked to cool the hot blood that rises from the heart. This viewpoint was called the cardiac hypothesis. The first recorded observation that the brain is the source of all behavior was produced by Pythagoras (580–500 BCE). Pythagoras and other scholars developed the idea of the brain hypothesis, which stipulated that the brain is the source of all behavior (Zillmer & Spiers, 2001).

Galen (130–201 AD), a Roman anatomist and physician, is a key figure in the history of neuropsychology. His observations of the human body came from his work as a surgeon who was appointed to gladiators (Finger, 1994a). Galen believed that the functioning of the body and brain resulted from the combination of the four elements, qualities, and humors (May, 1968). Galen’s view of humors became so ingrained that physicians barely elaborated on the role of the brain for the next thousand years. During the 16th century, Galen’s anatomical mistakes began to be corrected. Rene Descartes (1596–1650), a French philosopher and mathematician, is an important figure in the history of neuropsychology, in that he proposed a division between mental and physical processes. He viewed the human body as a material entity that functioned like a machine, where the mind was free to carry out the functions of consciousness. This idea is now referred to as interactive dualism (Benjamin, 1997).

As the 18th century approached, more accurate representations of the brain and its functions were occurring. This may have been related to the conviction that all things could be conceptualized as machines (Zillmer & Spiers, 2001). Emanuel Swedenborg (1688–1772) was likely the first to generate a theory of cortical localization of behavioral functions.
Swedenborg wrote that separate areas of the brain were necessary to prevent psychological chaos, and charted his ideas of discrete areas for vision and hearing based on his studies of pathology and anatomy (Finger, 1994b). Although ahead of his time, his ideas were not published until the end of the 19th century, when localization theory was broadly accepted. It was with the idea of brain localization in mind that Franz Gall (1758–1828) developed the science of phrenology. Phrenologists believed that the brain consists of a number of separate organs that are independently responsible for some aspect of behavior or personality. They stipulated that variations in brain functions among individuals led to variations in the shape or size of that organ of the brain. Hence, it was possible to detect variations in brain functions by looking for differences along the shape of the skull. Although today phrenology is referred to with contempt and humor, the advocates of phrenology made many important contributions to the study of the brain and how it affects behavior. Gall was among the first to propose that the cerebral cortex is not merely the outer area of the brain with no specific functions. Although the anatomical deductions of phrenology are erroneous, the determination to objectively study the mind without metaphysical conceptions is a landmark in the history of neuropsychology.

Paul Broca (1824–1880), a French surgeon-anthropologist, was able to identify specific functional areas within the cerebrum. He is best remembered for identifying an area that is related to expressive speech that produces a speech disorder we now commonly call Broca’s area. Damage to this area is called Broca’s aphasia, usually resulting from a lesion to the left hemisphere of the brain in either the frontal operculum, or the corticocortical association pathways in the white matter of the temporal, parietal, and frontal lobes that relate to the motor speech areas. Broca is also responsible for starting a decades-long trend that the left hemisphere was regarded as the dominant hemisphere. After performing an autopsy on his famous patient, Leborgne (also called Tan), who was suffering from a degenerative ability to produce speech, Broca was able to identify the area of the cerebrum, which bears his name, responsible for the damage. On an autopsy, Broca was able to identify several areas of the brain that were destroyed, which led him to conclude that the area of the brain which bears his name was responsible for causing the expressive language problem.

Another 19th century researcher, Carl Wernicke (1848–1904), was also to have an area of the brain named after him in honor of his findings. Wernicke postulated that the ability to understand spoken language had a specific localization site in the brain, in the posterior half of the left superior temporal gyrus. The disorder now known as Wernicke’s aphasia is characterized by defective comprehension of spoken words, and fluent yet incoherent speech. Wernicke was also responsible for casting light on a disorder that may have been previously referred to as madness in earlier centuries, which was actually a problem of the left hemisphere (Harris, 1999). Wernicke’s findings are important in brain localization theory, as, along with Broca, he was able to demonstrate that language is located in at least two different cortical areas. Wernicke’s findings cast a realistic shadow on 19th-century proponents of brain localization theory, who hypothesized functions had one specific location. In the case of speech, there were at least two areas of the cortex operating, Broca’s and Wernicke’s areas, as well as association pathways.

Early neuropsychologists were interested in studying other aspects of the brain aside from motor and sensory areas. The frontal lobes received a lot of attention, as many 19th century philosophers held that the frontal lobes are what separate man from the lower order species. Phineus Gage, a railroad worker suffered a traumatic brain injury when an explosion forced a large piece of metal into the front of his brain. Although he recovered with his lower order functions (respiration, heart rate) intact, he suffered a noticeable change in personality and behavior. This and other cases of people surviving injuries, led to speculation that elements of personality could be localized in the frontal lobes.

Hughlings Jackson (1835–1911) was an English neurologist who hypothesized that higher mental functions are not discrete actions unto themselves, but are combinations of a series of simpler mental processes. He disagreed with localization theorists who proposed that the brain has a single speech center. For example, he viewed speech as a sequence of simple mental abilities, such as hearing, fine motor movements, and kinesthetic control of the
mouth. Thus, if there is an injury to the brain that results in loss of speech, it does not necessarily occur in Broca’s or Wernicke’s area since the injury could disrupt any one of the many processes that are necessary to create speech. Jackson was not interested in answering the question, “Where is language located?”; he wanted to know “What is each region’s contribution to language?” (Harris, 1999).

Alexander Luria (1902–1977), a Russian neuropsychologist, built on Jackson’s theories to become one of the most prominent neuropsychologists of the 20th century. Luria did not view any complex higher cortical functions as products of a particular tissue or organ, but as the coordination of several different brain areas. Luria combined elements of localization, equipotentiality theory, and the work of Hughlings Jackson to create a conceptualization of a normally functioning brain as three units. The first unit regulates activation, muscle tone, and vigilance and consists of the reticular formation, limbic system, and mesial basal frontal lobes. Injuries to the first unit can result in lethargy and apathy, which will impair higher cortical systems, even though the areas related to higher cortical functions, may remain intact. The second unit is responsible for registration, analysis, and the storage of sensory information, and is comprised of the temporal, parietal, and occipital lobes. The third unit regulates complex mental activity, such as planning, abstract thought, and organization. This unit is dependent upon the integrity of the frontal lobes. All activities depend upon the cooperation of all three units. Luria’s theory hypothesizes that when a functional system ceases to operate correctly as a result of an injury, it is not obvious which cerebral structure in the brain is impaired. For example, a brain-injured patient may not be attending (Unit 1), he may not be able to analyze relevant stimuli (Unit 2), or he may not be actively trying to use the information; all three of these possibilities will have similar functional presentations (Gouvier et. al., 1997). No single unit or area of the brain is solely responsible for the execution of any activity. In order to assess which system is impaired, Luria proposed testing a series of hypotheses that call upon each unit to sequentially demonstrate its integrity. Luria’s idea of harmonious processing remains very relevant today, decades after he first published his ideas. His ideas have directly influenced modern neuropsychological tests such as the Luria-Nebraska Neuropsychological Test Battery (Golden, Purisch, & Hammeke, 1985) and the NEPSY: A Developmental Neuropsychological Assessment (NEPSY; Korkman, Kirk, & Kemp, 1998). More importantly, Luria’s idea of harmonious processing demonstrates some of the weaknesses regarding modern neuroimaging. Although functional neuroimaging is adept at showing regional processing, more widely used measures of static functioning (e.g., MRI, CT) only identify a lesion site and do not provide evidence of functional impairment. Thus, while the field of neuropsychology is likely to undergo significant changes in the next several years, the identification of functional implications and the interaction of the neurological impairment, behavior, and the environment are likely to remain the domain of the neuropsychologist.

Through modern neuroimaging analyses, we have been able to confirm the ideas proposed by Luria and Jackson regarding the overlapping of functional systems in producing behavior. As suggested by Luria (1964, 1966) the brain is best characterized as having harmonious functional systems that interact with one another to varying degrees to carry out all behavior and function. Clinically, a patient may present with dysnomia (i.e., difficulty in naming); however, this manifestation may originate from at least eight different sites of neuro-anatomical impact (e.g., Broca’s area, Wernicke’s area, arcuate fasciculus, Perisylvian region, anterior borderzone, posterior borderzone, angular gyrus, anterior, and posterior borderzone; Filley, 2001). Truly, assessment of additional domains of language functioning (e.g., spontaneous speech, auditory comprehension, repetition) may better establish regional differentiation; however, imaging can more accurately achieve this same differentiation when a lesion is viewable via imaging, which, in turn, the neuropsychologist may then use to guide their understanding of the individuals functional presentation. This understanding is of particularly great importance, as although the functional aftermath of two very different lesions may be similar, their responsiveness to methods of intervention will differ according to regional origin (see Crosson, Bacon-Moore, Gopinath, White, Wierenga, et al., 2005). Given this, it stresses the importance of utilizing neuroimaging findings in neuropsychological practice.
The following section will explain the mechanical and scientific underpinnings of modern neuroimaging techniques.

**NEUROPSYCHOLOGICAL PRACTICE**

Neuropsychology is best conceptualized as a mixture between behavioral neurology, clinical and experimental psychology, and objective measurement of human behavior. This is evident in many of the procedures that currently make up available neuropsychological test batteries. With few exceptions, current assessment procedures are either standardized versions of preexisting clinical procedures or adaptations of neuropsychological laboratory procedures for clinical use. Often seen as an expansion of the neurologic examination, neuropsychological assessment emphasizes standardized behavioral observations and interpretations that rely on normative standards and critical value cutting scores. This approach has been shown to be of value in diagnosing neurologic disorders and defining the behavioral effects of brain damage. In retrospect, one can criticize 19th and early 20th century methods that based conclusions about normal brain functioning on case studies of patients with diseased brains. Nevertheless, these early reports led to our present understanding of the relationship between clinically expressed behaviors and cerebral functions. The notion of a direct correspondence between behavior and localized microstructures of the brain seems naive by present standards. We now recognize that the magnitude, site, and chronicity of a brain lesion, developmental history, and individual differences in brain structure and chemistry all interact to make highly specific localization tenuous. The inflexible notions of a one-to-one correspondence between observable behavior and structures of the brain have been rejected by most neuroscientists. However, a quantitative-actuarial approach remains, which concentrates on the differential diagnosis of neurologically related conditions and their behavioral correlates. The emphasis on differential diagnosis in neuropsychological assessment is relatively recent in the history of the field, and grows out of a need to describe more objectively the behavioral effects of neurological and psychiatric presentations. Although the neurologist or radiologist may be able to document and localize lesions, rarely is it possible to make specific predictions about a patient’s behavioral functioning in their premorbid environment. Thus, neuropsychological assessment provides information useful in aftercare planning and following progressive disorders.

The scientific approach of identifying individual differences of the late 19th and early 20th centuries continues to influence psychometric theory in general and neuropsychological assessment specifically. From this perspective, various aspects of human behavior (e.g., memory) are viewed on a continuum rather than as a normal–abnormal dichotomy, with the majority of individuals clustering around a midpoint on a given ability spectrum. This approach to neuropsychological assessment has resulted in the scaling of functions and the interpretation of individual behaviors relative to normal cohorts.

Neuropsychological assessment comprises tasks examining a comprehensive array of behaviors that are compared with normative standards and those occurring in known neurologic conditions. Such information permits recognition of “minor” behavioral/cognitive impairment, often the early sign of neurologic disorders, which the cumulative literature over the past few decades has clearly linked with neurological substrates. Of use in differential diagnosis, these data also provide the clinician information concerning the extent of a patient’s behavioral impairment. Neuropsychological assessment provides the objectivity necessary in following the course of progressive or chronic disorders or presentations and offers the clinician a monitoring capability not available with other procedures. It also offers the opportunity for reassessment, which may be necessary in relation to (a) questionable validity on previous testing related to poor attention or motivation; (b) decline or improvement in cognition, (c) functional decline, (d) effects of a neurological event, (e) effects of substance abuse, (f) effects of cognitive interventions, (g) medication effects, and (h) test–retest for research purposes (Marcopulos et al., 2008). Within the cancer population, this is useful both within the experimental/scientific and clinical realms as it permits for the assessment of change over time in relation to an intervention (e.g., serial assessment), allows for pre- and postresection...
Neuropsychological examinations involve measures of cognitive, sensorimotor, and emotional functioning. Some of the tests are the same as those routinely administered in clinical evaluation. For example, the Minnesota Multiphasic Personality Inventory II (MMPI) and the Wechsler Intelligence Scales have been included as part of most neuropsychological evaluations after extensive research concerning the neurologic correspondence of these measures. These tests have allowed a more comprehensive view of the patient’s level of functioning. The tests used may vary somewhat with the individual laboratory or practitioner.

**Neuropsychological Practice in Oncology**

Within the domain of cancer and oncology, neuropsychological assessment may be pursued for both clinical and research purposes. In both instances, clinicians must be mindful of those areas most susceptible to the effects of treatment (e.g., attention, processing speed, executive functioning, memory, etc.). While measures such as the Mini Mental Status Examination may be a helpful initial screening tool for other presentations, it is unlikely to capture the functional deficits related to cancer and its treatment, aside from a few exceptions. This further emphasizes the importance of neuropsychological assessment as it provides a means of objectively identifying potential brain dysfunction, including mild or subtle cognitive disturbances such as those described in relation to cancer and oncology. Consequently, measures used should be sensitive to subtle changes across specified functional domains. The assessment must also be comprehensive as neuropsychological profiles related to cancer and its treatment can result in various impairments.

In general, assessments should (a) measure premorbid functioning, (b) assess a wide range of cognitive domains, (c) evaluate for potential malingering, (d) be mindful of examinee burden, and (e) be at the functional level of the client (Marcopulos et al., 2008). Within the cancer population, while particular domains may be focused on more than others because of the case presentation, we recommend that assessments include measures of intelligence, attention and processing speed, language, memory and learning, visuospatial/visuoperceptual skills, academic functioning, executive functioning, sensory-motor functioning, and mood. Inclusion of both objective measures and subjective report measures are essential as patients may often report greater impairments in everyday functioning than is revealed on objective assessment. For example, objective measures of executive functioning should be utilized while also including self-report measures such as the Behavior Rating Inventory of Executive Functioning (Roth et al., 2005) to obtain a quantification of the patient’s potential for daily problems in this domain. Inclusion of academic functioning measures is particularly important for children, adolescents, or others who may be in school or returning to school. However, academic functioning measures are also important from a functional standpoint given the potential for neurological features presenting in these domains (e.g., alexia, agraphia). Within the clinical setting, this comprehensiveness is more essential; within the parameters of a clinical study, the desired end points may direct assessment toward a more focused direction.

Interpretation must not simply focus on quantitative outcomes but also on the qualitative input and output, as task failure can stem from various cognitive processes and not necessarily a unitary function.

Table 1.1 includes a potential battery for a comprehensive neuropsychological assessment as well as a neuropsychological screening battery. An in-depth review of neuropsychological assessment can be found in other sources (e.g., Lezak et al., 2004).

**Competing or Influential Factors in Assessment and Interpretation**

*Premorbid and Neurodevelopmental History.* The impact of neurocognitive deficits within the cancer setting is dependent on the individual’s life stage, both in terms of chronological age and environmental demands of “normal” neurocognitive functioning. The timing of disease...
onset and treatment initiation should be taken into account when considering neuropsychological deficits. Discrepancies between children and adults should be anticipated as this reflects differences in exposing a developing brain to such insults compared to exposing a developed brain. A detailed developmental and premorbid history is critical to fully appreciate and conceptualize the potential impact of the cancer itself and the impact of the treatment delivered, and to understanding the interrelationship between cognitive, behavioral, biological, and environmental factors.

As is true in other clinical medical sciences, a patient’s presenting symptoms must be interpreted relative to their medical, social, and family history. Although it is often difficult to examine the effect of education, socioeconomic status, and occupation for the individual, each has been shown to be related to the performance on psychological measures in general, and on measures of neuropsychological functioning specifically, and may modify their interpretation. Prigatano and Parsons report a considerable relationship between the results on measures of neuropsychological functioning and the level of education for patients from a general medical service.

**TABLE 1.1 Brief and Comprehensive Neuropsychological Assessment**

<table>
<thead>
<tr>
<th>TYPE OF EVALUATION</th>
<th>TESTS</th>
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<tbody>
<tr>
<td>Neuropsychological Screen</td>
<td>• Wechsler Abbreviated Scale of Intelligence (WASI)</td>
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<td></td>
<td>• Wechsler Test of Adult Reading (WTAR)</td>
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<tr>
<td></td>
<td>• Repeatable Battery of Neuropsychological Status (RBANS)</td>
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<td></td>
<td>• Trails A and B or Comprehensive Trail Making Test (CTMT)</td>
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<td></td>
<td>• Stroop</td>
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<td></td>
<td>• Wisconsin Card Sorting Test</td>
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<td></td>
<td>• Grooved Pegboard</td>
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<tr>
<td></td>
<td>• Beck Depression Inventory-2</td>
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<td></td>
<td>• Beck Anxiety Inventory</td>
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<table>
<thead>
<tr>
<th>Comprehensive Neuropsychological Evaluation</th>
<th>TESTS</th>
</tr>
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<tbody>
<tr>
<td>• Wechsler Adult Intelligence Scale-IV (WAIS-IV) or Woodcock-Johnson-Ill-Tests of Cognitive Abilities (WJ-III-COG)</td>
<td>• Wechsler Test of Adult Reading (WTAR)</td>
</tr>
<tr>
<td>• California Verbal Learning Test-II (CVLT-II)</td>
<td>• Wechsler Memory Scale-IV (WMS-IV) or Wide Range Assessment of Memory and Learning-2 (WRAML-2)</td>
</tr>
<tr>
<td>• Rey Complex Figure Test</td>
<td>• Trails A and B or Comprehensive Trail Making Test (CTMT)</td>
</tr>
<tr>
<td>• Stroop</td>
<td>• Wisconsin Card Sorting Test</td>
</tr>
<tr>
<td>• Beck Depression Inventory-2</td>
<td>• Beck Anxiety Inventory</td>
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<tr>
<td>• MAE Token Test</td>
<td>• Boston Naming Test</td>
</tr>
<tr>
<td>• Verbal Fluencies (e.g., COWAT &amp; animals)</td>
<td>• Continuous Performance Test-II</td>
</tr>
<tr>
<td>• Wechsler Individual Achievement Test-III (WIAT-III) or Woodcock-Johnson-III-Tests of Achievement-Ill (WJ-III-ACH) or Kaufman Functional Academic Skills Test (K-FAST)</td>
<td>• Test of Memory Malingering (TOMM) and/or Word Memory Test</td>
</tr>
<tr>
<td>• Halstead-Reitan Sensory–Motor Battery or Dean-Woodcock Sensory-Motor Battery</td>
<td>• Grooved Pegboard</td>
</tr>
<tr>
<td>• Behavior Rating Inventory of Executive Functioning (BRIEF) / Minnesota Multiphasic Personality Inventory-II—Restructured Format (MMPI-2-RF)</td>
<td>• Beck Depression Inventory-2</td>
</tr>
<tr>
<td></td>
<td>• Beck Anxiety Inventory</td>
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</table>
Dean has argued that the adult patient’s premorbid occupation and the concomitant opportunity to refine academic skills may be a potent predictor of neuropsychological functioning. Indeed, there seems to be a substantial relationship between socioeconomic status, when measured by occupation, and normal individuals’ general cognitive abilities. The effect of race on neuropsychological functioning is not as clear. Although some have hypothesized a genetic component for race on such measures, the interaction of socioeconomic differences and aspects of cultural transmission make interpretation of these data for the individual patient tenuous.

As one would expect, the effects of age on neuropsychological performance are clearest at the two extremes with batteries developed exclusively for adults and exclusively for children. Although diminution in neuropsychological functions is known to exist with advancing years, the extent to which these results are dependent on past learning and experience is not clear. In one early study, Reed and Reitan reported a moderate negative correlation between age and scores on the neuropsychological battery. However, this summary statistic obscures the more interesting result that little dependable change in neuropsychological functioning was observed for abilities that depended most directly on past learning. This replicated finding was as clear as the decline with advancing years of performance on tasks requiring mental flexibility, new learning, and memory when not based on old associations.

Finally, in taking a patient’s developmental and premorbid history it is important to assess for preexisting and comorbid conditions. Histories of ADHD, learning disabilities, externalizing disorders, pervasive developmental disorders, or more general intellectual disabilities must be taken into account clinically and not ignored simply because these traits may not be the basis for the referral per se. Clearly, the patient’s developmental and medical history provides insight into their neuropsychological performance. Thus, the patient’s present functioning level must be evaluated in light of seemingly unrelated factors.

Timing of Assessment(s). Within the cancer population, the timing of assessments is a critical issue for clinicians. Differing opinions could likely be found within the profession. In reality, this decision is largely based on the purpose of the assessment. Within the research setting, with most studies focusing on either the impact of the disease itself or the treatment, we would argue that pretreatment assessment is always critical. If there is interest purely on the impact of the disease, assessment should be carried out prior to any treatment being delivered which itself could carry some degree of neuropsychological burden. Depending on the additional research interests, further assessments may be utilized. This could involve assessment during treatment, immediately following the completion of active treatment, and at key time points following treatment. This may even include assessments out to a year or more after treatment as latency effects have been reported. Due to the potential of practice effects across some measures, assessment timing and choice of measures may be modified. Emerging computer-based assessments, which report a greater control for practice effects may offer the best potential for minimizing these issues. In addition, given the potential impact of factors such as fatigue and sleep disturbance, mood, medicinal changes, anemia, and so on, these factors should be examined at the same time as the various assessments to offer some control over their potential confounding effects.

When the purpose of the assessment is purely clinical, one may argue that pretreatment assessment is not strongly warranted. However, we would argue, depending on the specifics of the case, that pretreatment assessment can be critical in many ways. Neuropsychological assessment has proven effective in the monitoring of disease status. Like in the case of CNS tumors, neuropsychological assessment has demonstrated the capacity to identify progression before MRI (Armstrong et al., 2003; Meyers, 2000; Meyers & Hess, 2003; Meyers et al., 2004). Consequently, this form of clinical tracking relies critically on baseline assessment. At the same time, with evidence demonstrating the potential of non-CNS cancers contributing to cognitive problems, pretreatment assessment remains critical. By having such data for comparison, one may better determine the potential toxicity of treatment if such concerns were raised by patients or providers. In the absence of such baseline data, one may view cognitive problems as potential evidence of toxicity of the treatment when, in reality, compared with baseline data, they may be improving. This has played out already, in some ways, within
the lung cancer population, where individuals have argued against the use of prophylactic cranial irradiation (PCI), stating the potential benefits did not outweigh the potential negative outcomes in neuropsychological functioning. These arguments were based on research where patients were just assessed following PCI. However, later studies, which included baseline assessments, revealed cognitive problems even prior to treatment that, in some instances, never worsened as a result of treatment. This is discussed in greater depth in the chapter on lung cancer within this text.

When assessment is carried out during treatment, just as in research, professionals should be mindful of fatigue, mood, medicinal changes, and anemia, as well as other factors, as they may have a direct influence on performance.

Following treatment, assessment can be carried out at different time points and is largely dictated by when the referral is received, unless pretreatment assessment has been utilized, which permits greater control on the part of the neuropsychologist as to when assessment would be appropriate. Given some patients experience a latency effect when it comes to the development of neuropsychological deficits (e.g., following radiation treatment), an assessment in closer proximity to the end of treatment and then one carried out months down the road may carry some utility. Whenever comparing repeated assessments to one another, utilizing a reliable change index calculation (e.g., Jacobsen & Traux, 1991) is essential to determine if change, whether positive or negative, is meaningful.

Motivation. Practicing neuropsychologists must always be mindful of potential confounds to assessment results. Exaggeration and malingering has been well discussed in the literature when it comes to forensic proceedings. These same issues can arise within the general clinical arena. While debate can be found in the literature, it is our professional belief that measures of symptom validity should be used in most every assessment scenario, as motivation toward assessment and specific assessment outcomes can vary for many reasons. In reality, before clear judgments can be made about objective data, one must be able to reasonably judge the reliability of that data and the likelihood that it represents the patient’s true abilities.

Neuropsychological assessment is an interactive process and the results are dependent on the patient’s motivation. The interpretation of neuropsychological functioning is predicated on the assumption that the patient has tried to cooperate. Although the patient’s motivation is continuously monitored during the examination and reinforcement is provided, secondary gains may influence the patient’s performance. Measures such as the Word Memory Test, Test of Memory Malingering, and even the validity scales of the MMPI are designed to predict purposeful aberrations in performance. At the same time, a deliberate effort to influence neuropsychological test results in any consistent manner is difficult for the patient. Malingering and factitious disorders can be detected with considerable accuracy. Even if there is not a forensic application to the assessment, patients within various settings can have a tendency toward exaggerating cognitive deficits as a means of demonstrating the degree of affliction they are experiencing related to their reported complaints. In the cancer population this may be seen in instances where patients are applying for disability or seeking particular medications (e.g., psychostimulants). Further, mental fluctuations related to their physical state can manifest as poor outcomes on measures of effort and thus call assessment outcomes into question.

Mood. Another issue within the cancer and oncology setting is the impact of mood on test performance and assessment outcomes. This is outlined in greater detail below, but must be noted within the context of this discussion. Neuropsychological examination requires the patient’s cooperation and concentration. Emotional disturbance may be important to consider in measuring neuropsychological function. Most research here has examined the relationship between measures of emotional disturbance and the results of neuropsychological tests. Emotional features such as depression, anxiety, as well as others commonly present within the cancer population and, as discussed below, may negatively impact test performance. Consequently, objective measures of mood should be included in assessments within the cancer population. This will not only assist in determining the possibility that neuropsychological problems are related to these mood disturbances, but also evaluate the severity of features that may themselves require clinical intervention.
Interpretation and Intervention Following Neuropsychological Assessment

Neuropsychological practice within any setting must go beyond descriptions and formulations of phenomenology. The relative importance of neuropsychology within the oncology setting is seen when the data obtained through assessment is used to develop appropriate cognitive remediation strategies. When done, the combination of neuropsychological assessment and functional intervention is amongst the most impactful services.

The intervention process starts with interpretation of the assessment results, as is the case with any neuropsychological evaluation. This should include a discussion of not only the cognitive strengths and weaknesses but also the functional implications of any impairments and recommendations to circumvent those difficulties to maximize functioning (Marcopulos et al., 2008). As previously noted, interpretation not only can focus on the quantitative results but must also take into account the qualitative input and output. This is best done through behavioral observation throughout the course of the assessment. This can help explain/understand variations in specific tests in the case of environmental distracters as well as offer qualitative judgment of the individual’s capacity for sustained effort.

Recent research has evaluated the utility and effectiveness of neuropsychological rehabilitation for neuropsychological impairments. Readers are directed to Chapter 20, which offers a thorough discussion of these principles and techniques.

NEUROPSYCHOLOGICAL IMPACT OF CANCER AND ONCOLOGY

Cognitive deficits are common within the cancer population and remain one of the most salient concerns of cancer survivors after treatment (Hewitt et al., 2006). Though cognitive dysfunction is most commonly reported during active treatment, deficits have been noted at all phases of the disease and treatment. That is, cognitive deficits have been noted prior to, during, and following treatment. The nature of these deficits may arise from both direct and indirect influences of both the disease itself and the various forms of treatment. Various causes have been discussed including the effects of CNS and non-CNS cancers, inflammatory and autoimmune responses, and the effects of treatment including surgery, chemotherapy, hormonal treatment, and radiation. These causes are discussed below.

While the cognitive deficits arising from these various sources may vary, deficits in attention, processing speed, and working memory, are the most common deficits. Individuals may report a wider variety of deficits in day-to-day life, such as executive dysfunction, which may come out on self-report measures, but are not necessarily identified on objective assessment. Furthermore, the impact of cognitive dysfunction on cancer patients depends on their developmental stage of life, the type of work they do, where they are at in school, and their preillness lifestyle. Those deficits that are found on standardized assessment are oftentimes mild in nature. Nevertheless, they commonly impede individuals functioning at home, at work, or in school.

Disease-Related Deficits

Cognitive deficits may arise prior to or in the absence of treatment. These disease-related deficits include the effects of primary and metastatic tumors of the CNS, the development of paraneoplastic syndromes, and inflammatory and autoimmune responses.

Primary and Metastatic CNS Lesions

A tumor is a mass of new tissue that persists and grows independently of its surrounding structures and has no physiological use. They vary in pathological origin as discussed below. The rate of the tumor’s growth varies greatly depending on the type of cell from which it grows. They are distinguished as being primary or secondary, or benign or malignant. Furthermore, malignancy is divided into low-grade and high-grade. A primary tumor is defined as a tumor that arises from substances within the brain itself. A secondary or metastatic tumor is carried through the blood to the nervous system from a primary tumor elsewhere (e.g., lungs or breasts). Brain metastasis actually represents the most common
intracranial tumor (Mehta & Tremont-Lucas, 2004). In reality, with improvements in treatment and increased length of survival after diagnosis increases, the risk of metastases to the brain also increases (Carney et al., 1999; Chidel et al., 2000).

When taken together, both primary and secondary tumors, the brain is the second most common site of tumors with the uterus being the first. Brain tumors are most common in early to middle adulthood. The overall incidence is nearly equal for males and females. Benign tumors may be as serious as malignant tumors because the site of the tumor may be inaccessible to the surgeon without risk to life.

As suggested, an initial means of classification is whether the tumor is primary or secondary, which coincides with its pathological origin. In addition, the area or tissue of invasion suggests underlying physiology. The combination of these factors results in various tumor classes including those discussed below. Tumor locality can be divided into (a) skull, (b) meninges, (c) cranial nerves, (d) supporting tissue, (e) pituitary or pineal body, and (e) congenital origin. The various tumors are discussed individually for clarity sake.

A tumor may develop as a distinct entity in the brain (encapsulated tumor) and put pressure on the rest of the brain. These are known as cystic tumors because they produce a fluid-filled cavity in the brain, usually lined with the tumor cells. The additional space occupied by these tumors compresses the brain, resulting in dysfunction. A second type of tumor is the infiltrating tumor. These tumors are not clearly marked off from the surrounding tissue. They may destroy normal cells and occupy their place or they may surround existing cells and interfere with normal functioning.

The gliomas are likely the most discussed tumors, as they constitute the greatest portion of primary tumors. They arise from glial cells and are classified as low-grade or high-grade. They are further divided as specific tumor types. These include astrocytomas, glioblastomas, oligodendrogliomas, medulloblastomas, and ependymomas.

Beyond the gliomas, multitudes of other tumors are important to mention. These include meningiomas, schwannomas, pituitary adenomas, primary CNS lymphoma, and metastatic tumors. Table 1.2 outlines the pathological features associated with these various tumors.

Emerging literature has suggested the potential role of genetics in the manifestation of primary CNS tumors, particularly malignant gliomas. Janus and Yung (2007) reported, to date, the most common alterations along these lines include deletions in chromosome 17p, 9p, 10q, and multiple copies of chromosome 7 across all types; 1p, 9p, 10p, 10q, 11p, 13q, and 17p in relation to astrocytomas; 19q in oligodendrocytes; and 22q in meningiomas.

Functionally, variability is seen in neuropsychological presentation and outcome based on the locality of the tumor(s) (Meyers, 2000, Meyers et al., 2000; Scheibel et al., 1996). While there is a tendency to conceptualize malignant tumors as most devastating from this perspective as well as from a mortality standpoint, benign tumors may be as serious as malignant tumors because the site of the tumor may be inaccessible to the surgeon without risk to life. As noted by Anderson and Ryken (2008), clinical presentation is consistent with a patternning consistent with expanding mass lesioning As the authors note, progressive neurologic deficit (68%), motor deficits or weakness (45%), headache (54%), and seizures (36%) are all common features across tumor types. In addition to the sequelae associated the tumor itself, there may be deficits arise from treatment, including surgical approach and chemotherapeutic and/or radiation therapy in cases of malignancy.

There is no unitary profile for intracranial brain tumors. Consequently, neuropsychological features vary. Anderson and Ryken (2008) said it best in noting that such tumors involve the potential for “virtually any neurological or neuropsychological sign.” However, as shown in Table 1.3, there are certain characteristics most commonly seen based on the locality of the tumor. While these features largely adhere to regional activation/localization theory, this is not always the case (Anderson, Damasio, & Tranel, 1990). Sometimes tumors do not produce the symptoms one would expect given their localities (e.g., a left frontal tumor may have only subtle effects on language based on the subtleties in its regional infiltrate). For example, tumors arising in the third ventricle tend to cause deficits in manual dexterity, memory, and executive functioning (Friedman et al., 2003). Oftentimes, sensory and motor features can be the first clinical symptoms seen and may serve as the most effective means of localization from
<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>NEUROPATHOLOGY/PATOPHYSIOLOGY</th>
<th>ADDITIONAL DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytomas</td>
<td>• Infiltrate and invade vital neural systems</td>
<td>• Usually develop slowly</td>
</tr>
<tr>
<td></td>
<td>• Characterized by increased cell number and nuclear pleomorphism without necrosis</td>
<td>• Account for about 40% of gliomas</td>
</tr>
<tr>
<td></td>
<td>• Mitotic figures should not be present</td>
<td>• Most common in adults over 30 years of age</td>
</tr>
<tr>
<td></td>
<td>• Uniformity of cells closely resembling mature resting or reactive, nonanaplastic astrocytes</td>
<td>• At times all the timorous infiltrates can be removed which can coincide with prognosis</td>
</tr>
<tr>
<td>Anaplastic Astrocytoma</td>
<td>• Increased cellular and nuclear pleomorphism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increased cell density</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increased mitoses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Vascular endothelial proliferation</td>
<td></td>
</tr>
<tr>
<td>Pilocytic Astrocytoma</td>
<td>• Most commonly found in the cerebellum, brain stem, thalamus, and optic nerve</td>
<td>• Rapidly growing gliomas</td>
</tr>
<tr>
<td></td>
<td>• Gelatinous appearance, often well circumscribed and can be fully removed if in an acceptable surgical plane</td>
<td>• They are highly malignant</td>
</tr>
<tr>
<td></td>
<td>• Histologically marked by fibrillary astrocytes and stellate cells, and often Rosenthal fibers and microsystic changes</td>
<td>• Represent about 30% of gliomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Most common in men over 35 years of age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sometimes considered a malignant form of astrocytomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prognosis is poor, life expectancy is short, usually less than one year after surgery</td>
</tr>
<tr>
<td>Glioblastomas</td>
<td>• Presents with all of the same features of astrocytomas and anaplastic astrocytomas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Grow far more rapidly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Demonstrates foci of coagulative necrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Infiltrate and migrate along white matter pathways</td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>• Arise from oligodendrocytes and thus develop in the white matter of the cerebrum</td>
<td>• Generally slow growing hemispheric tumors</td>
</tr>
<tr>
<td></td>
<td>• Most commonly present in frontotemporal regions simply due to the prominence of white matter and thus oligodendrocytes in these areas</td>
<td>• The grade may vary from 1 to 4 with grade 4 being rare. Survival may extend to 15 years Oligodendrogliomas represent about 5% of gliomas</td>
</tr>
<tr>
<td></td>
<td>• Demonstrate significant overlap with astrocytomas making differentiation difficult at times. When differentiation cannot be made it is termed an oligoastrocytoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Tumor cell infiltration in the cortex is seen in most cases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Many tumors show an artifactual halo around the nucleus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Vascular channels are common</td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>• The cerebellum is the most common site of origin</td>
<td>• Highly malignant tumor</td>
</tr>
<tr>
<td></td>
<td>• Appears on macroscopic exam as friable tumor with central necrosis</td>
<td>• Most commonly found in children and is the most common form of brain tumor in children</td>
</tr>
<tr>
<td></td>
<td>• Proposed as arising from the germinal neuroepithelium during embrogenesis permitting differentiation into tumor cells with neuronal, glial, or ependymal characteristics</td>
<td>• Approximately 80% of all cases occur during the first 15 years of life and mainly during the first decade</td>
</tr>
<tr>
<td></td>
<td>• Small blue cell tumors with little cytoplasm and pseudorosettas</td>
<td>• Boys are affected more than girls</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• They account for about 10% of gliomas. Survival beyond five years of age ranges between 18% to 38%</td>
</tr>
</tbody>
</table>

(continued)
### TABLE 1.2 Brain Tumor Types (continued)

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>NEUROPATHOLOGY/PATHOPHYSIOLOGY</th>
<th>ADDITIONAL DESCRIPTION</th>
</tr>
</thead>
</table>
| Ependymomas | • Associated with and arise in the cerebral ventricles from ependymal cells, particularly from the fourth ventricle  
• Marked by pseudorosettes, often located in the perivascular region  
• Blepharoplasts are present  
Anaplastic Ependymomas  
• Have increasing features of nuclear atypia, necrosis, and mitotic figures  
Myxopapillary Ependymomas  
• Usually confined to the filum terminale and have a distinctive fibrillary pattern with mucin secretion  
| • Represent about 10% of gliomas  
• Slow growing and tend to block the fourth ventricle, thus preventing the flow of CSF resulting in hydrocephalus  
• Such tumors are usually benign  
• Ependymomas constitute about 10% of all intracranial tumors in children with a peak incidence during the first decade  
• The 5-year survival rate in children with postoperative treatment is about 40%–50% |
| Meningiomas | • These are extrinsic tumors which grow from the arachnoid matter  
• They irritate the surface and compress the brain  
• Have a firm off-white appearance and are well demarcated from surrounding tissue as they are extra-axial in positioning  
• Demonstrates a whorled pattern with calcifications  
• Brain invasion and mitotic activity can be seen in aggressive tumors  
• Classified as fibroblastic, syncytial, transitional, and angioblastic  
| • They are the most benign of all brain tumors  
• Meningiomas can occur between the hemispheres  
• When surgically removed they generally will not recur |
| Schwannomas | • Sex hormone influence has been suggested due to predominance in females  
• Most commonly involve cranial nerves VIII, V, VII  
| • Tend to be slow growing  
• Benign  
• Intervention is not always needed beyond sequential monitoring of the tumor if individuals are not overly troubled by symptoms  
• Often found incidentally |
| Pituitary Adenomas | • These are neuroepithelial tumors of the pituitary region  
• Appear acophilic, basophilic, or chromophobic on staining  
• Vary in whether they secrete hormones  
| • A variety of problems arise with respect to growth characteristics of these tumors, including obesity, hairiness of the face, and amenorrhea  
• If they develop before puberty, the child may demonstrate gigantism  
• They can also cause acromegaly after puberty  
• These tumors are treatable and can be removed  
• Develop in a stepwise fashion |
| Primary CNS Lymphomas | • Mass lesion presenting in the periventricular white matter  
• Diffuse histological activity, even in tissues appearing normal macroscopically  
• Mechanisms of transformation largely unknown given there are no lymphatics in the CNS  
• Considered a non-Hodgkins Lymphoma, of B cell origin, which is perplexing as these cells are not usually present in the CNS  
• Aggregate near blood vessels  
• Stain positive for appropriate immunohistological B cell or T cell markers  
| • Commonly associated with immunocompromise or immunosuppression |

(continued)
pure functional assessment (not that this is needed per se given imaging techniques). It should be noted that the neurological and neuropsychological impairment resulting from metastatic lesions is similar to those arising from primary brain tumors (Hirsch et al., 1982).

Symptoms result from regional infiltration of the tumor, mass effect, and increased intracranial pressure caused by growth of the tumor and blockage of the flow of CSF through the ventricles. In some cases, the tumor presses upon or destroys parts of the brain, which produces effects which become gradually worse as the tumor grows. Consequently, common symptoms of intracranial tumors include headaches, especially after lying flat, increased by coughing or stooping; vomiting, this usually occurs at the peak of the headache; diplopia; blurred vision when moving the head; slowing of the pulse; increased drowsiness which progresses to coma; dilation of the pupils which fail to react to light; and papilledema. Convulsive seizures, focal or generalized, occur with cerebral hemisphere tumors and may precede other symptoms by months or years. They are most common with meningiomas and the slow growing astrocytomas.

In many instances, cognitive features are seen later as unrecognized tumors continue to grow and become more infiltrating, potentially causing mass effect. Yet, interestingly, subtle changes in cognition can be predictive of recurrence and/or tumor growth prior to it even being recognized on imaging (Armstrong et al., 2003; Meyers & Hess, 2003).

Cognitive issues have likely been historically underreported as neurologists and neurosurgeons who primarily serve these patients do not regularly seek neuropsychological consultation, relying on traditional mental status checks such as the MMSE. Emerging literature has demonstrated the relative insensitivity of such measures and practices to identifying cognitive deficits in tumors due to a low ceiling effect (Pahlson, Elk, Ahlstrom & Smits, 2003). Newer data suggests that nonspecific neurocognitive deficits present in upward of 90% of patients (Tucha et al., 2000) with nondominant hemisphere lesions constituting the majority of cases that do not present with cognitive deficits (Hahn et al., 2003). Approximately 91% of patients with primary brain tumors will present with at least one area of cognitive dysfunction at baseline and roughly 70% will present with at least three areas of dysfunction (Tucha et al., 2000). The frequency of cognitive deficits emphasizes the role of neuropsychological assessment in the care of patients. In fact, neuropsychological assessment in some ways is more powerful then neuroimaging. Meyers and Hess (2003) performed a baseline neuropsychological assessment on 80 patients with recurrent glioblastoma or anaplastic astrocytoma prior to beginning a clinical trial for recurrence. They found that 61% of patients who demonstrated measurable change in neurocognition on assessment prior to imaging could demonstrate significant change. In fact, neuropsychological assessment has demonstrated the ability to predict MRI evidence of tumor progression in both low-grade (Armstrong et al., 2003) and high-grade (Meyers, 2000; Meyers & Hess, 2003) gliomas and patients with brain metastases (Meyers et al., 2004).

Beyond deficits associated with tumors themselves, negative neuropsychological outcomes have also been linked with treatment modalities. In general, those clinical features apparently related to the hemispheric origin of the tumor oftentimes remain even following resection, but sometimes to a lesser extent. Where improvement is seen is in the reduction of mass effect and those residuals related to it (Duffau, 2006). This is in comparison to focal

<table>
<thead>
<tr>
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<th>ADDITIONAL DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastases</td>
<td>• Can present throughout the CNS • Associated with cancerous presentations of different organ sites with breast and lung cancers being the most common preceding cancer presentations • Also can occur in relation to skin, colorectal, and renal cancers</td>
<td>• The most common intracranial tumor</td>
</tr>
</tbody>
</table>

Source: Reproduced with Permission from Noggle & Dean (2011); Adapted from Janus & Yung (2007) and Anderson & Ryken (2008).
## TABLE 1.3 Common Symptoms Based on Tumor Location

<table>
<thead>
<tr>
<th>TUMOR LOCATION</th>
<th>SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral hemispheres—frontal lobes</td>
<td>- Hemiplegia, focal or generalized seizures, and mental changes&lt;br&gt;- Expressive aphasia may be present with tumors present in the dominate hemisphere&lt;br&gt;- Precipitate urination may be associated with a tumor on the medial surface&lt;br&gt;- Inattention, loss of motivation, and ataxic gait may be exhibited as the tumor spreads to both lobes</td>
</tr>
<tr>
<td>Cerebral hemispheres—parietal lobes</td>
<td>- Astereognosis and sensory impairment contralaterally&lt;br&gt;- Seizures may be either generalized or focal&lt;br&gt;- Anosognosia, apraxia, and denial of illness may be present&lt;br&gt;- Speech disturbances may be associated with a tumor in the dominant hemisphere</td>
</tr>
<tr>
<td>Cerebral hemispheres—temporal lobes</td>
<td>- Usually show few indications except for seizures&lt;br&gt;- Tumors involving the dominant hemisphere may produce mixed expressive and receptive aphasia or more pure receptive aphasia&lt;br&gt;- Memory deficits can occur</td>
</tr>
<tr>
<td>Cerebral hemispheres—occipital lobes</td>
<td>- Result in contralateral quadrant defect in the visual field&lt;br&gt;- Convulsion may have an aura of flashing lights</td>
</tr>
<tr>
<td>Cerebral hemispheres—subcortical</td>
<td>- Commonly contralateral hemiparesis is present—tumors which invade the thalamus produce contralateral cutaneous sensory impairment&lt;br&gt;- With basal ganglia involvement there is sometimes athetosis, bizarre tremors, or dystonic posturing</td>
</tr>
<tr>
<td>Pituitary and suprasellar region</td>
<td>- Headache and visual field defects, usually bitemporal hemianopia, are common&lt;br&gt;- Other endocrinopathies resulting from tumors of this region were mentioned under pituitary adenomas above</td>
</tr>
<tr>
<td>Pineal area</td>
<td>- Precocious puberty may result, more common in boys&lt;br&gt;- Hydrocephalus and papilledema result from compression of the aqueduct of Sylvius&lt;br&gt;- Paralysis of upward gaze, ptosis, and loss of pupillary light and accommodation reflexes result from compression of the pretectum&lt;br&gt;- There may be unilateral or bilateral paralysis of the 5th, 6th, 7th, and 10th cranial nerves and of lateral gaze&lt;br&gt;- Hemiplegia, hemianesthesia, ataxia, nystagmus, or intention tremor may be present</td>
</tr>
<tr>
<td>Cranial fossas</td>
<td>- Symptoms of increased intracranial pressure appear early&lt;br&gt;- Posterior fossa tumor has primary signs of ataxia and intention tremor&lt;br&gt;- Anterior fossa can have more cognitive issues similar to executive dysfunction and poor attention&lt;br&gt;- Hemiparesis, language deficits, and personality changes may be present</td>
</tr>
<tr>
<td>Cerebellopontine fossa</td>
<td>- Produce tinnitus, unilateral hearing impairment, and vertigo&lt;br&gt;- There will be loss of corneal reflex, facial palsy, anesthesiA, and signs of cerebellar dysfunction</td>
</tr>
</tbody>
</table>

Source: Reproduced with Permission from Noggle & Dean (2011).
deficits that present immediately following surgery and recover gradually over the course of 3 to 6 months (Duffau et al., 2003).

Whereas surgery contributes to focal deficits that are not necessarily new features, but likely a continuation of deficits owning to the locality of the tumor, radiation and chemotherapy coincide with more diffuse and potentially new deficits. Radiation of the brain has been associated with demyelination and small vessel damage, which coincide with a diffuse subcortical pattern of cognitive dysfunction. The most common features include slowed reaction time, diminished processing speed, retrieval-based memory deficits, diminished working memory capacity, slowed or impeded problem solving skills, diminished reading comprehension, reduced initial learning capacity, and varied executive deficits. Of interest, while some of these features present early on related to the demyelinating effects, some deficits do not come to light until months after treatment and are related to a diffuse encephalopathy (Armstrong et al., 2002). When it comes to chemotherapy, a similar diffuse pattern may be seen. This has included changes in working memory, executive functions, processing speed, and memory (Ahles & Saykin, 2002; Anderson-Hanley et al., 2003; Ferguson & Ahles, 2003; Tannock et al., 2004). While such deficits are most commonly noted acutely during chemotherapy (Ahles & Saykin, 2002; Ferguson & Ahles, 2003), some may persist at lesser levels following treatment discontinuation. Research in this area has however been plagued by flaws in methodology in addition to difficulties in controlling for confounds. There needs to be recognition that the idea of “chemo-brain” is not necessarily restricted to direct effect. Indirect effects due to fatigue, metabolic changes, and so forth must also be considered.

Paraneoplastic Syndromes and Cytokines

The role of an inflammatory response has been described in the literature (Lee et al., 2004; Meyers et al., 2005) as has an autoimmune response (Dropcho, 2005). Studies have revealed that even prior to chemotherapy, a greater than expected number of patients present with cognitive dysfunction (Meyers et al., 2005; Wagner et al., 2006; Wefel et al., 2004). These responses correspond with the manifestation of paraneoplastic syndromes and the impact of cytokines.

Paraneoplastic syndromes represent a group of disorders that are varied in their functional impact and clinical presentation. They may affect all levels of the central and peripheral nervous system. Paraneoplastic syndromes manifest as a result of the immune systems detection and response to a tumor antigen that cross-reacts with similar antigens expressed by the nervous system (Baehring, Quant, & Hochberg, 2007).

It is estimated that paraneoplastic syndromes affect up to 8% of patients with cancer (Baijens & Manni, 2006). Variability is seen based on the location of the onconeural antigen and thus impact on the system. Based on the clinical features that arise, paraneoplastic syndromes can be divided into four categories: Paraneoplastic Endocrine Syndrome, Paraneoplastic Hematologic Syndromes, Paraneoplastic Dermatologic and Rheumatologic Syndromes, and Paraneoplastic Neurologic Syndromes.

Individual discrepancies in physiology exist amongst the subtypes. As tumor cells invade the lymphatic system, this elicits the noted immune-detection. Baehring and colleagues (2007) note that onconeural antigens are classified by their location, either on the cell surface or intracellular, in addition to their subcellular expression pattern. The underlying mechanism across presentations appears to be a serological immune response, targeting intracellular antigens that activate cytotoxic T-cells directed at peptide sequences arising from the intracellular antigen (Yu et al., 2001).

Pathologically, paraneoplastic syndromes can correspond with neuronal loss that is fairly extensive and irreversible in combination with reactive gliosis, perivascular cuffing by lymphocytes, and meningeal infiltrates affecting the limbic system, brain stem, and spinal cord (Baehring et al., 2007). Again, variability is seen based on the syndrome type and its origin. Pelosof and Gerber (2010), in their review, offered a detailed synthesis of the literature in terms of the types of paraneoplastic syndromes that present, their features, pathology, diagnostic findings, and treatment options that have been adapted in Table 1.4. Paraneoplastic disorders are discussed throughout the book as they relate to particular neoplastic presentations or functional domains.

(text continues on page 27)
### TABLE 1.4 Paraneoplastic Endocrine Syndrome

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>PATHOLOGICAL CORRELATES</th>
<th>CLINICAL FEATURES</th>
<th>DIAGNOSTIC FINDINGS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIADH</td>
<td>Small cell lung cancer, mesothelioma, bladder, ureteral, endometrial, prostate, oropharyngeal, thymoma, lymphoma, thymoma, Ewing sarcoma, brain, gastrointestinal, breast, adrenal</td>
<td>Gait disturbance and falls, seizures, headache, nausea, fatigue, muscle cramps, anorexia, confusion, lethargy, respiratory depression, coma</td>
<td>Hyponatremia: mild, sodium: 130–134 mEq/L; moderate, sodium: 125–129 mEq/L; severe, sodium: &lt;125 mEq/L increased urine osmolality (&gt;100 mOsm/kg in the context of euolemic hyponatremia)</td>
<td>Restrict fluids (usually &lt;1,000 TdU/d) and encourage adequate salt and protein intake Demeclocycline: 300–600 mg, orally twice daily Conivaptan: 20–40 mg/d IV Tolvaptan: 10–60 mg/d orally Hypertone (3%) saline at &lt;1–2 mL/kg/h</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Breast, multiple myeloma renal cell, squamous cell cancers (especially lung), lymphoma (including HTLV-associated lymphoma), ovarian endometrial</td>
<td>Altered mental status weakness, ataxia, lethargy, hypertonia, renal failure, nausea/vomiting, hypertension, bradycardia</td>
<td>Hypercalcemia: mild, calcium: 10.5–11.9 mg/dL; moderate, calcium: 12.0–13.9 mg/dL; severe, calcium: &gt;14.0 mg/dL Low to normal (&lt;20 pg/mL) PTH level Elevated PTHrP level</td>
<td>Normal saline: 200–500 mL/h Furosemide: 20–40 mg IV (use with caution and only after adequate fluid resuscitation) Pamidronate: 60–90 mg IV Zoledronate: 4 mg IV Prednisone, 40–100 mg/d orally (for lymphoma, myeloma) Calcitonin: 4–8 IU/kg SC or IM every 12 h Mithramycin: 25 mg/kg IV (often requires multiple doses) Gallium nitrate: 100–200 mg/mVd IV continuous infusion for 5 d Hemodialysis</td>
</tr>
<tr>
<td>Cushing Syndrome</td>
<td>Small cell lung cancer, bronchial carcinoid (neuroendocrine lung tumors account for 50%–60% of cases of paraneoplastic Cushing syndrome), thymoma, medullary thyroid cancer, GI, pancreatic, adrenal, ovarian</td>
<td>Muscle weakness, peripheral edema, hypotension, weight gain, centripetal fat distribution</td>
<td>Hypokalemia (usually &lt;3.0 mmol/L), elevated baseline serum cortisol (&gt;29.0 ng/dL), normal to elevated midnight serum ACTH (&gt;100 ng/L) not suppressed with dexamethasone</td>
<td>Ketoconazole: 600–1200 mg/d orally Octreotide: 600–1500 mg/d SC or Octreotide LAR: 20–30 mg IM monthly Aminoglutethimide: 0.5–2 g/d orally Metyrapone: 1.0 g/d orally Mitotane: 0.5–8 g/d orally Etoposide: 0.3 mg/kg/h IV Mefepristone: 10–20 mg/kg/d orally Adrenalectomy</td>
</tr>
</tbody>
</table>

(continued)
TABLE 1.4 Paraneoplastic Endocrine Syndrome  (continued)

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>PATHOLOGICAL CORRELATES</th>
<th>CLINICAL FEATURES</th>
<th>DIAGNOSTIC FINDINGS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>Mesothelioma, sarcoma, lung, GI</td>
<td>Sweating, anxiety, tremors, palpitations, hunger, weakness, seizures, confusion, coma</td>
<td>For nonislet cell tumor hypoglycemia: low glucose, low insulin (often &lt;1.44–3.60 nIU/mL), low C-peptide (often &lt;0.3 ng/mL), elevated IGF-2:IGF-1 ratio (often &gt;10:1) For insulinomas: low glucose, elevated insulin, elevated C-peptide, normal IGF-2:IGF-1 ratio</td>
<td>Glucose (oral and/or parenteral) Dexamethasone: 4 mg 2 or 3 times daily Prednisone: 10–15 mg/d Diazoxide: 3–8 mg/kg/d orally, divided in 2 or 3 doses Glucagon infusion: 0.06–0.3 mg/h IV Octreotide: 50–1500 ng/d SC or Octreotide LAR, 20–30 mg monthly (often with corticosteroids) Human growth hormone: 2 U/d SC (often with corticosteroids)</td>
</tr>
</tbody>
</table>

PARANEOPLASTIC HEMATOLOGIC SYNDROMES

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>PATHOLOGICAL CORRELATES</th>
<th>CLINICAL FEATURES</th>
<th>DIAGNOSTIC FINDINGS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophilia</td>
<td>Hodgkin lymphoma, non-Hodgkin lymphoma (B- and T-cell), chronic myeloid leukemia, acute lymphocytic leukemia, lung, thyroid, GI (pancreatic, colon, gastric, liver), renal, breast, gynecologic</td>
<td>Dyspnea, wheezing</td>
<td>Hypereosinophilia (&gt;0.5 x 10^9/L); elevated serum IL-5, IL-3, IL-2, and GM-CSF</td>
<td>Inhaled corticosteroids Prednisone: 1 mg/kg/d orally</td>
</tr>
<tr>
<td>Granulocytosis</td>
<td>GI, lung, breast, gynecologic, GU, brain, Hodgkin lymphoma, sarcomas</td>
<td>Asymptomatic (no symptoms or signs of leukostasis such as neurologic deficits or dyspnea)</td>
<td>Granulocyte (neutrophil) count &gt;8 x 10^9/L, typically without a shift to immature neutrophil forms; elevated LAP; elevated serum G-CSF</td>
<td>Specific treatment not indicated</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td>Thymoma, leukemia/lymphoma, myelodysplastic syndrome</td>
<td>Dyspnea, pallor, fatigue, syncope</td>
<td>Anemia (hematocrit, &lt;20 not uncommon), low/absent reticulocytes, bone marrow with nearly absent erythroid precursors, platelet and white blood cell counts in normal ranges</td>
<td>Blood transfusions Prednisone: 1 mg/kg/d orally Antithymocyte globulin: 500 mg daily IV (with corticosteroids and/or cyclophosphamide) Cyclosporine A: 100 mg orally, twice daily Cyclophosphamide: 1–3 mg/kg/d orally</td>
</tr>
</tbody>
</table>
### TABLE 1.4 Paraneoplastic Endocrine Syndrome (continued)

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>PATHOLOGICAL CORRELATES</th>
<th>CLINICAL FEATURES</th>
<th>DIAGNOSTIC FINDINGS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytosis</td>
<td>GI, lung, breast, gynecologic lymphoma, renal cell, prostate mesothelioma, glioblastoma, head and neck</td>
<td>Asymptomatic (no bleeding or clotting abnormalities)</td>
<td>Elevated platelet count greater than 400 × 10³/L; elevated serum IL-6</td>
<td>Specific treatment not indicated</td>
</tr>
</tbody>
</table>

#### PARANEOPLASTIC DERMATOLOGIC AND RHEUMATOLOGIC SYNDROMES

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>PATHOLOGICAL CORRELATES</th>
<th>CLINICAL FEATURES</th>
<th>DIAGNOSTIC FINDINGS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthosis nigricans</td>
<td>Adenocarcinoma of abdominal organs, especially gastric adenocarcinoma (90% of malignancies in patients with acanthosis nigricans are abdominal); gynecologic</td>
<td>Velvety, hyperpigmented skin (usually on flexural regions); papillomatous changes involving mucous membranes and mucocutaneous junctions; rugose changes on palms and dorsal surface of large joints (e.g., tripe palms)</td>
<td>Skin biopsy: histology shows hyperkeratosis and papillomatosis</td>
<td>Topical corticosteroids</td>
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<tr>
<td>Dermatomyositis</td>
<td>Ovarian, breast, prostate, lung, colorectal non-Hodgkin lymphoma, nasopharyngeal</td>
<td>Heliotrope rash (violaceous edematous rash on upper eyelids); Gottron papules (scaly papules on bony surfaces); erythematous rash on face, neck, chest, back, or shoulders (the last of which is known as shawl sign); rash may be photosensitive; proximal muscle weakness; swallowing difficulty; respiratory difficulty; muscle pain</td>
<td>Laboratory findings: elevated serum CK, AST, ALT, LDH, and aldolase; EMG: increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves; Muscle biopsy: perivascular or interfascicular septal inflammation and perifascicular atrophy</td>
<td>Prednisone: 80–100 mg/d orally Methylprednisolone: up to 1 g IV Azathioprine: up to 2.5 mg/kg/d orally Methotrexate: up to 25 mg/wk orally Cyclosporine A: 100–150 mg orally twice daily Mycophenolate mofetil: 2 g/d orally Cyclophosphamide: 0.5–1.0 g/m² IVIG, 400–1000 mg/d to total 2–3 g</td>
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<tr>
<td>SYNDROME</td>
<td>PATHOLOGICAL CORRELATES</td>
<td>CLINICAL FEATURES</td>
<td>DIAGNOSTIC FINDINGS</td>
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<tr>
<td>Erythroderma</td>
<td>Chronic lymphocytic leukemia, cutaneous T-cell lymphoma (including mycosis fungoides), GI (colorectal, gastric esophageal, gallbladder), adult T-cell leukemia/lymphoma, myeloproliferative disorders</td>
<td>Erythematous, exfoliating, diffuse rash (often pruritic)</td>
<td>Skin biopsy: histology shows dense perivascular lymphocytic infiltrate</td>
<td>Topical corticosteroids</td>
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<td>Narrow-band UVB phototherapy</td>
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<td>Hypertrophic osteoarthropathy</td>
<td>Intrathoracic tumors, metastases to lung, métastases to bone, nasopharyngeal carcinoma, rhabdomyosarcoma</td>
<td>Subperiosteal new bone formation on phalangeal shafts (“clubbing”), synovial effusions (mainly large joints), pain, swelling along affected bones and joints</td>
<td>Plain radiography: periosteal reaction along long bones Nuclear bone scan: intense and symmetric uptake in long bones</td>
<td>NSAIDs</td>
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<td>Pamidronate: 90 mg IV</td>
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<td>Zoledronate: 4 mg IV</td>
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<td>Localized radiation therapy</td>
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<tr>
<td>Leukocytoclastic vasculitis</td>
<td>Leukemia/lymphoma, myelodysplastic syndromes, colon, lung, urologie, multiple myeloma, rhabdomyosarcoma</td>
<td>Ulcération, cyanosis, and pain over affected regions (especially digits); palpable purpura, often over lower extremities; renal impairment; peripheral neuropathy</td>
<td>Skin biopsy: histology shows fibrinoid necrosis, endothelial swelling, leukocytoclasia, and RBC extravasation</td>
<td>Methylprednisolone: up to 1 g/d IV</td>
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<td>Prednisone: 1.0—1.5 mg/kg/d orally</td>
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<td>Dapsone: -25–50 mg/d orally</td>
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<td>Colchicine: 0.5 mg orally</td>
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<td>two or three times daily</td>
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<td>Methotrexate: 5–20 mg/wk orally</td>
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<td>Azathioprine: 0.5–2.5 mg/kg/d orally</td>
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<td>IVIG: 400–1000 mg/d to total 2–3 g</td>
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<tr>
<td>Paraneoplastic pemphigus</td>
<td>Non-Hodgkin lymphoma, chronic lymphocytic leukemia, thymoma, Castleman disease, follicular dendritic cell sarcoma</td>
<td>Severe cutaneous blisters and erosions (predominantly on trunk, soles, palms); severe mucosal erosions including stomatitis</td>
<td>Serum antibodies to epithelia (against plakin proteins and desmogleins) Skin biopsy: histology shows keratinocyte necrosis, epidermal acantholysis, and IgG and complement deposition in epidermal and basement membrane zones</td>
<td>orally daily</td>
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<td>Azathioprine: -1.5 mg/ kg orally</td>
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<td>Cyclophosphamide: 100–150 mg/d orally</td>
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<td>Cyclosporine A (target plasma levels 100–150 ng/L) IVIG: 400–1000 mg/d to total 2–3 g</td>
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<td>Cyclosporine A (target plasma levels 100–150 ng/L) IVIG: 400–1000 mg/d to total 2–3 g</td>
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(continued)
### TABLE 1.4 Paraneoplastic Endocrine Syndrome (continued)

<table>
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<tr>
<th>SYNDROME</th>
<th>PATHOLOGICAL CORRELATES</th>
<th>CLINICAL FEATURES</th>
<th>DIAGNOSTIC FINDINGS</th>
<th>TREATMENT</th>
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</thead>
<tbody>
<tr>
<td>Polymyalgia rheumatic</td>
<td>Leukemia/lymphoma, myelodysplastic syndromes, colon, lung, renal, prostate, breast</td>
<td>Limb girdle pain and stiffness</td>
<td>Laboratory findings: elevated serum ESR (often not as high as in nonparaneoplastic PMR) and CRP</td>
<td>Prednisone: 15 mg/d orally</td>
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<td>Methotrexate: 10 mg/wk orally</td>
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<tr>
<td>Sweet syndrome</td>
<td>Leukemia (especially AML), non-Hodgkin lymphoma, myelodysplastic syndromes, genito-urinary, breast, GI, multiple myeloma, gynecologic, testicular melanoma</td>
<td>Acute onset of tender erythematous nodules, papules, plaques, or pustules on extremities, face, or upper trunk, neutrophilia, fever, malaise</td>
<td>Skin biopsy: histology shows a polymorphonuclear cell dermal infiltrate</td>
<td>Clobetasol propionate: 0.05% topical</td>
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<td>Triamcinolone acetonide: 3–10 mg/mL</td>
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<td>intralesional injection(s)</td>
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<td>Methylprednisolone: up to 1 g/d IV</td>
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<td>Prednisone: 30–60 mg/d orally</td>
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<td>Potassium iodide: 300 mg orally, 3 times daily (tablets) or 1,050–1,500 mg/d orally of saturated solution (Lugol solution)</td>
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<td>Colchicine: 0.5 mg orally 3 times daily</td>
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### PARANEOPLASTIC NEUROLOGIC SYNDROMES

<table>
<thead>
<tr>
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<th>CLINICAL FEATURES</th>
<th>DIAGNOSTIC FINDINGS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limbic Encephalitis</td>
<td>SCLC (~40%–50% of LE patients), testicular germ-cell (20% of LE patients), breast (8% of LE patients), thymoma, teratoma, Hodgkin lymphoma Associated antibodies: anti-Hu (typically with small cell lung cancer), anti-Ma2 (typically testicular cancer), anti-CRMP5 (anu-CV2) anti-amphiphysin</td>
<td>Mood changes, hallucinations, memory loss, seizures, and less commonly hypothalamic symptoms (hyperthermia, somnolence, endocrine dysfunction); onset over days to months</td>
<td>EEG: epileptic foci in temporal lobe(s); focal or generalized slow activity FDG-PET; increased metabolism in temporal lobe(s) MRI: hyperintensity in medial temporal lobe(s) CSF analysis; pleocytosis, elevated protein, elevated IgG, oligoclonal bands</td>
<td>IVIG, 400–1,000 mg/d to total 2–3 g Methylprednisolone, up to 1 g/d IV Prednisone, 1 mg/kg per day orally Plasma exchange Cyclophosphamide, -2 mg/kg/d orally Rituximab, 375 mg/m IV per dose</td>
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(continued)
**TABLE 1.4 Paraneoplastic Endocrine Syndrome (continued)**

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<tr>
<th>SYNDROME</th>
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<th>CLINICAL FEATURES</th>
<th>DIAGNOSTIC FINDINGS</th>
<th>TREATMENT</th>
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</thead>
<tbody>
<tr>
<td>Paraneoplastic cerebellar degeneration</td>
<td>SCLC, gynecologic. Hodgkin lymphoma. Breast Associated antibodies: anti-Yo anti-Hu anü-CRMP5 (anti-CV2) anti-Ma anti-Tr anti-Ri anü-VGCC anti-mGluRI</td>
<td>Ataxia, diplopia, dysphagia, dysarthria, prodrome of dizziness, nausea, vomiting</td>
<td>FDG-PET, increased metabolism (early stage) and then decreased metabolism (late stage) in cerebellum MRI. cerebellar atrophy (late stage)</td>
<td>IVIG, 400–1,000 mg/d to total 2–3 g Methylprednisolone: up to 1 g/d IV Plasma exchange Cyclophosphamide: -2 mg/kg/d orally Rituximab: 375 mg/m^2 IV per dose</td>
</tr>
<tr>
<td>Lambert-Eaton Syndrome</td>
<td>SCLC (-3% of patients have LEMS), prostate, cervical, lymphomas, adenocarcinomas Associated antibodies: anü-VGCC (P/Q type)</td>
<td>Lower extremity proximal muscle weakness, fatigue, diaphragmatic weakness, bulbar symptoms (usually milder than in MG) later in course, autonomy symptoms (ptosis, impotence, dry mouth) in most patients</td>
<td>EMG; low compound muscle action potential amplitude; décrémental response with low-rate stimulation but incremental response with high-rate stimulation</td>
<td>3,4-DAP: maximum of 80 mg/d orally Guanidine: -575 mg/d orally (with pyridostigmine) Pyridostigmine: -240–360 mg/d orally (with guanidine) Prednisolone: 60–100 mg orally every other day Azathioprine: up to 2.5 mg/kg/d orally IVIG: 400–1,000 mg/d to total 2–3 g Plasma exchange</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
<td>Thymoma (in -15% of MG patients) Associated antibodies: anti-AchR</td>
<td>Eatigable weakness of voluntary muscles (ocular-bulbar and limbs), diaphragmatic weakness</td>
<td>EMG: décrémental response to repetitive nerve stimulation</td>
<td>Thymectomy Pyridostigmine, -600 mg/d orally in divided doses Prednisone, -1 mg/kg/d orally Azathioprine, up to 2.5 mg/kg/d orally (with corticosteroids) Cyclosporine A, -3 mg/kg/d orally Tacrolimus, 3–4 mg/d orally Mycophenolate mofetil, 1–3 g/d orally Rituximab, 375 mg/m^2 IV per dose Cyclophosphamide, 50 mg/kg/d IV for 4 d Plasma exchange IVIG, 400–1000 mg/d to total 2–3 g</td>
</tr>
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(continued)
## TABLE 1.4 Paraneoplastic Endocrine Syndrome (continued)

<table>
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<tr>
<th>SYNDROME</th>
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<th>CLINICAL FEATURES</th>
<th>DIAGNOSTIC FINDINGS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic neuropathy</td>
<td>SCLC, Thymoma</td>
<td>Panautonomic neuropathy; often subacute onset (weeks), involving sympathetic, parasympathetic, and enteric systems; orthostatic hypotension; GI dysfunction; dry eyes/mouth; bowel/bladder dysfunction; altered pupillary light reflexes; loss of sinus arrhythmia CGP; constipation, nausea/vomiting, dysphagia, weight loss, abdominal distention</td>
<td>Abdominal radiography/barium studies/CT: GI dilatation but no mechanical obstruction (for CGP) Esophageal manometry: achalasia or spasms (for CGP)</td>
<td>For orthostatic hypotension: Water, salt intake Fludrocortisone: 0.1–1.0 mg/d orally Midodrine: 2.5–10 mg orally 3 times daily Caffeine: -200 mg/d orally For pseudoobstruction: Neostigmine: 2 mg IV</td>
</tr>
<tr>
<td>Subacute sensory neuropathy</td>
<td>Lung (-70%-80%), usually SCLC, breast, ovarian, sarcomas Hodgkin Lymphoma Associated antibodies: anti-Hu anti-CRMP5 (anti-CV2) anti-amphiphysin</td>
<td>Parasthesias/pain (typically upper extremities before lower), followed by ataxia; multifocal/asymmetric distribution; all sensory modalities decreased but especially deep sensation/pseudoathetosis of hands; deep tendon reflexes decreased/absent; onset over weeks to months</td>
<td>NCS: reduced/absent sensory nerve action potentials CSF analysis: pleocytosis, high IgG, oligoclonal bands</td>
<td>Methylprednisolone: up to 1 g/d IV Cyclophosphamide: -3 mg/kg/d orally IVIG: 400–1,000 mg/d. to total 2–3 g Plasma exchange</td>
</tr>
</tbody>
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Source: Adapted with Permission from Pelosof & Gerber (2010).
As suggested, evidence across cancer types now supports the idea that neurocognitive deficits may present without direct CNS involvement and prior to any treatment. Findings have been most commonly reported in relation to lung cancer, breast cancer, and hematological cancer patients (Meyers, Albitar, & Estey, 2005; Meyers, Byrne, & Komaki, 1995; Wefel et al., 2004). This has been associated with the influence of cytokines on the system and cognition and the influence on cytokines by systemic cancer.

Cytokines represent small proteins released by cells to mediate the interaction between cells and the behavior of cells. They are most commonly associated with the CNS as they have been shown to (a) influence synaptic transmission of serotonin and dopamine, (b) modify N-methyl-d-aspartate, glutamatergic, and c-amino butyric acid ion channels, and (c) activate and maintain inflammatory cytokine cascades secondary to the influence of norepinephrine (Hama et al., 1991; Ransohoff & Benveniste, 1996; Viviani, Gardoni, & Marinovich, 2007; Zalcman et al., 1994). B-cells have also been linked with proinflammatory cytokine secretion, including IL-6, TNF-α (Dalakas, 2006), and IL-12 (Stern, Magram, & Presky, 1996). This cytokine cascade occurs in response to the detection of the cancerous cells. Increases in cytokines, amongst other things, can cause an inhibition of cognitive functioning. Cytokine increases have been associated with problems in deficits in memory, processing speed, and executive functioning (Meyers et al., 2005; Rachal, Pugh, Fleschner, Watkins, Maier, & Rudy, 2001; Suarez-Krabbe et al., 2005). The impact of cytokines is discussed further throughout this text.

**Treatment-Related Deficits**

Advances in the successful treatment of cancer have been achieved largely by an increased aggressiveness of therapy, which now generally combines surgery, radiation, cytotoxic drugs, and immunotherapy. Unfortunately, cancer treatments are not highly specific and place normal tissues and organs at risk. The CNS is vulnerable to many types of cancer treatments, both systemic and those directed against CNS tumors. In addition, many adjuvant medications necessary for the treatment of medical complications also affect CNS function (e.g., steroids, antiepileptics, immunosuppressive agents, and drugs used for pain, nausea, and infection).

**Surgery**

Surgical intervention is most often associated with neuropsychological deficits when the surgical approach is directed at the CNS. In this case, the surgical effects largely extend those deficits experienced by the patient in relation to the brain tumor itself in a focal manner (Archibald et al., 1994; Levins et al., 2002). As previously noted, those clinical features apparently related to the hemispheric origin of the tumor oftentimes remain even following resection, but are sometimes to a lesser extent. However, tumors arising in areas with a difficult surgical approach, or tumors in ‘eloquent cortex’ not amenable to surgery, run increased risk of the surgery, damaging healthy tissue (Laws et al., 2003; Packer et al., 1998). In some instances, surgical intervention does improve symptoms, particularly when such intervention reduces mass effect (Duffau, 2006). Much of the impact of tumors on surrounding areas can correspond with the rate of tumor growth, such that slowly growing tumors may present with lesser impairments compared with more rapidly growing tumors due to the greater potential for functional displacement associated with the latter (Anderson et al., 1990). This is in comparison to focal deficits that present immediately following surgery and recover gradually over the course of 3 to 6 months (Duffau et al., 2003). Chapter 11 discusses this in further depth.

**Radiation**

Radiation has been regularly associated with neurocognitive deficits and structural changes on imaging, presenting in a dose dependent fashion. In general, effects are minimized if dosing does not exceed 2GY. Total dose, does per fraction, total time, volume, host factors, radiation quality and adjunctive therapies all influence CNS tolerability of radiation. Even when considering these factors, acute and chronic impairments are commonly reported, with some deficits developing in a latent fashion. Individuals older than 60 years of age are at additional...
risk of the neurotoxic effects of cranial irradiation. Deficits may develop over the course of a few weeks to several years following cranial radiation.

Meyers and colleagues (2000) revealed neurocognitive dysfunction in relation to direct or indirect cranial irradiation. Radiation induced progressive neurocognitive dysfunction, dementia, ataxia, and death have all been reported in the literature (DeAngelis, 1994; DeAngelis et al., 1989; Sheline et al., 1980; Sundaresan et al., 1981). In fact, deficits in attention, memory, information processing, executive functioning, and motor coordination have all been linked with cranial radiation (Archibald et al., 1994; Helfre & Pierga, 1999; Hochberg & Slotnick, 1980; Imperato et al., 1990; Lang et al., 2000; Lieberman et al., 1982; Salander et al., 1995; Scheibet al., 1996; Surma-Aho et al., Taphoorn et al., 1994). Many of these deficits have been noted in both pediatric and adult populations (Abayomi et al., 1996; Anderson et al., 2000).

In general, deficits are most commonly associated with white matter reductions (Roman et al., 1993). The basis for these structural changes however remains debated, with several reported contributors. Research suggests brain radiation leads to increased apoptosis and neuronal loss (Nakaya et al., 2005) along with decreased cell proliferation, and a decreased stem/precursor cell differentiation into neurons within the neurogenic region of the hippocampus (Monje et al., 2002; Snyder et al., 2003). Robbins and Zhao (2004) suggest radiation-induced CNS damage results from a combination of acute cell death and an induced intrinsic recovery/repair response in the form of specific cytokines, and may initiate secondary reactive processes that result in the generation of a persistent oxidative stress and/or chronic inflammation. Constine and colleagues (1988) suggested white matter changes were seen in 40% to 50% of patients postcranial irradiation.

Originally, a vascular basis was proposed. Admittedly, along with demyelination, vascular abnormalities are the most predominant biological change seen in radiation-induced CNS injury. Radiation-induced vascular changes including blood vessel wall thickening, vessel dilation, and endothelial cell nuclear enlargement have all been described (Reinhold et al., 1990; Schultheiss & Stephens, 1992). However, the vascular hypothesis has not bore fruit as white matter necrosis has been reported in the absence of vascular changes (Schultheiss & Stephens, 1992). Rather, a multidimensional model suggests many contributing factors, including the role of and impact on oligodendrocytes, endothelial cells, astrocytes, microglial, and neurogenesis.

Reduced numbers of oligodendrocytes and endothelial cells have been reported as a result of radiation-induced CNS injury (Van der Maazen et al., 1993; Calvo et al., 1988). These reductions have been found to precede necrosis. Reductions of oligodendrocytes may itself be a secondary manifestation as radiation has been found to diminish the reproductive capacity of the O-2A progenitor cells (van der Maazen et al., 1991a, b), which would, in turn, lead to a lack of replacement of oligodendrocytes resulting in demyelination.

While these previous factors may explain acute injury, they do not explain the late radiation-induced CNS injury per se. In this case, impeded neurogenesis may serve as a potential explanation. Radiation corresponds with an increased number of microglial, which has an inhibitory effect on neurogenesis (Nakagawa et al., 1996; Rola et al., 2004). This is particularly relevant to the hippocampus. Consequently, radiation induced changes in hippocampal cellular activity, synaptic efficiency, spike generation, and neuronal gene expression have all been reported (Pellmar & Lepinski, 1993; Surma-aho et al., 2001).

Findings of radiation-induced dysfunction are discussed throughout many of the additional chapters.

Chemotherapy and Biological Modifiers

Cross-sectional and longitudinal studies of cancer survivors have suggested detrimental effects of chemotherapy on cognitive performance (Ahles et al., 2002; Brezden et al., 2000; Castellon et al., 2004; Shilling et al., 2005). Chemotherapy-related cognitive dysfunction is reported in 15% to 70% of patients (Bender et al., 2006; Shilling et al., 2005; Wefel et al., 2004). These changes are usually subtle with patients often showing mildly reduced functioning in comparison to controls across an array of neurocognitive domains. The general pattern of chemotherapy-induced cognitive deficits is suggestive of preferential
dysfunction of frontal subcortical networks (Kayl et al., 2006). This has included changes in working memory, executive functions, and processing speed amongst others (Ahles & Saykin, 2002; Ferguson & Ahles, 2003; Tannock et al., 2004). Anderson-Hanley et al. (2003), in their meta-analysis, reported statistically significant deficits in memory, executive functioning, and motor functioning in cancer survivors, post-chemotherapy, when compared to normal controls. While such deficits are most commonly noted acutely during chemotherapy, long-term residuals have been reported in 17% to 34% of patients (Ahles & Saykin, 2002; Ferguson & Ahles, 2003). We place emphasis on these studies in particular, as confounding factors, including psychological status (e.g., depression and anxiety) and physical well-being (e.g., fatigue), were taken into account and controlled for.

Within the pediatric population, similar deficits have been reported. In addition, Mulhern and Butler (2005) found that pediatric patients who received chemotherapy for ALL presented with deficits in nonverbal memory, visual-motor integration, visual-spatial reasoning, and visual perceptual abilities. Findings of nonverbal memory deficits had been previously noted by Moleski (2000), who also reported deficits in attention as a key feature. Deficits in processing speed, working memory, vigilance, and cognitive flexibility have been reported in ALL survivors (Butler & Copeland, 2002; Langer et al., 2002; Schatz et al., 2000).

Certain factors have been associated with increased risk of chemotherapy-induced neurotoxicity. This includes but is not limited to (a) additive or synergistic effects of multimodality therapy that includes administration of chemotherapy either concurrently with or subsequent to cerebral radiation (Sul & DeAngelis, 2006), (b) additive or synergistic effects of multiagent chemotherapy, (c) exposure to higher dosing either due to planned use of high-dose regimens or higher concentrations of the parent drug and/or its metabolite secondary to disrupted systemic clearance and/or pharmacogenetic modulation of drug pharmacokinetics (Shah, 2005), (d) intra-arterial administration with blood–brain barrier disruption, and (e) intrathecal administration (Sul & DeAngelis, 2006; Taphoorn & Klein, 2004).

When deficits manifest, they have been associated with both direct and indirect causes of chemotherapy. We conceptualize direct causes as actual neurotoxic effects of the chemotherapeutic agents. In recent years, these effects have been visualized through advanced neuroimaging. We conceptualize indirect causes as secondary manifestations of chemotherapy, which themselves contribute to neuropsychological dysfunction. This includes but is not limited to fatigue, metabolic changes/abnormalities, anemia, and elevated cytokines related to a pro-inflammatory response.

Metabolic abnormalities have been associated with the use of chemotherapeutic agents and have also been linked with cognitive deficits. For example, methotrexate has been associated with hyperhomocysteinemia, which itself can lead to mineralizing microangiopathy in the white matter and alterations of monoamines such as norepinephrine, amongst other changes, which may contribute to neurocognitive changes and psychiatric manifestations (Haykin et al., 2006; Madhyastha et al., 2002).

Anemia is a very common side effect of chemotherapy, occurring in approximately 80% of patients (Cunningham, 2003). Anemia has been tied directly to cognitive dysfunction and also indirectly as it is strongly associated with fatigue, which also contributes to cognitive deficits (O’Shaughnessy et al., 2005; Wagner et al., 2005). Anemia also raises the risk for cerebral hypoxia, which overtime, at sub-threshold levels, can contribute to a slow deterioration of white matter.

Finally, just as increases in cytokines related to a proinflammatory response have been observed prior to treatment, as discussed previously, chemotherapeutic agents have also been linked with increases in various cytokines. Carboplatin, etoposide, paclitaxel, and docetaxel have all been associated with such a proinflammatory response that is associated with neurocognitive deficits, including deficits in memory and attention amongst other possible traits (Penson et al., 2000; Pusztai et al., 2004; Tsavaris et al., 2002).

When it comes to the direct physiological impact of chemotherapy, advances in neuroimaging and other neurodiagnostic technologies have allowed for the neurotoxic effects of chemotherapy to be visualized. The sum of these findings has demonstrated both structural and functional changes in the brain in relation to chemotherapy (Saykin et al., 2003b), with white matter abnormalities representing the most commonly reported trait (e.g., Hook et al.,
Most commonly, this is generalized as reductions in prefrontal regions and adjacent to lateral ventricles, though, specific abnormalities have been noted in the centrum semiovale and corpus collosum (Lien et al., 1991), as well as the parahippocampal, cingulated gyrus, and precuneus regions (Inagaki et al., 2007). To date, studies have been most commonly done within the pediatric and breast cancer populations, though other studies have been undertaken.

Ciesielski and colleagues (1999) found significant volumetric reductions in both the mammillary bodies and prefrontal cortices in a sample of children receiving chemotherapy without radiation therapy, for ALL using MRI morphometry, when compared with healthy controls. This sample was previously evaluated by Lesnik and colleagues (1998) whom at that time, noted smaller volumes in the PFC and cerebellar lobuli VI-VII. In this earlier study, structural changes were associated with deficits in short-term memory, visuospatial attention, visuomotor integration, and coordination corresponding with this cerebellar-frontal circuitry. Additional studies have also noted MRI abnormalities in relation to chemotherapy for ALL in pediatric samples (e.g., Harila-Saari et al., 1998; Kingma et al., 2001; Reddick et al., 2007). Across these additional studies, not surprisingly, it was demonstrated that combined cerebral radiation greatly increases the neurotoxic effects. Additionally, researchers found that changes related to chemotherapy, and even radiation, are not noted in all children (Harila-Saari et al., 1998; Kingma et al., 2001). This is an idea being increasingly discussed in the adult literature as well, with some suggesting that genetic polymorphisms may explain the susceptibility of some patients compared with others to the neurotoxic effects of chemotherapy (Largillier et al., 2006). Harila-Saari and colleagues (1998) specified that the two children, out of 15, who demonstrated structural changes after receiving chemotherapy alone were born prematurely and that this may be seen as an increased host risk factor.

An interesting finding noted by Kingma and colleagues (2001) was that while volumetric decreases in white matter and atrophy were observed in select patients, these structural abnormalities were not related to cognitive or academic deficits. Fliessbach and colleagues (2003) have also reported that while white matter pathology occurs in relation to chemotherapy, it does not necessarily manifest as neurocognitive dysfunction. Again, one might propose that just as one has a genetic susceptibility to displaying structural changes as a result of chemotherapy, there may too be a genetic predisposition for manifesting those changes as cognitive sequelae. However, some have demonstrated a link between structural changes and cognitive deficits (e.g., Reddick et al., 2006).

Reddick and colleagues (2006) offered good insights into the differential risk for neurotoxicity in chemotherapy alone compared with chemotherapy with cerebral radiation. In their study, Reddick and colleagues (2006) examined a large cohort of children treated with chemotherapy alone or combined chemotherapy and radiation for ALL, comparing them to healthy siblings. The researchers found both those with chemotherapy alone and those treated with both chemotherapy and radiation exhibited deficits on neuropsychological assessment. Comparatively, those receiving radiation in addition to chemotherapy presented with greater impairments. Those receiving chemotherapy alone demonstrated deficits in attentional functioning compared with healthy controls. This group also demonstrated significant volumetric reductions in white matter compared with healthy controls. Those receiving additive radiation therapy presented with significantly greater white matter reductions.

Within the adult population, structural abnormalities have still been observed. For example, Saykin et al. (2003a,b), using voxel-based morphometry (VBM) found volumetric reductions of local bilateral neocortical grey matter and cortical and subcortical white matter in several regions. This was noted in a sample of patients who had received chemotherapy for either lymphoma or breast cancer compared with healthy controls. In a later study, Saykin and colleagues (2007) also found reduced brain activation in frontal areas on fMRI during a working memory task in patients who had previously received chemotherapy. Silverman and colleagues (2007) have also demonstrated functional disruptions related to chemotherapy. Using PET, increased activation in the left inferior frontal gyrus and posterior cerebellum was noted in individuals who had underwent chemotherapy 5 to 10 years previously (Silverman et al., 2007). Related findings were noted by Kreukels and colleagues (2006) using EEG, in which decreased P3 amplitude was noted in chemotherapy survivors compared with controls.
Findings of chemotherapy-related dysfunction are discussed throughout many of the chapters.

Endocrine/Hormone Therapy

Though not as commonly discussed or considered as radiation or chemotherapy, endocrine/hormonal therapy is frequently used in both the breast cancer and prostate cancer populations. Wefel and colleagues (2004; Chapter 1) have discussed the potential influence of hormones and hormonal changes in the development of neurocognitive deficits within the cancer population. This is due to the relative importance of reproductive hormones in cognitive functioning (Bender et al., 2001), with some suggesting their roles in organizing neural systems leading to gender-based, neurological strengths (Maki et al., 2002; Sanders et al., 2002). For example, higher levels of estrogen appear to be beneficial to the performance on tasks such as verbal fluency and verbal memory (Maki et al., 2002), whereas higher levels of testosterone appear beneficial to performance on spatial perception and mental rotation tasks (Sanders et al., 2002). When the system, including the brain, is deprived of these hormones, deficits arise.

Within the prostate cancer population, research has long demonstrated the role testosterone plays in the development and growth of prostate cancer. Consequently, treatment success has been achieved with androgen deprivation therapy (ADT). While this is effective from an antineoplastic standpoint, negative consequences can be seen. Amongst the potential negative sequelae of ADT lies neurocognitive and psychiatric features. Both depression and anxiety have been associated with ADT (Di Blasio, Hammett, Malcolm, Judge, Womack, et al., 2008). Similarly, deficits in verbal memory, spatial reasoning, and attention have been associated with ADT (Beer, Bland, Bussiere, Neiss, Wersinger, et al., 2006; Cherrier, Rose, Higano, 2003; Green, Pakenham, Headley, et al., 2004; Herr, O’Sullivan, 2000; Holzebeierlein, Castle, Thrasher, 2004; Salminen, Portin, Koskinen, Helenius, & Nurmi, 2004; Thompson, Shanafelt, Loprinzi, 2003). This is discussed in greater depth in Chapter 2.

Regarding breast cancer population, tamoxifen, which is a selective estrogen receptor modulator, has shown significant benefit in reducing recurrence and mortality. However, it has also been linked with neurocognitive deficits. Paganini-Hill and Clark (2000) reported significantly more memory complaints on the part of women using tamoxifen compared with those who did not. In rodent models, memory deficits have also been shown in relation to tamoxifen use (Chen et al., 2002a,b). This is not that surprising given previous research has demonstrated declines in verbal memory following surgically induced menopause (Verghese et al., 2000). Eberling and colleagues (2004) not only found naming deficits in relation to the use of tamoxifen but also noted hypometabolism in the inferior and dorsolateral regions of the frontal lobes on PET related to tamoxifen. Chapter 3 discusses this in further depth.

Pharmacological Effects

In addition to the neurotoxic effects of primary cancer therapy, adjuvant medications such as steroids, anticonvulsants, and pain medications may also cause neurocognitive and neurobehavioral symptoms. The use of glucocorticoids is ubiquitous and is associated with a 5% to 50% incidence of steroid-induced psychiatric syndromes including euphoria, mania, insomnia, restlessness, and increased motor activity. Glucocorticoids have been implicated in the development of memory dysfunction across a variety of conditions including chronic stress and posttraumatic stress disorder. Certain anticonvulsants (e.g., topiramate, phenobarbital) are also known to have adverse neurocognitive effects. Both seizure frequency and the use of anticonvulsants have been demonstrated to adversely impact neurocognitive function in brain tumor patients. Pharmacologic intervention for symptoms of pain may cause sedation and associated diminution of cognitive function. The assessment of cognitive dysfunction secondary to cancer treatment is complicated by the use of supportive medications (e.g., steroids, immunosuppressive agents, anticonvulsants) that can alter cognitive function.

Pharmacologic intervention for symptoms of pain may cause sedation and associated diminution of neurocognitive function. Abnormalities in endocrinologic function secondary
to hypothalamic/pituitary injury are very common following radiotherapy. Thyroid dysfunction, loss of libido, and erectile dysfunction are present in a large proportion of patients. Endocrinologic replacement therapy has the potential to improve neurocognitive and neurobehavioral function in patients who have abnormal hormone levels. Anemia is a side effect of some chemotherapeutic agents/regimens that is associated with both fatigue and neurocognitive problems including decreased attention, processing speed, and memory.

Psychological Status
The word “cancer” itself elicits a cognitive and emotional reaction in many individuals. Within the clinical setting, once patients have a confirmed diagnosis, they may experience a wide range of emotions that are constantly changing as they proceed through their treatment. Depression and anxiety are by far the two most common psychiatric symptoms experienced within the cancer population, having been associated with the majority of disease sites and ages. As with other medical ailments, the experience of prominent psychological distress in cancer has been linked with poorer outcomes in terms of mortality and morbidity (Litofsky et al., 2004; Spiegel, 1996). Functionally, the negative impact of depression, anxiety, as well as other such features has been extensively described, including within the cancer population (Scheibel et al., 2004). For example, Scheibel and colleagues (2004) not only discuss the relative frequency of depression during chemotherapy but have also discussed depression’s role in the manifestation and maintenance of neurocognitive deficits. Airaksinen et al. (2004) found that depressed individuals and patients with mixed anxiety and depression demonstrated significant deficits in memory. Consequently, these factors must be considered in clinical evaluations and controlled for in empirical investigations. Chapter 18 discusses psychosocial functioning in cancer in greater depth.

Fatigue
When it comes to functional sequelae of cancer and the various forms of treatment, there is likely no symptom more common than fatigue. As previously suggested, fatigue is a primary residual of anemia and anemia presents in approximately 80% of patients. Hayes and colleagues (2003) have suggested that cancer-related fatigue (CRF) remains the most common and most debilitating side effect experienced by cancer survivors. In one study on older patients (>60 years), fatigue was nearly universal, significantly interfered with functional level, and was related to their level of reported depression (Respini et al., 2003).

McNeely and Courneya (2010) describes CRF as a multifactorial and multidimensional entity arising from biological, psychological, emotional, and/or behavioral factors. CRF is unique in that it is not responsive to increased sleep and can contribute to cognitive decline (Iop et al., 2004; Speck, et al. 2010; Tierney et al., 1991). Consequently, CRF can be quite debilitating and significantly affect an individual’s functional capacity and overall QOL. While CRF it is most often experienced during active treatment, many patients report CRF as a chronic and pervasive residual (Speck et al., 2010).

CRF has been regularly associated with neuropsychological deficits across cancer populations, though it often does not explain such deficits fully. Further, CRF is associated with most every treatment option for cancer, but is particularly relevant in certain therapeutic options. For example, Malik and colleagues (2001) reported 70% to 100% of patients receiving interferon-alpha will present with marked fatigue. In fact, these authors noted that 10% to 40% of these patients will present with such prominent symptoms that dose reduction is required. When considering neuropsychological status, fatigue must be considered, both in experimental investigations and in clinical evaluations. Interestingly, treatments that have shown promise in improving fatigue have also shown promise in improving cognitive deficits and vice versa. In particular, psychostimulants have shown promise both in the treatment of CRF and neuropsychological deficits related to treatment such as “chemo-brain.” CRF is discussed in greater depth in Chapter 22, and potential pharmacological interventions are discussed in Chapter 21.
SUMMARY

Over the past 20 years, antineoplastic treatments have grown by leaps and bounds. As a result, there has been a substantial growth in the number of cancer survivors. With advancements in medical therapies, we have seen an increased interest in the functional impact of cancer and its treatment on individual’s lives. Cognitive dysfunction is an area of growing interest as a majority of patients on active treatment and a fair portion of those posttreatment report cognitive problems. This is in addition to those deficits experienced prior to treatment, related to either tumors of the CNS or the negative influence of inflammatory/immune responses. Cognitive problems can thus be viewed as arising from direct and indirect features of both the cancer itself and its treatment. These deficits may range from prominent, focal impairments, to mild yet diffuse problems. In both instances, the effects these symptoms may have on individuals’ daily lives may be profound.

In this chapter, we discussed the common cognitive problems arising from cancer and its treatment and how neuropsychology, as a field, may address these issues both clinically and scientifically. In the following chapters, neuropsychological problems are discussed in relation to specific cancer types and particular cancer therapies related to those cancer types. The idea is that for professionals to fully appreciate the neuropsychological problems reported or demonstrated by patients, they must have an appreciation and understanding of the road the patient has traveled. Differential risks of neuropsychological problems have been associated with lung cancer versus prostate cancer as an example. Similarly, their methods of treatment vary and are also associated with different neuropsychological problems. One cannot adequately appreciate the subject matter clinically or scientifically if they simply lump all cancers and all treatments together. Discussion must be offered on both CNS and non-CNS cancers, and separation, as much as possible, amongst therapies must be offered. This book represents an attempt to discuss the effects of cancer and cancer treatment on cognition in this fashion. As the number of cancer survivors continues to grow, there will be continued growth in the need for services that address aspects of QOL. It is fairly clear that cognitive problems has been and will remain one of the main areas of concern for patients within this mindset.

REFERENCES


THE NEUROPSYCHOLOGY OF CANCER AND ONCOLOGY


