Neurocognitive Interventions for Children and Adolescents Surviving Cancer

Robert W. Butler,1 PHD, and Raymond K. Mulhern,2 PHD
1Oregon Health Science University, Portland, Oregon, and 2St. Jude Children’s Research Hospital, Memphis, Tennessee

Background It is well recognized that many cures for childhood leukemia and brain tumors entail some relatively permanent neurocognitive and psychological costs to the patient and family. As cure rates have improved over the past three decades, increasing efforts have been directed toward reducing treatment-related late effects. Objective The particular focus of this review will be on interventions for the neuropsychological late effects associated with the treatment of acute lymphoblastic leukemia (ALL) and malignant brain tumors. Summary We will first briefly review current approaches to the medical treatment of ALL and brain tumors to provide an appreciation of potential sources of brain injury. We will then summarize the existing literature on types of neuropsychological deficits found among survivors, with special attention to variables that place some children at greater risk. Then, there will be a discussion of approaches to intervention for these deficits—specifically, cognitive remediation, pharmacology, and ecological alterations in the classroom. Finally, we will present directions for future research in the field.

Key words pediatric brain injury, rehabilitation, childhood cancer.

Approximately 2,500 to 3,500 children and adolescents under the age of 20 are diagnosed each year with acute lymphoblastic leukemia (ALL), a malignant disorder of lymphoid cells found in the bone marrow that migrates to virtually every organ system, including the central nervous system (CNS), via the circulatory system. ALL accounts for one fourth of all childhood cancers and 75% of all cases of childhood leukemia. ALL is more common among white than black children and among boys than girls, with a peak incidence at 4 years of age. Although genetic, environmental, viral, and immunodeficiency factors have been implicated in the pathogenesis of ALL, the precise causes of most cases remain largely unknown (Margolin, Steuber, & Poplack, 2002).

Presenting symptoms include fever, fatigue, pallor, anorexia, bone pain, and bruising. Because the symptoms of ALL can mimic a number of nonmalignant conditions, definitive diagnosis, usually made by bone marrow aspiration, is sometimes delayed. The duration of treatment varies from 30 to 36 months and in the modern era is usually restricted to intervention with combination chemotherapy, reserving cranial irradiation for patients who experience a CNS relapse. A good prognosis is associated with female gender, age at diagnosis between 2 and 10 years, a low white blood cell count, and an early positive response to treatment, which can be divided into four phases: remission induction, CNS preventative therapy, consolidation, and maintenance. The purpose of the remission induction phase is to rapidly eradicate leukemia cells from the bone marrow and circulatory system. CNS preventative therapy is necessary because the CNS is a sanctuary for occult leukemia. Traditionally, CNS therapy has included cranial radiation therapy (CRT) and intrathecal chemotherapy, usually with methotrexate alone or combined with other drugs, including steroids. However, because of the risks for
CNS toxicity (to be discussed later in this chapter), treatment is now usually restricted to intrathecal and systemic chemotherapy with equivalent success in the prevention of CNS relapses. Consolidation may be used to intensify therapy following remission induction. Maintenance therapy is required for a prolonged period because of the presence of undetectable levels of leukemia that nevertheless have the capacity to be fatal. After the completion of treatment, approximately 20% of those children who will eventually relapse will do so in the first year off therapy, with a subsequent risk of relapse in the remaining patients of 2 to 3% per year for the next 3 to 4 years (Margolin, Steuber, & Poplack, 2002).

Pediatric brain tumors are considerably more heterogeneous than ALL in that they vary by histology as well as location. Next to ALL, brain tumors are the second most frequently diagnosed malignancy of childhood and are the most common pediatric solid tumor, with an annual incidence of 3.3 per 100,000. The etiology of most pediatric brain tumors is unknown, although brain tumors can appear as a second malignancy following the treatment of ALL with CRT. In relation to the tentorium, a membrane that separates the cerebellum and brain stem from the rest of the brain, tumors are oftentimes characterized as being above (supratentorial) or below (infratentorial). In approximate decreasing order of incidence, the most common tumors are supratentorial low-grade tumors, medulloblastoma, brain stem glioma, cerebellar astrocytomas, supratentorial high-grade tumors, and craniopharyngioma (Strother et al., 2002).

Among the more common symptoms of a brain tumor are morning headaches, nausea, lethargy resulting from tumor obstruction of the ventricles, and increased intracranial pressure. Problems with balance and cranial nerve findings are more common among patients with infratentorial tumors, whereas seizures are more common among patients with supratentorial tumors. Computed tomography and/or magnetic resonance imaging are critical to the diagnosis of pediatric brain tumors, although surgical resection or biopsy of tissue is usually necessary for definitive histological diagnosis. In addition to maximal safe surgical resection of the tumor, chemotherapy with or without cranial or craniospinal irradiation is indicated for malignant tumors. CRT is typically delivered once daily, 5 days each week for up to 6 weeks. The total dose delivered to the brain can be more than twice that once given in the treatment of ALL (Strother et al., 2002). Depending upon pathology, irradiation may involve whole brain fields with a boost to the tumor bed, or partial field treatments. Exciting advances in conformal field irradiation delivery are now being explored in order to reduce normal tissue damage. Fractionated delivery of CRT may also prove to be an important variable affecting neurocognitive outcome, and clearly deserves further study.

Prognosis varies with the tumor type. For example, medulloblastoma, the most common malignant brain tumor in childhood, has a prognosis of long-term survival greater than 65% for average-risk patients, whereas intrinsic brain stem glioma in children has a prognosis of less than 10%. Although this paper will address the neuropsychological toxicity of CRT and intrathecal chemotherapy, other potentially serious complications from irradiation (e.g., hormone deficiencies, growth retardation, second malignancies) are recognized in the literature, as well as hearing loss from cisplatin chemotherapy. There is also a growing concern that the use of steroids may result in neurocognitive deficits (Waber et al., 2000), but this literature is in its infancy.

Neurocognitive Late Effects

Despite the differences between ALL and malignant brain tumors, there are significant similarities among the symptoms comprising neurocognitive deficits, particularly with regard to the treatments of brain irradiation and intrathecal chemotherapy. While a considerable body of evidence has accumulated on the nature of white matter damage from those treatments, variations in tumor pathology and combined treatment protocols over time have made the need for further research necessary. In order to summarize our understanding of the neuropsychological impact of childhood cancers and their treatment, we have chosen to define core deficits, which involve executive functions, processing, and fluid abilities, and secondary deficits, which are knowledge based and oftentimes referred to as crystallized abilities. In the current conceptualization, it is the detrimental effects of cancer and cancer therapy on the biological substrates of core abilities that eventually result in more observable secondary deficits. Several excellent reviews are available supporting this approach to understanding neurocognitive deficits among children surviving ALL (Butler & Copeland, 1993; Moleski, 2000) and brain tumors (Ris & Noll, 1994), suggesting that children surviving brain tumors are at greater risk for more severe deficits because of the increased aggressiveness of their therapy and, in particular, the continued use of CRT. These reviews, and more recent studies, have further emphasized that the severity of deficits is also dependent upon patient age and gender, with girls and younger patients being more vulnerable (Butler, Rizzi, & Bandilla, 1999; Leung et al., 2000; Palmer et al., 2001;
Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001). While the late effects of CRT typically emerge within 1 to 2 years of administration, there is evidence that brain-damage effects may be delayed up to 7 years (Brouwers, Riccardi, Fedio, & Poplack, 1985). Furthermore, with brain tumors, infiltration of disease into normal brain parenchyma and the surgical resection process itself can also impact cognitive integrity.

Because of a consensus that CRT was harmful to intelligence and other neurocognitive functions in children with ALL, pediatric oncologists began substituting intrathecal chemotherapy. Initial studies reported an absence of neurocognitive toxicity with this approach (Butler, Hill, Steinherz, Meyers, & Finlay, 1994). Most current findings continue to document the fact that intrathecal chemotherapy is less harmful to the child’s neuropsychological status than is CRT. Nevertheless, at least 30% of the children who receive intrathecal chemotherapy go on to experience some degree of neurocognitive involvement (Copeland, Moore, Francis, Jaffe, & Culbert, 1996), and when compared with normative data, childhood cancer survivors from this population performed more poorly on nonverbal tasks (Brown et al., 1998). Other types of chemotherapy, such as with the corticosteroid dexamethasone, have also been reported to cause increased neurocognitive late effects (Waber et al., 2000). For many children with malignant brain tumors, CRT remains a primary therapeutic modality, along with resection and chemotherapy, because of the lack of success of approaches based on chemotherapy alone to preserve survival.

Most descriptions of core neurocognitive deficits in survivors of ALL and malignant brain tumors involve attention/concentration deficits. These were first reported by researchers at the National Institutes of Health (NIH) (Brouwers, Riccardi, Poplack, & Fedio, 1984). More recently, it has been determined that CRT results in significant impairment in attentional filtering, focusing, and automatic shifting (Lockwood, Bell, & Colegrove, 1999). Other researchers have documented (1) deficits in the ability to focus and execute under conditions of demanding attentional processing and (2) susceptibility to distraction (Rodgers, Horrocks, Britton, & Kernahan, 1999). These reports support the hypothesis of vulnerability of the pediatric brain to premature disengagement under conditions of vigilance following CNS treatments for a malignancy (Butler, Kerr, & Marchand, 1999).

In addition to core deficits in attention/concentration, relatively greater impairment of nondominant hemisphere functions has been consistently related to the effects of whole brain irradiation (Butler & Copeland, 1993; Fletcher & Copeland, 1988). More recent findings have suggested that the cognitive processes of working memory and information processing efficacy are also reduced following CRT in childhood (Schatz, Kramer, Ablin, & Matthay, 2000). Working memory appears to be particularly vulnerable to CRT, and working-memory deficits larger than predicted based on the degree of reduced information processing speed can be present. Another recent study similarly reported modest declines in nondominant hemisphere functions and arithmetic academic achievement following intrathecal CNS prophylactic treatment (Espy et al., 2001). Approximately two thirds of the studies reviewed of children treated for ALL reported intelligence declines, neuropsychological involvement, and delays in academic achievement, with the strongest findings for deficits in attention and nonverbal memory (Moleski, 2000). In terms of relevance to attention, it has been verified by other researchers (Posner & Raichle, 1994) that the nondominant hemisphere is extremely important to the processes that involve engagement, prevention of premature disengagement, and lack of perseverance.

In combination, deficits in these core areas are thought to be at least partially responsible for observed declines in intelligence (Schatz et al., 2000) and have recently been associated with quantitative loss of normal white matter in the brain among children with brain tumors treated with CRT (Mulhern et al., 2001; Reddick et al., 2003). As with CRT, it has been reported that intrathecal chemotherapy for ALL can be associated with brain abnormalities, including decreased cerebral perfusion, slower resting electroencephalogram (EEG) frequencies, white matter changes, and enlargement of the ventricles and cortical sulci (Moleski, 2000).

These core and secondary symptoms of neurocognitive deficits may also impact other areas of functioning, such as social interactions. Although completing treatment for childhood ALL is not generally associated with adjustment difficulties (Noll, Bukowski, Davies, Kooztz, & Kulkarni, 1993; Noll, LeRoy, Bukowski, Rogosch, & Kulkarni, 1991), children who survive a brain tumor do appear to be at risk for social difficulties following cessation of treatment, perhaps due to increased severity of neurocognitive injury (Vannatta, Gartstein, Short, & Noll, 1998).

### Approaches to Intervention for Cancer-Related Brain Injury

Table 1 presents a summary of commonly identified neuropsychological deficits among children surviving ALL and brain tumors, and the risk factors associated with these deficits.
The most direct approach to eliminating neurocognitive deficits would be primary prevention; that is, to reduce the occurrence of ALL or brain tumors. However, the etiology of most childhood cancers is unknown. Secondary prevention of neuropsychological deficits is currently a more realistic option, which involves the reduction of known sources of neurotoxicity, especially among patients known to be more vulnerable to neuropsychological late effects. These efforts have involved using chemotherapy to eliminate CRT, a strategy that has proved successful in the treatment of ALL but has had varying success in the treatment of brain tumors (Strother et al., 2002). When CRT cannot be eliminated, newer treatment techniques such as 3-D conformal methods offer the hope of sparing a greater proportion of normal brain from high doses of irradiation. Our current emphasis, however, will be on interventions for neuropsychological late effects that involve cognitive remediation, pharmacotherapy, and ecological manipulations directed at restoring areas of deficit or implementing compensatory activities.

Cognitive Remediation

Cognitive remediation refers to systematic attempts to improve cognitive functioning following a brain injury (Butler & Namerow, 1988). These methods typically involve massed practice and drill approaches, along with other psychologically based intervention methods. The theoretical basis for cognitive remediation can be traced to the work of Alexander Luria (1963). He proposed that the brain is not a static organ and that functional reorganization of neural pathways can occur after a CNS insult. Cognitive deficits must be analyzed and subdivided into their individual components. Retraining then involves extended practice and overlearning on tasks similar in nature to that of the component deficit. An NIH (1998) consensus statement concluded that while research methods remain somewhat equivocal, there is support for the use of cognitive rehabilitation methods. The clinical validity of these interventions is further advanced by a recent article documenting the effectiveness of remediation efforts to improve attention, memory, functional communication, and executive functioning in adults (Cicerone et al., 2000). A resurgence in the field of cognitive remediation is documented by the publication of five textbooks on this subject within the past half decade (Christensen & Uzzell, 2000; Prigatano, 1999; Raskin & Mateer, 2000; Sohlberg & Mateer, 2001; Stuss, Winocur, & Robertson, 1999). Of note, only three of these texts address rehabilitation issues in the pediatric population, and within each of these three texts only one chapter is devoted to interventions for the brain-injured child.

Cognitive Remediation After Childhood Traumatic Brain Injury

A relatively small number of research manuscripts have been published on the results of cognitive remediation following pediatric traumatic brain injury. Many of these studies are case report in nature. Crowley and Miles (1991) described a behavioral, individually tailored approach used with a 16-year-old male 1 1/2 years post-severe traumatic brain injury. Their results documented cognitive improvement with some generalization of skills to arithmetic academic achievement. In a case study (Campbell, 1990) it was reported that cognitive retraining improved attentional processes in an adolescent. A combination of traditional brain-injury cognitive rehabilitation (using massed practice drills) and instruction in metacognitive strategies was used to improve neuropsychological functioning. Williams (1989) investigated cognitive remediation in children with head traumas. Improvements in attention/concentration were reported, but generalization to school performance was not well documented.
Metacognitive strategies refer to teaching individuals to monitor their own thinking (Brett & Laash, 1998). These strategies have been documented to improve attentional processes in brain-injured children. Using a single-subject experimental design, Slifer et al. (1997) applied a behavior modification approach designed to reduce disruptive behavior and agitation in children and adolescents with serious brain injuries. Other researchers have established the usefulness of a behavioral approach to cognitive remediation (Silver, Boake, & Cavazos, 1994). Combining cognitive-behavioral therapy with instruction in metacognitive strategies and traditional behavior modification has also been shown to improve problem solving in children with acquired brain injuries, as seen in the study by Suzman, Morris, Morris, and Milan (1997), which also documented that patients, parents, and teaching staff all reported a high degree of satisfaction with the intervention and that generalization of the training program to classroom performance was likely. Also using a multimodal approach, Teichner, Golden, and Giannaris (1999) reported reductions in aggression in a severely brain injured adolescent. Their approach included contingency management, problem solving skills training, social skills training, relaxation training, and anger management, as well as working with the adolescent’s parents.

Psychological, behavioral, and psychiatric disturbances are frequently an outcome of childhood brain injury. A number of researchers have addressed the importance of these problems in addition to attempting to improve cognition and academic functioning. Behavior therapy and pharmacologic treatments have been shown to reduce aggressive behavior in children and adolescents who have experienced a traumatic brain injury (Deaton, 1987; Kehle, Clark, & Jenson, 1996). Children and adolescents who experience a traumatic brain injury are at risk for social skills deficits and withdrawal. Socialization is a major component of quality of life, and attempts at improving functioning in this area are showing promise (Warschauksy, Kewman, & Kay, 1999).

The importance and usefulness of supportive and analytic psychotherapeutic approaches with brain-injured adults have only recently been recognized. Prigatano (1999), who has written extensively about the manner in which psychotherapeutic intervention needs to play a central role in the rehabilitative process, described the suffering that occurs associated with the loss of self following a brain insult. The goal of psychotherapy with brain-damaged individuals is to restore a sense of purpose and meaning. The need for cognitive-behavioral therapy is also emphasized so that individuals can improve their verbal mediation skills and thus their self-control. The therapeutic alliance is also viewed as beneficial to the brain injury rehabilitation process. Psychotherapy will likely prove to be an equally important component of pediatric brain injury rehabilitation. Butler and Satz (1999) specifically addressed the need for psychotherapeutic interventions in children who experience depression as a result of brain injury. Adaptation to profound changes in cognition, academic status, socialization, and personality should be fostered. Psychotherapeutic interventions with brain-injured children must also address family issues, as the parents frequently experience traumatic stress associated with their child’s impairment (Leichtman, 1992).

Baron and Goldberger (1993) have written about the importance of ecological, or environmentally based, interventions with brain-injured children. Along with cognitive remediation, specific attention needs to be directed toward the child’s environment in order to facilitate rehabilitation. Frequently, children will need extended time limits for school examinations; the use of true/false and multiple-choice formats in testing, rather than essay examinations; and encouragement to tape-record classroom lectures for later review. Other ecological interventions recommended by the authors include using written handouts in order to decrease demands for copying from the blackboard, and substituting computer-driven for handwritten assignments. An important point made by Baron and Goldberger is that while cognitive remediation can benefit many children who suffer a brain injury, one should not expect a return to baseline, preinjury status. Thus, alterations in environmental demands combined with rehabilitation are most likely to result in maximal therapeutic gains.

Significant advances have occurred in the rehabilitation of neurocognitive and psychological functioning following a traumatic brain injury. Not only should the child and his/her family receive rehabilitative intervention, but the environment can also be manipulated in order to maximize functioning. The use of behavioral interventions, cognitive-behavioral therapy, instruction in metacognitive strategies, social skills training, traditional brain-injury rehabilitation techniques such as masked practice drills, and supportive and dynamic psychotherapeutic approaches all appear to be beneficial to the brain-injured patient. Research on the effectiveness of cognitive remediation with brain-injured children is a new and exciting field. There are clear indications that multimodal interventions in this population may be synergistic. From a methodological perspective, this suggests that additive approaches rather than the
dismantling of clinical outcome designs will be the preferred experimental paradigm. Given that trauma is the most common cause of brain injury in children, the majority of studies to date have been conducted on this population, with isolated case studies on children who have epilepsy or have experienced a hypoxic episode. The approaches used with traumatic brain injury would appear to have relevance for the pediatric oncology population. More specifically, the two most common malignancies of childhood—ALL and brain tumors—are, as noted above, frequently associated with neuropsychological and psychological disturbances very similar to those that occur in traumatic brain injury. Next, we will review neuropsychological rehabilitation efforts directed specifically toward childhood cancer survivors.

**Cognitive Remediation After Childhood Cancer**

The most systematic efforts in applying cognitive remediation principles to children with neurocognitive deficits associated with cancer and its treatment have been accomplished by Butler and Copeland (Butler, 1998; Butler & Copeland, 2002). These authors have developed an innovative tripartite model that uses techniques and methods from three disciplines: brain injury rehabilitation, special education/educational psychology, and clinical psychology. From brain injury rehabilitation, massed practice is used, and techniques developed by Sohlberg and Mateer (1996) are applied. This approach, called Attention Process Training (APT), exercises attentional processes in the areas of sustained, selective, divided, and executive attentional control. These tasks tend to be rather monotonous, and an alternating approach is advocated wherein APT exercises are used for 15 minutes and the child is then engaged in a more intrinsically interesting activity, such as various computer software programs and game activities. This alternating approach helps in maintaining the child’s stamina over the 20 two-hour sessions comprised by the Cognitive Remediation Program (CRP) developed by Butler and Copeland. Also, in order to maximize engagement, a 50–80% rule is followed. If a child is not able to obtain a 50%-correct level of responding to a task, the activity is substituted with a more basic task. Once the child reaches 80% accuracy, the next level of task difficulty is applied. All activities are described in a training manual available from the first author on request.

From special education/educational psychology, each CRP participant receives instruction in metacognitive strategies. Butler and Copeland (2002) currently have a dictionary of over 15 metacognitive strategies. These strategies are grouped within the three areas of task preparedness, on-task performance, and posttask strategies. Each CRP participant has an individual therapist who monitors the child/adolescent’s performance over the course of the drill activities. A strategy is taught, and if the child’s performance improves, then that strategy becomes part of the participant’s repertoire. Each strategy is individualized to the participant, and by observing performance over the course of remediation, frequently new and innovative strategies are developed that are unique to the individual.

From the clinical psychology discipline, a cognitive-behavioral approach is used (Meichenbaum, 1977). This approach embodies the concepts of reframing cognitive struggles into a positive light, psychotherapeutic support, acknowledging weaknesses and roadblocks to successful improvement in addition to strengths, monitoring internal dialogue, stress inoculation, becoming one’s own “best friend” rather than “worst enemy,” and ensuring realistic, positive, and optimistic self-statements. In the CRP, cognitive-behavioral methods are specifically directed toward the ability to withstand distraction. The therapist initially serves as a model for the CRP participant on how to overtly talk oneself through a distracting experience. Then the child practices this overt dialogue with the therapist serving as a distracter. Once overt dialogue is successfully incorporated, the child is then coached to internalize the dialogue and use it covertly.

Butler and Copeland (2002) summarized pilot data on the effectiveness of the CRP. Participation in this program resulted in significant improvement on a continuous performance test, thought to be most sensitive to the types of attentional disturbance that are present in the childhood cancer population. On initial examination there was no significant improvement in arithmetic academic achievement. Factors underlying treatment generalizability will need to be fully explored in order to ensure academic gains. The CRP is a team approach intervention. The team consists of the child/adolescent, therapist, parents, and teacher. The intervention involves contacting teachers at least, if not more than, three times over the course of therapy to ensure generalization of strategy use to the classroom. Parents are supplied with lists of strategies and encouraged to ensure their use in the household and on weekends. Clinically, teachers and parents consistently report improvement on the part of the child. Currently a Phase III clinical trial is being conducted on the CRP. This intervention is being administered at seven institutions across the United States: Oregon Health and Sciences University, Children’s Hospital—Los Angeles, the University of Texas’ M. D. Anderson Cancer Center, Cincinnati Children’s Medical
Neurocognitive Interventions

significant impaired memory. Academic achievement increased slightly when raw scores were evaluated. The authors report that, most importantly, the patient continued to use the memory notebook over 1 year after the initial training phase. Teachers were surveyed, and none indicated difficulty with class attendance or timely completion of assignments with appropriate submission to the teacher. Thus, the compensatory memory system appeared to benefit this individual, and it was successfully incorporated into her daily life.

Pharmacotherapy
Methylphenidate and Attention Deficit Hyperactivity Disorder

Among otherwise healthy children diagnosed with attention deficit hyperactivity disorder (ADHD), a large body of research over the past 50 years has documented the effectiveness of stimulant medications, most often methylphenidate hydrochloride (MPH), in improving cognitive performance (Brown, Dingle, & Dreelin, 1997; Brown & Sawyer, 1998). MPH is a mixed dopaminergic-noradrenergic agonist that is thought to enhance the function of the frontostriatal (anterior) attentional network (Weber & Lutschg, 2002). Oral MPH reaches peak bioavailability within 90 minutes and has a half-life of 4 hours. In general, strong dose-response relationships are found, with improvements in most cognitive functions at higher doses both in the laboratory and in school and home situations (Brown et al., 1997). Adverse side effects are rare but reversible with reduction or discontinuation of medication (Barkley, Edelbrock, & Robbins, 1990; Efron, Jarman, & Barker, 1997). The most consistent and significant benefits of MPH are found on measures of vigilance and sustained attention (Rapport, Denny, DuPaul, & Gardner, 1994; Rapport, DuPaul, Stoner, & Jones, 1986), but improvements in reaction time, paired-associate learning, and perceptual efficiency are also common (Brown & Sawyer, 1998; Rapport et al., 1986, 1994). Responsiveness to MPH appears equivalent among boys and girls (Pelham, Walker, Sturges, & Hoza, 1989). Although there has been one report of improved working memory abilities with MPH (Tannock, Ickowicz, & Schachar, 1995), positive effects of MPH on higher-order cognitive functions, such as problem solving or language processing, are rare (Brown & Sawyer, 1998).

Studies of the effects of MPH on actual academic achievement, as opposed to behavioral improvements in the classroom, are also equivocal (Brown & Sawyer, 1998). However, when academic learning is enhanced
by MPH, it appears that improvements in attention and concentration abilities are generally responsible because these abilities enhance efficiency on academic tasks (Tannock, Schachar, Carr, & Logan, 1989). Among children with ADHD, MPH may also improve their social relations with peers, as judged by behavioral observation and peer ratings (Whalen & Henker, 1991). All of the above studies excluded children with comorbid ADHD and mental retardation. However, some evidence of MPH efficacy has also been established among children with ADHD and abnormally low IQ. Handen, Breaux, Gosling, Ploof, and Feldman (1990) treated 12 children with ADHD and IQs in the range of 50–74 in a double-blind crossover trial of MPH and placebo. The investigators found that by parent report and objective performance, work output and attention to task increased with MPH, but no improvements were observed in social interactions or on a paired-associate learning task. The gold standard of research designs in drug trials for ADHD has been the randomized, double-blind, crossover trial that compares two or more doses of MPH to placebo (Rapport et al., 1986, 1994).

The number of studies of MPH effectiveness for attentional problems among children experiencing various forms of brain damage is extremely limited. However, the existing evidence suggests that MPH can be as effective for attentional problems among children with epilepsy as among children with ADHD without significantly lowering the seizure threshold (Weber & Lutschg, 2002). The effectiveness of MPH for attentional disorders associated with traumatic brain injury is equivocal, and no studies of MPH effectiveness for attention deficits associated with encephalitis or meningitis are known (Weber & Lutschg, 2002).

Methylphenidate and Cancer

Why should MPH help children treated for cancer who have attentional problems? We are aware of no evidence that these patients have neurotransmitter system deficiencies. One could depend upon a rationale that is purely empirical. That is, some children surviving cancer, particularly those surviving ALL and malignant brain tumors, exhibit behavioral symptoms similar to those of children with ADHD, especially symptoms of the inattentive type. Therefore, MPH is likely to ameliorate the symptoms. However, there is some emerging evidence of a neurobiological basis for attentional problems among survivors of childhood cancer involving intrahemispheric and interhemispheric white matter tracts (Mulhern et al., 2001), which have only recently been shown to mediate the relationship between the CNS treatment and cognitive outcomes, including academic achievement (Reddick et al., 2003).

Two preliminary reports were among the first to investigate the use of MPH in children with learning problems presumably secondary to their cancer treatment. DeLong, Friedman, Friedman, Gustafson, and Oakes (1992) at Duke University Medical Center treated 12 children surviving malignant brain tumors or ALL with MPH for 6 months to 6 years (median, 23 months) and found that 8 children had a good response, 2 had a fair response, and 2 had a poor response. No dosing information was given in their report. One of the 2 children with a poor response had MPH discontinued because of marked appetite loss. Torres and colleagues (1996) at the University of Rochester Medical Center reported on 6 children who had been given CRT 3 to 12 years earlier for malignant brain tumors. With a consistent dosing of 0.3 mg/kg MPH, they found no significant immediate or delayed benefit to the patients. Although laudable in their early attempts to help cancer survivors with attentional problems, these reports suffer from methodological problems, including a lack of objective measurement of response.

One open-label study has been published with adults treated for malignant brain tumors that used neuropsychological testing and objective inventories to quantify response to MPH (Meyers, Weitzner, Valentine, & Levin, 1998). Significant improvements in cognitive function—including psychomotor speed, memory, executive functions, and mood—and activities of daily living were found, oftentimes in the context of progressive disease.

Thompson et al. (2001) was the first to investigate MPH effects in a randomized, double-blind trial of MPH among survivors of childhood cancer. Evidence of efficacy was demonstrated in a 1-day laboratory study of the effects of MPH on learning-impaired children surviving leukemia or malignant brain tumor. Eligibility criteria included age over 6 years and completion of therapy 2 or more years earlier. Exclusionary criteria included uncorrected endocrinopathies; poorly controlled seizures or abnormal EEG; diagnosis of ADHD prior to diagnosis of cancer; current use of psychostimulants, antidepressants, or anxiolytic medications; or progressive disease. The investigators screened for a particular “cognitive phenotype” that was thought to be most responsive to MPH. Specifically, children with academic achievement deficits and a concurrent problem with vigilance were sought. To qualify for the MPH trial, patients were required to demonstrate on formal psychological testing an estimated IQ greater than 50, one or more academic.
achievement deficits (standard score less than 85 for age), and excessive errors of omission (greater than 84th percentile for age/gender) on the Conners’ Continuous Performance Test (CPT). Thirty-two children met the criteria for the medication trial and were randomized to receive placebo or MPH (0.6 mg/kg to maximum of 20 mg) in a double-blind design. The patients were then retested 90 minutes later. Significantly greater improvement occurred in the group receiving MPH on the CPT with regard to errors of omission and the overall index. No statistical difference was noted with regard to reaction time or errors of commission on the CPT, the overall score on the California Verbal Learning Test–Children’s, or the Visual-Auditory Learning Test on the Woodcock-Johnson Cognitive Battery. Two children exhibited transient side effects, one of which could be attributed to MPH.

These results encouraged us to design a multisite trial that included St. Jude Children’s Research Hospital as the coordinating site and Duke University Medical Center and the Medical University of South Carolina. Using similar eligibility and exclusionary criteria as the Thompson et al. (2001) study, children participate in a randomized, double-blind, 3-week home crossover trial taking two capsules daily for 5 weekdays: 1 week each of placebo, low-dose MPH (0.3 mg/kg to maximum of 10 mg), and moderate-dose MPH (0.6 mg/kg to maximum of 20 mg). At the end of each week, parents and teachers respond to the Conners Rating Scales and side effects rating scales. At the end of the 3rd week, the blind is broken and ratings compared. If the patient has shown objective improvement with MPH, the medication is continued for the next 12 months, at which time the patient’s attentional functioning and school achievement are reevaluated. Currently, preliminary analyses are in progress. Of the first 250 screened for participation, 43% qualified for MPH. Of those qualifying, 76% of parents and children agreed to the MPH trial. Of those participating in the home crossover trial, most have shown at least minimal response, and the overwhelming majority of those responding had parents who agreed to continue with MPH. Whether MPH ultimately facilitates academic achievement among survivors of childhood cancer who have attentional problems is not yet known.

**Ecological Interventions**

Whether the primary treatment approach is cognitive remediation, pharmacotherapy, or a combination, one cannot underestimate the importance of explaining the consequences of areas of neuropsychological deficit to patients, caretakers, and others in their community, such as primary health care providers and especially teachers. It has been recommended that all pediatric oncology centers have a structured school reentry program, one component of which is the education of the patient’s teacher about childhood cancer and the specific signs, symptoms, and special needs associated with the patient’s treatment and treatment outcome (Leigh & Miles, 2002). Some special accommodations are obvious—for example, allowing extra time for a patient with hemiparesis to change classrooms. On the other hand, some neurological and neuropsychological deficits are quite subtle, such as visual or hearing loss or slowed visual-motor production. In addition, the neuropsychological status of the patient may not remain stable after treatment has been completed, in that the onset of some deficits is delayed and others are not evident until the ability is normally expected (Armstrong, Blumberg, & Toledano, 1999). One of the greatest dangers in not communicating these new problems to the patient’s teachers is that the child’s struggles in the classroom can be falsely attributed to attitude problems, daydreaming, a lack of motivation, or emotional maladjustment. Simple classroom accommodations, such as reduced numbers of items on multiple-choice tests, preferential seating in the classroom, and decreased expectations for volume of homework, are oftentimes needed. The fact that most children have multiple teachers, most of whom will change with each school year, makes communication of the patient’s special needs more difficult. Many children undergoing treatment for cancer, as well as those who have completed treatment, will be classified as “other health impaired” by their local school systems as a means of accessing resources for their special needs.

**Future Directions**

Pediatric oncologists have been successful in reducing the frequency and severity of neurocognitive impairments associated with CRT as a prophylactic treatment for ALL. Nevertheless, the risk remains significant for those treated with intrathecal chemotherapy (Moleski, 2000). In contrast, CRT remains a curative modality for children with malignant brain tumors. A compromise has been to combine lower doses of CRT with chemotherapy and to attempt to reduce the volume of normal brain irradiated. Ongoing clinical trials are being conducted to determine whether these treatment alterations will result in decreased neurocognitive dysfunction.

These facts make the need for effective cognitive interventions with former patients a pressing problem,
and one that will likely continue into the advanced future. Initial efforts in this direction have been auspicious, but long-term efficacy data are lacking and we are not yet able to identify which children will benefit from a particular intervention. However, there is clearly a need to advance the impact of our efforts at improving cognitive functioning, especially for children who are school age. Successful completion of school and the acquisition of academic concepts and information is the foundation for adult productivity. Now that cure rates are high, waiting until the patient is known to be a long-term survivor before providing intervention for neurocognitive deficits is no longer defensible. As with the development of cognitive remediation and pharmacotherapy approaches to the treatment of neurocognitive problems in survivors of childhood cancer, we may need to look outside of pediatric oncology for new directions.

One potentially useful addition to the development of interventions for cognitive deficits has been an appraisal of the influence of the family environment and resources following recovery from traumatic brain injury. The importance of family cohesiveness and stability in recovery from brain injury has long been known. As early as 1958, it was reported that children who suffered a traumatic brain injury and developed psychiatric disturbance had greater degrees of family pathology than those who did not experience a mental disorder (Harrington & Letemendia, 1958). Other researchers have further demonstrated the relationship between family pathology and behavioral difficulties among brain-injured children (Lezak, 1978; Worthington, 1989). More recently, Yeates and colleagues (1997) have documented that chaotic and dysfunctional family environments have a significant adverse impact on neurological and neuropsychological recovery from traumatic brain injury among school-age children. This relationship appears to be valid even when severity of brain injury and other medical factors were experimentally controlled (Max et al., 1999). It appears that family burden, characterized by ratings from parents as to the negative impact of the child’s injury on the family, and overall family adjustment are significant predictors of continued neurobehavioral symptoms following childhood traumatic brain injury (Yeates et al., 2001).

How might these findings be relevant to survivors of childhood cancer having neurocognitive problems? One could speculate that the family environment might be of equal or greater importance in the treatment and recovery of a chronic life-threatening disease compared with an acute event such as a traumatic brain injury. Certainly, educating parents to be advocates for their children by giving them sufficient information and support should be a component of any clinical intervention. Whether formal training in special skills would facilitate recovery of function among children treated for traumatic brain injury or cancer is not yet known.

In summary, preliminary reports of interventions with children who experience attentional deficits, information processing speed and efficacy impairments, and other neurocognitive effects from cancer and cancer treatment suggest that there may be potential benefit. There are ongoing systematic efforts to improve attentional processes and neuropsychological functioning with these children and adolescents. The efforts are programmatic, and new directions are being explored in order to make the interventions more effective. Isolated reports have suggested that an intervention based on current standard of care may help prevent further decline in arithmetic achievement but does not result in improved academic functioning. It is possible that the combination of cognitive remediation with an education intervention would also prove to be of added rehabilitative benefit. Pharmacologic interventions need to be explored more fully. The past decade has resulted in the availability of a number of new stimulant medications that may result in even greater attentional improvement than that noted with the traditional medication for attentional disturbances: methylphenidate. An isolated case study suggests that adding compensatory memory devices to the remediation process, particularly with more impaired brain tumor survivors, may also result in increased academic performance and compliance to school scheduling regimens. Thus, we have a number of different avenues to explore that have the potential to successfully rehabilitate neurocognitive deficits. It is likely that the work conducted in the childhood cancer field will also be applicable to other areas, such as attention deficit disorder, ADHD, learning disabilities, traumatic brain injury, epilepsy, brain injuries associated with hypoxia, and perhaps even with children who have not experienced any neurocognitive insult. Conversely, brain injury rehabilitation is an evolving field, and clinicians/researchers in the pediatric oncology discipline need to stay abreast of work conducted with pediatric patients who have other CNS insults.

Acknowledgment

This work was supported by a grant from the NIH/National Cancer Institute (RO1 CA83936–01).
References


