Lessons in Pediatric Neuropsycho-Oncology: What We Have Learned Since Johnny Gunther

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Objective This article provides a commentary on the progression of research over the last six decades into the neurobehavioral outcomes of children treated for intracranial tumors. **Methods** Published studies and literature reviews are surveyed, with illustrations from the author's ongoing longitudinal study. **Results** Research on late effects in pediatric brain tumors continues to increase in both volume and quality. Samples are larger and more differentiated, scope of outcome measurement has increased, and more powerful developmental research designs are being used. Particularly promising recent developments are described, including research on: imaging–behavior relationships, improved modeling of dose-volume heterogeneity in radiation therapy, improved late effects measurement, and treatments for neurobehavioral sequelae. **Conclusions** There is now a large body of scientific evidence of increasing sophistication regarding the outcomes of patients receiving the most toxic treatments. It is argued that more research into the neuropsychological effects associated with ''benign'' tumors of childhood is needed.

Key words childhood cancer; late effects; neurocognitive outcome; oncology

A Historical Reference Point

In 1947, John Gunther, Jr, 17-year-old son of distinguished journalist John Gunther (author of such popular books as *Inside Europe*), died of a brain tumor after undergoing an incomplete resection of a right parietal-occipital glioblastoma multiforme (GBM). Through John Gunther's book, *Death Be Not Proud* (Gunther, 1949), Johnny's 15 month struggle with brain cancer was memorialized, telling the poignant story of a young man of uncommon intelligence and poise in the face of a devastating disease, painful treatments, and repeated setbacks. Among the notable figures that make appearances in Johnny's story are Wilder Penfield, who consulted on and followed Johnny's case closely, and Albert Einstein, with whom Johnny exchanged letters on a unifying theory of physics, the preoccupation of Einstein's later years. One of the last notes from Johnny conveyed his abiding faith in science —''Scientists will save us all,'' he wrote.

For neuro-oncology professionals, this book is an intriguing glimpse into the past and from the perspective of 60 years in the future, offers us a useful point for comparison. Some things have not changed all that much since Johnny Gunther's time. Radiotherapy (RT) is still the mainstay in the treatment of many pediatric brain tumors, and the long-term progression-free survival (PFS) for GBM remains poor—16% 5 year PFS for completely resected and 4% PFS for incompletely resected tumors (Wisoff et al., 1998). Also, just as the Gunthers sought dietary treatment in addition to the conventional treatments of that era, complementary and alternative therapies are continuing to be used by families of children with cancer—84% of them according to Myers, Stuber, Bonamer-Rheingans, and Zeltzer (2005). In other respects, though, the changes have been dramatic and this short paper cannot do justice to the advances in the diagnosis, treatment, and funding of cancer research that have transpired over the past 60 years. Rather, provided here is a commentary and historical perspective on developments in the neuropsychology of pediatric brain tumors (or, ''Pediatric Neuropsycho-Oncology'')—an account which, appropriately, also tracks the

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contributions of Raymond Mulhern, one of the preeminent contributors to this literature.

In 1947, the scientific literature on the behavioral aspects of pediatric neuro-oncology was meager, at best, and mental health/behavioral professionals played little role in the care of oncology patients. Leading neurosurgery and oncology textbooks of the time paid scant attention to neurobehavioral late effects, nor did the nascent field of neuropsychology venture into this territory. Neurological and neuropsychological research with adult brain tumor patients was related more to the explication of general principles of brain function than the unique characteristics of brain tumors. The long-term survival for many brain tumors of childhood was not sufficient to generate concern about the quality of that survival. In the foreword of the seminal book by Koocher and O'Malley (1981), psychiatrist Lean Eisenberg reflected on this early era of pediatric oncology: ''For the fact is that the investigation described in this book simply would not have been possible a generation ago . . . Simply put, there were so few survivors of childhood cancer when I graduated from medical school, that the identification of a cohort of suitable size would have been impossible at a single institution.''

Concerted efforts starting in the 1950s, including the initiation of cooperative groups by the National Cancer Institute, culminated in the 1970s in markedly improved survival rates, particularly for Acute Lymphoblastic Leukemia (ALL) as a result of the development of central nervous system (CNS) prophylaxis therapies. With this success came another challenge for the field, that being the quality of survival. An early paper by Bloom, Wallace, and Henk (1969) called attention to the late effects in pediatric brain tumors. But it was not until the mid-1980s that there developed a substantial literature with studies of varying degrees of neuropsychological sophistication on the neurobehavioral outcomes of long-term survivors of all and brain tumors.

Comparison of two reviews from the mid-1980s, one by Fletcher and Copeland (1988) on ALL and the other by Mulhern, Crisco, and Kun (1983) on brain tumors, would suggest that this literature developed somewhat faster in the case of ALL than in pediatric brain tumors, even after correcting for the different publication dates (Ris & Noll, 1994). Developments in ALL then, to some extent, paved the way for the more specialized field of pediatric neuropsycho-oncology and portended developments with brain tumor populations. In major cancer centers and within cooperative groups, such as Children's Cancer Study Group originally established by the National Cancer Institute in 1955 under the name Acute Leukemia Cooperative Chemotherapy Study Group A (renamed the Children's Cancer Group in 1992 and then later merging with the Pediatric Oncology Group to form the Children's Oncology Group in 2000) the expertise and capabilities for measuring long-term behavioral/psychosocial effects greatly expanded. The scientific ''yield'' of these developments was substantial and such research was essential for comprehensively ascertaining the effects of childhood cancers along with the neurodevelopmental toxicities of the treatments. Without the critical perspective provided by behavioral data, there would have been much less appreciation of the need to develop therapies with reduced toxicity. While psychologists could do little to help these patients once damage to the central nervous system had occurred, they have provided convincing evidence in recent decades of the untoward effects of neurotoxic treatments, and the benefits of protocols designed to reduce such toxicity.

Modern Era of Neurobehavioral Research in Pediatric Brain Tumors

Certain types of brain tumors offered more opportunities than others for late-effects research. While some of this early work was on diagnostically heterogenous samples, medulloblastoma (MB), in particular, was an obvious disease of interest in that it was the prototypical tumor of childhood, was one of the higher incidence pediatric brain tumors, a survival rate had been achieved that justified concern about the quality of survival, and treatment for MB involved radiotherapy, the neurobehavioral toxicity of which was becoming better known through the ALL experience. So, by the mid-1980s, large clinical trials for MB (CCG 923 and POG 8631) were underway in the two North American cooperative groups that incorporated neurocognitive endpoints (Albright et al., 1989; Deutsch et al., 1996). Overall, though, early research into late effects in pediatric brain tumors was characterized by heterogeneous samples, cross-sectional designs, and global outcome measures, as described in reviews by Mulhern et al. (1983) and then by Ris and Noll (1994). At that point (early 1990s), the conclusions arrived at in the latter review were modest: (a) supratentorial tumors were more disruptive to neuropsychological development/functioning than infratentorial tumors; (b) there was a dose–response effect with whole brain radiotherapy being most harmful; (c) younger children were at increased risk; (d) potential declines in IQ could be as great as 25–30 points;

(e) chemotherapy was less toxic, but also less established in the treatment of brain tumors than RT; and (f) more aggressive tumors produce more neuropsychological effects. Recommendations were offered in the review to increase the scope of outcome measurement, reference developmental neurobiological/neuropsychological models, study more differentiated samples, employ prospective-longitudinal designs, and capitalize on recent developments in statistics and methodology, such as growth curve analyses. It was also argued that there were inherent limitations to what behavioral scientists could accomplish in cooperative groups focused on survival, and that optimal progress would only be achieved through a balanced program of research at the institutional, small consortium, and large cooperative group levels (Ris & Noll, 1994).

Subsequently, in a symposium on pediatric brain tumors for the 2001 meeting of the International Neuropsychological Society (that also featured papers by Ray Mulhern, Bob Butler, Dean Beebe, and Brenda Spiegler), the lead paper (Ris, 2001) set the context with an update that demonstrated progress on many fronts. A computer literature search comparing two epochs, 1983–1992 (the years covered by the Ris & Noll review) and 1993–2000, revealed several changes in the volume and characteristics of the literature on pediatric brain tumors. The average number per year of published studies presenting new data on neurobehavioral outcomes had doubled from 2.3 to 5.7. Sample sizes tended to be larger and better differentiated in regards to tumor location and/or type. There was an increase in the scope of outcome measurement, although basic instruments, such as intelligence tests, were still preferred. Finally, there was greater use of prospective-longitudinal designs, although cross-sectional designs still predominated.

And so, by the new millennium, neurobehavioral research in pediatric brain tumors was clearly on the ascendancy, and was being looked to to provide critical outcome information. By this time, a deep experience with certain venerable outcome indexes, like IQ, had been achieved, and stronger research designs were being used.

Recent Advances in Pediatric Neuropsycho-Oncology

Since 2000, several papers have been published that cover developments in this field, but in a more circumscribed way than the aforementioned reviews. Mulhern and Palmer (2003) provided ''. . . an interpretation of findings within a conceptual framework . . . to accommodate new studies as well as guide further research'' (p. 178). They identified ''core'' (executive functions, attention, processing speed) and ''secondary'' (school failure, IQ loss) symptoms of a neurocognitive phenotype along with putative neurobiological (''brain reserve capacity''; Satz, 1993) and psychosocial (enriched environment) mitigating factors. In a 2004 *Lancet* article, Mulhern, Merchant, Gajjar, Reddick, and Kun reviewed the data on intellectual development of children treated for medulloblastoma and ependymoma concluding that neurocognitive impairment remains substantial for those treated aggressively and urging continued innovations in treatment that preserve cognitive development in these patients.

These more focused papers attest to a maturing of the science in this field insofar as they address better-defined questions in greater depth. The present commentary adds to these observations by highlighting four lines of research considered by the author to be most promising: (a) imaging–behavior relationships, (b) improved modeling of dose-volume heterogeneity, (c) improved late-effects measurement, and (d) treatments for neurobehavioral sequelae. Illustrations of these developments will be drawn from an ongoing longitudinal study at Cincinnati Children's Hospital Medical Center, as well as the recent work of prominent researchers in the field.

Imaging–Behavior Relationships

With the explosion in neuroimaging capabilities came a predilection to relate these radiographic findings to ''behavioral'' variables. This type of research continues at a brisk pace, particularly by the group at St Jude (e.g., Mulhern et al., 1999; Nagel et al., 2004; Palmer et al., 2002). The Cincinnati study, as well, is investigating brain changes over time in a mixed sample of brain tumor patients treated with RT using three Magnetic Resonance (MR) techniques—volumetrics, diffusion tensor imaging (DTI), and spectroscopy (MRS). The recent proliferation of novel imaging and behavioral methodologies has been a boon to brain research, allowing *in vivo* ''assays'' of brain structure and function as never before. But, the meanings/correlates of many of the scores, indexes, metrics, and ratios that can now be generated are yet to be discovered, and there is the temptation to engage in statistical ''trawling'' with these powerful methods. In this context, as in other areas of biobehavioral research, risk of Type 1 error can be managed in several ways including various statistical

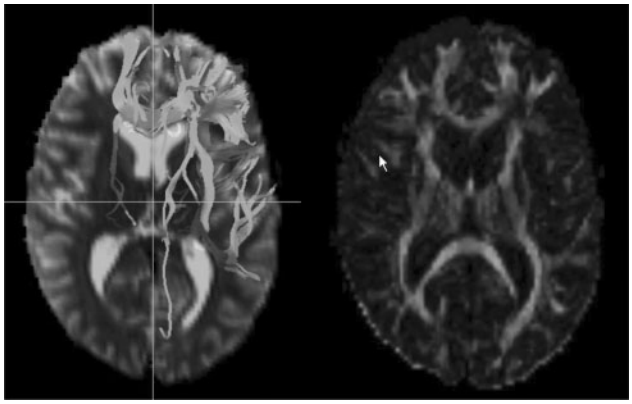

Figure 1. Diffusion tensor imaging showing frontal white matter pathways (left) and color-coded fractional anisotropy (right). Pathways are directionally coded by axis: superior–inferior pathways are blue, anterior–posterior pathways are green, and right–left pathways are red.

(e.g., factor analysis), rational (e.g., grouping by conventional neuropsychological domains), and hybrid statistical–rational data reduction methods, all of which have the effect of distilling many variables down to a few manifest indicators of latent constructs.

Hypothesis-driven research accomplishes this through a priori assignment of special significance to some variables over others. The Cincinnati study has narrowed the field of variables based on what is known about neural structures/tissues that are particularly vulnerable in this population, combined with knowledge of at-risk neuropsychological functions and their putative neural substrates (Ris et al., 2005). This has led to a multimodal imaging strategy that focuses on regions in the dorsolateral prefrontal cortex, anterior cingulate, parietal white matter, and total cerebral white matter. For each of these, there is a primary and secondary imaging modality. For example, the integrity of the cerebral white matter is measured through volumetrics and DTI, more specifically a quantitative derivative of DTI called fractional anisotropy (FA) (Khong et al., 2006). Figure 1 is an example of the DTI acquired from one of the Cincinnati study participants after treatment with 3-dimensional (3D) conformal radiotherapy for a medulloblastoma. The image on the left shows frontal white matter pathways while the image on the right is a color-coded FA map. RT-related changes soon after treatment are not expected, but when re-studied two years posttreatment, imaging changes are anticipated that not only relate to neurobehavioral changes over time, but also to parameters (i.e., dosimetry) from the original RT.

Improved Modeling of Dose-Volume Heterogeneity

Recent reports from Merchant and collaborators at St Jude have demonstrated how the detailed information about radiation gradients delivered to the brains of patients with tumors can be used to improve our modeling of RT late effects in patients with ependymoma (Merchant, Kiehna, Li, Xiong, & Mulhern, 2005) and craniopharyngioma (Merchant et al., 2006). Heretofore, most research has compared patients with very different radiation protocols (e.g., craniospinal RT vs. no RT; or standard dose RT vs. ''reduced dose'' protocols). With the advent of 3D conformal radiation therapy and other modern radiation oncology methods, researchers have access to highly differentiated radiation dose-volume information calculated on a fine spatial scale.

The Cincinnati longitudinal study is based on the premise that an understanding of the relationship between radiotherapy and late effects can only be as good as the precision of our modeling. Figure 2 illustrates the variability of dose distribution delivered to the brain despite these two patients having the same prescribed dose (50.4 Gy) and the same treatment region. The figure also shows the precision with which 3D contouring can map the radiation distributions. A further step involves the exploration of a radiobiologic metric, integral biologically effective dose (IBED), that combines into a single index information about the fractionation schedule, dose, and volume adjusted for biological effect (log cell kill) using the linear quadratic equation for cell survival (Barendsen, 1990). There is some evidence that this results in improved prediction of late effects in patients treated with radiation for brain tumors (Reimer et al., 2003; Ris et al., 2005).

As researchers attempt to make better sense of the neural processes of injury and repair that limit or promote behavioral recovery, recent investigations into radiation-induced depletion of neural precursor cells in accounting for learning deficits following irradiation (e.g., Otsuka et al., 2006) are particularly intriguing. These animal models under development have obvious implications for our understanding, in humans, of differential plasticity and recovery follow treatment for brain tumors. Combined with the increasing precision of radiation oncology, this research may provide important insights into ways to both limit damage and preserve the neural foundation of future development in children treated for brain tumors.

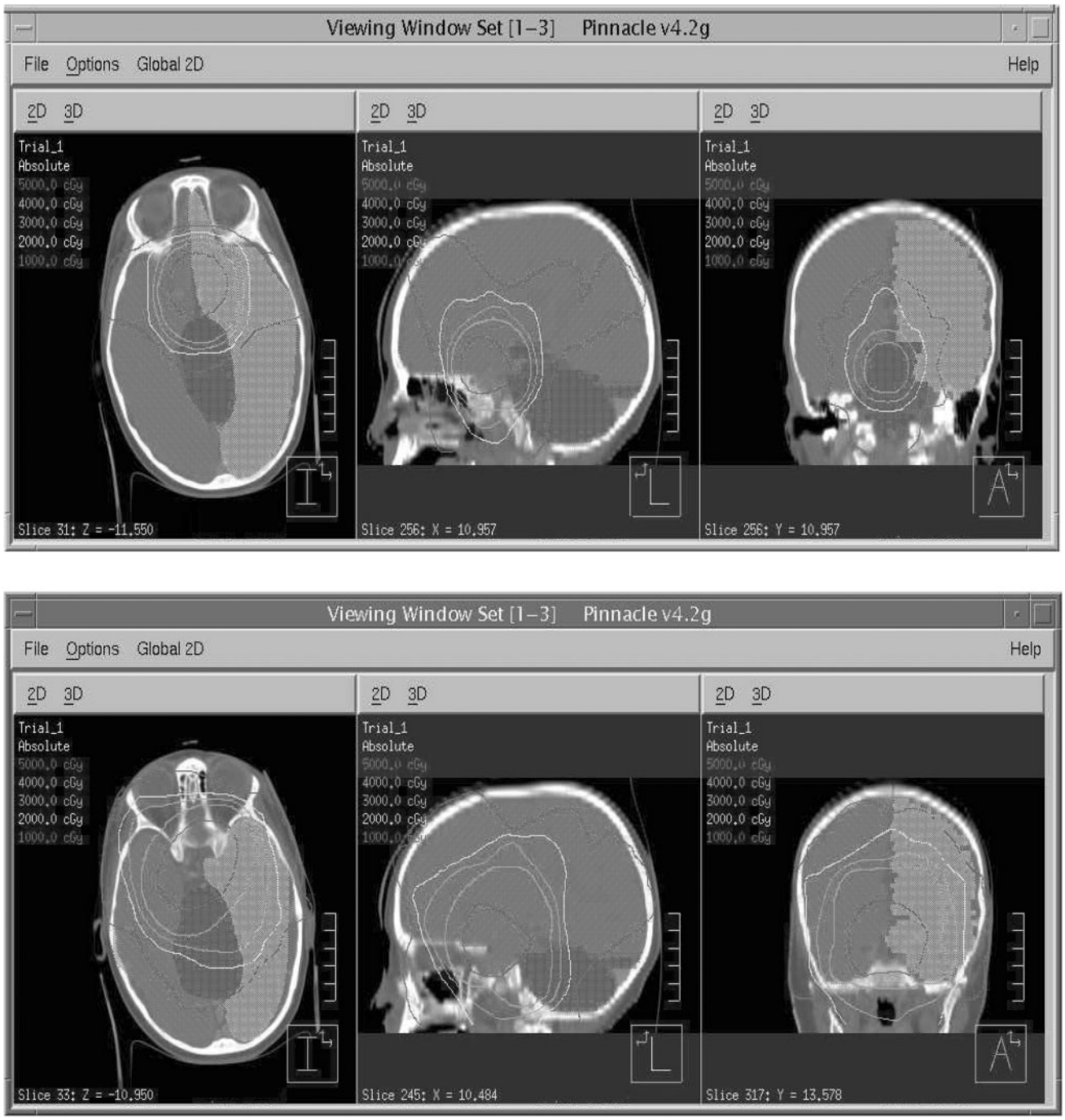

Figure 2. Differing dose contours for two patients treated with prescribed dose of 50.4 Gy for tumors in similar locations. Source: *Pediatric Blood & Cancer, 44*, 487–493, reprinted with the permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Improved Late–Effects Measurement

The recent pediatric brain tumor literature reflects several improvements in the measurement of outcomes. First, it is both more comprehensive and more focused on certain critical/vulnerable functions. Second, behavioral/functional outcomes are better appreciated. And third, advances in cognitive neuroscience are increasingly being applied. For example, the measurement strategy of the Cincinnati study concentrates on three critical constructs considered particularly vulnerable and foundational in the development of these children—attention, processing speed, and working memory. This is based on recent

research in neuropsycho-oncology (Schatz, Kramer, Albin, & Matthay, 2000; and nicely summarized by Mulhern & Palmer, 2003) and developmental psychology (Fry & Hale, 1996). One measure of attention in the Cincinnati study is a cueing reaction time and ''flanker'' task that comes from the work of Posner and colleagues (Fan, McCandliss, Sommer, Raz, & Posner, 2002) and allows attention to be parsed into separate components of alerting, orienting, and executive control, each of which appears to be supported by distinct neural systems.

The second point above is best illustrated by several lines of research, including research on peer relationships (Vannatta, Gartstein, Short, & Noll, 1998), adaptive behavior (Beebe et al., 2005) and quality of life (Palmer, Meeske, Katz, Burwinkle, & Varni, in press) all of which reflect increased appreciation that some of the critical morbidity in children with brain tumors cannot be captured with laboratory-based instruments. While the importance of direct measurement of neurobehavioral functions in children is well appreciated by researchers, there are distinct advantages to having readily available proxy reporters (parents and teachers) for which specialized instruments have been developed, such as the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Ratzlaff, & Espy, 2000). Such measures offer a degree of ecological validity that is difficult to approach with direct measurements in contrived testing conditions.

Treatments for Neurobehavioral Sequelae

The bulk of the neurobehavioral research in pediatric brain tumors has attempted to better define outcomes and use this information to inform the development of less toxic therapies. Intervention research to change these outcomes has been slow to emerge. One can surmise that this is because of a bias toward prevention—few would argue with the proposition that it is easier to limit damage to the CNS than to repair it. Indeed, success in prevention research is inversely related to the need for intervention studies. And then there are the inherent difficulties of conducting good clinical trials with such hard to measure (behavioral) outcomes. Not everyone, though, has been deterred by such challenges and there is a small but growing literature that promises to provide empirically validated interventions tailored, to varying degrees, to the pediatric brain tumor population. Exemplars of this research include the Butler and Copeland (2002) investigations into methods of cognitive rehabilitation/retraining, and Mulhern's clinical trial of methylphenidate pharmacotherapy for cognitive deficits associated with pediatric brain tumors (Mulhern et al., 2004). Noteworthy as well is Armstrong's work focusing on optimizing educational interventions (Armstrong, Blumberg, & Toledano, 1999). From the broader childhood cancer literature may someday come empirically validated interventions for the families of children with brain tumors (Kazak, 2005; Sahler et al., 2002) and treatments for social skills deficits in this population (Barakat et al., 2003). All of these approaches are predicated on the belief that advances in the treatment of brain tumors notwithstanding, these children will continue to suffer varying degrees of adverse neurobehavioral effects for which we need to develop better treatments.

Need for a Better Understanding of the Neuropsychological Effects Associated with ''Benign'' Tumors of Childhood

The accomplishments surveyed above are substantial and promise even greater insights in the ensuing years. With this progress, though, comes an emerging awareness of the relative neglect of tumors commonly referred to as ''benign,'' ''low-risk,'' or ''low-grade.'' There are several reasons for directing the late effects expertise acquired over the last 20 years on higher-risk tumors to pediatric tumors previously assumed to have minor to no long-term neurobehavioral morbidity. First, there is growing evidence that there are more late effects in these patients than was previously realized. Several studies now point to the likelihood of late neuropsychological effects in tumors such as low-grade cerebellar astrocytoma (Beebe et al., 2005; Ronning, Sundet, Due-Tonnessen, Lundar, & Helseth, 2005; Schmahmann & Sherman, 1998). This is consistent with evidence for the reciprocal interconnectivity of the cerebellum with diverse and remote structures of the brain and its corresponding role in what have been termed higher cognitive processes (e.g., Akshoomoff & Courchesne, 1992; Justus & Ivry, 2001). Second, smaller effect sizes notwithstanding, interventions to ameliorate brain tumor sequelae may be *more* effective when applied to these less-damaged children—moving more of them into the normal range, an important consideration for ''clinically significant'' change (Kendall, Marrs-Garcia, Nath, & Sheldrick, 1999). Third, this research offers a more sensitive metric for ascertaining costs and benefits associated with more and less aggressive surgery, as has been demonstrated in the case of craniopharyngioma where less aggressive surgery results in decreased morbidity (Merchant et al., 2002).

There is also the matter of the repeated treatments these patients often undergo. For patients with subtotal resections, half or more will have recurrences requiring further treatment (Palma & Guidetti, 1985). Presently, little is known about the neurobehavioral outcome after a single treatment, and almost nothing about morbidity associated with recurrences and subsequent therapies. Finally, low grade astrocytoma has the highest incidence and highest rate of long-term survival of any pediatric brain tumor. For this reason alone, it is deserving of greater attention from neurobehavioral late effects researchers.

Conclusions

A succinct reply to the question originally posed in the title of this article would be as follows: We have developed better methods for studying the sequelae of pediatric brain tumors including better research designs, improved measurement of behavioral dimensions, refinements in characterization of radiation injury to the brain, and improved models for relating ''proximal'' changes in the brain (via imaging) to ''distal'' alternations in neurodevelopmental trajectories. These advances have not only informed the development of less toxic treatments, but are beginning to yield interventions that change the outcomes for these children. Yet we are a long way from fulfilling Johnny Gunther's prediction about the triumph of science over disease. What has emerged over the last few decades, though, is a partnership between biomedical science and behavioral science that has helped to reframe the task before us from one of simply survival, to the quality of survival. Whereas early in the progression investigators applied generic methodologies in the measurement of behavioral late effects, there are now methodological and theoretical models increasingly tailored to pediatric brain tumors. While progress has been more incremental than dramatic, the suffering of patients and their families is slowly yielding to these efforts, and no one has worked at this task more earnestly and effectively than the man being honored in this special issue of the *Journal of Pediatric Psychology*.

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References

Akshoomoff, N. A., & Courchesne, E. (1992). A new role for the cerebellum in cognitive operations. *Behavioral Neuroscience, 106*, 731–738.

Albright, A. L., Wisoff, J. H., Zeltzer, P. M., Deutsch, M., Finlay, J., & Hammond, D. (1989). Current neurosurgical treatment of medulloblastomas in children. A report from the Children's Cancer Study Group. *Pediatric Neuroscience, 15(6), 276–282.*

Armstrong, F. D., Blumberg, M. J., & Toledano, S. R. (1999). Neurobehavioral issues in childhood cancer. *School Psychology Review, 28*, 194–203.

Barakat, L. P., Hetzke, J. D., Foley, B., Carey, M. E., Gyato, K., & Phillips, P. D. (2003). Evaluation of social skills training group intervention with children treated for brain tumors: A pilot study. *Journal of Pediatric Psychology, 28*, 299–307.

Barendsen, G. W. (1990). Mechanisms of cell reproductive death and shapes of radiation dose-survival curves of mammalian cells. *International Journal of Radiation Biology, 57*, 885–896.

Beebe, D. W., Ris, M. D., Armstrong, F. D., Fontanesi, J., Mulhern, R., Holmes, E., et al. (2005). Cognitive and adaptive outcome in low grade pediatric cerebellar astrocytomas: Evidence of increased risk in national collaborative research studies (CCG9891/POG9130). *Journal of Clinical Oncology, 23*, 5198–5204.

Bloom, H. J. G., Wallace, E. N. K., & Henk, J. M. (1969). The treatment and prognosis of medulloblastoma in children. *American Journal of Roentgenology, 105*, 43–62.

Butler, R. W., & Copeland, D. R. (2002). Attentional processes and their remediation in children treated for cancer: A literature review and the development of a therapeutic approach. *Journal of International Neuropsychological Society, 8*, 115–124.

Deutsch, M., Thomas, P. R., Krischer, J., Boyett, J. M., Albright, L., Aronin, P., et al. (1966). Results of a prospective randomized trial comparing standard dose neuraxis irradiation (3,600 cGy/20) with reduced neuraxis irradiation (2,340 cGy/13) in patients with low-stage medulloblastoma. A Combined Children's Cancer Group-Pediatric Oncology Group Study. *Pediatric Neurosurgery, 24*, 167–176.

Fan, J., McCandliss, B. D., Sommer, T., Raz, A., & Posner, M. I. (2002). Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience, 14*, 340–347.

Fletcher, J. M., & Copeland, D. R. (1988). Neurobehavioral effects of central nervous system prophylactic treatment of cancer in children. *Journal of Clinical and Experimental Neuropsychology, 10*, 495–538.

Fry, A. F., & Hale, S. (1996). Processing speed, working memory, and fluid intelligence: Evidence for a developmental cascade. *Psychological Science, 7*, 237–241.

Gioia, G. A., Isquith, P. K., Retzlaff, P. D., & Espy, K. A. (2002). Confirmatory factor analysis of the behavior rating inventory of executive function (BRIEF) in a clinical sample. *Child Neuropsychology, 8*, 249–257.

Gunther, J. (1949). *Death Be Not Proud*. New York: Harper Perennial.

Justus, T. C., & Ivry, R. B. (2001). The cognitive neuropsychology of the cerebellum. *International Review of Psychiatry, 13*, 276–282.

Kazak, A. E. (2005). Evidence-based interventions for survivors of childhood cancer and their families. *Journal of Pediatric Psychology, 30*, 29–39.

Kendall, P. C., Marrs-Garcia, A., Nath, S. R., & Sheldrick, R. C. (1999). Normative comparisons for the evaluation of clinical significance. *Journal of Consulting and Clinical Psychology, 67*, 285–299.

Khong, P. L., Leung, L. H. T., Fung, A. S. M., Fong, D. Y. T., Qui, D., Kwong, D. L. W., et al. (2006). White matter anisotropy in post-treatment childhood cancer survivors: Preliminary evidence of association with neurocognitive function. *Journal of Clinical Oncology, 24*, 884–890.

Koocher, G. P., & O'Malley, J. E. (Eds) (1981). *The Damocles syndrome: Psychosocial consequences of surviving childhood cancer*. New York: McGraw-Hill.

Merchant, T. E., Kiehna, E. N., Kun, L. E., Mulhern, R. K., Li, C., Xiong, X., et al. (2006). Phase II trial of conformal therapy for pediatric patients with craniopharyngioma an correlation of surgical factors and radiation dosimetry with change in cognitive function. *Journal of Neurosurgery, 104*, 94–102.

Merchant, T. E., Kiehna, E. N., Li, C., Xiong, X., & Mulhern, R. K. (2005). *International Journal of Radiation Oncology, Biology, and Physics, 63*, 1546–1554.

Merchant, T. E., Kiehna, E. N., Sanford, R. A., Mulhern, R. K., Thompson, S. J., Wilson, M. W., et al. (2002). Craniopharyngioma: The St. Jude Children's Research Hospital experience 1984–2001. *International Journal of Radiation Oncology, Biology, and Physics, 53*, 533–542.

Mulhern, R. K., Crisco, J. J., & Kun, L. E. (1983). Neuropsychological sequelae of childhood brain tumors: A review. *Journal of Clinical Child Psychology, 12*, 66–73.

Mulhern, R. K., Khan, R. B., Kaplan, S., Helton, S., Christensen, R., Bonner, M., et al. (2004). Short-term efficacy of methylphenidate: a randomized, double-blind, placebo- controlled trial among survivors of childhood cancer. *Journal of Clinical Oncology, 22*, 4795–4803.

Mulhern, R. K., Merchant, T. E., Gajjar, Reddick, W. E., & Kun, L. E. (2004). Late neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet Oncology, 5*, 399–406.

Mulhern, R. K., & Palmer, S. L. (2003). Neurocognitive late effects in pediatric cancer. *Current Problems in Cancer, 27*, 177–197.

Mulhern, R. K., Reddick, W. E., Palmer, S. L., Glass, J. O., Elkin, T. D., Kun, L. E., et al. (1999). Neurocognitive deficits in medulloblastoma survivors and white matter loss. *Annals of Neurology, 46*, 834–841.

Myers, C., Stuber, M. L., Bonamer-Rheingans, J. I., & Zeltzer, L. K. (2005). Complementary therapies and childhood cancer. *Cancer Control, 12*, 172–180.

Nagel, B. J., Palmer, S. L., Reddick, W. E., Glass, J. O., Helton, K. J., Wu, S., et al. (2004). Abnormal hippocampal development in children with medulloblastoma treated with risk-adapted irradiation. *American Journal of Neuroradiology, 25*, 1575–1582.

Otsuka, S., Coderre, J. A., Micca, P. L., Morris, G. M., Hopewell, J. W., Rola, R., et al. (2006). Depletion of neural precursor cells after local brain irradiation is due to radiation dose to the parenchyma, not the vasculature. *Radiation Research, 165*, 582–591.

Palma, L., & Guidetti, B. (1985). Cystic pilocytic astrocytomas of the cerebral hemispheres. Surgical experience with 51 cases and long-term results. *Journal of Neurosurgery, 62*, 811–815.

Palmer, S. L., Reddick, W. E., Glass, J. O., Gajjar, A., Goloubeva, O., & Mulhern, R. K. (2002). Decline in corpus callosum volume among pediatric patients with medulloblastoma: Longitudinal MR imaging study. *American Journal of Neuroradiology, 23*, 1088–1094.

Palmer, S. N., Meeske, K. A., Katz, E. R., Burwinkle, T. M., & Varni, J. W. (in press). The PedsQL brain tumor module: Initial reliability and validity. *Pediatric Blood and Cancer*.

Reimers, T. S., Ehrenfels, S., Mortensen, E. L., Schmiegelow, M., Sonderkaer, S., Carstensen, H., et al. (2003). Cognitive deficits in long-term survivors of childhood brain tumors: Identification of predictive factors. *Medical and Pediatric Oncology, 40*, 26–34.

Ris, M. D. (2001). Methodological developments in the neuropsychology of pediatric brain tumors. *Journal of the International Neuropsychological Society, 7*, 213.

Ris, M. D., & Noll, R. B. (1994). Long-term neurobehavioral outcome in pediatric brain-tumor patients: Review and methodological critique. *Journal of Clinical and Experimental Neuropsychology, 16*, 21–42.

Ris, M. D., Ryan, P. M., Lamba, M., Brenemen, J., Cecil, K., Succop, P., et al. (2005). An improved methodology for modeling neurobehavioral late-effects of radiotherapy in pediatric brain tumors. *Pediatric Blood & Cancer, 44*, 487–493.

Ronning, C., Sundet, K., Due-Tonnessen, B., Lundar, T., & Helseth, E. (2005). Persistent cognitive dysfunction secondary to cerebellar injury in patients treated for posterior fossa tumors in childhood. *Pediatric Neurosurgery, 41*, 15–21.

Sahler, O. J., Varni, J., Fairclough, D., Butler, R., Dolgin, M., Phipps, S., et al. (2002). Problem-solving skills training for mothers of children with newly diagnosed cancer: A randomized trial. *Developmental and Behavioral Pediatrics, 23*, 77–86.

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A reformulation and review of evidence for threshold theory. *Neuropsychology, 7*, 273–295.

Schmahmann, J. D., & Sherman, J. C. (1998). The cerebellar cognitive affective syndrome. *Brain: A Journal of Neurology, 121*, 561–579.

Shatz, J., Kramer, J. H., Ablin, A., & Matthay, K. K. (2000). Processing speed, working memory, and IQ: A developmental model of cognitive deficits following cranial radiation therapy. *Neuropsychology, 14*, 189–200.

Vannatta, K., Gartstein, M. A., Short, A., & Noll, R. B. (1998). A controlled study of peer relationships of children surviving brain tumors: Teacher, peer, and self-ratings. *Journal of Pediatric Psychology, 23*, 279–287.

Wisoff, J. H., Boyett, J. M., Berger, M. S., Brant, C., Li, H., Yates, A. J., et al. (1998). Current neurosurgical management and the impact of the extent of resection in the treatment of malignant gliomas of childhood: A report of the Children's Cancer Group trial no. CCG-945. *Journal of Neurosurgery, 89*, 52–59.