The direct, indirect, and treatment-related effects of cancer on the nervous system have received variable attention by neurologists over the past century. The diseases encompassed in the neuro-oncology field and our understanding of them have increased rapidly during the past 30 years. In part, progress has been driven by technological achievements in neuroimaging, in particular, computed tomography and magnetic resonance imaging. These advances have allowed unprecedented opportunities to view the anatomy and pathology of the central nervous system (CNS) and, to an extent, portions of the peripheral nervous system that could be affected by cancer or its treatment. Clear gains have occurred in diagnostic accuracy, neurosurgical safety, ease of tumor resection, and safer and more accurate radiotherapy. After carmustine chemotherapy was introduced in the late 1960s, neurosurgeons and a new breed of physician, the neuro-oncologist, investigated the clinical benefits of an increasing number of anticancer agents against gliomas, medulloblastomas, and metastatic tumors in the CNS. In parallel, another sector of neuro-oncology developed that was more closely allied with neurology. The focus of this activity was in correlative neurology and pain management issues.

To clarify the importance of the growth and success of the field of neuro-oncology, I will briefly address the (1) research being done to achieve a better understanding of how and why central nervous system (CNS) tumors grow, (2) therapeutic strategies used to improve survival for patients with CNS tumors, (3) methods for improving the neurocognitive function and quality of life of patients with CNS tumors, and (4) training of fellows and young faculty members to meet the demands of neuro-oncology in the 21st century. Thirty years ago, few physicians and doctorate degree holders were conducting brain tumor research—so few, in fact, that the first Conference on Brain Tumor Research and Therapy held at Asilomar, Calif, in 1975 attracted only 35 people. Today, there are neuro-oncology organizations in Europe, Japan, and North America, with combined membership estimates exceeding 1000. There are also separate sections of neurosurgical and neurological societies that represent hundreds of members who are also interested in the field of neuro-oncology. Also, in the United States alone, at least 4 philanthropic organizations raise millions of dollars yearly to support neuro-oncologic research (primarily for brain tumors). Neuro-oncology has come a long way over the past 25 to 30 years.

My contributions to and interest in the field of neuro-oncology have been narrowly focused on the treatment and evaluation of patients with cancers growing in the CNS and the optimization of their quality of life, on research that would enable better treatments, and on the training of physicians who wish to specialize in neuro-oncology. I have certainly not been alone in these endeavors and have had the good

From the Department of Neuro-Oncology, University of Texas M. D. Anderson Cancer Center, Houston.
fortune to have worked with outstanding clinicians and scientists at the University of California, San Francisco, Medical Center and the University of Texas M. D. Anderson Cancer Center, Houston. As we approach the next century, I take pride in my contributions to what is today the vocational subspecialty of neuro-oncology, but I remain impatient for more substantial progress in the treatment of CNS tumors.

I would like to take this opportunity to look forward to the challenges and opportunities that face neuro-oncologists in the 21st century. A quote from the opening line of Dickens’ *A Tale of Two Cities* aptly reflects my position, “It was the best of times, it was the worst of times.” The scientific knowledge of cancer and the nervous system that will allow medical scientists to devise better therapies for the treatment of neoplasia is moving forward with breathtaking speed. Although this technology is nearly palpable, our current knowledge is inadequate to improve the lot of the patient with CNS cancer. Some areas have advanced, while others have not. On the one hand, there has been virtually no improvement in the survival of patients with glioblastoma multiforme over the past 25 to 30 years (Table). On the other hand, the median survival for patients with anaplastic astrocytoma has increased from 82 weeks to 4 years, and patients with anaplastic oligodendroglioma have a median survival of more than 7 years. Unfortunately, the treatment of these cancers still requires that we irradiate the CNS (and peripheral nerves), but we have not yet found a way to avoid the resulting neurocognitive impairment and pain.

**RESEARCH TO UNDERSTAND HOW AND WHY CNS TUMORS GROW**

The convergence of research technologies and knowledge about cancer and the developmental biology of the supporting nervous system will define the best targets for anticancer therapies. The number of known genetic and heritable factors that lead to cancer in general, as well as those that lead to specific histologic cancers, grows weekly. Today, we can implicate the genes as being important in the genesis of astrocytic neoplasms. The importance of abnormalities in chromosomes 1 and 19 in oligodendrogliomas is being studied, but the genes involved have not yet been elucidated. The list of genes involved in glioma malignancy, lineage, and patterns of spread continues to grow as well.

Many of us in the cancer field expect that the National Genome Project and other research supported by the National Institutes of Health in Bethesda, Md, will likely provide most of the useful genetic information needed to fully conceptualize the genesis of primary gliomas and medulloblastoma within the next decade. To identify potential targets for antitumor drug development, the genetic information will have to be translated into a clear understanding of signaling pathways that regulate the cell cycle, apoptosis, and angiogenesis in each unique histologic type of brain tumor. Therefore, unless some unforeseen scientific discovery takes place in the near future, research to elucidate these targets and the development of therapeutic strategies to interfere with and/or mimic targets could, unfortunately, take decades.

**THERAPEUTIC STRATEGIES TO IMPROVE SURVIVAL IN PATIENTS WITH PRIMARY OR SECONDARY CNS TUMORS**

Even with the growing interest in and support for brain tumor research, there remains much that must be done to improve therapy. There is a consensus among those who are involved with chemotherapy for CNS tumors that the benefits of cytotoxic drugs have reached a plateau, and there is little expectation that more inventive cytotoxic drug combinations will lead to better control of CNS tumors. Where does the future of therapy lie? The direction of academic-industrial efforts is focused on drugs and antibodies that interfere with tumor angiogenesis, invasion, and receptor-initiated signaling. The reason for focusing on these targets is that the uncontrolled growth of tumor cells requires that their environment remain hospitable. Thus, if there is an insufficient supply of oxygen and other nutrients to support viability and growth, tumor cells become stressed and initiate strategies to survive. Such a survival repertoire causes tumor cells to (1) stop dividing and conserve energy (G₀ state), (2) secrete proteins that will stimulate new blood vessels (angiogenesis), (3) seek a more hospitable environment by active migration away from the main tumor mass (invasion), and/or (4) die for the good of the many (programmed cell death or apoptosis). Many of today’s therapeutic strategies are logically aimed at actively competing with this tumor survival repertoire.

Angiogenesis in gliomas is stimulated by vascular endothelial growth factor (VEGF) and, to a lesser extent, basic fibroblast growth factor and lesser cytokines. To counteract angiogenesis, a variety of drugs have been evaluated in patients. They include interferon alfa, interferon beta, 13-cis-retinoic acid, all-trans-retinoic acid, and thalidomide. Newer agents include a fumagillin analog (TNP-470), antibodies to compete with the vascular endothelial growth factor receptor, and drugs to block
the protein tyrosine kinase activity of the vascular endothelial growth factor receptor and/or the fibroblast growth factor receptor.

Today, drugs to block tumor cell invasion are directed toward protease secretion by tumor cells. There is an association among the various grades of astrocytic tumors and a large number of proteases such that the higher the grade of malignancy, the higher the level of protease. 4 Inhibitors directed against 72- and 92-kd gelatinases, such as collagenase type IV, appear to block the movement of invasion of glioma cells into cellular invasion models and to produce antitumor activity in animal models. The first clinical trial of such an inhibitor, marimastat, was recently completed in patients with glioblastoma. Other trials using protease inhibitors are being conducted or are being planned. Also, it appears that most of the anti-invasion drugs studied have antiangiogenic properties as well.

To maximize the antitumor activity of both antiangiogenic and anti-invasion drugs, it seems logical and experimentally feasible to combine other types of drugs to activate tumor cell apoptosis. Today, this can be achieved by the coadministration of DNA-damaging cytotoxic drugs. It is reasonable to assume that future drugs that effectively interfere with important signaling pathways may also work to effect apoptotic cell death with fewer systemic toxic effects.

If one views tumor cells in a hostile environment as being stressed, then a variety of strategies may lead the tumor cell to apoptosis. Someday, we should have drugs that can more selectively induce apoptosis in tumor cells without undue systemic toxic effects. As we learn more about apoptotic pathways, it becomes increasingly likely that drugs will be forthcoming to activate caspases and other important enzymes involved in apoptotic pathways.

There has been interest in drugs that can change the malignant tumor phenotype to a less malignant phenotype. 2 For high-grade gliomas, 13-cis-retinoic acid has been shown to be active in patients with glioblastoma. 6 From a treatment perspective, the fact that dedifferentiation leads to cytostasis rather than tumor cell death suggests that it may be inferior to a strategy that leads to apoptotic cell death.

The delivery of genes or gene products into tumor cells has received and will continue to receive a great deal of interest among the medical and lay communities. The problem with this approach is not what should be delivered into the tumor cell, but rather how to deliver the gene or gene product into all the tumor cells. 7 A variety of viral and nonviral vectors are under investigation. To date, however, no one has overcome the problem of the effective delivery of genes to the tumor cell. In brain tumors, local delivery of viruses and virus-producing cells by stereotactic administration, direct injection at the time of open surgery, or administration in the tumor cavity has been used, with evidence of only localized effect and no survival benefit. 8 If someone can develop a vector approach that allows the delivery and incorporation of gene or gene products into all tumor cells, the cure of CNS tumors will be a reality; if not, this approach will never be widely applicable.

IMPROVING THE NEUROCOGNITIVE FUNCTION AND QUALITY OF LIFE OF PATIENTS WITH CNS TUMORS

Had we more effective forms of chemotherapy, we could eliminate radiotherapy and neurotoxic chemotherapy for CNS tumors. Since we cannot yet replace these treatments, we must contend with the neurotoxic effects. From the results of careful magnetic resonance imaging and neurocognitive testing over the past 5 years, we know that more than 20% of people who receive cranial irradiation (frequently with cytotoxic chemotherapy) will suffer significant CNS damage and neurocognitive impairment. 9 We also know that a large number of patients who receive irradiation to peripheral nerves and their plexuses develop painful sequelae and decreased function. 10

Also, many of the drugs we administer impair neurocognitive function and are toxic to peripheral and cranial nerves. The list of drugs is quite long and appears to be increasing. Drugs in this group include interferon alfa, interferon beta, cisplatin, vincristine, procarbazine, paclitaxel, cytosine arabinoside, methotrexate, and many others.

It is clear that we must develop more selective and specific anticancer therapies to reduce neurotoxicity. At the same time, we need to devise approaches to deal as best as we can with neurological and behavioral/emotional deficits. One approach that we have taken is similar to that used in patients with brain injuries: the use of oral methylphenidate hydrochloride. We have found measurable improvement in neurocognitive testing, urinary continence, energy level, ability to work, and overall quality of life when this drug is used. 11 More efforts in this direction can lead to immediate benefit for the patient with brain tumor.

TRAINING OF FELLOWS AND YOUNG FACULTY MEMBERS TO MEET THE DEMANDS OF NEURO-ONCOLOGY IN THE 21ST CENTURY

Throughout the fields of medicine and scientific research, we see the value of and need for multidisciplinary practice and collaboration. The practice of clinical neuro-oncology is not a solo activity; it requires close and constant interaction with physicians in the specialties of neurosurgery, neuroradiology, neuropathology, radiation oncology, neuropsychology, and, depending on the practice and location, adult and pediatric medical oncology. The training of young physicians is not currently a board-approved subspecialty. There are several reasons for this; eg, physicians who enter the field of neuro-oncology come from adult and pediatric neurology as well as from adult or pediatric medical oncology, and the number of neuro-oncology practitioners needed is not great because primary CNS malignancies represent approximately 17 000 new cases per year in the United States and metastatic tumors in the CNS another 85 000 cases.

For the field of neuro-oncology to advance, we need to train good clinicians who are capable of diagnosis, treatment, and overall management of the direct and indirect neurological effects of cancer on the nervous system. Also, we must continue to produce outstanding physician-scientists
to do informative translational research. Given the breadth of effects that cancer has on the nervous system and the lack of fellowship candidates today whose research is focused on neuro-oncology, it will be important to create academic paths and provide support for those applicants with special research skills. In addition, it will be important to provide opportunities for those seeking to develop careers with research as a primary focus. The American Brain Tumor Association has been a strong advocate for research and has supported 134 researchers over the past 25 years. The National Institutes of Neurological Disease and Stroke has also supported, through training programs primarily in neurosurgery, postgraduate training in neuro-oncology. We need greater funding for these postgraduate opportunities, especially for neurologists. I also believe that we need support for entry-level faculty members to allow them the time and mentor guidance to hone their skills over the course of their assistant professorship. In 1998, the National Institutes of Health announced the creation of such a program. It may be, however, that we must look for other sources of support to increase the number of young faculty members with neuro-oncology interests.

CONCLUDING REMARKS

These are very exciting times in science and medicine. As neuro-oncologists, we must be thoughtful and innovative in the design of treatments and interventions for patients with CNS tumors and continue to use our skills to maximize the quality of life of our patients. As academicians, we must continue to encourage bright minds to enter the field of neuro-oncology, support their learning of multidisciplinary tools, and ensure opportunities for them after their training is completed.

Accepted for publication December 16, 1998.

Reprints: Victor A. Levin, MD, Department of Neuro-Oncology, Box 100, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

REFERENCES