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ELAINE C. JONES, MD
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I am a clinical neurologist. I’m not a health care economist or insurance policy expert. But, like most people, I have some moral code, and have read, with great anger, the various news reports of a handful of pharmaceutical companies destroying lives with price gouging.

I found the U.S. Senate’s Special Committee on Aging’s report on price gouging in the pharmaceutical industry (https://www.aging.senate.gov/imo/media/doc/Drug%20Pricing%20Report.pdf), summarizing some of the more outrageous behaviors I’ve read about before. This isn’t the routine sort of price gouging that has been the norm, where Americans are charged double or more than Canadians or Europeans, or the collusion that characterizes the otherwise peculiar paradox where the development of more drugs to treat multiple sclerosis increases rather than decreases their price, despite the development of generics, and the increased competition.

The Report focuses on only four companies, noting that three of them had been newly taken over by hedge funds, which had no experience with pharmaceutical companies or, apparently, with normal human values. The report opines that the funds were responding to their investors, although one assumes that the hedge fund managers, who take a percentage of the cut, are the major “deciders” of what happens and the investors close their eyes to the carnage in order to not sully the enjoyment of their increasing bank accounts.

The following characteristics are shared by the economic model: each drug was the “gold standard” treatment for a particular disorder, reducing the competition; the market was small, making it unlikely that a competing company would emerge or that the affected population would be able to mount a significant opposition; distribution of the drug was closed, that is, a designated distribution company was used, rather than general pharmacies, again, reducing competition; and, finally, price gouging.

The price gouging is impressive. Dara-prim’s price increased from $13.50 to $750 per tablet; Thiola went from $1.50 to $30.00 per tablet; Seromycin, a drug for multiple drug-resistant tuberculosis, an increasingly worrisome scourge for the whole world, particularly the poorer parts, went from $500/30 days to $10,800; Valeant, the only actual drug company among the four targeted by this report, increased the price of two drugs for Wilson’s disease, one of the rare, treatable neurodegenerative disorders, from $500/30 days to $24,000.

And, in case you think there have been typos with the number of zeros, you are mistaken. To top it off, all the drugs were available before 1990, some in the 1950s and ‘60s.

The Senate report indicates that the investors were fully aware of the business model and approved it. I am unsure if they would endorse the famous line of Gordon Gecko, in the movie, Wall Street, “Greed is good.” My guess is that they would not have used the word “greed,” and they would simply have said they were doing their job for their family, making them financially more secure. I doubt they actually took pleasure in thinking about the patients who would no longer be able to treat their disorders, about a 20-year-old girl whose liver and brain are failing, making her unable to care for herself, and, perhaps, ultimately, a ward of the state. I doubt they think about the implications of not treating multidrug-resistant TB for the whole world, including, perhaps their children.

The question is not why they do it. Bad, immoral people are part of humanity. The question is what can we do about it? It would be nice to post some photos in the post office, or in the local newspaper. One of the principal actors for two of the companies, Martin Skrelli, actually appears to enjoy the attention, apparently feeling, like book publishers, that a bad review is better than no review. The Senate committee’s report was a great first step. It recommended
further steps, of course. It felt that anti-trust laws were unlikely to be helpful, that price transparency would be extremely helpful, but unlikely without legislation and that coupons and cost sharing with the company would be counterproductive, increasing costs for insurers and increasing the amount of drug prescribed. Most helpful, I think, would be their recommendation to allow temporary imports of the drug from other countries. I am pleased to note that since I wrote the first draft of this that Valeant has been devastated by a number of revelations, causing a dramatic drop in its value. I am unsure of the fate of the other companies, but recent newspaper reports indicate that other investment groups have found this business model appealing and hope to cash in on our patients’ misery.

We must keep in mind that what these four companies are doing is not much different than what we’ve recently seen with EpiPens, Narcan injections and newer forms of insulin. Drug companies are supposed to make money, however, they also have some responsibility to their clients, perhaps not a lot, but some. They are bullies without a moral conscience. I am not a believer in violence and abhor the death penalty, but crimes like these make me doubt my resolve.

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Hospitals can be dangerous places and not only for patients.

The yearly incidence of physical abuse of nurses by patients is reported to be 30%. When asked about violence during their career, 61% of nurses who reported violent incidents indicated patients as the aggressors (families and others also were perpetrators). Drugs and alcohol were involved in 58% of the incidents. Emergency room nurses were most at risk.

Can we predict which patients are potentially violent?

That is not easy. Persons in police custody are prime candidates. In the 11 years ending 2011, there were 154 “shootings with injury” on US hospital grounds. Twenty-nine percent of shootings in the ER were by patients in police custody, a number of whom were violent while trying to escape. Patients with delirium, alcohol or drug intoxication and psychotic behavior are prone to violent behavior. Patients, friends and families stressed by bad news, long waits and other frustrations may act out their anger.

The Occupational Safety and Health Administration (OSHA) reports that in 2014 there were 8 cases per 10,000 health care employees with violent injuries (80% inflicted by patients) serious enough to require time away from work. The rate in private industry was less than 2 cases per 10,000.

In addition to being dangerous, workplace violence is expensive. In one hospital system 30 injured nurses in one year incurred expenses of $94,156 ($78,924 for treatment and $15,232 for lost wages). The cost of replacing a nurse can range up to $100,000.

The number of violent acts against health care workers (HCW) is elusive. First, there is a lack of a standard definition of violence. Nurses and doctors report less than 30% of the violent incidents suffered and many health care workers assume that these incidents are “part of the job.” Interestingly, urban and suburban hospitals did not vary in the rate of violent incidents, though “high volume ERs and residential and day social services present the highest risk.”

There is a reluctance to report due to the feeling that the hospital administration disapproves of such reports and may look adversely at HCWs who make such reports. The new emphasis on “customer satisfaction” is also a deterrent to reporting. The business maxim that the “customer is always right” has become prevalent in the medical enterprise, but is harmful in these cases.

A rapid response by security officers when a violent act seems imminent or has happened is standard practice. But this deprives other areas of the hospital of security protection. Security officers called to cope with an urgent situation will not be able to protect the parking lot, for example. The most frequent site of shootings (41%) in hospitals is on the grounds outside the building.

Violence impinges on patient care in number of ways. Medical personnel may be reluctant to care for potentially violent patients, thus decreasing the care available to these patients. And post-violence psychological trauma may impair the ability of HCWs to care for all patients.

So what can be done?

First, health care facilities should prohibit all firearms from their premises, except those carried by law enforcement. Metal detectors, however, are not in general use due to the many entrances to hospitals, high volume of persons and the cost of staffing.

OSHA has detailed guidelines about violence in the healthcare setting. They emphasize three steps: 1. Prevention (transfer patient to a safe environment, verbal de-escalation, etc.); 2. Work place adaptations (panic buttons, site specific issues such as accessible exit routes, etc.) and 3. Root cause analyses of all incidents.

Education of all HCWs in techniques of de-escalation should be universal. Verbal techniques to lessen the potential for violence may be effective. But training in self-defense may also be reasonable. The American Association for Emergency Psychiatry has a protocol for
such interventions. One RI health care system has initial mandatory training for nurses, PAs, etc. but not for doctors. Annual refresher training [best practice standard] is not offered due to lack of resources.

Simple approaches such as having security personnel wear clothing that is not the typical police uniform can avoid triggering violence in some persons [such as gang members, patients with criminal background, etc.] who react negatively to police. Uniformed security officers, however, are more effective in other situations, so this approach is possible only in units with dedicated security personnel.

Most states, including RI, classify assaults on HCWs as felonies. Assault means an action intended to cause bodily harm [even if no harm results]. In RI “any person” who “knowingly and willfully” assaults a “health care provider” during treatment may be “imprisoned for up to 3 years and fined not more than $1500.” While this law is not likely to deter a patient in the throes of delirium, it may be a deterrent to others.

Verbal and low level physical abuses are precursors to physical violence. A “zero tolerance” for all abusive behavior, no matter how minor, with appropriate interventions designed to de-escalate the situation may prevent major episodes of violence. This approach means reporting of all such behavior to the institution. Most importantly, the staff must have confidence that the institution truly believes in this approach and is fully committed to react promptly.

After a violent incident occurs it is critical that the staff have prompt therapeutic interventions to assist in coping with the stress. Trained “trauma-informed” teams with special expertise offering personalized treatment are already in place in many RI hospitals and are important to the health of the victims. In situations where violent patients require prolonged care, transfer to a specialized unit may be the best option. Just as cases with massive injury are best treated in a level 1 trauma center, violent behavior, not responsive to initial intervention, may be best treated in a unit with expertise and resources in the many facets of this behavior. Unfortunately, such units may not be readily available.

One hospital system [822 beds] reported 42 workplace violent incidents in 2012. After adopting a comprehensive approach to workplace violence there were 19 incidents yearly in 2015 and 2016.

These approaches work. Our patients and staff deserve no less.

Author
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Sarah Brooke Stevens checks the recent issue of RIMJ during Daffodil Days at the Cliff Walk in Newport.

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Introduction to Recent Advances in Neurosurgery

ZIYA L. GOKASLAN, MD
GUEST EDITOR

It is absolutely my pleasure to share with you in this issue some of the recent advances in treating a variety of neurosurgical conditions at the Department of Neurosurgery of Rhode Island Hospital and Brown University.

The following contributions are included in this special focus section of the Rhode Island Medical Journal:

**Current Treatment of Metastatic Spine Tumors – Surgery and Stereotactic Radiosurgery** by Jared S. Fridley, MD, Jaroslaw T. Hepel, MD, and Adetokunbo A. Oyel ese, MD, PhD, describes our multidisciplinary approach to patient care and the incorporation of stereotactic radiosurgery as well as other minimally invasive procedures into our surgical treatment paradigm in caring for patients with metastatic spinal tumors.

**The Role of Radiation Therapy in the Treatment of Metastatic Brain Disease** by Sohail Syed, MD, and Deus Cielo, MD, is a comprehensive review which describes the use of a variety of radiation treatment modalities in managing patients with single and multiple brain metastases.

**Current Strategies in the Surgical Management of Ischemic Stroke** by Cody A. Doberstein, BS, Radmehr Torabi, MD; Sandra C. Yan, BS, BA; Ryan McTaggart, MD; Curtis Doberstein, MD, and Mahesh Jayaraman, MD, summarizes the transformation we have witnessed over the last several years in treating patients with major cerebral vessel occlusion via emergency endovascular thrombectomy, resulting in truly amazing restoration of neurological function for patients who would have otherwise been left with devastating permanent neurological deficits. Our multidisciplinary team of physicians is leading the field in this very exciting area with some of the best outcomes in the world.

**Rhode Island Hospital’s Contribution to the Field of Endoscopic Spine Surgery** by Albert E. Telfeian, MD, PhD; Adetokunbo A. Oyel ese, MD, PhD, and Ziya L. Gokaslan, MD, is a description of the groundbreaking work by Dr. Albert Telfeian, the Director of the Center for Minimally Invasive Endoscopic Spinal Surgery at Rhode Island Hospital and Brown University, which allows outpatient endoscopic surgical treatment of spinal cord and painful nerve root compression, using pencil-tip size incisions. We are truly among the world leaders in this very exciting field, which has dramatically shortened the recovery time from surgery while drastically improving patient outcomes.

**Updates On Chimeric Antigen Receptor-Mediated Glioblastoma Immunotherapy** by George Mao, MD, Prakash Sampsath, MD, and Sadhak Sengupta, PhD, is again amazing work, outlining how the patient’s own immune system, specifically his/her own killer T-cells can be conditioned to recognize tumor-specific chimeric antigens in patients with glioblastoma. We are about to start clinical trials to translate this groundbreaking discovery to the care of our patients.

**A Comprehensive Approach to Deep Brain Stimulation for Movement Disorders** by Umer Akbar, MD, and Wael F. Asaad, MD, PhD, is a description of the multidisciplinary approach that our physicians employ in evaluating patients with movement disorders such as Parkinson’s disease and the state-of-the-art surgical methods and technology they use in the operating room, with intraoperative, image-guided navigation, and electrophysiological recordings for precise placement of the deep brain electrodes used for stimulation.

**Recent Advances in the Treatment of Gliomas – Comprehensive Brain Tumor Center** by Steven A. Toms, MD, MPH, and Nikolaos Tapinos, MD, PhD, is a comprehensive review of the whole spectrum of treatment options including radiation, chemotherapy and immunotherapy in patients with gliomas. The article also describes the multidisciplinary approach employed by the Comprehensive Brain Tumor Center at the Lifespan Cancer Institute of Rhode Island Hospital and exciting ongoing translational research projects in our Brain Tumor Research Laboratories.

**Current Concepts in the Pathogenesis, Diagnosis, and Management of Type I Chiari Malformations** by Cody A. Doberstein, BS, Radmehr Torabi, MD, and Petra M. Klinge, MD, is an excellent review of the topic on this rare and often poorly understood condition and its neurosurgical treatment. Dr. Klinge is a worldwide expert and leads the Center for CSF Disorders of the Brain and Spine, where we at Rhode Island Hospital and Brown University offer state-of-the-art care to our patients.

This is just a brief summary of some of the very exciting work we are doing here at the Department of Neurosurgery of Rhode Island Hospital, the Norman Prince Neurosciences Institute and Brown University, on a daily basis.
We are also pleased to share with you that we have just moved into a dedicated neuroscience floor at Rhode Island Hospital, which also houses an 18-bed Neuro Intensive Care Unit and highly specialized physician and nursing teams. Similarly, we have a dedicated spine floor with specialized nursing staff where we care for our patients with the whole spectrum of spinal disorders.

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Recent Advances in Neurosurgery

ABSTRACT

There has been significant progress and innovation in the treatment of patients with metastatic spinal tumors over the last two to three decades that has impacted our ability to provide individualized care that improves a patient’s quality of life and degree of neurologic impairment. Advances in surgical techniques and radiation delivery modalities have dramatically improved our ability to decrease local tumor recurrence rates, improve pain control, and provide more durable spinal stability. Modern day spine tumor resection and reconstruction techniques have been shown to improve and prolong patients’ ability to ambulate, maintain continence, and reduce the need for pain medications. Spinal radiosurgery, the focused delivery of radiation to a target in the spine, has significantly enhanced the ability to provide a high degree of local tumor control in a non-invasive manner, even for tumors that are deemed radioresistant by conventional radiation therapy standards. In most patients, a combination of treatment modalities, including both surgery and radiation, is the mainstay of any comprehensive treatment plan for metastatic spinal tumors.

KEYWORDS: spine metastases, separation surgery, spinal radiosurgery, spine tumor, spine decompression

INTRODUCTION

Metastases are the most common spine tumor, with up to 40% of cancer patients developing spinal metastases, and 5-10% developing symptomatic epidural spinal cord compression. The spine is the most common site of skeletal metastases, with the thoracic spine being the most frequently involved spinal segment, followed by the lumbar and cervical spine. Advances in the treatment of cancer has led to improved patient survival, but also a higher incidence of patients with spinal metastases. The treatment of these patients has evolved substantially over the past several decades, with dramatic advances in both surgical and radiation therapies. In this paper, we summarize some of the more important advances in these respective fields.

SURGICAL ADVANCEMENTS

For many years, patients with metastatic spine tumors causing epidural spinal cord or nerve root compression were treated with simple posterior spinal decompression followed by fractionated external beam radiotherapy. While some patients did improve in terms of ability to ambulate and bowel/bladder function, the results weren’t encouraging. When compared to radiation alone the addition of a simple posterior decompression was not found to add any significant benefit in terms of pain, sphincter function, or improved ambulation. The disheartening results of such studies led to a decline in surgical intervention.

The primary problem with a simple posterior decompression of the spinal cord, which is typically done via laminectomy, is that in many patients, epidural compression is ventral to the spinal cord, not dorsal. This means that many patients continue to have ventral spinal cord compression despite a posterior decompression. Following the disappointing outcomes of earlier studies examining laminectomy and radiation for tumor treatment, surgeons began developing techniques to directly decompress the spinal cord with ventral tumor resection. The hope was that circumferential decompression of the spinal cord with instrumented stabilization of the spine might lead to improved outcomes. This was confirmed in a landmark randomized, prospective trial published in 2009 by Patchell et al. comparing radiation alone to radiation plus circumferential surgical decompression in patients with a single spinal metastasis compressing the spinal cord. The authors found that 84% of patients treated with both circumferential decompression and radiation were able to ambulate after treatment versus 57% patients who underwent radiation alone. In the group of patients unable to walk before treatment, 62% in the surgery group regained the ability to ambulate versus 19% in the radiation only group. This contrasts with the results of performing a laminectomy alone with radiation in the study by Young et al. in which 45% of patients were able to ambulate after treatment. The surgery plus radiation group was also able to walk for a longer period of time after treatment versus the radiation only group (122 days vs. 13 days). This study provides the best evidence to date that circumferential spinal cord decompression can significantly improve patient quality of life.

Pathologic fractures in patients with metastatic spine...
tumors without epidural compression often present with significant back pain. When unstable these fractures tend to be managed via surgical instrumentation. However, when neither gross instability nor significant epidual spinal cord compression exist, percutaneous vertebral body cement augmentation is a non-invasive method that can provide back pain relief. There are two primary methods of cement augmentation: balloon kyphoplasty and vertebroplasty, both of which have been shown to be effective for treating pain from pathologic fractures. These procedures involve injection of polymethylmethacrylate (PMMA) through the percutaneous insertion of a small metal trocar into the vertebral pedicle, followed by injection of cement under fluoroscopic guidance. With balloon kyphoplasty, a small inflatable balloon is inserted into the vertebral body and inflated to augment vertebral body height prior to injection of cement. Even in patients with significant vertebral body collapse, cement augmentation can be an effect option for pain relief, with a low overall complication rate.

**ADVANCES IN RADIATION TREATMENT**

Radiation delivery for spinal metastases has evolved substantially since the end of the 20th century. Traditional external beam radiation therapy (EBRT) consists of radiation delivered in a fractionated dose, typically 30 Gy over 10 fractions, and using simple one to two portal configurations that encompasses the area of disease with a wide margin of 1 vertebral level above and below. EBRT has been shown to be effective in treating very radiosensitive tumors such as multiple myeloma and lymphoma as well as moderately radiosensitive tumors such as breast and prostate cancer. However, EBRT has been shown to not be as effective in the treatment of more radioresistant tumors, such as sarcoma, melanoma and renal cell carcinoma. To maximize the dose of radiation delivered to a tumor target and minimize radiation toxicity to surrounding healthy tissues, advances in both computing hardware and radiation planning software were incorporated into treatment planning. This led to the development of conformal radiotherapy such as intensity modulated radiation therapy (IMRT), which utilizes sophisticated 3D planning and multi-leaf collimators that focus radiation to the intended tumor target and minimize dose to adjacent normal tissues. However, the radiation sensitivity of the spinal cord and its intimate location to metastatic disease in the vertebra, limits the safe delivery of only moderate doses of radiation (45-50 Gy in standard fractionation) with this technique.

The next significant advance in radiation therapy was the development of stereotactic radiosurgery to be delivered to spine lesions akin to stereotactic radiosurgery for brain metastases in the late 20th century. Radiosurgery consists of a single or hypo-fractionated dose of radiation delivered with extreme precision to the tumor target. Unlike cranial stereotactic radiosurgery, spinal radiosurgery has unique technical challenges. This includes dose limitations due to proximity of the spinal cord and spinal motion during radiation delivery. Unlike the head, which can be fixed in place using a stereotactic frame, the spine is more difficult to constrain. To overcome the problem of motion, immobilization devices coupled with real-time image guidance during treatment have been developed which allow for targeting accuracy to 1 mm or less. The extreme precision combined with sophisticated dose modulation allows for the delivery of high doses of radiation while still relatively sparing the spinal cord. This results in safe delivery treatment that is effective even for radiation-resistant histologies. Using single fraction dose equivalents of 18-24 Gy, studies have demonstrated a local tumor control rate of 80-96%, and a 86% chance of long-term pain relief.

**A NEW PARADIGM**

The success of spinal radiosurgery in terms of local control and pain relief of spinal tumors has dramatically altered treatment paradigms. It has supplanted both EBRT and surgery in the primary treatment of solitary spine tumors without significant epidural compression. In those patients with significant neural element compression, or in those patients with spinal instability due to an unstable pathologic fracture, surgery remains the gold standard. Similarly, EBRT continues to be used for the treatment of radiosensitive spinal metastases. To minimize surgical morbidity from an extensive circumferential decompression including vertebral body resection, Laufer et al have advocated ‘separation surgery’ which entails circumferential resection of epidural tumor, a limited resection of vertebral body tumor, followed by adjuvant radiosurgery to the remaining tumor and resection cavity. In their series of patients, Laufer et al reported a 4.1 – 22.6% local recurrence rate at 1 year depending on the radiation dose/fraction regimen utilized post-operatively. Despite these impressive results, further study is needed to determine whether this is a more efficacious strategy versus a more aggressive surgical resection and spinal reconstruction.

**CONCLUSION**

Recent advances in the surgical and radiation management of patients with spinal metastases has led to significant improvement in patient outcome. Despite these advances, treatment remains palliative. The goals of care should be to minimize patient morbidity, and maximize patient quality of life in terms of pain, mobility, and neurologic function. A multi-disciplinary approach to management of these patients that incorporates medical oncology, radiation oncology, and neurosurgery is necessary for optimal treatment planning in this complicated group of patients.
References


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ABSTRACT
Brain metastasis is the most frequent central nervous system malignancy. Although surgery and chemotherapy have roles to play in the treatment of brain metastasis, radiation therapy remains a mainstay of therapy. We will review the role of fractionated radiotherapy and stereotactic radiosurgery in the treatment of newly diagnosed and recurrent brain metastasis.

KEYWORDS: brain metastasis, radiotherapy, stereotactic radiosurgery

INTRODUCTION
In adult patients with cancer, 20-40% of ultimately develop brain metastases. Patterns of intracranial disease and factors influencing survival become important considerations when examining potential treatment options. METHODS: The records of 729 patients with metastases to the brain treated during the period between 1973 to 1993 were reviewed. RESULTS: Primary tumor histologic type in order of descending frequency included nonsmall cell lung carcinoma (NSCLC). Historically, the prognosis for these patients was poor, ranging from one month for untreated patients to four-to-six months in patients who received corticosteroids and whole brain radiation therapy (WBRT). Recently, changes in management have significantly improved the prognosis of patients, especially those with high functional status at time of diagnosis. While surgical resection has been increasingly employed for patients with limited disease, radiation therapy remains the mainstay of treatment for patients, either as a primary or adjuvant therapy. While the precise role of stereotactic radiosurgery (SRS) is still evolving, considerable body of evidence has confirmed the efficacy of both SRS and WBRT. In fact, the persistence of radiation therapy over time despite the emergence of alternative therapeutic modalities suggests that SRS and WBRT are likely to continue to play critical roles in the treatment of this patient population well into the future.

Brain metastases are the most common form of intracranial tumors. With an annual incidence of at least 200,000 cases in the United States, they are nearly ten times more common than primary malignant brain tumors. In 85% of cases, they are found in the cerebral hemispheres, but they can also involve the cerebellum and, very rarely, the brainstem. While brain metastases most commonly originate from primary tumors in the lungs, breast, or skin (melanoma), they can ultimately originate from any type of cancer. Patterns of intracranial disease and factors influencing survival become important considerations when examining potential treatment options. METHODS: The records of 729 patients with metastases to the brain treated during the period between 1973 to 1993 were reviewed. RESULTS: Primary tumor histologic type in order of descending frequency included nonsmall cell lung carcinoma (NSCLC). With improved management, a significant number of patients with brain metastases are living considerably longer compared to historic figures. In 2008, Sperduto et al. published a new prognostic assessment tool for patients with brain metastases called the Graded Prognostic Assessment (GPA). The GPA takes four aspects of a patient’s clinical status into account: age, Karnofsky Performance Status (KPS), the number of intracranial metastases, and the presence of extracranial metastases and found that a substantial number of patients with brain metastases, especially those with the highest GPA scores, were living longer than one year.

THE TREATMENT OF BRAIN METASTASES
Treatment regimens for brain metastases are frequently complex and multimodal. For symptomatic relief from brain edema, corticosteroids are used. Antiepileptics are often useful in controlling seizures in symptomatic patients. For definitive treatment, chemotherapy, radiation therapy, and surgery may be used.

Historically, radiation has played a dominant role in the treatment and palliation of brain metastases and was first described as a treatment for brain metastases in 1954 by Chao et al. In the 1980s, SRS was widely adopted to treat patients with a limited number of brain metastases. In 1990, the role of surgery was first established by Patchell et al., who demonstrated that patients with a solitary brain metastasis who underwent surgical resection and WBRT had lower rates of local recurrence, longer periods of functional independence, and improved overall survival as compared to patients who received WBRT alone. We randomly assigned patients with a single brain metastasis to either surgical
removal of the brain tumor followed by radiotherapy (surgical group) Numerous clinical trials have reinforced the roles of surgery and radiation in the management of these patients.

**WBRT**

Tumor metastases to the brain disseminate hematogenously and may thus seed broadly within it. The role of WBRT in the treatment of patients with brain metastases is thus twofold: to target both the macrometastases seen on imaging, as well as any micrometastases undetected by current diagnostic testing. By treating both visible and occult lesions, WBRT can improve neurologic symptoms in 63% of the patients treated. Further studies have found that WBRT decreases local recurrence rates, improves neurologic function, and improves overall survival in patients with brain metastases. Multiple clinical trials have established the efficacy of WBRT. Nonetheless, there is no Class I evidence that suggests that there is an advantage of a specific dose regimen with respect to overall survival, local control, or neurocognitive function. In common practice, though, the two most common schedules remain 30 Gray delivered in 10 fractions or 37.5 Gray delivered in 15 fractions.

Unfortunately, WBRT can cause side effects by causing tissue damage in its intended target or the surrounding tissues. In the acute period after receiving WBRT, days to weeks after treatment, patients most commonly may experience fatigue, nausea and vomiting, radiation dermatitis, and alopecia. Within one to six months of treatment, patients may experience a transient worsening of symptoms and, rarely, somnolence syndrome. In the delayed period, six months or more after treatment, patients can develop more permanent side effects, including radiation necrosis, vascular abnormalities, and cognitive deficits. Just six months after receiving WBRT, in fact, 50–90% of patients show evidence of radiation-induced cognitive impairment, including effects upon verbal and spatial memory, attention, and novel problem-solving ability. As patients with brain metastases live longer, increasing attention is being paid to the neurocognitive sequelae associated with WBRT. Not surprisingly, two controlled trials found worse neurocognitive outcomes in patients treated with WBRT and SRS compared to those treated with SRS alone.

Patients were stratified by recursive partitioning analysis class, number of brain metastases, and radioresistant histology. The randomisation sequence was masked until assignment, at which point both clinicians and patients were made aware of the treatment allocation. The primary endpoint was neurocognitive function: objectively measured as a significant deterioration (5-point drop compared with baseline) In response to these neurocognitive outcomes, hippocampal-sparing WBRT has been advocated and seems to have improved neurocognitive outcomes compared to traditional WBRT. Nonetheless, it is the total burden of brain metastases that is the most important factor in predicting the cognitive outcome in patients with brain metastases. Despite its adverse effects, WBRT remains a cornerstone of management of patients with brain metastases. WBRT is especially useful in treating patients who are not candidates for SRS or surgery due to a large number of intracranial metastases, poor performance status, tumor location, or leptomeningeal spread. Unfortunately, WBRT suffers from high rates of recurrence which are highly tumor histology dependent. Especially of tumor volume, on remission and to evaluate whether particular subgroups of metastases are controlled by low-dose radiotherapy.

The use of WBRT has also been explored as an adjuvant to surgery or SRS. In patients with 1–3 brain metastases, the addition of adjuvant WBRT to SRS or surgery has been shown to improve local control and decrease the risk of neurologic death, but it does not appear to extend the length of functional independence or improve overall survival. 199 underwent radiosurgery, and 160 underwent surgery. In the radiosurgery group, 100 patients were allocated to OBS, and 99 were allocated to WBRT. After surgery, 79 patients were allocated to OBS, and 81 were allocated to adjuvant WBRT. The median time to WHO PS more than 2 was 10.0 months (95% CI, 8.1 to 11.7 months)

**Stereotactic Radiation Surgery**

Gamma Knife, first developed by the Swedish neurosurgeon Lars Leksell in 1951, is the most widely used SRS device. 192 sources of cobalt-60 are organized around a circular frame that is secured to the patient’s head by four screws to ensure immobilization. During treatment, the sources of cobalt-60 produce gamma ray beams with an average energy of 1.25 MeV. The intersection of the beams, known as the isocenter, can be manipulated to ensure adequate coverage of the targeted lesion. While treatment time is variable, and depends on factors such as the number and morphology of the lesions to be treated, therapeutic radiation is delivered in a high-dose, single fraction. As a result, patients generally may return home on the same day of treatment.

Linear accelerator-based radiosurgery may be delivered in many different forms utilizing rigid, frame-based patient immobilization or mask-based frameless immobilization systems. CyberKnife, first developed by John Adler at Stanford University, utilizes image-guidance technology and a 6-MV linear accelerator with 12 circular collimators mounted upon a robotic arm to compensate for target movement when delivering treatment. Emerging technology that is a significant departure from current stereotactic radiosurgery and external beam radiotherapy technologies.
In its clinical application and quality assurance [QA X-ray images taken by mounted cameras during treatment adjust beam trajectory to ensure accuracy.31] Frameless SRS may enhance patient comfort and allows radiation treatment to be delivered in multiple fractions with impacting outcomes.32-34 Proximity to critical structures and variable tumor volumes. In this study, we investigate whether acceptable treatment plans with excellent conformity and homogeneity can be generated for complex skull base tumors using the Cyberknife® 4 In light of the complexity of treating patients with brain metastases, the input and cooperation of neurosurgeons, radiation oncologists, and medical physicists is required to assess the feasibility of SRS treatment plans.

SRS is increasingly being utilized and is capable of delivering high, focal doses of radiation that rapidly drop off outside of the targeted treatment volume. Patient survival with SRS treatment of brain metastases appears to be less influenced by tumor histology than WBRT and offers high rates of local control.35-37 The primary therapeutic aim is symptom palliation and maintenance of neurologic function, but in a subgroup, long-term survival is possible. Local control in the brain, and absent or controlled extracranial sites of disease are prerequisites for favorable survival. Stereotactic radiosurgery (SRS) Patients who receive SRS in the absence of adjuvant WBRT have an increased risk of recurrence in untreated areas of the brain.35,36 The primary therapeutic aim is symptom palliation and maintenance of neurologic function, but in a subgroup, long-term survival is possible. Local control in the brain, and absent or controlled extracranial sites of disease are prerequisites for favorable survival. Stereotactic radiosurgery (SRS) Despite this finding, there is no difference in overall survival between patients who received SRS alone and those who received SRS and WBRT.21,28,38 2001, to September 14, 2007. Patients were stratified by recursive partitioning analysis class, number of brain metastases, and radiosensitive histology. The randomisation sequence was masked until assignation, at which point both clinicians and patients were made aware of the treatment allocation. The primary endpoint was neurocognitive function: objectively measured as a significant deterioration [5-point drop compared with baseline.

Although SRS may be used as monotherapy, avoiding the negative neurocognitive effects associated with WBRT, it should be noted that SRS monotherapy increased overall survival in patients under 50, but decreased survival in patients over the age of 50 in one study.39 Additionally, SRS is not recommended for tumors greater than 40 millimeters in diameter because of the risk of radionecrosis in neighboring tissue. RTOG 90-05 found that the risk of neurotoxicity in patients treated with SRS was related to the size of metastases and established appropriate dose limits for SRS: 24 Gray for tumors less than 20 millimeters in diameter, 18 Gray for those 21–30 millimeters in diameter, and 12 Gray in those 31–40 millimeters in diameter.40 The efficacy of SRS monotherapy in patients with multiple brain metastases is the subject of ongoing research. A recent multi-institutional, prospective observational study in Japan found that the use of SRS alone was non-inferior in patients with 5–10 brain metastases as compared to its use in patients with 2–4 brain metastases. While more data is required to establish the superiority of SRS monotherapy over SRS and WBRT combination therapy in patients with 5–10 brain metastases, this study suggested that SRS alone may be a feasible treatment strategy in patients with up to 10 brain metastases.41

Since WBRT often fails to control local disease, the use of SRS as an adjuvant to WBRT alone was explored in RTOG 9508 in patients with 1–3 brain metastases. Both local control and KPS were improved in patients receiving SRS and WBRT versus those who received WBRT alone and patients with solitary metastasis, favorable tumor histology, or Recursive Partitioning Analysis Group 1 who received adjuvant SRS had a survival benefit.32 Similarly, a trial that analyzed patients with 2–4 brain metastases found that those who received WBRT and adjuvant SRS had lower rates of local recurrence and longer progression-free survival as compared to those who received WBRT alone; however, no statistically significant differences in overall survival were found.42 Frequently diagnosed in patients with cancer, the prognosis, even after treatment with whole brain radiation therapy (WBRT Likewise, after surgical resection, SRS has been found to increase rates of local control.43 SRS may also be used in the salvage setting. Untreated, recurrent brain metastases are typically fatal within 2–4 months. A retrospective review by Caballero et al. that analyzed 310 patients who received SRS for brain metastases after prior WBRT found that overall median survival was 8.4 months after receiving SRS. Patients with a solitary brain metastasis had a higher median survival at 12.0 months, while those with multiple brain metastases had a median survival of 7.9 months. In this study, every patient, regardless of the total number of brain metastases, benefited from receiving salvage SRS.45

CONCLUSION

While the treatment of patients with brain metastases remains challenging, the prognosis for these patients has improved significantly over the past two decades. Despite the many improvements in management that have been made, radiation therapy remains a cornerstone of treatment. For a significant number of these patients, including those with a large number of brain metastases, poor performance status, and leptomeningeal spread, WBRT remains a clearly-defined, first-line treatment option. The role of SRS, in contrast, is rapidly evolving. While SRS monotherapy is appropriate for properly selected patients with 1–4 brain metastases, its sole use in the treatment of patients with
5-10 brain metastases is the subject of ongoing investigation. Additionally, SRS has been shown to increase rates of local control as an adjuvant and salvage treatment in patients receiving WBRT or surgery. As further advances are made in the medical management of patients with brain metastases, including in the emerging field of immunotherapy, radiation therapy is likely to remain a useful tool in treating this population of patients.

References


Current Strategies in the Surgical Management of Ischemic Stroke
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ABSTRACT
Stroke is a major cause of death and disability in the United States and rapid evaluation and treatment of stroke patients are critical to good outcomes. Effective surgical treatments aim to restore adequate cerebral blood flow, prevent secondary brain injury, or reduce the likelihood of recurrent stroke. Patient evaluation in centers with a comprehensive stroke program and a dedicated neurovascular team is recommended.

KEYWORDS: stroke, embolectomy, cerebrovascular occlusion

INTRODUCTION
Stroke is the leading cause of long-term adult disability in North America and the fifth leading cause of death. Although some strokes are hemorrhagic, the majority (87%) are ischemic due to insufficient cerebral blood flow secondary to occlusion or flow limiting stenosis. Brain tissue is exquisitely sensitive to ischemia, and an estimated 1.9 million neurons die every minute that blood flow is not restored. Time is brain.

Surgical treatment for stroke can be classified into acute (emergent) or non-acute. Acute interventions, initiated within hours of stroke onset, are aimed at reestablishing cerebral blood flow, restoring lost neurologic function, and preventing permanent tissue damage. Non-acute surgical therapies focus on reducing secondary injuries resulting from brain swelling or preventing recurrent stroke.

The effective surgical management of stroke requires continuous and immediately available treatment by dedicated personnel specializing in complex cerebrovascular interventions. These requirements may be best accomplished in facilities with a dedicated neurovascular center and stroke program.

EMERGENT EMBOLECTOMY FOR STROKE
Intravenous tissue plasminogen activator (IV-tPA) remains an effective medical treatment in stroke patients if administered within 4.5 hours of symptom onset. However, 20–30% of acute ischemic stroke patients have evidence of large vessel occlusion (LVO) involving a major proximal intracranial artery and the efficacy of IV-tPA is significantly reduced in these cases. Furthermore, many patients do not fit the strict time window and inclusion criteria for the administration of IV-tPA and therefore are ineligible to receive treatment.

The recent refinement of endovascular catheter-based surgical techniques, which use a stent-retriever device to directly remove clots from occluded vessels and restore blood flow, have proven effective in reducing morbidity and mortality in stroke patients with LVO. Several recent randomized studies have demonstrated a significant benefit of embolectomy compared to standard medical treatment alone. Due to improved outcomes, embolectomy in combination with IV-tPA has now become the standard of care for patients with LVO stroke. Figure 1 demonstrates pre- and post-angiographic images in a patient who underwent emergent embolectomy and shows the dramatic improvement of cerebral perfusion following recanalization.

In addition to improving outcomes, embolectomy has less restrictive enrollment criteria and a longer time treatment window (usually 6 hours from stroke onset, though 12 or more hours in suspected basilar artery occlusion). It is estimated that the likelihood of a good outcome decreases by 10% for every 30-minute delay in recanalization from embolectomy, making efficient diagnosis and management critical. Computed tomographic angiography (CTA) can rapidly and accurately demonstrate the presence of an occlusion, and should be part of the minimum imaging workup for suspected stroke patients. A national study in 2015, led by members of our neurovascular team, identified several elements that are required to achieve timely revascularization in LVO patients. Expanding upon these findings, our Comprehensive Stroke Center (CSC) developed a standardized practice to decrease procedure times and initiated a protocol for LVO patients who first presented to an outside primary stroke center (PSC) to facilitate quick treatment (Figure 2). This method was designed to minimize waiting times for suspected LVO patients, getting them closer to intervention as soon as possible. Initial results demonstrate that when fully executed, median time from PSC arrival to CSC intervention was reduced from 151 to 111 minutes (p<0.0001). This protocol also made patients twice as likely to have a favorable outcome (50% vs. 25%). Evidence
strongly supports that prompt evaluation and treatment of stroke patients with documented LVO in centers capable of performing embolectomy is crucial to obtaining optimal clinical outcomes.

**DECOMPRESSIVE HEMICRANIECTOMY**

Despite acute interventions such as IV-tPA and embolectomy, up to 10% of ischemic strokes result in large areas of infarction. This can lead to significant brain swelling, raised intracranial pressure (ICP), and in severe cases, life-threatening herniation syndromes. These conditions are associated with worse outcomes, as they promote further reductions in cerebral blood flow leading to additional ischemic tissue damage (secondary brain injury).

Significant edema that occurs in the supratentorial space after a stroke is referred to as malignant infarction of the middle cerebral artery (MCA). This condition is associated with CT evidence of infarction involving at least 50% of the MCA territory or an infarct volume of greater than 145 cm³ on diffusion weighted magnetic resonance imaging (MRI). Despite aggressive medical management including hyperventilation, barbiturates, hyperosmolar therapy, and corticosteroids, malignant MCA infarctions have been associated with an 80% fatality rate. However, recent multi-center trials and pooled analyses strongly support the role of surgical intervention, consisting of a decompressive hemicraniectomy (DHC), in reducing mortality and disability after malignant MCA infarction in select patients. The surgical procedure involves removal of a large bone flap, followed by insertion of a dural patch. This results in reduced constriction of the injured brain and culminates in lower ICP and reduced risk of brain herniation.

Three European prospective, multi-center, randomized controlled trials have investigated the benefit of DHC versus medical treatment in patients with space-occupying hemispheric strokes and altered level of consciousness. The DESTINY trial enrolled patients, between 18 and 60 years of age, within 36 hours of stroke onset. The trial was terminated per the study protocol when statistical significance was reached for reduction in 30-day mortality in the surgical arm (88% of patients randomized to DHC versus medical treatment).
47% receiving conservative therapy survived after 30 days. DECIMAL randomized 38 patients, 18–55 years old, within 24 hours of stroke onset. There was a 52.8% absolute reduction in death in the surgical cohort. Lastly, the HAMLET trial included 64 patients between 18 and 60 years of age treated within 96 hours of symptom onset and found that DHC reduced case fatality by 38%. A pooled analysis of 94 patients from all three trials demonstrated a significant increase in favorable outcome in the DHC cohort. However, there was no statistically significant evidence in any individual trial regarding improved functional outcomes for patients undergoing DHC.

Current evidence suggests a role for DHC in patients younger than 60 with malignant infarction of the MCA associated with altered consciousness who are treated within 48 hours of stroke onset. For patients older than 60, surgical decompression is controversial. There are notable improvements in mortality, but many of the surviving patients have severe disability.

CAROTID ENDARTERECTOMY AND CAROTID STENTING

Carotid artery stenosis causes up to 10% of all ischemic strokes. The risk of recurrent stroke is significantly higher in patients who have previously suffered an initial stroke or transient ischemic attack (TIA). It is estimated that 25% of patients presenting with a stroke are suffering from a recurrent ischemic episode. The risk of stroke is particularly high in symptomatic patients who have severe narrowing of the extracranial internal carotid artery, and several large randomized studies have demonstrated the effectiveness of carotid endarterectomy (CEA) in reducing future stroke risk in these patients. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) reported that in symptomatic patients with greater than 70% carotid stenosis who undergo CEA, the absolute risk of future stroke is reduced by 17% compared to medical therapy alone, which has been confirmed by other large studies. Pooled analysis of three large trials of CEA versus medical therapy has shown a 16% absolute risk reduction when CEA was performed in patients with symptomatic stenosis of 70% or more. For patients with 50–69% stenosis, there was still a benefit but to a lesser degree. Patients with less than 50% narrowing of the carotid artery do not appear to benefit from surgical intervention.

Despite the proven effectiveness of CEA, carotid artery stenting (CAS) has been promoted as an attractive, less invasive option for revascularization. Potential advantages of CAS include decreased patient discomfort and a shorter recuperation period. Early studies indicated a higher procedural risk during CAS compared to CEA, but these studies have been criticized for inadequate and non-uniform operator experience. Furthermore, advances in endovascular techniques and devices used for CAS have made the procedure safer.

The largest trial to date, the Carotid Revascularization Endarterectomy versus Stent Trial (CREST) was a prospective, randomized trial of 2,502 patients comparing the efficacy of CAS with CEA. The primary endpoint was the composite of any stroke, myocardial infarction, or death during the periprocedural period and ipsilateral stroke within 4 years thereafter. The study found that CAS and CEA had similar outcomes, although there were varying complications with each intervention. The rate of any periprocedural stroke or post-procedural ipsilateral stroke within 30 days was significantly higher in the CAS group than in the CEA group (5.5% versus 3.2%). However, the rate of myocardial infarction was higher in the CEA group (2.3% versus 1.0%). Overall, the CREST study demonstrated that CAS and CEA had similar short- and long-term outcomes. Carotid artery stenting may prove especially useful in cases of surgically inaccessible lesions, radiation-induced stenosis, or in patients with severe cardiac or pulmonary disease.

To date, studies have shown that surgical interventions aimed at preventing stroke in patients who have already suffered a stroke or TIA from extracranial carotid stenosis have proven more effective than medical treatment alone. However, previous studies did not include optimal medical therapies such as statins. As advances in the medical treatment of stroke continue, it is imperative to compare these with both CEA and CAS. The CREST 2 trial currently underway attempts to compare current best medical therapy versus CEA and CAS.

EXTRACRANIAL TO INTRACRANIAL ARTERIAL BYPASS

Extracranial-intracranial (ECIC) bypass surgery has not been shown to provide any benefit for patients with atherosclerotic carotid occlusion or carotid artery narrowing distal to the carotid bifurcation. However, in patients with moyamoya disease or syndrome, ECIC bypass has been shown to be effective at reducing stroke risk.

Moyamoya can occur in children and adults and is a cerebrovascular condition that predisposes affected patients to stroke due to progressive stenosis of the intracranial internal carotid arteries and their branches (Figure 3a). Genetic factors play a role, and moyamoya can be associated with other conditions such as Down’s syndrome, sickle cell disease, neurofibromatosis, or previous cranial irradiation. If the disease is unilateral, or is associated with one of these conditions, it is called moyamoya syndrome. Moyamoya disease is bilateral and is not associated with other risk factors. Most patients present with stroke or ischemic symptoms with 50–75% of known moyamoya patients experiencing ischemic stroke.

It has been estimated that up to two-thirds of patients...
with moyamoya have symptomatic progression over a 5-year period with poor outcomes without treatment. Medical therapies have not been shown to be beneficial in reducing stroke risk and surgical revascularization (ECIC bypass) is the primary treatment for moyamoya. This procedure utilizes extracranial arterial supply (usually the superficial temporal artery) which is either directly or indirectly anastomosed to an intracranial cortical artery. Following ECIC bypass, there is a 96% probability of remaining stroke-free over the subsequent 5 years, and a meta-analysis concluded that 1003 of 1156 patients (87%) derived symptomatic benefit from surgical revascularization.

**FUTURE DIRECTIONS**

Time to treatment is a critical factor in improving outcomes in acute stroke, and the development of additional strategies to decrease time to intervention are warranted. Field triage based on clinical severity to a Comprehensive Stroke Center can help decrease time to treatment. Perhaps the ultimate solution, Mobile stroke ambulances (composed of trained medical personnel, a CT scanner, and telecommunications) can allow ultra-rapid patient assessment, in-field administration of IV-tPA, and rapid transport to a dedicated neurovascular center. Only a few units currently exist, but preliminary reports show improvement in treatment times and clinical outcomes.

The precise time window for acute embolectomy has not been fully evaluated. A select group of patients, with defined areas of reversible ischemia, may benefit from recanalization outside of the current time recommendations. Further refinement of patient selection using advanced CT or MR based imaging will likely allow us to offer treatment to a greater group of patients. In addition, as endovascular technologies continue to improve, treatment of non-LVO stroke patients with occlusion in smaller, more distal vessels may benefit from embolectomy.

Despite treatment, many stroke patients have permanent neurologic deficits such as hemiplegia, aphasia, or visual loss. Surgical techniques to restore function are needed. Stem cell transplantation, neuromodulation and cortical stimulation techniques, and brain-computer interface technologies have potential to improve neurorestoration and warrant future investigation.

**References**


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**Figure 3.** A) Lateral left ICA angiogram in a patient with moyamoya disease. The MCA is occluded and there is poor angiographic filling in the MCA territory. Small collateral vessels develop at the ICA terminus (arrow). B) Lateral left ICA angiogram in a patient who underwent a STA-MCA bypass for the treatment of moyamoya disease.


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A Comprehensive Approach to Deep Brain Stimulation for Movement Disorders

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ABSTRACT
Deep brain stimulation (DBS) is a well-established form of neuromodulation, used primarily for movement disorders such as Parkinson’s disease (PD) and Essential Tremor (ET). The selection of patients who will benefit most from DBS depends on a team of clinicians from various disciplines, including neurology, neurosurgery, psychiatry, neuropsychology and rehabilitation specialists. The actual surgical procedure can take many forms. We apply a combination of multidisciplinary, team-based evaluations and intra-operative neurophysiology, test stimulation and imaging to optimize DBS therapy for individual patients.

KEYWORDS: movement disorders, Parkinson’s disease, Essential Tremor, Deep Brain Stimulation, neurosurgery

INTRODUCTION
Neurosurgery for movement disorders has evolved dramatically over the past century culminating in the widespread acceptance and use of deep brain stimulation (DBS). While DBS has been and is being tested for a wide variety of neurological and psychiatric conditions (Figure 1), DBS is most widely used to treat the motor symptoms of two common movement disorders, Parkinson’s disease (PD) and Essential Tremor (ET). DBS surgery entails the insertion of electrodes (“wires”) into the brain through a small burr-hole and connected subcutaneously to a pacemaker-like battery powered device implanted in the chest wall. The implanted pulse generator battery is then programmed to deliver electrical stimulation to the brain to regularize, or at least limit, abnormal brain activity.

PD affects over 1 million people in the United States (US) and the prevalence is expected to double over the next two decades. The cardinal motor symptoms of PD – bradykinesia, tremor and rigidity – are often adequately treated with medications early in the course of the disease. As the disease progresses, patients develop medication-refractory tremor, motor fluctuations (early “wearing-off” of medication benefit) and dyskinesias, in addition to non-motor symptoms such as mood, cognitive, sleep and autonomic symptoms. The efficacy of DBS for these medication-refractory motor symptoms has been well established through several high-quality, randomized controlled trials.1-3 A meta-analysis of 22 studies demonstrated that subthalamic nucleus (STN) DBS improved motor symptoms (Unified PD rating scale, part 3) by 52%, dyskinesias 69%, off-periods 68%, and activities of daily living by 50%.4 Gpi DBS is also effective and is often favored for more severe dyskinesias or dystonias, and may have a slightly lower risk of cognitive- and mood-related adverse effects.5-7 Non-motor symptoms of PD do not directly respond to DBS but can improve indirectly. For example, a patient with difficulty sleeping or depressed mood due to excessive slowness and stiffness may feel improvement in these symptoms after DBS because of improved overall mobility and physical comfort.

In contrast to the resting tremor of PD, ET tremor is typically postural and worsens with movement. Early in the disease, patients with ET often manage their symptoms with behavioral modifications, without medications. Over time, increasing tremor amplitude may lead to difficulty with fine motor tasks, such as handwriting, eating, drinking and dressing. Medications can reduce tremor by about 50%, but benefit wanes over time as the tremor worsens. In these patients, DBS of the ventral-intermediate nucleus of the thalamus can reduce tremor by ~80% (range ~50–100%).8,9

Figure 1. Approved and Experimental Applications of DBS.

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* Approved under FDA Humanitarian Device Exemption (HDE)
** Approved in Europe; USA FDA approval anticipated
DBS for movement disorders should be considered when the quality of life becomes impaired by motor symptoms that are refractory to medical therapy. Patients should generally have preservation of mood and cognitive functions, and should be medically able to undergo surgery.

**THE COMPREHENSIVE FAST-TRACK PRE-OPERATIVE EVALUATION**

Even though quality of life in many domains improves with DBS, some areas may worsen. A 4-year follow up study of STN vs. globus pallidus interna (GPI) DBS showed increased risk of speech, gait, cognitive and mood adverse effects, and up to 30% of patients undergoing DBS may have negative outcomes due to inappropriate screening. However, comprehensive and thorough pre-operative screening can detect problems and stratify the risk of post-operative worsening based on baseline functioning. To achieve this, our institution utilizes a unique, multi-disciplinary, pre-operative DBS clinic in which patients are evaluated by neurology, neurosurgery, psychiatry, neuropsychology and rehabilitation services (physical therapy, speech therapy and swallowing assessment); these are typically conducted at a single, convenient location in a one-day visit.

- **Neurology** – confirm diagnosis; ensure medical optimization; assess severity of disease and appropriateness for surgical intervention; identify motor symptom[s] to be treated by surgery; discuss unilateral vs. bilateral; discuss target selection; discuss risks/benefits;
- **Neurosurgery** – discuss surgical options; discuss surgery-related risks; assess overall medical condition to undergo surgery; discuss contraindications for surgery;
- **Psychiatry** – screen for mood and behavioral problems; ensure chronic, underlying mood issues are adequately treated; discuss risk of mood and behavioral problems with DBS;
- **Neuropsychology** – conduct a thorough assessment of cognitive functions; compare baseline performance to peers; discuss risk of cognitive decline after DBS;
- **Physical therapy** – assess baseline gait and balance; make recommendations to optimize gait before DBS; discuss risk of worsening after DBS;
- **Speech therapy** – assess baseline speech function; make recommendations to optimize speech before DBS; discuss risk of worsening after DBS;
- **Swallowing assessment** – assess baseline swallowing function; make recommendations to optimize swallowing function before DBS; discuss risk of worsening after DBS.

The multidisciplinary team discusses the candidacy of each patient in a meeting at the conclusion of the clinic. The patient is rated on a scale of low, medium or high risk by each specialist based on their evaluations, and the final recommendation is communicated to the patient.

**DBS SURGERY: BENEFITS, RISKS AND OPTIONS**

The primary goals of DBS surgery are safety and accuracy. The risk profile of DBS surgery has been extensively studied. Some risks, such as hemorrhage, are significant and potentially life threatening, but are fortunately rare. Other risks include seizure, hardware infection, discomfort, hardware failure and suboptimal electrode placement (Figure 2). This last risk is minimized by careful design and meticulous execution of the surgical procedure. There are many different ways to “do” DBS surgery. Individual surgeons often develop customized, stereotyped workflow preferences to promote reproducibly good results.

DBS is currently approved by the FDA to be implanted while the patient is awake in order to confirm neurologic benefit without intolerable side effects. Nonetheless, there is a growing utilization of asleep procedures for the implantation of DBS as an off-label approach. But even within these categories of “awake” vs. “asleep” there are many different ways in which surgeons can perform the procedure.

The main technical goal is accurate placement of electrodes within a target, typically with about 1mm precision. Classically, this is achieved with the use of a stereotactic frame affixed to the head while a scan (MRI or CT) is obtained. The target location is then computed with respect to the frame coordinates, and these x, y and z values are manually dialed into an arc attached to the frame. More recently, some centers including ours, have switched to using a different system consisting of a patient-customized 3D-printed stereotactic platform [FHC Inc, Bowdoin, ME]. Here, temporary skull screw fiducial markers are implanted a week prior to electrode implantation. These then serve as the reference coordinate system for selecting targets and trajectories by co-registering a CT scan showing these fiducials with a “clean” pre-operative MRI. Computer assisted design (CAD) software then designs a frame specifically for that patient and the planned trajectories. While adding an extra step, this approach reduces the potential for human or mechanical error (because the targets and trajectories need not be manually transferred to a mechanical frame, which itself would have moving parts and mechanical backlash). It also may increase patient comfort during awake procedures.

**Figure 2. Major Surgical Complications of DBS.**

These data are summarized from Zrinzo et al., and Boviatis et al.12,13

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence: Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic Hemorrhage</td>
<td>6.5% (3-34.4%)</td>
</tr>
<tr>
<td>Symptomatic Hemorrhage</td>
<td>2.6% (0-6.9%)</td>
</tr>
<tr>
<td>Infection</td>
<td>6.4% (0 - 16.2%)</td>
</tr>
<tr>
<td>Electrode Breakage</td>
<td>4.2% (0 - 15.2%)</td>
</tr>
<tr>
<td>Electrode Misplacement</td>
<td>5.4% (0 - 18.8%)</td>
</tr>
</tbody>
</table>
because it does not apply intense pressure to the skull as does a classical stereotactic frame.

In an awake procedure, microelectrode recordings are typically used to map the target region using a combination of neurophysiological patterns and neuronal responses to interactive patient testing. Once the target has been characterized, the permanent DBS electrode lead is placed according to those findings and test stimulation is delivered. Because the patient is awake, neurologic benefit with no or minimal side effects can be assessed. If these results are satisfactory, the lead is locked in-place. If results are suboptimal, a different location can be assessed for lead implantation.

Awake procedures are feasible because only the skin perceives pain (although some patients will report brief discomfort upon passing through the dural), generous infusion of local anesthetic typically eliminates most discomfort. PD patients, because they are off medications for neurologic assessment during the procedure, typically experience discomfort mostly due to the primary disease symptoms, such as rigidity and dystonia.

The need for empirical assessment of lead placement derives from two main factors: first, once the skull is opened for insertion of electrodes, there may be an egress of cerebrospinal fluid (CSF) and an ingress of air. Good surgical technique aims to minimize these factors but even a slight change in skull contents can cause brain shift of a magnitude which, although small in absolute terms, may diminish surgical accuracy in a clinically meaningful way. Second, there is debate in the field over the question of whether the visually identified “optimal” target on imaging is truly the best target for that individual patient, both in terms of maximizing benefit and minimizing side effects. Therefore, empirical assessment of potential targets adds a level of certainty that is otherwise unavailable.

The first factor, brain shift, can be addressed by the use of intra-operative imaging. Indeed, asleep procedures typically use this as the primary method of achieving accurate electrode placement. Many major academic centers now have intra-operative MRI suites which allow visual confirmation of targeting during the electrode implantation procedure. However, many centers use intra-operative CT imaging; the brain tissue resolution of CT, especially intra-operative CT, is less than that of MRI, and so these CT scans are often co-registered with pre-operative MRI. Because most co-registration algorithms are “rigid” (in the sense that they cannot account for brain movement with respect to the skull), brain shift is potentially a limitation with this approach. Yet even procedures performed with intra-operative MRI cannot address the second factor, that is, whether the visually identified target truly represents the optimal brain circuit for patient-specific neuromodulation. So far, several studies have compared results of awake vs. asleep DBS and, according to the fairly course measures used, there do not seem to be major differences. However, one study has observed that thresholds to motor side effects may not be predictable based upon the imaging alone, and so clinical assessment of these side effects in an awake patient may in some cases yield a larger available dynamic range of stimulation and thus potentially more optimal results.

Most centers implant the battery in a delayed fashion, typically one week later. In the case of awake DBS surgery, this allows continuous neurological monitoring of the patient without a period of general anesthesia for battery implantation.

**DBS Surgery at Rhode Island Hospital**

Our preference is to perform DBS as an awake procedure in order to maximize the possibility of obtaining optimal results for each individual patient. We typically perform microelectrode recordings along three tracks on each side, aligned according to the dimension of highest anatomical-radiographic uncertainty about the target. The best track in terms of neurophysiological patterns and responses is selected first for test stimulation using the permanent DBS electrode. If results are good, the electrode is locked in-place at that location; otherwise additional locations are tested in order of the quality of their neurophysiological signals. In addition, we perform most of our procedures with the aid of an intra-operative CT scanner. This adds an extra level of safety and certainty regarding our targeting, should there be any question about the signals we are observing or about the patient’s condition.

Many of our procedures are performed as a collaboration between our lead movement disorders neurologist and functional neurosurgeon. Both have extensive experience interpreting neurophysiological signals and assessing clinical responses. This team-based approach affords an added level of confidence about the quality of these procedures and the ultimate clinical benefit.

**Conclusion**

DBS is potentially a valuable therapy for patients whose movement disorders are poorly managed on medications alone. Comprehensive, multidisciplinary evaluation of patients pre-operatively maximizes good outcomes by screening out those who are more likely to decline after surgery. The surgery itself can be performed using a variety of approaches, but ultimately, surgical safety and precision are the main goals. Throughout this process, a team-based approach works to ensure the best course of treatment for each patient.
References


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Rhode Island Hospital’s Contribution to the Field of Endoscopic Spine Surgery

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ABSTRACT
The first academic program in endoscopic spine surgery in the United States opened its doors at Rhode Island Hospital in 2012. Published advances in the field since its inception have included treatments for a myriad of pathologies including lumbar and thoracic disc herniations, spondylolisthesis, spine tumors as well as treatments for complications of other spinal procedures including spinal fusion, kypholasty, and total disc replacement. In this issue of the Rhode Island Medical Journal we summarize the history of the procedure as well as some of the interesting progress going on in this field in Rhode Island.

KEYWORDS:  endoscopic discectomy, minimally-invasive, transforaminal

INTRODUCTION
“Necessity is the mother of invention,” is a proverb that dates back to 16th century England and describes well the challenge that faces those practicing medicine today and the generation who follow us. With health care costs rising, how will we face the upcoming challenge of providing care to our patient population?

Patients who would have had open-heart surgery in the past, are now candidates for outpatient interventional cardiology procedures. Complex intracranial vascular pathologies and skull base tumors that would have been treated with lengthy intracranial surgeries in the past are now treated with interventional radiology procedures and stereotactic radiosurgery. But what is being done in the field of spine surgery? For the answer to that question, much of the world looks to the research coming out of the institution that is at the center for publishing the latest advances in endoscopic spine surgery: The Department of Neurosurgery at Rhode Island Hospital and Warren Alpert Medical School of Brown University.

PERCUTANEOUS LUMBAR ENDOSCOPIC DISCECTOMY — THE HISTORY
The natural history of surgical techniques seem to be an evolution of “big to small.” But the history of endoscopic spine surgery is really an evolution of “small to big.” Early practitioners developed needle-based procedures to try to decompress the disc nuclear material to relieve back and radicular symptoms. Needles got bigger and the first endoscopic views of a herniated disc were published by Kambin in 1988, and the first reported introduction of a modified arthroscope into the intervertebral disc space was reported by Forst and Hausman in 1983.

In 1990, Parvis Kambin described a triangular safe zone bordered by the exiting root anteriorly, the traversing root medially, and the superior endplate of the lower lumbar vertebra inferiorly. The anatomic description of this safe zone allowed the advancement of the field of endoscopic spine surgery to outgrow the technique of percutaneous nucleotomy which was limited by the use small needle-like instruments. Kambin’s triangle was a working corridor that allowed the introduction of larger instruments and working channels to be introduced even closer to foraminal pathology without injuring the exiting nerve.

With the idea of a safe working triangle between the exiting and traversing roots in the foramen, the field of endoscopic spine surgery started to leave the safety of the indigo carmine blue stained nucleus and explore the foramen. An angled lens scope was used by Mayer and Brock in 1993 that allowed more dorsal visualization of annular pathology. Foraminoscopy was described by Mathews in 1996 and Ditsworth in 1998. Kambin and Zhou in 1996 described lumbar nerve root decompression by annulectomy and decompression of lateral recess stenosis with the use of forceps and trephines. Schubert and Hoogland in 2005 described their technique for transforaminal endoscopic removal of a sequestered disc fragment using reemers to expand the foraminal window by removing the ventral portion of the superior articular process. Multichannel endoscopes with larger working channels were introduced by Tsou and Yeung in 1997 and Reuten et al in 2007. What would follow would be multiple reports of the clinical success of direct endoscopic decompression of foraminal pathology: Yeung and Tsou in 2002, Reuten et al 2007, Reuten et al 2008, Jasper et al 2013.

THE CLINICAL SUCCESS OF ENDOSCOPIC SURGERY
Seven papers published between 2013 and 2014 on awake endoscopic spine surgery indicated the possible efficacy of this procedure performed through a 5 mm incision for the
treatment of Lumbar radiculopathy. For patients with single level disc disease, the success rate reported was an 84% reduction in pain, and for patients with multi-level pathology, the average pain relief was 70%. In a series of 50 consecutive patients over the age of 75, over 80% of patients described either a “good” or “excellent” outcome: many of these patients were offered fusion surgeries at other centers before being considered for endoscopic surgery. Patients who underwent endoscopic treatment for radicular symptoms due to spondylolisthesis reported a 72% reduction in pain – up front instrumented fusion is currently a mainstay treatment for this pathology. Figure 1 displays in a step-by-step manner how the endoscopic technique is used to treat a patient (former NFL player) with lumbar radiculopathy in the setting of spondylolisthesis.

The mainstay for the treatment of lumbar degenerative pathology is conservative treatment with weight loss uniformly recommended for lumbar radicular symptomatology in the setting of morbid obesity. But the success of conservative management in reducing obesity is difficult. 82 patients in one study published showed pain reduction close to 70% for patients with BMIs between 30 and 40 but closer to 45% for patients with BMIs over 40.

The first paper in the world describing the feasibility and technical steps that enable a surgeon to circumnavigate and reach into the epidural space for intracanal pathology was also published in these period, opening the possibility for treating more than routine herniated lumbar discs.

**FAILED BACK SURGERY**

There has been a 15-fold increase in complex spinal fusion procedures in the past decade. But innovative treatment strategies for treating the complications from these procedures has lagged. In 2015 a series of 3 papers have described innovative minimally invasive treatments for herniated

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**Figure 1.**

A. Preoperative sagittal T2 MRI showing pathology of L4-5 spondylolisthesis.

B. Spinal needle entry into L4-5 disc on lateral fluoroscopic view.

C. Small dilator and large crown reamer in L4-5 foramen during foraminoplasty on AP fluoroscopic view.

D. Bevelled working canulla in L4-5 foramen on AP fluoroscopic view.

E. Endoscopic view of the residual reamed ventral border of the SAP (white arrow) and ligamentum flavum (black arrow).

F. Endoscopic view of the ligamentum flavum (black arrow), traversing nerve root (black border arrow), and herniated disc (red arrow).

G. Intraoperative photograph of the L4-5 herniated disc fragment removed with an endoscopic forceps during the procedure.
Figure 2.

A. Sagittal T1 MRI with gadolinium of the thoracic spine demonstrating recurrence of the ventral extradural tumor.

B. Axial T2 MRI with gadolinium showing preoperative planning for spinal needle trajectory for transforaminal approach.

C. Intraoperative AP fluoroscopic image demonstrating passage of spinal needle into the left T5-6 neural foramen.

D. Intraoperative AP fluoroscopy showing reaming of the superior articular process.

E. Intraoperative AP fluoroscopic image showing working channel within the left T5-6 neural foramen, along with ball probe passed to confirm position of T6 pedicle.

F. Intraoperative AP fluoroscopy confirms position of malleable curved grasping forcep.

G. Patient positioned prone with working channel 5cm lateral to midline and communicating author shown manipulating bendable grasper in working channel.

H. Intraoperative endoscopic view with ball probe pushing on the dorsal aspect of the tumor capsule.

I. Intraoperative endoscopic view demonstrating the bendable grasper reaching inside the tumor capsule.
discs after fusion,20 lumbar radiculopathy after instrumented fusion,21 and lumbar radiculopathy after interbody fusion.22 All of these “rescue” or “salvage” procedures were performed without general anesthesia on outpatients.

SPINAL TUMORS
In the international journal Clinical Neurology and Neurosurgery in July 2015, the first report in the world of performing a resection of a spinal canal tumor endoscopically in an awake patient was reported.23 The case was performed on a 15-year-old patient who underwent the procedure in order to avoid a complex instrumented fusion procedure. Figure 2 shows the patient’s MRI, intraoperative x-rays, a photograph from the operating room, and endoscopic images from the surgery. The NBC news story of this historic surgery was shared around the world.

THORACIC DISC SURGERY
Surgery for the treatment of thoracic disc herniations has for years meant operating through a thoracotomy to remove disc pathology and fuse the spine. In 2016 the first 2 descriptions of technical nuances for performing awake endoscopic surgery for thoracic and thoracolumbar disc herniations were published in the Journal of Neurosurgery24 and World Neurosurgery.25 The advances in this area were the result of a collaboration between physicians at Rhode Island Hospital and surgeons in Germany and the Netherlands.

ENDOSCOPIC SURGERY TO TREAT OTHER SPINE SURGERY COMPLICATIONS
Kyphoplasty is a treatment for painful compression fractures of the osteoporotic spine. Cement leakage can be a disastrous complication that results from the procedure because an open laminectomy and instrumented fusion can be necessary to remove the extravasated cement. This surgery is made even more complicated by the fact that these osteoporotic patients are not favorable candidates for instrumented fusion procedures. In 2016 the first paper in the world describing an endoscopic solution for this problem in an awake patient was published.26

Artificial lumbar discs or total disc replacement surgery is performed more popularly in Europe than in the United States because of difficulty getting this non-fusion technology approved by insurance carriers. Patients interested in this surgery in the U.S. will sometimes travel to Europe for the procedure. Approximately 10% of these surgeries ultimately go on to need instrumented fusion due to complications from the original implant. In 2016 the first endoscopic treatment for a total disc replacement surgery was published in the Journal of Neurosurgery.27 The surgery in Germany to place the artificial disc dislodged a fragment of bone that caused nerve compression. With the patient awake, an endoscope was used to drill out the fragment to free it and then remove it. The patient was able to avoid a laminectomy and fusion and ultimately benefited from a successful total disc replacement. The future of total disc replacement surgery in the U.S. remains to be seen but certainly endoscopic surgery may have a role in treating the complications seen in this procedure.

CONCLUSION: THE FUTURE OF SPINE SURGERY
Laser spine surgery that is advertised ubiquitously is not, in fact, performed with a laser. It is, in fact, an aggressive marketing program for a minimally invasive open surgical procedure that is performed with the patient under general anesthesia. Endoscopic spine surgery is performed with a working channel rigid endoscope, high definition camera, drills, trephines, articulated graspers, and sometimes, yes, a laser. But it has at its endpoint, the same surgical goal as many more open surgical spine procedures. The essence of what makes it different and the heart of what may be at the future of spine surgery is moving the point of visualization from the surgeon’s eye to the endoscopic camera, which allow us to move the “eye’s” lens remotely to the site of the surgical pathology. Innovation that brings the surgeon’s “eye” to within millimeters from the patient’s pathology allows complex spine surgery to be performed in awake patients through a tube the size of a pencil.

References
11. Yeung AT, Tsou PM. Posterolateral endoscopic excision for lumbar disc herniation: surgical technique, outcome, and

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Updates On Chimeric Antigen Receptor-Mediated Glioblastoma Immunotherapy

GEORGE MAO, MD; PRAKASH SAMPATH, MD; SADHAK SENGUPTA, PhD

ABSTRACT
Glioblastoma multiforme (GBM) is the most malignant of the primary central nervous system (CNS) neoplasms, accounting for nearly 80% of all primary brain tumors and is associated with high morbidity and mortality. Immunotherapy is proving to be a fertile ground for next-generation GBM therapy, with large translational research projects and clinical trials currently underway. One particularly promising area is the chimeric antigen receptors (CARs) in the context of lymphocyte adoptive cell therapy (ACT), which has achieved success in the treatment of hematological malignancies. In this review, we will discuss CARs and review current challenges facing their use in GBM therapy.

KEYWORDS: glioblastoma, immunotherapy, CAR

INTRODUCTION
Glioblastoma (GBM) is the most common and most malignant of all the primary cancers of the central nervous system. It is an aggressive and heterogeneous cancer characterized by densely packed pleomorphic cells with high mitotic activity, necrosis, and high degree of vascularization. GBM most commonly strikes older individuals, with a slight predilection for males over females. The current standard of care therapy for GBM, which consists of maximum allowable surgical resection, focal beam radiation, and chemotherapy with temozolomide, is not curative. Survival remains abysmal, as fewer than 10% of patients survive after 5 years. The difficulty in treating GBM arises from the cancer’s cellular heterogeneity, their diffuse infiltration into the brain, protection provided by the blood-brain barrier, the chemotherapeutic resistance and regenerative capacity of glioma stem cells.

With these barriers in mind, immunotherapy may offer an avenue of treatment for GBM that may be both safer and more effective. Immunotherapy offers a targeted approach to treatment, via utilization of unique molecular and genetic signature of tumor cells. It has been noted in several malignancies that cancer patients who had more activated immune systems seem to have better outcomes. Thus, techniques have been developed to enhance a patient’s immune response against GBM. Immunotherapy encompasses a wide variety of techniques, which are beyond the scope of this review. The most developed of these immunotherapeutic methods is the use of monoclonal antibodies (mAbs). While mAbs have been developed against multiple GBM-specific antigens, they have not yet enjoyed wide success due to a combination of tumor and host factors. Other areas of immunotherapy for GBM under current active investigation include dendritic cell vaccines derived from lysed tumor cells, immunomodulatory checkpoint inhibitors, and engineered T-cell based therapies, which will be the focus of this paper.

CARs
Recently reported success of clinical CAR-T cell therapy of GBM [4] has generated hope in the use of this technology for GBM immunotherapy. CAR-T cell offers an attractive alternative to a limitation inherent in the other T-cell receptor (TCR) dependent cellular immunotherapeutic approaches, namely, that of MHC independent antigen presentation. Precluding the need for TCRs, CAR-T cell strategies greatly improve the diversity of antigen targets, and bypasses a mechanism of GBM immune evasion through MHC down-regulation [5]. Engineered CAR-Ts have much higher affinity to their targeted antigens than T cells. The antigen binding can be further modulated in subsequent development of the CAR-T cells to prevent overly strong immune responses that can result in the potentially fatal cytokine release. Since CAR-Ts are artificially constructed from functional polypeptide domains, the receptors can be configured by the addition of new effector domains, adding novel features to the CAR-T cell. Thus, CAR-T cells can be precisely tailored to the goals of therapy, and be individualized to the particular patient and clinical scenario.

CAR-Ts are very similar to TCR in structure and function, as they both combine an antigen-binding domain with downstream signal transduction domains. The antigen-binding domain of CAR can be a heavy chain and the light chain fusion protein (scFv) of a prototypical antibody, and the most common design is an scFv domain joined to a transmembrane CD3-ζ signaling domain and costimulatory domains that couple extracellular antigen recognition to intracellular signal transduction, which subsequently affect T-cell immune response [Figure 1]. One can also look beyond the traditional antigen-antibody paradigm...
for ligand-binding motifs. For example, the natural receptor of a particular tumor specific antigen may be utilized as the ligand-binding domain, thus permitting CARs to bind to non-immunogenic peptides as well as carbohydrate and even lipid-based antigens.

The MHC independent nature of CAR-mediated antigen presentation and their inherent modular properties engineered into these cells make the receptors far more versatile than TCRs. After the CAR design is decided upon, the underlying genetic sequence that encodes for the CAR is encoded and transfected into the T-cell usually via a viral vector. The modified T-cells are then expanded in vitro and subsequently re-introduced back to the patient [6, 7].

**CARs for GBM Immunotherapy**

Initially achieving success for the treatment of hematologic malignancies, adoptive CAR-T cell therapy is now under active investigation for a variety of solid tumors, including GBM. Presently, CARs have been developed against six GBM-associated antigens, with four having passed animal trials and currently in clinical trials. These include: EGFRvIII [8-13], IL13Rα2 [4, 14-16], HER2 [17, 18], and EphA2 [19].

Epidermal growth factor receptor, or EGFR, is directly implicated in GBM through either over-amplification of the gene (HER2/neu) or through constitutively active mutant variants, both of which result in increased growth and survival of the GBM tumor cell [10]. EphA2 is a cell-surface receptor that regulates proliferation, migration and angiogenesis, which ultimately affects the invasive and metastatic potential of GBM [20, 21]. IL13Rα2 is a unique decoy receptor for IL13, and binding of the cytokine to the decoy receptor terminates the chain immuno-stimulatory signals that lead to the generation of an appropriate immune response [22].

Currently, there are three major clinical trials involving CAR-T cells against EGFRvIII on GBM. All three are in preliminary stages, only one is currently recruiting participants, whereas the two others have not yet started or have suspended patient recruitment [23-25]. There have been two CAR-T-cell clinical trials involving the use of IL13Rα2 as the target and two clinical trials involving anti-HER2 CAR-T cells. Lastly, there is currently one clinical trial with the goal of establishing EphA2 as a safe and feasible CAR-Target, which is presently in recruitment [30] (Table 1).

**Table 1. List of CAR-T cells currently undergoing clinical trials.**

<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>CAR Target(s)</th>
<th>Current Status</th>
<th>Special Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01454596</td>
<td>EGFRvIII</td>
<td>Suspended recruitment</td>
<td>Status unclear</td>
</tr>
<tr>
<td>NCT02664363</td>
<td>EGFRvIII</td>
<td>Not yet started recruitment</td>
<td>Neoadjuvant ACT</td>
</tr>
<tr>
<td>NCT02209376</td>
<td>EGFRvIII</td>
<td>In recruitment</td>
<td>Safety/feasibility study</td>
</tr>
<tr>
<td>NCT02575261</td>
<td>EphA2</td>
<td>In recruitment</td>
<td>Safety/feasibility study</td>
</tr>
<tr>
<td>NCT02442297</td>
<td>HER2</td>
<td>Not yet started recruitment</td>
<td>Inhibitory CAR model</td>
</tr>
<tr>
<td>NCT01109095</td>
<td>HER2</td>
<td>Ongoing, not accepting new patients</td>
<td>Modification of preselected CMV specific T cells</td>
</tr>
<tr>
<td>NCT01082926</td>
<td>IL-13Rα2</td>
<td>Completed</td>
<td>T cells also engineered with HyTK suicide switch and resistance to steroids</td>
</tr>
<tr>
<td>NCT02208362</td>
<td>IL-13Rα2</td>
<td>In recruitment</td>
<td>Safety/feasibility study</td>
</tr>
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</table>
LIMITATIONS OF CARS FOR GBM IMMUNOTHERAPY

So far, the use of adoptive CAR-T cell therapy for GBM has not yet enjoyed the level of success seen in the treatment of lymphoproliferative disorders such as in ALL and CLL. This is due to a combination of tumor and host factors, the most relevant of which is GBM’s ability to evade immune surveillance and even achieve active suppression of the local immune response. GBM can actively shield itself from immune assault by concealment of targeted cell-surface antigens (including MHC proteins) and active secretion of various ligands that induce T-cell apoptosis and further inhibit the immune response [31-33]. Furthermore the intrinsic cellular heterogeneity of GBM provides further passive immunoresistance and immune escape mechanisms.

OVERCOMING THE LIMITATIONS

One of the most obvious ways to counteract the problem of tumor heterogeneity is the use of CAR T cells that recognize multiple tumor antigens. By designing CARs with multiple distinct antigen-binding domains and through the introduction of multiple different CARs onto the surface of a single T cell, there is more opportunity to overcome intratumor antigen heterogeneity [34]. CAR-T cells can be further modified to render them unresponsive to the various immunosuppressive and apoptotic-inducing signals secreted by GBM [35, 36]. In addition, checkpoint inhibitors such as nivolumab, which suppress such interaction between the inhibitory ligand and its associated receptor on the T cell, can be given in conjunction with CAR-T cell administration to impair GBM’s immunosuppressive capabilities [37-39].

Further engineering of the CAR-T cells allows for potential improvement in their immune response. Examples include the addition of co-stimulatory domains to the intracellular portion of the CAR construct to amplify the immune response generated by the CAR-T cell [Figure 1B]. Further amplification may include designing CARs that can independently secrete critical pro-inflammatory cytokines [40], priming CAR-T cells with viral particles, and/or the appropriate pre-selection of T cells for CAR engraftment, such as the use of particular T cell subsets that have greater capacity to replicate in vivo after exposure to GBM antigens. In addition, CAR-T cells can also be rendered resistant to various chemotherapeutic agents, so that chemotherapy may be given in conjunction with adoptive T cell therapy [41-43].

One of the major issues confronting CAR-T cells is stimulating the appropriate level of immune response that kills the tumor, while causing minimal damage to normal tissues. While in vitro CAR-T cells demonstrate specificity for target antigen, in vivo studies have shown that CAR-T cells have resulted in systemic toxicity. Three classes of toxicities are seen with CAR-T cell therapy. Off-target-off-tumor toxicity is cross-reactive due to qualitative defects in scFv design and/or production. Since these antibody fragments are often derived from murine immune systems, human toxicity resulting from murine derived antigen cross-reactivity will likely become less of an issue. A more serious problem is the on-target, but off-tumor toxicity observed with CAR-T cell therapy, as the tumor antigens are sometimes expressed in or cross react with non-neoplastic cells [44]. One way to offset this type of toxicity is designing a CAR-T cell that becomes activated only when it interacts with multiple different GBM antigens on the surface of the glioma cell [45, 46]. Because there is a dearth of antigens that are only expressed in GBM and nowhere else, investigators have turned to utilizing antigens that are highly expressed in glioma cells, but are also expressed at lower levels elsewhere in the body. By modulating the affinity of the CAR so that T cell activation occurs only after a defined threshold of binding is reached between the T-cell and its target, this type of toxicity may be abrogated [47]. The last category of toxicity due to a dysregulated immune response can range from a mild systemic flu-like illness to a massive overwhelming cytokine release that can result in multiorgan failure, and ultimately death. This may be addressed through the introduction of safety suicide switches into the adoptive T cell, which, when turned on by an exogenous signal (usually introduced by a clinician), results in the death of the T cell.

CONCLUSION

The unique modular nature of CARs allows them to be tailor-made to match the need of any particular clinical scenario and nature makes CAR-T cell therapy a good potential complement to existing conventional therapies. Protocols are in place to determine their efficacy when used in conjunction with Temozolomide. However, the full potential of CAR-T therapy will not be realized until they are designed for the individual patient. Because technology now exists to allow for rapid genome-wide sequencing of individual cells, CAR-T cell therapy allows for targeting of targets unique to the individual cancer patient. And as the patient’s GBM evolves over time, due to selection pressure during therapy, new CAR-T cells may be prepared and reintroduced to the patient in response to the antigenic shift. Of course, to identify these shifts, fresh tumor samples and genetic sequencing will be required to identify antigenic changes over time in the tumor organ.

Currently, there are still major challenges facing CARs that prevent their widespread use; however, solutions are in development that address most of these hurdles. With the cost of genomic sequencing rapidly decreasing due to technical innovations and economy of scale, a personalized approach to glioblastoma therapy is nearing. CAR-T cells represent a novel therapeutic option that may soon be ready for widespread use in this and other diseases.
References


References 26–47

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ABSTRACT
Gliomas are a class of primary brain tumors arising from the supporting structures of the brain, the astrocytes and oligodendrocytes, which range from benign lesions to its most malignant form, the glioblastoma. Treatment for these lesions includes maximal surgical resection, radiotherapy, and chemotherapy. Recently, novel therapies such as immune modulatory therapies and electrical field treatment of the most malignant form, the glioblastoma, have shown promise in improving survival. We will review recent advances in clinical trials, explore the role of multimodal care in brain tumor therapy, as well as explore advances in molecular biology and nanotechnology which offer new hope for treatment of this class of disease.

KEYWORDS: glioblastoma, immunotherapy, tumor treating fields, nanotechnology, drug delivery

INTRODUCTION
Gliomas are a class of tumors which arise from the supporting structures of the brain, astrocytes and oligodendrocytes. They range in behavior from benign lesions with distinct borders such as juvenile pilocytic astrocytomas, curable with surgical resection alone, to more diffusely infiltrative cancerous lesions, astrocytomas, oligodendrogliomas, and glioblastoma, all uniformly lethal in a matter of several to many years. In this brief review, we will focus on the most lethal of these, the glioblastoma (GBM).

GBM is the most devastating primary malignancy of the central nervous system in adults. Currently, standard treatment consists of maximal safe surgical resection or a diagnostic biopsy, followed by radiotherapy [60 Gray] with concomitant daily temozolomide chemotherapy, followed by maintenance treatment with temozolomide for 6- to 12 months. However, most patients will die within 1 to 2 years. Median progression-free survival from diagnosis of 6.2 to 7.5 months and median overall survival from diagnosis of 14.6 to 16.7 months have been reported in clinical trials. The reported 2- and 5-year survival rates are 27% and 10%, respectively. During the last decade, all attempts to improve outcomes for patients with glioblastoma have failed when evaluated in large randomized trials. Most recently, the development of electric current loco-regional antimitotic therapy (“tumor-treating fields”) led to the first reported survivals exceeding 20 months.

In the United States alone, 12,000 new cases of GBM are diagnosed each year. One reason cited for the failure to improve survival has been the presence of a robust blood-brain barrier within the tumor, which impedes delivery of traditional cytotoxic and novel molecular therapies. Most chemotherapeutic agents are hydrophilic, and do not penetrate the blood brain barrier well. Attempts to deliver chemotherapeutic molecules into the brain have included both osmotic, chemical, and ultrasound mediated opening of the blood brain barrier to improve drug delivery, but none have improved clinical outcomes. A novel method to bypass this barrier, [i.e., convection enhanced delivery], met with success in delivering high drug concentrations of hydrophilic drugs to brain tumors and led to several clinical trials. However, convection-enhanced delivery has not yet been associated with improved clinical response. This failure has been ascribed to inhomogeneous delivery of the drug to the entire tumor, as well as difficulty in modeling the bulk flow of infusate:drug to the tumor volume.
is undertaken to map out motor and sensory areas [See Figure 2] or nearby cranial nerve nuclei. If the lesion is near language areas, an awake craniotomy with speech mapping may be required to achieve maximal safe resection while minimizing the risk of language deficits.

After biopsy or resection, the tissue is studied by a dedicated neuropathologist for both histopathology and molecular markers. A detailed description of the molecular pathology of glioma is beyond the scope of this manuscript. Postoperative MRI is reviewed for completeness of resection and a care plan is formulated by the team. This care plan may include radiation therapy, chemotherapy, tumor treating fields, or clinical trials. Further discussion with the family is begun to deliver the diagnosis and care plan, as well as to engage the patient and family with resources such as local and virtual brain tumor support groups to aid in the social support network for these patients.

Follow-up routinely is weekly during radiation therapy, monthly during active chemotherapy and every three months for high-grade gliomas. Routine surveillance scanning is often used to identify progression of the disease and allow for more timely intervention upon therapeutic failure.

LANDMARKS IN THE CARE OF GLIOMA

For both low-grade glioma as well as glioblastoma, survival is dependent upon age, the patient Karnofsky Performance Score, as well as a host of histopathological and molecular pathological factors. The most important factor in the control of clinicians, is, of course, the percentage of tumor
which can be surgically resected. It has been clearly demonstrated that for all types of glioma, the improvement in patient outcomes achieved by the cytotherapy of tumor cells gained is nonlinear and that maximum benefit to the patient is achieved when all tumor which can be removed up to the point of causing a postoperative neurological deficit is beneficial for the patient.

The most important clinical advances in glioma therapy have occurred within the past 15 years. The molecular biology of gliomas involves a host of genetic and epigenetic alterations which are of prognostic importance to tumor classification as well as patient survival. For low-grade gliomas, the most important of the diagnostic and prognostic markers are those of gene rearrangement studies, which suggest the classical oligodendroglioma phenotype and predict responsiveness to chemotherapy, that of chromosome 1p and 19q allelic loss. Loss of 1p/19q alleles predict both sensitivity to chemotherapeutic agents as well as a prognosis which is nearly double that of low-grade gliomas without this genomic loss.

In GBM, attempts have been made to characterize multiple molecular phenotypes, but the single gene with the most prognostic value is IDH1. Mutations in IDH1 are associated with improved prognosis. The other commonly cited prognostic factor in GBM is the epigenetic alteration of methylation of the methyl guanine methyl transferase (MGMT) gene promoter. The MGMT methylation at the promoter reduces the expression of the MGMT gene, needed to repair the damage caused by the chemotherapy temozolomide. Thus, patients with methylated MGMT promoter are more susceptible to the effects of the chemotherapeutic temozolomide and are in a better prognostic category.

Prognosis for GBM patients has been among the worst of all malignancies until recently. Survival was less than 12 months as recently as 20 years ago, and progress has been slow. The work of Roger Stupp, who showed that concurrent temozolomide along with radiation therapy improved prognosis over sequential radiotherapy followed by temozolomide marked the first major advance in glioblastoma survival (to 14.6 months) since the advent of radiotherapy and the introduction of nitrosoureas in the 1970s and 1980s”. More recently, a series of novel devices, drug therapies and immune strategies have begun to improve survival beyond this mark.

**NOVEL THERAPEUTIC ADVANCES**

The most recent therapeutic advance to be approved for clinical use in glioma is that of a novel antimitotic therapy called tumor treating fields (TTFs). TTFs are an antimitotic therapy consisting of an alternating electrical current of 100 – 300 kHz delivered via transducer arrays placed on the scalp. In both recurrent and newly diagnosed GBM, TTFS delivered for at least 18 hours per day have been shown to improve survival. In newly diagnosed GBM, the addition of TTFS to radiation and temozolomide improved survival to 24.3 months in treated patients versus 20.4 in the control group. One might note that even the control group with radiation and temozolomide were surviving longer than those from a decade ago.

A host of other small molecule inhibitors and novel drug delivery systems such as convection enhanced delivery have been tried in the past several decades but have failed to show meaningful improvements in survival of GBM. More recently, techniques such as immunomodulatory molecules, such as the PD-1 and CTLA-4 inhibitors have shown improvements in survival of melanoma, lung and renal cell carcinoma and are in trials for GBMs.

In addition to immune checkpoint inhibitors, other immune strategies such as peptide vaccines, dendritic cell vaccines, and Chimeric Antigen Receptor T-cell (CAR T-Cell) strategies have shown early promise in improving survival for patients with glioma. These topics will be reviewed in another manuscript in this issue.

**THE ROLE OF RESEARCH IN GLIOMA – INSIGHTS FROM OUR LABORATORY**

Despite many decades of work and recent advances, glioma remains a fatal disease. Thus, no development of a comprehensive brain tumor program would be complete without a research effort. This includes clinical trials with industry and large cooperative groups, but some of the most exciting prospects for improvements in glioma therapy lie within the laboratory. It is the goal of our group to bring several of these to clinical trial within the next several years. With this in mind, we will preview two fields of investigation, glioma migration and micro ribonucleic acid (miRNA) of glioblastoma stem cells.

One of the most vexing aspects of gliomas is that they migrate away from the solid tumor and diffusely infiltrate well beyond apparent margins on MRI. Thus, for anything other than compact, Grade I [benign] gliomas, surgery alone will never be curative. Therefore, we have studied within our laboratory how glioblastoma cells interact with the brain environment to migrate as well as how we might manipulate these pathways to aid in therapy. We are manipulating these pathways to promote the return of remaining cancer cells to the resection site by placing a pro-migratory protein (LCN2) in a slow release hydrogel placed within the resection cavity to hopefully improve the results of radiation therapy. In addition, we have found a small molecule inhibitor of a tyrosine kinase (Lck), which enables pseudopodia extension and migration in GBM stem cells. We feel that manipulation of the “On” and “Off” pathways for migration can be used to
improve patient outcomes and expect to begin clinical trials after we complete our small animal model data.

In addition, our laboratory is investigating the role of miRNA – the regulators of RNA transcription – to identify how regulation of these small switches controls the ability of cancer cells to self renew and replicate in GBM stem cells. Thus far, we have narrowed the control of this crucial feature of cancer – the ability of cells to remain stem-like and resist therapy – to 9 likely miRNA candidates. Our preliminary work suggests that miRNA-mediated control of RNA methylation may be the molecular switch that changes GBM stem cells to the cancer cells we typically associate with GBM. We hope that this signature may yield prognostic data and reveal pathways for therapeutic intervention.

Of course, none of this has much meaning without educating the future generation of oncologists and neurosurgeons to care for patients with glioma. We anticipate beginning advanced training of neurosurgical oncology fellows within the year. Once this is complete, the comprehensive brain tumor center will close the circle from the patient, to the student, to the laboratory, and back, to be able to provide the best care for patients afflicted with glioma.

References

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Current Concepts in the Pathogenesis, Diagnosis, and Management of Type I Chiari Malformations

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ABSTRACT

Type 1 Chiari malformations (CMs) are a group of congenital or acquired disorders which include the abnormal presence of the cerebellar tonsils in the upper spinal canal, rather than the posterior fossa. The resulting anatomic abnormality causes crowding of the structures at the craniocervical junction and can impair the normal flow of cerebral spinal fluid (CSF) in this region. This impairment in CSF flow dynamics can lead to the development of syringomyelia or hydrocephalus. Type 1 CMs have been associated with a wide array of symptoms resulting from either cerebellar and brainstem compression and distortion or disturbances in CSF dynamics, and can affect both children and adults. The clinical diagnosis may be difficult. Age usually matters in the clinical presentation, and in symptomatic patients, surgical intervention is usually required.

KEYWORDS: Chiari I Malformation, cerebrospinal fluid, hydrocephalus, syringomyelia

INTRODUCTION

Chiari malformations are a group of disorders defined by structural defects of the cerebellum, pons, fourth ventricle, and upper spinal cord in relation to the foramen magnum and the skull base. In 1891, Chiari was the first to describe and define hindbrain herniation, representing downward displacement of the cerebellum, fourth ventricle, and brainstem.1 Type 1 CMs are characterized by herniation of the cerebellar tonsils through the foramen magnum into the upper spinal canal. The resulting compaction and crowding at the craniocervical junction can disrupt normal cerebrospinal fluid flow, produce the so-called “Valsalva-induced” headaches, and may lead to the formation of a spinal cord syrinx or hydrocephalus.2

Chiari malformations are still listed as a rare disease by the Office of Rare Diseases of the National Institutes of Health. The estimated prevalence in the United States of type 1 CMs is less than one percent with a slight female predominance.2 Speer et al. have estimated that 215,000 Americans may harbor a type 1 CM.4 However, the routine use of magnetic resonance imaging (MRI) has led to more frequent identification of this disorder and type 1 CMs can be seen incidentally in approximately 1% to 4% of patients undergoing brain or cervical spine magnetic MRI studies.4

Most cases of type 1 CM are sporadic. Type 1 CMs can be found in association with other conditions such as neurofibromatosis, idiopathic intracranial hypertension (IIH), tethered spinal cord, connective tissue disorders, craniosynostosis and skull base abnormalities, intracranial hypotension and cerebellar hypertrophy in polymicrogyria.5 It is still not fully understood whether these co-existing conditions are mere coincidences or true co-morbidities. The precise natural history of this disorder remains unclear although patients generally have symptomatic progression. There have been a few published reports of spontaneous resolution of type 1 CMs but most symptomatic cases require surgical intervention.5,6

PATHOGENESIS

Most cases of type 1 CM are congenital. Skull base abnormalities are seen in approximately 50% of type 1 CM cases, (i.e., basilar invagination, retroflex odontoid, platybasia etc.).7 Although the exact etiology is unknown, this condition is thought to be secondary to insufficiency of the paraxial mesoderm after neural tube closure with underdevelopment of the occipital somites.7,8 Milorat and coworkers examined reconstructed CT and MRI images in 388 patients with classic type 1 CMs, and morphometric analysis revealed reductions in the posterior cranial size and volume.7 In severe cases, downward herniation of the brainstem may occur and is sometimes referred to as a type 1.5 CM.7 Despite evidence supporting a genetic contribution to type 1 CMs (i.e., twins, familial clusters, and co-segregation with known genetic syndromes), limited research has been conducted to identify the specific genetic factors involved.8

Acquired type 1 CMs can occur when there is a significant cerebrospinal fluid (CSF) pressure gradient across the craniocervical junction, i.e., CSF leakage or lumboperitoneal shunts can produce negative downward pressure gradients leading to the development of a type 1 CM. In addition, conditions associated with raised intracranial pressure, such as hydrocephalus and IIH, can promote downward pressure gradient. The association of CM1 with tethered cord has led to the “caudal traction theory.”6

Syringomyelia is identified in 30-85% of patients.5,10,11 There are many hydrodynamic theories to explain the formation of syringomyelia11. Abnormal and increased pulsatile
motion of the cerebellar tonsils (“tonsillar pistoning”) can produce selective obstruction of CSF flow during systole. The increased systolic CSF waves are then transmitted to the spinal subarachnoid space and drive the CSF into the central canal of the spinal cord through engorged perivascular and interstitial spaces and lead to syrinx formation.12,13

**DIAGNOSIS**

The clinical findings vary dependent on the age at presentation. Occipital headache and neck pain are the most common symptoms in adults.10 In infants, oropharyngeal dysfunction or sleep apnea and other cranial nerve findings, i.e., strabismus, are the most common presenting symptoms, while older children often present with headaches aggravated by “Valsalva maneuvers” during coughing and sneezing or strain, and scoliosis.14,15 Symptoms are based on the structural and functional [impaired “CSF-dynamics”] pathologic associated with CM, which often leads to a wide spectrum of focal and non-focal findings in the clinical and neurological presentation, making it difficult to diagnose. Even more challenging is the often reported “brain fog” that has been largely attributed to chronic pain, depression and anxiety associated with the unknowns and physical challenges of this disorder. In traditional thinking, a disorder like Chiari affecting the craniocervical junction and the cerebellum, has not been thought to affect cognitive function: Altered MRI diffusion tensor imaging [DTI] metrics in the genu of the corpus callosum, splenium, fornix have been correlated with cognitive neurocognitive function in Chiari.16

Magnetic resonance imaging is the widely accepted diagnostic tool for type 1 CMs. The McRae line is a radiographic line drawn on a lateral midsagittal section of CT or MRI joining the basion and opisthion representing the level of the foramen magnum. The traditional definition of type 1 CM as greater than 5 mm displacement of the cerebellar tonsils below the foramen magnum is challenged.15 Even a “mild” displacement of 3-5 mm may be considered significant in the presence of neurological signs or symptoms or in the presence of syringomyelia. Also, the level of tonsillar ectopia evidenced in the sagittal MRI varies based on head position, and whether the measurement of the tonsillar position is based on a brain or spinal MRI. Recently, upright MRIs have challenged this view also, as gravity might reveal tonsillar displacement that was not seen in the traditional supine MRI versions.

The future lies in computation of the CSF space at the craniocervical junction and the resulting altered compliance and failure to synchronize transmission of systolic CSF pressures between the cranial and cervical subarachnoid space.12

**SURGICAL MANAGEMENT**

The management of acquired forms of type 1 CM is directed at correcting the primary causative condition. For example, ventricular shunting for the treatment of hydrocephalus, repairing spinal CSF leakage, or correcting a tethered spinal cord usually results in anatomic and physiologic correction of the acquired CM. Intervention to directly treat the acquired CM is typically not necessary.

Asymptomatic patients who have an incidental finding on imaging are usually observed and monitored with follow-up MRI studies. Most patients with symptoms, or those who harbor a large associated spinal cord syrinx, should be recommended surgical intervention. Close follow-up and serial MRI imaging is required in patients who undergo observation alone in the presence of a syrinx. Appropriate management of an asymptomatic patient with a small syrinx is controversial.17,18

Many different surgical techniques are utilized to treat type 1 CMs, and there is no consensus. Surgical correction of type 1 CMs may include bony decompression of the posterior fossa with or without duraplasty, arachnoid dissection, or shrinking of the cerebellar tonsils. The goal of any of these operations is to restore adequate CSF flow at the level of the foramen magnum and establishment, basically an “anatomical reconstruction,” of the Cisterna magna (Figure 1A, B). Bony decompression alone has been associated with a decreased risk of CSF related complications such as pseudomeningocele, meningitis, and hydrocephalus.

**Figure 1.** (A) Sagittal T2 STIR magnetic resonance imaging showing Chiari I with significant cervical syringomyelia (black asterisk) and the classical “crowding” of the cerebellum and the brain stem at the level of the foramen magnum (dashed white line equals the McRae line, which indicates the level of the foramen magnum on a midsagittal section of CT or MRI joining the basion and opisthion). (B) At 3 months follow-up, there is evidence of restored CSF signal anterior to the brain stem, decompression of the obex and restoration of the cisterna magna associated with an almost complete resolution of the syrinx.
However, multiple studies have shown that reoperation rates are higher for patients who have undergone bony decompression alone.\textsuperscript{19,20,21} Duraplasty involves the use of autologous pericranium or allografts, none of which have been found superior to the other. More involved arachnoid dissection to ensure flow through native CSF channels may be required, particularly if scarring or webbing is restricting CSF flow. Shrinking of the cerebellar tonsils using meticulous bipolar cautery is also controversial, although we do advocate this approach in select cases. A recent meta-analysis suggested shrinking the cerebellar tonsils during the procedure showed better clinical results in patients with syringomyelia.\textsuperscript{20} Shunting of an associated spinal cord syrinx has been largely abandoned. CM1.5 and associated skull base anomalies may require occipital-cervical fusion and instrumentation due to associated craniocervical instability.

**FUTURE DIRECTIONS**

All efforts need to be directed to identify potential subgroups of type 1 CMs. This will result in better diagnostic methods and treatment that will eventually be tailored to the individual anatomic and physiologic characteristics. This includes experimental and molecular studies to further our understanding of the genetics and pathophysiology of type 1 CMs. Also, MRI studies need to advance imaging to allow computation of cerebrospinal fluid space before and after surgery and provide a reliable “disease biomarkers.” A large randomized, prospective study evaluating available surgical techniques is required to definitively determine the most successful and safest treatment options for type 1 CMs.

The Center for CSF Disorders of the Brain and Spine at the Warren Alpert Medical School of Brown University supports these endeavors, and has recently started exploring cognitive mechanisms in conditions such as hydrocephalus, CM and syringomyelia and optogenetic manipulation of chondroitin plexus cells to gain new insights into CSF physiology in collaboration with the Brown Institute for Brain Sciences and the Neuroscience Department. The annual CSF disorder symposium at the Brown medical school supports the interdisciplinary management of Chiari and related CSF disorders in collaboration with the Chiari and Syringomyelia Foundation (http://csfinfo.org/).

**References**


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Smoking is one of the most common preventable causes of poor pregnancy outcomes and is associated with maternal, fetal, and infant morbidity and mortality. Smoking before pregnancy can cause reduced fertility, infertility, and ectopic pregnancy. Smoking during pregnancy increases the risk for pregnancy complications (e.g., placental previa, placental abruption, and premature rupture of the membrane) and poor infant outcomes (e.g., low birth weight, preterm birth, restricted fetal growth, sudden infant death syndrome [SID], born with a cleft lip or cleft palate, and preterm related death). Maternal smoking after delivery increases an infant’s risk for respiratory tract infections, ear infections, severe asthma, and death from SIDS through exposure to secondhand smoke. In 2002, it was estimated that 5%–8% of preterm deliveries, 13%–19% of term low birth weight deliveries, 23%–34% of SIDS, and 5%–7% of preterm-related deaths were attributable to prenatal smoking in the United States. Two Healthy People 2020 national health objectives address smoking and smoking cessation during pregnancy; 1) reducing the prevalence of cigarette smoking among pregnant women to 1.4% (MICHI-11.8), and 2) increasing smoking cessation during pregnancy to 30.0% (TU-6). The purpose of this study was to examine the effects of smoking and smoking cessation during pregnancy on adverse birth outcomes in Rhode Island. In addition, it described the prevalence of and disparities in cigarette smoking during pregnancy.

**METHODS**

We analyzed aggregate data from the 2012-2014 Rhode Island Pregnancy Risk Assessment Monitoring System (PRAMS) (n=3,642; average weighted response rate=62.9%). PRAMS is a collaborative surveillance project of the Centers for Disease Control and Prevention (CDC) and state health departments, which collects state-specific, population-based data on maternal behaviors and experiences before, during, and shortly after pregnancy. Self-reported survey data are linked to selected birth certificate data and are weighted to represent all women delivering live infants in Rhode Island.

To estimate the prevalence of prenatal smoking, and to determine prenatal smoking status, the following survey questions were analyzed: “Have you smoked any cigarettes in the past 2 years?” “In the 3 months before you got pregnant, how many cigarettes did you smoke on an average day?” “In the last 3 months of your pregnancy, how many cigarettes did you smoke on an average day?” Prenatal smoking status was classified as “did not smoke during pregnancy,” “smoked before pregnancy but quit smoking by the last 3 months of pregnancy” and “smoked throughout the pregnancy.” Three measures of adverse birth outcomes collected from the birth certificate files were used in this study: low birth weight (<2,500 grams), preterm birth (<37 weeks’ gestation), and small-for-gestational-age (<10th percentile). To identify disparities, the prevalence of prenatal smoking was examined by various socio-demographic characteristics (maternal age, race/ethnicity, education, marital status, household income, health insurance type, parity, and assistance from WIC program). These characteristics were also used as covariates in the logistic regression model.

All data analyses were performed using SUDAAN release 11.0, which accounts for the complex sample design of PRAMS. Logistic regression was performed to assess the effects of smoking and smoking cessation during pregnancy on each measure of adverse birth outcomes, while controlling for all covariates. The p-values <.05 are considered statistically significant.

**RESULTS**

**Prevalence of Smoking during Pregnancy, 2012–2014**

Overall, 8.5% (95% CI: 7.5%-9.5%) of Rhode Island women who delivered a live infant between 2012 and 2014 smoked during the last 3 months of pregnancy. The prevalence of smoking during pregnancy varied significantly among populations (Figure 1). Women who were aged 20–29 years (11.1%), were White (10.0%), were non-Hispanic (9.9%), were unmarried (14.2%), were on WIC program (13.5%), were publicly insured (14.1%), were multiparous (10.5%), had < high school education (17.6%), had an annual household incomes < $26,000 (15.4%) were more likely to smoke during pregnancy, compared to their counterparts. None of the groups presented in Figure 1, except one group with an annual household income > $67,000, achieved the Healthy People 2020 goal of reducing the prevalence of cigarette smoking among pregnant women to 1.4%.

**Prenatal Smoking and Adverse Birth Outcomes, 2012–2014**

Among women who delivered a live birth during 2012–2014, 80.5% (95% CI: 79.0%-81.9%) were classified as “did not smoke during pregnancy,” 11.1% (95% CI: 10.0%-12.3%) were classified as “quit smoking during pregnancy,” and 8.5% (95% CI: 7.5%-9.5%) as “ smoked throughout the
Figure 1. Prevalence of smoking during the last 3 months of pregnancy by socio-demographic characteristics, Rhode Island women who delivered a live birth, RI PRAMS, 2012–2014 combined

Figure 2. Prevalence of adverse birth outcomes by maternal smoking status during pregnancy, Rhode Island women who delivered a live birth, RI PRAMS, 2012-2014 combined

Table 1. Adjusted Odds Ratio (AOR) and 95% Confidence Interval (CI) for Each Adverse Birth Outcome, Rhode Island women who delivered a live birth, RI PRAMS, 2012–2014 combined

<table>
<thead>
<tr>
<th></th>
<th>Low Birth Weight</th>
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<tr>
<td>Did not smoke during pregnancy</td>
<td>AOR 1</td>
<td>AOR 1</td>
<td>AOR 1</td>
</tr>
<tr>
<td>Quit smoking during pregnancy</td>
<td>1.05 0.84-1.31</td>
<td>0.9 0.62-1.31</td>
<td>1.22 0.81-1.84</td>
</tr>
<tr>
<td>Smoked throughout pregnancy</td>
<td>2.04* 1.57-2.65</td>
<td>1.30 0.87-1.95</td>
<td>2.55* 1.65-3.94</td>
</tr>
</tbody>
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* p<.0001

AOR: Adjusted Odds Ratio; Adjusted for Maternal Age, Race, Ethnicity, Education, Marital Status, Household Income, Health Insurance, Parity, and WIC participation.

During 2012-2014, 6.4% (95% CI: 6.3%–6.5%) of Rhode Island mothers had a low birth weight baby, 8.6% (95% CI: 7.9%–9.3%) had a preterm delivery, and 10.1% (95% CI: 9.2%–11.1%) had a small-for-gestational-age baby.

Figure 2 presents the prevalence of each adverse birth outcome in relation to prenatal smoking status. Compared to women who did not smoke during pregnancy, women who smoked throughout the pregnancy were significantly more likely to have a low birth weight baby (6.0% vs. 10.7%), a preterm baby (8.2% vs. 12.9%), and a small-for-gestational-age baby (9.1% vs. 18.5%). However, there were no significant differences between women who did not smoke during pregnancy and women who quit smoking during pregnancy in the prevalence of all three measures of adverse birth outcomes.

Table 1 presents the adjusted odds ratios (AOR) and 95% confidence intervals (CI) from the logistic regression analyses for each adverse birth outcome measure. After adjusting for all socio-demographic factors shown in Figure 1, women who smoked throughout the pregnancy had twice the odds of having a low birth weight baby (AOR=2.04; 95% CI=1.57-2.65; p<.0001) and 2.6 times the odds of having a small-for-gestational-age baby (AOR=2.55; 95% CI=1.65-3.94; p<.0001), compared with women who did not smoke during pregnancy. However, preterm birth became not significant when all covariates were controlled for. Consistent with the results in Figure 2, there were no significant differences between women who did not smoke during pregnancy and women who quit smoking during pregnancy in the odds of adverse birth outcomes for all three measures.

**LIMITATIONS**

The findings in this article are subject to at least two limitations. First,
the smoking data in this study relied on self-reporting. Pregnant women might under-report smoking and over-report quitting smoking during pregnancy. Second, the PRAMS sample includes only women who delivered a live infant, and excludes women who experienced a miscarriage or still-birth that is likely related to smoking during pregnancy. Therefore, the actual prevalence of smoking among all pregnancies might be higher than the estimates presented here.

**DISCUSSION**

The main finding of this study is that although smoking during pregnancy significantly increases the risk for certain adverse birth outcomes, quitting smoking during pregnancy substantially reduces these risks. Women who smoked throughout their pregnancy, compared with women who did not smoke during pregnancy, had significantly higher odds of poor birth outcomes (e.g., low birth weight and small-for-gestational-age). However, when comparing women who quit smoking during pregnancy with women who did not smoke, no differences were found in the odds of low birth weight, preterm birth, and small-for-gestational-age. The results of this study provide a compelling message that smoking cessation is not only possible, but critical, for pregnant smokers to reduce the risk of adverse birth outcomes. In addition, our data also show that 1 in 12 Rhode Island women who delivered a live infant during 2012-2014 smoked in the last 3 months of pregnancy, and there were significant disparities among populations in prenatal smoking prevalence.

These new data can be strategically used by providers to communicate the benefits of quitting, increase motivation to quit, and engage pregnant smokers in supportive services that help them quit and stay quit. For example, the Rhode Island Tobacco Control Program coordinates with the WIC program to promote motivating cessation messages that link pregnant smokers to free, evidence-based telephonic counseling specifically tailored to the needs of pregnant women. Through the Rhode Island Quitline (1-800-Quit-Now), women can access extended counseling during pregnancy and receive relapse prevention counseling through post-partum. When offering cessation services to patients, providers can refer pregnant smokers to the Quitline by fax referral so they have extra support.

Pregnancy appears to motivate women to quit smoking: 55% of Rhode Island women who smoked before pregnancy stopped smoking by the last 3 months of pregnancy in 2014.4 While effective interventions such as motivational interviewing, brief cessation counseling (the 5 A’s) and supplementary referral to the Quitline help many women, some pregnant women are highly addicted to nicotine and require consistent intervention at each health care encounter.3 Health care providers can help increase smoking cessation among pregnant women by routinely integrating tobacco use assessment and cessation interventions into each prenatal care visit.4 As most women have more than 10 prenatal care visits during pregnancy, providers have multiple opportunities [from the first prenatal care visit throughout the course of pregnancy] to motivate smokers to quit and provide effective cessation interventions.3 It is also recommended that since nearly 40% of pregnancies in Rhode Island are unintended, public health efforts should target all reproductive-age women, regardless of pregnancy status or pregnancy intention, to refrain from smoking to reduce maternal, fetal, and infant morbidity and mortality.

**References**

1. CDC. PRAMS and Smoking. Available at www.cdc.gov/prams/tobaccoandprams.htm
6. CDC. PRAMS. Available at www.cdc.gov/prams/

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**Disclosure of Financial Interests**

The authors have no financial interests to disclose.

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Rhode Island Monthly Vital Statistics Report
Provisional Occurrence Data from the Division of Vital Records

<table>
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<tr>
<th>VITAL EVENTS</th>
<th>REPORTING PERIOD</th>
<th>12 MONTHS ENDING WITH DECEMBER 2016</th>
<th>Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DECEMBER 2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>Number</td>
<td></td>
</tr>
<tr>
<td>Live Births</td>
<td>924</td>
<td>11,655</td>
<td>11.0*</td>
</tr>
<tr>
<td>Deaths</td>
<td>928</td>
<td>10,014</td>
<td>9.5*</td>
</tr>
<tr>
<td>Infant Deaths</td>
<td>11</td>
<td>66</td>
<td>5.7#</td>
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<tr>
<td>Neonatal Deaths</td>
<td>7</td>
<td>52</td>
<td>4.5#</td>
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<tr>
<td>Marriages</td>
<td>376</td>
<td>7,085</td>
<td>6.7*</td>
</tr>
<tr>
<td>Divorces</td>
<td>261</td>
<td>3,002</td>
<td>2.8*</td>
</tr>
<tr>
<td>Induced Terminations</td>
<td>237</td>
<td>2,278</td>
<td>195.5#</td>
</tr>
<tr>
<td>Spontaneous Fetal Deaths</td>
<td>57</td>
<td>522</td>
<td>44.8#</td>
</tr>
<tr>
<td>Under 20 weeks gestation</td>
<td>52</td>
<td>448</td>
<td>38.4#</td>
</tr>
<tr>
<td>20+ weeks gestation</td>
<td>5</td>
<td>74</td>
<td>6.3#</td>
</tr>
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</table>

* Rates per 1,000 estimated population
# Rates per 1,000 live births

<table>
<thead>
<tr>
<th>Underlying Cause of Death Category</th>
<th>REPORTING PERIOD</th>
<th>12 MONTHS ENDING WITH JUNE 2016</th>
<th>Rates (b)</th>
<th>YPPL (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JUNE 2016</td>
<td></td>
<td>Number (a)</td>
<td></td>
</tr>
<tr>
<td>Diseases of the Heart</td>
<td>149</td>
<td>2,363</td>
<td>223.7</td>
<td>3,846.0</td>
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<tr>
<td>Malignant Neoplasms</td>
<td>190</td>
<td>2,243</td>
<td>212.3</td>
<td>5,444.5</td>
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<tr>
<td>Cerebrovascular Disease</td>
<td>34</td>
<td>436</td>
<td>41.3</td>
<td>505.0</td>
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<tr>
<td>Injuries (Accident/Suicide/Homicide)</td>
<td>79</td>
<td>866</td>
<td>82.0</td>
<td>12,604.0</td>
</tr>
<tr>
<td>COPD</td>
<td>31</td>
<td>452</td>
<td>42.8</td>
<td>387.5</td>
</tr>
</tbody>
</table>

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.
(b) Rates per 100,000 estimated population of 1,056,298 (www.census.gov)
(c) Years of Potential Life Lost (YPPL).

NOTE: Totals represent vital events, which occurred in Rhode Island for the reporting periods listed above.
Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.
First, do no harm.

Second, have great insurance.

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Informative.

Respectful of your time.

**RIMS NOTES**
is published electronically on alternate Fridays.

Contact Sarah if you’ve missed an issue, sstevens@rimed.org.
Working for You: RIMS advocacy activities

May 1, Monday
AMA Advocacy Resource Center
Executive Committee conference call
RIMS Board of Directors meeting:
Sarah J. Fessler, MD, President

May 2, Tuesday
RIMS Physician Health Committee:
Herbert Rakatansky, MD, Chair
Meeting with Chairman Miller, Senate
Health and Human Services Committee
regarding legislation
Department of Health Health Services
Council regarding Rhode Island Hospital
and Women & Infants obstetrics
Certificates of Need
Anti-conversion Therapy press
conference at the State House
Legislative hearings

May 3, Wednesday
Legislative Hearings
RIMS Patient Safety Initiative
committee meeting

May 4, Thursday
Legislative Hearings

May 5, Friday
New England Delegation to the AMA
and Council of New England State
Medical Societies reception

May 6, Saturday
New England Delegation to the AMA
and Council of New England State
Medical Societies spring meeting

May 8, Monday
Department of Health
Board of Nursing meeting
Legislative Hearings

May 9, Tuesday
AMA Advocacy Resource Center
conference call
Legislative hearings
RIMS Foundation Strategic
Planning meeting

May 10, Wednesday
Board of Medical Licensure
and Discipline Task Force
Meeting of the Governor’s Opioid
Overdose Prevention Task Force:
Sarah J. Fessler, MD, President;
Gary Bubly, MD, Past President
AMA Conference Call regarding
federal health care reform
Legislative hearings
RIMS Nominating Committee:
Sarah J. Fessler, MD, President
Citizen Physicians at WAMS

May 11, Thursday
Consultation with Anchor Medical
Associates regarding diabetes prevention
strategies
Legislative hearings
SIM Grant Steering Committee:
Peter A. Hollmann, MD, Vice President
Senator Archambault fundraiser

May 12, Friday
Conference call with RI ACEP regarding
political fundraising
Diabetes Prevention Stakeholders’ Group
Bryant University PA Program fundraising
gala for Heart Association, Officers' Club,
Newport

May 16, Tuesday
CME Directors’ meeting, Waltham, MA:
Patrick J. Sweeney, MD, MPH,
RIMS CME Chair; RIMS staff
OHIC Health Insurance Advisory
Committee
Senate Majority Leader McCaffrey
fundraiser

May 17, Wednesday
RI Department of Health’s Primary Care
Physician Advisory Committee
Meeting with Brown medical students
regarding Citizen Physician
Governor’s Food Strategy event,
State House
Legislative Hearings
Senator Goldin fundraiser

May 18, Thursday
RIMS Foundation consultant interview
Legislative hearings
House HEW Chair McNamara fundraiser

May 19, Friday
RI Workers Compensation Reform
25th Anniversary celebration
Conference call with Blue Cross dental
coverage

May 23 Tuesday
Legislative hearings

May 25, Thursday
RIMS Foundation strategic planning

May 26, Friday
Presentation of two RIMS awards
to graduating medical students:
Sarah J. Fessler, MD, President

May 30, Tuesday
Meeting with WAMS faculty
regarding special projects

May 31, Wednesday
Senator Lombardi fundraiser
Non-Patient Centered Medical Home
(PCMH) Small Practice Engagement
meeting
MACRA Symposium planned for June 20

Are you ready for MACRA? Are you struggling to understand what MACRA means for your organization? Are you having trouble preparing for this new payment program?

Our MACRA Symposium will provide expert guidance to help you to better understand the quality payment program, the impact on healthcare providers, and how you can best prepare. A panel discussion of local healthcare professionals will discuss their concerns and how they’re preparing.

**JUNE 20, 7:30AM**
New England Institute of Technology
1 New England Tech Boulevard
East Greenwich

**AGENDA**

7:30–8:00 am
Registration/ Breakfast/Networking

8:00–9:00 am
The Mechanisms of MACRA Reporting: MIPS and APM Tracks
Leila Volinsky, MHA, MSN, RN
Program Administrator, Massachusetts, Healthcentric Advisors

9:10–10:10 am
Demystifying MACRA
Terrence McWilliams, MD, MSJ, FAAFP
Chief Clinical Consultant, HSG

10:20–11:50 am
Panel Discussion
Rhode Island Responses and Perspectives
Moderator:
Peter Hollmann, MD
Chief Medical Officer, University Medicine

Panelists:
Alan Kurose, MD, MBA, FACP
President & CEO, Coastal Medical
Ann Kashmanian, CPA, MBA
Chief Financial Officer & Compliance Officer
University Medicine
Lauren Capizzo, MBA, PCMH CCE
Director, Practice Transformation
Healthcentric Advisors

Healthcentric Advisors is accredited by the Massachusetts Medical Society to provide continuing medical education for physicians.

This program has been developed and is presented locally by ACHE-RI. The American College of Healthcare Executives has awarded 1.5 ACHE Face-to-Face Education Credits to this program.

As an independent chartered Chapter of the American College of Healthcare Executives, ACHE-RI is also authorized to award two hours each of ACHE Qualified Education credit toward advancement or recertification in the American College of Healthcare Executives. Participants in this program who wish to have it considered for ACHE Qualified Education credit should list their attendance when they apply to the American College of Healthcare Executives for advancement or recertification.

The event is co-sponsored by:
Rhode Island Medical Society
Hospital Association of Rhode Island
Healthcentric Advisors

**Click here to register**

For further information, contact:
Amanda Barney
amandab@hari.org.
It’s a new day.

The Rhode Island Medical Society now endorses Coverys.

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Doctor’s Choice provides no cost Medicare consultations. Doctor’s Choice was founded by Dr. John Luo, a graduate of the Alpert Medical School at Brown University to provide patient education and guidance when it comes to choosing a Medicare Supplemental, Advantage, or Part D prescription plan. Doctor’s Choice works with individuals in RI, MA, as well as CT and helps compare across a wide variety of Medicare plans including Blue Cross, United Health, Humana, and Harvard Pilgrim.

Neighborhood Health Plan of Rhode Island is a non-profit HMO founded in 1993 in partnership with Rhode Island’s Community Health Centers. Serving over 185,000 members, Neighborhood has doubled in membership, revenue and staff since November 2013. In January 2014, Neighborhood extended its service, benefits and value through the HealthSource RI health insurance exchange, serving 49% the RI exchange market. Neighborhood has been rated by National Committee for Quality Assurance (NCQA) as one of the Top 10 Medicaid health plans in America, every year since ratings began twelve years ago.

RIPCPC is an independent practice association [IPA] of primary care physicians located throughout the state of Rhode Island. The IPA, originally formed in 1994, represent 150 physicians from Family Practice, Internal Medicine and Pediatrics. RIPCPC also has an affiliation with over 200 specialty-care member physicians. Our PCP’s act as primary care providers for over 340,000 patients throughout the state of Rhode Island. The IPA was formed to provide a venue for the smaller independent practices to work together with the ultimate goal of improving quality of care for our patients.

The Rhode Island Medical Society continues to drive forward into the future with the implementation of various new programs. As such, RIMS is expanded its Affinity Program to allow for more of our colleagues in healthcare and related business to work with our membership. RIMS thanks these participants for their support of our membership.

Contact Marc Bialek for more information: 401-331-3207 or mbialek@rimed.org
RIMS: Your Voice for 200+ Years
Join your colleagues and add your voice

Membership in The Rhode Island Medical Society (RIMS) makes you a part of a dynamic network of physicians, residents, students, physician assistants, and healthcare professionals who represent, like you, the best of the profession.

The ABCs of membership

Advocacy: RIMS membership offers a cohesive platform for its members to speak with a unified voice on local, state and national issues through committee participation, policy development, legislative representation, educational conferences, and stakeholder seminars.

Benefits: CME sessions, physician health services, preferred career, financial and personal services from our sponsors, membership portal.

Collegiality: Social events, networking opportunities, professional development.

Strength: In numbers. If you are already a member, thank you for your support. If you’re not, join us today. Group, military and new practitioner discounts; medical students join for free.

Click here to learn more.

Contact Mark Bialek, Director of Membership

A Rhode Island Academy of Physician Assistants (RIAPA) town hall meeting was held April 11 at Kent Hospital on PA practice in the state. Representatives from the state and national PA organizations and the Rhode Island Department of Health and the Rhode Island Medical Society participated in a series of meetings and updates on recertification and looking at the future of PA practice in the state.

A RIMS Mix and Mingle event was held at the Chapel Grille restaurant in Cranston on April 11.
RIMS gratefully acknowledges the practices who participate in our discounted Group Membership Program

For more information about group rates, please contact Marc Bialek, RIMS Director of Member Services
Washington Trust is actively lending to local healthcare providers throughout the region, financing solutions that allow them to provide exceptional quality client care and remain competitive, just as we have done for more than 200+ years. For more information, call us at 401-348-1200 or 401-331-5090.
Alpert Medical School, 6 foundations partner to form Brown Physicians, Inc.

Physician groups include: The Neurology Foundation, Inc.; University Emergency Medicine Foundation; University Medicine Foundation; University Surgical Associates, Inc.; Brown Urology, Inc.; and Brown Dermatology, Inc.

PROVIDENCE — Six physician practice foundations have agreed to form a new physician-led federation, Brown Physicians, Inc., in partnership with the Warren Alpert Medical School of Brown University.

Members of the Corporation of Brown University joined the presidents of the six foundations in signing a formal agreement at a ceremony at Brown May 25, to create the nonprofit Brown Physicians, Inc. (BPI). The foundations are: The Neurology Foundation, Inc.; University Emergency Medicine Foundation; University Medicine Foundation; University Surgical Associates, Inc.; Brown Urology, Inc.; and Brown Dermatology, Inc.

The agreement will take effect on July 1, 2017. At the outset, the foundations will retain their status as individual corporations within the BPI federation. Caliendo said the agreement outlines parameters for further integration in the future to achieve evolving goals for expansion and growth.

In forming the partnership, both the physician practice foundations and Brown’s medical school will invest financially to ensure BPI’s success in both the short and long term. The University will contribute funds toward operations during BPI’s first decade and raise funds to endow professorships and make new hires within the partnership. Meanwhile, the members of the foundations will contribute a modest percentage of revenues toward supporting research and other academic activities.

Together, the six foundations employ more than 500 doctors, all of whom are also members of the Warren Alpert Medical School faculty, and many of whom work side-by-side in local hospitals with physicians and other health care providers employed by the hospitals.

DR. JACK A. ELIAS, senior vice president for health affairs and dean of medicine and biologic sciences at Brown, will join the presidents of the foundations and a second Brown appointee to form BPI’s board of directors. He said the new organization will enable enhanced partnership between the foundations, Brown and its affiliated hospitals as they seek to develop new therapies in laboratories and deliver the best medical care in clinical settings.

“I look forward to working with my colleagues to identify and implement a strategic approach that will help clinicians across important specialties identify efficient, effective ways to improve care for patients across the region,” Elias said. “BPI will yield new opportunities for our Brown medical students, focus resources on urgent areas of innovative research and enhance our ability to hire the best physician-scientists.”

Discussions on the effort to form BPI began among Brown’s medical school leaders, clinical faculty and affiliated health care providers approximately five years ago, Elias noted, and the partners worked over the last 15 months to outline an agreement.

DR. ANGELA CALIENDO, vice president of University Medicine and BPI’s interim executive director, said the foundations and their physicians will experience many benefits from sharing administrative resources, such as greater operating efficiency.

“Forming BPI is an important step, as it provides the foundations with the opportunity to enhance coordination of care, improve the quality of care for patients in RI and the region, better position us for success in the changing healthcare environment, and facilitate partnerships with the hospitals,” said Caliendo, who is also a professor of medicine at Brown.

“The creation of BPI also underscores our commitment to the research and teaching missions of the medical school.”

Elias and Caliendo noted that the potential for improved patient care in the region is an important focus of the agreement. While patients of the six foundations will face no practical changes to how they receive care, they stand to benefit from enhanced administrative and medical coordination. Over the longer term, greater collaboration on research can lead to the development of advanced therapies that will ultimately benefit patients.

“We believe that collaborating with our clinical partners to more tightly integrate patient care, research and education will result in a significant and positive impact on the local community,” said University President Christina Paxson.

The creation of BPI will enhance the ability of its members to serve the community’s health care needs, Paxson explained, to optimally educate the next generation of medical professionals, to grow combined research portfolios, and to contribute to the state’s plans to cultivate a thriving biomedical economy in Providence and the greater region.

Dr. Jack A. Elias, senior vice president for health affairs and dean of medicine and biologic sciences at Brown, signs a new agreement creating BPI as Dr. Angela Caliendo, vice president of University Medicine Foundation and interim executive director of BPI looks on.
In The News

New Secretary of Veterans Affairs, Dr. David J. Shulkin, visits Providence VA, Veterans Home

Dr. Susan D’Andrea, director of the Virtual Reality and Motion Analysis Rehabilitation Laboratory, demonstrates to Veterans Affairs Secretary Dr. David Shulkin and Sen. Jack Reed a virtual reality system that creates virtual environments and uses motion-capture cameras to animate an avatar in the virtual environment based on the motion of an individual walking on a treadmill in the real world. She said the system provides effective training by creating realistic and challenging environments with accurate visual perception of a motor task being performed by the user.

Shulkin concluded his visit by challenging Providence VAMC and Rhode Island officials to effectively end Veterans homelessness in the state within the next few years, noting the progress already made and how close they are to the goal.


Scheduled to open in the fall, the facility is being built using new federal design guidelines that maximize independent living.

PROVIDENCE – The new Secretary of Veterans Affairs, Dr. David J. Shulkin, visited Rhode Island May 5 to participate in a cornerstone ceremony at the Rhode Island state Veterans Home and visit the Providence VA Medical Center.

After the ceremony, the secretary traveled to the Providence VAMC, and received a tour of the Virtual Reality lab. Dr. Noah Philip, director of the Neuromodulation Clinic, described non-invasive brain stimulation research that will help Veterans suffering from PTSD.

Shulkin was then shown DEKA, the first computer-driven prosthetic arm capable of multiple simultaneous movements.

Next was a tour of the Virtual Reality and Motion Analysis Rehabilitation Laboratory. Dr. Susan D’Andrea, lab director, said the system creates realistic and challenging virtual environments for training and rehabilitation.

The secretary then received briefings on selected research and facility achievements, and discussed his priorities.

Shulkin said that VA strategy is focused on transparency, and that new access and quality of care information is now available to Veterans on the VA access website, www.accesstocare.va.gov.

Dr. Leigh Hochberg, director of the VA Center for Neurorestoration and Neurotechnology, gave a presentation on BrainGate, a neuroscience consortium that includes Brown University and the PVAMC, and research on new technologies for brain-computer interface.

Dr. James Rudolph, director of the Center of Innovation in Long-Term Services and Supports for Vulnerable Veterans, gave a briefing on research to improve the access, quality and value of care for Veterans in nursing homes.

Dr. JAMES RUDOLPH, director of the Center of Innovation in Long-Term Services and Supports for Vulnerable Veterans, gave a briefing on research to improve the access, quality and value of care for Veterans in nursing homes.
WE QUIT is enrolling women who want to quit smoking and are concerned about gaining weight after quitting.

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WE QUIT is funded by the National Institutes of Health
Health insurers to end prior authorization for opioid dependency medications

Agreements reached with all of Rhode Island’s major commercial insurers

Cranston – Dr. Kathleen Hittner, Health Insurance Commissioner for the State of Rhode Island, has executed agreements with all major commercial health insurers in the state to end the practice of requiring prior authorization for certain prescription drugs used to treat patients with opioid dependence disorders.

“I am very pleased to announce these agreements, which will greatly improve access to necessary medications for patients with opioid dependence disorders,” Dr. Hittner said. “Working together with Rhode Island’s health insurers, we’ve found a way to streamline processes for coverage of these treatments. I am grateful for the insurers’ collaboration and commitment to fighting this public health crisis.”

All four major health insurers – Blue Cross & Blue Shield of Rhode Island, Neighborhood Health Plan of Rhode Island, Tufts Health Plan, and United Healthcare – joined in the agreement to eliminate prior authorizations for patients prescribed medications such as buprenorphine and Suboxone. The agreements will allow opioid dependent patients more timely access to medications.

The Office of the Health Insurance Commissioner is currently conducting a Market Conduct Examination for Mental Health and Substance Abuse Parity. Commissioner Hittner said the ongoing examination “led my staff and me to reach out to the insurance carriers and begin to consider ways to improve access to MAT.”

Southcoast Health opens Urgent Care center in Seekonk

Seekonk – Southcoast Health opened its new Urgent Care center May 1. The 4,800 square-foot center provides immediate, non-emergency care. It is staffed by a specialized team of physicians, mid-level providers and a number of ancillary and support staff, and offers a full array of services including on-site radiology and laboratory services, basic orthopedics, gynecologic and minor surgical treatments, and medications.

Open seven days a week, the center treats both adults and children (6 months of age and older). Walk-ins are welcome, and no appointment is needed. Patients are not required to have a Southcoast primary care physician, and the patient’s primary care physician is electronically alerted to the visit.

Patients seeking services can now use a new online check-in system. Visitors to www.southcoast.org/urgentcare can find the closest center, its current wait time and click “Save My Spot” to get in line electronically.

The new facility in Seekonk is Southcoast Health’s fourth Urgent Care center.
Southcoast Health partners with Stratus Video to improve care for limited English proficiency and Deaf/Hard-of-Hearing patients

Health system offers video remote interpretation for patients throughout Southeastern Mass.

NEW BEDFORD – Southcoast Health has partnered with language access and telehealth company, Stratus Video, to better serve its limited English proficiency (LEP) and Deaf/Hard-of-Hearing patients. The community-based health system now provides easy access to video remote interpretation (VRI) at all three of its hospitals in Southeastern Massachusetts.

Ever-expanding language diversity, coupled with evolving federal regulations of the Americans with Disabilities Act (ADA), has brought on-demand interpreting from a “nice-to-have” to “mission-critical” for health systems looking to provide quality care for all patients. For Southcoast Health, there were 42,195 interpretation requests across all of its hospitals in FY 2015, of which 24,486 were for Spanish, alone. The health system realized the need to offer its diverse patient population access to a broader array of simple and effective communication tools.

“We are very focused on leveraging innovation to promote health and well-being in the communities and populations we serve, and our LEP population is no exception,” said DR. ROBERT CALDAS, Chief Medical Officer and Senior Vice President of Southcoast Health. “We have been so pleased with how Stratus Video Interpreting has helped enhance communication and care delivery in our hospitals that we are now beginning to discuss rolling the VRI technology out to our affiliated physician practices.”

Stratus Video Interpreting combines the benefits of face-to-face interpretation with the on-demand nature of over-the-phone interpretation. The mobile app is easy to use and can be loaded onto any tablet, smartphone, desktop or laptop, giving users instant access to medically qualified interpreters at a push of a button. On the back-end, the technology incorporates sophisticated automation and intelligent routing, enabling easy integration into existing processes and workflows.

www.rimed.org | archives | june webpage

IN THE NEWS
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Blackstone Valley Surgicare acquired by CharterCARE Health Partners

“CharterCARE’s breadth of services, contracting expertise and capital strength will ensure stability and growth for our organization in the years ahead.”

Blackstone Valley Surgicare is fully licensed by the state of Rhode Island, certified by Medicare and accredited by AAAHC, and accepts all major insurance.

Ann Dugan, administrator, is pictured discussing Blackstone Valley Surgicare’s capabilities with Johnston Mayor Joseph Polisena and John Holiver, CharterCARE CEO.

JOHNSON – Blackstone Valley Surgicare, an ambulatory surgery center in Johnston, has been acquired from Surgical Care Affiliates by CharterCARE Health Partners. The purchase was approved by the Rhode Island Department of Health last month.

“This acquisition will ensure CharterCARE patients with direct access to a complete range of outpatient surgery procedures and will continue the process of completing our service capabilities,” said CharterCARE President and CEO John Holiver.

“We are delighted to become part of the CharterCARE network”, said Blackstone Administrator ANN DUGAN.

OFFICE SPACE AVAILABLE

The Rhode Island Medical Society has 442 square feet of newly renovated office space (3 contiguous offices of 200 sq ft, 121 sq ft and 121 sq ft), complete with convenient sheltered parking and the opportunity for tenants to share three well-equipped meeting spaces, break room, office machinery, etc. on the western edge of downtown Providence. Suitable for a small non-profit organization, boutique law firm, CPA firm or other office-based small business.

Inquiries to Newell Warde, nwarde@rimed.org
Rhode Island’s Medical Staffing Experts!

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Research evaluates effectiveness of yoga in treating major depression

When treating depression, traditional treatment such as medication or psychotherapy is effective for many patients, some may not fully recover even with these treatments. Researchers sought to determine if the addition of hatha yoga would improve treatment outcomes. They found that the benefits of yoga were less pronounced early in treatment, but may accumulate over time.

The research, entitled “Adjunctive yoga v. health education for persistent major depression: a randomized controlled trial,” has been published in Psychological Medicine. The research was led by Lisa Uebelacker, PhD, a research psychologist in the Psychological Medicine.

“Adjunctive yoga v. health education for persistent major depression: a randomized controlled trial,” explained Dr. Uebelacker.

“We did not see statistically significant differences between hatha yoga and a control group (health education) at 10 weeks, however, when we examined outcomes over a period of time including the three and six months after yoga classes ended, we found yoga was superior to health education in alleviating depression symptoms.”

According to Dr. Uebelacker, this is the largest study of yoga for depression to date. The team enrolled individuals with current or recent major depression who were receiving antidepressant medication and continued to have clinically significant depression symptoms. Participants were randomized into two groups – those who participated in a hatha yoga class and a control group who took part in a health education class. The intervention phase lasted 10 weeks and participants were followed for six months afterward.

“We hypothesized that yoga participants would show lower depression severity over time as assessed by the Quick Inventory of Depression Symptomatology (QIDS), as well as better social and role functioning, better general health perceptions and physical functioning, and less physical pain relative to the control group,” said Dr. Uebelacker. “We found that yoga did indeed have an impact on depression symptoms.

The team also included Gary Epstein-Lubow, MD; Ana M. Abrantes, PhD; Audrey Tyrka, MD, PhD; Brandon A. Gaudiano, PhD; and Ivan W. Miller III, PhD, of Butler Hospital and the Warren Alpert Medical School; Geoffrey Tremont, PhD and Tanya Tran of Rhode Island Hospital and the Warren Alpert Medical School; Tom Gillette of Eyes of the World Yoga; and David Strong of the University of California, San Diego.

Women & Infants awarded $12.2M NIH grant

First COBRE of its size, only one in the U.S. to focus on women’s health

Women & Infants Hospital has been awarded a $12.2 million National Institutes of Health (NIH) Center of Biomedical Research Excellence (COBRE) grant to boost interdisciplinary research related to women’s reproductive health. This is the first COBRE of its size and the only one to focus on women’s health.

“We’re very excited about this opportunity,” said SURENDRAR SHARMA, MD, PhD, a research scientist and professor in the Department of Pediatrics at Women & Infants Hospital and The Warren Alpert Medical School.

“The question that remains unanswered is how complications suffered by a woman during pregnancy provide insight into other future adverse health outcomes.”

Dr. Sharma will serve as the principal investigator for the COBRE for Reproductive Health. MAUREEN G. PIPPS, MD, MPH, chief of obstetrics and gynecology at Women & Infants, will serve as Deputy Director of the program.

Four investigators will be participating at Women & Infants Hospital:

LYNAE BRAYBOY, MD, a reproductive endocrinologist, proposes a study on the prediction of preeclampsia and gestational diabetes in in vitro fertilization (IVF) patients.

SHIBIN CHENG, MD, PhD, a research scientist, will continue his studies into preeclampsia, which also focuses on the concept that preeclampsia may be a prelude to Alzheimer’s disease, a significant disease affecting women later in life.

BEATRICE LECHNER, MD, a neonatologist, will continue her studies into complications causing pre-term birth. Along with a high rate of mortality in newborns, preterm birth has also been associated with a high rate of mortality in mothers, suggesting its long-term health effects on women.

JESSICA S. SCHUSTER, PhD, instructor of pediatrics and a computational biologist in the Department of Pediatrics, will continue her study which focuses on women diagnosed with severe preeclampsia and on using contemporary mathematical and computer science approaches to find answers to scientific questions related to preeclampsia.

IN THE NEWS
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**Appointments**

**Jonathan Kurtis, MD, PhD, named inaugural Stanley M. Aronson Professor**

Jonathan Kurtis, MD, PhD, director of the Center for International Health Research (CIHR), Rhode Island Hospital, and Professor of Pathology and Laboratory Medicine at the Alpert Medical School, has been appointed the inaugural Stanley M. Aronson Professor. The professorship was established by Alice Montag Tisch ’18, P’20 and Thomas Tisch ’76, P’18, P’20 in honor of the founding dean of Brown’s medical school, the late Stanley M. Aronson, MD.

**Dana Levy Guyer, MD, named medical director, Hope Hospice & Palliative Care**

Dana Levy Guyer, MD, has been named medical director of Hope Hospice & Palliative Care Rhode Island, where she will serve as the physician member of the Rhode Island Hospital interdisciplinary palliative care team.

Formerly, Dr. Guyer worked as a primary care physician and palliative care consultant at Martha’s Vineyard Hospital. She served as medical director at Hospice of Martha’s Vineyard and was the palliative care consultant at Martha’s Vineyard Hospital Oncology Clinic.

**Jack A. Elias, MD, named inaugural Senior Vice President for Health Affairs**

Dean of Medicine and Biological Sciences Jack A. Elias, MD, has been appointed the inaugural Senior Vice President for Health Affairs at Brown University. In this position, Dean Elias will continue to oversee the Alpert Medical School and the Division of Biology and Medicine’s components of the Brown Institute for Brain Science (BIBS). He will also oversee the newly constituted Brown Institute for Translational Sciences (BITs) and Brown Biomedical Innovations Inc. (BBII).

**Recognition**

**Elaine C. Jones, MD, honored by American Academy of Neurology**

Elaine C. Jones, MD, FAAN, has received the Kenneth M. Viste, Jr, MD “Patient Advocate of the Year Award for 2017” from the American Academy of Neurology (AAN). She currently serves on the AAN Board of Directors.

Dr. Jones has served as president of the Rhode Island Medical Society, treasurer of the RI Medical Political Action Committee, [RIMPAC], vice-chair of the Public Laws Committee and co-chair of the Membership Committee.

**Dr. Kenneth Chen receives Beckwith Family Award**

Kenneth K. Chen, MD, was recently presented with the Department of Medicine’s Beckwith Family Award for Outstanding Teaching at The Warren Alpert Medical School.

Dr. Chen is director of the Division of Obstetric and Consultative Medicine and co-director of the Integrated Program for High-Risk Pregnancy at Women & Infants Hospital.

Recipients of the award are nominated and chosen by students, residents, fellows, physicians, and program/course directors in Brown’s Department of Medicine.

**Dr. Linda Resnik recognized for work with veterans**

Dr. Linda Resnik, a research scientist with the Providence VA Medical Center, has been awarded the Paul B. Magnuson Award for her work with veterans who have experienced upper-limb loss. It is presented annually to a VA investigator who exemplifies entrepreneurship, humanitarianism and dedication to veterans.

Resnik directed the Department of Veterans Affairs (VA)-funded optimization study, which led to the approval of the Life Under Kinetic Evolution Arm for Veterans with upper-limb amputation.

**William H. Sabina, MD, named Physician of the Year at South County Hospital**

William H. Sabina, MD, chief of emergency medicine at South County Hospital, was named 2016 Physician of the Year. CEO Lou Giancola described Dr. Sabina as “incredibly dedicated,” making a positive impact on South County Health as chief of the emergency department, past president of the medical staff, chairman of the utilization review committee and as a former member of the board of trustees.
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ROBERT EMMETT CURRAN, JR, MD
76, of Seekonk, MA, passed away peacefully at his home on May 2, 2017 with his family by his side.

He graduated cum laude from the College of the Holy Cross in Worcester, MA in 1962. He graduated from Cornell Medical College in New York City in 1966 where he was inducted into the Alpha Omega Alpha Academic Honor Society in his third year.

He completed residencies at Cornell/New York Hospital Medical Center in New York City; the National Cancer Institute at the National Institutes of Health in Bethesda, MD; and The Wilmer Institute at The Johns Hopkins Hospital and University in Baltimore, MD; and completed a fellowship at The Children’s Hospital Medical Center in Boston, MA.

Dr. Curran had a private ophthalmology practice in Pawtucket, for 42 years. He served as the Chief of the Division of Ophthalmology at Memorial Hospital in Pawtucket from 1977–2013.

He was also Clinical Assistant Professor of Surgery in ophthalmology at Brown Medical School from 1977–2016 where he was awarded multiple distinctions for teaching at the Eye Clinic at Rhode Island Hospital.

Over the course of his career, Dr. Curran published sixteen scientific papers on topics ranging from internal medicine to pediatric ophthalmology.

He is survived by his wife, Margareta “Peggy” Cox Curran; his children Robert Emmett Curran, III and wife Meredith Wirsching, Trevor McIntosh Curran of Seekonk, and Victoria Cox Curran and husband Trevor Eppehimer of Salisbury, NC; his grandchildren Grace and Nicholas, his sister Kitty Barrett; his brothers-in-law Robert Cox, Esq., Douglas Cox, and Jack Gallagher; his sisters-in-law Kate Cox, Dr. Kathryn Cox, and cousin Richard Curran. He also leaves numerous nieces and nephews who loved their Uncle Bob.

Donations in his memory may be made to the Comprehensive Cancer Center at The Miriam Hospital Cancer Center, 164 Summit Avenue, Providence, RI 02906.
**Editorial**

**Scientific feeding of the people in wartime**

Much has been written in these anxious times concerning the conservation of food, and the necessity for planting a greatly increased acreage in this country in order to offset the losses occasioned by decreased planting in Europe, by submarine activities and by poor crops. More important than the conservation of food, as necessary as that is known to be, is the proper nutrition of the people. This can be accomplished by an intelligent supervision of the dietary, so that the greatest number of caloric units may be obtained from the smallest intake of food, and the elimination of expensive food and those of low caloric value. The greater necessity of proper nutrition for everyone in these times of unusual stress has been appreciated by local organizations of which the Housewives League is an example. In conjunction with other organizers working along similar lines, a series of demonstrations on the proper selection of a dietary are being planned at neighborhood clubs, factories and department stores. This is an endeavor in which physicians can be of especial help. It should be a patriotic duty for us to offer gratuitous advice on the proper feeding of the family in every home we visit. We can outline a proper diet producing the greatest caloric value which will at the same time be palatable and help to conserve the food supply of the country. Special attention should be paid to the diet of babies and in growing children in order that the unfortunate experience of some European countries shall not be repeated in this country. It is more important than ever before that the milk supply shall be maintained at the highest possible standard.

*Poster from the U.S. Department of Agriculture encouraging Americans to grow their own food to combat the shortages.*
Doctor, have **you** ever suffered from **throat irritation** due to smoking?

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Miscellaneous

Hospital units for mental and nervous disorders
The National Committee for Mental Hygiene has created a subcommittee on furnishing hospital units for nervous and mental disorders to the United States government; the project has been approved by Surgeon General W.C. Gorgas of the US Army.

This subcommittee is authorized to secure the services of alienists and neurologists to be commissioned in the Officer Reserve Corps, medical section, to serve in the neuropsychiatric units which are to be attached to the base and other hospitals of the military services of the United States. Further information will be given, and application forms sent to physicians qualified in this branch of medicine, on application by letter or in person to the National Committee for Mental Hygiene, 50 Union Sq., New York City.

Newport Medical Society
A meeting was held May 17, 1917 at 8:30 PM at the Historical Society building. Dr. H.G. Giddings of the Boston City Hospital spoke on drug store prescribing in venereal diseases. Mary E Baldwin, MD, secretary

St. Joseph’s Hospital
The graduating exercises of the Training School for Nurses were held on the evening of May 22 at the Eloise, Franklin Street. The class consists of nine nurses. Dr. Arthur H. Harrington of the State Hospital for the Insane delivered the graduation address.

Providence City Hospital
Arrangements have been made with the naval authorities at Newport whereby cases of contagious diseases, including tuberculosis, will be cared for in the City Hospital if the necessity arises.

Necrology
Dr. Henry W. Burnett, widely known as a specialist in children’s diseases, died at his home, 167 Lloyd Ave., May 7, 1917. Dr. Burnett was born in New York City in 1873. He graduated from Long Island College Hospital and later attended King’s County Hospital and Harvard Graduate School of Medicine.

He served as resident physician in Butler Hospital, physician in charge of children’s diseases in Rhode Island Hospital, the North End Dispensary, and the St. Vincent DePaul Infant Asylum.

Dr. Burnett was a member of the board of managers of the Providence District Nursing Association, chairman of Baby Welfare committee, Rhode Island Medical Society, Providence Medical Association, American Medical Association, Association of Military Surgeons and the New England Pediatric Society.

He was formerly a captain in the Medical Corps, Rhode Island National Guard, and was recently appointed assistant surgeon general of the state. He leaves a widow, mother, two brothers and two children.

St. Joseph’s Hospital graduated nine nurses on May 22, 1917. Many expressed an interest in participating in the war effort.
In 1917, charts that accompanied clinical articles looked like this. These appeared in the June 1917 issue of the Rhode Island Medical Journal with “A Study of Cardiorenal Types” by H.P. Lovewell, MD, of Providence. The review was based on 250 cases from a course in medicine and pathology at the Massachusetts General Hospital, using a classification of Dr. R. Cabot, from a paper read before the AMA in 1914. Dr. Cabot found that 93% of the “failing hearts” fell into four groups: rheumatic, arteriosclerotic, nephritic and syphilitic. Of the 250 cases, Dr. Lovewell would put 70 under these four types.
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Hopeworth Sanitarium in Bristol offered rest and work cures

Founder grew up in Civil War field hospitals, orphan asylum

MARY KORR
RIMJ MANAGING EDITOR

When Herman Canfield, Sr., a prominent Ohio lawyer, mayor, senator and Abolitionist was killed at the Battle of Shiloh during the Civil War, his wife Martha packed up her two boys and headed South, to use her nursing skills to tend the war wounded in field hospitals. The boys trailed after their mother, and the generals as well.

After the war, she opened the Canfield Colored Orphan Asylum in Memphis, Tennessee, which became home to her two young sons and an army of ‘siblings,’ many street urchins orphaned during the war.

The Canfield boys would eventually wind up in Bristol, RI, as the physician directors of the Hopeworth Sanitarium.

Hopeworth was situated on 65 acres of seashore, woodlands, fields and gardens. The main building consisted of 24 bedrooms, sitting rooms, treatment areas, and dining, music and billiard rooms.

Dr. Herman Canfield, Jr., first came to Bristol in 1879, several years after graduating from the University of New York Medical Department (1876). He was determined to open a sanitarium. With $12 in his pocket, he settled into the town by the bay with his wife and child, and after two years of practice rented the Gen. Burnside estate to open his sanitarium. Within 18 months, he purchased a large parcel of land and buildings along the shores of Mount Hope Bay and established the Hopeworth Sanitarium in 1883.

Hopeworth was billed as a respite for the “weary invalid.” Accepted were chronic “nervous cases, other than the insane,” patients who suffered from rheumatism, gout, diabetes, diseases of the kidney, stomach and bladder, heart disease – in short, just about everyone, with the exception of those with tuberculosis, infectious diseases, and epilepsy. The sanitarium was also open to selected recovering alcoholics and those with drug addictions, but only with prior screening.

Electrical Room: A brochure sent to physicians advertised the various treatments offered, which included: massage, medical gymnastics, mechanical vibration, and electricity in its various forms (galvanic, faradic, static, etc.).

Solarium: (Right) An 80-foot conservatory of flowers was often used as a solarium and area for the “rest cure.”
In 1885, Herman’s brother, **Dr. William E. Canfield**, joined him. One of their rules was to offer care for two deserving patients who are unable to meet the regular charges. The costs were:

- Single room, $15–$30 per week, only general medical direction
- Suites: $35–$75 week
- Additional medical treatment: $20 per week and upward
- Weekly settlement of bills required.

The consulting physicians included:

- George W. Porter, MD, gynecologist, Providence
- George L. Shattuck, MD, neurologist, Providence
- George S. Matthews, MD, general medicine, Providence
- John W. Keefe, MD, surgeon, Providence
- H.C. Pitts, MD, gynecologist

The salty air and temperate summers mitigated by bay breezes was proclaimed in the sanitarium’s advertisements, as well as its accessibility. It could be reached by electric trains from Providence, which left every hour to the Bristol station on Franklin Street, where a carriage would be awaiting.

For out-of-towners, the Federal Express train left Washington D.C at 4:20 p.m. and arrived in Providence (without changing trains!) at about 6 a.m. For New Yorkers, the Providence Steamboat Line and the Fall River Steamboat Line left Pier 18 in that city at 5 p.m. daily.

In addition, according to the brochure, residents had the luxury of making local and long-distance telephone calls.

Martha Canfield became a permanent resident at Hopeworth, until she died there in 1889, according to one account, “from the effects of exposure in her work for the soldiers during the war.”

The Canfields sold the facility in 1909, when Herman opened a smaller facility in Newton, Mass. He also opened facilities in the Caribbean, and died in Florida at the age of 60 in 1914.

In 1959, the main building of the former sanitarium was destroyed in a fire. Eventually the land was divided into home parcels and scattered throughout the area are remnants of the old stone-walls and pillars, crumbling sentinels of a bygone era.

**Bath House:** The Bath House was situated along the shoreline. Hydrotherapy in full tubs, with or without electricity, douches, sprays, packs and rubs, vaporizers, etc. at varying temperatures, was offered to residents in the warm weather.

**Outdoor life:** Built on the shoreline of Narragansett Bay in Bristol, the sanitarium offered the use of a sloop for the nautical-minded.


Updates On Chimeric Antigen Receptor-Mediated Glioblastoma Immunotherapy


