SPECIAL SECTION

UPDATES in ONCOLOGY: PART II

GUEST EDITORS KIMBERLY PEREZ, MD; MURRAY B. RESNICK, MD, PhD
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Ebola vaccine and corporate responsibility

JOSEPH H. FRIEDMAN, MD
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The head of the world Health Organization (WHO) once again denounced the large pharmaceutical corporations for not having created an Ebola vaccine. As she noted, they put profit over everything. No surprise there, as this is, alas, how capitalism works. Corporations are apparently people to Mitt Romney, money-making, amoral people, and few are dedicated to the public good. Not to say that some, perhaps many companies, don’t have the public good as their mission, but the mission of most corporations is to maximize the return for the shareholders. It is not to help poor or sick people. It is not to improve quality of life. It is not to clean the environment.

I believe that the resource-rich west has been remiss in almost every way in their dealings with the poor countries. These countries only exist when there’s a problem or some group has a politically important base in the U.S. Ebola was not a western problem until Americans contracted it. Western aid to the poor, which may sound like a lot in terms of dollars, is miniscule and often is used to reward the lender anyway by forcing the borrower to buy American products, thereby rewarding American interest groups under the guise of helping the poor.

However, unlike the WHO, I do not believe the pharmaceutical corporations are obliged to create vaccines or therapies for the common good. It would be nice if they did, but this is not their mission. I do not say this lightly. I just don’t think that pharmaceutical companies are different than other corporations. Even doctors turn away poor patients. Are large contractors obligated to build housing for poor people? Do we expect Toyota to give cars to poor people because they can’t find a job unless they have a car? Should a private corporation be obliged to help the poor? Should manufacturers of sewage treatment plants be forced to create plants in an impoverished area with sewage problems, which would probably be medically much more cost effective than developing vaccines anyway?

In the 19th century, when fire companies were first begun, they were private. People paid a local fire company to provide their service. If you paid and had a fire you were protected. If you didn’t belong then your house burned down. Fire companies became public when it became clear that each house was better protected when everyone else’s was too.

Yet, drug companies have developed vaccines. Companies that develop vaccines have gotten waivers against lawsuits that may occur if adequate safety testing did not reveal evidence of rare side effects. In addition, the government has subsidized pharmaceutical research and development for vaccines.

Most Americans, and probably the vast majority of the world’s population, believe that the development of vaccines for poor regions and treatment for diseases of poor areas is a responsibility of wealthy governments, whether the problem is within their country or not. They should also fund the research independently or in collaboration with pharmaceutical companies. Aside from the obvious good of enhancing health, epidemics, even in poor areas, may destabilize large regions of the world and lead to chaos and terrorism, posing a threat to national defense. Even the possibility of Ebola’s spreading to the U.S. caused terror in our country, leading to a large outlay of money for training, treatment and disease assessment, and quarantine. In the Ebola case, the outlay for a response, while very large, may not equal the investment required for a vaccine, but, on the other hand, it certainly will have been seen as a wise investment if not doing it leads to an epidemic in the U.S. There is no reason the wealthy world cannot come together to develop vaccines or better treatments for the major killers in the world: malaria, TB, cholera, and some minor ones as well, like Ebola. Until the Ebola scare, U.S. government investment in vaccines actually dropped over the last few years.

The reader should be aware that I have received money for consultations from pharmaceutical corporations and hedge funds as well as research funds from drug companies. I used to give promotional talks, but no longer, due to hospital bylaws.

Author
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Dissent as a Prelude to Advancement

STANLEY M. ARONSON, MD

Those admitted to the inner precincts of Academia will readily acknowledge that their exalted status carries weighty responsibilities. These new burdens inevitably include a sense of noblesse oblige, attendance at torture sessions called committee meetings and, of course, carrying the weight of the academic robes on days of solemn purpose.

The daily calendar of the typical faculty member is peppered with committee assignments. These involuntary assemblages are conducted in large rooms, typically bereft of windows, with portraits of their bearded predecessors on the walls, a long rectangular table often covered with green fabric, and with a fresh pad of paper, a disposable pen and the day’s agenda at each participant’s seat.

What is the ultimate purpose of these gatherings? Veterans of committee servitude will sigh and declare that such a discussion is pointless. But if pressed, they may mention a few customary chores undertaken by committees: to provide reluctant approval for unpleasant actions already established by the administration; to debate the merit of abhorrent practices that have little bearing upon the primary mission of the college; and if refreshing ideas should, by happenstance, appear on the agenda, to see them quietly strangled by means of delays, remote contingencies, wearisome debate and the proposal of meaningless appendices.

Faculty have consistently viewed committee assignments as something akin to coal mining or required attendance in a catechism class. As scholars faithful to the demands of independent reasoning, they are aware that the word, committee, originally defined the person fully committed to a higher authority. Passive agreement and unanimity in voting is abhorrent to the typical scholar whose academic advancement is based upon his independent thinking. They remember that ‘it stands to reason’ provides its user with the advantage of having invoked reason while simultaneously refusing to listen to it. Yet when gathered into a conclave, these faculty are expected to surrender their idiosyncratic ways, ignore one of their fundamental precepts that skepticism is the chastity of their intellect; and then lapse into a lower state of consciousness as they relinquish their alertness and capacity to reason.

And so, in self-defense, universities have now assembled a roster of alternative names to give the impression these gatherings are not mere timeworn committees but assemblages with prestigious missions.

Some institutions now refer to periodic faculty gatherings as boards, conclaves, councils, consistories, congresses, retreats, missions or even panels. The word conclave, they will recall, derives from the Latin literally meeting ‘he who has the key’; and over the centuries has defined secret gatherings of sinister intent. Consistory, historically, has provided the name of a church gathering whose purpose is to ‘stand firm’, and in practice ‘to block any new scriptural interpretation.’ And a consortium stems from the Latin meaning partner, comrade or consort; in practice, it defines a gathering solely of males.

There are still other names of serious purpose that might be employed; but again, many have a tainted past. A cabal, for example, descends from the Hebrew word meaning ‘doctrine received’, but in practice defines a secret group intent on intrigue.

In desperation, university administrations may seek more exalted titles such as synod, from the Greek meaning ‘a gathering’, but historically a name reserved for infrequent gatherings of
dedicated ecclesiastics. Or they may glance momentarily at the word synagogue coined by the Hellenic translators of the Old Testament and meaning an assembly, with no sectarian hint, but would refrain from using it because of its currently narrow interpretation.

Many of the nouns used to define scheduled meetings do not come freshly born; rather, they carry baggage of implicit subtexts well beyond their etymological roots. Some suggest a theological mission, others hint that only males shall attend, and still other names speak darkly of subversive conspiracy. Some have used that grand word symposium for their periodic gatherings, a title which by custom is confined to more open assemblies and incidentally, from the Greek, literally meaning ‘a get together for a drink.’

In their relentless search for a pleasingly non-toxic name for their faculty working groups, university authorities have quickly discarded such vernacular titles as pow-wow, huddle, liaison, and even tryst. And so, after a fruitless search, they have returned to their original appellation: committee, in the hopes that these future gatherings will fulfill its intent.

Universities, in sadness, have concluded that no grand idea ever arrives from the committee of passive souls. Conformity, they conclude, is the death knell of a group asked to seek iconoclastic ideas. And the birth of innovative visions may best be encouraged in an atmosphere of skepticism, rebellion, disenchantment with current rules and a will to find a better way of doing things.

Author
Stanley M. Aronson, MD, was Editor emeritus of the Rhode Island Medical Journal and dean emeritus of the Warren Alpert Medical School of Brown University.
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Growing Up and Aging with Progressive Hearing Loss

ANNAL ALBRECHT PARISI, RN, MSN

[Editor’s Note: This commentary was submitted to RIMJ by Dr. Alfred Parisi (Professor Emeritus of Medicine, Brown University), husband of the late Anna Albrecht Parisi, who passed away in 2011 after a lengthy illness. He recently came across this recollection and thought it would be of interest to RIMJ readers. Anna was supervisor of the cardiac rehabilitation program at The Miriam Hospital and also worked as a research project nurse at the Miriam Hospital Centers for Behavioral and Preventive Medicine.]

One wonders what life would be like if I could hear everything that was said and selectively omit what I don’t want to hear. Individuals with normal hearing take for granted the many challenges that face those of us who have hearing loss. Hearing loss is a chronic disability that has no cure. The treatment includes many visits to a hearing professional to get fitted for the latest hearing aids that do little when compared to normal hearing.

Don’t get me wrong – there are some advantages to hearing loss. Rarely do I wake up at night because of thunder and lightning. But I sometimes wonder if I would hear the house alarm. I now have to worry about hearing the alarm clock in the morning. When I stay at a hotel, I have to set two alarms because I rarely hear the wake-up call. Add to that the ringing that never stops in your ears (tinnitus) and you sometimes feel like you will go crazy.

In grade school I was not yet aware that I had a hearing loss. Because my first and last name starts with an ‘A’ I was always assigned a front-row seat. That was quite lucky in hindsight because it allowed me to hear well. The hearing tests we had at school were conducted in a group. You would be exposed to different sounds and raise your hand when you heard them. It didn’t take me long to figure out that if I wanted to pass the test, I had to raise my hand when everyone else did. You see, I didn’t want to be different than my peers. Back then, I never understood why I couldn’t hear what they did.

I should have figured this out because my father couldn’t hear and my mother always spoke loudly. My father didn’t want a hearing aid, so everyone in the family had to pipe up. I was always amazed when I visited other homes and people talked so softly. I wondered if this was normal. As a child sometimes the obvious just isn’t so obvious.

In high school, I remained in the front row during most of my classes. I didn’t feel that my hearing loss was having a negative effect on my school work because I wasn’t that motivated in high school and was more engaged in the social aspects. I managed to graduate as an average student. When I entered college, I am not sure why I chose nursing, except that it was not uncommon for women to choose nursing in the 1970s.

Early in my training I had an instructor that learned of my hearing loss and she strongly encouraged me to change professions; she said this would be a huge handicap and that I would ultimately have to leave the profession. Being somewhat stubborn, I decided to ignore her suggestion. I graduated magna cum laude.

For many years I worked as a nurse in a variety of positions. I obtained a special stethoscope that amplified sound and always made sure that I put myself in the best position to hear.

At that time I was still able to get by without a hearing aid. I am sure I missed some things but didn’t feel that I was endangering my patients. Initially I worked in the intensive care unit; I found that to be the most challenging. As time went on I thought I needed to do more with my career and headed to graduate school. I was still able to get by adequately without hearing aids. Eventually I accepted a position in cardiac rehabilitation and found this to be quite challenging for many years.

My hearing loss gradually increased over the years. For a short time I worked as a clinical instructor of nursing and this was probably the most challenging position I have had, compounded by the fact that I was now wearing a hearing aid. I was in constant fear that one of my students would say something quickly and run off to do something that would harm the patient. If you have ever taught nursing students on a busy unit, you know how hectic it can be when multiple people are talking to you at the same time. It was largely because of my hearing that I left teaching for a position that didn’t require hearing processing skills.

One can argue that very successful people have coped with hearing loss, so what is the big deal? Bill Clinton comes to mind. I remember when he got his hearing aids. I thought they must be the best if he purchased them and I tried them for myself. I always wondered how he did so well and I was still struggling.

I have been told numerous times that my hearing loss is particularly difficult to fit. I have a reverse-sloped condition and most hearing aids are designed for high-frequency hearing loss. As you age, you are more likely to develop high-frequency loss due to exposure to loud sounds and the natural aging process.

Why am I writing this story? I guess I’ve been trying to put into words what it’s like to have experienced a lifetime of hearing loss. As I write this, I still hope for a better hearing aid in the future. I still worry about not being able to hear as I get older and how that will impact the quality of my life. I still wonder who will help me put my batteries in the hearing aid when my fingers are arthritic. Lastly, but more than anything, I wonder who will take the time to talk to me because I can’t hear.

”
We are read everywhere

NARRAGANSETT BAY, RHODE ISLAND
Cheryl Turcotte, of RIMS-IBC, shows off the October issue while enjoying a sunset cruise of the upper bay on the Save the Bay vessel “Elizabeth Morris” as part of RIMS annual meeting and members’ Convivium.

SANTORINI, GREECE
Speaking of Convivium, Michael Migliori, MD, spotted this restaurant in Fira on the Island of Santorini. The town was built on the edge of a 1000-foot cliff, on the rim of a crater overlooking a caldera, the remnants of a volcano that collapsed into the sea after it erupted 3600 years ago. The eruption was the largest in human history, contributed to the demise of the Minoan culture, and is believed by many to be the origin of the legend of Atlantis.

BAR HARBOR, MAINE
Former AMA President Robert McAfee, MD, viewed the October issue during the 162nd Annual Session of the Maine Medical Association in Bar Harbor. Dr. McAfee was President of the MMA in 1980-1981.

Wherever your travels take you, be sure to check the latest edition of RIMJ on your mobile device and send us a photo: mkorr@rimed.org.
We are read everywhere

ATHENS, GREECE
In appears as if Asklepios himself is trying to get a look at the October issue on the phone held by Michael Migliori, MD, at the National Museum of Archaeology in Athens. Asklepios, a son of Apollo, was a god of medicine in ancient Greek mythology, representing the healing arts. His staff with its entwined snake is still used as a symbol of the medical profession today. One of his daughters, Hygeia (goddess of cleanliness and sanitation – hygiene) is depicted in the RIJM seal. This statue, carved from Pentelic marble, was found at the Sanctuary of Asklepios at Epidaurus and is believed to be a circa 160 CE copy of a 4th century BCE original.

Michael Migliori, MD, consults RIJM at the Sanctuary of Asklepios, under reconstruction on the south slope of the Acropolis below the Parthenon. This important sanctuary and healing center in Athens was founded in 420 BCE, when a statue of Asklepios was brought from the temple at Epidaurus. Under a “stoa”, or covered walkway, beside the sanctuary, patients would wait to be cured by the apparition of Asklepios in their dreams.
Updates in Molecular Pathology of Central Nervous System Gliomas in Adults

MICHAEL PUNSONI, MD; JOHN E. DONAHUE, MD; HEINRICH D. ELINZANO, MD; TIMOTHY KINSELLA, MD

ABSTRACT
Central nervous system (CNS) tumors are a heterogeneous group of neoplasms divided into two broad categories, glial and non-glial. Non-glial tumors are derived from such diverse structures as the pineal gland, meninges, germ cells, and hematopoietic cells, as well as metastases. Primary glial neoplasms, or those which originate from astrocytes, oligodendrocytes, or ependymal cells, include astrocytomas, oligodendrogliomas, ependymomas, and mixed gliomas. Each entity has a unique morphology and pattern of biologic behavior which portends a distinct prognosis and outcome. Individual outcomes show some variability based on tumor location and age of symptom onset; however, the underlying aggressiveness of the tumor often dictates the time course of the disease. With the advent and widespread use of fluorescent in-situ hybridization and polymerase chain reaction (PCR) techniques, molecular phenotyping of brain tumors has become mainstream and is now an integral part of patient care. The molecular genetics of CNS tumors is a rapidly growing field, and the volume of discoveries is growing at an ever increasing rate, compelling the need for updates in this exciting area of science.

KEYWORDS: Glioma, astrocytoma, oligodendroglioma, glioblastoma, 1p19q, MGMT, IDH1

INTRODUCTION
Within the broad spectrum of central nervous system (CNS) tumors, a number of common neoplasms carry a high rate of morbidity and mortality. In 2014, an estimated 22,850 adults in the United States were diagnosed with primary tumors of the brain and spinal cord. It was estimated that 15,320 of those affected would die of their disease that same year [1]. Furthermore, currently there are nearly 700,000 people in the U.S. living with a brain tumor [2]. While primary brain tumors are a diverse group of entities, with over 120 types of neoplasms, among the commonest, and one of the most studied, are the gliomas. Each neoplasm has a unique morphology and pattern of biologic behavior that shapes the clinical outcome of the individual. New discoveries in the molecular biology of these diverse brain tumors may offer advanced targeted therapies leading to decreased complication rates and improved quality of life.

Epidemiology
The incidence of CNS malignancies has been increasing. Most commonly, CNS tumors arise from glial cells, particularly astrocytes and oligodendrocytes. Gliomas account for approximately 77% of primary malignant brain tumors [3]. Most patients present between the fifth and seventh decade of life. High-grade tumors are more common than low-grade and present a high risk of morbidity and mortality. The World Health Organization (WHO) in 2000 formulated a classification system based on histologic findings that is used to stratify brain tumors into prognostic grades. High-grade gliomas (WHO grade III and IV) are most commonly seen in middle-aged to older adults, while grade II astrocytomas mainly affect younger adults. Management for low-grade neoplasms involves either observation or surgical excision, while high-grade tumors often require aggressive regimens involving chemotherapy and radiation after surgical debulking.

Pathology
CNS tumors are classified according to their predominant cell type. Therefore, most gliomas can be classified as astrocytic, oligodendrogial, or mixed oligo-astrocytic tumors. Furthermore, criteria such as atypia, mitoses, endothelial proliferation, and/or necrosis allow for application of the WHO grading scheme, which gives prognostic information based on tumor grade.

Diffuse gliomas are devastating cancers due to their locally aggressive behavior, insidious infiltration into the adjacent brain tissue, and resistance to current treatment options. In addition, low-grade gliomas have a tendency to progress to anaplastic (grade III) gliomas, with anaplastic astrocytomas ultimately progressing to glioblastomas (WHO grade IV).

Molecular alterations, such as changes in chromosomal copy number, deletions, and duplications, are common events in gliomas. In recent years, molecular analysis of tumors has sharply increased in terms of available molecular studies and their impact on diagnosis and prognostication. Currently, it is believed that changes in gene expression and other genetic abnormalities may underlie transformation and progression of gliomas. Some of the most common molecular changes that are tested in gliomas are co-deletion of 1p19q, O6-methylguanine-DNA methyltransferase (MGMT) methylation, and Isocitrate dehydrogenase 1 (IDH1) mutation.
**1p/19q**

The combined loss of chromosomal arms 1p and 19q are commonly seen in oligodendrogliomas and are thought to be a marker of good prognosis. Oligodendrogliomas derive their name from their non-neoplastic counterpart, the oligodendroglial cell, a native support cell of the central nervous system. These tumors are diffusely infiltrating, well-differentiated [WHO grade II] gliomas, often occurring in adults. They tend to arise in the cortex and white matter of the cerebral hemisphere, with the majority of cases in the frontal lobes. Oligodendrogliomas are slow-growing tumors that are well-demarcated, non-enhancing mass lesions on radiologic scans. Grossly, the tumors may show mucoid changes, with areas of cystic degeneration, hemorrhage, and calcification. Microscopically, they are diffusely infiltrating glial tumors composed of monomorphic cells with uniform round vesicular nuclei, distinct small nucleoli, and a classic perinuclear halo which is an artifact of fixation [giving rise to the name “fried egg” cells]. This is often accompanied by a delicate capillary (“chicken wire”) vasculature. These neoplasms infiltrate the adjacent cortex, specifically via perineural, perivascular, and subpial spread. Grade II tumors may progress to grade III tumors, which are known to have increased cellularity, nuclear atypia, and mitotic figures. A common molecular alteration in oligodendrogliomas is co-deletion of the 1p and 19q chromosomal arms. This combined loss is rare in astrocytomas and glioblastomas [GBM]; however, it is seen in approximately 40–70% of classical forms of oligodendroglioma [4]. The incidence of 1p/19q loss is much lower in cases of mixed oligoastrocytoma [20–30%] [5]. Patients with anaplastic (grade 3) oligodendrogliomas whose tumors harbor the 1p/19q co-deletion have a more favorable prognosis if treated with chemotherapy and radiation therapy with an overall survival approaching 15 years compared to similarly treated patients whose tumors do not demonstrate the co-deletion in a large randomized clinical trial [overall survival of 7.5 years] [6]. While histopathology is the gold standard for diagnosis, molecular testing for the combined loss of 1p/19q is used as an adjunct for prognostication and treatment selection.

**MGMT**

MGMT [O6-methylguanin-DNA-methyltransferase], a DNA repair enzyme located on chromosome 10q26, is involved in repairing damaged DNA from toxic effects of alkylating reagents. In addition, this enzyme contributes to drug resistance of gliomas by protecting tumor cells from alkylating agents. MGMT promoter hypermethylation and epigenetic silencing lead to MGMT gene inactivity and loss of protein expression. In effect, methylation leads to susceptibility of tumor cells to the alkylating effects of agents such as temozolomide, thereby allowing for more effective treatment of high-grade gliomas that are methylated. A study by Heigi et al. showed a survival benefit among patients whose glioblastoma [grade IV] contained a methylated MGMT promoter. In those treated with temozolomide and radiotherapy, the median survival was 21.7 months compared to 15.3 months among those who only receive radiotherapy [7].

MGMT inactivation is an important marker of therapeutic application, commonly tested in GBM. GBM is a malignant primary brain tumor [WHO grade IV] that is often supratentorial. It may occur de novo [primary] or progress from lower-grade gliomas, such as an anaplastic astrocytoma [WHO grade III]. GBM is an aggressive neoplasm that shows contrast enhancement on radiologic scans, often with large areas of peritumoral edema and mass effect on surrounding brain tissue. Grossly, the tumors are variegated with necrosis and hemorrhage. Microscopic features include hypercellularity with atypia, mitoses, endothelial proliferation, and either geographic or pseudopalisading necrosis. Due to their aggressive nature, early diagnosis with proper therapeutic management is essential.

In recent studies, MGMT was methylated in approximately 45-50% of glioblastomas and irrespective of treatment, MGMT promoter methylation was an independent favorable prognostic factor. Furthermore, a survival benefit was observed in that same group of patients following treatment with temozolomide and radiotherapy [7-8].

**IDH1**

IDH1 [isocitrate dehydrogenase-1], a metabolic enzyme, is known to undergo mutations that are associated with gliomas and are thought to give prognostic implications to the diagnosis. The most common mutation affects codon 132, which causes conversion of arginine to histamine (R132H). Immunohistochemical analysis can detect mutant IDH1, which is found in neoplastic gliomas cells and not in reactive gliosis. IDH1 mutations are frequently found in low-grade gliomas and to a lesser extent high-grade gliomas, including secondary GBM, and are associated with a favorable prognosis when compared to IDH1 wild-type [9–11]. A study by Ichimura et al. showed that codon 132 mutations were seen in up to 65% of oligodendrogial tumors, 54% of astrocytomas and 6% of glioblastomas [3% of primary GBM and 50% of secondary GBM] [12]. Using current WHO grading schemes, anaplastic astrocytoma [WHO grade III] has a better prognosis than GBM [WHO grade IV]. Some research supports combining histologic grading of tumors with molecular phenotype, thereby creating a combined classification that gives a clear diagnostic and prognostic picture of each entity. For example, Hartmann et al. [13] proposed a sequence of favorable [median survival of 18–24 months] to clearly less favorable [median survival of 6–9 months] outcomes based on histologic and molecular status that ranged from anaplastic astrocytoma with IDH1 mutation, GBM with IDH1 mutation, anaplastic astrocytoma without IDH1 mutation and finally GBM without IDH1 mutation. Future randomized trials are needed to further elucidate the interaction and prognostic implications of this molecular alteration.
CONCLUSION

CNS tumors are a heterogeneous group of neoplasms with a wide array of histologic subtypes and an increasingly complex group of molecular abnormalities. Current standards of practice dictate that diagnosis is based primarily on histopathology; however, it is becoming increasingly common to order molecular studies to further characterize, classify, and prognosticate tumors. The vast catalogue of molecular alterations is steadily increasing, and further studies will be necessary to determine their significance in terms of diagnosis and prognosis.

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Molecular profiling helps define the phenotype of a cell and is designed to aid in early cancer detection, risk assessment, and targeted therapies. Profiles should be measurable across populations, useful for detection of cancer at an early stage, or assist in identification of high-risk individuals. As technology has developed, so has our ability to explore tumor biology down to the level of gene expression.

Endometrial cancer is the most common gynecologic malignancy in developed countries and the second most common in developing countries. Patients typically present with symptoms such as postmenopausal bleeding, which allows for detection at an earlier stage. Ovarian cancer is less common but carries a poorer prognosis given its typical late stage of diagnosis. This section will discuss developments in the treatment of endometrial and ovarian cancer at a molecular level. Considerable breakthroughs have been made in the area of poly ADP-ribose polymerase (PARP) inhibitors in BRCA mutated ovarian, fallopian tube, and primary peritoneal cancers. Epithelial cellular adhesion molecule (EpCAM) overexpression has been a target for the treatment of malignant ascites in ovarian cancer. There has been utility in targeting hormone receptors in the setting of recurrent endometrial cancer while the role of human epidermal growth factor 2 (HER2) and mTOR inhibitors shows promise but remains investigational.

**POLY ADP-RIbose POLYMERASE (PARP) INHIBITORS**

PARPs are a constitutive factor of the DNA damage surveillance network developed to cope with numerous environmental and endogenous toxic agents. In particular, the roles of PARP 1 and 2 in the base excision DNA repair pathway have been elucidated. Inhibition of the PARP enzyme leads to persistence of spontaneously occurring single-strand breaks and subsequent formation of double-strand breaks. PARP inhibitors were found to have anti-cancer activity both in vitro and in vivo in germline BRCA mutated cancer. BRCA1 and BRCA2 mutations act on the cellular level as tumor suppressor genes involved in double-stranded DNA (dsDNA) break repair. Using the concept of synthetic lethality, which is defined as the situation when mutation in either of two genes individually has no effect but combining the mutations leads to death, the use of a PARP inhibitor in patients with an existing BRCA mutation should disable the back-up repair mechanism thus leading to cell death. The implication is that targeting one of these genes in a cancer where the other is defective should be selectively lethal to the tumor cells but not toxic to the normal cells. In December 2014, olaparib (Lynparza™) became the first PARP inhibitor approved by the FDA in the treatment of advanced ovarian cancer in patients with a known BRCA mutation who have received three or more prior lines of therapy. Approval is contingent upon the demonstration of positive results in two ongoing phase III clinical trials with olaparib limited to patients with BRCA mutations. Other PARP inhibitors such as veliparib have shown promising results in a phase II Gynecology Oncology Group (GOG) trial of patients with persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer with a BRCA 1 or 2 mutation.

**EpCAM**

EpCAM is abundantly expressed on human cancers and EpCAM overexpression has been associated with a poor prognosis in patients with ovarian, breast, prostate and gallbladder carcinoma, both functioning as an oncogene and suppressing CD4+ T-cell-dependent immune responses. Tumor cells in malignant ovarian cancer-associated ascites have been shown to express EpCAM in 70–100% of cases, while the mesothelial cells lining the peritoneal cavity lack expression. Catumaxomab is a trifunctional monoclonal antibody with two different antigen-binding sites and a functional Fc domain: one binds to epithelial tumor cells via EpCAM and the other to T cells via CD3. Catumaxomab was evaluated as part of a phase I/II dose-escalating study for intraperitoneal application in patients with ovarian cancer who had EpCAM-positive tumor cells. Treatment with catumaxomab resulted in significant and sustained reduction of ascites. In April 2009, the European Union approved catumaxomab for the intraperitoneal treatment of malignant ascites where standard therapy was not feasible. It has not been FDA approved in the United States but is in clinical trials.

**HORMONE RECEPTORS**

The presence of progesterone receptors has been found to correlate with low-grade histology and overall more favorable outcomes. Receptor expression can be lost in either the
primary tumor or in metastatic disease, its loss is associated with disease progression and decreased patient survival. Progestins have been employed to exploit the presence of progesterone receptors, however they paradoxically down regulate receptors when given continuously. The addition of tamoxifen to counter the progesterin induced down regulation has shown clinical benefit. Megesterol acetate (megace) and tamoxifen for the treatment of metastatic endometrial cancer is based on a Gynecologic Oncology Group (GOG) study where patients alternated three-week courses of megest and tamoxifen with an overall response rate of 27%, a median progression-free survival of 2.7 months and median overall survival of 14 months. This is a viable treatment option in patients who are not eligible for secondary cytoreduction or multidrug cytotoxic chemotherapy, which has demonstrated a response rate from 33–57%. Endocrine therapy has shown some, albeit limited, clinical utility in the treatment of relapsed epithelial ovarian, fallopian tube, and primary peritoneal cancers. Studies using tamoxifen, thalidomide, and letrozole have shown improvements in progression free survival [PFS] and overall survival [OS].

**HER2**

Although currently investigational, the role of human epidermal growth factor 2 (HER2) was shown to be a potential target in women with uterine serous carcinomas that overexpress HER2. A small GOG trial of 34 women with advanced or recurrent endometrial cancer showed no responses but 12 patients with overexpression of HER2 had stable disease. A clinical trial evaluating the role of trastuzumab in combination with chemotherapy in uterine serous papillary carcinoma is ongoing. Single agent lapatinib in one trial of patients with endometrial cancer showed that 3 out of 30 patients were progression free after 6 months, 1 patient had a partial response, and 7 had stable disease. Although these appear to be modest results, treatment options in the platinum resistant setting are needed. These women have a poor prognosis. The limited data suggest that the most likely response to second line treatment is stable disease at best and overall survival is usually less than a year.

**mTOR INHIBITORS**

Overactivation of the PI3K/AKT/mTOR pathway, a signaling pathway that plays an important role in cellular growth and survival, has been implicated in endometrial cancer pathogenesis. In a phase II study of previously treated recurrent or metastatic endometrial carcinoma patients, 25mg of IV temsirolimus showed a response rate of seven percent, however, 44 percent had stable disease, with a median duration of 5.1 to 9.7 months. These results have been promising enough to proceed with a clinical trial. GOG 86-P incorporates temsirolimus into one of three treatment arms for women with advanced, recurrent, or metastatic endometrial cancer not previously treated with chemotherapy. Results are anticipated in the near future.

**CONCLUSION**

Biomarkers for gynecological cancers, especially ovarian cancer, are the subject of multiple ongoing and planned clinical trials. Targeted therapies for these biomarkers are in rapid development and are hoped to improve the prognosis of women with gynecological malignancies by providing improvement in outcomes and treatment tolerability.

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Genetics and diffuse large B-Cell lymphoma
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ABSTRACT
Diffuse large B-Cell lymphoma (DLBCL) is one of the most common and aggressive subtypes of non-Hodgkin’s lymphoma (NHL). Gene expression profiling (GEP) studies have identified at least two distinct molecular subtypes of DLBCL termed as germinal center B-cell (GCB) and activated B-cell (ABC). These molecular subtypes represent lymphomas that are driven by very different intracellular oncogenic signaling pathways which have prognostic value and could potentially be exploited for therapeutic benefit in future. There are other oncogenes, namely BCL-2, BCL-6 and MYC, which have been associated with the pathogenesis of DLBCL. Concurrent presence of two oncogenes is present in about 5% of DLBCL and it is termed “double hit lymphoma” (DHL). DHL are associated with an aggressive clinical course and do not respond well to the standard DLBCL immune-chemotherapy regimen, RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). Other aggressive therapeutic approaches including autologous bone marrow transplant have not shown any survival benefit in this subgroup of DLBCL patients. New strategies in development to address this resistance in DHL include the regimen DA-EPOCH-R (dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab). Recent studies have shown increased sensitivity of DHL to DA-EPOCH-R chemotherapy and will likely be the new standard of care in this subset of DLBCL patients in the future.

KEYWORDS: Diffuse large B cell lymphoma, Activated B-Cell, Germinal center B-Cell, MYC, BCL-6 and BCL-2 oncogenes, RCHOP, DA-EPOCH-R.
kinase (SYK), Phosphatidylinositol3kinase (PI3K), bruton tyrosine kinase (BTK) and protein kinase C b (PKCb). Other mutations that have been observed in varying frequencies are mutations in MYD88, loss of TNFAIP3 which result in up-regulation and loss of inhibition respectively of NF-kB and Janus kinase pathways.8

Along with the identification of intracellular oncogenic pathways, GEP studies have also identified molecular signatures related to the microenvironment of the tumor cells that are independent of these molecular subtypes. Stromal-1 signature reflects extracellular matrix deposition and infiltration of the tumor by macrophages and stromal-2 signature identifies tumors associated with high level of angiogenesis and high density of blood vessels. These molecular subtypes have been correlated with outcome; stromal 1 represents a prognostically favorable group compared to stromal 2 subtype.5 In addition to these, recurring lesions in the genes involved in immune recognition and antigen presenting functions have been recognized, suggesting that escape from immune surveillance plays an important role in the pathogenesis of DLBCL.9 There are, however, a subset of DLBCL whose biology cannot be explained by genomic events and transcriptional programs that are identified on the GEP, suggesting an additional layer of regulation. Recently somatic mutations in the epigenetic machinery have been identified suggesting the significance of epigenetic regulation in the normal B cell development and in lymphomagenesis. These epigenetic subgroups of DLBCL reflect the variability in DNA methylation, which has also been associated with clinical outcome.10

The growing understanding of the molecular pathways in DLBCL has provided an opportunity to pharmacologically target these pathways to improve clinical outcomes in DLBCL. However, further work is needed to translate the recent discoveries to the clinical setting; this can be done by clinical trials, which support the use of tumor genetics in the formulation of therapeutic plans. There are many ongoing trials which are looking at agents that target various molecules in the oncogenic pathways of DLBCL. Immuno-modulatory agents which target the NFkB pathways like bortezomib and lenalidomide have been looked in non GCB DLBCL in retrospective studies. One study showed a higher response rate of 83% vs. 13% (p<0.001) and overall survival of 10.8 vs. 3.4 months (p=0.003) with the addition of bortezomib to chemotherapy in relapsed/refractory DLBCL.11 Similarly, studies using lenalidomide have demonstrated a high response rate in relapsed/refractory setting. Numerous phase III trials are ongoing which are looking at addition of these immunomodulatory agents with standard chemotherapy in non GCB DLBCL in first line setting.

One of the better-understood aspects of the pathogenesis in DLBCL is the alteration in the oncogenes and tumor suppression genes. Three such oncogenes are c-MYC, BCL-2 and BCL-6, key regulation of cellular proliferation(c-MYC) and apoptosis (BCL-2 and BCL-6). BCL-2 and BCL-6 translocations are present in about 15 and 29% of DLBCL respectively.12,13 The c-MYC translocation is present in about 5-10% of DLBCL.14 Isolated presence of BCL-2 genetic aberration does not have independent prognostic value. Furthermore, it is controversial whether the c-MYC translocation alone has prognostic value in patients with DLBCL. However, recent studies have revealed that the impact of MYC is strongly influenced by BCL-2 or BCL-6. The presence of concurrent MYC and BCL-2 or BCL-6 translocation in patients with DLBCL, also known as “double hit lymphoma” (DHL), which has been associated with a very aggressive clinical course and an overall worse survival with standard R-CHOP chemotherapy. DHL occurs in nearly 5% of cases of DLBCL.15

Numerous studies have correlated the presence of MYC rearrangement and BCL-2 or BCL-6 with a poorer outcome in DLBCL treated with standard chemotherapy RCHOP.15,16 One example is a retrospective study by Akyurek et al investigating the impact of c-MYC, BCL-2 and BCL-6 rearrangements in 239 patients with DLBCL treated with RCHOP therapy. In patients with DHL, outcome was extremely poor with a median survival of 9 months and a 2-year overall survival (OS) rate of only 14% vs. 78% for non-DHL patients [Progression free survival, p = 0.003 and OS, p < 0.001].17 Given the extremely poor outcome seen for this subset of DLBCL patients, clearly newer therapies are needed for DHL patients.

However, even though the double hit lymphoma have unacceptably poor cure rate with standard therapy, the optimal management approaches in this population of patients remains to be defined. As this subtype of lymphomas is rare, there are no large prospective studies evaluating the role of alternative forms of therapy in this poor prognosis group. One approach has been to use more aggressive chemotherapy treatments strategies, such as chemotherapy regimens used to treat the more aggressive form of NHL, Burkitt lymphoma, which consist of higher doses and more intensive chemotherapy cycles. However, one limiting factor is the high median age of patients with DLBCL, who due to co-morbidities may not be able to tolerate more aggressive regimens. One such attempt at this approach is the use of the aggressive chemotherapy regimen R-Hyper-CVAD (rituximab, fractionated cyclophosphamide, Adriamycin, dexamethasone alternating with high dose methotrexate, cytarabine and vincristine) frequently used to treat Burkitt lymphoma. However, the recent experience with this regimen in patients with DHL is not promising. For example, Li et al reported on a retrospective series of 52 patients with DHL treated with R-Hyper-CVAD regimen and found median OS in these patients was only 18.6 months.18 Other studies have reported similar poor outcomes with R-Hyper-CVAD in DHL patients.

Another approach to improve the outcome of DHL patients is to intensify therapy with the use of autologous bone marrow transplantation (BMT). However, two retrospective
series investigating the role of autologous BMT did not demonstrate an advantage over standard immunotherapy regimens.19

However, one very promising approach in patients with DHL is the use of prolonged infusional chemotherapy. One such regimen is dose-adjusted EPOCH with rituximab or DA-EPOCH-R. In this regimen the chemotherapy agents are similar to RCHOP with the addition of etoposide. However, the agents vincristine, adriamycin and etoposide are given as continuous infusional therapy over a period of 4 days rather than the standard one day bolus regimen of RCHOP. Evidence for this approach comes from in vitro data that suggests that lymphoma cells of high proliferation rates may be more sensitive to a continuous exposure to chemotherapy rather than the more traditional bolus chemotherapy. Furthermore, DA-EPOCH-R has been used successfully in the more aggressive c-MYC positive Burkitt lymphoma and it has been postulated that c-MYC positive lymphoma cells may show more susceptibility to infusional regimens such as DA-EPOCH then other DLBCL cells. Moreover, DA-EPOCH-R has been shown to be well tolerated in elderly patients. One other advantage to DA-EPOCH-R is that the doses of the chemotherapy agents are adjusted up or down depending on absence or presence of associated toxicities, thereby, theoretically tailoring therapy to minimize toxicity while maximizing the doses of the chemotherapeutic agents.

One retrospective study published by Oki, et al has shown a superior rate of complete remissions (CR) with DA-EPOCH-R compared to R-CHOP in DHL patients. In this analysis, CR rates were found to be approximately 68% for DA-EPOCH-R compared to 20% for the more traditional RCHOP (p = 0.008).20 Preliminary data from a recent multicenter Phase II study has shown promising activity with DA-EPOCH-R with progression free survival at 1 year of 87%.21 These data appear to show patients with DHL maybe more sensitive to DA-EPOCH-R chemotherapy versus the standard RCHOP regimen. However, longer follow-up of this prospective study will help us identify if this increased sensitivity results in a survival benefit for patients with DHL treated in this manner.

CONCLUSION

DLBCL is a very treatable and frequently curable NHL. GEP has helped us identify at least two subtypes of DLBCL (ABC and GCB) based on their different stages of lymphoid differentiation. Each of these molecular subtypes of DLBCL has different intracellular oncogenic signaling pathways. ABC subtype is associated with poor prognosis and has poor outcomes with standard chemo immunotherapy compared with GCB subtype. Along with the cells of origin, molecular signatures related to the microenvironment of the tumor cells and mutation in the epigenetic machinery have also been implicated in the prognosis of DLBCL which are independent of these molecular subtypes. Given the poor prognosis in these subtypes of DLBCL, numerous ongoing studies are looking at agents targeting the oncogenic signaling pathways. There is another known subtype of DLBCL called double hit lymphoma which has the presence of c-MYC rearrangements in association with BCL-2 or BCL-6 rearrangements in patients with DLBCL. This delineates a population with an overall dismal prognosis for which new treatment strategies are needed. One promising mode of therapy is infusional therapy in the form of DA-EPOCH-R; however, we will need to await the results of prospective trials to ultimately determine if this regimen offers an improvement over standard approaches.

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Genomics in acute myeloid leukemia: from identification to personalization

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ABSTRACT
Acute Myeloid Leukemia (AML) is an aggressive bone marrow malignancy that is fatal if left untreated. Previous classification was strictly based on morphology, which gave little information in terms of prognosis or guide to treatment. Recent research has provided vital information into the chromosomal and molecular pathogenesis of leukemia development. The discovery of these abnormalities via proteomics and genomics have provided two key insights. First, these novel discoveries provide prognostic significance into the predictive result of chemotherapy. Second, these chromosomal and protein abnormalities have provided potential drug targets for new treatment modalities. This article will elaborate on many of these new molecular findings and discuss their implications on the treatment of AML.

KEYWORDS: Acute Myeloid Leukemia, AML treatment

INTRODUCTION
Over the past several decades, the field of oncology has transitioned from non-specific cytotoxic treatments to a more personalized approach to therapy. From the discovery of the Philadelphia chromosome in chronic myeloid leukemia to lung cancer’s EGFR gene mutations, every malignancy is unique—each with its own set of cytogenetic anomalies and molecular mutations that provide each patient with an individualized collection of prognostic and therapeutic implications.

Acute myeloid leukemia, or AML, is no exception to this generalization. AML is a heterogeneous disease with many different pathogenic etiologies, clinical presentations and responses to treatment. Standard karyotypic analysis of the blast cells from AML patients indicate a large number of cytogenetic abnormalities among different patients, and it allows clinicians to stratify their patients into favorable-, intermediate- and unfavorable-risk groups, based on studies that looked at response to chemotherapy.1 For example, “favorable” cytogenetics include Inv(16), t(8;21) or t(15;17), although the later entity is classified as acute promyelocytic leukemia, which is treated as a completely separate entity altogether. “Unfavorable” cytogenetics include a complex karyotype (>= 3 clonal chromosomal abnormalities), -5, -7, t(9;22) and many others. Included in the “intermediate”-risk cytogenetic class are those patients whose leukemic cells possess a normal karyotype [NK]. Interestingly, NK patients have demonstrated a consistently variable response to standard treatment,2 which typically consists of induction chemotherapy, followed by either consolidation chemotherapy versus allogeneic hematopoietic stem-cell transplantation (allo-HSCT), based on clinical risk and individual patient factors. Thus, much of the recent research in molecular genetics within AML has the ultimate goal of better risk-stratifying these patients in order to provide better clinical outcomes.

Advances within the field of genomics have allowed for the detection of several different recurring genetic mutations in leukemic myeloblast cells of patient’s with normal cytogenetics. Typically, these genes increase signal transduction (leading to cellular proliferation) or affect transcription (causing impaired differentiation). While many of these molecular genetic changes do not impact clinical outcome, several mutations have been shown to significantly alter a patient’s ability to achieve a complete remission (CR), worsen the chance of relapse or effect overall survival (OS).3,4 Moreover, these studies have allowed clinicians to further risk-stratify NK patients, which subsequently may alter treatment decisions or make the patient eligible for novel small molecule inhibitors.5 Pertinent mutations that will be discussed in further detail below are FLT3-ITD, NPM1, CEBPA, DNMT3A, IDH1/2, TET2, ASXL1 and RUNX1, as well as the novel treatments available for these patient populations.

FMS-LIKE TYROSINE KINASE 3 (FLT3)
FLT3 (also known as CD135) is a tyrosine kinase receptor that is expressed on the surface of many hematopoietic progenitor cells. It activates signal transduction and is involved in cellular proliferation and differentiation. The FLT3-ITD (internal tandem duplication) mutation can be found in approximately 28-30% of NK AML.5,6 It has been shown to be an independent risk factor for poor outcome, specifically increased relapse rate and decreased OS. The adverse effect demonstrated by FLT3-ITD has suggested that NK patients with this mutation may be better classified as adverse-risk, allowing for clinicians to consider more aggressive therapy, such as allo-HSCT, based on known poor outcome with conventional chemotherapy. A second FLT3 mutation demonstrates a point mutation in the tyrosine kinase domain [FLT-TKD], although its prognostic significance is more clinically variable.7
Not surprisingly, FLT3-ITD has become a novel target with several different therapeutics currently involved in clinical trials. The most widely studied is sorafenib, a non-specific tyrosine kinase inhibitor approved for renal cell carcinoma, hepatocellular carcinoma and thyroid cancer. Sorafenib has been proven safe and effective in relapsed/refractory AML. It also may have some possible benefit for maintenance therapy after allo-HSCT. Midostaurin, another relatively non-selective FLT3-inhibitor, was shown in a phase I/II clinical trial to have high (92%) CR in younger patients with newly-diagnosed AML when combined with standard chemotherapy. The phase IIb trial by the same group demonstrated a decrease in blast count with midostaurin treatment, revealing better responses in the FLT3-mutated population compared to the FLT3 wild type population. A phase III trial (CALGB 10603) is currently ongoing. Finally, quizartinib, a highly-selective FLT3-inhibitor has proven effective in relapsed/refractory AML with a 53% response rate in FLT-3 positive patients, and is currently being tested in combination with standard therapy (NCT01390337).

**NUCLEOPHOSMIN 1 (NPM1)**

The NPM1 gene encodes for a protein [nucleophosmin] with many functions, including nuclear transportation and regulation of tumor suppressor genes. It can be found in 45-64% of all NK AML, and approximately 33% of all cases of AML. Mutations in NPM1 lead to abnormal cytoplasmic localization of the protein that can be diagnosed with immunohistochemistry on bone marrow samples. While the NPM1 mutation has been shown to often be associated with other mutations, such as FLT3-ITD, DNMT3A and IDH1/2, it has been associated with a favorable prognosis with higher relapse-free survival and OS in patients without co-occurring FLT3-ITD mutations. This benefit is seen not only in younger patients, but also in older patients, even those over the age of 70. Thus, patients with NPM1 mutations, without FLT3-ITD or other poor prognostic features, can likely pursue standard chemotherapy (with induction followed by consolidation), without necessarily needing allo-HSCT.

<table>
<thead>
<tr>
<th>Gene Mutation</th>
<th>Effect</th>
<th>Incidence</th>
<th>Potential Therapy Implications</th>
</tr>
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<tbody>
<tr>
<td>Fms-like tyrosine kinase 3 (FLT3)</td>
<td>Tyrosine kinase receptor that activates signal transduction and cellular proliferation</td>
<td>Approximately 30% NK AML</td>
<td>Phase II success with TKI [sorafenib, midostaurin, quizartinib]; clinical trials ongoing.</td>
</tr>
<tr>
<td>Nucleophosmin 1 (NPM1)</td>
<td>Protein involved in transportation and regulation of tumor suppressor genes</td>
<td>45-64% NK AML</td>
<td>Potentially favorable prognostic factor.</td>
</tr>
<tr>
<td>CCAAT/Enhancer binding protein alpha (CEBPA)</td>
<td>Transcription factor involved in differentiation of myeloid precursors</td>
<td>10-18% NK AML</td>
<td>Potentially favorable prognostic factor.</td>
</tr>
<tr>
<td>DNA-methyltransferase 3A (DNMT3A)</td>
<td>Enzyme involved in epigenetic modification (methylation) of DNA</td>
<td>25% NK AML</td>
<td>Patients may benefit from high-dose anthracyclines in induction therapy; 5-azacytidine/decitabine currently used for MDS and being studied for AML.</td>
</tr>
<tr>
<td>Isocitrate dehydrogenase 1/2 (IDH1/2)</td>
<td>Mutant enzymes that produce d-2-hydroxoglutarate, an oncometabolite that interferes with histone function and leads to oxidative stress</td>
<td>10-14%, 10-19% NK AML, respectively</td>
<td>Phase I trials ongoing with IDH1/2 inhibitors, AG-120 and AG-221.</td>
</tr>
<tr>
<td>Additional sex combs-like 1 (ASXL1)</td>
<td>Protein involved in chromatin modification and remodeling</td>
<td>3% NK AML &lt; 60 years of age; 16% NK AML &gt; 60 years of age</td>
<td>Poor prognostic factor.</td>
</tr>
<tr>
<td>Ten-eleven-translocation-2 (TET2)</td>
<td>Enzyme involved in epigenetic modification (deoxygenation) of DNA</td>
<td>18-23% NK AML</td>
<td>Poor prognostic factor.</td>
</tr>
<tr>
<td>Runt-related transcription factor 1 (RUNX1)</td>
<td>Transcription factor involved in hematopoiesis</td>
<td>8% NK AML &lt; 60 years of age; 16% NK AML &gt; 60 years of age</td>
<td>Poor prognostic factor.</td>
</tr>
</tbody>
</table>

NK AML, normal karyotype acute myeloid leukemia; TKI, tyrosine kinase inhibitors.
**CCAAT/ENHANCER BINDING PROTEIN ALPHA (CEBPA)**

CEBPA is a gene that encodes for CCAAT/enhancer binding protein alpha (CEBPα), a transcription factor protein that binds to promoter regions of DNA leading to growth arrest and cellular differentiation of myeloid precursors. The mutation can be found in 10-18% of adult patients with NK AML, and is also associated with the 9q deletion. Like NPM1, patients with CEBPA gene mutations, without concomitantly occurring FLT3 mutations, have a decreased relapse rate and increased OS. Patients can have either one or two allelic mutations, and patients with two mutations have been shown to carry the improved prognosis. This mutation has already been incorporated into the European LeukemiaNet classification, although a therapeutic target is not currently known at the time of writing this article.

**ISOCITRATE DEHYDROGENASE 1/2 (IDH1/2)**

IDH1 and IDH2 are homologs of the enzyme isocitrate dehydrogenase occurring in the cytosol and mitochondria, respectively. These mutant enzymes catalyze the conversion of α-ketoglutarate to 2-oxoglutarate (2-HG), an oncometabolite. Mutations in IDH1/2 have been known to occur in various types of brain tumors, but have also been found in approximately 10-14% [IDH1] and 10-19% [IDH2] of NK AML. Both mutations have been found to carry poorer prognosis in patients with NK AML. These mutations and 2-HG are currently of great clinical interest, as they may be used monitor treatment response and become targets of novel therapies. Currently, there are inhibitors to IDH1 [AG-120, Agios, Cambridge] and IDH2 [AG-221] under evaluation for AML. Although the pharmacokinetics data from the phase I trial of AG-120 has been presented, the early studies for AG-120 [NCT02074839] and AG221 [NCT01915498] are ongoing.

**ADDITIONAL SEX COMBS-LIKE 1 (ASXL1)**

ASXL1 encodes for a protein that is involved in chromatin modifications and remodeling. Mutations in this gene have been studied in other hematologic malignancies, but have only recently been identified as an adverse prognostic indicator in AML. ASXL1 mutations occur in approximately 8-13% of patients with NK AML, although it has been demonstrated more frequently in abnormal karyotype intermediate-risk cytogenetics, such as trisomy 8, and MDS-related AML. It is also notable that ASXL1 mutations occur with a 5-fold higher frequency in patients over 60 years of age compared to patients younger than 60. Patients with ASXL1 mutations demonstrate both a lower CR and OS.

**DNA-METHYLTRANSFERASE 3A (DNMT3A)**

Genomic studies have identified a mutation in the DNMT-3A gene that has become a significant negative prognostic indicator for AML. This key enzyme is involved in epigenetic regulation via DNA methylation. There are two mutations with DNMT3A – one which affects codon R882 that has a worse prognosis for older patients, while other DNMT3A mutations are related to a worse prognosis in younger patients. Mutations in this gene occur in approximately one-quarter of patients with NK AML and are associated with an OS of 12.3 months compared to 41.1 months. These patients were more likely to be older, and also more commonly had concomitant mutations in NPM1, FLT3, and IDH1 as well as more frequently noted to be in the NPM1-FLT3 low-risk group.

**TEN-ELEVEN TRANSLOCATION-2 (TET2)**

TET2 is an oncogene that has been identified in myelodysplastic syndromes and 18-23% of de novo NK AML. It has been strongly associated with secondary AML, older AML patients and a higher pretreatment white blood cell count. A recent CALGB study demonstrated that in NK patients, who would be otherwise categorized as having a favorable mutational profile, the presence of the TET2 mutation led to lower response rates and a high risk of relapse or death. This may lead clinicians to suggest more aggressive treatment regimens, rather than standard chemotherapy, which would typically be offered to patients with an otherwise favorable risk.

**RUNT-RELATED TRANSCRIPTION FACTOR 1 (RUNX1)**

The RUNX1 mutation involves the α-subunit of core binding factor, which takes part in the differentiation of hematopoietic progenitor cells. It is associated with NK AML in 8% of patients under the age of 60, yet 16% of patients over 60. The RUNX1 mutation was associated with inferior CR rates [47% versus 77%] and shorter disease-free survival. Most importantly, patients with RUNX1 mutations had a markedly decreased 5-year overall survival rate, with RUNX1 mutated patients at 2% while non-mutated at 30%. RUNX1 mutations were also found with concomitant mutations in ASXL, MLL, and IDH2, but less likely to be present in patients with NPM1 and CEBPA.

**CONCLUSION**

While many recurring mutations have been identified, adequate studies have yet to determine which specific mutations have clinical relevance. Moreover, several studies have demonstrated the frequent co-occurrence or mutual exclusivity of several mutations, which leads to further questions regarding which particular mutations may be oncogenic initiators versus subclonal variations or downstream mutations. Although multiple mutations have been described here and in the literature, only NPM1 andFLT3 have clinical studies available, while IDH1 and IDH2 have small
molecule inhibitors in clinical trials. As genomic testing becomes commercially available, newly diagnosed patients with AML should have molecular studies performed, in addition to the standard karyotype analyses. Genomic advances have allowed clinicians to more appropriately risk-stratify patients, and future utilization of novel targeted inhibitors will likely lead to the development of successful personalized treatment plans for patients with AML.

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**Melanoma Genomics and Immunotherapy**

**MARIA CONSTANTINOU, MD**

**ABSTRACT**

Over the last decade the molecular characterization of melanoma has progressed. Since a majority of melanoma cases arise from repeated intermittent ultra violet radiation (UVR) exposure, the role of UVR has been evaluated extensively. Recent work has identified two mechanisms in which the carcinogenesis of melanoma may result; Ultra violet radiation has been demonstrated to lead to down regulation in immune responses and result in pyrimidine dimerization. Given these links and more significant immunogenic antigen profile of melanoma, as compared to other malignancies, there has been significant therapeutics breakthroughs based on these molecular pathways.

**KEYWORDS:** Tumor profiling, Melanoma, Immunotherapy

**MELANOMA RATES ARE RISING RAPIDLY**

Over the past 30 years, the incidence has doubled among women and tripled among men. More than 75,000 new cases of invasive melanoma will be diagnosed in the US in 2015. Melanoma claims 8,776 lives annually. The cost of treatment for melanoma is 3.3 billion per year and continues to rise. 

In the majority of cases, melanoma arises from repeated intermittent sun exposure especially in individuals with a history of multiple severe sunburns in childhood and adolescence. Melanoma is associated with a more immunogenic antigen profile compared to other malignancies. Ultra Violet radiation exposure leads to down regulation in immune responses. The absorption of UV radiation leads to a release of mediators that can affect antigen-presenting cells locally and systemically. This generates antigen specific T-cells capable of regulating immunity. In addition, UV exposure can lead to pyrimidine dimerization on DNA. If these products are not removed by cellular repair activities, after DNA replication, they may cause mutations.

Regardless of the cause of the rise there has been an increase in survival due to the development of new treatments. The new treatments are targeted therapies which have emerged from advances in genetic profiling of molecular targets. Three key molecular pathways have been identified as highly deregulated in melanoma and include: mitogen-activated protein kinase (MAPK), PI3K/AKT and CDKN2A [p16] pathway.

I. MAPK Pathway

Advances in melanoma have emerged from an increased understanding of melanoma biology and signaling pathways. The mitogen activated protein kinase (MAPK) pathway is a signaling cascade that has been studied extensively in melanoma. Deregulation occurs as a result of acquired mutations along this pathway.

This cascade includes several upstream signals that are funneled through RAF, MEK and ERK. Downstream molecules such as phosphatases, communicate with higher levels in the pathway to appropriately reduce signaling in normal cells. In melanoma, cells with an activating BRAF mutation, feedback is inhibited, which keeps the pathway switched on. The most prevalent are the BRAF mutations seen in at least 45% of cases. RAS mutations have a prevalence of 15% and the surface receptor tyrosine kinase, c-Kit is rare with 2-3% prevalence. Downstream mutations include amplification of CDK4 [30%], CCND [10%] and the survival oncogene microphthalmia associated transcription factor [MITF] [10%].

BRAF is a serine/threonine kinase, a component of the MAPK pathway downstream of RAS. BRAF activation is a very strong signal, when it is activated it triggers the phosphorylation of MEK. BRAF mutations occur early in melanogenesis. About 50% of all melanomas have BRAF mutations. V600E mutations represent 80-90% followed by V600K, V600D and V600R that account for 5-15% of all BRAF mutations. These are more common in intermittently sun exposed skin and superficial spreading melanomas.

BRAF inhibition is associated with a robust clinical
response. Vemurafenib and Debrafenib inhibit cells with a BRAF mutation. Immunohistochemistry of tumor biopsies showed a positive association between tumor response and the percentage decrease in cytoplasmic phosphorylated ERK supporting the proposed mechanism of action. A 3-year overall survival rate of 30% was observed in long-term follow-up with a significant improvement over standard therapy, Dacarbazine [DTIC]. BRAF inhibition response is heterogeneous and rapid but resistance to therapy is seen within a year.

Within the MAPK pathway 37% of patients have a secondary RAS mutation that co-exists with the BRAF mutation. Alternative splicing, which allows BRAF to dimerize and increase signaling occurs in 20% of patients. BRAF amplification, which may produce a 50-fold increase in BRAF copies, occurs in 30% of patients. Downstream mutations in MEK 1/2 (2%) and cdk4 (11%) are less common. 7,8 The pattern of acquired BRAF inhibitory resistance follows a branched rather than linear path. This heterogeneity supports the rationale for early use of combined BRAF and MEK inhibitors in pursuit of a durable response. When resistance-related disease progression occurs while taking a BRAF inhibitor a secondary response may occur when a MEK inhibitor is added. 9,10,11

Debrafenib, a BRAF inhibitor, used in combination with Trametinib, a MEK inhibitor, is associated with an improved 12-month OS of 72% vs 63% in the monotherapy group and a MPFS [Median Progression Free survival] of 11 months vs 7.3 months. The combination therapy delays resistance and is associated with lower treatment-related toxicity. 12

II. PI3K/AKT: RAS and PTEN

The RAS proteins belong to a family of p21 proteins. These are all part of a complex network of pathways resulting in the release of nuclear transcription factors leading to expression of genes involved in mitogenesis and apoptosis. 8,13 Three closely related proto-oncogenes encoding the HRAS, KRAS and NRAS are found in mutated forms in human tumors. NRAS mutations are common in myeloid leukemia and melanomas. About 20% of melanomas have NRAS mutations. NRAS and BRAF mutations are mutually exclusive. There are no successful therapeutic targets for mutant NRAS mutant melanomas.

The pathways that could be targeted in NRAS mutant melanoma include MEK, P13K/m-TOR and cell related targets. Monotherapy with MEK inhibitors was associated with partial responses of 20% in this group of patients.

The PTEN gene is located on chromosome 10. Mutations in PTEN are found in 10%-20% of melanomas. PTEN has lipid phosphatase activity, which prevents formation of intracellular signaling molecules required for conformational change, which results in activation of the AKT protein kinase family. Activation of AKT pathway suppresses apoptosis through phosphorylation and inactivation of pro-apoptotic proteins. DNA copy gain of the AKT3 locus is found in 40%-60% of melanomas and results in activation of the AKT protein kinase. AKT3 expression correlates with melanoma progression. Thus, inactivation of PTEN allows signaling through the AKT pathway, which contributes to cell growth and anti-apoptosis. Evidence suggests that there is cooperation between loss of PTEN and BRAF mutations. 14

Adaptive responses by the tumor are reflected in pathway alterations contributing to acquired resistance to therapy. In more than half of the cases, the MAPK pathway, previously blocked by the BRAF inhibitors is reactivated, and p13k-PTEN-AKT alteration is involved in 4% of resistance development.

III. AKT: CDKN2A/p16

The CDKN2a gene products, p16 [tumor suppressor molecule] and p14 are cell cycle regulators that are frequently nonfunctional, especially in tumors arising from chronically sun-damaged skin. CDK4 and CDKN2A mutations are more common in acral and mucosal melanomas. The p16 protein binds to CDK4/6 kinase, blocking phosphorylation of the retinoblastoma protein and therefore leading to cell cycle arrest and inhibition of melanogenesis. Dysfunction in the proteins involved in this pathway promotes cell growth. P14 protein inhibits oncogenic activity of Bax/bcl-2 proteins that are responsible for effective apoptosis and are associated with resistance to anti-cancer therapy. 15

OTHER MOLECULAR PATHWAYS

C-Kit is a receptor tyrosine kinase [RTK] activated by binding of a stem cell factor. C-Kit plays an important role in proliferation, development, and survival of melanocytes, hematopoietic cells and germ cells. C-Kit mutations or amplifications activate a signal transduction pathway that ultimately leads to melanogenesis. Mutations in C-Kit are found in mucosal, acral and permanently exposed skin melanomas. C-Kit mutations or copy number gains are found in 39% of mucosal melanomas and 36% of acral melanomas. C-Kit mutations have also been shown to occur in up to 88% of oral mucosal melanomas and 15% of anal melanomas. Acral melanomas and mucosal surfaces appear to be the most aggressive subtypes. C-Kit mutations are rare in melanoma but inhibitors such as Imatinib and Nilotinib have shown promising activity in patients with exon 11 and 13 mutations. Phase II data showed overall disease control rate of 50%. 16 The presence of NRAS mutations is associated with resistance to Imatinib in the C-Kit mutant melanomas. BRAF mutations are less frequent in these melanomas.

Uveal melanoma arises from melanocytes of the choroid, ciliary body, and iris. Unlike cutaneous melanomas, which more frequently metastasize to lymph nodes, lung and brain, uveal melanomas often spreads to the liver. Metastatic disease is aggressive and with no effective treatment options for this group of patients. GNAQ and GNA11 pathway dysregulation appears to be responsible for the development of uveal
melanomas. GNAQ and GNA11 are genes that up-regulate the MAPK pathway when constitutively active. Mutations in GNAQ and GNA11 are mutually exclusive and found in more than 80% of uveal melanomas. These mutations are potential targets of therapy through blockade of the mutated proteins or other signaling molecules downstream in the same signaling pathways.7,16

**IMMUNOTHERAPY**

Over the past decade, new developments in T cell immunology have changed treatment algorithms and led to significant improvements in survival in patients with metastatic melanoma. T cell activation and proliferation are upregulated or down-regulated by checkpoint proteins that originate during distinct phases of the T cell response. Several immune checkpoint molecules have been identified many of which are co-expressed on cancer specific T cells. T cell activation occurs away from the target tumor Cytotoxic T lymphocyte associated molecule-4 (CTLA-4). CTLA-4 is a negative regulatory molecule that is translocated to the surface of the T cells after activation. This molecule ligates receptor B7 on antigen presenting cells (APC) and down-regulates T cell responses within 72 hours after activation. Blocking the ligation of CTLA-4 to the APC permits proliferation of activated cells.17

Ipllimumab

Ipllimumab is a monoclonal antibody to CTLA-4 approved for treatment of metastatic or unresectable melanoma. This therapy is associated with a disease control rate of about 30% and a 2-year survival of 29%, with a long-term durable response achieved in 20% of patients. There are no clear markers to predict response to therapy.18

**Anti PD1/L1 immune blockade**

Cytokines activate T cells that subsequently proliferate and migrate to the tumor microenvironment, where terminal inhibition of activated T cells occurs. PD1 and its ligand PD L1 which is up regulated on the tumor cells upon T cell recognition, are important immune checkpoint proteins. Whereas anti CTLA-4 inhibition occurs at the lymph node checkpoint, PD1 blockade occurs in the tumor microenvironment.

Nivolumab is an anti PD1 humanized monoclonal antibody approved for treatment of metastatic melanoma in patients who failed prior therapy with Ipllimumab or other targeted therapies. Nivolumab achieved response rates of 32% with durability ranging from 2.6–10+ months. Pembrolizumab is another IgG4 human programmed death receptor-1 engineered blocking antibody approved for patients with unresectable or metastatic melanoma and disease progression following Ipllimumab or BRAF targeted therapy. Overall response rate was 24% with ongoing responses 6 months or longer.19

PD-L1 is an inducible ligand with several immune system functions. When expressed on tumor cells this protein down regulates the immune response. Histologic studies have shown that PD-L1 expression on the leading edge of the growing tumor further supporting the role that PD-L1 plays in the suppression of the immune system.19 Treating patients with compounds known to induce tumor PD-L1 has been suggested and this strategy is currently being investigated in clinical trials.

PD-L2 is a homologue ligand of PD-L1 both of which have normal physiologic functions in humans. Dendritic cells and macrophages express high levels of PD-L2 after immune challenge. Therefore specificity of PD antibodies is important. Results from a phase 1 study on anti PD-L1 antibodies suggested similar responses to that achieved with anti PD-1 antibodies; an overall response rate of 32 % was observed and several patients achieved durable responses. Patients with >5% cell expression of the PD-L1 had better disease control rates (80%), compared to those with <5% PD-L1 staining.20

**OTHER IMMUNE MODULATORY RECEPTOR TARGETS**

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<thead>
<tr>
<th>GITR (glucocorticoid induced TNF receptor)</th>
<th>Increases expansion of the T cell population</th>
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**CONCLUSIONS**

Molecular differences among melanoma are extremely valuable for best therapeutic options and targets. Despite the recent advances in this field most patients ultimately relapse because of resistance. Many studies are underway investigating mechanisms and pathways to prolong treatment response and combat resistance.

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Oral Hygiene in Patients with Parkinson’s Disease
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ABSTRACT
Parkinson’s disease is a chronic progressive neurodegenerative disorder with a multifactorial etiology. The symptoms are characterized by motor disorders – tremor, rigidity, bradykinesia and postural instability, which hinder oral hygiene. Oral and dental health in Parkinson’s disease has been under-documented and findings are conflicting. Moreover, a number of dentists have limited experience regarding the management of these patients. This article reviews literature published within the last fifteen years, to better understand the impact of this disease in oral health. A literature search (MEDLINE and PUBMED), using keywords Parkinson Disease and Oral Hygiene, yielded 27 articles, from which 20 were selected. All of the articles were published in English in the last 15 years.

KEYWORDS: Parkinson’s disease, oral hygiene, oral health

INTRODUCTION
Parkinson’s disease (PD) has a prevalence of greater than 1% in people over 65 years old. This illness results in selective destruction of mesencephalic dopaminergic neurons located in the substantia nigra.¹ The classic motor presentation, characterized by tremor, rigidity, bradykinesia, and postural instability, reduces dexterity, making oral hygiene challenging. Additionally, other risk factors for oral disease in PD patients have been documented, such as craving for sweets and medication-induced salivation changes.²,³

Although there are increasing data on the subject, oral health in Parkinson’s disease is still poorly documented and findings have been contradictory. This may affect the level of expertise and, consequently, the level of comfort that dentists have in the management of these patients. Oral health professionals rarely perform complex dental procedures in PD patients, and sometimes they may disregard an essential step of the treatment: motivation and instructions for oral hygiene. These limitations in treatment may also help to explain the increase, sometimes reported, in tooth loss in this population. On the other hand, patients with PD have also been reported to have a smaller number of teeth decayed.²,⁴,⁵

Almost half of patients with PD have some difficulty with daily oral hygiene habits, and although there is no absolute consensus in the literature about the link between a higher prevalence of oral disease and PD, it is essential for health care providers to be aware of the potential oral health hazards that PD patients have.

METHODS
We performed a systematic review of articles published in English in the last 15 years that connect Parkinson’s disease and oral hygiene. Using MEDLINE and PUBMED with the keywords Parkinson Disease and Oral Hygiene, articles were included if they were published in English within the last 15 years. The search yielded 27 articles, from which 20 were included based on the aforementioned criteria.

LITERATURE REVIEW
Parkinson’s disease is characterized by cardinal motor impairments noted above, but other findings may also be present including dysphagia, gait instability/shuffling gait, and masked facial expression. Although they produce less saliva than normal, they swallow less, which may lead to drooling. It is an irreversible, slowly progressive disorder.⁶,⁷,⁸,⁹

There is some concordance in the literature on risk factors that PD patients have to develop oral diseases: mechanical inability to perform proper oral cleaning, medication use that can cause dry mouth by reducing saliva formation, physical and behavioral changes that complicate professional dental service, cognitive changes that prevent patients from reporting dental symptomatology including pain, and an elevated number of appointments missed with the dentist.²,³

Almost half of patients with PD have some difficult in daily teeth cleaning. For instance, PD patients are less likely than healthy patients of the same age: to brush their teeth, to use dental floss, and to clean their dental prosthesis.⁴,⁵,¹¹

The reduction of salivation caused by anticholinergic medications and also by possible malnutrition, and the habit of eating sweets and sticky foods, may contribute to the formation of dental caries, periodontal disease and eventual tooth loss.⁵,¹² Some patients have decreased appetite. This problem, associated with proper motor function required for proper chewing, cause patients to avoid nutritious foods such as vegetables and grains. Additionally, PD patients are also known for their “sweet tooth,” a predilection which can increase the risk of developing dental caries.¹³,¹⁴
Behavioral changes may also increase the risk of oral health problems. Apathy, depression and forgetfulness, for instance, may cause patients to neglect their oral hygiene as well as hamper professional dental care. Patients may develop cognitive impairment, which tends to be reflected in the decline in the practice and effectiveness of activities of daily living, including self-care routines, such as dental hygiene. For these same reasons, PD patients can also lose more appointments with the dentist and may not accurately report their dental symptoms to their caregivers and dentists.

In some studies, comparing patients with PD and healthy populations, PD patients have a higher number of missing teeth, more dental plaque, more dental caries, more pronounced bone loss, deeper periodontal pockets and overall worse oral hygiene. In these studies, salivation rates were essentially the same for groups with and without Parkinson’s disease, which can be a surprising finding given that PD patients may sometimes either present with reduced salivation due to some anti-parkinsonian medications or even as an early autonomic manifestation of PD, or have drooling due to a reduced rate of swallowing.

Some interventions have been proposed to improve oral hygiene and the care of these patients: the use of an electric toothbrush provides precise and repetitive movements, cleaning and protecting teeth more effectively; treatment with stannous fluoride dental gel is a good strategy for daily use at home, as well as in periodic visits to the dentist, because stannous fluoride gel is stronger than the fluoride component found in toothpastes; treatments with chlorhexidine, which can chemically reduce the plaque index in patients with motor deficiencies; appointments preferably scheduled for about an hour after patients have taken their PD medications, to take advantage of a peak response period, leading to better cooperation with the dental procedures; the use of mouth opening devices to facilitate procedures; the use of appropriate local anesthetics (e.g. Lidocaine with adrenaline) in the lowest effective dose. Dentists should stimulate and guide their PD patients, family and caregivers to practice appropriate techniques of dental hygiene.

**DISCUSSION**

Studies that outline the habits and the special needs of patients with PD are still scarce and fairly discordant. Nevertheless, there seems to be agreement on the many predisposing factors for oral cavity diseases in PD, including: 1) the difficulty performing proper oral hygiene because of motor limitations; 2) propensity for deleterious food habits such as high ingestion of sweets; 3) the use of drugs that reduce salivation; 4) physical and behavioral deficiencies that hinder adequate professional dental procedures; 5) cognitive changes, which make patients more likely to miss dental visits and less likely to report dental pain/symptomatology to their caregivers or dentist, among other factors.

However, contrary to what one could expect, patients with Parkinson’s disease have been reported as having less decayed teeth but an increased prevalence of periodontal disease when compared to a normal control group. The authors also found that the frequency of brushing was higher among patients with Parkinson’s disease, with an average of two daily brushings. The results of increased rates of gingivitis and periodontitis, with a significant increase of the depth of periodontal pockets serves as a reminder that chronic plaque accumulations may cause not only tooth decay but also bone loss in this special patient group, because of their presumed difficulty with daily oral hygiene.

While oral hygiene was reportedly poor in PD patients, the number of caries were at least as high as in control groups, suggesting that PD patients are not invariably associated with a protective factor against decay. Furthermore, the authors also found that the subjects were invariably associated with the need for good oral hygiene. Although individuals with PD have been reported to brush their teeth at least as often as the comparison subjects, and they also seem to be aware of the need of proper oral hygiene, this was clearly not always particularly effective. Published reports in which individuals with PD used electric toothbrushes and even flossed, still noted that the results were still not satisfactory for efficient plaque control. Because the inability to perform oral hygiene well due to their motor limitations, the authors identified a need to further strengthen oral hygiene in this group, through a combination of physical methods and chemical control of the plaque, with chlorhexidine or a similar agent. Furthermore, regular monitoring by a dentist or dental hygienist to ensure that patients are able to maintain a reasonable oral hygiene appears to be a sensible recommendation.

There is general agreement on the need for greater participation of dentists in the planning and delivery of health care to patients with PD, as an essential team player in the multidisciplinary task force in PD. Oral health professionals are also essential to motivate and educate these patients and their caregivers on the importance of maintaining good oral hygiene habits. Deficient dental and periodontal health may be a risk factor for progression of associated systemic diseases such as diabetes, pulmonary disease, atherosclerosis, cardiovascular disease and stroke in any population. Moreover, a good control of the PD itself prevents deterioration of the patient's oral health, which can often be neglected as a result of the evolution of the disease.
as how to achieve good oral hygiene in PD. Additionally, dentists need to understand the disease and the limitations it imposes to properly participate in the care of PD patients, helping them to achieve a better quality of life.

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ABSTRACT

CASE: A 53-year-old male sustained a high-pressure water injection injury to his foot while working in a river. He was taken to the operating room for emergent irrigation and debridement of copious riverbed sediment. Cultures taken from the operating room were positive for multiple anaerobes, fungus and mold and he was treated with appropriate antibiotics. To date, his only residual deficit is a 1 cm area of numbness at the entrance wound.

CONCLUSION: High-pressure water injections to the foot are uncommon injuries. These are serious injuries that require emergent antibiotics, tetanus and surgical debridement.

KEYWORDS: Trauma, Emergency Care, Orthopedics, High-Pressure Injection Injury

INTRODUCTION

High-pressure injection injuries (HPII) of the foot are uncommon injuries, and are usually the result of industrial work accidents. A HPII to the foot, as in the hand, may have devastating consequences. Sequelae of these injuries include serious injury to the soft tissues, neurovascular structures, decreased long-term function and may ultimately result in amputation. 1 HPII most commonly occur in men, with the non-dominant hand being the most frequent location; however, injuries have also been reported in the feet, legs, abdomen and face. 2-5 The injected material provokes an inflammatory response causing pain and swelling and can often lead to irreversible tissue destruction. 1 There continues to be a question in the literature as to whether injections with certain materials such as water necessitate operative intervention.

CASE REPORT

We present a case of a 53-year-old healthy male who was volunteering in a local river-cleaning project (Blackstone River, Rhode Island). He was attempting to clean a turbine in the riverbed when he sustained a power washer injury to his foot. He was submerged to his waist in the river and was wearing thick rubber boots. Given the cold temperature of the water, the patient continued working for one hour after the time of injury. He only noticed the extent of the injury after he had exited the river. He then realized the pressure washer had perforated his rubber boot and two pairs of socks. Upon inspection of his foot he noticed a small hemorrhagic lesion and consequently presented to Rhode Island Hospital (RIH), four hours after injury.

At presentation to RIH ED, the urgency of his HPII was noted immediately and the patient was taken emergently to the OR for irrigation and debridement. Upon arrival in the OR, the foot presented with a pinhole injury [assumed entrance wound] and streaking proximal erythema [Figure 1]. The foot was neurovascularly intact, however, he had exquisite tenderness proximal to the zone of injury. In the OR an extensive debridement was performed. Debris was noted on his radiographs as well as grossly during initial debridement.

Figure 1. The patient’s foot at presentation with a pinhole injury (assumed entrance wound) and streaking erythema.
and had infiltrated vascular structures (Figure 4). All gross debris was excised at the initial debridement (Figure 5). Cultures were sent from the OR, and the wound was copiously irrigated and washed in a betadine/lactated ringsers solution and primarily closed with interrupted nylon suture. The patient remained hospitalized for three days,

Figure 2. The initial radiograph showing debris tracking proximally from injection site.

Figure 3. Gross debris noted at initial debridement.

Figure 4. Debris tracking along and infiltrating vascular structures.

Figure 5. Wound after all gross debris was excised at the initial debridement.

to allow daily examination of the wound. He was seen in consultation by the infectious disease team and was started empirically on IV levofloxacin 750mg IV daily and Zosyn 4.5g q6h. He was made non-weight bearing for three weeks to allow the soft tissue to heal and was discharged on levofloxacin 500mg daily.

Cultures grew multiple anaerobes (B. cereus, Bacillus sp. not Anthrasis, Cornybacterium sp, Clostridium sp) and Stenotrophomonas maltophilia, requiring the addition of Flagyl 500mg q8h. Approximately two weeks after injury the cultures began to grow 1+ Fusarium and 1 colony mold consistent withacremonium species; consequently Voriconazole was added. At three weeks post-op, his wound continued to heal with a 2 cm zone of eschar focused around the initial injection injury. At six weeks his incision had almost fully healed with a half-centimeter eschar remaining. His antibiotics were continued for a total of six weeks for levofl oxacin and flagyl and four weeks for voriconazole. His recovery after initial debridement was uneventful; at no time did he present with systemic signs of infection. CBC, ESR, and CRP were followed throughout his recovery and all had returned to baseline normal by four weeks post injury. He was made weight bearing as tolerated three weeks after injury. His only residual symptoms are localized numbness approximately 1 cm in diameter centered over the initial injection wound.
DISCUSSION

HPII are associated with irreversible tissue ischemia with several described mechanisms. First, the injected material dissects through tissue planes of least resistance and can lead to compression of neurovascular structures and vasospasm causing tissue ischemia. Second, the injected material may create enough pressure to decrease tissue perfusion, resulting in a local compartment syndrome. Third, the material itself may result in a localized toxicity secondary to the chemical properties of the injected material. Lastly, ischemia and tissue necrosis set the stage for secondary infection which is frequently encountered with these injuries. As our case report demonstrates, river water should be considered a potent biological and chemical toxin.

On first inspection of HPII, the entry wound is a small, benign appearing puncture. Additionally, patients initially have little to no pain, which may explain delays in seeking medical attention as well as missed diagnoses. An accurate history should be obtained at presentation to determine the material injected, the pressure of the gun and the distance of the extremity from the gun. A thorough physical examination should include the entry and exit wounds if present, neurovascular status, and the presence of the injected material. Additionally, radiographs are necessary to determine the extent of the injected material, assess for other foreign bodies and exclude fractures. Broad-spectrum antibiotics and tetanus prophylaxis are mandatory. Surgical debridement is necessary, although there are reports of successful conservative management of high-pressure injuries with water, air, and vaccine.1,2,7,10,11

The degree of tissue damage depends on the pressure of the injection and the amount and type of injected material. The most frequent injected agents are grease, paint, paint-thinner, diesel oil, hydraulic fluid, and gasoline, while reports of water and air are less common. Significantly, this is only the second report we were able to find on injected river water, although similar to the report of sea mud injection by marine, a second report was able to find on injected river water, but reports of river water and air are less common. Significantly, this is only the second report we were able to find on injected river water, although similar to the report of sea mud injection by marine, diesel oil, hydraulic fluid, and gasoline, while reports of water and air are less common.

A meta-analysis of high-pressure injection injuries concluded that the type of injected material was the most important factor affecting outcomes. The authors found that 4 of 5 [80%] patients injected with paint thinner or turpentine required eventual amputation. Whereas only 9 of 40 [22.5%] patients injected with grease, a much less caustic agent, required amputation. A review by Hogan et al had similar findings and found that organic solvents such as paint, paint-thinner, diesel fuel, gasoline and oil resulted in amputation 40% of the time. They concluded that these agents cause an inflammatory response that promotes vasoconstriction and tissue necrosis. Additionally, paint is considered by some to be the most toxic injected agent. However Hogan et al found the rate of amputation with latex-based paints was only 6%, whereas it was 58% with oil-based paints. While strong solvents to clean oil-based paints such as toluene and turpentine are discouraged due to risk of further tissue damage, a study by Urso-Baiarda et al found that the use of butter to emulsify and facilitate solvent removal enhanced tissue cleansing. Additionally, many painters find that baby oil is useful to emulsify oil paints and may have a role to play in gentle tissue cleansing of oil-based paints. In our case, we irrigated the wound with a mixture of lactated ringers and betadine solution. Subjectively we felt that the yellow coloring of the betadine/lactated ringers irrigant made visualizing the small dirt particles easier. It is possible that this is a result of enhanced contrast due to blue-light filtering, similar to the effect of wearing yellow-lensed glasses.

There are few other case reports of HPII with water. A report by Bussewitz et al detailed an incident of a 40,000-psi pressure water washer injury to the hallux. The patient did well after aggressive multiple debridements, foot and lower extremity fasciotomies, antibiotics and eventual primary closure. The pressure of the injection injury is an important factor to consider. A recent review demonstrated that when the pressure of the injection was less than 1000-psi for all injected materials the amputation rate was 19%. With pressures greater than 1000 psi, the amputation rate increased to 43%, demonstrating increased injury to the soft tissues and neurovascular structures. However, it is important to note that in the same review no cases of injection with water or air resulted in amputation, independent of pressure or surgical versus nonsurgical treatments.

The question of when to treat high-pressure water injuries with surgical debridement continues to be debated. The most important factor to consider is the source of water. Water sources for high-pressure sprayers can come from enclosed containers, or may be siphoned from nearby water sources such as rivers, lakes, and ponds. Even the water from enclosed containers poses a threat as these containers can grow bacteria from sewage and industrial waste. Additionally, water from a presumed safe water supply may lead to infection from atypical bacteria. Although water is not overly inflammatory, most high-pressure guns are lubricated with oils that may consist of inflammatory agents such as carbons, sulfur, and vanadium.

CONCLUSION

All patients with a HPII should be admitted to the hospital, given broad-spectrum antibiotics to cover both gram-negative and gram-positive organisms, and in our opinion, should undergo thorough surgical exploration and debridement. All devitalized tissue and foreign material should be removed, and cultures should be sent. We recommend using a betadine-saline solution for both its antimicrobial properties and improved visualization of dark colored foreign material. Additionally, we think there may be a role for the use of less harsh solvents, such as baby oil, for aiding in removal of oil-based paints despite previous literature supporting the contrary. Post-operatively the patient should be monitored...
closely for signs of infection and compartment syndromes. Re-exploration should be utilized if any signs of infection develop, or to reassess the wound if a large amount of foreign material was initially encountered.

References

Authors
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**Chest Pain and a Sore Throat**

**COURTENEY MACKUEN, MD; JEFFREY FEDEN, MD; BONNIE MARR, MD; WILLIAM BINDER, MD**

 chops records of the brown university residency
in emergency medicine

**dR. COURTENEY MACKUEN:** The patient was a 36-year-old man who presented to the Emergency Department (ED) with the sudden-onset of substernal chest pain that woke him from sleep just prior to arrival. The pain was sharp and radiated down his left arm. It was associated with shortness of breath and diaphoresis. He had never experienced similar pain previously. The patient was otherwise a healthy, employed, married man with two children at home. He reported subjective fevers and chills three days prior to his visit and had had several loose stools. He also complained of a sore throat and headache for the past several days. He denied cough or runny nose, and he denied abdominal pain. He stated that he had been taking ibuprofen for the past 24 hours because he was simply not feeling “well.” The patient denied any illicit drug use and is a former smoker. Ill contacts included his 9-year-old son who was diagnosed with streptococcal pharyngitis approximately two weeks prior to presentation and was treated with amoxicillin for ten days. His family history is only significant for coronary disease in his father at the age of 55. The patient has two dogs and keeps an aquarium.

**dR. WILLIAM BINDER:** Can you describe his exam?

**dR. MACKUEN:** This gentleman appeared uncomfortable, and diaphoretic. His blood pressure was 94/64 mmHg, heart rate at 114 beats per minute, temperature of 102.7 degrees Fahrenheit, and oxygen saturation 98% on room air. The patient’s exam demonstrated an erythematous posterior pharynx with minimal exudate and mild nasal discharge. He had no cardiac murmurs, rubs, or gallops and his pulses and blood pressures were equal bilaterally. The lung exam was unremarkable and his abdomen was soft, nontender, and nondistended. There was no hepatospleno-megaly. There was no edema in the legs. His neurologic exam was normal.

**dR. FRANTZ GIBBS:** What were your initial concerns in the evaluation of this patient?

**dR. MACKUEN:** Of the 130 million emergency department visits in the US, chest pain is one of the most frequently encountered complaints, accounting for over 6 million visits to the nation’s EDs annually. The initial focus among emergency physicians is to consider life-threatening conditions, such as acute coronary syndrome (ACS), pulmonary embolism, and aortic dissection. Though sharp pain is atypical for ACS, radiation of pain into the left arm has an odds ratio of 1.7 for ACS. (1) The patient’s relatively young age and lack of risk factors reduced the likelihood of ACS, and his fever prompted a broader differential diagnosis.

**dR. ALEXIS LAWRENCE:** What studies were performed and how did the results affect the differential diagnosis?

**dR. JEFFREY FEDEN:** National guidelines mandate a 12-lead electrocardiogram (ECG) within ten minutes of ED arrival for all patients presenting with chest pain or possible anginal symptoms. Our patient’s ECG [Figure 1] shows striking ST segment abnormalities which are generalized to the limb and precordial leads and not associated with the characteristic reciprocal changes suggestive of acute ST-elevation myocardial infarction. ST segment changes like these may be seen in acute pericarditis and benign early repolarization. The ECG changes prompted additional testing including a complete blood count (CBC), basic metabolic panel, and

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**Figure 1.** 12-lead electrocardiogram demonstrating diffuse ST segment changes suggestive of pericarditis rather than myocardial infarction.
myocarditis, pericarditis, and myopericarditis. (2, 3) Approximately 10-20% of cases are associated with connective tissue diseases, cancer, radiation, and post-cardiac injury syndromes. (4, 5) Additional causes include bacterial, protozoal, and parasitic disorders, in addition to medications. (3)

In the developing world, rheumatic fever, dengue and Chagas disease remain important causes of myocarditis. The patient did not report any travel history; therefore, a monoclonal illness such as CMV, EBV, or HIV is a more likely cause of his illness. I would also consider checking a throat culture for more than 150 years, the exact pathogenesis remains elusive. An autoimmune response causing ARF may be triggered by molecular mimicry between group A streptococcus antigenic determinants and human cardiac tissue. (13) The primary preventive method is treatment of pharyngitis with appropriate antibiotics.

**DR. BRUCE BECKER:** How does one contract acute rheumatic fever? Can it be prevented?

**DR. MACKUEN:** Acute rheumatic fever is a delayed inflammatory sequela of GABHS and often occurs about two weeks after the initial pharyngitis. Although ARF has been studied for more than 150 years, the exact pathogenesis remains elusive. An autoimmune response causing ARF may be triggered by molecular mimicry between group A streptococcus antigenic determinants and human cardiac tissue. (13) The primary preventive method is treatment of pharyngitis with appropriate antibiotics.

**DR. BRIAN CLYNE:** Was an echocardiogram performed? Did the patient meet the Jones criteria?

**DR. MACKUEN:** An echocardiogram showed no evidence of valvular disease and further demonstrated normal left ventricular function. However, the patient’s myopericarditis [with an initial troponin elevation] certainly qualifies as one of the major Jones criteria. In combination with elevated inflammatory markers and fever, our patient met two minor criteria for ARF.

**DR. FEDEN:** There are some limitations to the Jones criteria. As the incidence of ARF has decreased in developed

---

**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
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</tr>
<tr>
<td>Troponin</td>
<td>10.44 ng/mL</td>
</tr>
<tr>
<td>TSH</td>
<td>1.31 IU/mL</td>
</tr>
<tr>
<td>CRP</td>
<td>227.5 mg/L</td>
</tr>
<tr>
<td>ESR</td>
<td>65 mm/h</td>
</tr>
<tr>
<td>HIV</td>
<td>Non reactive</td>
</tr>
<tr>
<td>Rapid Strep A antigen</td>
<td>Positive</td>
</tr>
<tr>
<td>Heterophile antibody</td>
<td>Negative</td>
</tr>
</tbody>
</table>

troponin. The CBC revealed leukocytosis with 13% bands, and the troponin was elevated (Table 1). A portable chest radiograph was unremarkable. The elevated troponin, taken along with the ECG findings and febrile illness, suggested myopericarditis as a leading diagnosis.

In the United States and other developed countries, viral infections including Coxsackie A and B, Echoviruses, Hepatitis C, Epstein-Barr virus [EBV], Cytomegalovirus [CMV], Respiratory syncytial virus [RSV], Influenza, and many others are the most common causes of myocarditis, pericarditis, and myopericarditis. (2, 3) Approximately 10-20% of cases are associated with connective tissue diseases, cancer, radiation, and post-cardiac injury syndromes. (4, 5) Additional causes include bacterial, protozoal, and parasitic disorders, in addition to medications. (3)

In the developing world, rheumatic fever, dengue and Chagas disease remain important causes of myocarditis. The patient did not report any travel history; therefore, a monosporadic illness such as CMV, EBV, or HIV is a more likely cause of his illness. I would also consider checking a throat culture for more than 150 years, the exact pathogenesis remains elusive. An autoimmune response causing ARF may be triggered by molecular mimicry between group A streptococcus antigenic determinants and human cardiac tissue. (13) The primary preventive method is treatment of pharyngitis with appropriate antibiotics.

The original Duckett Jones criteria were published in 1944, modified in 1992, and have traditionally been used to diagnose ARF. Diagnosis requires evidence of GABHS infection [positive throat culture or rapid antigen test, or elevated antistreptolysin O antibody titer] in addition to one major and two minor criteria, or two major and one minor criteria. The major criteria include carditis, arthritis, chorea, subcutaneous nodules, and erythema marginatum. The most common findings are carditis [50-70%] and arthritis [33-66%]. The minor criteria consist of fever, arthralgia, elevated ESR/CRP, and PR interval prolongation. (8)

There have been several updates to these criteria, most recently in 2015. (12) The criteria now include echocardiogram as a diagnostic tool for subclinical carditis. Since 1992, there has been increasing debate about the utility of echo in diagnosing subtle heart disease. Previously, carditis was diagnosed using cardiac biomarkers [i.e., troponin] or auscultation for valvular abnormalities. With the 2015 update, echocardiogram may be used to diagnose valvular involvement in the absence of clinical symptoms [Level I evidence].

Although the addition of echocardiography was a major change in 2015, several other small changes are noteworthy. (12) New guidelines separate minor criteria into greater detail depending on the population prevalence of ARF. For example, “arthritis” in low-risk populations was changed to “polyarthritis.” Low-grade fever is included in the minor criteria in high-risk populations and ESR must be greater than 60 in low-risk populations.

**DR. ANDREW NATHANSON:** The patient meets some of the criteria for Acute Rheumatic Fever [ARF]. How common is ARF and can you review the Jones criteria?

**DR. MACKUEN:** Rheumatic heart disease still reaches epidemic proportions in low-income and socially-disadvantaged populations worldwide. (6) It is estimated that nearly 20 million people in total are affected globally, and rheumatic heart disease remains a leading cause of heart failure through the 5th decade of life. (7, 8) In the United States [US], the prevalence is much lower at approximately 2 per 100,000. (9, 10) This low prevalence is attributed to better living conditions, antibiotic use against Group A β hemolytic Streptococcus [GABHS] and, more fundamentally, to a shifting [non-rheumatogenic] GABHS serotype. (6, 11)
countries, the Jones criteria are increasingly specific but have reduced sensitivity. An alternative cause can be considered in this case – myopericarditis due to acute streptococcal pharyngitis – but the evidence for this diagnosis is indirect. The absence of valvular disease is occasionally noted in acute rheumatic fever but is an uncommon finding. [9]. Additionally, ARF has a median onset of two weeks after an episode of overt or subclinical pharyngitis, unlike this patient who presented acutely.

The pathogenesis of nonrheumatic streptococcal myocarditis has not been elucidated, but it may be due to both cross-reactivity between cardiac M proteins and streptococcal antigens, in addition to a direct insult of pyogenic exotoxins and hemolysins on the myocardium. [14, 15] It is a rarely reported diagnosis. [14, 15, 16]

DR. THOMAS HARONIAN: What happened to your patient?

DR. MACKUEN: The patient was treated with penicillin in the ED, and admitted to the hospital. His troponin peaked at 86.7 ng/mL on hospital day 3, and his symptoms subsided by hospital day 4. He was discharged to home. An echocardiogram one month later still showed no evidence of valvular disease or left ventricular dysfunction. His ECG normalized.

FINAL DIAGNOSIS: Acute rheumatic fever causing myopericarditis without valvular involvement versus nonrheumatic streptococcal myocarditis.

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2. LeWinter MM. Acute Pericarditis. NEJM. 2014; 371: 2410-2416

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Intimate partner violence (IPV) is defined as violence or threat of violence in a close relationship, including current/former spouses or dating partners. IPV affects females and racial/ethnic minorities disproportionately in the U.S. Societal costs of IPV victimization approach $6 billion every year based on the Centers for Disease Control and Prevention (CDC) data. There are many risk factors for IPV, including low education, unemployment, poor neighborhood, public assistance receipt, alcohol abuse, prior domestic violence or forced sex, abusive relationship, access to firearms, and previous mental health problems of the suspect. IPV causes a substantial burden on individuals, families, and communities. Because of the prevalence and associated costs, IPV has been recognized as a major public health problem.

Recent research on IPV is focusing on evidence that it can be prevented and interventions that can stop IPV before it happens. In order to prevent IPV, we need to know the facts about IPV-related deaths. The Rhode Island Violent Death Reporting System (RIVDRS) is a statewide active surveillance system that links multiple data sources, collects information such as demographic characteristics, substance use, and circumstances including mental health status on all suicides, homicides, legal intervention deaths, unintentional firearm deaths, and undetermined deaths. RIVDRS data can provide insight into IPV deaths that can inform prevention efforts at the state level. For this study, we will estimate the prevalence of IPV using the 2005 Behavioral Risk Factor Surveillance System (BRFSS) data and examine the characteristics of IPV/intimate partner problem (IPP)-related deaths by manner of death in Rhode Island using the 2004-2013 RIVDRS data.

METHODS
Data sources
Two data sources were employed. The first was the Rhode Island BRFSS, a random-digit dialed telephone survey that collects statewide data on health risk behaviors and preventive health practices linked to chronic conditions, injuries, and preventable infectious diseases in the adult population. The 2005 survey included an IPV module, consisting of seven questions. We utilized the 2005 BRFSS data to provide information on the prevalence of IPV and to create a profile of this population.

RIVDRS was the second data source we used and contains data on violent deaths from multiple Rhode Island agencies, including the Office of State Medical Examiners (autopsy reports), law enforcement (incident and investigatory reports), and the Office of Vital Records (death certificates). Specifically, RIVDRS includes data on victims, suspects, the manner of death, substance use, city of residence, as well as the circumstances surrounding the death. Trained abstractors identified eligible incidents by matching medical examiner information and death certificates using manner of death and ICD-10 codes selected by the National Violent Death Reporting System.

Measures for IPV/IPP
In the 2005 BRFSS, an intimate partner was defined as any current or former spouse, boyfriend, or girlfriend, including someone they dated. Four of the seven questions in the IPV module about violence in relationships with an intimate partner were: “Has an intimate partner ever threatened you with physical violence? This includes threatening to hit, slap, push, kick, or physically hurt you in any way.”; “Has an intimate partner ever hit, slapped, pushed, kicked, or physically hurt you in any way?”; “Has an intimate partner ever attempted physical violence against you? This includes times when they tried to hit, slap, push, kick, or otherwise physically hurt you, but they were not able to.”; and “Have you ever experienced any unwanted sex by a current or former intimate partner?” If any one of these four questions was answered affirmatively, the victim was defined as an IPV victim.

IPV/IPP-related cases were selected from RIVDRS if the deaths indicated that the victim-suspect relationship was a current/former spouse or intimate partner, or if any of the five circumstances were noted: 1) intimate partner problem was a crisis; 2) jealousy (lovers’ triangle) was a crisis; 3) problems with a current or former intimate partner appear to have contributed to the suicide or undetermined death; 4) homicide or legal intervention death was related to immediate or ongoing conflict or violence between current or former intimate partners; 5) cases in which jealousy or distress over a current or former intimate partner’s relationship or suspected relationship with another person led to the incident. IPV is a circumstance for homicide only and IPP is a circumstance for suicide only. We selected victims linked to IPV/IPP from 2004 to 2013 for analysis. We examined socio-demographics, manner of death, means of death,
location of injury, weapon type, toxicology test, and other circumstances among these cases.

**Data Analysis**

A ten-year period was used for data analysis since small numbers of Rhode Island violent deaths lead to substantial year-to-year fluctuations. Statistics were generated from multiple years of data to correct for the annual fluctuations in the data (e.g., there were a total of 59 IPV-related homicides in Rhode Island for the ten-year period 2004–2013.) The number of IPV/IPP-related deaths was summed across the years to mitigate the problem of small numbers.

We used descriptive statistics to report prevalence of IPV victims and victims’ characteristics by manner of death. For the BRFSS data, we calculated frequencies, weighted frequencies, and weighted prevalence. Significance was assessed using a Chi-square test statistic. For the RIVDRS data, we calculated percentages of characteristics by manner of death among IPV/IPP-related victims. All analyses were conducted by using SAS software (release 9.4, SAS Institute Inc., Cary, NC, 2014), which can account for the complex sample design of the BRFSS.

**RESULTS**

An estimated 17.3% (105,175) of adults in Rhode Island reported IPV (Table 1). The 18-34 years age group had the highest prevalence of persons who reported IPV [22.2%] and the 45 years and over age group had the lowest [12.8%]. Females were almost two times more likely than males to experience IPV. Those who were divorced or separated had the highest prevalence of reported IPV compared to married or widowed persons (33.8% vs. 12.1%). Persons with low education or income were more likely to report IPV than those having high education or income.

Characteristics of IPV/IPP decedents by manner of death in Rhode Island between 2004 and 2013 are presented in Table 2. Of the 406 IPV/IPP-related deaths, 76.1% were suicides, 14.5% were homicides, and 9.4% were categorized as undetermined intent. There were seven victims who were less than 18 years old. For IPP-related suicide, the majority of deaths were male (80.9%); non-Hispanic whites (89.3%); resided in non-core cities (70.1%); 72.8% of the victims injured in a residence; and suicides were more likely to die via asphyxia (50.5%) as cause of death compared to poisoning or firearms. For IPV-related homicide, the majority of decedents: were 18-34 years old; were female (74.6%); were minorities (52.5%); were never married or single (47.5%); resided in Rhode Island's high poverty ‘core’ cities (52.5%); and died from firearms (44.1%).

Substance use was high and similar among all groups. Deaths of undetermined intent had the highest percentages of alcohol or drug use except for marijuana (Table 3). Current mental health problems and treatment were higher among suicide victims. Compared to other suicide deaths, those IPP-related deaths were more likely to have had a crisis in the past or impending two weeks, having left a suicide note, or having disclosed intent to commit suicide. An argument or conflict leading up to the victim’s death occurred in over one quarter of the IPV-related homicides.

**DISCUSSION**

Our findings showed differences between IPP-related suicide and IPV-related homicide victims in age, sex, race/ethnicity, marital status, and city/town of residence. Victims of IPP-related suicide were more likely to be older and white as compared with IPV-related homicide deaths in Rhode Island. Previous research has revealed that males

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**Table 1. Prevalence of adult victim of IPV by demographic characteristics in RI, 2005 BRFSS**

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Intimate Partner Violence</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n</td>
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<tr>
<td>Total</td>
<td>521</td>
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<td>Age group (years)</td>
<td></td>
</tr>
<tr>
<td>18-34</td>
<td>129</td>
</tr>
<tr>
<td>35-44</td>
<td>135</td>
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<tr>
<td>45 and over</td>
<td>256</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
<td>386</td>
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<tr>
<td>Race/Ethnicity</td>
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<tr>
<td>Non-Hispanic white</td>
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<tr>
<td>Minorities</td>
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<td>Marital status</td>
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<td>Married/Widowed</td>
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<td>Divorced/Separated</td>
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<tr>
<td>Never married/Unmarried couple</td>
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<td>City/Town of residence</td>
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<tr>
<td>Core cities a</td>
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<tr>
<td>Non-core cities</td>
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<td>Education level</td>
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<td>Less than college</td>
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<td>Annual household income</td>
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<td>Less than $50,000</td>
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<tr>
<td>$50,000 and higher</td>
<td>186</td>
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IPV, Intimate Partner Violence; BRFSS, Behavioral Risk Factor Surveillance System.

a Core-cities: Central Falls, Pawtucket, Providence and Woonsocket.
### Table 2. Percentages of characteristics by manner of death among IPV/IPP victims, 2004-2013 RIVDRS

<table>
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<tr>
<th>Characteristics</th>
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<th>IPP-related Suicide</th>
<th>IPV-related Homicide</th>
<th>IPV/IPP-related Undetermined</th>
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<tr>
<td>Total</td>
<td>406</td>
<td>76.1</td>
<td>14.5</td>
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<td><strong>Age group (years)</strong></td>
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<tr>
<td>16-17</td>
<td>7</td>
<td>2.3</td>
<td>0.0</td>
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<td>18-34</td>
<td>121</td>
<td>25.9</td>
<td>54.2</td>
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<td>35-44</td>
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<td>45 and over</td>
<td>174</td>
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<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
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<td>19.1</td>
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<td>Minorities</td>
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<td><strong>Marital Status</strong></td>
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<td>139</td>
<td>32.4</td>
<td>47.5</td>
<td>29.7</td>
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<td></td>
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<tr>
<td>Core cities(^a)</td>
<td>114</td>
<td>23.1</td>
<td>52.5</td>
<td>31.6</td>
</tr>
<tr>
<td>Non-core cities</td>
<td>265</td>
<td>70.1</td>
<td>44.1</td>
<td>60.5</td>
</tr>
<tr>
<td>Out of state</td>
<td>26</td>
<td>6.8</td>
<td>3.4</td>
<td>7.9</td>
</tr>
<tr>
<td><strong>Injury Location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>House, apartment</td>
<td>327</td>
<td>78.2</td>
<td>88.1</td>
<td>92.1</td>
</tr>
<tr>
<td>Other</td>
<td>77</td>
<td>21.8</td>
<td>11.9</td>
<td>7.9</td>
</tr>
<tr>
<td><strong>Injured at Victim Home</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>292</td>
<td>72.8</td>
<td>69.0</td>
<td>79.0</td>
</tr>
<tr>
<td>No</td>
<td>109</td>
<td>27.2</td>
<td>31.0</td>
<td>21.1</td>
</tr>
<tr>
<td><strong>Weapon Type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Firearm</td>
<td>95</td>
<td>22.3</td>
<td>44.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Asphyxia(^b)</td>
<td>166</td>
<td>50.5</td>
<td>13.6</td>
<td>5.9</td>
</tr>
<tr>
<td>Poisoning</td>
<td>90</td>
<td>19.1</td>
<td>0.0</td>
<td>91.2</td>
</tr>
<tr>
<td>Other</td>
<td>51</td>
<td>8.1</td>
<td>42.4</td>
<td>2.9</td>
</tr>
</tbody>
</table>

RIVDRS has collected data on violent deaths since January 1, 2004.
IPP, Intimate Partner Problem; IPV, Intimate Partner Violence; RIVDRS, Rhode Island Violent Death Reporting System.
\(^a\) Core-cities: Central Falls, Pawtucket, Providence and Woonsocket.
\(^b\) Asphyxia: hanging, strangulation, or suffocation.

### Table 3. Percentages of toxicology test and circumstance by manner of death among IPV/IPP victims, 2004-2013 RIVDRS

<table>
<thead>
<tr>
<th>Toxicology Test and Circumstance(^a)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPP-related Suicide</td>
<td></td>
</tr>
<tr>
<td>IPV-related Homicide</td>
<td></td>
</tr>
<tr>
<td>IPV/IPP-related Undetermined</td>
<td></td>
</tr>
<tr>
<td><strong>Toxicology test positive</strong></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>39.1</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>23.4</td>
</tr>
<tr>
<td>Opiates</td>
<td>15.8</td>
</tr>
<tr>
<td>Marijuana</td>
<td>12.2</td>
</tr>
<tr>
<td>Cocaine</td>
<td>10.2</td>
</tr>
<tr>
<td><strong>Mental health/substance abuse context</strong></td>
<td></td>
</tr>
<tr>
<td>Current depressed mood</td>
<td>58.9</td>
</tr>
<tr>
<td>Current mental health problem</td>
<td>50.5</td>
</tr>
<tr>
<td>Current mental health/substance abuse treatment</td>
<td>40.8</td>
</tr>
<tr>
<td>Alcohol problem</td>
<td>25.6</td>
</tr>
<tr>
<td>Other substance abuse problem</td>
<td>19.1</td>
</tr>
<tr>
<td><strong>Interpersonal circumstance</strong></td>
<td></td>
</tr>
<tr>
<td>Had relationship problems with a family member</td>
<td>12.3</td>
</tr>
<tr>
<td>Problems with a friend or associate</td>
<td>11.0</td>
</tr>
<tr>
<td>An argument or conflict led to the victim’s death</td>
<td>7.4</td>
</tr>
<tr>
<td><strong>Life stressor circumstance</strong></td>
<td></td>
</tr>
<tr>
<td>Crisis in past or impending two weeks</td>
<td>39.8</td>
</tr>
<tr>
<td>Job problem</td>
<td>17.5</td>
</tr>
<tr>
<td>Financial problem</td>
<td>15.2</td>
</tr>
<tr>
<td>Recent criminal legal problem</td>
<td>9.4</td>
</tr>
<tr>
<td>Physical health problem</td>
<td>6.5</td>
</tr>
<tr>
<td><strong>Suicide event circumstance</strong></td>
<td></td>
</tr>
<tr>
<td>Left a suicide note</td>
<td>40.8</td>
</tr>
<tr>
<td>Disclosed intent to commit suicide</td>
<td>33.0</td>
</tr>
<tr>
<td>History of suicide attempt(s)</td>
<td>23.0</td>
</tr>
</tbody>
</table>

RIVDRS has collected data on violent deaths since January 1, 2004.
IPP, Intimate Partner Problem; IPV, Intimate Partner Violence; RIVDRS, Rhode Island Violent Death Reporting System.
\(^a\) Subcategories do not sum to 100% because test results of victims can be positive for alcohol or multi-drugs.
\(^b\) Percentages might exceed 100% because multiple circumstances might have been coded.
are overwhelmingly represented in suicide deaths and multiple-death incidents where a suspect is also a victim. The research also revealed that females are more likely to be victims of IPV-related homicides and males are more likely to be suspects.2 Our data found that 80.9% of the IPP-related suicide victims were male and 74.6% of the IPV-associated homicide victims were female. Our data also found that 85.2% of IPV-related homicide suspects were male during 2004-2013 (data not shown). To prevent IPV/IPP injury or death, intervention programs need to target high-risk vulnerable populations.8-10

National data from the Smith study reveals that most IPV-related homicides occur in homes and are more likely to involve firearms than other weapons.2 IPV involving a firearm are 12 times more likely to result in death than incidents not involving a firearm.2, 11 Some states have laws giving police the authority to remove firearms when responding to a domestic violence crisis and authorizing courts to remove firearms when issuing protective orders.2, 11 A recent study shows that having such laws can decrease 19% of IPV-related homicides.11 Rhode Island state laws prohibit suspects who have been issued certain types of domestic violence protective orders from purchasing or possessing firearms and/or ammunition, and require or authorize the removal or surrender of firearms or ammunition when a protective order is issued.11 Enhancements to Rhode Island's domestic violence laws addressing access to firearms may lead to a reduction of incidents of IPV-related homicides.

Those who die directly of IPV are not the only IPV victims.2 Our data showed that some victim and suspect relationships consisted of acquaintance, child, friend, stranger, and other person known to the victim. Corollary victims represented almost 20% of IPV-related homicide victims in the RIVDRS data. Among the 59 IPV-related homicides, 12 suspects were also victims (data not shown). In some cases, the homicide victim attempted to intervene in an IPV situation and was murdered.2 Strategies that promote bystander intervention in situations where IPV exists should be an integral part of any IPV prevention program.2

Primary prevention of IPV needs to target adolescents before they have intimate relationships.2 Our 2013 Youth Risk Behavior Survey data showed that the percentage of students who reported dating violence or forced sex during the past 12 months was 13.8% among all public high school students and 28.1% among lesbian/gay/bisexual/unsure students in Rhode Island (data not shown). The majority of these victims were 15-18 years old. In order to prevent adolescent dating violence and sexual violence, Rhode Island schools can integrate IPV prevention information into existing curricula and work with parents to develop in-home activities that are prevention focused.3

There are two limitations to this study. First, because of missing values of circumstances and relationship between suspect and victim, accurately identifying IPV cases presented a challenge that might have led to under-identifying IPV-related victims. Second, although RIVDRS has ten years of data, the number of IPV-related victims is still very small compared to other states.

In summary, the impact of IPV extends beyond the intimate partners involved. Shelters, the criminal justice system, children’s protective services, behavioral health and healthcare systems (including primary care providers), and schools/universities interact with IPV victims routinely. Each of these systems presents opportunities to identify IPV, assess the potential danger to victims, and protect them from harm.2 The increase in IPV victims’ services and changes in criminal justice responses to IPV crises can effectively decrease IPV.1 Effective IPV prevention strategies could avert serious and fatal injuries.2 IPV interventions that focus on identification of abusive relationships and bystander intervention may be effective with youth and families exposed to IPV.1, 2

Acknowledgments

The analyses are in response to a request made by the Rhode Island Coalition Against Domestic Violence (RICADV). This brief was funded by a Centers for Disease Control and Prevention (CDC) grant (1U17CE002615-01 Revised) awarded to the Rhode Island Department of Health, Office of State Medical Examiners. We would like to thank the Office of Vital Records, the Office of State Medical Examiners, the Rhode Island State Police and local law enforcement agencies, and the crime laboratory who provided data in a timely manner and without which RIVDRS would be non-existent. We would like to express our special thanks to data abstractors Karen Foss and Shannon Young who spent hours compiling the data and constructing sound narratives to make Rhode Island's program one of the best. Without their daily efforts throughout the years, the data and reports would not be as accurate or complete. We gratefully appreciate Edward Donnelly, the previous RIVDRS epidemiologist, Rhode Island Department of Health, for his generous help. We also thank Jana Hesser for her contribution as the BRFSS coordinator during the time the 2005 BRFSS data were collected.

References


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Samara Viner-Brown, MS, is the Chief of the Center for Health Data and Analysis at the Rhode Island Department of Health.

Disclosure
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

### Reporting Period: May 2015

<table>
<thead>
<tr>
<th>VITAL EVENTS</th>
<th>MAY 2015</th>
<th>12 MONTHS ENDING WITH MAY 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>Rates</td>
<td></td>
</tr>
<tr>
<td>Live Births</td>
<td>930</td>
<td>11,424</td>
</tr>
<tr>
<td>Deaths</td>
<td>856</td>
<td>10,228</td>
</tr>
<tr>
<td>Infant Deaths</td>
<td>6</td>
<td>61</td>
</tr>
<tr>
<td>Neonatal Deaths</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>Marriages</td>
<td>635</td>
<td>6,771</td>
</tr>
<tr>
<td>Divorces</td>
<td>231</td>
<td>2,994</td>
</tr>
<tr>
<td>Induced Terminations</td>
<td>178</td>
<td>2,747</td>
</tr>
<tr>
<td>Spontaneous Fetal Deaths</td>
<td>42</td>
<td>623</td>
</tr>
<tr>
<td>Under 20 weeks gestation</td>
<td>38</td>
<td>566</td>
</tr>
<tr>
<td>20+ weeks gestation</td>
<td>4</td>
<td>57</td>
</tr>
</tbody>
</table>

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

### Reporting Period: November 2014

<table>
<thead>
<tr>
<th>Underlying Cause of Death Category</th>
<th>NOVEMBER 2014</th>
<th>12 MONTHS ENDING WITH NOVEMBER 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (a)</td>
<td>Number (a)</td>
</tr>
<tr>
<td></td>
<td>Rates (b)</td>
<td>YPLL (c)</td>
</tr>
<tr>
<td>Diseases of the Heart</td>
<td>198</td>
<td>2,313</td>
</tr>
<tr>
<td>Malignant Neoplasms</td>
<td>169</td>
<td>2,287</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>36</td>
<td>397</td>
</tr>
<tr>
<td>Injuries (Accident/Suicide/Homicide)</td>
<td>57</td>
<td>769</td>
</tr>
<tr>
<td>COPD</td>
<td>44</td>
<td>517</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 1,055,173 (www.census.gov)
(c) Years of Potential Life Lost (YPLL).

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.
It’s a new day.

The Rhode Island Medical Society now endorses Coverys.

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401-331-3207
RIMS and Coverys announce new partnership

In October 2014, the Medical Society entered into a new strategic partnership with Coverys, the 40 year-old medical liability insurance giant headquartered in Boston.

Coverys and RIMS have pledged to combine and coordinate their complementary strengths for the purpose of enhancing patient safety. The two organizations share the conviction that safety is fundamental to promoting and maintaining the kind of professional liability environment that everyone wants for Rhode Island: one that is stable and responsive to the needs of the medical profession and the public. RIMS and Coverys are uniquely positioned to support each other in this endeavor.

Key elements of the new collaboration will be peer review, risk management and continuing education. RIMS’ peer review prowess is well established, particularly in the highly sensitive and all-important area of physician health. In addition, RIMS is recognized by the American Council for Continuing Medical Education (ACCME) as the agency responsible for accrediting the CME programs of all the hospitals within the state of Rhode Island. RIMS has been a consistent star nationally in earning an unbroken string of long-term recognitions from ACCME.

For its part, Coverys is one of a tiny number of medical professional insurers that have devoted the necessary and substantial resources to gaining and maintaining full accreditation by the ACCME as a source of Category 1 CME credits for physicians. RIMS regards this extraordinary commitment to CME as particularly meaningful and praiseworthy in an insurance company. Of course, medical peer review and continuing medical education, each in its own way, provide targeted risk management and serve to enhance quality and safety.

RIMS has also agreed to advise Coverys and to offer the company additional eyes and ears focused on the evolving insurance market, the medical practice environment and the medical liability climate, as each of these is affected by legislative, regulatory, judicial, economic, demographic and political developments in the Ocean State. In recognition of their strong relationship and mutual support, RIMS and Coverys will also engage in joint marketing.

Coverys is the sixth largest medical liability insurer in the nation. It protects more than 32,000 physicians, dentists and other health professionals nationally, as well as over 500 hospitals, health centers and clinics. It is rated A (“excellent”) by A.M. Best. It writes over $400 million in premium, has net assets of $3.5 billion, and maintained a policyholder surplus of $1.5 billion as of the end of last year. Member companies include Medical Professional Mutual Insurance Company (“Promutual”) and the ProSelect Insurance Company.

Coverys is the dominant insurer of physicians and surgeons in Rhode Island. The Rhode Island Medical Society Insurance Brokerage Corporation (RIMS-IBC) is proud to have been appointed as an agent for Coverys three years ago. The RIMS-IBC is a full-service agency that specializes in medical professional liability.

Robert A. Anderson, Jr, Director of the IBC, can be reached at 401-272-1050.
Working for You: RIMS advocacy activities

October 2, Friday  
Administrative Simplification Task Force: Office of the RI Health Insurance Commissioner (OHIC)

October 5, Tuesday  
RI Community Health Centers Association Annual Meeting  
Certified Diabetes Outpatient Educator licensing; Healthcentric Advisors

October 6, Tuesday  
RIMS Physician Health Committee: Herbert Rakatansky, MD, Chair  
RIMS headquarters relocation, New address: 405 Promenade Street, Suite A, Providence RI 02908

October 7, Wednesday  
State Innovation Model (SIM) Measurement Harmonization Working Committee: Peter A. Hollmann, MD, and RIMS staff  
Governor’s Working Group for Healthcare Innovation

October 8, Thursday  
Physician Assistants’ Week observances: RI Academy of Physician Assistants

October 13 Tuesday  
Governor’s Working Group for Healthcare Innovation: Spending Cap Subgroup, RI State House

October 14, Wednesday  
RI Quality Institute Board of Directors  
Governor’s Overdose Prevention & Intervention Task Force: Josiah Rich, MD, Chair, RI Dept. of Administration  
Special Legislative Commission to study the Rules and Regulations of the Board of Medical Licensure and Discipline, Rep. Michael Chippendale, Chair, RI State House

October 15, Thursday  
Administrative Simplification Work Group: Office of the Health Insurance Commissioner (OHIC)  
State Innovation Model (SIM) Steering Committee: Hewlett-Packard Co., Warwick  
Alliance for Healthy RI: obesity prevention legislation

October 19, Monday  
Groundbreakings at Roger Williams Medical Center and Fatima Hospital

October 20, Tuesday  
RI Public Health Association Annual Meeting: Chelo, Warwick

October 21, Wednesday  
RI Medical Society Insurance Brokerage Corp. Board of Directors: Peter Hollmann, MD, President & Chair

October 23, Friday  
US Senator Sheldon Whitehouse, former CMS Administrator Dr. Donald Berwick, Coastal Medical ACO: press conference and panel. Providence Hilton

October 25–26, Sunday and Monday  
American College of Emergency Physicians Annual Scientific Assembly, Boston, MA

October 26, Monday  
RIMS Board of Directors, RIMS Offices, Providence

October 27, Tuesday  
Governor’s Working group for Healthcare Innovation: Provider Advisory Committee; EOHSS Secretary Elizabeth Roberts, Chair; Health Director Nicole Alexander-Scott, MD, MPH, guest; RIMS offices  
RI Drug Policy Alliance: draft recommendations of Governor’s Overdose Prevention and Intervention Taskforce

October 29, Thursday  
RI Coalition for Mental Health and Addiction Recovery, Steve DeToy, Chair

October 30, Friday  
Administrative Simplification (OHIC) and Measurement Harmonization Subgroup (SIM)
We are past the SGR hurdle. The path is clear for what’s next.

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For more information about group rates, please contact Megan Turcotte, RIMS Director of Member Services
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- Powerful advocacy at every level
  - Advantages include representation, advocacy, leadership opportunities, and referrals
- Complimentary subscriptions
  - Publications include Rhode Island Medical Journal, Rhode Island Medical News, annual Directory of Members; RIMS members have library privileges at Brown University
- Member Portal on www.rimed.org
  - Password access to pay dues, access contact information for colleagues and RIMS leadership, RSVP to RIMS events, and share your thoughts with colleagues and RIMS
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IN THE NEWS

CharterCARE announces $17.5M capital investment in RI facilities

Providence – CharterCARE Health Partners has announced the next phase of its capital investment program, a $17.5 million facility improvement plan to dramatically enhance both hospital campuses. The investments were announced at a press conference on October 19, 2015 attended by Rhode Island Governor Gina Raimondo, Congressman James Langevin, Congressman David Cicilline, and Gregory Mancini, executive director BuildRI, along with hospital and medical staff leadership, board members, and more than 100 employees and guests.

The projects announced are:

• Expansion and renovation of the Emergency Department at Roger Williams Medical Center. This approximately 23,000 square-foot project will significantly increase the capacity and efficiency of the Emergency Department and will also provide state-of-the-art emergency medical technologies to the staff of the emergency room. This project first requires state approval through the Health Services Council and Certificate of Need process.

• Renovation and modernization of the Emergency Department at Fatima Hospital. Improvements will include upgrades to the core nursing area to enhance patient care and workflow, expanded treatment space for behavioral health patients and separate access for both patients and EMS professionals.

• Construction of a new lobby and entrance to Roger Williams Medical Center. This project will feature a covered entrance and a new elevator that connects a modern lobby with the diagnostic wing of the hospital. The project will dramatically improve the patient and visitor experience with improvements designed for greater accessibility.

• Construction of a new main entrance at Fatima Hospital. This project will re-locate the main hospital entrance to the southern side of the facility to provide more convenient access and parking for patients and visitors. It will also consolidate and improve registration and business office functions to better accommodate patients.

With these projects nearing the final stages of design development, construction is scheduled to begin on the new entrances and is expected to be completed in phases by the end of 2016. The projects will create approximately 235 direct and indirect construction jobs.  

Pictured at the groundbreaking ceremony, from left to right, are: Thomas Hughes, Fatima Hospital president; Kimberly O’Connell, Roger Williams Medical Center president; Congressman David Cicilline, Edwin J. Santos, chairman of the board, CharterCARE; Governor Gina Raimondo, Lester P. Schindel, CharterCARE CEO; Congressman James Langevin; Dr. Cynthia Alves, medical staff president, Roger Williams Medical Center; Dr. Raffi Calikyan, medical staff president, Fatima Hospital, and Gregory Mancini, executive director BuildRI.
Southcoast Health unveils Lash Heart and Vascular Center at Charlton

FALL RIVER, MASS. — Southcoast® Health unveiled the Harold and Virginia Lash Heart and Vascular Center at Charlton Memorial Hospital on October 22. The new venue will house Southcoast Health’s expanding cardiovascular services, including a state-of-the-art hybrid operating room and new electrophysiology lab.

The hybrid OR is a cardiovascular surgical theatre equipped with advanced medical imaging devices to enable minimally-invasive surgery while bringing together doctors of different disciplines in the same operating room. The hybrid OR will support Southcoast Health’s structural heart procedures, vascular surgery and endovascular medicine.

The new electrophysiology lab will be dedicated exclusively to performing more advanced procedures, such as cryo-ablation and convergent hybrid ablation for patients with atrial fibrillation. Southcoast is also currently one of only three hospitals in New England implanting Watchman, a device that reduces stroke in AFib patients and allows them to discontinue use of blood thinners. According to the CDC, an estimated 2.7 to 6.1 million people in the United States have AFib. In 2012, Southcoast discharged more than 700 atrial fibrillation cases, the second highest number of all the state’s hospital systems.

“As we look to the future, and continue to strive for excellence, the Harold and Virginia Lash Heart and Vascular Center will always be the place where our community will find the latest and best in cardiovascular care – the care our patients deserve, right here, close to home,” said DR. MARGARET FERRELL, Physician-in-Chief of Cardiovascular Services at Southcoast Health.

The Center will cost approximately $14 million to complete. Southcoast Health is currently conducting a major capital campaign in support of the new facility. The construction was made possible in large part by a donation from the Harold and Virginia Lash Trust and other major commitments from the Auxiliary of Charlton Memorial Hospital, BayCoast Bank, Anesthesia Associates of Massachusetts, BankFive and the Oliver S. and Jennie R. Donaldson Charitable Trust.

Coastal ranks in top 1 percent nationwide for quality; announces $15.3M in shared savings program

PROVIDENCE – Coastal Medical has been rated in the top 1 percent for quality nationwide in 2014 among the 333 Medicare Shared Savings Program Accountable Care Organizations (MSSP ACOs), it was announced at a press conference held Oct. 23 at the Providence Hilton.

The group also saved a combined $15.3 million across their federal and commercial shared savings contracts over the same one-year period.

Coastal Medical has been engaged in shared savings contracts with various payers since the beginning of 2012. Its current partners include Blue Cross Blue Shield of RI, UnitedHealthcare, Tufts Health Plan, and the Centers for Medicare and Medicaid Services (CMS).

Each contract contains specific quality measures that relate to patient care, and Coastal strives to meet or exceed the target for a total of 143 quality measures, while at the same time attempting to reduce the overall cost of care for their patient population. The MSSP quality score was based on a set of 33 measures specified by CMS.

“These results are astounding and hard won,” said ALAN KUROSE, MD, president and CEO. “We’ve learned that providing more clinical services to patients is the best way to reduce the total cost of care for a population of patients. We are spending more to save more. That seems counterintuitive, but efforts like our Coastal 365 clinic, our diabetes management program, and our team based model of care all help to ensure that we are delivering the right care, in the right place, at the right time. That makes care more cost efficient, and gets better outcomes for patients. That said, there is still much work left for us to do to improve the affordability of care and to ensure a more seamless experience of care for patients across the entire healthcare delivery system here in Rhode Island.”

Speakers also included Sen. Sheldon Whitehouse, and Donald M. Berwick, MD, President Emeritus and Senior Fellow, Institute for Healthcare Improvement.
Newly approved hearing-impaired device available at Rhode Island Hospital

Demand for hybrid cochlear implants continues to grow

PROVIDENCE – Nearly 3,000 Rhode Island adults have hearing loss so severe that the most powerful hearing aids on the market can’t help them hear much. These adults have a new reason to seek reevaluation of their hearing loss: Hybrid cochlear implants, now available at Rhode Island Hospital. The device, approved by the Food and Drug Administration last year is a combination of a hearing aid and a traditional cochlear implant for those with some residual hearing function but not enough loss to be a traditional cochlear implant candidate.

“For persons with severe hearing loss, this new hybrid device can restore the ability to hear mid- and high-frequency sounds,” said BRIAN DUFF, MD, chief of otolaryngology at Rhode Island Hospital. “For the 1.2 million Americans who suffer hearing loss that cannot be improved with hearing aids and who aren’t eligible for traditional cochlear implants, this device brings new hope.”

The Cochlear Nucleus Hybrid L24 Cochlear Implant System combines the functions of a traditional cochlear implant with a hearing aid. The device is surgically implanted through an opening in the mastoid bone into the cochlea (inner ear) and later calibrated by an audiologist.

Most patients who benefit from this type of implant have difficulty understanding speech or listening where high background noise impedes their ability to interact with others and remain independent. Fewer than six percent of potential cochlear implant candidates have one.

“Studies have shown that those with even a mild hearing loss, if left untreated, are twice as likely to develop dementia,” said Dr. Duff. “Importantly, there’s a 95 percent chance of the implant functioning effectively during the patient’s lifetime.”

The outpatient surgery takes approximately two hours. After a four-week healing period, the audiologist turns the device on and adjusts the levels to the comfort of the patient. Additional adjustments are performed as patients adapt to their listening environments. The devices can even sync with smartphones and iPods.

Total Joint Center at Miriam launches quality improvement initiative

National database helps assess pain, function before and after joint replacement surgery

PROVIDENCE – The Total Joint Center at The Miriam Hospital has implemented a new data collection and analysis system that delivers real-time information on patients’ pain and physical function. Known as the Function and Outcomes Research for Comparative Effectiveness in Total Joint Replacement (FORCE-TJR), this database registry enables Total Joint Center physicians to target the best methods for relieving pain and improving patients’ activity and track and report functional patient outcomes.

“We care about our patients and how they are doing,” said JOHN FROEBLICH, MD, program director of the Total Joint Center, “and by readily accessing this important patient assessment information – often direct from the patient – we will be better able to help them regain that sense of independence that is so important to them.”

Developed by The University of Massachusetts Department of Orthopedics and Physical Rehabilitation, the FORCE-TJR system guides best total joint replacement surgical practices by ensuring primary joint replacement patients achieve optimal pain relief and functional gain with minimal adverse events and implant failures. The tool measures patient-reported outcome data, as well as surgeon performance, and rates hospitals against national standards. Protected data is collected largely from voluntary patient surveys. It includes patient-reported outcomes of pain, function, and other conditions that could impact a patient’s individualized treatment plan, such as early post-operative adverse events and implant failures – and includes corrective measures to address them.

The benchmark database for FORCE-TJR includes a nationally representative sample of patients with complete outcomes from more than 85 percent of total joint replacement patients – more than any U.S. registry. Patient-reported data is augmented with clinical data, allowing surgeons to monitor patient progress and evaluate treatment effectiveness. The database also provides surgeons with comprehensive and comparative arthroplasty practice feedback to support quality improvement efforts.

FORCE-TJR originated in 2010 with an award from the Agency for Healthcare Research and Quality (AHRQ) and includes a national sample of U.S. patients and surgeons. As of 2015, more than 25,000 patients have been enrolled from more than 150 surgeons in 23 states. The unique AHRQ cohort forms the basis for clinical benchmarks in TJR outcomes and risk-adjustment models. In 2015, FORCE-TJR opened membership to additional surgeons and patients from members across the country and is currently enrolling new members.

“This is about quality of life for our patients,” said ROY AARON, MD, director of research at The Total Joint Center at The Miriam Hospital, “and always seeking implementation of the newest best practices and standards of care that enable us to continue to deliver the highest quality of care to our patients.”
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Miriam receives $1.3M NIH bariatric surgery grant

Data from the three-year study will focus on understanding how to help maximize weight loss using mobile technology

PROVIDENCE – The National Institute of Diabetes and Digestive Kidney Diseases (NIDDK) – part of the National Institutes of Health (NIH) – has awarded a $1.3 million research project grant to The Miriam Hospital and Beth Israel Deaconess Medical Center to use advanced monitoring technology to examine behavioral, psychosocial and environmental predictors of weight loss following bariatric surgery.

“Very little is known about why some people are more successful than others at keeping weight off after having bariatric surgery,” said DALE BOND, PhD, lead researcher and faculty in the Department of Psychiatry and Human Behavior at The Miriam Hospital’s Weight Control and Diabetes Research Center. “Behavioral factors are thought to be very influential, but guidelines for behavior changes among bariatric surgery patients are often vague and not well supported by scientific research. Our goal is to collect data to improve behavioral guidelines and help increase weight loss after bariatric surgery.”

In this study, wristwatch-like sensor devices and smartphones will be used to measure factors such as eating and physical activity behavior, mood, hunger and cravings in approximately 100 bariatric surgery patients at the Miriam Hospital and also Beth Israel Deaconess Medical Center, a second data collection site for the study. Patients, who will be recruited beginning in early 2016, will be followed before surgery and four times over the year after surgery. Researchers will collect information about environmental factors, such as foods available to patients and support from family and friends, to assess which factors predict weight loss.

“The study is exciting because this could lead to improved behavioral guidelines and new behavioral treatments, strategies and tools to maximize weight loss after bariatric surgery,” said GRAHAM THOMAS, PhD, also a lead researcher on the study and faculty in the Department of Psychiatry and Human Behavior at The Miriam Hospital’s Weight Control and Diabetes Research Center.

This project is an extension of existing research Bond and Thomas have conducted using real-time data collection methodologies to analyze weight-related behaviors associated with bariatric surgery. That includes Bond’s study of physical activity and sedentary behavior and Thomas’ use of mobile health (mHealth) technology to measure and intervene on behaviors in real time.

“Not enough research has been conducted on behavioral, psychological, and environmental predictors of weight loss after bariatric surgery,” added Bond. “This study will help to fill the gap using a unique and highly innovative mobile health platform combining sensor technology with a smartphone-based, self-reporting tool to measure behavioral, psychological and environmental predictors of weight loss continuously – in real time – in the patient’s natural environment.”

“Bariatric surgery is a powerful tool for weight loss,” said SIVA VITHIANANTHAN, MD, chief of minimally invasive and bariatric surgery at The Center for Bariatric Surgery, a program of Rhode Island and The Miriam Hospitals, also a researcher on the study. “By making key behavior changes, it may be possible for patients to get the greatest health benefit – and at the same time – we may have more information to better inform patients about steps they can take to boost weight loss after bariatric surgery.”

In addition to their primary affiliation at The Miriam Hospital, Bond and Thomas are, respectively, associate professor and assistant professor of psychiatry and human behavior at The Warren Alpert Medical School of Brown University.

RIQI receives $8.3M Transforming Clinical Practice Initiative Award

Statewide collaborative will join federal government and other partners in supporting large-scale health care transformation among clinician practices

PROVIDENCE –The Rhode Island Quality Institute (RIQI) is one of 39 health care collaborative networks selected to participate in the Transforming Clinical Practice Initiative, announced recently by Health and Human Services Secretary Sylvia M. Burwell. RIQI will receive up to $8.3M over four years to provide technical assistance to help equip clinicians in Rhode Island with tools, information, and network support needed to improve quality of care, increase patients’ access to information, and spend health care dollars more wisely.

As a Practice Transformation Network, Rhode Island Quality Institute will support 1,500 clinicians to expand their quality improvement capacity, learn from one another, and achieve common goals of improved care, better health, and reduced cost. The network will provide practice transformation assistance, care coordination tools and services, and performance measurement, reporting and evaluation to help participating clinicians meet the initiative’s phases of transformation and associated milestones, clinical and operational results.

“This four-year award will allow us to significantly strengthen and expand the support we’ve been able to offer providers through RIQI’s Regional Extension Center (RIREC) and to lever CurrentCare’s data sharing capabilities to achieve the triple aim of better health, better healthcare and lower per capita costs,” said LAURA ADAMS, President and CEO, RIQI. “Moving into new payment models that reward value and not volume is extremely challenging for providers. We’re delighted to be able to offer them the opportunity to be supported by a national network of experts in cooperation with local ‘boots on the ground’ assistance.”

For more information on the Transforming Clinical Practice Initiative, visit: http://innovation.cms.gov/initiatives/Transforming-Clinical-Practices/
Ruben Alvero, MD, publishes research on unexplained infertility in NEJM

**PROVIDENCE** – It is estimated that approximately 10 percent of women of child-bearing age may be unable to get pregnant or to carry a pregnancy to term. While recent years have seen a tremendous growth in fertility treatments and options, many assisted reproductive technologies like in vitro fertilization (IVF) and embryo transfer are very expensive and not often covered by insurance.

Many women, especially those with unexplained infertility, are commonly treated with ovarian stimulation medications – letrozole, gonadotropins or clomiphene citrate. Not only is this course of treatment quite successful, it is also significantly less costly. The challenge has been to determine which medication is best at achieving and maintaining pregnancy while reducing multiple gestations.

Research entitled “Letrozole, Gonadotropins, or Clomiphene Citrate for Unexplained Infertility” has been published in the *New England Journal of Medicine* (NEJM). The research was co-led by Ruben Alvero, MD, FACOG, FACS, director of the Division of Reproductive Endocrinology and Infertility (REI) in the Department of Obstetrics and Gynecology at Women & Infants and was funded by a grant from the National Institutes of Health Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The research was conducted when Dr. Alvero was at the University of Colorado School of Medicine.

“Ovarian stimulation medication promotes pregnancy by increasing the number of eggs that a woman ovulates and by enhancing implantation through hormonal effects in the endometrium. Unfortunately, ovarian stimulation can be complicated by ovarian hyperstimulation syndrome, which results in multiple gestations with increased risk of preterm birth,” explained Dr. Alvero. “We designed this trial to assess whether ovarian stimulation with letrozole, as compared with clomiphene or gonadotropins would result in lower rate of multiple gestations without lowering the likelihood of pregnancy. What we found is that clomiphene citrate should be used as the first line agent for patients with unexplained fertility,” said Dr. Alvero.

Dr. Alvero’s team performed a multicenter randomized trial of couples with unexplained infertility – those who have not been diagnosed with a particular problem that is causing their infertility. Women age 18 to 40 who were ovulating and had at least one Fallopian tube were randomized to up to four cycles with ovarian stimulation with gonadotropins, clomid or letrozole. The primary outcome being observed was the frequency of multiple gestations among women with clinical pregnancies.

The research team concluded that standard treatment with clomiphene is better than the proposed alternative for unexplained infertility. They wrote, “In women with unexplained infertility, ovarian stimulation with letrozole resulted in significantly lower frequency of multiple gestations, but also a lower frequency of live births, as compared with gonadotropins, but not as compared with clomiphene.”

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Hasbro expands medical/psychiatric programs with Bradley Hospital

Renovations help double the number of inpatient beds and dramatically increase partial program capacity

PROVIDENCE—The Medical/Psychiatric Program at Hasbro Children’s Hospital has recently completed renovations on both its inpatient unit and its partial hospitalization program to accommodate an increased demand for integrated medical/psychiatric care for children and teens.

“Within the past year, our Medical/Psychiatric Program has received patients sent to us from some of the largest academic medical centers nationwide – places like North Carolina and California,” said Henry Sachs, MD, chief medical officer at Bradley Hospital. “Here in Rhode Island, we are uniquely equipped with a program that can meet a growing local and national need for this type of care, and this expansion allows us to help more children in need.”

The Medical/Psychiatric Program at Hasbro Children’s Hospital addresses the needs of children and adolescents between the ages of 6 and 18 with complex pediatric illnesses. Diagnoses might include eating disorders, medical illness complicated by psychiatric co-morbidity, chronic pain and somatiform disorders. It is the only program in the region designed to provide family-based, integrated care for this patient population.

A collaboration between Bradley Hospital, the only hospital in New England dedicated exclusively to children’s mental health, and Hasbro Children’s Hospital, the program is staffed by a multidisciplinary team of pediatricians, child psychiatrists, psychologists, advanced practice psychiatric nurses, social workers, pediatric nurses, mental health workers and nutritionists. Coordination of care also occurs with hospital-based rehab specialists and pediatric subspecialists as needed.

Patients requiring inpatient treatment are admitted to the Inpatient Medical/Psychiatric Program at Hasbro Children’s Hospital, a secure unit located on the sixth floor of Hasbro Children’s Hospital. The recently completed renovation expanded the program from eight to 16 beds, offering both private and semi-private rooms and areas for family, group and milieu therapy.

“To provide optimal treatment for children with psychiatric and medical illness, the inpatient unit was designed with input from both pediatric and psychiatric experts,” said Phyllis Dennery, MD, pediatrician-in-chief of Hasbro Children’s Hospital. “This integrated care model is critically important to children who would not otherwise be able to heal unless they can receive total treatment of both body and mind.”

Also expanded during the renovation is the Hasbro Children’s Partial Hospital Program, which has extended capacity from 16 patients to 24. The partial program, opened in 1998, is the only day treatment program in New England for children with combined medical and psychiatric illness.

It offers a safe, nurturing environment that allows children and families to participate in activities and therapy in a climate of healing five days per week, while also providing access to the same range of services available to patients admitted to the inpatient unit, including consultation with specialists and comprehensive diagnostic testing.

“Children in our partial program may not require an inpatient stay, but do require a high level of support due to impaired functioning in the home and school settings, or limited response to outpatient intervention,” said Michelle Rickerby, MD, psychiatric director of Child Med/Psych Services for Lifespan. “Some patients may step down to the partial program after a stay as an inpatient, while others at high risk for hospitalization may be able to avoid an inpatient stay by participating.”

Both programs specialize in family-based, integrated care. Families are involved in the creation of an individualized treatment plan, incorporating a balance of medical and psychological support with the goal of the child’s successful transition to full functioning at home and school. Family involvement includes nursing and nutrition education sessions, multidisciplinary team meetings, family therapy and involvement in multifamily groups. For more information about the Medical/Psychiatric Program at Hasbro Children’s Hospital, visit: http://www.hasbrochildrenshospital.org/Medical-Psychiatric-Program.html

Hasbro introduces new pediatric spinal surgery

IN THE NEWS

Magnetic growing rod surgery allows in-office spine lengthening versus bi-annual returns to the operating room

PROVIDENCE—Craig Eberson, MD, chief of pediatric orthopedics at Hasbro Children’s Hospital, has performed the first magnetic growing rod surgery in Rhode Island on an eight-year-old boy with a muscle disorder. The surgery eliminates the need for patients to return to the operating room twice a year under general anesthesia, as is the case with standard growing rods. Instead, the patient can be lengthened with an external magnet during an outpatient office visit.

“Children have a severe case of scoliosis, or an abnormal curvature of the spine, the current treatment plan involves surgically attaching a rod along the spine to control the curvature and prop up their chests,” said Dr. Eberson. “Twice per year, those patients must go back into surgery to manually extend those rods. This new technology can completely avoid those trips to the operating room, thereby reducing infection risk and recovery time, while increasing quality of life.”

This new magnetic rod, such as the one implanted in Dr. Eberson’s young patient, can be lengthened during an office visit every several months using a hand-held magnetic device placed along the patient’s back. No anesthesia is necessary.

Dr. Eberson’s patient will now be able to grow and remain seated upright, which will greatly preserve his lung function. “It is the mission of our department to be able to provide the highest level of pediatric spine care,” he said. “This new treatment option allows patients with scoliosis to manage their care in a five-minute outpatient procedure with no pain medication, no recovery time and no absence from school.”
Jennifer F. Friedman, MD, at RIH confirms anti-parasitic drug safe for pregnant women after first trimester

Finding could spur improved access to treatment to millions of women in developing countries

PROVIDENCE – A study by Rhode Island Hospital researchers confirmed that a drug used to treat a disease affecting millions of people in developing countries is safe to give pregnant women following their first trimester. The finding could prove critical to the care of pregnant women and lactating women with schistosomiasis, a disease caused by a parasitic worm, who were denied the drug out of concern for their health and the health of their fetuses.

Authored by JENNIFER F. FRIEDMAN, MD, PHD, MPH, director of clinical studies for the Center for International Health Research at Rhode Island Hospital, the study found that praziquantel does not lead to adverse events for the pregnant woman or her newborn. The study was published today in The Lancet Infectious Diseases.

“Millions of women, many of whom are in a multi-year, cyclical pattern of pregnancy and breast-feeding, are denied praziquantel,” said Dr. Friedman. “The accumulation of evidence shows that commencement of this treatment after the first trimester does not adversely affect the mother or fetus. We wanted to conduct this study to demonstrate that this drug is safe after the first trimester, and we remain hopeful that public health policies will change. Deferring treatment only exacerbates the morbidity of the patients.”

Nearly 40 million women of reproductive age are infected with schistosomes. They are a significant cause of disease in developing countries. Despite World Health Organization recommendations to offer pregnant women treatment with praziquantel, many nations continue to withhold treatment, awaiting safety and efficacy data from controlled drug trials such as this one.

Schistosomiasis is transmitted during contact with freshwater containing snails that have been infected due to poor sanitation practices. It is known to cause damage to the kidneys, liver, bladder and other organs. After malaria, schistosomiasis is the most common parasitic disease, affecting 200 million people throughout the world and kills approximately 280,000 people annually.

No previous study has examined whether praziquantel treatment at 12–16 weeks gestation improves pregnancy outcomes or whether the use of a higher dose of praziquantel recommended to treat Asian schistosomiasis can be safely administered without adverse newborn or maternal outcomes. This research study, conducted in the Philippines, found that treatment did not positively impact birth weight, however, the iron status of the mothers and newborns improved in the treated group.

RIH, Hasbro EDs to participate in research trial for seizure medicines

PROVIDENCE – The emergency departments of Rhode Island Hospital and its pediatric division, Hasbro Children’s Hospital, are participating in a research study to compare three seizure medications administered during emergencies. The seizure study, known as Established Status Epilepticus Treatment Trial (ESETT), is sponsored by the National Institutes of Health.

Fosphenytoin, levetiracetam, and valproic acid are used to treat seizures in the U.S. emergency departments. However, it is not known which drug is the best drug to stop persistent seizures, a condition called status epilepticus. A clinical trial to study these drugs will be initiated at Rhode Island and Hasbro Children’s hospitals. Persons affected by seizures can decline enrollment in the ESETT study by contacting the study leadership and requesting an “opt out” medical bracelet.

Eligible patients who present to the emergency department with a seizure that does not respond to standard first line therapy [a drug called a benzodiazepine] will be enrolled in the ESETT study. One of the three study medicines will be provided. The ESETT study will assess which seizure medication is the best at stopping the seizure. As soon as possible after enrollment, the hospitals will attempt to obtain consent from the patients or their legal representatives for continued participation in the study. Patients may withdraw from the study at any time.

Hospitals are required to inform the community when the U.S. Food and Drug Administration authorizes a study to be conducted under exception from informed consent. This study meets all four criteria for such exception because: 1) the patient’s life at risk; 2) the treatments currently used are unproven; 3) the best treatment is not known; and 4) it is not possible to get permission from the patient because of his or her medical condition or from the person’s legally authorized representative because the medical problem must be treated very quickly.

ICDs approved for use in MRI scans now being implanted at CNE hospitals

PAWTUCKET – Care New England Cardiovascular Care is now offering patients an implantable cardioverter defibrillator (ICD) system approved by the FDA for use with magnetic resonance imaging (MRI) scans. The first implant of this type of device in Rhode Island was performed recently at Memorial Hospital in Pawtucket.

“Patients with ICDs are often older adults with other serious medical conditions that require an MRI for diagnosis,” said BRUCE KOPLAN, MD, MPH, director of Cardiac Arrhythmia Services for Care New England and a member of the Brigham and Women’s Cardiovascular Associates at Care New England, who performed the procedure. “We’re grateful to have this new technology that helps treat cardiac arrest and still enables patients to access MRIs.”

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IN THE NEWS

November 2015

RHODE ISLAND MEDICAL JOURNAL 65
Memorial researchers note connection between sleep apnea and nighttime urination in postmenopausal women

PAWTUCKET – Thousands of postmenopausal women have obstructive sleep apnea (OSA) and researchers with the Center for Primary Care and Prevention (CPCP) at Memorial Hospital have now connected the risk factors for OSA with nighttime enuresis, or waking to urinate at night. Treatment for one condition, they claim, will help both.

The CPCP research team, which included PATRICK KOO, MD, F. DENNIS MCCOOK, MD, LAUREN HALE, PhD, KATIE STONE, PhD, and CHARLES B. EATON, MD, MS, recently published “Association of obstructive sleep apnea risk factors with nocturnal enuresis in postmenopausal women” in Menopause: The Journal of the North American Menopause Society.

The team mined the data made available by the landmark national study Women’s Health Initiative (WHI), which maintained a clinical presence at Memorial from 1993 to 2005, and created a cohort of 2,789 women aged 50 to 79 years of age for this study.

“What we found suggests that a history of nighttime urination, including leakage, in postmenopausal women places them at increased risk of OSA,” explains Dr. Koo, who is also an assistant professor of medicine (clinical) at The Warren Alpert Medical School of Brown University. “Therefore, primary care providers should consider assessing for OSA risk factors in at-risk postmenopausal women with nocturnal enuresis.

“Most importantly, postmenopausal women with nocturnal enuresis should report it to their physician.”

The connection between OSA and nocturnal enuresis is as basic as understanding that apnea-associated changes in a person’s intrathoracic pressure causes increased urine output. Although it is typically more common in men, OSA increases in women after menopause. If it is left untreated, OSA can lead to the development of high blood pressure and cardiovascular disease. Treatment of OSA with a continuous positive airway pressure (CPAP) machine not only improves blood pressure control and cardiovascular health, but, as the CPCP research team discovered, nocturnal enuresis as well.

“The incidence of nocturnal enuresis increases with age but not necessarily after menopause. The fact that women think this an expected sign of aging means that they do not mention it to their primary care providers,” Dr. Koo says. “In our research, however, we found that OSA risk factors – such as obesity, snoring, poor sleep quality, sleep fragmentation, daytime sleepiness, and hypertension – are clearly associated with nocturnal enuresis in post-menopausal women.”

Medical licensure and discipline legislative commission meets

STATE HOUSE – A newly created special legislative commission that will study and review current rules and regulations pertaining to the Rhode Island Board of Medical Licensure and Discipline held its first meeting next on Oct. 14.

The commission was formed due to legislation, 2015-H 5500A, sponsored by Rep. Michael W. Chippendale. The legislation created a nine-member special legislative study commission whose purpose is to study and analyze the rules and regulations pertaining to the Rhode Island Board of Medical Licensure and Discipline and to assess the fairness of the application of the rules and regulations regarding the discipline and counseling of any medical professional in the practice of medicine.

“Quality patient care is an issue that is of great importance to everyone – especially good doctors,” Representative Chippendale states. “Just as important is how our state treats the doctors responsible for the delivery of that care and it was brought to my attention late last year that there seems to have been a breakdown in the process of how fairly doctors are treated whenever a disciplinary or license-related issue arises,” continues Rep. Chippendale.

“It would be devastating to Rhode Islanders in need of high quality medical care if our state inadvertently developed a reputation for being unjustly zealous in the application of our disciplinary standards which could drive good doctors out of, or keep good doctors from coming to our state to practice,” concluded Rep. Chippendale.

The nine-member commission will consist of:
- Rep. Michael W. Chippendale (R-Dist. 40, Foster, Coventry, Glocester)
- Rep. Gregg Amore (D-Dist. 65, East Providence)
- Rep. Thomas Winfield (D-Dist. 55, Smithfield, Glocester)
- Rep. Samuel A. Azzinaro (D-Dist. 37, Westerly)
- Rep. Patricia L. Morgan (R-Dist. 26, West Warwick, Coventry, Warwick)
- Patricia Recupero, MD, former President of Butler Hospital
- Debbie McInteer, MD, Psychiatrist
- Elizabeth Galligan, public member
- Dean Lees, public member

The commission will also be meeting on Wednesday, November 4 at 3 pm and Wednesday, December 16 at 3 pm.
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Appointments

David Anthony, MD, named editor-in-chief of fmCASES educational tools

Pawtucket – DAVID ANTHONY, MD, a family medicine physician at Memorial Hospital, was named editor-in-chief of Family Medicine Computer-Assisted Simulations for Educating Students (fmCASES) used by more than 100 medical schools to teach the Society of Teachers of Family Medicine (STFM) Family Medicine Clerkship Curriculum.

The content for fmCASES’s 40 interactive virtual patient cases draws heavily from other STFM projects including Family Medicine Curriculum Resources and the Future of Family Medicine.

An fmCASES subscription includes cases that help cover the family medicine core learning objectives. These cases help build clinical competency, fill educational gaps, and instill the core values and attitudes of family medicine. fmCASES fosters self-directed and independent study, builds clinical problem-solving skills, and teaches an evidence-based and patient-centered approach to patient care.

Dr. Anthony is also director of Predoctoral Education and an associate professor of family medicine at the Warren Alpert Medical School of Brown University.

Dr. Sarah M. Davis joins division of Maternal-Fetal Medicine At Women & Infants

Providence – SARAH M. DAVIS, MD, has joined the staff in the Division of Maternal-Fetal Medicine in the Department of Obstetrics and Gynecology at Women & Infants Hospital.

Dr. Davis is board certified in obstetrics and gynecology nationwide and maternal-fetal medicine in Pennsylvania and Rhode Island. Her clinical and research interests include fetal sonography and maternal infectious complications of pregnancy.

She received her medical degree from Penn State College of Medicine. She completed her residency in obstetrics and gynecology at the University of Utah Health Care and fellowship in maternal-fetal medicine with the University of Vermont.

Since 2013, Dr. Davis has served as assistant professor in the Division of Maternal-Fetal Medicine in the Department of Obstetrics and Gynecology at the Penn State Milton S. Hershey Medical Center.

Steve Louvet, DO, family medicine physician, joins Newport Hospital

Newport – Newport Hospital announced that STEVE LOUVET, DO, has joined the Newport Hospital medical staff as part of Family Physicians of Newport and NHCC Medical Associates. He began seeing patients on October 6.

Dr. Louvet received his medical degree from Western University of Health Sciences, College of Osteopathic Medicine of the Pacific. He completed his postgraduate training at Aria Health and the Children’s Hospital of Philadelphia, both in Philadelphia, Pennsylvania.

He is board certified in emergency and family medicine.

Julia Tassinari, MD; James Valente, MD, general surgeons, join Newport Hospital

Newport – Newport Hospital announced that JULIA TASSINARI, MD, and JAMES VALENTE, MD, have joined the Newport Hospital medical staff as general surgeons. They began seeing patients in early September.

Dr. Tassinari, who is board eligible, received her medical degree from Temple University School of Medicine in Philadelphia, Pennsylvania, and completed her internship and residency at St. Elizabeth’s Medical Center in Boston, Massachusetts.

Dr. Valente received his medical degree from the Tufts University School of Medicine and completed his residency at Morristown Medical Center, formerly Morristown Memorial Hospital in Morristown, New Jersey. For the past 25 years, he has cared for members of the U.S. military and their families, most recently as head of general surgery at Naval Health Clinic New England. He is board certified.

Dr. Valente has expertise across a broad range of general surgical services, including management of conditions affecting the breast and thyroid and diseases of the intestinal tract; hernia repair; endoscopic procedures; management of skin and subcutaneous lesions; and advanced laparoscopic surgery, including gallbladder and colon surgery, and surgery for acid reflux.

Among Dr. Tassinari’s interests and expertise are minimally invasive surgery, including hernia repair, and colon and foregut surgery (esophagus, stomach and upper small intestines); breast surgery; and skin and soft tissue surgery.
Appointments

Women’s Care introduces four new providers

The Women & Infants Health Care Alliance has welcomed four new providers to its Women’s Care, Inc. office. The Alliance is a group of four obstetrics/gynecology practices which have partnered with Women & Infants Hospital, with offices in Providence, Pawtucket, Woonsocket and East Greenwich, Rhode Island.

Jennifer L. Hopley, RN, MSM, comes to Women’s Care, Inc. from Baystate Midwifery and Women’s Health of Springfield, MA, where she completed her midwife student clinical experience in ambulatory women’s health. Hopley received her bachelor’s degree from Quinnipiac University and her master’s in midwifery from Philadelphia University.

Lisa H. Pile, RN, MSN, received her master’s in nursing from Chamberlain College of Nursing. She currently serves as clinical adjunct faculty for Maternal Child Health at Aurora University in Illinois and Chamberlain College of Nursing. She joins Women’s Care, Inc. after serving as relief charge, triage, OR circulator and staff RN for the Labor and Delivery Unit at Central DuPage Hospital in Winfield, IL.

Tania Richardson, MSN, CNM, joins Women’s Care from OB/GYN Associates, Inc. Richardson earned her bachelor’s of science in nursing at South University and her master’s of science in nursing and master’s in health sciences at Georgetown University. She is a member of the American College of Nurse Midwives (ACNM) and the American Congress of Obstetricians and Gynecologists (ACOG).

Christian F. Roman-Rodriguez, MD, received his bachelor’s degree from Boston College and his medical degree from the Ponce School of Medicine in Puerto Rico. Dr. Roman-Rodriguez completed his residency in obstetrics and gynecology at Nassau University Medical Center where he served a stint as administrative chief resident. Dr. Roman-Rodriguez’ research interests include polycystic ovarian syndrome and high blood pressure in pregnancy, and medical education. Additionally, he is fluent in Spanish and consistently strives to close communication gaps with the Hispanic patient community.

Dr. Vincent Armenio named Chairman of Medicine at Roger Williams

Providence – Vincent Armenio, MD, has been named Chairman of the Department of Medicine at Roger Williams Medical Center following an extensive national search.

As Chairman, Dr. Armenio will be responsible for providing leadership within the Department of Medicine, including oversight of clinical affairs, quality care, program development, and outreach to community physicians and other providers.

Dr. Armenio is a widely-respected Hematologist/Oncologist who has held a number of leadership roles at Roger Williams including Vice Chairman of the Department of Medicine and Associate Director of the Cancer Center.

Board certified in Internal Medicine and Medical Oncology, Dr. Armenio received his fellowship training in Hematology/Medical Oncology and Pediatric Hematology/Oncology at Brown University School of Medicine. After graduating from Ross University School of Medicine in Dominica, he completed a residency in Internal Medicine through Mount Sinai School of Medicine at Englewood Hospital in New Jersey. Dr. Armenio’s research interests include medical oncology and clinical trials.

Dr. Armenio has served on numerous committees at Roger Williams related to cancer care and quality and currently serves as Chairman of the Quality Oncology Practice Initiative [QOPI] committee at the Cancer Center.

Herbert Aronow, MD, MPH, named director of interventional cardiology at Cardiovascular Institute

Providence – The Cardiovascular Institute [CVI] of Rhode Island Hospital, The Miriam Hospital and Newport Hospital named Herbert Aronow, MD, MPH, of East Greenwich as director of interventional cardiology. An expert in cardiovascular disease, and coronary and vascular intervention, he will practice at all three hospitals.

Dr. Aronow will also serve as director of the cardiac catheterization laboratories at Rhode Island and The Miriam hospitals.

He earned a medical degree from the University of Michigan Medical School and a master’s degree in epidemiology from the University of Michigan School of Public Health in Ann Arbor. He completed his residency at the University of Michigan Medical Center, and fellowships in cardiovascular medicine and interventional cardiology at the Cleveland Clinic Foundation in Cleveland, Ohio.

Dr. Aronow is board certified in cardiovascular disease and interventional cardiology. He is a fellow of the American College of Cardiology, a former member of its board of governors and the current chairperson of its peripheral vascular disease section. He is also a fellow of the Society for Cardiovascular Angiography and Intervention and secretary of the Society for Vascular Medicine’s board of trustees.
Appointments

Dr. Jessica Pineda joins Center for Women’s Medicine

PROVIDENCE – JESSICA PINEDA, MD, has joined the Center for Women’s Medicine at Women & Infants Hospital. Dr. Pineda will be seeing patients at the Center for Primary Care and the Center for Women’s Behavioral Health.

Dr. Pineda received her bachelor’s degree from Luther College and her doctor of medicine from the Medical College of Wisconsin in Milwaukee. She completed an internship and residency at the University of Cincinnati in psychiatry and family medicine. Dr. Pineda’s recent resident work experience includes serving as a psychiatrist for the Inpatient Forensic Unit at Summit Behavioral Health, physician at Deerfield Urgent Care, addiction psychiatrist at the Prime Health Group, and volunteer physician at LifeSpring NCH Free Clinic.

In addition to her clinical practice, Dr. Pineda’s research interests include women’s behavioral health surrounding obstetrics and overall mental health for the underserved in the community.

Lynn Pesta, MD, primary care physician, joins Women’s Medicine Collaborative

PROVIDENCE – LYNN PESTA, MD, has joined the Women’s Medicine Collaborative Women’s Primary Care team.

Dr. Pesta received her medical degree from the Wayne State University School of Medicine in Detroit, Michigan. She completed her residency at Fletcher Allen Health Care in Burlington, Vermont.

She is board eligible in internal medicine. Among her clinical interests are preventive medicine and cancer screening. In 2015, she received the Arnold P. Gold Foundation Humanism and Excellence in Teaching Award, as well as the Richard E. Bouchard Primary Care Excellence Award from The University of Vermont.

Zsolt Orban, MD, appointed to Memorial Hospital

PAWTUCKET – Memorial Hospital of Rhode Island recently appointed ZSOLT ORBAN, MD, FACE, to its medical staff in the Department of Endocrinology. Dr. Orban is a member of Affinity Physicians and will work out of Memorial Hospital.

Dr. Orban earned his medical degree Summa Cum Laude from Semmelweis University Medical School, Budapest. He completed his Internal Medicine residency at Henry Ford Hospital, Detroit, MI and pursued a clinical endocrinology fellowship at the National Institutes of Health. After completion of his training, he had been in private practice as an internist and endocrinologist, for over 15 years.

Dr. Orban is a Fellow of the American College of Clinical Endocrinologists. His clinical interests include: diseases of the thyroid, parathyroid and pituitary, osteoporosis, and male hypogonadism. He is fluent in Portuguese.

Rep. Kazarian elected chairwoman of rare disease commission

STATE HOUSE – REP. KATHERINE S. KAZARIAN (D-Dist. 63, East Providence) was elected chairwoman of the legislative commission tasked with examining care administered to individuals with rare diseases during the commission’s first meeting at the State House. REP. DAVID A. BENNETT (D-Dist. 20, Warwick, Cranston) was elected vice-chair of the commission.

“I’d like to thank my colleagues on the commission for having the confidence in me to act as their chairwoman during this important study commission regarding an often underrepresented group within our state’s healthcare system,” said Representative Kazarian. “Living with any disease is a burden, but, to the few in the state affected with uncommon and rare diseases, the burden significantly increases, often without any clear course of action for treatment. Just because a patient is the only person in Rhode Island suffering from a particular rare ailment, does not mean they should be left alone to fend for themselves. My hope is that this commission can change that tragic reality for those who suffer from rare diseases,” added Kazarian.

The commission was the result of legislation [2015-H 5297A] that Representative Kazarian sponsored after hearing the story of Patricia Weltin, an East Providence resident and fellow commission member, who is the caregiver to two young daughters who each suffer from rare diseases. The legislation created a nine-member special legislative study commission whose purpose is to study and make recommendations for coordinating the necessary resources to provide care to individuals with rare diseases.
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**Recognition**

**Women’s Medicine Collaborative earns facility bone densitometry reaccreditation**

PROVIDENCE – The Bone Health Program at the Women’s Medicine Collaborative has been reaccredited for five years by the International Society for Clinical Densitometry. This distinction recognizes the facility’s quality and technical excellence in assessing skeletal health. The Women’s Medicine Collaborative first achieved accreditation in bone densitometry in May, 2012.

“Our goal is to provide our patients the best possible care with their distinctive needs in mind,” said GEETHA GOPALAKRISHNAN, MD, CCD, medical director of the Bone Health Program and an endocrinology specialist at the Women’s Medicine Collaborative.

A DXA is recommended for:
- Women age 65 or older
- Men age 70 or older
- Menopausal women with risk factors
- Postmenopausal women under age 65 with risk factors
- Men age 50-69 with risk factors
- Anyone with a broken bone after age 50

**Southcoast Breast Center recognized by the American Cancer Society**

DARTMOUTH, MASS. – The Southcoast Breast Center, a part of Southcoast® Health, was recognized by the American Cancer Society at its annual Making Strides Against Breast Cancer [MSABC] walk recently in Providence, for its extraordinary efforts supporting breast cancer patients and caregivers, while also embracing the Society’s mission to help people stay well, get well, find cures and fight back. The recognition was accepted by DR. MAUREEN CHUNG, Medical Director of Southcoast Breast Center.

The Society also recognized the Southcoast Breast Center for recently receiving a three-year full accreditation by the National Accreditation Program for Breast Centers, a program administered by the American College of Surgeons. Accreditation by the NAPBC is only given to those centers that have voluntarily committed to provide the highest level of quality breast care and that undergo a rigorous evaluation process and review of their performance.

**Four Women & Infants nurse-midwives earn national recognition with Clinical Star Award**

PROVIDENCE – Four certified nurse midwives [CNMs] at Women & Infants Hospital of were honored with the Clinical Star Award from the American College of Nurse-Midwives [ACNM] Foundation. The Award is given in honor of midwives in clinical practice for 25 or more years who have demonstrated excellence in clinical practice and positive mentoring in the profession.

DIANE ANGELINI, CNM, EDD, FACNM, FAAN [retired]; DEBRA ERICKSON-OWENS, CNM, PHD, of North Kingstown; JUDITH MERCER, CNM, PHD, FACNM, of Cranston; and LINDA NANNI, CNM, MS, FACNM, of Wesport, MA, were honored during National Midwifery Week at Women & Infants Hospital.

“It’s providers like Diane, Deb, Judy and Linda who dedicate so much of their professional lives to nursing excellence that make Women & Infants the model in midwifery and all nursing disciplines when it comes to the care of women and newborns,” said ANGELLEEN PETERS-LEWIS, RN, PhD, chief nursing officer and senior vice president of patient services at Women & Infants Hospital.
Recognition

Southcoast Health named one of America’s 100 Best Hospitals for Cardiac Care for the 5th year in a row by Healthgrades

Recognized for outstanding cardiovascular services in 7 categories including the treatment of heart attacks

Fall River, Mass. – Southcoast® Health today announced that it has been recognized as one of America’s 100 Best Hospitals for Cardiac Care for the fifth year in a row by Healthgrades®[2012-16], the leading online resource for healthcare consumers. Southcoast Health is one of just four hospitals in Massachusetts to receive this distinction for five consecutive years.

In all, Southcoast Health was recognized for superior cardiovascular services in seven areas of care, including receiving the Healthgrades Cardiac Care Excellence Award for the 10th year in a row (2007–16).

“These recognitions are a much-deserved acknowledgement of the tremendous dedication of the team of physicians, nurses and clinical staff at the Southcoast Health Cardiovascular Care Center,” said DR. MARGARET FERRELL, Physician-in-Chief of Cardiovascular Services at Southcoast Health. “Our team provides the highest level of cardiac care to the patients of our region on a daily basis, and so it’s gratifying to see their hard work recognized.”

Southcoast Health also received awards in pulmonary, neurosciences, women’s health, gastrointestinal, orthopedics and critical care, as well as for patient safety. (See the full list below)

These achievements are part of new findings and data released this week on Healthgrades.com and in the Healthgrades 2016 Report to the Nation. For its analysis, Healthgrades evaluated approximately 40 million Medicare-patient records for nearly 4,500 short-term acute care hospitals nationwide, assessing hospital performance relative to each of 33 common conditions and procedures.

Healthgrades recognizes a hospital’s quality achievements for cohort-specific performance, specialty area performance and overall clinical quality. Individual procedure or condition cohorts are designated as 5-star (statistically better than expected), 3-star (statistically as expected) and 1-star (statistically worse than expected) categories.

The following is a full list of recognitions received by Southcoast Health:

**Cardiovascular Services**
- One of Healthgrades America’s 100 Best Hospitals for Cardiac Care™ for five years in a row (2012–16)
- Recipient of the Healthgrades Cardiac Care Excellence Award™ for 10 years in a row (2007–16)
- Top 10% in the Nation for Overall Cardiac Services for 10 years in a row (2007–16)
- Top 10% in the Nation for Cardiology Services in 2016
- Five-Star Recipient for Coronary Bypass Surgery for five years in a row (2012–16)
- Five-Star Recipient for Treatment of Heart Attack for 2016
- Five-Star Recipient for Treatment of Heart Failure for two years in a row (2015-16)
- Five-Star Recipient for Defibrillator Procedures in 2016

**Pulmonary**
- One of Healthgrades America’s 100 Best Hospitals for Pulmonary Care™ for two years in a row (2015–16)
- Recipient of the Healthgrades Pulmonary Care Excellence Award™ for seven years in a row (2010–16)
- Top 5% in the Nation for Overall Pulmonary Services for three years in a row (2014–16)
- Top 10% in the Nation for Overall Pulmonary Services for seven years in a row (2010–16)
- Five-Star Recipient for Treatment of Chronic Obstructive Pulmonary Disease for eight years in a row (2009–16)
- Five-Star Recipient for Treatment of Pneumonia for six years in a row (2011–15)

**Neurosciences**
- Recipient of the Healthgrades Stroke Care Excellence Award™ in 2016
- Top 10% in the Nation for Treatment of Stroke in 2016
- Five-Star Recipient for Treatment of Stroke for five years in a row (2012–16)

**Women’s Health**
- Recipient of the Healthgrades Women’s Health Excellence Award™ in 2015
- Top 5% in the Nation for Women’s Health in 2015

**Critical Care**
- Five-Star Recipient for Treatment of Respiratory Failure in 2016

**Gastrointestinal**
- Five-Star Recipient for Esophageal/Stomach Surgeries in 2016

**Orthopedics**
- Five-Star Recipient for Hip Fracture Treatment in 2016

**Hospital Wide**
- Recipient of the Healthgrades Patient Safety Excellence Award™ for two years in a row (2014-15)
- Top 5% in the Nation for Patient Safety for two years in a row (2014-15)

Detailed performance information, such as cohort-specific outcomes data and quality achievements, as well as more information on the Healthgrades 2016 Report to the Nation, including the complete methodology, can be found at: www.healthgrades.com/quality
Recognition

Rhode Island Hospital earns national cancer award

The honor from the American College of Surgeons’ Commission on Cancer recognizes cancer programs that achieve excellence in providing highest quality cancer care

PROVIDENCE – The Comprehensive Cancer Center at Rhode Island Hospital was recently presented with the Midyear 2015 Outstanding Achievement Award by the American College of Surgeons’ Commission on Cancer. Rhode Island Hospital is one of only 23 health care facilities in the country – and the only in Rhode Island – to receive this national honor for excellence in providing quality care to cancer patients.

The award recognizes the significant commitment by the Rhode Island Hospital team in providing superior cancer care to patients while meeting and exceeding the standards set by the Commission on Cancer.

Comprehensive Cancer Center on Top 100 List

Becker’s Hospital Review taps hospital systems with great oncology programs

PROVIDENCE – Becker’s Hospital Review has published the 2015 edition of its list of “100 Hospitals and Health Systems With Great Oncology Programs” and the Comprehensive Cancer Center (CCC) of Rhode Island Hospital, The Miriam Hospital and Newport Hospital is on the list.

The CCC is the only Rhode Island health system on this year’s list.

The list features organizations dedicated to treating cancer patients as well as researching the deadly disease. The hospitals and cancer centers stand out in terms of quality patient care, clinical outcomes and research achievements.

“One again, an independent organization has scrutinized cancer programs across the country and includes ours as among the best,” said DAVID WAZER, MD, interim medical director of the CCC. “We acknowledge this recognition with pride and renew our steadfast commitment to providing high-quality care and support systems to our patients.”

The Becker’s Hospital Review editorial team selected hospitals for inclusion based on recognition received, accreditations earned, and memberships held in cancer care-oriented groups. Specifically, the Becker’s team examined U.S. News & World Report’s hospital rankings for treating cancer, CareChex cancer care rankings, BlueCross BlueShield Association Blue Distinction Center designation, National Cancer Institute designations, and Commission on Cancer accreditations and awards received, as well as membership in the National Comprehensive Cancer Network. Hospitals on this list have several of these recognitions.

The full list features individual profiles of all 100 organizations and can be read here: http://bit.ly/1itn5Zb

Women & Infants Physicians win best poster award at IDSOG annual meeting

PROVIDENCE – Brenna L. Hughes, MD, MSC, of the Division of Maternal-Fetal Medicine and Director of the Women’s Infectious Disease program presented at the 42nd Annual Meeting of the Infectious Diseases Society for Obstetrics and Gynecology (IDSOG) in Portland, OR. IDSOG brings together professionals in the field of obstetrics and gynecology who are interested in the scientific study of infectious diseases in women.

One of two poster presentations by the group took home the Best Poster Award, “Longitudinal cohort study of association of HIV infectivity with pregnancy.” The study examined epidemiologic data that currently conflicts as to whether pregnancy increases the risk of HIV acquisition. To measure this, the team compared the protection against infectivity conferred by cervicovaginal secretions among pregnant and non-pregnant women using a novel in vitro model.

The sample included 40 pregnant women with the mean gestational age of 12 weeks and 37 non-pregnant women. There were no significant differences between groups in most demographic characteristics. Pregnant women were followed across gestation and non-pregnant women across the menstrual cycle. Cervicovaginal lavage (CVL) was performed at each visit. CVL fluid from both groups significantly inhibited HIV infectivity compared to the control group.

“The median percent inhibition of HIV infectivity at enrollment did not differ between pregnant and non-pregnant women. The findings were similar at each follow-up visit and infectivity did not change significantly across time within groups,” said Dr. Hughes, who served as principal author on the study. “Our data doesn’t support the data saying that pregnant women are at higher risk of contracting HIV. This suggests that we need to study that question more thoroughly.”

Erica Hardy, MD, MA, MMSc, co-Director of the Women’s Infectious Disease program, served as presenting author for the second poster presentation “Uptake of Third Trimester HIV Testing Program at a Tertiary Care Hospital.” In addition, oral presentations at the meeting included “Inflammatory Mediators in Cervicovaginal Secretions and Association with HIV Infectivity among Pregnant and Non-pregnant Women,” Dr. Hughes as primary author. Catherine Albright, MD, fellow in the Division of Maternal Fetal Medicine, was presenting author for the oral presentation “Use of Cefazolin for Group B streptococcal Prophylaxis in Women Allergic to Penicillin Without Anaphylaxis.”

Women & Infants Physicians win best poster award at IDSOG annual meeting
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Recall

Robert Goldman, PhD, Memorial researcher, earns subcontract to study pain indices

Providence – Roberta Goldman, PhD, director of Community Participatory Research at the Center for Primary Care and Prevention at Memorial Hospital, recently earned a subcontract from Southern California University to help her pursue qualitative research into the different ways pain is recorded. This includes investigating which methods for measuring and reporting pain impact patients’ experiences of pain, and which are most important for their physicians to understand.

To advance the measurement of pain, Dr. Goldman and other researchers will develop a set of indices representing new ways to consider pain experiences. These will involve gauging various measurements of pain intensity, environmental setting, and time-related components. “These innovative indices will go well beyond the relatively simple conceptualization of average pain to explore a broader selection of potentially useful ways to report pain,” Dr. Goldman explains. “Finding ways to more effectively understand both patients’ pain and the effect of treatment on that pain is critical for clinicians as they work with patients to improve their health and reduce their pain.”

Her study, “Innovative pain outcomes derived from patients’ real-time pain reports,” is funded by a three-year grant from the National Institutes of Health. As co-investigator of the study, she will serve as the lead for all qualitative components of the research, which will involve in-depth interviews with a national sample of patients with chronic pain, clinicians who treat patients with chronic pain, U.S. and European governmental prescription drug regulators and clinical trial researchers.

Dr. Goldman is also a clinical professor of family medicine in the Warren Alpert Medical School of Brown University and director of the Scholarly Development Program in the Brown Family Medicine Residency Program at Memorial, a Care New England hospital.
Memorial Hospital School Of Nurse Anesthesia Program graduates 8

PAWTUCKET—Ceremonies for the 49th graduation of the Memorial Hospital School of Nurse Anesthesia Program took place on October 23, 2015 in the hospital’s Medical Staff Auditorium. Hospital administration, staff, family and friends were on hand to honor the eight graduates.

This year’s graduates are: Tyler Berch of Littleton, CO; Kathleen Bourski of Warwick, RI; Kathryn Foster of Hershey, PA; Bryana Gillespie of Calais, ME; Ewa Korzeniowska of Tacoma, WA; Kenneth Leeberg of Lombard, IL; Marwan Rayan of Roanoke, VA; and Austin Smith of Big Sandy, TX.

MARK A. FOSTER, APRN, CRNA director of Memorial’s School of Nurse Anesthesia Program, recognized the accomplishments of the eight nurse anesthetists. He noted how the graduates devoted the past 29 months to a comprehensive didactic and clinical curriculum, earning a Master of Science Degree in Biological Sciences/Anesthesia.

Dr. Juan Sanchez-Esteban awarded $25,000 to investigate fetal lung development

PROVIDENCE – JUAN SANCHEZ-ESTEBAN, MD, an associate professor of pediatrics at The Warren Alpert Medical School and staff neonatologist at Women & Infants Hospital, was awarded a $25,000 grant in support of his project titled “Role of Exosomes in Fetal Lung Development.” This is a pilot project funded by Center of Biomedical Research Excellence (COBRE) to investigate the role of exosomes in fetal lung development.

“This pilot study will investigate whether isolated lung cells exposed in the lab to stretch, mimic the stretch that normally occurs in lung development releasing exosomes. We will also test whether these isolated exosomes given to the cells stimulate development,” said Dr. Sanchez-Esteban.

The results of these investigations regarding the administration of exosomes to fetus or preterm newborns could be the next step in accelerating lung development in high-risk cases, explained Dr. Sanchez-Esteban.

Dr. Sanchez-Esteban received his medical degree from the Universidad Autonoma De Barcelona in Spain. He went on to complete his internship at the Metropolitan Hospital Center and his residency at the Metropolitan Health Medical Center in New York. His fellowship was completed with Women & Infants Hospital.
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Obituaries

DR. ROBERT P. CURHAN, 83, of Narragansett died October 10, 2015 at home surrounded by family. He was the beloved husband of Adele (Pearlman) Curhan. They were married for 60 years. Born in Detroit, MI, a son of the late Joseph and Pauline (Pevin) Curhan, he lived in Narragansett for 40 years.

Dr. Curhan was an OB-GYN at South County Hospital for nearly 40 years. He served in the Air Force and was a member of Congregation Beth David. He was the devoted father of Michael Curhan and his wife, Suzan, of West Bloomfield, MI; Gary Curhan and his wife, Sharon, of Lincoln, MA, and Amy Freedman and her husband, Alan, of Canton, MA, and is survived by 11 grandchildren.

In lieu of flowers, contributions in his memory may be made to Congregation Beth David, 102 Kingstown Rd., Narragansett, RI 02882.

OWEN B. GILMAN, MD, 77, died peacefully on October 16, 2015 in his Buttonwoods home, with his family at his side. He was the beloved husband of Katherine E. (Hand) Gilman for 52 years. Born in Providence, the son of the late Hector A. and Sally E. (Thornton) Gilman, he lived in Warwick for 45 years.

After graduating from the College of the Holy Cross, he received his medical degree from Tufts University School of Medicine. He completed Internal Medicine Residency at New England Deaconess and Rhode Island Hospitals, followed by Nephrology Fellowship at Rhode Island Hospital.

He served as a Major in the US Army Medical Corps at Tripler Army Medical Center and also as Clinical Instructor of Medicine at the University of Hawaii. He was a Diplomate of the American Board of Internal Medicine and American Board of Nephrology. After completion of his medical training and military service, he was appointed to the medical staff of Kent County Memorial Hospital and Rhode Island Hospital in the Departments of Medicine in 1970.

At Kent County Hospital he founded the Dialysis Unit where, under his direction, the first dialysis machine was purchased and used to treat patients. He served as the Director of the Kent County Hospital Dialysis Unit and as the Medical Director of the Kent County Hospital Home Care Division. For 39 years he dedicated his career to the care of his medical and nephrology patients. One of his greatest rewards and privileges was caring for the patients in his medical practice.

His greatest joy in life was his family. He loved spending time with his children and grandchildren, of whom he was extremely proud. He was an avid reader, lover of Irish poetry, dedicated and accomplished fisherman, and he loved music. He was a devout Catholic and an extraordinary minister of the Eucharist. Besides his wife, he is survived by his sons, Owen B. Gilman Jr. and Matthew D. Gilman MD, and his daughters, Beth M. Simpson and her husband Trevor, Melia Flynn and her husband Gerald, and Katherine M. Cooney and her husband Edward. He was the grandfather of Jessica C. Gilman, Max W. Gilman, Jack O. Flynn, Kaylin M. Flynn, and Edward J. Cooney III. He was the brother of Sheila Gilman Falconer and the late Robert T. Gilman, MD.

In lieu of flowers, contributions in his memory may be made to the Kent Hospital Foundation, for Kent Dialysis Unit, 455 Toll Gate Road, Warwick, RI 02886.

DAVID E. MAGLIO, JR., DO, 77, of Providence, passed away September 29, 2015. He was the husband of Alice T. (Ash) Maglio. They had been married for 55 years. Born in Dorchester, MA, he was a son of the late David and Angela (Guarcello) Maglio.

Dr. Maglio graduated in 1959 from Providence College, and received his degree from the Kirksville College of Osteopathic Medicine in 1963. He and his wife came to Rhode Island in 1964 where he practiced family medicine in East Greenwich for 25 years.

In 1989, he began a ministry providing medical and spiritual care for the needy at St. Vincent dePaul Ministry on Dexter Street in Providence until retiring in 2013.

Besides his wife, he leaves two sons, David Maglio and his wife Jane Maglio of Barrington, and Joseph Maglio, MD, and his wife Nancy Maglio of CT; three daughters, Gia Maglio, Elise Maglio, and Laura Sullivan and her husband Keith Sullivan, all of Providence; a sister, Ursula Lyons and her husband Frank Lyons of MA; and eight grandchildren.

In lieu of flowers, donations in his memory may be made to St. Vincent dePaul Ministry, 178 Dexter St., Providence, RI 02907.
Josh Schiffman, MD: Genetic clues as to why elephants rarely get cancer

Providence native hopes research will help target pediatric cancers

MARY KORR
RIMJ MANAGING EDITOR
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When **DR. JOSHUA SCHIFFMAN**, [Brown ’96, Alpert Medical School ’00], took his three kids to the Hogle Zoo in Utah several years ago, he paused in front of the massive African elephants and pondered the conundrum: “Why do elephants rarely get cancer?”

Despite their massive size, which can reach a whooping 14,000 pounds, just 4.8 percent of known elephant deaths are cancer-related, as compared to between 11% and 25%, for people.

“Nature has already figured out how to prevent cancer. It’s up to us to take a lesson from Nature’s playbook and adapt those strategies to prevent cancer in people,” Dr. Schiffman said.

He hopes his study, of which he is senior co-author, recently published in JAMA online on the elephant genome, will translate into arresting cancer in children.

Titled “Potential Mechanisms for Cancer Resistance in Elephants and Comparative Cellular Response to DNA Damage in Humans,” it reported that elephants have 38 additional modified copies (alleles) of a gene that encodes *TP53*, a well-defined tumor suppressor, as compared to humans, who have only two.

In addition, elephants may have a mechanism for killing damaged cells at twice the human cell rate, suggesting the extra *TP53* could explain elephants’ enhanced resistance to cancer.

Dr. Schiffman hopes his and his co-researchers’ surprising study on the elephant genome will translate into arresting cancer in children. To that end, he and the Greatest Show on Earth have teamed up, along with researchers at the Utah Zoo and a Ringling Bros. elephant conservation center, as well as the Huntsman Cancer Institute in Utah, to further investigate the findings.

It’s a JUMBO tale – full of hope and wonder for kids of all ages, and RIMJ asked Dr. Schiffman, who is now medical director of the High Risk Pediatric Cancer Clinic at the Huntsman Cancer Institute in Utah, to discuss his personal and professional path which led him to pediatrics and pachyderms.
Q. What in your background in RI, for example, as the son of a prominent oncologist, and a PLME student at Brown medical school — influenced and informed your decision to become a pediatric oncologist?

A. When I was fifteen years old, I was diagnosed with Hodgkin’s Lymphoma, first by my own father and then later confirmed by Dr. Edwin Forman. As a PLME student at Brown medical school, I had the very meaningful experience of shadowing Dr. Forman at Hasbro Children’s Hospital. When it came time to choose a career, I wanted to deliver the same type of compassionate care that I had always witnessed growing up which my father delivered to his own patients, and then personally experienced as one of Dr. Forman’s own patient, and then later witnessed Dr. Forman delivering to his other patients while a medical student. Truly, when I grew up, I wanted to be just like Dr. Forman (and my dad!). There is no substitution for the truly wonderful, talented, dedicated, and caring mentors at Brown!

Q. What was the genesis of this study? Did you see an elephant and wonder why they were not prone to cancer?

A. After medical school, I trained in Pediatrics and Pediatric Hematology/Oncology at Stanford University. Although I initially wanted to just take care of patients (like my father and Dr. Forman), I was very much attracted to the potential of translating laboratory science to our patients in the clinic. I moved to Primary Children’s Hospital and the University of Utah in Salt Lake City, Utah, to start a translational genomics laboratory to better understand the origins of pediatric cancer. Along the way, our lab became very interested in understanding increased cancer risk in other animals (I had minored in animal behavior while an undergraduate at Brown). We were very focused on cancer predisposition in humans and dogs.

While attending an evolution and medicine conference in Bar Harbor, Maine (sponsored by Dr. Randy Nesse, one of the founders of the field of Evolutionary Medicine), I learned that elephants rarely develop cancer and it might be due to extra copies of TP53. This intrigued me because we care for children and families with Li-Fraumeni Syndrome who are missing functional TP53 and have nearly 100% lifetime risk of cancer as opposed to elephants with extra TP53 who almost rarely develop cancer. This was “a-ha moment” for me when I realized we can focus on cancer resistance instead of cancer risk, and see what we could learn to apply to our patients.

We immediately began a collaboration with the speaker from this evolution and medicine conference (Dr. Carlo Maley, Arizona State University), and then reached out to Utah Hogle’s Zoo to get fresh elephant blood to do our functional DNA repair experiments. Eventually, the Ringling Bros. and Barnum & Bailey Circus reached out to us, and we have developed an extremely productive partnership including tremendous research support and collaboration with their Center for Elephant Conservation. Link: https://www.ringlingelephantcenter.com/cancer-research/

Q. Is evolutionary medicine an emerging field and can you explain the conceptual approach?

A. This is the idea that if you look at why disease occurs (or doesn’t occur) from an evolutionary perspective, that you may gain clinical insight into how to apply these evolutionary mechanisms to patients.

Q. What is the next step in this research?

A. We are now trying to raise enough support and awareness to continue to...
fund this research. We want to search for natural or synthetic compounds that will mimic the effects of extra copies of TP53 (i.e., shift all of the cells to apoptosis instead of just DNA repair). We also are working with collaborators from Israel to try to use novel genomic technology to deliver elephant TP53 to human cells as potential therapeutic for either cancer prevention or treatment. We don’t want to overpromise; we have not found the cure to cancer, although we do believe we may have discovered one of the potential mechanisms for how elephants are protected from cancer (multiple copies of TP53, the “guardian of the genome”). Now we want to work as hard as we can – and as fast as we can – to see if we can apply this discovery to humans.

This will require significant philanthropic funding. However, one child with cancer is one child too many, and we now want to take advantage of 55 million years of elephant evolution to try to figure out how to prevent cancer in people.

Q. When you meet with your little patients, do you share elephant stories with them?

A. Yes, absolutely! This has been one of the unexpected joys of this research. I can now take a situation that is desperate and full of fear and anxiety, and just by sharing the research that we’re doing, we are now able to turn the situation into a happy discussion that leaves everyone smiling and wanting to visit elephants at the zoo or circus.

Q. Do your children think you are really cool now that you are a researcher in the Animal Kingdom?

A. They think that I am a mixture of coolness and weirdness that I am so interested in elephants and other animals! They do like seeing me discuss the research, and are particularly amused by the cartoon explanation made by Ringling Bros [see link above]. Personally, I am just pleased that my children are able to learn a little bit more about what I do for a living. Maybe, one day, they will want to continue to help patients and their families just like I grew up wanting to help continue what my father does through his dedication to his own patients that he demonstrates on a daily basis [like father, like son, except for the elephant part!].

WATCH THE VIDEO: https://www.youtube.com/watch?v=ThRRIVSH?wk
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1780: American dentistry had its roots in RI during the Revolution

MARY KORR
RIMJ MANAGING EDITOR

When Count Rochambeau sailed into Newport on July 11, 1780 to aid the Continental Army, it was a seminal moment for dentistry in America, thanks to French Navy surgeon-dentist DR. JOSEPH LEMAIRE.

Rochambeau’s force remained in Rhode Island for more than a year. During the winter of 1781–1782, at Brown’s University Hall, which served as a military hospital, Dr. LeMaire, with Rochambeau’s approval, trained two young men in the dental arts.

According to “Patriot and Pioneer Surgeon-Dentist” by Burton Lee Thorpe, DDS, published in Oral Hygiene (1920):

“During the winter of 1781 Dr. LeMaire tutored two fellow-patriots in the art of dentistry, one a fellow countryman, physician and surgeon James Gardette, aged 25, the other an American Josiah Flagg, eighteen years of age, both of whom afterward proved a credit to American dentistry.”

The article further noted Dr. LeMaire’s skill in transplanting teeth and carving artificial teeth from ivory. It cited him as “the first and original dental preceptor and his coming marked the commencement of dentistry as a profession in America.”

Josiah Flagg of Boston was the first American-trained dentist, who apprenticed during the American Revolution in Providence, RI, with a French dentist.

This broadside of Dr. Flagg’s advertises: “Cash given for handsome and healthy live teeth.” The reverse offers instructions on brushing teeth.
Beecher’s Manual and Dental Directory of the United States (1884) credits JOSIAH FLAGG as the first American-trained dentist “as far as is known.”

Transplants and Teeth Whitening
Immediately after the war, various dental journals relate, Flagg traveled as an itinerant dentist and for a time practiced in Rhode Island and surrounding areas before setting up a practice in Boston.

The contents of a circular he distributed from 1790, stated:

Dr. Flagg transplants teeth, cures ulcers, fastens those that are loose, mends teeth with gold to be as useful and lasting as sound teeth, and without pain in the operation, makes artificial teeth and secures them in a lasting and serviceable manner.

He also advertised teeth whitening without “the use of saws, files, acids and such abusives as have shamefully crept into the profession and which have destroyed the confidence of the public.”

Flagg was also a purveyor of dental appliances: tinctures, chewsticks (which were a branch of the creeping shrub of the West Indies buckthorn family), masticks (a Mediterranean evergreen) and teeth and gum brushes “suitable for every age and climate.”

According to the Massachusetts Historical Society archives, he constructed the first dental chair in the United States by using a Windsor chair and configuring it with an adjustable horsehair and leather headrest, an extended armrest and drawers under the armrest and seat for dental tools.

During the War of 1812, Flagg enlisted and was captured by the English fleet and sent to England, where he made the most of his captivity by studying with European dentists and practicing. After the war, he was shipwrecked on the voyage home, off New York harbor.

Several years later, in 1816, he died of yellow fever in Charleston, SC, where he had gone in search of a warmer clime. His profession was carried on by several of his sons, who became noteworthy in the field.

For photos, more information on Flagg’s dental tools and chair, visit the historical dental museum collection at Temple’s Kornberg School of Dentistry, http://temple.pastperfect-online.com.

Contrary to popular legend, George Washington’s teeth were not made of wood. During his lifetime he used dentures made of bone, ivory, human teeth, brass screws, lead, and gold metal wire.