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All doctors deal with obtaining prior authorizations for medically indicated tests, medications and therapy. In some cases these are reasonable attempts to reduce costs. In most cases they feel like they are simply impediments to make a doctor think twice about whether the test or medication is worth the time and effort. Recently I gave up after spending 20 minutes attempting to make an appointment with the physician at the insurance company to request an MRI, not even to actually speak with the person. My secretary was not sympathetic. She does this all the time. Yesterday I wrote an appeal for a denial for a lift seat for an 83-year-old woman with advanced Parkinson’s disease. Evidently this wasn’t considered a “severe neuromuscular problem.” The goal is cost reduction by attrition rather than cost reduction through quality control. But a recent denial was different. It forced me to balance the needs of the one versus the many. I was integrally involved in the decision-making. It is a paradigm of what managed medical care should really mean.

My patient has tardive dyskinesia (TD), a medication-induced movement disorder. She had required the psychiatric medication that caused the problem. Her treatment had been exemplary. Her medications had been used sparingly and reduced when possible, leading to early recognition of her disorder, which, while not disabling in the sense that it restricted her movements, was disabling in the sense that she could not function well around other people due to her odd facial movements. There is no cure for TD.

There is data suggesting that if she can remain off the medication that caused her TD, she has a 50-50 chance of recovering to normal or near normal, but this might take over a year. In the meantime, there’s a drug that might mask the movements, without making them worse in the long term. This approach would allow her to function normally while her TD, hopefully, resolves. She has a medical insurance plan for the indigent, and the drug of choice is very expensive. Since TD is not an approved indication for the drug, insurance plans are well within their rights to deny the prescription. In this case the issue was cost relative to demonstrated efficacy. Here’s where I was challenged: the insurer would agree to cover the drug, but the annual cost would equal the cost of insuring 20 people. While this would not affect the number of people covered during the current year, no one could predict whether such costs carried forward would mean a drop in the number of insured next year.

This is a difficult situation to be put into, but no different than the doctor at the other end of the telephone, an old friend, a thoughtful and fine physician, who was clearly torn between doing the best he could for his insured patient and doing the best he could for the poor, otherwise uninsured, of Rhode Island. This was a different interaction than the numerous calls to one of the big insurance companies or the companies they contract with to review the prior authorization requests.

Yesterday I wrote an appeal for a denial for a lift seat for an 83-year-old woman with advanced Parkinson’s disease.

Yesterday I wrote an appeal for a denial for a lift seat for an 83-year-old woman with advanced Parkinson’s disease.
Not only that, but we quite reasonably discussed the pros and cons of different approaches to treating the problem, and he even faxed me an article suggesting a different (and much less expensive) approach to treating the problem. Alas, that faxed article wasn’t useful, but the intention was the same as it was when we began our discussion. How can we balance the needs of the patient with the needs of the community? This is not a discussion we get into with other insurers. When we deal with the large, nameless companies we never perceive the tradeoff in services. The large insurers are not necessarily benign.

I have no complaint. As much as I do not like being involved in making these types of decisions, I prefer being a part of the decision-making process to being a faceless drone, appealing a denial, knowing that the particulars of the case may have no influence on the decision. And I recognize that colleagues working for the insurers are trying to make our insurance payments go further and the only way this can be done is through denials. There is, however, a difference between the clear balance required for my patient, and the random patient denied a lift seat because the guidelines evidently did not list her disease. If the hurdle is too low premiums rise, fewer government-insured patients get covered, and physician reimbursement rates go down. Or, the insurer makes more money and its stock market value increases. There is a different feel to the interaction when one concretely weighs this one patient vs. 20 unknown poor people who may pay the price next year.

We do have to get our priorities re-ordered. We have to understand what evidence does and doesn’t show, when and where costs become untenable. We need to protect treating physicians and nurses from lawsuits when they do consider cost cutting in decision-making. There is only so much in the pot. We are not doing a good job confronting this issue. v

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A Tree-bark and its Pilgrimage through History
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The armies of Nebuchadnezzar II besieged the kingdom of Judah in 589 BCE and conquered Jerusalem three years later, exiling its resident Jews to the Mesopotamian plains of Babylon. And so the psalmist lamented [Psalm 137]:

By the rivers of Babylon, there we sat down, yea, we wept. When we remember Zion, We hanged our harps upon the willows in the midst thereof.

The trees of ancient Babylon, modern Iraq, were likely not willows (genus Salix) but rather the closely related poplars (Populus euphratica). But Carolus Linnaeus (1707-1778) named them, nevertheless, Salix babylonica to acknowledge this Scriptural reference. Linnaeus believed that willows with pendulous branches, the weeping willows, appear as though they are in mourning. But long before the exile of the Hebrews, willows had occupied a special place in the daily lives of ancient cultures.

Willow trees are nearly global in their distribution; and documents from ancient Egypt, Sumer, Assyria, Greece and China all indicate a familiarity with the sap derived from the tree bark. As a remedy it served two principal uses: it reduced fever (as a febrifuge) and it allayed aches and pains (as an anodyne). Nor was the medicinal use of willow bark confined to the cultures of the Eastern Hemisphere. Many Native American tribes had also been familiar with its salutary actions long before European colonists felt morally obliged to educate them in the ways of civilization.

Despite the widespread use as a folk remedy and despite the extensive writings of Hippocrates, it was not until the 18th Century that willow bark extract finally entered the formal repertory of prescribed medicinals. Edward Stone (1702–1768), an Oxfordshire cleric and amateur scientist, was interested in the pharmacological qualities of tree bark. England, in the 18th Century, was still burdened by malaria; and quinine, the drug of choice for its treatment, was increasingly scarce since Spain controlled access to this substance obtained, then, from Peruvian cinchona tree bark. And so nibbling on tree bark – any tree bark – was a common occurrence in England. Rector Stone found the tree bark of Salix alba, the English willow, to be intensely bitter and since quinine was also bitter, he reasoned, willow bark might also share in quinine’s ability to suppress fevers.

Stone gathered a pound of willow bark and extracted a powdered residue which he tried on 50 of his church congregants. (A crude field test perhaps with neither control groups nor ethical considerations but still an earnest beginning.) He found his experimental medication “to
be a powerful astringent and very efficacious in curing agues and intermitting disorders.” And on April 25, 1763, he announced his discovery to the Royal Society in the form of a letter.

Other scientists found similar fever-allaying substances in meadow-sweet, a widely distributed, deciduous shrub of the *Spiraea* genus. It became apparent that this elusive chemical, first encountered in willow bark, was present in many botanical species, although its specific chemical structure had to await the labors of 19th Century German, Italian and French scientists who identified this bitter substance as salicylic acid (named after the willow tree genus, *Salix*).

Pure salicylic acid proved to be much too toxic as an oral medication but a variant of it, sodium salicylate, worked reasonably well. The 19th-Century discovery of coal tar as a source of dyes for textile factories created a vast new industry in Germany, employing many chemists seeking to exploit the many hidden chemicals within coal tar.

Two German industrialists, Friedrich Bayer and Friedrich Weskott, envisioned the commercial potential in marketing a salicylate-derived product for the alleviation of arthritis aches. One of their chemists, Felix Hoffman, then assessed the clinical merits of acetylsalicylic acid (ASA), a substance that had been synthesized by other chemists decades before but had not been explored clinically. The new trials were eminently successful and the Bayer Company then sought a distinctive commercial name for ASA. They fused the letter ‘a’ (from the word, acetyl), to ‘spir’ (from the genus name, *Spiraea*) and the chemical suffix, -in, to form the contrived name, aspirin. In the next century, it became the world’s most commonly employed medication.

Despite the discovery of alternate substances, aspirin continues to be guaranteed a place in the family medicine chest as a febrifuge, an anodyne and now as a prescribed anticoagulant. And the willow, once but an ornamental tree used occasionally to hang harps upon, has now made a major contribution to the comfort of humanity.

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**Disclosures**

The author has no financial interests to disclose.
Testing, Testing, Testing – When Will the Madness Stop?
LEONARD MERMEL, DO, SCM

I f you ventured upon my father, his wrinkleless face and sharp wit, you’d think he’s doing well for a man of 70 or so. He is 90. He was liberated from Buchenwald concentration camp on April 4, 1945, contracted meningitis shortly thereafter, and was one of the fortunate few to receive life-saving intravenous penicillin. He walks on his treadmill 45 minutes each morning and then briskly completes the jumbo word puzzle in the daily paper. He can converse in 8 languages, chants innumerable biblical psalms by memory, plays bridge twice weekly and he still goes to work every Friday.

Recently, my father called to tell me that he had his yearly cardiology appointment. The cardiologist performed a carotid ultrasound and my father was later called by the physician’s office with a message that the cardiologist needed to talk with him about the findings. My father is stoic but I could discern some angst in his voice. I told him that a few years ago I had spoken with his cardiologist and requested that he not do any more carotid ultrasounds on my asymptomatic father.

I called the cardiologist. He told me that my father had some unilateral stenosis, worse than in the past, and he was planning on a CT angiogram or MRI with gadolinium. I reminded him that my father is 90, he has not a hint of symptoms, he is medicated (aspirin and Plavix), and his creatinine is elevated. I said that he’d likely put him into renal failure if he proceeded and I reminded him that a few years ago I had requested that he not do any more carotid ultrasounds on my father. He said OK, he’d skip additional diagnostic tests and send my father to a very good vascular surgeon near his California home. I said no, please don’t do that. He has no symptoms and my memory is stained with the recollection of the elderly father of my dearest friend who had a stroke and died after he had an endarterectomy some years ago. As a result of this conversation, the physician said he would call my father and tell him not to worry.

My father then told me that he had his yearly cardiology appointment. The cardiologist performed a carotid ultrasound and my father was later called by the physician’s office with a message that the cardiologist needed to talk with him about the findings. My father is stoic but I could discern some angst in his voice. I told him that a few years ago I had spoken with his cardiologist and requested that he not do any more carotid ultrasounds on my asymptomatic father.

I then told my father that it took 90 years to develop some blockage in his carotid artery, so in another 90 years or so we may have to deal with it.

The future of medicine is grim unless we can encourage its practitioners to uphold the values that drove each of us to become physicians and to withstand the urge to do more, when doing less is in the best interest of our patients.

Author
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Quotes: Rx for life
“Medicine is the art of engagement with the human condition rather than with the disease.”
— Bernard Lown, MD
Nobel Peace Prize recipient, professor of cardiology emeritus at the Harvard School of Public Health; author: The Lost Art of Healing

Submitted by: Barbara H. Roberts, MD, FACC, Director, the Women’s Cardiac Center at The Miriam Hospital

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TO THE EDITOR:

Major depression is a common and debilitating illness. Over recent years, new pharmacologic treatments have been approved for this disorder, including the atypical antipsychotics. One of the benefits of these medications is their significant efficacy as augmenting agents for unipolar, nonpsychotic major depressive disorder (MDD). Aripiprazole (marketed as Abilify, Bristol-Myers Squibb/Otsuka Pharmaceuticals) was the first medication of this class approved for adjunctive treatment of MDD, and is the 5th most commonly prescribed medication in the United States in 2010. However, despite the frequency of its use, little has been described regarding events surrounding aripiprazole discontinuation. Here I describe what is, to my knowledge, the first reported case of an aripiprazole discontinuation syndrome. While directly relevant to psychiatrists and behavioral specialists, the symptoms described here are pertinent for internists and neurologists who may encounter this medication in their clinical practice.

Noah S. Philip, MD
Assistant Professor of Psychiatry and Human Behavior (clinical), Alpert Medical School of Brown University, Butler Hospital

KEYWORDS: akathisia, Aripiprazole, major depression

CASE REPORT

Ms. L, a 20-year-old Caucasian woman with MDD, was admitted to the inpatient psychiatry service for depression and suicidality. Admission physical examination and laboratory measures were normal. Admission medications were aripiprazole 15 mg/day, clonazepam 1 mg three times a day, citalopram 80 mg/day, trazodone 50 mg at bedtime, and topiramate 100 mg twice daily for migraines. There had been no changes in her medications in 4 months, which indicated that the current regimen provided little or no relief from her depression. On further evaluation, the patient reported that she had been feeling “restless inside” since aripiprazole initiation, and that this symptom contributed to severe anxiety. Aripiprazole was tapered over 48 hours and her akathisia resolved. Over the following three days her citalopram was tapered to 40 mg, in anticipation of a medication switch. On the fourth day after aripiprazole discontinuation, she reported anxiety, irritability, “feeling shaky and jittery,” which increased in intensity throughout the day. Physical and motor examinations were unremarkable and vital signs were stable. A diagnosis of serotonin reuptake inhibitor discontinuation syndrome was made, and a one-time dose of fluoxetine 20 mg was given. Lorazepam 1mg prn was provided. These symptoms continued over the following 24 hours. Citalopram was subsequently increased up to 60 mg with no effect. Lorazepam was only moderately effective, at doses up to 4 mg/day. A presumptive diagnosis of aripiprazole discontinuation syndrome was made. She was given aripiprazole 5 mg, which resulted in prompt symptomatic improvement.

DISCUSSION

To my knowledge, this is the first report of an “aripiprazole discontinuation syndrome,” characterized by anxiety and restlessness without psychomotor findings. Aripiprazole is a dopamine partial agonist, with high affinity for the D2 and 5-HT1A receptors, and antagonism at the 5-HT2A receptor. Elimination half-lives of aripiprazole and its metabolite, dihydro-aripiprazole, are 75 and 94 hours, respectively. Although the aripiprazole package insert does not report side effects that occurred after discontinuation of the medication during registration trials, there have been previous reports...
of withdrawal dyskinesias with atypical antipsychotics with prominent motor symptoms. Internet searches of lay-person message boards describe aripiprazole withdrawal, with similar reports to those described here. While aripiprazole has a high rate of discontinuation due to akathisia, this is the first case of discontinuation-induced symptoms.

I hypothesize these symptoms are etiologically related to akathisia, within the spectrum of withdrawal dyskinesias induced by an abrupt loss of antagonism at nigrostriatal D2 receptors. The patient’s presentation, with symptoms emerging at approximately the elimination half-life of aripiprazole, lack of effect of other interventions, and prompt response to re-initiation of treatment support this observation. I hope that my experience is useful, in that caution should be employed when abruptly discontinuing this frequently prescribed medication.

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2. IMS Institute for Healthcare Informatics, April 2011.

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Showcasing Bioscience in Rhode Island

DENICE SPERO, PhD
GUEST EDITOR

There are a number of well-recognized bioscience companies located in the greater Providence area. They represent a significant and growing source of jobs and future revenue, which promises to play a role in the revitalization and expansion of Rhode Island’s economy. In an effort to support these companies and to showcase their research, the Rhode Island Medical Journal is highlighting five of these innovative enterprises in this issue. The companies selected are members of the Rhode Island BioScience Leaders organization, and their research spans a wide range of science, from biologics and informatics to innovative coatings for medical devices. They include ProThera Biologics, EpiVax, Tivorsan Pharmaceuticals, BioIntraface, and VeroScience.

COMPANIES AT A GLANCE

PROTHERA BIOLOGICS was founded in 2002 by Yow-Pin Lim, MD/PhD, and Douglas Hixson, PhD, to commercialize their research on Inter-alpha Inhibitor Proteins (IAIP) for the treatment of pathological conditions caused by dysregulated inflammatory response such as sepsis/septic shock, Anthrax infection/intoxication, necrotizing enterocolitis and acute ischemic stroke.

EPIVAX, INC., founded by Anne De Groot, MD, William Martin and attorney Fred Stolle, has developed a set of immunoinformatics tools and is leveraging these tools to design better vaccines, de-immunize protein therapeutics and to develop new immune modulatory therapies (T Regulatory Epitopes) to treat a wide variety of diseases.

TIVORSAN PHARMACEUTICALS, formed by Justin Fallon, PhD, professor of neuroscience at Brown University, is a protein therapeutics company pioneering a unique approach to treating serious neuromuscular disorders, including Duchenne Muscular Dystrophy (DMD) and Becker muscular dystrophy (BMD). This method, using recombinant human biglycan (rhBGN), is based on 24 years of basic science work in the Fallon laboratory at Brown University.

BIOINTRAFACE, founded by John Jarrell, PhD, utilizes platform technologies to create economical metal oxide and polymer materials and coatings to control the bioactivity and antimicrobial properties of medical devices and implants.

VEROSCIENCE, founded by Anthony Cincotta, PhD, is developing drugs to treat metabolic and immune system disorders such as type 2 diabetes, obesity, and cancer through its platform technology, Neuroendocrine Resetting Therapy (NRT). This Tiverton-based company has the distinction of being granted FDA marketing approval for its drug Cycloset in May of 2009. Cycloset is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The Bioscience industry represents a significant part of the future knowledge economy of Rhode Island, and its continued growth and success will lead us into a future with an expanded business base creating new drugs and devices to ultimately improve human health.
ProThera Biologics, Inc.: A Novel Immunomodulator and Biomarker for Life-Threatening Diseases
YOW-PIN LIM, MD, PhD

ABSTRACT
ProThera Biologics is a development stage bio-therapeutics company in East Providence, Rhode Island. The company was founded in 2002 to focus on the critical role and commercial potential of Inter-alpha Inhibitor Proteins (IAIP) for treating acute life-threatening inflammatory diseases. The discovery research originated in the basic research laboratories of the co-founders, Yow-Pin Lim, MD, PhD, and Douglas C. Hixson, PhD, at Rhode Island Hospital, a Lifespan partner. The company is backed by the Slater Technology Fund and has received research grants from the Rhode Island State Science and Technology Council (RI STAC) as well as continuous funding from the National Institutes of Health (NIH), with several Phase I and II Small Business Innovation Research (SBIR) grants over the past 10 years. ProThera has developed a novel process to purify Inter-alpha Inhibitor Proteins from source material, and has conducted groundbreaking research into the usage of IAIP to fight systemic inflammation.

KEYWORDS: inter-alpha inhibitor proteins, sepsis, septic shock, anthrax

INTER-ALPHA INHIBITOR PROTEINS: ENDOGENOUS PROTECTIVE MOLECULES
Sepsis and Systemic Inflammatory Response Syndrome (SIRS) both refer to a severe physiochemical reaction that may occur following exposure to an infectious agent (e.g. bacterial, viral, fungal) or injury such as burn, or trauma. This systemic hyper-reaction typically includes an excessive production of cytokines, known as a “cytokine storm,” and destructive proteases, with disturbances in metabolic, oxygenation, coagulation, and vascular functions leading to multi-organ dysfunction. Consistent findings in the complex pathophysiology of systemic inflammation/sepsis has shown that SIRS activates excess systemic protease activity, neutrophil proteases, proteases of the complement and coagulation systems and matrix metalloproteinases. An array of endogenous protease inhibitors has evolved to prevent excess activation of proteases and to limit the potential injurious actions of protease activation on endothelial and epithelial tissues. Many of these protease inhibitors, such as antithrombin, alpha-1 antitrypsin, C1 esterase inhibitor, tissue inhibitor of metalloproteinases, and secretory leukocyte protease inhibitors are rapidly consumed in acute inflammatory states, often leading to a failure to appropriately regulate protease activity.

One endogenous plasma protease inhibitor family that has recently received increased attention is Inter-alpha Inhibitor Proteins (IAIP). IAIP are a family of trypsin-type protease inhibitors composed of a unique combination of polypeptide subunits (light and heavy chains) covalently linked by a chondroitin sulfate chain. Two major forms of IAIP are found circulating in human plasma:

Inter-alpha-Inhibitor (IαI), a larger molecule with 250 kDa composed of two heavy chains [H1 & H2] and a single light chain [L].

Pre-alpha-Inhibitor (PaI), a smaller molecule with 125 kDa composed of one heavy [H3] and one light chain [L].

The light chain [also termed ‘bikunin’=bi-kunitz=inhibitor with two Kunitz domains] is known to have broad inhibitory activity against plasma serine proteases such as trypsin, elastase, plasmin, cathepsin G and furin. Upon cleavage, the light chain, or bikunin, is released from the IAIP complex and rapidly excreted in urine. The high level of IAIP normally circulating in plasma, coupled with the fact that persons lacking IAIP have never been reported, suggests that these proteins have an essential physiological role. Relevant in this regard are our previous studies demonstrating that plasma IAIP level in infants are independent of gestational age and that even premature infants born at 24 weeks have similar levels to those found in adults.

Although the full extent of the physiological functions of IAIP remains to be established, numerous studies have implicated that IAIP, or the lack thereof, play a significant role in systemic inflammation. Findings from ProThera and other laboratories have shown that IAIP comprise a crucial component of the body’s protective defenses critical to modulating host response to pathological insults.
Decreased IAIP levels in life-threatening diseases

In healthy individuals, the amount of circulating IAIP in blood is relatively high (between 300-600 mg/L). However, IAIP levels rapidly decrease during systemic inflammation and sepsis. In more severe cases, IAIP may be depleted up to 90% of the baseline value found in plasma of septic patients. To date, IAIP levels have been measured in over 2,000 patients serving as study participants in systemic inflammation following bacterial and viral infections. The decreased levels of IAIP correlate strongly with the progression of the disease. As the diseases progress to more advanced and life-threatening levels, IAIP levels drop precipitously, suggesting IAIP’s clinical utility as a prognostic and therapeutic tool for monitoring disease progression and making informed treatment decisions.

Moreover, we recently studied the receiver operating characteristics of IAIP levels in 573 high-risk infants with suspected sepsis and demonstrated that IAIP level is a reliable biomarker with high sensitivity and specificity (89.5% and 99%) and a high positive and negative predictive value (85% and 98%) for neonatal sepsis. Studies have also demonstrated that the IAIP level is significantly reduced in neonates with necrotizing enterocolitis (NEC), a devastating acute inflammatory condition of the gastrointestinal tract commonly found in premature infants with birth weights of less than 1500 grams. IAIP blood levels in infants with the confirmed NEC (Bell stage 2 and 3) was found significantly lower compared to the matched age control infants with non-specific gastrointestinal disorders.

Thus, IAIP have proven to be a reliable diagnostic marker for neonatal sepsis and systemic inflammatory conditions like NEC. Since these acute conditions present a very serious threat to neonates, there is an urgent need to obtain confirmation as soon as possible. ProThera is currently conducting an NIH-funded project to develop a rapid point-of-care IAIP test that can be used to identify sepsis and necrotizing enterocolitis in high-risk infants with a simple, user-friendly and portable device suitable for use in the NICU setting.

BenEFICIAL EFFECTS OF IAIP THERAPY IN SYSTEMIC INFLAMMATION

As IAIP are found abundantly in human plasma and can be extracted and purified in high yield by a scalable production process similar to other blood derived products such as albumin and immunoglobulin (IVIg), a replacement IAIP therapy to reverse the decrease in systemic levels in pathological conditions is feasible.

Using a rat model of polymicrobial sepsis (Cecal Ligation and Puncture), we demonstrated dramatic improvements following treatment with human plasma derived IAIP administered 1 hour after sepsis induction as evidenced by recovery of hemodynamic stability, decreased organ injury, increased survival (2-3 fold) and arrested progression of sepsis. Similar beneficial effects were achieved even if the IAIP administration was delayed 10 hours after the sepsis challenge, although at this point, the disease had progressed to a severe stage with at least one organ dysfunction.

Similarly, studies in the neonatal model of endotoxin-induced systemic inflammation revealed that administration of IAIP significantly improves survival of the experimental animals. The therapeutic effects of IAIP were also demonstrated in live organism models of sepsis using E. coli and Group B hemolytic Streptococcus (GBS), two of the most relevant pathogens in sepsis in human infants. Moreover, IAIP was found to attenuate the marked increase in pro-inflammatory cytokine TNF-alpha and to augment anti-inflammatory cytokine IL-10 in the septic animals. These results suggest that administration of IAIP exerts potent immunomodulatory activity that leads to a significant beneficial effect in adult and neonatal sepsis models. At least three distinct mechanisms in the inflammatory pathways contribute to the protective effects of IAIP: 1) inhibition of the serine proteases [elastase, cathepsin G, and several others]; 2) modulation of pro-inflammatory cytokines (TNF-alpha) and 3) blockage of excess complement activation (C5a).

IAIP IN BIODEFENSE APPLICATIONS

Some scientific progress has been made in developing countermeasures for various biowar pathogens in the post-9/11 era. However, it is becoming clear that the “one bug-one drug” approach such as vaccines or antiserum specific against a single agent is not a practical or sustainable approach.

The life-threatening consequences following exposure to biowar pathogens do not typically arise directly from the causative agent, but from dysregulated host response leading to lethal systemic inflammation. As potent immunomodulators, IAIP can serve as a “first line of defense” in providing crucial protection against deadly acute systemic inflammation triggered by biowar pathogens. In addition, as a broad-spectrum serine protease inhibitor, IAIP has a capability to block furin, a cell membrane-associated endogenous serine protease that plays a critical role in the anthrax pathogenesis and several viral diseases. As ProThera’s IAIP therapy is independent from the causative agent [bacterial/viral or toxin], it can be applied immediately following exposure without risk of overdosing or misdiagnosis. Subsequently, once the causative agent is identified and confirmed, a more specific and targeted therapy with antibiotics or antiviral drugs to eliminate the pathogens can be initiated.

ProThera’s current focus is targeted on Anthrax intoxication and infection, where the company has generated robust and promising data in the experimental animals, and is conducting confirmatory studies in large animals including non-human primates (baboons). As the biodefense focus has shifted from the “single agent specific” countermeasures...
to more “universal” defenses that address multiple pathogens, IAIP not only can potentially serve as an effective broad-spectrum therapy against biothreat pathogens (CDC Category A, B and C) but also against naturally emerging pathogens. To this end, early investigations have also indicated encouraging protective effects of IAIP in viral diseases [Influenza A and Dengue virus infection].

**IAIP IN OTHER ACUTE INFLAMMATORY DISEASES**

While ProThera is mainly focusing on the development of IAIP as novel therapeutic proteins in systemic inflammation/sepsis and Anthrax biodefense, recent investigations of IAIP effects in hypoxic and ischemic brain injury have revealed exciting results as well. In collaborations with Barbara Stonestreet, MD, at Women & Infants Hospital and Steve Threlkeld, PhD, at Rhode Island College, ProThera has been able to demonstrate the beneficial effects of IAIP in hypoxic and ischemic brain injury models in fetal sheep and neonatal/adult rats.

IAIP have been detected in neurons, astrocytes, and meningeal cells of the brain and, may function as endogenous neuroprotective molecules. Moreover, studies have observed significant decreases of IAIP in brain tissues of experimental animals following ischemia-reperfusion injury. IAIP might serve as a novel agent to prevent/attenuate brain damage in infants at risk for mental/developmental disorders such as cerebral palsy and in adults following acute ischemic stroke.

**SUMMARY**

ProThera Biologics develops novel products that are based on its proprietary technology to produce and treat using Inter-alpha Inhibitor Proteins. The key to ProThera’s strategy is a single biological product to be developed for the treatment of widespread pathological conditions caused by dysregulated inflammatory response such as sepsis/septic shock, Anthrax infection/intoxication, necrotizing enterocolitis and acute ischemic stroke. ProThera offers a rational targeted solution to treat deadly diseases by combining both the predictive test and the effective replacement therapy of natural occurring Inter-alpha inhibitors. The successful development of an efficient and scalable manufacturing process combined with the implementation of viral inactivation steps will ensure a safe and effective IAIP product for testing in humans.

**References**


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Building Better Biotherapeutics and Vaccines by Design: EpiVax, Inc., an Immunology Company

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ABSTRACT

EpiVax, Inc., is an early-stage informatics and immunology biotechnology company in Providence, Rhode Island. It applies computational tools to harness immunity in three major areas: immunomodulation, biotherapeutic immunogenicity risk assessment and de-risking, and vaccine development. Immunotherapy, bio-better and vaccine candidates under development at EpiVax promise to improve the health outcomes of millions of people affected by devastating immune-related diseases.

KEYWORDS: vaccines, immunoinformatics, immunotherapy, immunomodulation, autoimmune diseases

A BRIEF HISTORY OF EPIVAX

A talented post-baccalaureate, a statistics major, and a professor who aspired to develop an HIV vaccine are at the root of EpiVax. Gabriel Meister, Bill Jesdale and Anne S. De Groot, MD, were members of the TB/HIV Research Lab team in Brown University’s BioMed Center that created two novel computer-driven tools, EpiMer and EpiMatrix, between 1992 and 1996. These ‘epitope discovery’ algorithms generated the foundation for a whole suite of advanced in-silico tools that now form the core of EpiVax, Inc., a privately held immunoinformatics company in Providence. The late Michael Lysaght, an approachable and optimistic Brown professor of biotechnology, was another instrumental person in the company’s establishment; he recognized the promise of EpiVax and connected the founders to the Slater Center for Biotechnology, a source of funding that brought the technology out of the academe into the entrepreneurial world in 1998. With the addition of a programming expert (Bill Martin) and a formidable lawyer (Fred Stolle), a company was born.

Fifteen years later, EpiVax has evolved into a powerhouse of ideas that is changing the way that we think about vaccines and biotherapeutics. EpiVax has also been the source of an unusual spin-out, the Institute for Immunology and Informatics [established in 2008] at the University of Rhode Island, which has exclusive access to the EpiVax technology to research and develop vaccines for neglected tropical diseases and other targets. Team members at EpiVax are now working on a second spin-out devoted to another promising technology that may change the treatment of autoimmune disease.

IN-SILICO DESIGN FOR VACCINES AND PROTEINS

Vaccines are among the most important inventions of modern medicine, but the technology for making vaccines was based on empirical rather than hypothesis-driven science until 1996, when molecular biology made bacterial and viral proteins interpretable by computers. EpiVax has harnessed the availability of whole genomes to develop bioinformatics algorithms and apply them to a four-point vaccine design strategy. Immunoinformatics tools are first used to sort through thousands of potential vaccine candidates in a pathogen’s genome, comparing those sequences to similar pathogens and identifying sequences that would trigger a human immune response. Protein sequences are then mapped for short, linear, putative T cell epitopes. These epitopes are synthesized as peptides and evaluated in vitro and in vivo for human leukocyte antigen (HLA) binding and antigenicity in survivors of infection or vaccinees. Finally, the optimal composition of immunogenic sequences to drive an effective human immune response is computationally derived (iVAX software suite), and prototype epitope-based vaccines are
evaluated for immunogenicity and efficacy in humanized transgenic mice. Using this approach, we have demonstrated pre-clinical proof-of-concept for smallpox and tularemia prophylactic vaccination and therapeutic immunization for *H. pylori* infection.1-4

The genomes-to-vaccine strategy has two important advantages. First, it strips a pathogen down to the minimal essential antigens, eliciting robust and sustained protective immunity while eliminating non-essential information that could lead to diminished protective immunity and/or immunopathology sometimes associated with whole organism vaccines. This approach may appear to handicap vaccine design because vital elements (i.e., adjuvant, carrier structure) that are normally part of a pathogen are removed, but it creates a valuable opportunity that forms the second advantage. One can combine this novel approach with best-in-class adjuvant and delivery technologies for optimal vaccine construction.

This methodology also forms the core of immunogenicity screening, the process by which protein therapeutics are evaluated for their potential to elicit harmful responses that would impede their effectiveness. Non-vaccine protein therapeutics risk causing harmful immunoreactions, which can render a biologic ineffective and severely compromise patient health. For example, the induction of antibodies known as “inhibitors” against factor VIII in the treatment of hemophilia is a sign of therapeutic protein immunogenicity.5,6 In 2001, antibodies to a commonly used therapeutic protein drug Erythropoietin, were linked to transfusion dependent anemia.7 Consequently, unwanted immunoreactions to biologics are a major concern for physicians and drug developers.

EpiVax has thus developed an entire suite of immunoinformatics tools for prospectively identifying and reducing protein therapeutic immunogenicity “in silico,” a process that dramatically reduces the time and effort involved, allowing drug developers to accelerate the pre-clinical development of their protein products. The tools are organized in an interactive website called the ISPRI [Interactive Screening and Protein Reengineering Interface] system. Using the ISPRI system, researchers have the ability to screen the protein sequences of product candidates for the presence and immunogenic potential of putative T cell epitopes [EpiMatrix] and epitope clusters [ClustiMer]. Protein sequences can be ranked for immunogenic potential in comparison to known proteins on a normalized scale, and an interactive protein reengineering tool [OptiMatrix] allows researchers to modify, or deimmunize, T cell epitope clusters in real time by optimizing the amino acid sequence so that it is no longer able to interact with T cells.

The EpiMatrix toolkit has been extensively validated internally and externally, with several key publications demonstrating the technology and rigorous testing procedures using known protein therapeutic targets.8,9 In addition, EpiVax incorporates exclusive knowledge of the impact of Tregitopes (T cell regulatory epitopes) on the immunogenicity of protein therapeutics in clinical use, leading to higher accuracy in immunogenicity predictions.

**TREGITOPES: AN EPIVAX DISCOVERY AND IMMUNOMODULATION POWERHOUSE**

The discovery of Tregitopes, or “T Regulatory Epitopes” in one of the most common proteins found in blood (immunoglobulin G, or IgG) can be attributed to keen observation on the part of the scientific team at EpiVax. Tregitopes turned up regularly in the immunogenicity screens that were performed by the scientists at EpiVax as soon as the ISPRI tools were being applied to monoclonal antibody therapeutics, but were only recognized for their regulatory potential by De Groot and Martin in 2008.10 Tregitopes act as a natural ‘off switch’ for the immune system. They are naturally part of the arms (Fab) and stem (Fc) of human IgG and are thought to balance the inflammatory triggers that are present in the re-arranged, or hypervariable segments [variable loops] of the antibody arms. Tregitopes are also found in Intravenous IgG (IVIG), a blood-derived product that is used clinically to control autoimmune conditions.11 Indeed, some of the anti-inflammatory activity of IVIG may be due to the presence of Tregitopes.12

The Tregitope discovery has been validated in a range of standard preclinical models and by collaborating laboratories, where Tregitopes have been shown to suppress and treat autoimmune disease and allergies,13 and to effectively suppress the immunogenicity of co-administered proteins.14,15 In addition, Tregitopes have been shown to modify immune
responses to biotherapeutics, such as FVIII. In vitro, co-incubation of proteins with Tregitopes leads to suppression of effector cytokine and chemokine secretion, reduced proliferation of effector T cells, and expansion of antigen-specific adaptive Tregs. In vivo, co-administration of Tregitopes with a wide range of proteins (e.g., FVIII, ovalbumin, and auto-antigens) leads to antigen-specific suppression of T cell and antibody responses.

Funding for research on Tregitopes has been flowing. For example, EpiVax recently received a Small Business Innovation Research (SBIR) grant for $600,000 to explore the use of Tregitope in facilitating tolerance to the life-saving enzyme replacement therapy for Pompe’s disease. In 2012 alone, EpiVax scientists were able to obtain $3.4 million in National Institutes of Health (NIH) funding for development of Tregitope therapies; the group has been awarded more than $6 million in grants to develop Tregitopes over the past few years. Once the right formulation of Tregitopes is identified, they pass the usual regulatory hurdles, their use is expected to have a radical impact on the clinical management of autoimmunity, transplant rejection, and protein replacement therapies.

CONCLUSION

EpiVax will continue to apply the experience gained from these basic research efforts to practical problems in immuno-therapy and vaccine design. In the field of protein therapeutics, we are broadly recognized as thought leaders, and we expect to maintain this position through our discovery work on Tregitopes and tolerance. In addition, our work on epitope-driven vaccines – such as the smallpox, Tularemia, and H. pylori vaccines in our pipeline – has begun to demonstrate the power of T cell epitopes to generate protective immune responses. We will combine these breakthroughs with advancements in delivery and formulation to bring novel immunomodulatory therapies and vaccines to market.

References


Authors

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On the Path to a Duchenne Muscular Dystrophy Therapy

JUSTIN R. FALLON, PhD

ABSTRACT
Duchenne Muscular Dystrophy (DMD) is a devastating inherited disease of children with no effective therapies. Here I discuss the landscape for new treatments and the history, current status and prospects for our work developing recombinant biglycan as DMD therapy.

KEYWORDS: Biglycan, Duchenne Muscular Dystrophy, neuromuscular disorders

INTRODUCTION
Duchenne Muscular Dystrophy (DMD) is the most common form of muscular dystrophy. DMD is caused by mutations in dystrophin, a protein that is essential for maintaining the integrity of both cardiac and muscle cells [Emery, 2002; Nowak and Davies, 2004]. Starting at about age four, the affected boys exhibit muscle weakness and most are in wheelchairs by their teens. Death is usually caused by failure of the diaphragm and/or cardiomyopathy. Patients rarely survive past their mid-twenties. Effective treatments for this devastating disease are urgently needed.

Current therapies for muscular dystrophies are not disease-modifying and have limited impact on the clinical outcome. The current standard of care is steroids, either prednisone [Mendell et al., 1989] or Deflazacort [a synthetic prednisolone; Biggar et al., 2004]. These agents impede inflammatory fibrosis and improve muscle strength. Unfortunately, after an initial increase in strength in the first six months to one year, patients on these medications often exhibit a slow decline after 18 months [Griggs et al., 1991]. Both these drugs have significant side effects that can limit their use. Physical rehabilitation, including stretching exercises, can maintain greater flexibility in muscles susceptible to contracture formation. However, most methods of rehabilitation become ineffective once the disease reaches its greatest severity by the second decade of life.

The good news is that a wide range of DMD therapeutic strategies are under investigation, with some promising compounds in late-stage clinical trials. Gene therapies seek to replace, repair or override the mutated dystrophin gene. The most advanced of this class employ a dystrophin minigene delivered by adeno-associated viral vectors [Blankinship et al., 2006]. Since muscle is a regenerative tissue, cell-based therapies have drawn much attention. However, it has been difficult to achieve sufficient engraftment of the transplanted cells. Recent approaches using mesangioblasts in mouse models have started to break down this barrier [Sampaiolesi et al., 2003], but human studies are still in the planning stages.

Pharmacological interventions include small molecule drugs to induce stop codon read through, which would be effective for ~15% of DMD patients. Ataluran, whose development was inspired by the observation that gentamicin has such activity [Wagner et al., 2001], has been tested in a large clinical trial [PTC Therapeutics]. Other pharmacological therapies are also being pursued that either improve muscle performance or mitigate the pathological process in DMD muscle. These include using humanized antibody fusion proteins that neutralize myostatin and related inhibitors of muscle growth. Unfortunately, this class of compounds has not yet proven effective in clinical trials.

Finally, treatments aimed at reducing muscle fibrosis are also in development. Since scarring interferes with the function of remaining normal muscle and degrades the stem cell niches necessary for regeneration, such treatments could confer significant benefit to the patients.
Exon skipping is an exciting new approach that employs synthetic oligonucleotides to excise selected regions of the mutated dystrophin mRNA by regulating alternative splicing (Ci-rak et al., 2011). The product is a ‘Becker-like’ dystrophin protein that, while truncated, harbors activity that would be expected to confer significant benefit to patients. Early small-scale studies in humans targeting exon 51 using two different oligonucleotide chemistries have yielded encouraging results and late-stage trials are currently underway [drisapersen and etepliren; GlaxoSmithKline and Sarepta, respectively]. Both studies have shown that the expression of (truncated) dystrophin is restored in a subset of muscle fibers. Most importantly, the subjects have maintained ambulation to a remarkable degree when compared to historical controls. These compounds are a leading example of personalized medicine, since the therapy is tailored to specific mutations. However, since mutations can occur virtually anywhere in the very large dystrophin gene, a given compound can only target a subset of patients. For example, exon 51-targeted oligonucleotides could benefit about 15% of patients. With current methodology it is estimated that additional compounds could be developed that would collectively target about 50% of patients. A further limitation of exon skipping is that none of the current oligonucleotide chemistries target the heart.

One of the most long-standing and appealing pharmacological approaches to treat DMD is the upregulation of utrophin, an autosomal homolog of dystrophin (Khurana and Davies, 2003). Utrophin is normally expressed at high levels during fetal development and in early childhood, but in the mature animal it is restricted to the neuromuscular and myotendinous junctions. The high levels of utrophin in young children is likely one of the reasons that the clinical manifestations of DMD only appear after about 4 years of age. Genetic studies have shown that if utrophin is up-regulated it can functionally replace dystrophin in mdx mice [Tinsley et al., 1998]. Muscle death is prevented and muscle function is restored to wild-type levels. A utrophin-targeted approach is also appealing since it targets an endogenous, fetal program that could compensate for the loss of dystrophin. Finally, a utrophin-based therapy should target all DMD patients, regardless of mutation.

**THE PATH TO BIGLYCAN AS A DMD THERAPEUTIC**

Our laboratory is developing a recombinant form of the endogenous extracellular matrix protein biglycan as a DMD therapeutic. Although I did not know it at the time, this idea can be traced back to when I was a postdoctoral fellow with U.J. McMahan at Stanford. The goal of these studies was to identify and characterize the proteins that organize the muscle cell membrane at the synapse. We discovered agrin, an extracellular matrix protein that organizes acetylcholine receptors into discrete domains on the muscle cell surface [Fallon et al., 1985; Nitkin et al., 1987]. In my own laboratory we went after the cell surface proteins that bind agrin and
mediate its activity. This effort led to dystroglycan, which had just been found to be a key member of the complex of proteins that associate with dystrophin [Bowe et al., 1994]. Utrophin was known to be at the neuromuscular junction – even in DMD. We began to wonder whether we had tapped into a mechanism that regulates utrophin expression. If so, we realized that it might be possible to harness this pathway to create a new DMD treatment.

We sought to explore this new hypothetical pathway. This work was carried out in my laboratory at Brown University. I have been incredibly fortunate to work with a team of remarkably talented and dedicated scientists. These include Mark Bowe, Katherine Deyst, Mike Rafii, Hiroki Hagiwara, Mary Lynn Mercado, Beatrice Lechner, Sarah Mentzer, Carolyn Schmiedel and Alison Amenta. An especially important member of the team is Beth McKechnie, who has been on this project for over 20 years and has contributed many of the key insights that have brought us to the cusp of clinical trials.

The first clues came from biochemistry; we looked for additional dystroglycan binding proteins and discovered biglycan in this complex [Bowe et al., 2000]. Continuing down this biochemical path, we found that biglycan also binds to alpha and gamma sarcoglycans [Rafii et al., 2006]. This result was exciting because these sarcoglycans are only found in the two tissues affected by DMD: skeletal muscle and heart. We went on to investigate biglycan function using mutant mice created by Marian Young at the NIH [Young and Fallon, 2012]. These studies yielded the critical information that biglycan is important for the proper expression of several dystrophin-associated proteins such as the sarcoglycans and an intracellular signaling complex including nNOS (neuronal nitric oxide synthase; Mercado et al., 2006). However, from a DMD therapy viewpoint, the critical finding was that biglycan also regulates utrophin in early development [Amenta et al., 2011]. We now had a link to a potential therapeutic pathway.

The transition from an idea to a viable therapeutic is complex and lengthy. However, the first question is simple – can we produce a candidate compound and show that it can be delivered in a form, route, dose and frequency that is amenable to use as a drug? We therefore produced recombinant biglycan (rhBGN) and asked if it was active in mouse models of DMD. Remarkably, systemically-delivered rhBGN up-regulated utrophin at the muscle membrane and improved the health and function of the dystrophic muscle (Amenta et al., 2011). Equally important, rhBGN was active at doses [2-10mg/kg] and frequencies (once injection every two weeks) that are suitable for use in patients.

With these first results in hand we began a concerted effort to bring rhBGN to clinical trials. These efforts require expertise beyond that of an academic laboratory. Therefore I cofounded Tivorsan Pharmaceuticals, a Rhode Island-based company committed to develop rhBGN as a therapeutic for DMD (www.tivorsan.com). Tivorsan has marshalled the necessary regulatory, manufacturing and clinical expertise that will be needed to complete preclinical work and initiate clinical testing.
FUTURE DIRECTIONS

Biglycan could have therapeutic benefit in amyotrophic lateral sclerosis (ALS). ALS is a neurodegenerative disease marked by the loss of upper and lower motor neurons (Pasinelli and Brown, 2006). However, the first sign of pathology is destabilization of the nerve-muscle synapse, resulting in deafferentation and muscle paralysis. A therapy that stabilizes this synapse could thus prolong function in ALS patients.

As discussed above, our path to biglycan stemmed from an inquiry into the how nerve-muscle synapses are formed. In an exciting recent finding we showed that biglycan binds to the receptor tyrosine kinase MuSK, the central organizer of this synapse. Further, biglycan is important for synapse stability. These basic science findings raise the possibility that rhBGN could stabilize the compromised synapses in ALS patients and delay the progress of the disease. Experiments to test this idea in mouse models of ALS are underway in the laboratory. If these studies in model organisms are favorable, we will be well positioned to initiate testing of rhBGN in ALS patients.

References


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BioIntraface®: The Next Quantum in Medical Devices

JOHN D. JARRELL, PhD, PE

ABSTRACT
BioIntraface®, Inc., located in Riverside, Rhode Island, was formed in February of 2009 to commercialize its biomaterials surface treatment technologies. The platform technologies involve the creation of economical, multifunctional metal oxide and polymer materials and coatings to control the bioactivity and antimicrobial properties of medical devices and implants. Biointraface® has continued optimizing and validating coatings for promising applications in orthopaedics, dentistry, catheters, wound dressings, topical antimicrobial products, and cosmetics applications. It has also obtained third-party verification of ISO biocompatibility testing for eight coatings with increasing levels of antimicrobial agents, where no cytotoxicity was indicated and similar tests showing long lasting antimicrobial efficacy against multiple strains of bacteria.

KEYWORDS: antimicrobial coatings, medical devices, metal oxide and polymer coatings

UPGRADING THE SURFACE OF MEDICAL DEVICES
Silicones, such as polydimethylsiloxane (PDMS), have a long history of use in medical applications, beginning with a bile duct repair by Lahey in 1946, an artificial urethra in 1948 by DeNicola and a hydrocephalus shunt constructed by Holter for his son in 1956. The wide applicability of PDMS to tissue contact is due to its generally low toxicity and biocompatibility, which was investigated in a publication by Rowe, Spence and Bass in 1948 and continues to be extensively studied for general biomedical suitability and specific implant applications.\(^1\) From the perspective of chemistry, the strength of the two oxygen and two carbon (methyl group) bonds per silicon atom gives the material thermal stability up to 400°C, allowing autoclave sterilization, and preventing chemical decomposition under most physiological conditions.\(^7\) This inertness has a downside for some applications; PDMS tends to poorly facilitate protein and cell attachment, resulting in poor soft-tissue integration, a lack of skin sealing around percutaneous devices and localized foreign body response with subcutaneous implants.\(^8\)

Titanium has been recognized as the material of choice for many implant applications, especially when contacting bone or to limit contact with nickel. More recently, it has been applied to osseointegrated trans-epithelial prosthetic fixation for dentistry and experimental limb attachment.\(^9\) It is the presence of a spontaneous and self-regenerating passive oxide layer on titanium’s surface that is primarily responsible for the corrosion resistance and biointegrative properties of this metal.\(^10\-13\) Titanium oxide reduces local inflammatory responses, lowers the presence of local reactive oxygen species, and dynamically incorporates elements from surrounding tissues after implantation.\(^14\) Because of the properties of this (and other) refractory metal oxides, the problem of aseptic osseointegration of medical devices is all but solved.

Polyether ether ketone (PEEK) is increasingly finding use in orthopaedic applications like spinal and trauma implants. PEEK has a good combination of formability, mechanical properties, biocompatibility and radio transparency, but lacks some of the bioactive and integrative properties identified with titanium-based implants. Here we explore the use of metal-organic derived, hybrid coatings, as a means of creating antimicrobial treated PEEK biomaterials with a titanium oxide surface interface.

BIOMATERIALS AND BIOFILMS
While biomaterials like titanium, stainless steels, cobalt chrome, polyether ether ketone (PEEK), silicone and polyvinyl chloride (PVC) have been widely used for medical devices, catheters and implants, none of these materials provide active resistance to bacterial infection or prevents biofilm formation. Biofilm formation is a five-step process involving reversible attachment, irreversible attachment, maturation I, maturation II and dispersion.\(^1\) Identification of the mechanisms at work in each of these steps has aided investigators in developing targeted approaches.\(^1\-3\) These include prevention of bacterial attachment, encouraging release,
BI's coatings are based on a new hybrid materials technology using metal-organic precursors to create both metal oxide and polymer coatings from liquid solutions. Each component of the coating is already in common use in other medical devices. The prospective coatings are optimized using an innovative rapid screening cell culture platform, inspired by the approaches used by large pharmaceutical companies for new drug discovery.

These promising in vitro results (Figure 1) have been followed by several small animal studies conducted at both Brown University and Rhode Island Hospital. Early applications that have been considered include catheters, fracture fixation devices, and transcutaneous osseointegrative devices (bone-anchored prosthetics for limb replacement).

**BIOSCIENCE**

**FIGHTING INFECTION**

Several types of surface treatments have been investigated to reduce bacterial growth and infection, including: the introduction of nano surface topography, manipulation of surface chemistry and the permanent attachment of antibiotic drugs to implants to inhibit bacterial attachment, growth and resulting biofilm formation. Nano surface modifications are well-developed and have been demonstrated to facilitate healing and reduce the growth of bacteria, but not at the log scale level. University of Pennsylvania researchers developed methods for permanently attaching antibiotic drugs to medical devices with good in vitro results against bacteria, but raise the concern of preferentially selecting and encouraging development of drug resistant bacterial infections. Due to the recent increased number of antibiotic resistant bacteria, silver has been studied extensively as an alternative to antibiotics. Silver ion delivery has a history of use on medical devices, does not contribute to drug resistance and provides broad spectrum antimicrobial protection

**BIOACTIVE AND ANTIMICROBIAL COATINGS**

Research conducted at Brown University, Rhode Island Hospital and in collaboration with the U.S. Department of Veterans Affairs shows that metal oxide and polymer hybrid surface treatments have the ability to prevent bacterial attachment and eliminate bacterial growth on the log-scale, while promoting healthy cell growth. These coatings are based on a new hybrid-materials technology using metal-organic precursors to create both metal oxide and polymer matrix coatings from liquid solutions. Each component of the coating is already in common use in other medical devices. The prospective coatings are optimized using an innovative rapid screening cell culture platform, inspired by the approaches used by pharmaceutical companies for new drug discovery. Promising in vitro results have been followed by several small and large animal studies conducted at both Brown University and Rhode Island Hospital and third-party in vitro ISO biocompatibility testing and AATCC antimicrobial testing. The coating matrices have novel electro-chemical and controlled release properties to deliver bioactive agents, including metal ions like silver. The main advantages of these treatments over competitive delivery technologies is the ability to control the silver release properties and balance them with the bioactive properties of titanium oxide, the economical methods of application and the formation of a chemical bond between the treatment and the surface of the medical device.

**Figure 1.** In vitro results with glass discs with no coating (A), Hybrid #1 coating (B), amorphous Titanium Dioxide only (C), and Hybrid #2 coating (D) incubated in Petri dish with E. Coli-coated agar. Note large zone of bacterial inhibition surrounding disc coated with Hybrid #1 and smaller zone surrounding disc coated with Hybrid #2 (arrows). Right image is a close up view of bacteria free zone around Hybrid #1.
BioIntraface®, Inc. (BI), was formed in February of 2009 to commercialize the biomaterials surface treatment technologies. The platform technologies involve the creation of economical, multifunctional metal oxide and polymer materials and coatings to control the bioactivity and antimicrobial properties of medical devices and implants. In 2009, the BI team won the Rhode Island Business Plan Competition, which was followed in 2010 by a Rhode Island Innovation Award in the category of Health Care & Biotechnology Innovations. In 2011, BI was issued two U.S. patents from their original filings and their first international patent claims were allowed in Australia and Mexico, with additional applications pending in the United States, the European Union and six additional industrialized nations. BI has continued optimizing and validating coatings for promising applications in orthopedics, dentistry, catheters, wound dressings, topical antimicrobial products, and cosmetics applications. It has also obtained third-party verification of ISO biocompatibility testing for eight coatings with increasing levels of antimicrobial agents, where no cytotoxicity was indicated and similar tests showing long lasting antimicrobial efficacy against multiple strains of bacteria. On the strength of this technology, BI is raising additional funding to launch multiple companies focused on specific antimicrobial product lines. In 2011, the establishment registered with the FDA as an initial importer of medical devices and plans to begin to obtain FDA approval for upgraded revision of specific device lines for distribution into the United States, Germany, France and the United Kingdom once adequate funding is obtained.

The initial management objective has been to create the infrastructure to warehouse and distribute branded devices into markets ready for a high-value line of antimicrobial devices and implants, while adding in-house manufacturing, quality and R&D capacity. In 2012, BI moved into a pilot manufacturing facility at Quonset to expand processes and research capacity to facilitate rapid growth and a robust new product pipeline.

Leadership

BI management is led by John D. Jarrell, PhD, PE, who is president and founder, with 25 years of experience in failure analysis and product liability of medical devices.

Christopher T. Born, MD, FAAOS, FACS, professor of orthopedics at Brown University, is head of the BI Clinical Advisory and Chief Technical Officer (CTO).

Brown University Associate Professor of Medical Science and Engineering Jeffrey Morgan, PhD, is a co-founder and head of the Scientific Advisory Board. For more information: www.biointraface.com

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VeroScience: Applying Nature’s Genius to Help Improve the Human Condition

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ABSTRACT

VeroScience is a biotechnology company in Tiverton, Rhode Island, focused on the development of therapies and products to improve human health. The company has a strong pipeline of metabolic disease products and therapies for immunological disorders. A major platform technology of the company, Circadian Neuroendocrine Resetting Therapy, is utilized as a generator of multiple therapeutic strategies to treat a variety of disease states. The circadian timed daily [morning] administration of Cycloset\textsuperscript{®}, a quick release formulation of bromocriptine mesylate, a dopamine agonist, was developed for the treatment of type 2 diabetes using this platform technology.

KEYWORDS: Neuroendocrine Resetting Therapy, type 2 diabetes, cycloset, glycemic control

INTRODUCTION

Since 2001, VeroScience has been in the business of developing drugs to treat metabolic and immune system disorders such as type 2 diabetes, obesity, and cancer through its platform technology, Neuroendocrine Resetting Therapy (NRT). The platform technologies of the company were co-developed by its founder, Anthony Cincotta, PhD, largely in academia during the 1980s, incorporated into a biotechnology company that he founded in 1990 and directed until 2000, ErgoScience, and then ultimately transferred to VeroScience in 2006. NRT is based on research demonstrating that normal physiology is regulated in large part by the temporal interactions of circadian neuroendocrine oscillations within certain centers of the brain. Alterations in the phase relations of these circadian activities alter physiological status of the organism. Resetting aberrations in these activities is an effective means of treating several neuroendocrine disorders.

In 1997, data presented at the 57th Annual Scientific Sessions of the American Diabetes Association (ADA) reported the results of three nationwide, multi-center trials, known as “TRIAD – Time Regulated Intervention in Adult Diabetes” conducted by ErgoScience demonstrating that Ergoset, a timed quick-release formulation of a dopamine agonist [bromocriptine mesylate], used alone or in combination with oral antidiabetic agents, was shown to produce statistically and clinically meaningful reductions in blood sugar levels in obese, type 2 people with diabetes when compared to placebo. In 1998, ErgoScience filed for Food and Drug Administration (FDA) approval of the drug. The FDA initially issued a non-approval letter, owing to concerns about safety of the active agent, bromocriptine. ErgoScience appealed that decision and the FDA issued an approvable letter to ErgoScience for Ergoset in 1999. Thus began efforts for the successful transition of NRT, including Ergoset, to VeroScience and eventual approval of the drug marketed as Cycloset.

After securing private funding in 2003 and 2006, VeroScience was able to initiate the required FDA 3,000-person, one-year trial to evaluate the overall safety and cardiovascular safety of Cycloset. The trial was conducted at 74 sites in the United States, including 22 Veterans Affairs Medical Centers. Briefly, patients with type 2 diabetes were randomized 2:1 to bromocriptine-QR (Cycloset) or placebo in conjunction with the patient’s usual diabetes therapy (diet controlled only or up to 2 anti-diabetes medications, including insulin). The all-cause safety endpoint was the occurrence of any serious adverse event (SAE). In a pre-specified analysis, the frequency of cardiovascular (CVD) events defined as a composite of myocardial infarction, stroke, coronary revascularization, hospitalization for angina or congestive heart failure was evaluated.
RESULTS

Results showed that 176 (8.6%) people in the bromocriptine-QR group reported SAEs compared to 98 (9.6%) in the placebo group, and a lower percentage of people reported a CVD endpoint in the bromocriptine-QR group; 37 (1.8%) versus placebo, 32 (3.2%). In fact, these results demonstrated a 40% relative risk reduction in the CVD endpoint among those taking bromocriptine-QR. Nausea was the most commonly reported adverse event in the bromocriptine-QR group. Mean HbA1c was lower in the bromocriptine-QR group than in the placebo group at one year. 3

Based on these safety and efficacy results, the FDA granted marketing approval to VeroScience for Cycloset in May of 2009. Cycloset is approved by the FDA, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It has been shown to reduce post-prandial hyperglycemia without increasing insulin levels and while not increasing the risk for hypoglycemia or weight gain. 2 Cycloset was the first diabetes therapy to be approved under the FDA's new cardiovascular guidelines (December 2008) requiring evidence that type 2 diabetes medications do not increase the risk of cardiovascular disease. 4 In additional analyses, five times as many Cycloset-treated patients achieved an A1C goal of ≤7.0% compared to placebo. 5 Cycloset is marketed in the United States by Santarus Pharmaceuticals, Inc., in San Diego, California.

BACKGROUND – PRECLINICAL STUDIES AND DEVELOPMENT RATIONALE

Decades of work investigating animals in the wild that undergo marked annual cycles of metabolism revealed that seasonal shifts from the obese, insulin-resistant condition to the lean, insulin-sensitive state are driven by shifts in the circadian phase relations of specific hypothalamic neurophysiological events.

By mimicking this neurophysiological shift by pharmacological interventions, it is possible to effectuate the predicted shift in seasonal metabolism in either direction, to or from the insulin-sensitive state. Similar approaches in a variety of genetic and diet-induced animal models of type 2 diabetes have produced similar results. 1

Animals in the wild under natural conditions express a marked annual cycle of metabolism, shifting between lean insulin-sensitive, and obese insulin-resistant states at specific times of year. Seasonal insulin resistance imparts the ability to withstand long periods of ensuing low food availability and this seasonal mechanism appears to have evolved as a survival strategy to circumvent such an environmental stress. Among the many examples of such seasonal variations in metabolism are bear hibernation, bird migration, and squirrel overwintering. Available evidence indicates that this seasonal mechanism evolved and has persisted over at least 400 million years. Neuroendocrine and neurophysiological studies of seasonal animals among all the major vertebrate classes have implicated an important role for circadian dopaminergic input to the hypothalamus and specifically to the mammalian biological pacemaker (the suprachiasmatic nuclei, SCN) in the regulation of whole-body fuel metabolism. 1

METABOLIC DISEASE

By employing methods that mimic the neurobiochemical physiology responsible for the seasonal shift from the obese, insulin-resistant condition to the lean, insulin-sensitive state common among vertebrate species in the wild, it is possible to develop new treatment strategies for human metabolic diseases such as type 2 diabetes, obesity, and metabolic syndrome. Changes in the circadian phase relations of distinct neuroendocrine rhythms drive the annual cycle of metabolism among vertebrates in the wild.

Consequently, it is not merely supplying the neuroendocrine factors of the “lean” season that produces leanness but rather supplying the circadian neuroendocrine blueprint that accomplishes this shift. Methods aimed at doing so can function to alleviate and induce the obese, insulin-resistant condition as is the case in the wild. VeroScience is developing different ways of applying this science to provide effective and practical means of treating human metabolic diseases.

ABOUT THE COMPANY

VeroScience is a hybrid of traditional academic inquiry and industrial focus within a small and efficient organization of six full-time employees in the 27,000 sq. ft. building. The facility houses an animal lab, bench laboratory, greenhouse and offices. There are scientists, an animal care professional and a medical/clinical affairs group within the company and several worldwide consultants. The company conducts preclinical and clinical research nationwide, utilizing strong academic and pharmaceutical industry collaborations to advance its development programs.

VeroScience is headquartered in Tiverton.

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METABOLIC AND IMMUNE DISEASE RESEARCH AND THERAPY DEVELOPMENT

VeroScience is committed to developing novel, practical, and effective therapies for chronic debilitating human diseases such as type 2 diabetes, metabolic syndrome, autoimmune disease, and cancer through interdisciplinary basic research.

Our approach to achieving these goals focuses in large part upon readjusting aberrant central nervous system [CNS] modulation of neuroendocrine activities etiologic in or supportive of these disease states.

VeroScience researchers study biological clocks in vertebrates and their organizational influence on neuroendocrine regulation of physiology to develop new treatment strategies for metabolic and immune disorders.

By investigating and mimicking nature’s means of regulating biochemical physiology for survival of vertebrates in the wild, VeroScience develops treatment strategies, not products per se, aimed at re-directing pathological biochemistry back towards its ‘normal’ physiological organization.

IMMUNE DISORDERS

Immuno-suppression and autoimmune diseases are both associated with derangements in the circadian neuroendocrine axis. Once again, it is the critical role of the brain-neuroendocrine axis to regulate and orchestrate the complex immunological interactions that occur at the cellular and tissue levels for the production of an organismal level immunocompetence.

Rather than focusing on specific immunomodulators such chemokines or lymphokines to boost immuno-reactivity, VeroScience focuses on resetting circadian neuroendocrine events that organize overall global immunophysiology to treat immuno-suppressed states. Similarly, autoimmune disorders with genetic components manifest as alterations in the neuroendocrine axis which in turn potentiate the underlying disorder.

Consequently, autoimmune diseases may be improved by appropriately resetting specific aberrations in the circadian neuroendocrine axis. Our interventions are not just pharmaceutica compounds but rather therapeutic treatment regimens employing such compounds in a particular manner to reprogram the master control centers in the brain for the production of whole-body immunological status.

References


Authors

Donna Cowan, a Certified Clinical Research Coordinator, is project manager for VeroScience’s Medical Affairs and Clinical Research Operations.

Anthony Cincotta, PhD, is the Founder of VeroScience.

Correspondence

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Fax 401-816-0524
donna_cowan@veroscience.com

Important Safety Information

Contraindications

CYCLOSET is contraindicated in:
• Patients with known hypersensitivity to bromocriptine, ergot-related drugs, or any of the excipients in CYCLOSET.
• Patients with syncopal migraine. Bromocriptine increases the likelihood of a hypotensive episode among patients with syncopal migraine. Loss of consciousness during a migraine may reflect dopamine receptor hypersensitivity. CYCLOSET is a dopamine receptor agonist, and may, therefore, potentiate the risk for syncope in these patients.
• Women who are nursing their children. CYCLOSET may inhibit lactation. There are postmarketing reports of stroke in this patient population although causality has not been proven.

Warnings and Precautions
• Hypotension: Can cause orthostatic hypotension and syncope, particularly upon initiation or dose escalation. Use caution in patients taking anti-hypertensive medications. Assess orthostatic vital signs prior to initiation of CYCLOSET and periodically thereafter. Advise patients during early treatment to avoid situations that could lead to injury if syncope was to occur.
• Psychosis: May exacerbate psychotic disorders or reduce the effectiveness of drugs that treat psychosis. Use in patients with severe psychotic disorders is not recommended.
• Somnolence: May cause somnolence. Advise patients not to operate heavy machinery if symptoms of somnolence occur.
• Interaction with dopamine antagonists: Concomitant use with dopamine antagonists such as neuroleptic agents may diminish the effectiveness of both drugs. Concomitant use is not recommended.
• Other dopamine receptor agonists: Effectiveness and safety are unknown in patients already taking dopamine receptor agonists for other indications. Concomitant use is not recommended.
• Macrovacular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with CYCLOSET or any other anti-diabetic drug. CYCLOSET does not increase the risk of macrovascular events.
Barriers to Completion of Desired Postpartum Sterilization

REBECCA H. ALLEN, MD, MPH; MICHAEL DESIMONE, BS; LORI A. BOARDMAN, MD, SCM

immediately after vaginal delivery up to 2 days postpartum. The advantages of doing the procedure immediately postpartum are that existing epidural anesthesia can potentially be used and the woman does not have to restrict food and drink in preparation for the procedure another day. Of note, sterilizations funded by Medicaid require that the woman be at least 21 years old and wait at least 30 days between signing the Medicaid consent form and having the procedure. Exceptions can be made for emergency abdominal surgery or preterm deliveries. If the sterilization is not performed postpartum and the woman still desires the procedure, it can be done at least 6 weeks after delivery either through a laparoscopic or hysteroscopic approach. This requires that the patient use reliable contraception postpartum until the sterilization can be performed and have extra visits to arrange the surgery.

Many women who initially request postpartum sterilization antenatally do not obtain the procedure. While some women change their mind after delivery, other women confront barriers to completing the procedure. The purpose of this analysis is to determine the frequency with which desired postpartum sterilizations are not fulfilled, the reasons why these procedures are not performed, and to identify predictors of incompletion. Secondary aims include assessing whether women received an interval sterilization or any other form of long-term contraception within a year of delivery, and determining whether these women became pregnant again within a year of delivery.

METHODS

We performed a retrospective cohort study examining women from a single obstetrics practice who delivered between 1/1/07 and 6/30/07 at Women and Infants Hospital in Providence, RI. During the study period, 626 women in the practice delivered. Of these subjects, 87 (14%) desired postpartum sterilization. Of these 87, 45 (51.7%) underwent sterilization as planned. In multivariable analysis controlling for age, BMI, delivery mode and marital status, older age (OR 2.15, 95% CI 1.12, 4.12, p=0.02) and cesarean delivery (OR 19.65, 95% CI 3.75, 103.1, p < 0.001) were associated with completion of postpartum sterilization and being married (OR 0.10, 95% CI 0.02, 0.56, p=0.009) and having a higher BMI (OR 0.60, 95% CI 0.39, 0.91, p=0.02) were associated with incompletion. Only half of women who request postpartum sterilization antenatally end up obtaining the procedure.

KEYWORDS: postpartum sterilization, barriers, contraception, unintended pregnancy

INTRODUCTION

Tubal sterilization is a highly effective, permanent, and safe method of contraception. Tubal sterilization is the second most common method of contraception used by women in the United States and the most common among women over 30 years of age. Approximately half of all tubal sterilizations are performed in the immediate postpartum period, following nearly 10% of all births in the United States. Postpartum tubal sterilization can be performed during cesarean section or after vaginal delivery through a minilaparotomy. The procedure is convenient for the mother as she is already in the hospital for the delivery. Sterilizations after vaginal delivery are performed through a small infra-umbilical incision as the enlarged postpartum uterus facilitates access to the fallopian tubes. The procedure can be performed from

PRESENTATION AT MEETINGS: This abstract was presented at the 67th annual meeting of the American Society of Reproductive Medicine on October 18, 2011.

ABSTRACT

Tubal sterilization is a highly effective, permanent, and safe method of contraception. Many women who desire postpartum sterilization do not obtain the procedure due to barriers. We performed a retrospective cohort study examining patients from a single obstetrics practice who delivered between 1/1/07 and 6/30/07 at Women and Infants Hospital in Providence, RI. During the study period, 626 women in the practice delivered. Of these subjects, 87 (14%) desired postpartum sterilization. Of these 87, 45 (51.7%) underwent sterilization as planned. In multivariable analysis controlling for age, BMI, delivery mode and marital status, older age (OR 2.15, 95% CI 1.12, 4.12, p=0.02) and cesarean delivery (OR 19.65, 95% CI 3.75, 103.1, p < 0.001) were associated with completion of postpartum sterilization and being married (OR 0.10, 95% CI 0.02, 0.56, p=0.009) and having a higher BMI (OR 0.60, 95% CI 0.39, 0.91, p=0.02) were associated with incompletion. Only half of women who request postpartum sterilization antenatally end up obtaining the procedure.

KEYWORDS: postpartum sterilization, barriers, contraception, unintended pregnancy

METHODS

We performed a retrospective cohort study examining women from a single obstetrics practice who delivered between 1/1/07 and 6/30/07 at Women and Infants Hospital in Providence, RI. The Women and Infants Hospital Institutional Review Board granted approval for the study protocol. Prenatal records for these women were reviewed and subjects who expressed a desire for postpartum sterilization during antepartum care were identified. Data collected included completion of required consent forms, whether or not the procedure was performed and if not, the reason why. For those subjects who did not receive desired postpartum sterilization, we recorded whether the patient received interval sterilization or any other method of long-term contraception within one year of delivery, and whether they had a repeat
pregnancy within one year of delivery. Other data collected included age, race/ethnicity, obstetric history, marital status, BMI, insurance status, trimester at initial prenatal visit, trimester at request for sterilization, gestational age at delivery, mode of delivery, and use of epidural analgesia.

Comparisons were made between women who did obtain their desired postpartum sterilization and those who did not. Descriptive statistics (means and percentages) for the baseline characteristics of the two study groups were compared using chi-square tests for categorical data and t tests for continuous data. Multivariable logistic regression was used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for completion of postpartum sterilization. Variables associated with the outcome with p<=0.1 in the crude models were considered for the multivariable model. Some variables were collapsed for the regression analysis.

Table 1. Selected Clinical Characteristics According to Study Group

<table>
<thead>
<tr>
<th></th>
<th>Sterilization Completed</th>
<th>Sterilization Not Completed</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>45</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>30.2 ± 5.2</td>
<td>26.6 ± 3.9</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>15 (34.1)</td>
<td>17 (40.5)</td>
<td>0.50</td>
</tr>
<tr>
<td>Black</td>
<td>4 (9.1)</td>
<td>8 (19)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2 (4.5)</td>
<td>1 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>22 (50)</td>
<td>16 (38.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (2.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>8 (17.8)</td>
<td>15 (35.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Divorced</td>
<td>4 (4.4)</td>
<td>4 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>35 (77.8)</td>
<td>23 (54.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Insurance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>41 (91.1)</td>
<td>36 (85.7)</td>
<td>0.70</td>
</tr>
<tr>
<td>Private</td>
<td>3 (6.7)</td>
<td>5 (11.9)</td>
<td></td>
</tr>
<tr>
<td>Self Pay</td>
<td>1 (2.2)</td>
<td>1 (2.4)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>31.1 ± 7.8</td>
<td>34.4 ± 7.2</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td>2.98 ± 1.94</td>
<td>2.45 ± 1.09</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Trimester of Request for Sterilization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>4 (8.9)</td>
<td>3 (7.1)</td>
<td>0.70</td>
</tr>
<tr>
<td>Second</td>
<td>15 (33.3)</td>
<td>11 (26.2)</td>
<td></td>
</tr>
<tr>
<td>Third</td>
<td>26 (57.8)</td>
<td>28 (66.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Gestational Age at Delivery (weeks)</strong></td>
<td></td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>38.3 ± 2.02</td>
<td>38.7 ± 3.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Delivery Mode</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>24 (53.3)</td>
<td>37 (88.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cesarean</td>
<td>21 (46.7)</td>
<td>5 (11.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Use of epidural</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (66.7)</td>
<td>34 (81)</td>
<td>0.13</td>
</tr>
<tr>
<td>No</td>
<td>15 (33.3)</td>
<td>8 (19)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation or n (%)
Missing data no greater than 3.4%
BMI, body mass index

The statistical software packages SPSS 16.0 [SPSS, Inc., Chicago, IL] and STATA 10.0 [StataCorp, College Station, TX] were used for all data analyses.

RESULTS

During the study period, 626 women in the practice delivered. Of these subjects, 87 (14%) desired postpartum sterilization. Of these 87, 45 (51.7%) underwent sterilization as planned. Of the 42 women who did not receive the procedure, 22 (52.4%) changed their mind, 8 (19%) did not have the required Medicaid consent form signed, 4 (9.5%) had prior abdominal surgery that caused the provider to cancel the procedure due to anticipated difficulty, 2 (4.8%) had significant anemia causing the elective procedure to be cancelled, 2 (4.8%) were considered too obese to be able to technically perform the procedure, 2 (4.8%) had chorioamnionitis, 1 (2.4%) had an intrauterine fetal demise at term, and 1 (2.4%) had no documentation. Of those women who did not undergo a planned sterilization, 5 (12%) underwent an interval sterilization and 6 (14%) were pregnant again within a year after delivery. Table 1 compares selected clinical characteristics between those who did and did not receive a desired postpartum sterilization.

In multivariable analysis controlling for age, BMI, delivery mode and marital status, older age [OR 2.15, 95% CI 1.12, 4.12, p=0.02] and cesarean delivery [OR 19.65, 95% CI 3.75, 103.1, p < 0.001] were associated with completion of postpartum sterilization and being married [OR 0.10, 95% CI 0.02, 0.56, p=0.009] and having a higher BMI [OR 0.60, 95% CI 0.39, 0.91, p=0.02] were associated with incompletion. Parity, race, ethnicity, insurance type, gestational age at delivery, trimester of initial prenatal visit, and trimester of request for postpartum sterilization were not significantly different between the two groups; however, due to the population of predominantly Medicaid patients, the influence of insurance type could not be assessed.

DISCUSSION

Our study found that only half of women who request postpartum sterilization antenatally end up obtaining the procedure. While many women changed their mind at the time of delivery, failure to sign the required Medicaid consent form 30 days in advance was a significant contributor to incompletion. In addition, we found that women who have had prior abdominal surgery or are obese should be counseled that postpartum sterilization may not be possible unless cesarean delivery occurs.
The strengths of this study include a detailed review of prenatal and hospital records to identify women who requested postpartum sterilization and the reasons why the procedure was not performed. Limitations of the study include the small sample size and retrospective data collection. In addition, our study population was limited to a single obstetrics practice that serves women predominantly on Medicaid and may not reflect other obstetric practices. Furthermore, our hospital does not perform postpartum sterilization on the same day as vaginal delivery, unlike many other institutions. This may have influenced the completion rate, as women who had undergone vaginal delivery had to wait until postpartum day one to obtain their procedure. This increases obstacles such as operating room availability and patient convenience.

Other institutions have reported similar findings. A study of 712 women at a Chicago hospital showed that 46% of women requesting postpartum sterilization did not obtain the procedure. The investigators found that lack of valid Medicaid sterilization consent forms, a medical condition precluding the procedure, and lack of availability of an operating room were the most common reasons why the procedures were not performed. The same investigators also found that young age (21 to 25 years), African American race, request for sterilization in the second trimester, and vaginal delivery rather than cesarean section were risk factors for not obtaining a desired postpartum tubal sterilization. It is not surprising that cesarean section facilitates the completion of postpartum sterilization since the fallopian tubes are accessible through the Pfannensteil incision while a separate procedure is required after a vaginal delivery. The requirement for Medicaid consent at least 30 days prior to the procedure was developed to provide a window for women to think about their decision and prevent coerced sterilizations that had occurred in the past among disadvantaged populations. Nevertheless, our study and others demonstrate that this requirement often becomes a barrier for women who desire the procedure.

Another study of 429 women from San Antonio, Texas, found completion of desired postpartum sterilizations to be 69% and was more likely among women who were documented U.S. residents, married, of lower parity, and who had received prenatal care, and had private health insurance. In this study, completion of postpartum sterilization at the time of cesarean section was no different between documented and undocumented U.S. residents; however, after vaginal delivery, significantly more documented U.S. residents obtained the procedure. This is because undocumented U.S. residents on emergency Medicaid must pay out of pocket for sterilization after vaginal delivery but not at the time of cesarean delivery. Their follow-up study reported that, of the women who did not receive the requested sterilization, 46.7% became pregnant in the year after delivery.

Our study was not able to show any differences in completion between types of insurance but most of our population was on Medicaid. We are unable to explain why being married was associated with failure to complete postpartum sterilization in our study.

In conclusion, signing Medicaid consent forms in a timely fashion should be a priority during prenatal care and women should be counseled about effective alternatives to sterilization such as intrauterine devices and implants so that they can choose another method if needed. While some women may obtain sterilization after the postpartum period, those who do not are at risk for pregnancy. Improving access to postpartum sterilization, especially after vaginal delivery, is an important step towards reducing unintended pregnancy rates in the United States.

References

Acknowledgments
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Disclosures
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Sources
RHODE ISLAND MEDICAL JOURNAL
Decade of HIV in Rhode Island: Demographic and Clinical Characteristics of Patients Diagnosed in 2001 and 2010

SARAH LEEPER, MD; KATIE FILLION, MD; FIZZA GILLANI, PhD; HEATHER ROSS, LICSW; AADIA RANA, MD; KAREN TASHIMA, MD

ABSTRACT
This article provides an overview of the current epidemiology of HIV infection in Rhode Island, summarizes disease trends over the last decade, and describes circumstances surrounding patient diagnosis.

METHODS: We performed a retrospective chart review of patients newly diagnosed with HIV who presented to the Immunology Clinic of The Miriam Hospital in 2001 and 2010.

RESULTS: From 2001 to 2010 there was an increase in patients reporting MSM (men who have sex with men) as their primary risk factor, and in diagnosis occurring at outpatient sites (p=.03). CD4 count at diagnosis was highest when diagnosed at an HIV testing site and lowest in inpatients (p=.0003). Late presenters were more likely to be tested because of illness (p=.001), as inpatients (p=.000), and heterosexuals (p=.017).

CONCLUSIONS: MSM and minorities are overrepresented in the RI HIV population. Patients without traditional risk factors are more likely to present late and are poorly served by historic screening practices.

KEYWORDS: HIV/AIDS, CD4, MSM

INTRODUCTION
The number of Americans living with HIV is higher than ever before. In 2006, approximately 1 million people in the United States were infected with HIV,1 with 1 in 5 unaware of their status.2 Despite aggressive education and prevention campaigns, the incidence rate is not slowing down. According to the most recent estimates, incidence has remained relatively stable over the past decade, accounting for 56,000 new infections per year.3 Furthermore, immune status at presentation to care has not improved4 despite a growing body of evidence showing that earlier diagnosis and treatment provides numerous individual health and lifestyle benefits as well as decreased transmission to sexual partners.5,6,7

To address these challenges, new strategies to encourage earlier HIV testing and referral into care have been implemented locally and nationally over the last decade. In 2006, the Centers for Disease Control and Prevention (CDC) published revised recommendations for HIV testing in all healthcare settings.8 New guidelines endorse universal screening for patients in all healthcare settings with opt-out verbal consent in lieu of opt-in written consent, and eliminate counseling requirements. In 2009, Rhode Island passed legislation allowing providers to offer opt-out HIV testing with verbal consent alone.9 In theory, these changes would facilitate universal outpatient HIV testing, leading to earlier diagnosis and care.

Despite the static nature of incidence and prevalence data over the past decade, national and regional epidemiological data have reflected a constantly changing epidemic with implications for targeted prevention and testing in certain high-risk populations.10 This article provides an overview of the current epidemiology of HIV infection in Rhode Island, summarizes disease trends over the last decade, and describes circumstances surrounding patient diagnosis. We also describe symptoms, acute and chronic medical illnesses, and psychiatric illnesses present at the time of diagnosis. We hypothesized that more patients would present to care after testing positive at outpatient screening sites, and that this would result in improved clinical status at presentation.

METHODS
Setting and Population
The Samuel and Esther Chester Immunology Clinic of Miriam Hospital provides comprehensive care for approximately 1,500 HIV-positive patients from Rhode Island and surrounding states, comprising over 75% of HIV care within Rhode Island.11 Services are provided regardless of patient insurance status or ability to pay, and include primary care, case management and counseling, opportunities to participate in research trials, hepatitis screening and coinfection care, and substance abuse education and treatment referrals.

Data Collection
We performed a retrospective chart review of patients newly diagnosed with HIV presenting to the clinic in 2001 or 2010. Exclusion criteria included an HIV-positive test result more than 12 months prior to presentation or transfer of care from another site. Data collection included demographics, details surrounding patient diagnosis, clinical presentation, and initial lab work. “Late diagnosis” was defined as CD4<200 and/or an AIDS-defining condition at diagnosis. Physician and social work notes were reviewed up to 12 months following the initial presentation and lab values were recorded up to 6
months following the initial presentation. This study was approved by the Lifespan IRB.

**Statistical Analysis**

Data was aggregated for each study year, and Chi square or Fisher Exact Tests were used to compare demographics, immunological status at diagnosis, HIV risk behaviors, testing site, and testing motivation. A two-sample t-test was used to examine continuous variables. Analyses were performed using STATA10.

**RESULTS**

**Demographics**

The demographic and selected clinical characteristics of the study populations for each year are shown in Table 1. Statistically significant increases have occurred in the proportion of patients who self-identify as gay males/lesbians/bisexuals/other (p=.016) and patients who list the United States as their country of origin (p=.043). Distribution of risk factors has changed significantly (p=.001), most notably with an increase in the proportion of patients who report MSM (men who have sex with men) as their primary risk factor for transmission. Statistically significant changes were not seen in terms of patient age, gender, or race/ethnicity. Mean CD4 increased from 349 to 454 (p=.042). Although the data shows a moderate decrease in the proportion of patients presenting with a CD4 count <200 and/or an AIDS-defining condition, these results do not achieve statistical significance (Figure 1).

**Test Location and Motivation for Testing**

Location of diagnostic test and motivation for seeking the test are shown in Table 2 and Figure 2. A marked increase is seen in the proportion of patients who report MSM [men who have sex with men] as their primary risk factor for transmission. Statistically significant changes were not seen in terms of patient age, gender, or race/ethnicity. Mean CD4 increased from 349 to 454 (p=.042). Although the data shows a moderate decrease in the proportion of patients presenting with a CD4 count <200 and/or an AIDS-defining condition, these results do not achieve statistical significance (Figure 1).

**Risk Factors for Late Diagnosis**

The cohorts from 2001 and 2010 were combined in order to identify groups at

| Table 1. Demographic and Clinical Characteristics of the Study Population, by Year of Diagnosis |
|---------------------------------|---------------------------------|-----------------|
|                                 | 2001 (n= 52)                   | 2010 (n= 69)    |
| **Demographics**                |                                |                 |
| Age, Median (IQR)               | 36.7 (30,42)                   | 37.1 (27,45)    |
| Gender                         |                                |                 |
| Male                           | 34 (65.4%)                     | 53 (76.8%)      |
| Female                         | 18 (34.6%)                     | 16 (23.2%)      |
| **Race/ethnicity**             |                                |                 |
| White                          | 20 (38.5%)                     | 27 (39.2%)      |
| Black                          | 17 (32.7%)                     | 17 (28.3%)      |
| Hispanic                       | 11 (21.2%)                     | 18 (26.5%)      |
| Other                          | 4 (7.7%)                       | 5 (8.8%)        |
| **Nationality**                |                                |                 |
| USA                            | 15 (38.5%)                     | 40 (58.8%)      |
| Other                          | 24 (61.5%)                     | 28 (41.2%)      |
| **Sexual Identity**            |                                |                 |
| Heterosexual                   | 30 (66.7%)                     | 28 (40.6%)      |
| Gay male, lesbian, bisexual, or other | 15 (33.3%)       | 41 (59.4%)      |
| **HIV transmission risk group**|                                |                 |
| MSM                            | 16 (30.8%)                     | 43 (66.2%)      |
| IVDU                           | 2 (3.9%)                       | 2 (2.9%)        |
| IVDU and MSM                   | 2 (3.9%)                       | 0               |
| Heterosexual                   | 20 (57.7%)                     | 24 (34.8%)      |
| Other                          | 2 (3.9%)                       | 0               |
| **Clinical Presentation at Diagnosis** |                  |                 |
| CD4 Count, Median (IQR)        | 349.8 (102-550)                | 454.4 (190-671) |

*Late diagnosis is defined as CD4 count of <200 and/or the presence of an AIDS-Defining Condition present at the time of diagnosis.*
a higher risk of late diagnosis. Patients presenting late were more likely to have been motivated to test because of illness (p=0.001), to have been tested as inpatients (p=0.0004), to self-identify as heterosexual (p=0.017), and to list heterosexual transmission as their primary infection risk (p=0.025). CD4 count at diagnosis (Figure 3) varied widely across diagnosis sites, with the highest mean CD4 reported by patients tested at HIV/STD testing sites and the lowest by patients tested as inpatients (p=.0003).

AIDS Defining Illness and Symptoms Present at Diagnosis

Signs and symptoms were catalogued for all patients presenting with any illness prompting their diagnosis. Symptoms presented varied significantly and were frequently related to AIDS defining illnesses or other conditions present at the time of diagnosis. Opportunistic infections were the most common AIDS defining illness at presentation and dropped by nearly half from 2001 to 2010. In 2010, 18% of symptomatic patients presented to the Rhode Island Hospital or The Miriam Hospital Emergency Department on one or more occasions in the six months prior to their diagnosis with no documentation of any HIV test being performed.

Non-HIV Chronic Diseases Present at the Time of Diagnosis

Table 3 shows patients presenting with a history of or diagnosed with a chronic condition in the first 6 months of their HIV care. Laboratory data was reviewed and diagnoses of lipid disorders, diabetes, and chronic hepatitis B and C were made based on that data. Reported percentages include only patients where lab data was available. There was a significantly higher rate of reported psychiatric disease (p=0.001) and substance abuse, both active (p=0.017) and prior (p=0.0005). Overall there was no significant change in any medical illnesses reviewed, including diabetes, hypertension, or lipid disorders. Patients presenting in 2010 were significantly more likely to report one or more chronic illness (p=0.002).
LIMITATIONS

Our study was limited by a relatively small sample size. We captured two single “snapshots” in time, which may not accurately reflect epidemic trends or which may represent outlying patient populations. Our study was observational, and thus any changes in demographics, clinical presentation, or diagnostic methodology cannot definitively be attributed to modifications in CDC guidelines or RI legislation. Finally, data for the 2010 cohort was collected shortly after the 2009 RI legislative changes, and so the full impact of that reform may not yet be evident.

DISCUSSION

Demographic changes

Many of the demographic trends suggested by these two data points mirror state-wide and national trends over the past decade. In Rhode Island, analysis between 2003 and 2007 showed a greater than 30% increase in the proportion of MSM patients, coinciding with a decrease in the proportion of patients infected via IVDU.11 Nation wide, the proportion of new infections attributable to male-to-male sexual contact has increased rapidly over the past decade, accounting for over half of new infections in 2006.12 Concurrently, surveys of sexual risk behavior in the MSM population have described increases in high-risk behaviors and other STDs.13

In Rhode Island, black and Hispanic patients accounted for roughly 50% of the new infections in Rhode Island over the time period studied, despite making up only 14% of the state’s population.11 In 2006, the nationwide incidence among blacks was 7 times the rate among whites, and the incidence among Latinos was 3 times the rate among whites.14 Ongoing research highlighting the specific factors that put MSM and ethnic minority populations at heightened risk for HIV infection is essential for targeted prevention, testing, and treatment campaigns.

Clinical changes

Immunological status at presentation in our cohort (as indicated by mean CD4 count at diagnosis as well as proportion of patients meeting criteria for “late”

Table 3. Chronic Diseases Present at the Time of Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>2001</th>
<th>2010</th>
<th>p</th>
</tr>
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<tr>
<td>PCP identified</td>
<td>18(35%)</td>
<td>35(51%)</td>
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<tr>
<td>Psychiatric</td>
<td>1(1.9%)</td>
<td>15(19%)</td>
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</tr>
<tr>
<td>Substance Use</td>
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<tr>
<td>Substance abuse- active</td>
<td>4(10%)</td>
<td>21(30%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Substance abuse- prior</td>
<td>9(23%)</td>
<td>40(58%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Smoking History</td>
<td>9(22%)</td>
<td>26(38%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes history</td>
<td>3(6%)</td>
<td>6(9%)</td>
<td>0.54</td>
</tr>
<tr>
<td>New Diabetes Diagnosis</td>
<td>2(4%)</td>
<td>5(8%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Total Diabetes</td>
<td>5(10%)</td>
<td>11(16%)</td>
<td>0.31</td>
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<tr>
<td>Thyroid disorder</td>
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<td>4(6%)</td>
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</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension History</td>
<td>6(12%)</td>
<td>10(15%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Lipid Disorder- History</td>
<td>1(4%)</td>
<td>4(6%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Lipid Disorder- New</td>
<td>2(18%)</td>
<td>10(25%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Lipid Disorder- Total</td>
<td>3(27%)</td>
<td>14(20%)</td>
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<tr>
<td>Low HDL</td>
<td>4(36%)</td>
<td>29(73%)</td>
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<tr>
<td>Co-infections</td>
<td></td>
<td></td>
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<tr>
<td>Hepatitis C</td>
<td>5(10%)</td>
<td>6(10%)</td>
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<td>10(15%)</td>
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<td>Seizure Disorder</td>
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<td>4(6%)</td>
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<tr>
<td>Other Illness</td>
<td>13(25%)</td>
<td>15(22%)</td>
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<td>Total Number of Chronic Illnesses</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>24(46%)</td>
<td>14(20%)</td>
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</tr>
<tr>
<td>1</td>
<td>11(21%)</td>
<td>23(33%)</td>
<td>0.14</td>
</tr>
<tr>
<td>2</td>
<td>4(8%)</td>
<td>14(20%)</td>
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<td>3-4</td>
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<tr>
<td>5+</td>
<td>2(4%)</td>
<td>6(8%)</td>
<td>0.29</td>
</tr>
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</table>
diagnosis appears to have marginally improved over the past decade, although many of the changes in our data set do not achieve statistical significance. Although we are in the midst of a national effort to bring about earlier diagnosis for people with HIV exemplified by the 2006 CDC guidelines as well as the 2009 RI legislation, our data cannot definitively demonstrate a beneficial result. This failure to make gains in the arena of earlier diagnosis has been well documented at other clinical sites. For example, Keruly et al in their report of the Johns Hopkins Clinical Cohort from 1990 through 2006 show a marked decrease in the median presenting CD4+ cell count, from 371 cells/mm3 during 1990–1994 to 276 cells/mm3 during 2003–2006 [P < .01].

We were able to identify demographic groups particularly vulnerable to delayed diagnosis. Compared with those patients diagnosed early, patients who presented to care late were more likely to self-identify as heterosexual with no additional HIV infection risk factor. In contrast, neither race, non-US origin, nor gender was significantly associated with early or late diagnosis. These data are consistent with a multi-site study in the United States from 2000-2003, which also found heterosexual contact to predict late diagnosis. Theoretically, a full transition from targeted HIV testing to adoption of the 2006 CDC recommendations for routine screening of all patient populations would minimize this disparity. Until then, it is important for providers to be aware that absence of “traditional” risk factors for HIV infection may actually place patients at a higher risk of late diagnosis.

### Diagnosis site/reason

To our knowledge, motivation for HIV test and HIV testing site have not previously been described in the Rhode Island population, and so we are unable to compare our data points to larger trends. Our data suggests that not only is the proportion of outpatient tests growing, but that patients diagnosed at outpatient sites are generally diagnosed at higher CD4 counts. Additionally, patients who are motivated by illness to test themselves for HIV generally have a lower CD4 count at diagnosis than those motivated by other reasons. This data, while limited, indicates that policies supporting outpatient testing as well as routine screening might improve rates of early diagnosis and entry into care.

### Chronic Disease

Our data shows a striking increase in the presence of chronic disease, specifically psychiatric illness and substance abuse present at the time of HIV diagnosis. The potential explanations for this were not further explored; however in 2010 patients were asked to provide a more extensive psychosocial history during the initial visit to the Immunology Center. With 30% of new patients reporting active substance abuse, and 19% with psychiatric illness, it is of utmost importance that we are prepared to treat these illnesses alongside the HIV and other medical illnesses present in this population.

### CONCLUSIONS

More Americans are living with HIV than ever before, and a large portion remains unaware of their infection. Groups in Rhode Island that are overrepresented in terms of new infections include men who have sex with men as well as patients of African-American or Hispanic ethnicity. Groups overrepresented in terms of late diagnosis of new infection include heterosexual patients without “traditional” risk factors. Historic screening practices based on risk factors or HIV-associated illnesses are poorly suited to identify patients at early stages of infection. Widespread adoption of the new CDC guidelines regarding universal screening is likely to result in an increase in outpatient diagnoses as well as diagnoses at earlier stages of infection. These trends are suggested by this data but further analysis of larger cohorts over time is necessary to confirm these outcomes.

### References


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**Disclosures**
The authors have no financial interests to disclose.

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ABSTRACT
Measles is a highly contagious viral disease and rapid identification and control of cases/outbreaks are important global health priorities. Measles was declared eliminated from the United States in March 2000. However, importations from endemic countries continued throughout the last decade and in 2011, the United States reported its highest number of cases in 15 years. With a global snapshot of current measles epidemiology and the persistent risk of transnational spread based on population movement as the backdrop, this article describes the rare event of a measles case identification in the state of Rhode Island and the corresponding public health response. As the global effort for measles elimination continues to make significant progress, sensitive public health surveillance systems and strong routine immunization programs will be important to ensure we maintain local and regional control.

KEYWORDS: measles, eradication, outbreak investigation, Rhode Island, GIS

INTRODUCTION
Measles is one of the most contagious diseases known to mankind. In spite of the progress achieved over the past few decades in eliminating and controlling the disease from many parts of the world through immunization, regions of high measles transmission still exist. Global migration and international travel to and from such regions pose a constant threat of re-introduction of virus transmission in regions that have eliminated measles. This article describes the rare event of detection of a confirmed measles case in Rhode Island and the public health response that followed. Focusing on the current re-emergence of measles in parts of Europe and the United States, it also reviews the critical importance of maintaining surveillance competence in the medical and public health community to disease events that are sporadic in terms of local and regional transmission, but are still relevant from a global epidemiological perspective.

Measles was declared eliminated from the United States in March 2000, nearly three decades after the initial control efforts began in the early 1960s when the first measles vaccine was licensed in the country. In 2002, the World Health Organization (WHO) geographical Region of the Americas achieved measles elimination by interrupting transmission of the endemic strain of measles virus. However, importations from endemic countries continued throughout the last decade and a median of 56 cases of measles were reported in the United States during the 2001-2008 period. A major resurgence of measles occurred in the WHO European Region in 2011, with more than 13,000 laboratory-confirmed cases, nearly three times higher than the total number of laboratory-confirmed cases reported in 2010. Ninety percent of the measles cases reported from the WHO European Region in 2011 had not been vaccinated or had no documentation of prior vaccination. Two-hundred and sixteen laboratory-confirmed cases were reported in the United States in 2011, the highest number of cases since 1996. Rhode Island reported its first case of measles since 1996 in April 2011.

CASE REPORT
On April 13, 2011, the RI Department of Health (HEALTH) received a call from a primary care physician reporting a suspected case of measles in a foreign traveler. The patient was a 28-year-old female who flew from Italy and landed at John F. Kennedy International Airport in New York City at around 2 pm on April 12. A friend picked her up and then they drove towards Rhode Island. Their only stop while in transit was at a restaurant in Connecticut. At 7 pm she checked into a hotel in Newport. Approximately 2 hours later, she developed a generalized, non-pruritic, maculopapular rash on the face and trunk, with moderate fever. On April 13, she visited the reporting physician with complaints of cough and coryza, beginning April 9. Clinical examination did not reveal any Koplik’s spots. There was no history of exposure to a known case of measles. No documented evidence of prior immunization could be elicited. Serum tested courtesy of the Massachusetts State Laboratory on April 14 yielded a positive IgM result. Two weeks later, the Centers for Disease Control and Prevention (CDC) confirmed the genotype of the measles virus from this case as D4 (Enfield Strain), the predominant strain circulating in Europe in 2011.

EPIDEMIOLOGY
A virus of the paramyxovirus family causes measles. It is characterized by a prodrome of 3-4 days with fever, cough,
coryza and conjunctivitis followed by a maculopapular rash that usually appears first on the face and then spreads distally. A case of measles is infectious for a period of 4 days prior to the onset of rash until 4 days after the onset of rash. Airborne spread through aerosolized droplet nuclei has been documented in closed environments (e.g., clinics or waiting rooms) for up to 2 hours after the infected person has left the area. The incubation period is 7 to 21 days with an average of 14 days. The rates of hospitalization due to complications can be as high as 40% even in developed countries, as noted during the first quarter of 2011 in the United States. The \( R_0 \) [expected number of secondary cases resulting from a primary case in the absence of community immunity] for measles is approximately 15, more than 10 times higher than that of the swine-origin H1N1, and three times higher than smallpox. Thus, controlling the spread of such a contagious disease that has an 8-9 day-long period of infectiousness remains a major public health challenge. In addition to the isolation of all laboratory-confirmed cases, post-exposure immunization of susceptible contacts with a single dose of measles-containing vaccine within 72 hours of exposure has been demonstrated to decrease transmission and is a standard recommendation. Both serologic and epidemiologic evidence suggest that the immunity induced by the vaccine remains effective long term and possibly for life, in most individuals.

**PUBLIC HEALTH RESPONSE**

Within a few hours of the case notification, HEALTH activated an emergency public health response to ensure efficient coordination among the operational areas [case management and isolation of index patient, laboratory testing, contact evaluation and immunization]. Voluntary isolation was negotiated with the patient and she was kept confined to her hotel room April 13-17, after which she was allowed to board a flight to return to Italy. Immediate notifications were made on April 13 to CDC Quarantine Stations in New York City and Boston, which took on the responsibility of tracking all airline passengers exposed. The Department of Public Health in Connecticut was notified on the same day for tracking contacts at the restaurant where the patient and her friend had stopped for dinner. In-state contacts were rapidly identified by a team of HEALTH investigators and included her friend, staff at the doctor’s office, and hotel staff. Exposed susceptible individuals (n=3) in the doctor’s office

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Figure 1. Distribution of Laboratory-Confirmed Measles Cases by WHO Region, 2011.*

Laboratory-confirmed measles per 100,000 population by WHO Region, 2011

(WHO Regions, rates)

- **Americas:** <0.2
- **Western Pacific:** 0.2 - 0.3
- **South-East Asia:** 0.5 - 0.6
- **African:** 0.7 - 0.8
- **Eastern Mediterranean:** 0.9 - 1.0
- **European:** >1.0

* As of January 11, 2012. The six WHO regions have been resized based on rates of laboratory-confirmed measles, using the cartogram tool of ArcGIS. Data Source: World Health Organization
and her friend were vaccinated with one dose of Measles, Mumps and Rubella (MMR) vaccine within 24 hours of initial exposure. An immunization clinic was set up in the hotel in Newport on April 15, and all 14 hotel staff who were considered exposed and susceptible were vaccinated with one dose of MMR. Enhanced surveillance with regular telephone calls was implemented for exposed in-state contacts for 2 incubation periods (42 days from April 17). No secondary cases were identified in any RI resident.

GLOBAL SITUATION AND RISK OF U.S. IMPORTATION

In 2011, more than 40,000 laboratory-confirmed cases of measles were reported globally. Global data were processed in Microsoft Excel® and ArcGIS® version 9.3.1 to calculate rates by WHO Regions and a map was created using the cartogram tool of ArcGIS® following the Gastner-Newman method (Figure 1). In this map, WHO Regions have been resized using ArcGIS® based on the number of laboratory-confirmed measles in each Region, adjusted for the population. Thus, European and the Eastern Mediterranean Regions appear larger and more prominent than the other Regions because of the high rates of laboratory-confirmed cases in 2011. The highest number of clinically confirmed and epidemiologically linked cases of measles was still reported from the African Region. Also, there has been a striking increase in the proportion of cases in the Region of Americas, and the European Region from 2010 to 2011 (Figure 2). Approximately 32% of all laboratory-confirmed cases were reported from the European Region in the year 2011, compared to 17% in 2010. Similarly, there has been a near three-fold rise in proportion of laboratory-confirmed cases from the Region of the Americas compared to the other Regions, the United States reported its highest number (n=216) of cases in 15 years during 2011. Fifty-five percent (n=118) of these cases were reported during the first 5 months of 2011 and 90% of these cases were associated with importation from other countries. The resurgence of measles in Europe coupled with the ever-increasing trend of global migration and international travel poses a continued threat to measles control in the United States, and emphasizes the need for pre-travel vaccinations.

DISCUSSION

Measles is highly communicable and can cause complications such as otitis media, pneumonia, severe diarrhea, and encephalitis leading to hospitalization and death in severe cases. Due to its high communicability, even a minor drop in immunization coverage can result in rapidly spreading outbreaks and re-establishment of endemic transmission, as noted in the United Kingdom in the recent past. Unvaccinated children and young adults are at a higher risk of developing measles and they place vulnerable groups such as infants and persons with contraindications to immunization at risk. During the first half of 2011, 15% of all measles cases and 15% of all post-measles hospitalizations in the

Figure 2. Laboratory-Confirmed Measles Cases by WHO Region, 2010 and 2011.*

*As of January 11, 2012, Data Source: World Health Organization
United States were noted in infants.4 Similarly in Europe, measles has caused high fatality in recent years in children and adolescents who could not be vaccinated due to underlying immune-compromised conditions.6,11 Maintaining high immunization levels with MMR vaccine is of critical importance to prevent the re-introduction of measles transmission in countries that are considered measles-free. Currently Rhode Island has a 91% immunization rate by age 36 months and a 2-dose rate at kindergarten entrance of 92%, and the goal is to improve on this rate.13 Rhode Island is a universal vaccine supply state and mandates completion of a 2-dose schedule for children entering kindergarten and university, as well as mandated age-appropriate vaccination for day care attendees.

Swift control efforts by public health agencies, as described here, are time and resource intensive, and costly. Moreover, appropriate inter-sectoral coordination is essential to ensure rapid communication and implementation of control strategies, as noted in this case response that involved coordination among multiple state agencies, physician and laboratory networks, regional quarantine stations and Federal disease control staff. Although this was the first case of laboratory-confirmed measles in Rhode Island since 1996, timely reporting by an astute clinician followed by a prompt public health investigation and response completed within 3 days of notification ensured there were no secondary cases in the state. This response underscores the importance of maintaining awareness in the clinician community and the need to sustain epidemiologic capacity for rapid detection and control of rare but serious disease events such as measles.

Due to the continued risk of importations of measles into the United States, health-care practitioners should “think measles” in patients of any age presenting with a febrile rash illness associated with cough, coryza, or conjunctivitis, particularly those with a history of recent travel abroad. Such suspected cases should be isolated and reported immediately to public health authorities, so that an urgent mitigation response can be initiated. As well, exposures to measles might occur in various settings during travel. Therefore, physicians should recommend vaccination before travel for international travelers including for infants aged ≥6 months.13 These actions will assure maintenance of local control while the global eradication strategy is being implemented.

References

Acknowledgements
Paul Vincent Del Guercio, MD, Jason Weisfeld, MD, MPH; Department[s] of Public Health: Massachusetts, Connecticut, New York and New Jersey, Quarantine Station[s]: New York and Boston [CDC’s Division of Global Migration and Quarantine], CDC’s National Center for Viral and Respiratory Diseases, RI Department of Health’s Division of Infectious Disease and Epidemiology, Center for Emergency Preparedness and Response and Immunization Program.

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

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<td>Number</td>
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<td>Deaths</td>
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<tr>
<td>Infant Deaths</td>
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<tr>
<td>Neonatal Deaths</td>
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<td>Induced Terminations</td>
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* Rates per 1,000 estimated population
# Rates per 1,000 live births

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<td>Diseases of the Heart</td>
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<td>2,420</td>
<td>229.8</td>
</tr>
<tr>
<td>Malignant Neoplasms</td>
<td>176</td>
<td>2,209</td>
<td>209.7</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>33</td>
<td>406</td>
<td>38.5</td>
</tr>
<tr>
<td>Injuries (Accident/Suicide/Homicide)</td>
<td>66</td>
<td>739</td>
<td>70.2</td>
</tr>
<tr>
<td>COPD</td>
<td>63</td>
<td>538</td>
<td>51.1</td>
</tr>
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</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 1,052,567 (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.
A 53-year-old man had fine needle biopsy of a left parotid mass showing “cellular components with mucoid material consistent with pleomorphic adenoma.” The gland was reworked, revealing a 2.9 x 2.4 x 2.0 cm well circumscribed tan-grey opaque mass with a myxoid appearance on cut surface (Figure 1). The frozen section slides demonstrated mixed epithelial and myxoid areas. The extensive myxoid stroma contained characteristic red to pink crystalloid deposits arranged in floret-like patterns (Figure 2). The intraoperative consult diagnosis was “myxoid lesion suggestive of mixed tumor on representative section.”

Pleomorphic adenomas, also known as benign mixed tumors, are the most common tumors of the parotid gland. They have variable morphologic features with matrices that can be cartilaginous or myxoid. The characteristic floret-like crystals present in the parotid are an uncommon finding and are more often present in pleomorphic adenomas (benign mixed tumor) than any other tumor of the parotid gland, and are generally found in the myxoid areas. They are reported to have a frequency of 1.5-21% but we have found them to be much more infrequent.

The crystalloids seen in this case are tyrosine-rich crystals. They are refractile with light microscopy and some may contain a dominant component of arginine rather than tyrosine. They are thought to result from the precipitation on stromal collagen of products secreted by neoplastic myoepithelial cells. Two other types of crystals have been described in pleomorphic adenomas. The most common are eosinophilic, needle-shaped crystals that may diminish when tissue undergoes routine processing and fixation. The third type resembles calcium oxalate crystals.

REFERENCES

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DISCLOSURES
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RI Physician Traces Tragedy, Triumphs in ‘Man with Bionic Brain’

MARY KORR
RIMJ MANAGING EDITOR

PROVIDENCE PHYSICIAN JON MUKAND, MD, PhD, has written a heart-wrenching story of tragedy tempered by hope and the promise of biotechnology in The Man with the Bionic Brain and Other Victories over Paralysis.

A Fourth of July weekend beach party in 2001 turned deadly for 21-year-old Matt Nagle. When a brawl erupted, the former high school football player from Weymouth, Mass., dove into the melee to rescue a buddy and was stabbed with a hunting knife. The eight-inch blade severed his spinal cord and paralyzed the 6-foot, 2-inch young man from the neck down.

Matt had just taken the police cadet entrance examination. He wanted to follow in the footsteps of his father, a police sergeant in Cambridge, Mass. Dr. Mukand, medical director of the Southern New England Rehabilitation Center (SNERC) in Providence, would come to know Matt and his family well. In the book, he recounts Matt’s memory of the attack:

I was dead for an instant or an hour. I don’t know how long. Katie [a friend] held me as I turned blue and died. My lungs collapsed, but the paramedics saved me and got me to Boston Medical. Someone said, ‘Come on man, pull through,’ and I’m glad I did. I tell my parents [Patrick and Ellen Nagle] I love them every time I see them. You can’t take anyone for granted, you can’t take life for granted – life’s too short. Too short …’

Matt, writes Dr. Mukand, “was in a race against time, a race to get a computerized brain implant, an electrode system, stem cells, or any other technology that could cure his spinal cord injury — before he died from its many complications.

“Based on his clinical status, Matt could expect to live to forty-five. With paralysis, sensory loss, abnormal movements, bowel and bladder incontinence, pain and sexual dysfunction, Matt was one of the most disabled people I had ever met.”

JON MUKAND, MD
About the author
A graduate of the Medical College of Wisconsin, Jon Mukand, MD, PhD, is a rehabilitation medicine specialist and medical director of the Southern New England Rehabilitation Center and serves on the clinical faculty of Brown University and Tufts University. He has edited three additional books and published research articles, poems, and reviews in Nature, New England Journal of Medicine, and the Journal of the AMA, among others.

He holds a PhD in English literature from Brown University.
Three years later, Matt became the first volunteer recipient of the investigational BrainGate implant, a neural interface system developed by John Donoghue, PhD, professor of neuroscience at Brown University, and a cofounder of the company Cyberkinetics, formed to advance the technology.

Dr. Mukand served as BrainGate’s FDA-approved study’s first clinical investigator. Matt called him his “research doctor.”

On June 22, 2004, the surgery was performed at Rhode Island Hospital. Neurosurgeons situated the pill-sized BrainGate sensor on the surface of Matt’s right brain in the motor cortex area.

“A hundred microelectrodes thinner than a hair and a millimeter long sent fine wires to a titanium pedestal that protruded from Matt’s head,” Dr. Mukand writes.

When the surgical site healed, a fiber optic cable connected Matt to a computer that analyzed and stored his brain’s electrical nerve signals. The system tethered Matt to a cart operated by a clinical systems engineer.

When the system was first turned on, nothing but gibberish registered. Weeks later, after troubleshooting and tightening the connection, the BrainGate system finally displayed activity in Matt’s brain cells as he imagined different movements. The computer then interpreted the nerve signals and translated these activities into action.

Dr. Mukand describes Matt’s first response when he moved the cursor with only his thoughts: “Holy shit!”

Through long sessions with the BrainGate’s system engineer, Matt’s successes with the technology grew. He played video games, opened and closed a prosthetic hand and controlled a robotic arm.

At the same time he struggled with depression, suicidal thoughts, raging anger and roaring fits. At times, he urged friends who came to visit him in the rehabilitation facility where he lived to pull the plug on his ventilator. Once, Matt told his mother he wanted to die. She said, “Then I’ll go with you.”

On October 18, 2005, Matt returned to Rhode Island Hospital for removal of the BrainGate implant. He wanted to be off the system so he could have a phrenic pacemaker implanted in his chest in order to breathe on his own; another implant was not allowed on the BrainGate study protocol. The pacemaker implant was successful and Matt was able to be off the ventilator for as long as 36 hours at a time.

On July 23, 2007, complications from an infection claimed Matt’s life. He had lapsed into a coma several days prior.

When no brain activity was detected, his mother held him as he was disconnected from the ventilator. His final act was to donate his organs.

Matt hoped that by volunteering for experimental therapies such as BrainGate, others would be inspired. Robbed by a violent act of who he was and who he was meant to be, within the prison of his body he glided on the currents of hope afforded by medical science and biotechnology.

Throughout the book, the author intersperses accounts of other patients such as Floyd, who suffered a spinal cord injury and uses robotic braces for legs. Dr. Mukand hopes their stories, as well as Matt’s, will be useful for physicians who treat patients impaired by spinal cord injury, brainstem stroke, amyotrophic lateral sclerosis, Parkinson’s disease and other movement disorders.

And he hopes others who read it will be inspired by Matt, as he was.
PROVIDENCE — Amid rapid changes in health care policy that are increasing the need for leaders in community-based primary care, the Warren Alpert Medical School of Brown University has begun to develop a novel MD/ScM program in Primary Care and Population Health. The plans underway would create a four-year, dual degree program for 24 students a year beginning in fall 2015.

“Primary care is a vitally important area of medicine in Rhode Island and around the country,” said Dr. Edward Wing, dean of medicine and biological sciences. “The best care will come from doctors who are trained to understand and improve the community health of their patients. Future primary care doctors must therefore be trained in population health, policy, epidemiology, technology, and teamwork.”

Treating a patient with high cholesterol is not only a matter of prescribing a pill or telling a patient to change behavior, but also of understanding the barriers in the patient’s neighborhood to exercise, the local availability of healthy food options, and cultural influences on diet and activity.

New models of health care are designed not only to treat individual patients but also to encourage medical teams to produce high-quality outcomes across entire patient communities. Meanwhile, as more patients gain access to health care, the Association of American Medical Colleges estimates that the nation will face a shortage of 45,000 primary care physicians in 2020, a year after the first students would graduate from the Alpert Medical School’s new program.

“We desperately need to control health care costs in Rhode Island and across the United States,” said Brown University President Christina Paxson, a health economist. “By training more primary care physicians, we can contribute to controlling costs while maintaining high-quality care.”

A new dual-degree program being planned by the Alpert Medical School would provide a new approach to educating primary care physicians. The Association of American Medical Colleges estimates that the nation will face a shortage of 45,000 primary care physicians in 2020.

**A new student experience**
The pedagogical emphasis across the program’s four years would be on teaching students not only the medical knowledge they need
to become physicians, but also public health policy, leadership skills, and how to work with other health professionals who are part of the broad care teams that serve patients.

“The proposed integration of a rich population health curriculum into students’ training would be unique among medical school programs,” said Jeffrey Borkan, MD, whom Dr. Wing has appointed assistant dean to spearhead the effort. Dr. Borkan has also served as chair of the Alpert Medical School’s Department of Family Medicine since 2001.

In the current working proposal, classes in the new program will emphasize active learning rather than passive lecture-style teaching, Dr. Borkan said. And rather than structuring student clerkships as a string of separate rotations through specialty clinical settings for six weeks at a time (for example, internal medicine followed by pediatrics followed by surgery) students would instead engage in nine-month, physician practice-based clerkships, where they follow a cohort of patients through their various interactions with the health care system, under the mentorship of local primary care physicians.

“In these longitudinal clerkships, students would experience a continuity of relationships with their patients and mentors,” Dr. Borkan said. “They could observe the natural history of disease and wellness over time and learn the continuum of care as it is encountered by patients and their care teams.”

After months of planning, medical school officials including Drs. Wing, Borkan, Paul George, MD, assistant professor of family medicine, and Philip Gruppuso, MD, associate dean for medical education, held their first meeting on Jan. 8 to gather feedback from a newly formed advisory board charged with providing the dean with advice and recommendations. The school is continuing to work on several other fronts, including deeper planning of the curriculum, identifying sites and practices for clerkships and residencies, and steps toward obtaining accreditation for the program.

A successful program will not only add to the ranks of primary care physicians in Rhode Island, Dr. Borkan said, but also improve the quality of care around the state and perhaps inspire similar programs at other medical schools. “When the first class graduates in 2019, we hope they will not only become leaders in a new model of primary care, but that their education itself will have become a model,” he said.
Public Health Program at Brown Launches Healthy Aging Initiative

Diamond Fund gift estimated at $4-$7 M

MARY KORR
RIMJ MANAGING EDITOR

PROVIDENCE – Thanks to an estimated $4 to $7 million gift from the Irene Diamond Fund, Brown University’s Program in Public Health will undertake a broad-based healthy aging initiative linking public health strategies and care to the elderly.

The funds, which will come from a 12.5 percent share of a limited partnership interest in a building on Roosevelt Island in New York City, will be disbursed after the sale of the building. It is the largest gift the Brown public health program has received to date, and it couldn’t be timelier. The Brown Corporation will vote this month on a plan to transform the program into a School of Public Health. If approved, the school would be launched on July 1st and will be located at 121 South Main St., where the educational program, departments and 11 public health research centers are located. It is anticipated that the two-year accreditation process will also begin in July.

Terrie Fox Wetle, PhD, associate dean of medicine for public health and public policy, will co-direct the Diamond Healthy Aging Initiative with Richard Besdine, MD, director of the Center for Gerontology Healthcare Research. (See Spotlight page 53.)

The gift recognizes Brown’s national leadership in aging research and teaching. “Most public health programs in the country focus on younger populations, such as child and maternal health,” said Wetle, who is former deputy director of the National Institute on Aging.

The numbers
Rhode Island is a fertile incubator for aging research, with its rapidly aging population.

A report on population projections issued by the Rhode Island Statewide Planning Program (www.planning.ri.gov) estimates that there will be more than 29,000 residents in the state who are 85 and older by 2015, and 18,277 in the 80–84 age group.

The United States Bureau of the Census figures (estimates as of 2012) show that 14.7 percent of Rhode Islanders are 65 and older. That compares with 13.3 percent nationwide.

Statewide population projections show that by 2030, the number of persons 65 years and older is expected to reach 233,749, and represent 20 percent of Rhode Islanders.

Nationwide, the census figures project that:

By 2030, the number of adults aged 65...
and older will be more than 72 million, an increase from 13 percent of the U.S. population to almost 20 percent.

By 2050, the population aged 85 and over could grow to nearly 19 million.

The first pilot project of the initiative, even before receiving income from the Diamond gift, is being planned with the Rhode Island Dept. of Health. A Brown graduate student will be assigned to work with Health department staff on the project. They will review data relating to hundreds of older people who are frequent users of 911 and emergency departments, and who have made at least four such costly trips within a year’s time.

“What are the reasons for multiple 911 calls for these older people and how might we intervene to improve health and avoid emergency calls?” Wetle said in a discussion of the project. “We want to be able to work with this population and identify ways of supplementing their health care. It could be connecting them with a PCP or community health center. If we can provide evidence-based strategies to improve health and reduce expensive emergency room visits and hospitalizations, it will be a positive first step for the initiative,” she said.

In addition to working with Health and community organizations, the Diamond healthy aging initiative will focus on expanding and innovating Brown’s public health and medical school curricula, relevant to aging population health. It will also support student and faculty research in this area, with the goal of implementing healthy aging programs statewide with community partners.

The Diamond Fund committed the balance of its endowment, $40 million, at the end of 2012 to grants for healthy aging projects. Other beneficiaries include Weill Cornell Medical College, the American Federation for Aging Research and Columbia University.

The 2003 New York Times obituary of the late Mrs. Diamond, who in her earlier years was an editor and film scout responsible for acquiring the script Casablanca, quotes her as saying: “Philanthropy is a lot like Hollywood: You find a good script, you support it.”

The Diamond Healthy Aging Initiative at Brown will focus on identifying opportunities for preventive health interventions for older people, in order to improve their quality of life and reduce health care costs.
Q & A with Dr. Richard Besdine

MARY KORR
RIMJ MANAGING EDITOR

PROVIDENCE – Richard Besdine, MD, director of the Center for Gerontology and Healthcare Research at Brown University, recently sat down for a candid conversation about geriatrics and his personal path into the field, which took root in the Scottish city of Glasgow in 1972.

1. Who has influenced you the most in your life, both professionally and personally?
My Scottish mentor, Sir Ferguson Anderson, known to all as Fergie, was my first professional mentor. I began my career as a basic scientist and in ID [infectious disease]. I became less and less fulfilled as a scientist and did some soul searching. I realized my greatest satisfaction was in figuring out the toughest and most complicated patients – most were older – and improving their lives. Howard Hiatt [later dean of public health at Harvard], my Chair of Medicine, told me about Fergie.

I went to the University of Glasgow in 1972 and did a geriatrics fellowship with Fergie, who was Europe’s first professor of geriatrics. He inspired me and I came home determined to build one of the nation’s first academic geriatrics programs in the United States, which I did with Jack Rowe at Harvard Medical School.

My second mentor was Bruce Vladbeck at what was then known as HCFA [Health Care Financing Administration, today’s Centers for Medicare and Medicaid Services], I was on a one-year sabbatical (1995) from UConn. [At the time, Dr. Besdine was chief of the division of geriatrics at the University of Connecticut.]

Bruce was a brilliant visionary and introduced me to the world of health care policy. He eventually offered me the position of director of HSQB [Health Standards and Quality Bureau] and first chief medical officer at HCFA. It was the bulliest pulpit for geriatrics and the most exciting job I’ve ever had.

And my treasured wife Fox has been a powerful influence in my life. I first met Fox in 1978. I was a young and arrogant Harvard faculty member. She taught me to look for the good in people. Here at the Center, people do good work and care for and about each other. It’s important to publicly recognize their accomplishments. That’s paying it forward.

2. What distinguishes a geriatrician from an internist or primary care physician?
What makes the field of geriatrics different? Pure aging in the body happens no matter how healthy a person is. Diseases common in the 60s, 70s, 80s, and 90s almost always also occur in middle age. But when major diseases are super-imposed in the older population, they present differently. Increasingly, subspecialists are recognizing this. The management of complex and chronic diseases in older people is the bread and butter of geriatricians.

A good solid educational program can prepare future doctors in treating these patients. We’ve put this into the core curriculum at Brown’s medical school.

3. In your experience, who are the predominant referral sources for geriatricians?
We get referrals from well-read family members and patients. Surgeons are a large source of our referrals, both general and orthopedic, neurosurgeons, neurologists and other subspecialists.
4. Should all elderly patients have a geriatrician as their PCP?

No. We usually see 5 to 10 percent of the very elderly, with multiple health problems on a variety of medications. We see a patient in referral, do a comprehensive assessment, and return them to their internist or PCP, if they have one.

5. To what extent do you involve hospice care and particularly our local Home & Hospice Care (HHCRI) in your attempts to lessen the costs of health care while simultaneously improving the emotional well-being of your patients?

We facilitated the affiliation of HHCRI with Alpert Medical School, based upon its huge capacity and activities as a teaching center for hospice and palliative care for Brown medical students, residents and faculty. We now have a fellowship in palliative care. I’m a zealot for palliative care.

The primary goal is not saving money. It is delivering the care that patients and their families want once they are informed of all their choices. Geriatricians often begin the conversations on palliative care and advanced directives with patients and families. We need to have patients and families begin to have these conversations earlier, while the patient is capable and able to communicate his/her choice. An advanced care directive is not a single sheet of paper. It’s a conversation. Things change over time.

6. Do you have a favorite quote on aging?

I have several. One is from George Burns at 95: “If I had known I was going to live this long, I would have taken better care of myself.”
RIMS Reschedules Neuroscience and Society Lectures

PROVIDENCE – Harvard psychologist and author Steven Pinker, and New York University Professor Paul Glimcher, author of several books on neuroeconomics, will be speaking at Brown University on February 13 and March 4 respectively.

The talks conclude the Rhode Island Medical Society’s 2012 Bicentennial lecture series, developed by RIMS’ Bicentennial committee chaired by the Society’s president, Diane Siedlecki, MD, and its symposium subcommittee, chaired by Herbert Rakatansky, MD.

The series is co-sponsored by the Brown Institute for Brain Science and the Norman Prince Neuroscience Institute. All lectures are open to the public.

MARCH 4
WHO: Paul W. Glimcher, PhD, professor of economics and chief investigator, Center for Neural Science, New York University
WHEN: Monday, March 4 5 to 6 p.m.
WHERE: Brown University, Metcalf Chemistry Building, Friedman Auditorium, 190–194 Thayer Street.

VIDEO Paul W. Glimcher, PhD

FEBRUARY 13
WHO: Steven Pinker, PhD, professor of psychology at Harvard University and author of The Better Angels of Our Nature: Why Violence Has Declined [Penguin, 2011]. Pinker was named one of Time magazine’s “100 most influential scientists and thinkers,” and was listed in “Top Global Thinkers” by Foreign Policy magazine.
WHEN: Wednesday, February 13 5 to 6 p.m.
WHERE: Brown University, Salomon Center for Teaching, DeCiccio Family Auditorium, Room 101, College Green, 69–91 Waterman Street.
Bubly, Rich, Simon Named ‘Public Health Heroes’

PROVIDENCE – The Association of State and Health Territorial Officials (ASTHO) has designated three Rhode Island physicians as “Public Health Heroes.” The three designees — Gary Bubly, Josiah D. Rich and Peter Simon — were nominated for this distinction by the Rhode Island Department of Health (HEALTH).

“Each of these three doctors brings a high degree of dedication and professionalism to his public health work,” said Michael Fine, MD, director of HEALTH. “They are examples of the great resource that is Rhode Island’s primary care and medical community, as well as examples of how much progress can be made through the partnership of primary care and public health.”

GARY BUBLY, MD, FACEP, is director of the Department of Emergency Medicine at The Miriam Hospital and is a clinical associate professor of emergency medicine and medicine at the Warren Alpert School of Medicine at Brown University. HEALTH nominated Dr. Bubly for his assistance in writing regulatory language regarding emergency dispensing of medications from emergency rooms and for his assistance in developing the state’s legislation on its new Prescription Monitoring Program.

JOSIAH D. RICH, MD, MPH, is professor of medicine and epidemiology at the Warren Alpert School of Medicine at Brown University and an attending physician at The Miriam Hospital. HEALTH nominated Dr. Rich for his work in advancing for health policy changes to improve the health of people with addiction, including improving legal access to sterile syringes and increasing drug treatment for the incarcerated and formerly incarcerated populations. He has also been instrumental in developing Project Bridge, an outreach and intensive case management program for HIV-positive ex-offenders moving back into the community, and serves as co-director of the Center for Prisoner Health and Human Rights, based at Miriam.

PETER SIMON, MD, MPH, is the medical director of the Division of Community, Family Health, and Equity at HEALTH. HEALTH nominated Dr. Simon for his work as a national leader in the areas of childhood lead poisoning prevention, newborn screening, and environmental health, and for his passion and commitment to public health.

The United Health Foundation (UHF), with the help of ASTHO, has posted a list of public health heroes who serve as examples of the important work public health professionals carry out in our communities and across the United States. These individuals were included in press releases and announcements in coordination with the release of the 2012 edition of UHF’s America’s Health Rankings.

Overall, only 41 physicians and researchers nationwide have been recognized for their public health service.
Recognition

Dennehy receives distinguished service award from Pediatric Infectious Disease Society

Award from the Pediatric Infectious Disease Society [PIDS]. The award recognizes a Society member who has made an outstanding contribution to the specialty of pediatric infectious diseases and to the Society. She is past president of PIDS and has been involved in the society for more than 20 years.

“The impact of Dr. Dennehy’s tireless efforts in preventing childhood illness can be seen most evidently in her actions during the H1N1 flu outbreak. Rhode Island had the highest overall H1N1 vaccination rate in the country, as well as leading the nation in vaccinating children six months through 17 years of age,” said Robert Klein, MD, pediatrician-in-chief at Hasbro Children’s Hospital.

Dr. Dennehy founded and directed the clinical virology laboratory at Rhode Island Hospital, where she began her work on rotavirus. Her primary areas of research include the study of viral gastroenteritis and viral respiratory diseases. She is currently a member of the National Institutes of Health’s Collaborative Antiviral Study Group.

Dr. Dennehy has authored numerous peer-reviewed publications, written book chapters, and presented many lectures at national and international venues. She is also the recipient of five Dean’s teaching excellence awards from the Warren Alpert Medical School.

She is a graduate of Tufts University School of Medicine and completed her pediatric residency at Rhode Island Hospital, and then pursued fellowship training in infectious diseases at Children’s Hospital Medical Center–Beth Israel Hospital in Boston.

Fatima honors Testa for excellence in service

The medical staff of St. Joseph Health Services/Fatima Hospital recently honored DR. ANTHONY TESTA for excellence in service. At the ceremony were, from left, Ed Santos, Chairman of the Board, CharterCARE; Dr. Roberto Ortiz, medical staff president; Dr. Testa and Kenneth H. Belcher, president & CEO.
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National Appointments

W&I’s Frishman leads national council
PROVIDENCE – GARY N. FRISHMAN, MD, a reproductive endocrinologist at Women & Infants Hospital of Rhode Island, recently started a term as president of the national Council of Gynecologic Endoscopy (CGE).

Dr. Frishman, who is affiliated with Women & Infants’ Center for Reproduction & Infertility, is also actively involved with the hospital’s resident and medical student education and research and is a professor of obstetrics and gynecology at The Warren Alpert Medical School of Brown University.

The CGE is part of the American Association of Gynecologic Laparoscopists, established in 1971 to advance minimally invasive gynecology in the United States.

Migliori elected president of American Society of Ophthalmic Plastic and Reconstructive Surgery
PROVIDENCE – MICHAEL E. MIGLIORI, MD, FACS, ophthalmologist-in-chief at Rhode Island Hospital and its director of ophthalmic plastic and reconstructive surgery, has been elected the 45th president of the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS).

Dr. Migliori, clinical professor of ophthalmology at the Warren Alpert Medical School at Brown University, is also on the staff of the Providence Veterans Administration Medical Center.

He has written numerous peer-reviewed publications and book chapters, and lectures nationally and internationally on both clinical and advocacy topics. His research interests include anophthalmic socket rehabilitation, cosmetic laser surgery, and orbital oncology.

He has been active in both medical education and advocacy, serving as Rhode Island Delegate to the American Medical Association House of Delegates, on the Board of Directors of the American Medical Association Political Action Committee. He is past president of the Rhode Island Medical Society and the Rhode Island Society of Eye Physicians and Surgeons.

Dr. Migliori lives in Providence with his wife, Marianne, and their four children.

Founded in 1969, ASOPRS’ mission is to advance training, research, and patient care in the fields of aesthetic, plastic, and reconstructive surgery specializing in the face, orbits, eyelids, and lacrimal system.

Obstetrics journal names Rouse associate editor
PROVIDENCE – DWIGHT J. ROUSE, MD, a specialist in the Division of Maternal-Fetal Medicine at Women & Infants Hospital, has been named an associate editor for obstetrics of Obstetrics & Gynecology, the official journal of the American College of Obstetrics and Gynecology.

Dr. Rouse, a professor of obstetrics and gynecology at The Warren Alpert Medical School, is the Brown/Women & Infants principal investigator for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Research Network.
## Featured Online CME Programs February 2013

### WEBINAR

**FEBRUARY 26, 2013**  
**2013 CPT Coding Changes for Cardiology Services**  
11:00 AM - 12:30 PM (Eastern)  
1.5 AAPP Credits  
This webinar will address the latest updates on noninvasive cardiology, electrophysiology, pacemakers and implantable devices, heart catheters, interventional cardiology, PCI codes and new category 1 codes for VAD implantations and more.

### ONLINE CME

- **Best Biopsy Techniques for General Practice**  
  1 AMA PRA Category 1 Credit™ (Enduring)

- **Documentation and Procedures for Effective Pain Management**  
  1 AMA PRA Category 1 Credit™ (Enduring)

- **Fraud and Abuse: Compliance is the Key to Prevention**  
  1 AMA PRA Category 1 Credit™ (Enduring)  
  1 Ethics | 1 TMLT

- **Is That Health Plan Contract Good for Your Practice?**  
  1 AMA PRA Category 1 Credit™ (Enduring)

- **Privacy and Security: The New Regulatory Environment**

- **Risk Analysis and Meaningful Use: How to Get Your Practice Ready**

### PUBLICATION

- **How to Create and Maintain Life Balance**  
  1 AMA PRA Category 1 Credit™ (Enduring)  
  1 Ethics

### QUICK LINKS

- RIMS' Online CME Calendar
- RIMS Website

### SUBJECT AREAS

- Billing
- Cancer
- Ethics
- Leadership
- Legal
- Patient Safety
- Physician Health
- Primary Care
- Risk Management
Area Appointments

St. Anne’s names Katz orthopedics chief
FALL RIVER – JERALD W. KATZ, MD, has been appointed chief of orthopedics at St. Anne’s Hospital.

A resident of Barrington, RI, Dr. Katz is certified to perform MAKOplasty® knee and hip procedures. His clinical interests include general and pediatric orthopedic surgery, including surgical treatment of scoliosis and other spinal conditions.

A member of Saint Anne’s Hospital’s medical staff since 1990, he is a fellow of the American Academy of Orthopedic Surgeons and a diplomate of the American Board of Orthopedic Surgery.

He has served as a clinical instructor in the Department of Orthopedics at Brown University’s Alpert Medical School and the Department of Pediatrics at Tufts University School of Medicine. He maintains his office practice with Coastal Orthopaedics in Fall River.

Southcoast appoints Pricolo chief of general surgery
NEW BEDFORD, MASS. – Barrington resident VICTOR PRICOLO, MD, has been appointed chief of general surgery at Southcoast Health System. He is a surgeon with Southcoast General Surgery, a practice of Southcoast Physicians Group.

In his new role, Dr. Pricolo will lead the development of a system-wide program for general surgery and the creation of a system-wide colorectal center of excellence, working with surgeons in the community to provide full service, integrated colorectal care.

Dr. Pricolo has been a pioneer of minimally invasive surgery and continence-preserving procedures in colon and rectal surgery for decades.

He received his medical degree from the University of Milan, Italy, and completed a surgical residency at Rhode Island Hospital. He had additional training in surgical research and metabolism, gastrointestinal endoscopy and colon and rectal surgery. He is a diplomate of the American Board of Surgery.

Pulicken joins staff at Memorial Hospital
PAWTUCKET – Memorial Hospital of Rhode Island recently appointed MATHEW PULICKEN, MD, an assistant professor of neurology at the Warren Alpert Medical School, to its medical staff in the Department of Neurology.

Dr. Pulicken completed his neurology residency at Tufts University and a fellowship in electroencephalography and epilepsy from the Massachusetts General Hospital. He holds a master’s in health sciences from the Johns Hopkins Bloomberg School of Public Health in Baltimore.

Kozel joins Wood River Health
HOPE VALLEY – Pediatrician MAGGIE KOZEL, MD, has joined the staff at Wood River Health Services.

Dr. Kozel, formerly of Narragansett Bay Pediatrics, served as a Navy physician for eight years before entering private practice in Washington, D.C., and Rhode Island. She also teaches and writes about health care reform, has written a memoir, The Color of Atmosphere: A Doctor’s Journey In and Out of Medicine, and blogs for the Huffington Post and the New York Times’ Well blog.

She holds a medical degree from Georgetown University School of Medicine and lives in Jamestown with her family.
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LAURA KIBUUKA, 26, a student at the Alpert Medical School of Brown University, died on January 2, 2013 after being struck by an Amtrak Acela Express train on the train track at the South Attleboro, Mass., station. The MBTA Transit Police and the Bristol County District Attorney’s office are investigating the incident.

She was a 2009 graduate of the University of Massachusetts, Boston, with a degree in biology. According to a report in the Brown Daily Herald, Kibuuka entered the medical school with the class of 2015, but took a year off and was not on campus this fall. During her time at Brown, Kibuuka served as a representative for her class on the Student Health Council.

She is survived by her parents, Diana and Samuel Kibuuka, and six siblings. A native of Uganda, she lived with her family in Watertown, Mass. Students and administrators at the medical school organized remembrances in her honor and helped collect money to return Kibuuka’s remains to Uganda.

ERNEST P. MENNILLO, MD, 90, died on January 22, 2013. Dr. Mennillo is survived by his loving wife of 60 years Joanne (Macomber) Mennillo.

Dr. Mennillo was a WWII veteran having piloted a B-17 with the 490th bomb group of the 8th Air Force, US Army Air Corps in England. Upon returning from the war, Dr. Mennillo earned his medical degree from the University of Rochester and came to Rhode Island to do his pediatric residency at Rhode Island Hospital. Dr. “Ernie” practiced pediatrics in Cranston for over 50 years, including many years as the pediatrician for the Cranston school system, and later served as chief of pediatrics at Kent County Memorial Hospital where he had also served 13 years in the emergency room.

He leaves four sons: Ernest P. (Paul) Mennillo Jr. of Warwick, Dr. Roger Mennillo of Barrington, Dana Mennillo of Warwick, Todd Mennillo of Newport, a daughter Melissa Day of Cranston, as well as 11 grandchildren and 5 great-grandchildren.

JOHN A. ROQUE, MD, 96, of Naples, Florida, and formerly of Plum Beach, North Kingston, died on January 17, 2013 at the Massachusetts General Hospital in Boston. He was the husband of the late Elizabeth (Bolton) Roque. Born in Providence, he lived in Plum Beach for many years before moving to Naples 10 years ago.

A graduate of Providence College and Tufts University Medical School, Dr. Roque served his internship at Philadelphia General Hospital and his residency at Henry Ford Hospital in Detroit. He was a U.S. Navy veteran of World War II. Following his naval service, he established his medical practice in Cranston, where he maintained his office until his retirement 30 years ago.

He was affiliated with Rhode Island Hospital and St. Joseph Hospital, and was president of the medical staff at St. Joseph Hospital in 1975 and 1976. He was a member of the American Medical Association, the Rhode Island Medical Association, and the Catholic Physicians Guild.
The Words of Disordered Consciousness

STANLEY M. ARONSON, MD

Medicine provides its practitioners with a spectrum of useful words to describe the many possible states of disordered consciousness. And we define consciousness as the patient’s level of alertness, awareness of, and responsiveness to, his immediate environment.

The most profound loss of consciousness, short of cerebral death, is called coma, a word descending directly from a Greek word originally meaning a state of insensibility, and related to the Greek term, comein, meaning to lie down or to sleep. This root word, somehow, also defines hair; and so, acomia describes a state of baldness (a-, being a privative prefix); and those mobile astronomic bodies of the autumn night skies, because of their visible tails resembling hair, are hence called comets.

Stupor, defined as a state of torpor, numbness or inattention, comes from the Latin, stupere, meaning possessing a dull demeanor. The same Latin root gives rise to a cluster of pejorative words such as stupid; but also to words such as stupefy, a term defining a state of astonishment rather than bland numbness of affect.

Lethargy is defined as a drowsiness and slowness in response. It derives from the Greek, lethe, meaning oblivion, and earlier, from the mythic river in Hades, called Lethe, whose waters when consumed cause forgetfulness. The word, lethal, on the other hand, is from the Latin, letalis, meaning deadly. And litharge, the lead monoxide ore, is from a compounded Latin word, lithargyrus, meaning, literally, stone silver.

Sedative, an adjective describing an agent capable of calming, is from the Latin, sedare, meaning to allay, to sit down. A number of English words are cognate with sedate: assiduous, dissident, sediment, insidious, sedulous but not sedition, which stems from the Latin, sedetio.

Delirium, defined as a mental state of inappropriate excitement and agitation, is from the Latin, delirare, meaning to turn aside from an agricultural furrow or, more metaphorically, deviating from a straight track. And thus the term, delirium, becomes a poetic representation for departure from an allegedly normal state. Nor should one forget Hypnos [the Greek god of sleep] and his Roman equivalent Somnos whose brother, incidentally, was Thanatos. And thus arose such medically relevant words as hypnosis, somnolence and thanatology.

And finally, the word, conscious. It is derived from the Latin compound, conscius, which in turn represents the merger of con [meaning with] and scire [to know].
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Antiseptic Glee Club performs at RIH Club fete

On February 13, 1913, the 13th annual dinner of the Rhode Island Hospital Club was held at the Crown Hotel on Weybosset Street. According to a subsequent report in the Providence Medical Journal, “the hoodoo suggested by the numerical anniversary, the day of the month and the year, was not in evidence, as under the timid but altogether satisfactory guidance of Dr. Charles H. Higgins, as President and toastmaster, the unlucky anniversary was passed with great enjoyment…”

Not quite. The first tenor in the Antiseptic Glee Club [under Dr. Rice’s leadership] “suffered a rupture of the left posterior crico-arytenoid,” according to the article.

Nevertheless, the 100 guests enjoyed the repast: Blue Point oysters, Mock Turtle Amontillado, Pommes Saratoga, mashed turnip, chiffonade salad, followed by harlequin ice cream and demi-tasse.

At the fete, Professor Courtney Langdon spoke on the demise of the general practitioner. However, stated the article, “he evidently did not appreciate the fact that half the audience was engaged in special practice when he stated that when he was alive he wanted the general practitioner but when ready to die, it was necessary to call the specialist to insure a thoroughly good job.”

Sailing on the SS Moltke

Drs. J.M. Peters and E.B. Smith sailed on February 22, 1913, by the Hamburg-American steamer, the S.S. Moltke, for a trip to the West Indies.

Pulmotor in RI

The Pulmotor was used for the first time in Rhode Island to resuscitate a case of asphyxiation by illuminating gas on January 15, 1913. Heinrich Drager patented the Pulmotor in 1907, considered the first ventilator to be used worldwide in the history of medicine.