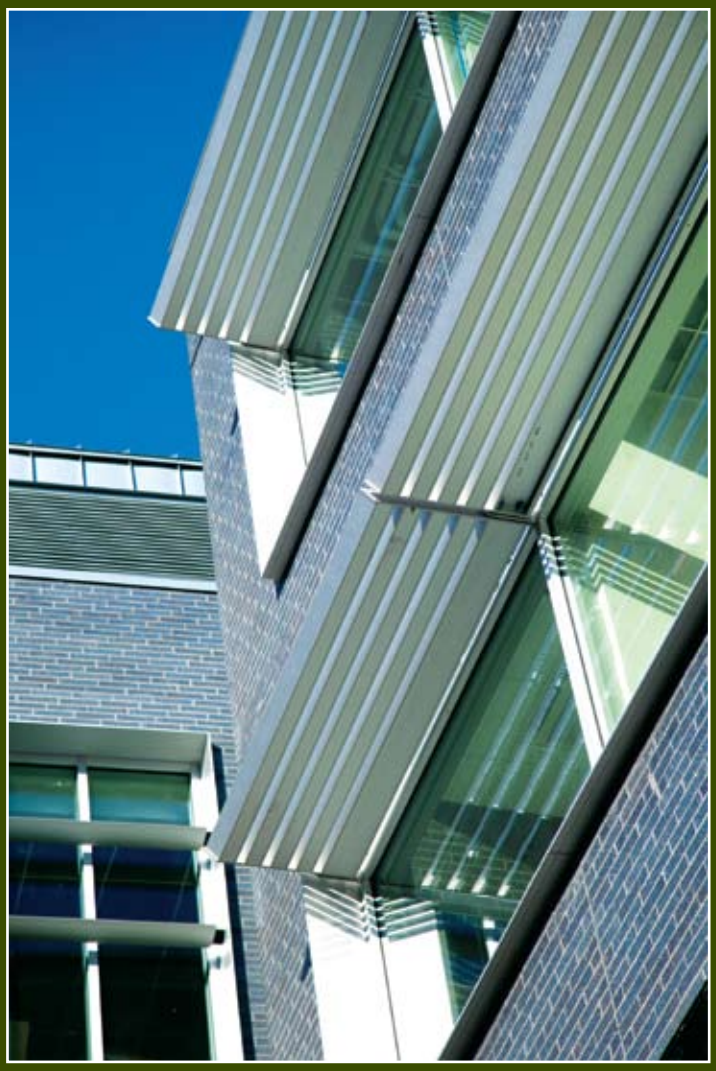
Volume 95 No. 9 September 2012

Medicine & Health RHODE ISLAND



University of Rhode Island College of Pharmacy

Isn't it time you got your own second opinion?

The Rhode Island Medical Society has partnered with Butler & Messier Insurance to provide an exclusive **CONCIERGE PROGRAM** for all your insurance needs. Everyone in the Rhode Island medical community is eligible for the best rates for your home and auto insurance, as well as your office policies.

For your own FREE – *NO OBLIGATION* – SECOND OPINION call John Divver at 401.728.3200

RHODE ISLAND MEDICAL SOCIETY
RIMS-INSURANCE BROKERAGE CORPORATION

BMI BUTLER & MESSIER, INC. INSURANCE

www.ButlerandMessier.com

Cover: "University of Rhode Island College of Pharmacy," digital photo used with permision of the University of Rhode Island College of Pharmacy.

Medicine & Health RHODE ISLAND VOLUME 95 NO. 9 September 2012

PUBLICATION OF THE RHODE ISLAND MEDICAL SOCIETY

COMMENTARIES

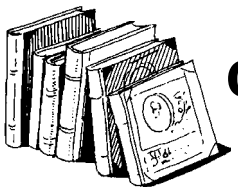
CONTRIBUTIONS

SPECIAL ISSUE: University of Rhode Island College of Pharmacy
Guest Editor: **Norma J. Owens, PharmD, BCPS, FCCP**

COLUMNS

Medicine and Health/Rhode Island *(USPS 464-820), a monthly publication, is owned and published by the Rhode Island Medical Society, 235 Promenade St., Suite 500, Providence, RI 02908, Phone: (401) 331-3207. Single copies $5.00, individual subscriptions $50.00 per year, and $100 per year for institutional subscriptions. Published articles represent opinions of the authors and do not necessarily reflect the official policy of the Rhode Island Medical Society, unless clearly specified. Advertisements do not imply sponsorship or endorsement by the Rhode Island Medical Society. Periodicals postage paid at Providence, Rhode Island. ISSN 1086-5462. POSTMASTER: Send address changes to Medicine and Health/Rhode Island, 235 Promenade St., Suite 500, Providence, RI 02908. Classified Information: Cheryl Turcotte/Rhode Island Medical Society, phone: (401) 331-3207, fax: (401) 751-8050, e-mail: cturcotte@rimed.org. Information on permissions and reprints available from jdteehan@rimed.org.*

Note: *Medicine & Health/Rhode Island* appears on www.rimed.org, under Publications.



Commentaries

Voter Restrictions in Florida (and elsewhere in the United States)

I'VE BEEN WRITING A MONTHLY COLUMN for this journal, *Medicine and Health/Rhode Island*, since 1999 and have assiduously avoided political issues for several reasons, the two most important being that I don't want to upset people, and there's no reason to think that I know more or better about most political topics than the readers. As someone recently put it in a newspaper op/ed piece, "the predictions of political writers have been no better than those of trained chimps." However, and with some trepidation, I wish to express my thoughts, as a neurologist on the issue of voter fraud in the US.

This issue, guided almost entirely by nativist anti-illegal immigrant sentiment, is allegedly an attempt to disenfranchise voters believed to have been voting illegally, but more clearly aimed at the poor and uneducated. How Rhode Island came to join this group is something I don't understand, and since I'm only a neurologist, and not a tea-leaf reader, will leave this to trained columnists (and chimps) to figure out. The state that has attracted the most attention has been Florida, probably because the Obama administration has challenged them in court. Under the guise of removing illegal alien voters from the voting rolls, a rather bald-faced attempt was made to remove as many likely Hispanic voters as possible. Since illegal aliens are presumably Hispanic, the names to be investigated were largely Hispanic.

The state of Florida investigated 2,500 people and found 50 who should not have been qualified for voting rights. Actually, it turns out that the original list of people to be investigated was believed to be 180,000. As most of us recall, the presidential election of 2000 turned on a few hundred votes and a Supreme Court decision. So even 50 votes, which doesn't sound so important, may be, whereas 180,000 clearly is.

So, why am I writing about this? The reason is neurological, where I do know something. Florida has the relatively oldest population in the US. There are more than three million people over the age of 65 in Florida, about 17% of the population. Using the figure that applies in general to the US, about 13% of people over the age of 65 have Alzheimer's disease. Since there are other causes for dementia, 13% is a significant underestimate. This means that over 400,000 potential voters in Florida are demented.

If Florida or other states are serious about restricting voting to people who "should" vote, they should have taken on the difficult task of trying to exclude people who shouldn't be voting, whether legal or not. This is not an easy exercise. About 20% of voting is now done by absentee ballot. Nowhere is the possibility of voter fraud higher than with the demented. Dementia appears in mild as well as severe forms. Mildly demented people may interact in a seemingly normal fashion until stressed by some unexpected problem or memory lapse. Severe dementia, on the other hand, is always obvious, due to inappropriate behavior, problems following conversations, difficulties of expression and memory impairment. The demented generally do not apply for absentee ballots, but their caretakers may, on their behalf. In some cases the spouse, or child, or best friend, truly knows how the person would have voted and votes the same way. After all, barring a remarkably unusual candidate, a life-long Democrat or Republican is unlikely to change stripes late in life. But sometimes the choices may not be so clear, or the person controlling the ballot has a major interest in the election outcome, enough to trump a consideration for how the demented person would have voted, or sometimes there is no way to determine how the person would have voted and the child simply gets to vote twice.

I don't pretend to have an answer to the question of how we keep demented people from voting that would satisfy everyone. It is a topic of interest to many and has been addressed by lawyers, ethicists and geriatricians resulting thus far in little legislative action. Not too many years ago, Strom Thurmond, the senator from South Carolina, died in office, demented. His dementia probably didn't matter to his staff, and maybe not to his constituents either, since his staff had done the work and decision-making for years. I doubt that anyone knows how many members of the Congress are demented, but when you see photos of the US Senate, "the world's greatest deliberating body," it looks remarkably like an advertisement for a well-healed nursing home.

Politicians who are trying to rid the voting rolls of illegal voters would better serve their constituents by trying to reduce voting by people who are no longer mentally competent. This is not an easy road, and may be more challenging for theoretical legal reasons than the task of limiting driving by the demented, an extraordinarily difficult task which no state has yet tackled.

The reasons, I believe, that the elderly have, probably largely to their own detriment, been able to avoid restrictive driving and tests on voting competency is their power in numbers. They, unlike the poor and uneducated, actually vote, and sometimes this means that their family gets to vote twice.

– JOSEPH H. FRIEDMAN, MD

Disclosure of Financial Interests

Lectures: Teva, Ingelheim Boehringer; General Electric

Consulting: United Biosource; Bubaloo, Halsted, Reitman LLC; EMD Serono; Genzyme; Teva; Acadia; Addex Pharm; Schwarz Pharma

Research: MJFox; NIH: Cephalon; EMD Serono; Teva; Acadia

Royalties: Demos Press

CORRESPONDENCE

e-mail: joseph_friedman@brown.edu

Individuals: Each a Majority of One

Ronald Reagan once declared that you can tell a lot about a man by the way he eats jelly beans. The "Reagan Jelly Bean Consumption Test" may not be the most critically diagnostic of behavioral tests to reveal something about a person's character, but it represents a beginning. The test may, for example, reveal hidden traits of avarice, covert leanings toward hoarding, color blindness, perhaps an indifference toward dental hygiene, even a subversive streak of generosity.

Human character, and the attributes that make each of us distinguishable from the crowd, is an impossibly complex field of inquiry. And therefore the Reagan Test, while not very sophisticated, nonetheless gets us started. Will Rogers judged people by seeing their reaction to his offer of chewing tobacco, currently a rarely employed test of character. Some sociologists believe that much of a person's character may be divulged by asking, "When confronting a new problem, what is the very first step that you would undertake ?" These social scientists would then divide the many responses into two major categories: Those responses that point to the recruitment of oneself as their best source: "the Lone Wolf Response"; and, in the second category, those responses that would first enlist the advice and counsel of others; in essence, convening a gathering to address the problem: "the Committee Response."

Thus, by this wretchedly simple criterion, we can assign humanity to but one of two crude categories: Those who believe that great things in life are best accomplished by individuals acting as solitary, inward-seeking vanguard agents, depending primarily upon their own accumulated experience and inner capabilities (The Lone Wolves); and the contrary belief, that only through the constructive cooperation of the many may humanity achieve its highest purposes in life (The Committee Seekers.).

The Lone Wolves disparage committees stating that their sole purpose is to entice creative ideas from the open marketplace; and then, through collective action, choke them to death. The Lone Wolves also denounce the tendency of committees to confront societal problems by reducing the aggregate of humanity into something they call the masses. And then, by calling them 'the masses' they may then deride them as people with no faces, no individuality, no idiosyncratic thought.

The effective functioning of a society of humans has always depended upon a relentless yet healthy tension between those two opposing social forces: the need for people to work together, coordinating their creative skills while subordinating their sense of individuality for the greater good of the community. And in creative opposition to this, the equally paramount need to protect our nascent sense of individuality, nurturing it and defending it from the efficiency experts of society who daily pray at the altar of ergonomics.

If one extreme is reached, we end up witnessing a society with but one faith, one political doctrine, one language and probably one beloved leader-for-life. And the other extreme ? Total, permissive anarchism with not even the most rudimentary of communal regulations, a chaotic society that would offend even the most troglodyte libertarian. And, in all of this, the Lone Wolf folk are labeled as eccentrics, potential heretics, bohemians who tend to sulk, anti-social deviants who avoid mass rallies and will argue with anyone, even the Good Fairy. While the committee-loving crowd are seen as excessively gregarious, lovers of parties, life members of the Klu Klux Klan, and inclined to compromise on all issues even the content of the Ten Commandments.

Where in this distressing dichotomy stands the earnest individual seeking what is best for himself, his family and his community ? His personal views overlap those of the Lone Wolf persuasion as well as the views of the Committee-loving crowd. He proclaims, first, that he is a freely thinking individual rather than an adherent; and he recalls that the word 'individual' is derived from a Latin word describing a human who cannot be divided into many factions, one who is ultimately indivisible; and thus he realizes ruefully that no one philosophy can possibly define him.

This person, this "individual", vividly recalls that individuality is at the very core of both the arts, the creative sciences and social innovation; and that the collectivist states fear most the specter of individuality arising amidst its citizens. Nikita Khrushchev (1894-1971), in a memorable 1956 speech, declared: "Comrades ! We must abolish the cult of the individual decisively, once and for all." And, an opposing, but less amplified, voice: "The enduring merit of any nation, in the long run, is the worth of the individuals composing it." (John Stuart Mill (1806-1873).

– Stanley M. Aronson, MD

Stanley M. Aronson, MD is dean of medicine emeritus, Brown University.

Disclosure of Financial Interests

The author and his spouse/significant other have no financial interests to disclose.

Correspondence

e-mail: SMAMD@cox.net

The University of Rhode Island College of Pharmacy

Bongsup Cho, PhD, and Norma J. Owens, PharmD, BCPS, FCCP

The University of Rhode Island College of Pharmacy (www.uri.edu/pharmacy/) will begin its 55th year at the University in a $75 million research and teaching facility. The new pharmacy building is the largest academic building on the Kingston campus. To mark the occasion, we planned a ribbon-cutting ceremony on September 4, a one-day symposium on *Drug Therapy in the 21st Century* for September 14, 2012, and an international scientific conference featuring researchers from around the world from September 28–30, 2012.

The College includes more than 50 faculty who are leading experts in pharmacology, toxicology, medicinal chemistry, natural product chemistry, pharmaceutics, pharmacokinetics, clinical sciences and practice, epidemiology, and pharmacoeconomics. These individuals conduct cutting-edge research in areas that range from the neurosciences, HIV, diabetes, and cancer to pharmacoeconomic management of pharmaceuticals. We are also passionate about mentoring and training the next generation of scientists, practitioners, and academics by offering highly-specialized graduate MS and PhD degrees in pharmaceutical sciences. More than 20 practice-based faculty are located in health settings across the state where they teach and provide clinical services to the people of Rhode Island. The healthcare settings for practice faculty include acute care hospitals, long term care institutions, clinics, physician offices, community pharmacies, as well as consulting practices with the state.

The new pharmacy building is the largest academic building on the Kingston campus.

In the 2011–12 academic year, we had 572 **Doctor of Pharmacy (PharmD)**, 77 **Bachelor of Science in Pharmaceutical Science (BSPS)**, and 66 graduate students in the College. Since 2000, the College has received over $83 million in private and federal funds to support research in the biomedical, pharmaceutical and clinical sciences. In this edition of *Medicine & Health/Rhode Island*, we highlight the research and clinical practice work of several junior faculty at the College. In addition, the College has a large group of senior faculty who are actively engaged in funded research on drug discovery and development in cancer, HIV, and Alzheimer's disease, as well as molecular toxicology, nanotechnology and geriatrics.

We thank *Medicine & Health/Rhode Island* for the opportunity to showcase just a small sample of the work at the College. We would also thank the citizens of Rhode Island for supporting the 2006 bond that provided funding for the new College of Pharmacy building. Please come and visit the College at our new facility.

Bongsup Cho, PhD, is a Professor in the Department of Biomedical and Pharmaceutical Sciences and Associate Dean for Research and Graduate Education.

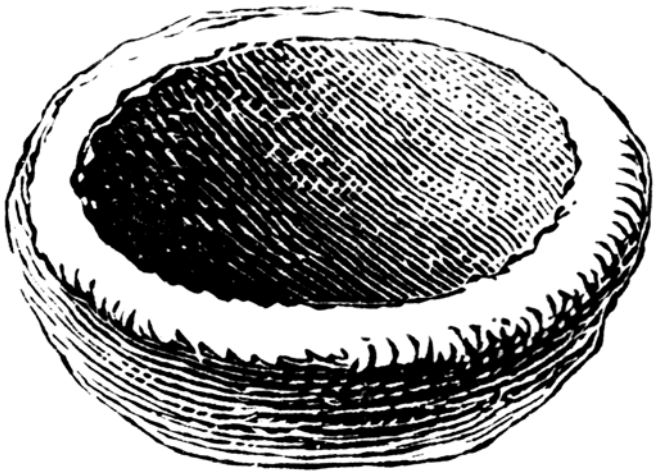
Norma J. Owens PharmD, BCPS, FCCP is a Professor in the Department of Pharmacy Practice. She has a clinical practice in Geriatrics at the Steere House Nursing Home and Rehabilitation Center in Providence.

Disclosure of Financial Interests

The authors and/or their spouses/significant others have no financial interests to disclose.

Correspondence

Norma J. Owens, PharmD, FCCP
Department of Pharmacy Practice
College of Pharmacy
University of Rhode Island
7 Greenhouse Rd
Kingston RI 02881
phone: (401) 874-2964
e-mail: Normaowens@uri.edu



The Role of Comparative Effectiveness Research in Medicine and Health

Aisling R. Caffrey, PhD, MS

Today, more than ever, healthcare systems need to do more with less. Clinicians, decision-makers, and other stakeholders are seeking evidence-based healthcare practices that control expenditures while improving patient care. Of particular concern is the paucity of supportive clinical data related to alternative therapeutic options for the treatment of acute and chronic conditions. The demand for high-quality pharmacoepidemiologic and pharmacoeconomic research is at unprecedented levels, with government agencies, foundations, and private industry collectively committing billions of dollars in funding for studies examining the beneficial and unintended effects of medications.[1,2] Pharmacoepidemiology provides vital insights into effectiveness and safety, while pharmacoeconomics addresses value and costs given limited healthcare resources.

What is Comparative Effectiveness Research?

Often, the selection of the most appropriate treatment is complicated by limited efficacy, effectiveness, and safety data. In efficacy trials, the capability to produce the planned effect under ideal conditions is typically assessed in an active study drug compared to a placebo comparator. Alternatively, comparative effectiveness focuses on head-to-head comparisons between two or more active treatments in the real-world clinical setting. While randomized controlled trials provide evidence for the drug approval process, there is a lack of comparative data on which agents produce the most favorable clinical outcomes with the fewest side effects in various real-world clinical populations. Realizing the need for evidence supporting prescribing decisions and the importance of comparative effectiveness research, programs developed under the 2009 American Reinvestment and Recovery Act and 2010 Patient Protection and Affordable Care Act, as well as initiatives from other public and private agencies, have sought to fill critical gaps in knowledge regarding best treatment practices.

Study Designs and Cautions of Comparative Effectiveness Research

Comparative effectiveness research can be carried out with various study designs including clinical trials and observational studies, as well as meta-analyses and systematic reviews. Study design selection depends on the research question, exposure prevalence, primary and secondary outcomes, data availability, existing knowledge, costs, and limitations of each design. One of the greatest challenges for comparative effectiveness clinical trials and observational studies relates to the comparability of patients in different treatment groups. Confounding by indication is a primary concern in comparative effectiveness research. The likelihood of receiving different drugs directly relates to the indication for treatment, patient characteristics, provider characteristics, and facility characteristics which can confound the observed relationship between exposure and outcome.[3] Further, it is often difficult to conceptualize and define these potential external influences.

Often, the selection of the most appropriate treatment is complicated by limited efficacy, effectiveness, and safety data.

Clinical trials rely on randomization to balance baseline patient characteristics between study drugs. Whereas observational studies use analytic techniques and other study design approaches to mitigate the impact of confounding by evenly distributing significant variables associated with the exposure and outcome.[3] Randomization is considered the gold standard approach to balancing patient characteristics, including both measured and, more importantly, unmeasured confounders, in order to evaluate the impact of treatment on the study endpoints. However, residual confounding can occur through the omission of a key confounder analytically or in cases of randomization failure. Indeed, subgroup analyses are highly criticized as the effects of randomization may have failed in the subgroups assessed, resulting in analyses of nonrandomized data.

Imbalance in clinically significant variables can bias the results of both clinical trials and observational studies. Usually it is difficult to assess whether these variations were due to chance or selection bias, particularly when statistically significant differences remain after randomization in clinical trials or analytic adjustment in observational studies. Such variations may indicate residual confounding, for example, if additional differences existed between treatment groups in variables that were not assessed (unmeasured confounders), or may even indicate effect modification. When significant baseline imbalances are observed between treatment groups, regardless of study design, assessments of residual confounding should be completed.

In general, the resources required for large clinical trials, particularly those powered to detect superiority, are cost prohibitive and patient enrollment can be slow. Additionally, non-inferiority is easier to detect than superiority. Due to these limitations, there may be reluctance to fund head-to-head active comparator trials. A major strength of observational comparative effectiveness research is that it uses existing data to discern important real-world differences in effectiveness and safety. To improve the efficiency of comparative effectiveness clinical trials, observational research can be used to guide the development and design of randomized trials.

Components of a Successful Comparative Effectiveness Research Program

Properly designed, conducted, and interpreted comparative effectiveness research can provide evidence-based knowledge for clinical decision-making that optimizes patient outcomes. As researchers and consumers of healthcare research, the best resources for comparative effectiveness technical reports and methods guides include the Agency for Healthcare Research and Quality Effective Healthcare Program, the Institutes of Medicine, the Patient-Centered Outcomes Research Institute, and the National Information Center on Health Services Research and Health Care Technology. Other resources that assist in the critical evaluation of the literature include the GRACE principles, Good Research Practices for Comparative Effectiveness Research from the International Society for Pharmacoeconomics and Outcomes, and the Guidelines for Good Pharmacoepidemiology Practices from the International Society for Pharmacoepidemiology.[4-6]

For comparative effectiveness research, a strong, interdisciplinary research team is needed, and core contributors should include physicians, pharmacists, and pharmacoepidemiologists. Also, patients are increasingly recognized as key stakeholders in designing clinical research.[2] With the tremendous growth in health outcomes and health economics, there is record demand for trained professionals in these fields, though few universities in the country offer such programs. The Program in Pharmacoepidemiology and Pharmacoeconomics of the University of Rhode Island College of Pharmacy engages in the focused, interdisciplinary training of the next generation of pharmacoepidemiologists and pharmacoeconomists.

My research program has focused on the comparative effectiveness of antimicrobials for the treatment of infectious diseases.[7] The goal of this research is to provide insight into the optimal treatments for invasive infections, enhancing patient safety by reducing treatment failures and adverse outcomes, through the use of rich data sources and sophisticated analytical techniques.[8,9] To address potential biases, the most accurate sources available for defining exposures, outcomes, and potential confounders are used, including pharmacy data, microbiology data, laboratory results, and records of inpatient and outpatient care from electronic medical records. Further, we utilize advanced statistical methods, including propensity scoring, calibration, and assessments of residual confounding, to mitigate confounding and achieve balance between treatment groups.

In summary, with the proper study team, study design, study methods, and resources, comparative effectiveness research plays an important role in evidence-based medicine. Evidence-based pharmacotherapy is necessary for maximizing positive clinical outcomes and minimizing negative effects to better inform and improve clinical practice.

Acknowledgements

The views expressed are those of the author and do not necessarily reflect the position or policy of the United States Department of Veterans Affairs.

Dr. Caffrey is supported in part by a Department of Veterans Affairs Career Development Award. Dr. Caffrey thanks Dr. Kerry LaPlante, Dr. Stephen Kogut, and Dr. Brian Quilliam for their thoughtful review of the manuscript.

References

1. Institute of Medicine. Initial national priorities for comparative effectiveness research. Washington, DC: Institute of Medicine, 2009.
2. Patient-Centered Outcomes Research Institute. Pre-public comment draft report of the Patient-Centered Outcomes Research Institute Methodology Committee. Washington, DC: Patient-Centered Outcomes Research Institute; 2012.
3. Strom B, Kimmel S, eds. *Textbook of Pharmacoepidemiology*. Chichester, West Sussex: John Wiley & Sons, Ltd; 2006.
4. Dreyer NA, GRACE Initiative Collaborators and Supporters. GRACE Principles: Good ReseArch for Comparative Effectiveness. 2010.
5. Berger ML, Dreyer N, Anderson F, Towse A, Sedrakyan A, Normand SL. Prospective observational studies to assess comparative effectiveness: the ISPOR good research practices task force report. *Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2012;15:217–30.
6. International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices. *Pharmacoepidemiol Drug Saf*. 2008;17:200–8.
7. Caffrey AR, Quilliam BJ, LaPlante KL. Comparative effectiveness of linezolid and vancomycin among a national cohort of patients infected with methicillin-resistant Staphylococcus aureus. Antimicrob Agents *Chemother*. 2010;54:4394–400.
8. Caffrey AR, Quilliam BJ, LaPlante KL. Risk factors associated with mupirocin resistance in meticillin-resistant *Staphylococcus aureus*. *J Hosp Infect*. 2010;76:206–10.
9. Caffrey AR, Laplante KL. Changing epidemiology of methicillin-resistant Staphylococcus aureus in the Veterans Affairs Healthcare System, 2002-2009. *Infection*. 2012;40:291–7.

Aisling R. Caffrey, PhD, MS, is Assistant Professor of Pharmacoepidemiology at the University of Rhode Island College of Pharmacy and an Investigator in the Infectious Diseases Research Program at the Providence Veterans Affairs Medical Center.

Disclosure of Financial Interests

Aisling R. Caffrey, PhD, MS, receives grant support from Pfizer, Inc.

Correspondence

Aisling R. Caffrey, PhD, MS
URI College of Pharmacy
7 Greenhouse Road
Kingston, RI 02881
phone: (401) 874-5320
e-mail: Aisling.Caffrey@uri.edu

Pharmacists as Diabetes Educators and Diabetes Disease Managers

Lisa Cohen, PharmD, CDE, CDOE

Diabetes is a complex condition that requires patients to perform many self-care activities. Prescribers must manage diabetes patients with nine different categories of diabetes medications, nine combination oral medications, four different categories of insulin and three combination insulin products available on the US market. The prices of these medications and diabetes supplies costs the average person with diabetes approximately $2,900 to $3,100 per year in direct pharmacy costs services in Rhode Island, not including any medical services or medications for diabetes complications.[1] In addition to prescribing and managing medications, providers are responsible for the patient's overall quality measures such as hemoglobin A1C monitoring, foot screenings, cholesterol measurements, and ensuring their patients obtain their yearly dilated eye exam. Endocrinologists, diabetes education centers, and pharmacists are available throughout the state of Rhode Island and nationally to assist patients and primary care providers.

Currently, pharmacists completing their Doctor of Pharmacy degree and/or residency programs are highly trained providers with the necessary skills to co-manage and educate patients on a wide variety of diabetes issues. Pharmacists are successfully involved in many aspects of diabetes care such as outpatient clinics, community pharmacies, pharmacist-led group medical appointments at the Veterans Affairs Medical Center, patient-centered medical homes, surgical units, home telehealth monitoring, and diabetes education.[2-5] Locally, many pharmacists have obtained the **Rhode Island Certified Diabetes Outpatient Educator** (**CDOE**) certification as well as the nationally recognized **Certified Diabetes Educator** (**CDE**) certification.

Certified Diabetes Outpatient Educator Pharmacist vs. Certified Diabetes Educator Pharmacist

Nationally, the **National Certification Board of Diabetes Educators** (**NCBDE**) has been certifying diabetes educators since 1986. As of July 2011, there is one CDE pharmacist in Rhode Island out of 51 total CDEs (2% of the CDE professionals) and 26 CDE pharmacists in Massachusetts out of 499 total CDEs (5.2% of the CDE professionals). **Certified Diabetes Educators** (**CDEs**) may be clinical psychologists, nurses, dietitians, pharmacists, occupational therapist, optometrists, physical therapists, physicians, or social workers. These practitioners must have two years of diabetes education experience prior to the CDE exam. In addition, they must be employed performing 1,000 hours of **diabetes self management education** (**DSME**) including educational interventions, personalized follow up plans, and documentation of these interactions. Four hundred of the 1,000 hours must be accrued within the year prior to application for the exam. This would mean that the practitioner must be employed eight hours per week performing DMSE with patients. Most community pharmacists would be precluded from obtaining these hours due to their other generalized practice responsibilities. For example, a community pharmacist may speak to a patient for five to ten minutes regarding their diabetes medications and glucose monitoring, establish individual goals, and document the intervention. These types of interventions would need to be more than 20% of a 40-hour-work week of a community pharmacist. While this could happen, it is probably a rare occurrence. The time can be counted towards the 400 hours if the patient has set goals for follow up and the pharmacist has scheduled time to follow up with the patient on these issues. As of 2007, **American Diabetes Association** (**ADA**) recognized sites as single-discipline or multidiscipline sites and may employ one discipline to supply all of the education or a combination of any of the approved providers. This was a change from the past, in which, each ADA recognized site had to have a nurse and a dietitian with no mention of a pharmacist as part of the healthcare team. Now, each discipline could set up its own ADA recognized site, if desired. The ADA recognized site allows diabetes education billing to Medicare-eligible enrollees, for individual and group education.

Certified Diabetes Outpatient Educators (**CDOE**) organization was established in Rhode Island in 1980.[6] It was created to help certify nurses, dietitians and pharmacists as diabetes educators. The CDOE organization provides continuing education to their educators as well as assistance in procedures such as billing for services and obtaining provider status for third party payers. The CDOE does not include an hourly requirement to test for competency. Rather, the CDOE requirement includes successful completion of five-weekly all-day workshops, a CDOE competency exam, teaching one session of the respective discipline, and/or 12 hours of volunteer diabetes education. In order to become a CDOE certified site, the practice must employ a nurse, dietitian, and a pharmacist.

Pharmacists as Diabetes Educators and Disease Managers

Understanding the importance of their medications, how they work, and what to expect from taking them is crucial to the patient's medication adherence. Adherence rates of studies, with adherence rates higher than the average adherence rate due to study related follow up, are approximately 71% ± 17% (range 34-97%).[7] Low adherence rates of all medications is often due to patient fear of adverse effects, not knowing why they were prescribed certain medications or dosages, high medication burden, cost of the medication, and not understanding the progression of the condition, such as type 2 diabetes. Pharmacists are utilized in many outpatient diabetes centers, such as Endocrine Treatment Centers, Inc. in Providence where I inform patients about their medications, explain side effects and expectations from the medications, and improve knowledge of the progression of their condition and the necessity of multiple medications or insulin as part of a multidisciplinary team of a nurse

practitioner, nurse, dietitian, physician, and pharmacist. In addition, I can educate the patient on other information such as exercise, monitoring, coping, managing sick days, nutrition, utilizing diabetes technology, problem solving, eating healthy, problem solving and goal setting. Frequently, if the patient understands why they were prescribed the medication and can see the results on their blood sugar readings or improve their quality of life by reducing hyperglycemia symptoms, then they become more successful with adherence with their medications and they become a reliable part of their treatment plan.

Commonly, non-dispensing pharmacists located within a medical practice, diabetes education, or at the **Veterans Administration Medical Center (VAMC)** are not expected to maintain the same patient load as primary care providers. Therefore, pharmacists have more time to discuss and counsel patients on their medications and review patient medications for appropriateness, pharmacokinetic and pharmacodynamics interactions as well as research the pharmacoeconomic impact of a medication choice for a patient. Nationally, many pharmacists at VAMC have a scope of practice that includes limited prescribing privileges. My colleagues and I are involved in many research-based pharmacist-led programs at the Providence VAMC, including a cardiac risk reduction clinic for patients with diabetes and cardiac risk factors, pharmacist-led group medical visits, pharmacist-led metabolic clinics, and pharmacist-led telehealth. These clinics have data to support their benefit.[5,8-12] For patients in these pharmacist clinics, we have shown that at six months, significant improvements were achieved for exercise, foot care, and goal attainment of hemoglobin A1C, LDL cholesterol and blood pressure, versus those in the control group who did not have pharmacist-led group medical visits.[11] In addition, we have shown that although coexisting mental health conditions attenuate treatment of diabetes, our pharmacist-led cardiovascular risk reduction clinics improve their United Kingdom Prospective Diabetes Study risk change and when discharged from the program (after achieving clinic goals), they have similar rates of decline for maintenance of systolic blood pressure and hemoglobin A1C readings as compared to patients without mental health conditions.[4,12]

After patients meet with pharmacists to discuss their medications and diabetes, the time spent at follow up visits with their primary care provider and specialist can be used for specific questions and higher-level questioning for the provider. For physicians and primary care providers, the medication prescribing process can be burdensome. Pharmacists with CDE and CDOE credentials can work collaboratively with prescribers to improve the medication process and contribute to high quality disease state management for patients with diabetes who require complex medication regimens. Pharmacists can also help select lower cost alternatives for patients who are on fixed incomes and for those who want to save money on co-pays and other medication expenses. Pharmacists are familiar with third party formularies and can let patients know when lower-tiered medications may be available.

Conclusion

Pharmacists who are certified as diabetes educators or disease managers can be a great resource for primary care providers and other allied health professionals. Locally and nationally, pharmacists have been an integral part of the diabetes management team. Since the prevalence of diabetes is expected to continue to rise over the next few decades, we need to utilize pharmacists. All patients should have the opportunity to sit down with a pharmacist at a physician practice or medical facility and learn about their medications and their condition.

References

1. Kogut SJ, Johnson S, Higgins T, Quilliam BJ. Evaluation of a program to improve diabetes care through intensified care management activities and diabetes medication copayment reduction. *J Manag Care Pharm*. 2012;18(4):297–310.
2. Choe HM, Farris KB, Stevenson JG, Townsend K, Diez HL, Remington TL, Rockafellow S, Shimp LA, Sy A, Wells T, Standiford CJ. Patient-centered medical home: developing, expanding, and sustaining a role for pharmacists. *Am J Health Syst Pharm*. 2012;69(12):1063–71.
3. Mularski KS, Yeh CP, Bains JK, Mosen DM, Hill AK, Mularski RA. Pharmacist glycemic control team improves quality of glycemic control in surgical patients with perioperative dysglycemia. *Perm J*. 2012;16(1):28–33.
4. Taveira TH, Dooley AG, Cohen LB, Khatana SA, Wu WC. Pharmacist-led group medical appointments for the management of type 2 diabetes with comorbid depression in older adults. *Ann Pharmacother*. 2011;45(11):1346–55.
5. McFarland M, Davis K, Wallace J, Wan J, Cassidy R, Morgan T, Venugopal D. Use of home telehealth monitoring with active medication therapy management by clinical pharmacists in veterans with poorly controlled type 2 diabetes mellitus. *Pharmacotherapy*. 2012;32(5):420–6.
6. http://ridiabeteseducators.org/ (accessed May 31, 2012).
7. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 2001;23(8):1296–310.
8. Taveira TH, Wu WC, Martin OJ, Schleinitz MD, Friedmann P, Sharma SC. Pharmacist-led cardiac risk reduction model. *Prev Cardiol*. 2006;9(4):202–8.
9. Martin OJ, Wu WC, Taveira TH, Eaton CB, Sharma SC. Multidisciplinary group behavioral and pharmacologic intervention for cardiac risk reduction in diabetes: a pilot study. *Diabetes Educ*. 2007;33(1):118–27.
10. Taveira TH, Friedmann P, Cohen LB, Dooley AG, Khatana SA, Pirraglia PA, Wu WC. Pharmacist-led group medical appointment model in type 2 diabetes. *Diabetes Educ*. 2010;36(1):109–17.
11. Cohen LB, Taveira TH, Khatana SA, Dooley AG, Pirraglia PA, Wu WC. Pharmacist-led shared medical appointments for multiple cardiovascular risk reduction in patients with type 2 diabetes. *Diabetes Educ*. 2011;37(6):801–12.
12. Cohen LB, Taveira TH, Wu WC, Pirraglia PA. Maintenance of risk factor control in diabetic patients with and without mental health conditions after discharge from a cardiovascular risk reduction clinic. *Ann Pharmacother*. 2010;44(7-8):1164–70.

Lisa Cohen, PharmD, CDE, CDOE, is an Associate Professor of Pharmacy at the College of Pharmacy at the University of Rhode Island, and a Research Pharmacist for the Veterans Affairs Medical Center, and the CVS Regional Business Office (Lincoln, RI).

Disclosure of Financial Interests

The author and/or their spouse/significant other have no financial interests to disclose.

Correspondence

Lisa Cohen, PharmD, CDE, CDOE
Department of Pharmacy Practice
College of Pharmacy
University of Rhode Island
Kingston, RI 02881
phone: (401) 874-2734
e-mail: lisacohen@mail.uri.edu

Rhode Island's Interprofessional Education Initiatives

Celia P. MacDonnell, PharmD, Paul George, MD, and Kara Misto, RN

The Committee of Health Professions Education, as part of the Institute of Medicine, held a summit in 2002 in which 150 multidisciplinary heath care educators discussed strategies for integrating a core set of competencies into the curriculum of future healthcare professionals. The resultant publication, *Health Professions Education: A Bridge to Quality* recommended that a core set of competencies be integrated into curricula for health care professionals.[1] One of the core areas described was the ability of professionals to cooperate, collaborate, communicate, and integrate care as part of an interdisciplinary healthcare team. The World Health Organization has long espoused the belief that **Interprofessional Education (IPE)** is necessary in preparing health care providers for effective collaborative practice which will ultimately improve patient health outcomes.[2]

Three years after the symposium, **University of Rhode Island (URI)** College of Pharmacy began an initiative to develop a series of interdisciplinary practice laboratory modules to be held with students in URI's College of Nursing. A brief presentation on caring for patients with diabetes was first presented and included a seminar with both pharmacy and nursing implications. Following this, groups of nursing and pharmacy students participated in various interactive learning stations. These stations enabled students to test themselves with blood glucose meters, handle insulin pens, and practice subcutaneous injections in interprofessional teams. There was also a station where students could prepare the contents of a sick day management kit for patients with diabetes. The station had items such as: a thermometer, notepad and pen, various food choices, sports drinks and gelatin. The collaboration was regarded as highly successful by not only the faculty facilitating this seminar, but also the students from each discipline.[3] It remains an essential part of the curriculum of the respective programs to this day.

Interprofessional Work with Medicine: Methods and Results

In 2008, in an effort to continue to grow student learning partnerships, we approached the Director of the Office of Medical Education and the Associate Director of Preclinical Curriculum at the **Warren Alpert School of Medicine at Brown University (AMS)** to discuss the potential to provide new collaborative learning opportunities for students in the health-care programs in the state. AMS embraced the proposal, and the process of working together to develop an expanded, team-based, educational program for students prior to concentrated clinical training began. We hoped to impact students early in their training so that interprofessional teamwork became the norm when they entered their clinical training.

There are clear benefits to interprofessional education.

Over the past five years faculty members from AMS and URI's College of Pharmacy and College of Nursing worked together to develop a curriculum containing content that naturally lends itself to the expertise of each student group. The overarching goal is for students to develop interprofessional skills through active and problem-based learning. This educational concept has been used for many years in Canada, and is known as "Seamless Care".[4] With this model as a conceptual framework, the three schools introduced introductory IPE experiences to pharmacy, medical and nursing students.

Our current curriculum for PharmD students includes the required participation of second year medical students, 4th year (senior) nursing and 5th year pharmacy students (the PharmD students are in their 3rd year of pharmacy coursework). The students participate in a half-day workshop where they are assigned to equally balanced, interdisciplinary teams. In these teams, the students begin to gain a greater understanding of the knowledge and skills *each* healthcare practitioner brings to patient care.

We assign students to interprofessional teams prior to the workshop. Students then work together within their teams to discuss paper problem-based learning scenarios and teach each other about the medical, therapeutic and nursing aspects of chronic obstructive pulmonary disease and asthma. We carefully crafted and refined these cases so health issues important to each discipline are highlighted. In addition, each learning station is also supplied with a variety of teaching tools such as placebo inhalers. This allows the groups to work together on demonstration of inhaler technique and patient teaching points.

Running parallel to case-based work, one-third of the interdisciplinary student teams meet with a standardized patient (an actor portraying a patient) who presents to them with pneumonia. They take a history, perform a physical examination, determine a diagnosis and select "appropriate" therapy together as a team. Sometimes the students are correct, and sometimes they miss the mark (they are preclinical students after all). However, the most valuable component of this introductory encounter is *how well they work together as a team and if they were aware of any benefit to patient outcomes with this approach.*

After the workshop, we asked students to complete a survey with both closed ended and open ended questions indicating their satisfaction with the workshop. The results of this initiative have been very positive. Survey data over the last three years has confirmed the students' overwhelming approval of the interprofessional team-based learning approach. Greater than 80% of the students agreed or strongly agreed that "workshops such as these promoting teamwork among different disciplines are important for professional development. ($p < 0.001$) The

results also verify that at the workshops conclusion, each of the disciplines had a greater understanding of the each other's knowledge and skills.[5] The students were also asked if workshops likes these should be required during their "pre-license" education and 63.7% responded that they *strongly agreed* that it should be part of the required curriculum. ($p < 0.001$) Qualitative data also reflect the success of the workshop. As an example, one student wrote in a reflection, "In the future, I will take advantage of the other medical professionals to improve my patient's care."

Advantage to an Interprofessional Approach

There are clear benefits to interprofessional education. The importance of interprofessional healthcare teams in the provision of patient care is well recognized for improved patient outcomes.[6] Teams composed of healthcare professionals from different disciplines who conduct individual assessments and develop patient care plans independently *are not* considered interprofessional teams.[7] As a result of the success of our single workshop, we added a second workshop in 2012 where students from AMS and URI work together as a team (using a standardized patient once again).

Barriers to implementation of programs such as this include: space (although this is less of a concern now with the opening of AMS's new medical school in downtown Providence), and proximity of academic institutions (although separated by less than 30 miles, transporting nursing and pharmacy students to Providence is difficult). Challenges to a program such as this are many. The scheduling logistics of holding this one-day practicum are daunting, as each if the three discipline's class size is approximately 100 students.

We worked diligently to determine the appropriate level of education for the three student disciplines. This has been challenging. In the first year of the workshop, third year nursing students participated. Through our survey data, we determined that this cohort of students did not yet have the same level of educational experience to feel comfortable participating in the workshop activities with the other disciplines. Conversely, the following year, students from the College of Nursing's Family Nurse Practitioner Graduate Program participated, and were at a much higher practice level than the students in the other two disciplines. It is clear in the literature that if one student in the group is unable to contribute, it negatively reinforces the stereotypes of that entire profession.[9] We finally settled on fourth year nursing students to work with second year medical students and third professional year pharmacy students. We believe this combination works well for our workshop.

A final challenge comes from faculty and practitioners. We cannot expect students to adopt an *esprit des corps* if we do not fully embrace it ourselves. Teaching, research and practice often takes place in silos. We also may benefit from interprofessional training to be able to effectively work as a team to model for our students even further the benefits of interprofessional teamwork. Plans are underway to provide faculty development in this arena.

Finally, the authors recently attended the Interprofessional Education Institute in Washington DC. There, as a team we developed the framework of an interprofessional education curriculum to be disseminated to administrators at AMS, URI and Rhode Island College (we included nursing students from Rhode Island College to participate in our last workshop). Our plans for the two workshops next year include the addition of graduate students from the School of Social Work at Rhode Island College as part of the interprofessional team. Additionally, we plan on developing both preclinical and clinical electives (that count as part of student grades) for nursing, medical, pharmacy and social work students to take jointly.

We can no longer expect students in the healthcare field to go from the classroom directly into a clinical setting, and to *then* be able to function as a patient focused team, with no cohesive training.

Educational experiences, such as this initiative, foster interprofessional trust and the necessary communication skills for students to effectively participate as active members of healthcare teams in the future as healthcare providers.

We believe that team-based, patient-centered care *must* begin with undergraduate (pre-licensure) interprofessional education. Educational experiences such as this furnish students with the confidence and the skills needed for the pursuit of post-graduate inter-professional collaborations and will ultimately serve to enhance any patient centered care program.

References

1. Summit CotHPE. *Health Professions Education: A Bridge to Quality*: The National Academies Press; 2003.
2. Framework for Action on Interprofessional Education and Collaborative Practice, World Health Organization. 2010:63.
3. MacDonnell CP JA, Lavin M, Cohen S, Cohen L. Impact of an Interdisciplinary Practice Laboratory on Pharmacy and Nursing Students' Perceptions of Health Care Roles. *Int Journal Pharm Ed and Pract.* 2011;7(1).
4. Mann KV M-DJ, Martin-Misener R, Clovis J, Rowe R. Interprofessional education for students of the health professions: the "Seamless Care" model. . *J Interprofessional Care.* 2009;23(3):224–33.
5. MacDonnell CP RS, Misto K, Dollase R, George P. Evaluating healthcare students' response to an introductory interprofessional exercise and their team dynamics. . *Am J Pharm Ed.* 2012. Pub pending.
6. Reeves S, Russell A, Zwarenstein M, et al. Structuring communication relationships for interprofessional teamwork (SCRIPT): a Canadian initiative aimed at improving patient-centred care. *J Interprofessional Care.* Feb 2007;21(1):111–4.
7. Buring SM, Bhushan A, Broeseker A, et al. Interprofessional education: definitions, student competencies, and guidelines for implementation. *Am J Pharm Ed.* Jul 10 2009;73(4):59.
8. Hoffman B. Why Simulation Can Be Efficient: on the Preconditions of Efficient Learning in Complex Technology Based Practices. *BMC Medical Education.* 2009;48(17):1515–19.
9. Tunstall-Pedoe S, Rink E, Hilton S. Student attitudes to undergraduate interprofessional education. *J Interprofessional Care.* May 2003;17(2):161–72.

Celia P. MacDonnell, PharmD, is a Clinical Associate Professor in the Department of Pharmacy Practice at the University of Rhode Island College of Pharmacy, and maintains a clinical practice at the South County Hospital Medication Management Clinic.

Paul George, MD, is an Assistant Professor of Family Medicine at the Warren Alpert Medical School of Brown University.

Kara Misto, RN, is an Instructor; PhD(c) at the University of Rhode Island College of Nursing.

Disclosure of Financial Interests

The authors and/or their spouses/significant others have no financial interests to disclose.

Correspondence

Celia P. MacDonnell, PharmD
e-mail: cmac@uri.edu

A Ten-Year Experience of a Pharmacist Consulting Team for Statewide Bioterrorism and Emergency Preparedness

Brett Feret, PharmD, and Jeffrey Bratberg, PharmD, BCPS

The tragic events of September 11 and subsequent anthrax attacks in the fall of 2001 changed the nation. These events also changed the profession of pharmacy by expanding their roles in emergency and disaster planning and response.[1] The American Society of Health System Pharmacists state "On the basis of their education, training, experience, and legal responsibilities, pharmacists should have a key role in the planning and execution of (a) pharmaceutical distribution and control, and (b) drug therapy management of patients during disasters."[2] The purpose of this paper is to describe innovative ways that pharmacists in the state of Rhode Island are involved in emergency preparedness planning.

Introduction of Pharmacists in Rhode Island Preparedness Activities

After a successful multidisciplinary education seminar led by **University of Rhode Island** (**URI**) College of Pharmacy on bioterrorism agents and their public health implications, the **Rhode Island Department of Health** (**RIDOH**) decided to explore adding pharmacists to a team of health professionals who were preparing the state for an intentional outbreak of a biological agent. Initially, RIDOH sought a pharmacist to assist them to repackage bulk medications supplied from the **Strategic National Stockpile** (**SNS**), a federal cache of medical supplies.[3] The initial group included five pharmacists with a variety of backgrounds and specialties, including community pharmacy, pharmacoepidemiology, and infectious diseases. In early 2002, this group developed a process to effectively package multiple doses of antibiotics.

In October 2002, the first dispensing exercise with a local municipality and RIDOH was conducted to simulate a response to a terrorist attack using *Yersinia pestis*, the causative agent of plague, a Category A biowarfare agent. An ice skating rink in Pawtucket, RI was turned into a **point of dispensing** (**POD**) for either doxycycline or ciprofloxacin, both recommended antibiotics for prophylactic treatment of pneumonic plague.[4] This comprehensive response plan was called the **Medical Emergency Distribution Plan** (**MEDS**). The MEDS plan exists as a way to maintain control of all state-level medical emergency supply resources and to deliver those resources during an emergency, including the mass distribution of antibiotics to the entire population.[5] Our role during this initial exercise was limited to staffing the pharmacy where the "patients" received their medication and were counseled on appropriate medication use.

Participation in National Training

During the summer of 2003, our group of pharmacists as well as members of the Board of Pharmacy traveled to the Noble Training Center in Anniston, Alabama for the Strategic National Stockpile Preparedness Course sponsored by the **Centers for Disease Control** (**CDC**) **and Prevention**. This course educated attendees on the administration of a quick and efficient medical response to a terrorist attack, natural disaster, or any other accident where medical personnel were needed. The majority of the course was concentrated on the design of a comprehensive system for the rapid distribution of prophylactic medications or vaccinations to the public. This included developing and determining the most appropriate location, site design, and ideal characteristics of POD's. Other crucial operational and logistical issues such as internal and external communications, staffing levels and roles, security, patient flow, and volunteer and resource management were discussed and practiced in both tabletop (response capability simulations) and live POD exercises and evaluations.

This course was a significant turning point in our roles as pharmacists with RIDOH in preparedness issues. During our time in Alabama, we realized our

Rhode Island Department of Health emergency preparedness consultant pharmacists Brett Feret (left) and Jeffrey Bratberg (right) pause for a photo at the pharmacy station during the mass dispensing of antibiotics for at Greenwood Elementary School in Warwick, RI in January 2007.

responsibility should be much more than medication repackaging supervisors. Now, as professionals with advanced training on the SNS, our roles changed from repackaging supervision to emergency planners with expertise from drug selection to POD site security and evaluation.

Activities to help Rhode Island Communities in Emergency Preparedness

In late 2003, the pharmacy emergency preparedness consultants began to help revise and update the state's MEDS plan. A comprehensive manual and template for POD set-up and training for each municipality throughout the state of Rhode Island was developed that outlined all the necessary steps to open a POD for the public.[5] POD workflow diagrams, medication selection algorithms, drug information sheets, and volunteer job descriptions were all included in this document. Each pharmacist was then assigned a group of municipalities to work with each year to develop, maintain, and improve each municipality's MEDS plan to meet federal and state SNS requirements. In order to receive federal and state funding, each municipality is scored on a local technical assistance review. Each pharmacist grades the municipality using this tool annually. Currently, this is one primary role for each pharmacist.

Examples of Emergency Preparedness in Local Outbreaks of Infection

Several real-life events were interspersed throughout the consulting period. Each pharmacist was heavily involved in preparing and responding to the atypical *Mycoplasma* outbreak in Warwick, RI in January 2006. During that event, each pharmacy consultant worked to develop the POD flow in the Greenwood School and staffed the pharmacy, while providing counseling to families regarding the antibiotic course. The MEDS plan was put to the test for each municipality during the 2009–2010 H1N1 pandemic. During this event, each pharmacist worked closely with their assigned municipalities to quickly and efficiently set-up their vaccination POD's in communities and pandemic regional hospitals. The MEDS program helped Rhode Island lead the nation in vaccination coverage for adults with chronic health conditions (57.5%) and Rhode Island was estimated to have the highest H1N1 vaccination coverage rate in the country for anyone older than six months at 38.8% compared to the national median of 23.9%.[7] Pharmacists now immunize over 45% of all adults against influenza in Rhode Island, likely due to increased recognition of their role in public health (unpublished data). At URI College of Pharmacy, Dr. Bratberg has developed an innovative elective course in public health preparedness and all-hazards emergency preparedness and response. In various semesters student pharmacist teams not only have developed and tested pandemic influenza and hurricane preparedness plans, but also have designed and participated in full-scale, University-wide live exercises testing the rapid distribution of medical countermeasures to students exposed to inhalational anthrax. In 2012, students facilitated their own tabletops to emerging infectious disease outbreaks in class, and designed a full-scale exercise of an outbreak of a hypothetical infection that creates zombies, thus mimicking an outbreak of an unknown, yet highly communicable and terrifying infectious disease.

Conclusion

Pharmacists' knowledge and skills in emergencies have transformed from a purely dispensing, logistical role to all-hazard preparedness planners and evaluators. Based on lessons learned from past national and local disasters, pharmacists continue to demonstrate their value to the healthcare system by leading all-hazard public health emergency preparedness and response efforts in Rhode Island.

References

1. Babb J & Down K. Fighting Back: Pharmacists' roles in the federal response the September 11 attacks. *J Am Pharm Assoc*. 2001; 41(6):834–7.
2. American Society of Health-System Pharmacists. ASHP statement on the role of health-system pharmacists in emergency preparedness. *Am J Health-Syst Pharm*. 2003; 60:1993–5.
3. Strategic National Stockpile [Internet]. Centers for Disease Control and Prevention; c2012 [updated March 8th 2012; cited May 28th 2012]. Available from http://www.cdc.gov/phpr/stockpile/stockpile.htm.
4. Inglesby TV, Dennis DT, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Fine AD, et al. Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA*. 2000; 283(17):2281–90.
5. Banner G. The Rhode Island Medical Emergency Distribution System (MEDS). *Disaster Manage Response*. 2004;2:53–7.
6. MEDS Guidelines and Supplemental Information. 3rd Edition. *Consensus Guidelines from the Rhode Island Department of Health Pharmacist Consultants*. Rhode Island Department of Health, Providence, RI. August 2006.
7. RI.Gov [Internet]. Rhode Island Government Press Release; c2010 [updated April 1 2010; cited May 28 2012]. Available from http://www.ri.gov/press/view/11080.

Brett Feret, PharmD, is a Clinical Associate Professor of Pharmacy Practice at the University of Rhode Island, College of Pharmacy.

Jeffrey Bratberg, PharmD, BCPS, is a Clinical Associate Professor of Pharmacy Practice at the University of Rhode Island, College of Pharmacy; an Adjunct Associate Professor of Medicine, Division of Infectious Diseases at the Warren Alpert Medical School of Brown University; and an Infectious Diseases Specialist, Department of Pharmacy, Roger Williams Medical Center/CharterCare.

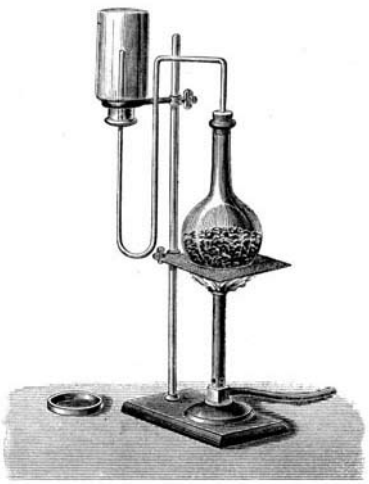
Disclosure of Financial Interests

Brett Feret, PharmD, consults for the Rhode Island Department of Health.

Jeffrey Bratberg, PharmD, BCPS, consults for the Rhode Island Department of Health and is on the speakers bureau for Merck and Co., Inc.

Correspondence

Brett Feret, PharmD
Clinical Associate Professor
URI College of Pharmacy
phone: (401) 874-2320
fax: (401) 874-2717
e-mail: bferet@uri.edu



Medication Therapy Management in Community Pharmacy Practice

Ginger Lemay, PharmD, CDOE

Community pharmacists are often the first point of contact for patients with health-related and medication questions. The *2007 Wilson Rx Pharmacy Customer Satisfaction Survey* reports that the average pharmacy customer visits their pharmacy an average of two to three times per month, which is greater than ten times the number of times they visit their primary care physician and greater than 15 times more often than they visit a specialist physician in a year. Community pharmacists are faced with the challenge of identifying and resolving medication-related problems for prescription, nonprescription, herbal, and dietary supplements on a daily basis. In an often fast-paced, busy environment such as a community pharmacy, it is critical for pharmacists to be afforded face-to-face, uninterrupted, quality time with their patients. However, broad scale reimbursement mechanisms for such services were lacking until the establishment of The Medicare Modernization Act of 2003. Effective January 1 2006, this act established a prescription drug benefit for 25 million Medicare beneficiaries. In addition, it afforded pharmacists a platform for reimbursement for the identification and resolution of medication-related problems, entitled **Medication Therapy Management** (**MTM**).[1]

Components of Medication Therapy Management

The Centers of Medicare & Medicaid Services requires Medication Therapy Management as a component of all Medicare Part D prescription drug benefit plans. The goals of MTM services are to improve collaboration among pharmacists, physicians, and other healthcare professionals; enhance communication between patients and their healthcare team; and optimize medication use for improved medication outcomes.[2] Integral to the provision of MTM services is that they are distinct from the medication dispensing process. Therefore, the services provided are patient-centered as opposed to a prescription-focused approach.[3] Though the look and feel of MTM services may vary in the menu of services offered within the pharmaceutical care model, the framework of delivery is consistent and reproducible. In 2004, a joint initiative by The American Pharmacists Association and the National Association of Chain Drug Stores Foundation established a service model document supported by many pharmacy organizations across the spectrum of pharmacy practice. This document, entitled Medication Therapy Management in Pharmacy Practice: Core Elements of an MTM Service Model, updated in 2008, defines the five core elements of an MTM practice.[2] (Table 1)

The hallmark of an MTM service is the **Comprehensive Medication Review** (**CMR**). A CMR is "a review of the beneficiary's medications, including prescription, over-the-counter medications, herbal therapies and dietary supplements, that is intended to aid in assessing medication therapy and optimizing patient outcomes."[4] In short, just as a patient is recommended to see their primary care physician each year for a complete physical, they are also encouraged to see their pharmacist each year for a complete "medication check-up". Once the community pharmacist gathers the medication-related information from the CMR, he/she assesses, identifies, and prioritizes medication-related problems. (Table 2)

Once the medication-related problems have been prioritized, a plan is developed for the resolution of each problem identified. This plan is documented on the patient-centered **Medication-related action plan** (**MAP**) which is created by the pharmacist in conjunction with their patient. The MAP is a list of "to-do's" for the patient to use with their pharmacist, primary care physician, physician specialists, and other healthcare providers to ensure they are working toward their specific health goals. In addition to the MAP, the community pharmacist also creates a **Personal Medication Record** (**PMR**) which is a list of all the patient's medications, both prescription and nonprescription. The MAP and PMR are fluid documents and must be updated regularly with any changes in health status and medication therapy. After the community pharmacist completes a comprehensive medication

Table 1. Core Elements of Medication Therapy Management

Medication Therapy Review (MTR) , also referred to as Comprehensive Medication Review (CMR)
Personal Medication Record (PMR)
Medication-related Action Plan (MAP)
Intervention and/or referral
Documentation and follow-up

Table 2. Possible Medication-related Problems

Medication without an indication
Indication without a medication
Adverse Drugs Effects
Wrong Medication
Wrong Dose
Adherence to therapy
Drug-drug, drug-food, drug-herbal interactions

review, a copy of the medication action plan and the personal medication record are given to the patient, and copies faxed to the primary care physician. These documents are designed to be shared and utilized within all facets of the patient's "medical home." If the community pharmacist identifies medication-related problems that require intervention, such as a potentially harmful drug-drug interaction, the prescriber is immediately contacted. In addition, if referral to another healthcare provider is warranted, such as a dietician for a patient with type 2 diabetes mellitus, the community pharmacist assists the patient with this referral to ensure continuity of care. The last step of the MTM service is documentation and billing. The community pharmacist uses the SOAP note format along with the supporting documents of the medication action plan and personal medication record. The patient's insurance dictates the method in which the community pharmacist bills for their service. In October 2007, three Category I CPT codes were established for MTM services provided by a pharmacist for face-to-face education. These codes opened the door for private payers and the Medicare Part D plans to reimburse community pharmacists for this valuable service.[5]

Advantages of Medication Therapy Management

The benefits of pharmacist delivered MTM services have been documented repeatedly. Specifically, the well known Asheville Project enlisted 12 community and hospital settings over a six-year period to significantly improve the clinical and economic outcomes in a cardiovascular risk reduction educational program.[6] In addition, data from the Connecticut Medicaid transformation project demonstrated, among other things, a 50% increase in the number of Medicaid patients who achieved their therapeutic goals, as a result of face-to-face pharmacist MTM services.[7] When the Medicare Modernization Act opened the door for reimbursable, pharmacist-delivered MTM services, pharmacists passionately embraced their expanded scope of practice. The Affordable Care Act, which places the coordination of care for patient outcomes in the patient-centered medical home, recognizes the value of the pharmacist as the "medication expert." Incorporation of the pharmacist in a patient-centered medical home holds the promise of enhanced communication and collaboration with the primary care physician as well as improved medication-related outcomes.

References:

1. Isetts BJ. Pharmaceutical care, MTM, & Payment: The past, present, & future. *Ann Pharmacother*. 2012;46(suppl 1):S47–56.
2. American Pharmacists Association, National Association of Chain Drug Stores Foundation, et al. Medication therapy management in pharmacy practice: core elements of an MTM service model (version 2.0). *J Am Pharm Assoc*. 2008;48:341–53.
3. Cipolle RJ, Strand LM, Morley PC. *Pharmaceutical Care Practice: The Patient Centered Approach to Medication Management*. New York: McGraw-Hill, 2012.
4. Centers for Medicare and Medicaid Services. Medicare Part D Medication Therapy Management (MTM) Programs. 2011 fact sheet, updated June 30, 2011. https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/downloads/MTMFactSheet2011063011Final.pdf (accessed 2012 June 2nd).
5. Isetts BJ, Buffington DE. CPT code-change proposal: national data on pharmacists' medication therapy management services. *J Am Pharm Assoc*. 2007;47:491–5.
6. Bunting BA, Smith BH, Sutherland SE. The Asheville Project: clinical and economic outcomes of a community-based long-term medication therapy management program for hypertension and dyslipidemia. *J Am Pharm Assoc*. 2008;48:23–31.
7. Smith MA, Giuliano MR, Starkowski MP. In Connecticut: improving patient medication management in primary care. *Health Affairs*. 2011;30:646–54.

Ginger Lemay, PharmD, CDOE, is a Clinical Assistant Professor at the University of Rhode Island College of Pharmacy, and a Community Pharmacist for Rite Aid Pharmacy.

Disclosure of Financial Interests

The author and/or their spouse/significant other have no financial interests to disclose.

Correspondence

Ginger Lemay, PharmD, CDOE
University of Rhode Island
College of Pharmacy
7 Greenhouse Road
Kingston, RI 02881
e-mail: glemay@uri.edu

Pharmacy Research at URI: Mining Red Maple (*Acer rubrum*) Trees for Novel Therapeutics to Manage Diabetes

Navindra P. Seeram, PhD, Jialin Xu, PhD, Liya Li, PhD, and Angela Slitt, PhD

Type 2 diabetes mellitus (T2DM) accounts for about 90% of all diagnosed cases of diabetes in adults. Over 200 million people suffer from this disease worldwide. In the United States alone, in 2007, 10% of American adults had diabetes and the cost of management was $174 billion and this figure is expected to skyrocket (Centers for Disease Control and Prevention, 2010). Plants and their derived products have been used for centuries by various cultures as traditional medicines for the management of diabetes. Plants contain secondary metabolites (known as phytochemicals; 'phyto' means plant), which are implicated in the prevention and treatment of several chronic human diseases, including diabetes. Among these natural products, polyphenols and phenolic glycosides, have attracted significant interests for their anti-diabetic properties.

Plant polyphenols as α-glucosidase inhibitors. Dietary carbohydrates are hydrolyzed by pancreatic α-amylase with absorption aided by α-glucosidases and thus, inhibition of the activities of these enzymes is a promising approach for managing T2DM. In fact, the clinical α-glucosidase inhibitor, acarbose, has been shown to effectively reduce glycated hemoglobin levels when given as monotherapy or as an add-on to other antidiabetic drug treatment.[1] Additionally, a fixed dose combination of acarbose and metformin was reported to be superior to metformin alone in controlling HbA1c, fasting blood glucose, and post prandial blood glucose levels in T2DM patients,[2] as well as, enhancing the blood glucose control.[3] Multiple plant-derived polyphenols have been investigated as α-glucosidase inhibitors. Extracts from grape seeds and green tea been demonstrated to exert inhibition on α-glucosidase activity.[4] We recently have shown a similar activity for phenolic-enriched extracts from the bark of *Acer rubrum*, commonly known as red maple.

Study of maple for novel therapeutics. The sugar maple (*Acer saccharum*) and red maple plant species are native to eastern North America and highly regarded for their sap which is used to produce the natural sweetener, maple syrup. Our laboratory has recently identified a number of phenolic compounds native in maple plant parts that are also present in maple syrup.[5]

Here we report a case study in which the ability of **red maple bark extract (MBE)** to decrease elevation of blood glucose levels was investigated. Male adult C57BL/6 mice were administered MBE in combination with a bolus sucrose challenge to evaluate the effect of MBE or acarbose on α-glucosidase activity *in vivo* according to described methods.[6] As expected, mice receiving a bolus sucrose challenge increased blood glucose concentration 30, 60, and 90 minutes after administration compared to initial blood glucose concentration. (Figure 1) Both MBE and acarbose significantly lowered blood glucose concentrations at these time intervals after the sucrose challenge. Compared to acarbose, MBE was less effective, but did impart a significant inhibitory effect. We now hope to further purify and evaluate individual phytochemicals of MBE to evaluate for activity against sucrose-induced glucose elevation.

We have demonstrated that phenolic glycosides are present in various maple constituents. The isolated compounds and extracts inhibit α-glucosidase activity *in vitro*.[7,8] Recently, multiple gallotannins, named maplexins A-E, were isolated from red maple stems and bark.[7,8] These maplexin compounds were shown *in vitro* to possess more activity than acarbose for inhibition of α-glucosidase activity (IC_{50} = 8 vs. 160 μM; maplexin E vs. acarbose, respectively). These interesting maplexin compounds, that are as effective as acarbose *in vitro*, will be further evaluated and developed to determine whether they impart beneficial properties in preventing blood glucose elevations *in vivo*. Overall, we determined that MBE contains bioactive constituents that can potentially aid

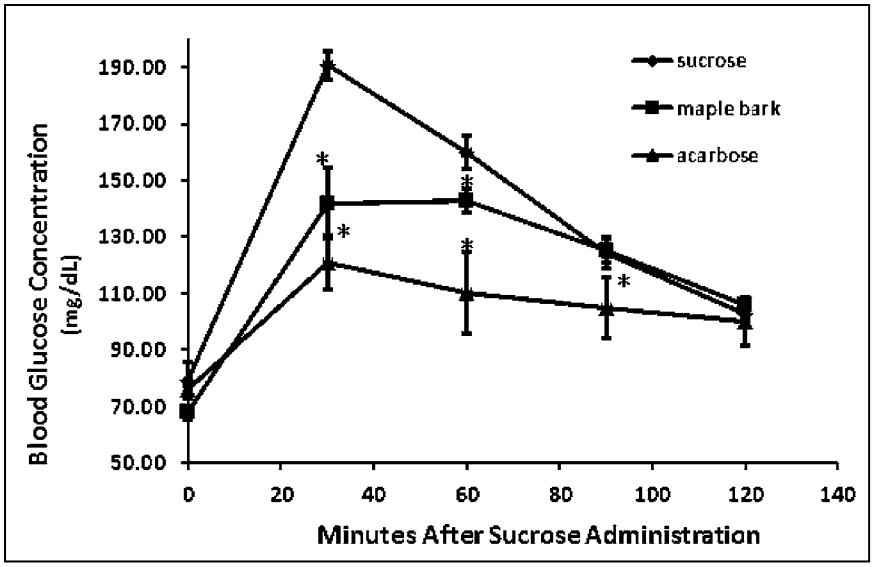


Figure 1. Adult male C57BL/6 mice were administered sucrose (3g/kg BW), sucrose and acarbose (3g/kg BW + 3 mg/kg BW), or 3) sucrose and maple bark extract (3g/kg BW+150mg/kg BW) by oral gavage. Blood glucose levels were determined by tail bleed at 0, 30, 60, 90, and 120 minutes post sucrose administration. An asterisk (*) denotes statistical significance ($p<0.05$) from the sucrose treatment group.

in the regulation of blood glucose control after a carbohydrate challenge.

We will continue to explore how bioactive extracts and molecules isolated from plants can impart beneficial effects on metabolic syndrome. As metabolic syndrome encompasses T2DM, dyslipidemia, systemic inflammation, and non-alcoholic fatty liver disease, the potential therapeutics isolated will be tested in various cell-based and in vivo models. We are currently exploring anti-inflammatory effects of maple-derived extracts and compounds, as well as, the potential for plant-derived extracts to augment weight loss and T2DM therapies. Ultimately, we hope that identification of beneficial components in foods commonly consumed can arm the consumer with information to make better food choices that can be synergistic with drug therapies used to treat T2DM. We also will continue to mine botanicals for potential therapies to treat T2DM or enhance activity of commonly prescribed anti-diabetes therapies.

Funding Sources

This project was supported by funding provided by Agriculture and Agri-Food Canada through the **Developing Innovative Agri Products (DIAP)** initiative and, in part, by The National Institute of Health (ES-016042-03 and ES-016042-2S2). The authors would like to thank Mr. J. Peter Morgan for assistance with plant authentication.

References

1. Derosa G, Maffioli P. Efficacy and safety profile evaluation of acarbose alone and in association with other antidiabetic drugs: a systematic review. *Clin Ther.* Jun 2012;34(6):1221–36.
2. Jayaram S, Hariharan RS, Madhavan R, Periyandavar I, Samra SS. A prospective, parallel group, open-labeled, comparative, multi-centric, active controlled study to evaluate the safety, tolerability and benefits of fixed dose combination of acarbose and metformin versus metformin alone in type 2 diabetes. *J Assoc Physicians India.* Nov 2010;58:679–82, 687.
3. Schnell O, Mertes G, Standl E. Acarbose and metabolic control in patients with type 2 diabetes with newly initiated insulin therapy. *Diabetes Obes Metab.* Nov 2007;9(6):853–8.
4. Yilmazer-Musa M, Griffith A, Michels AJ, Schneider E, Frei B. Grape seed and tea extracts and catechin 3-gallates are potent inhibitors of alpha-amylase and alpha-glucosidase activity. *J Agric Food Chem.* Jun 15 2012.
5. Li L, Seeram NP. Further investigation into maple syrup yields 3 new lignans, a new phenylpropanoid, and 26 other phytochemicals. *J Agric Food Chem.* Jul 27 2011;59(14):77–16.
6. Honma A, Koyama T, Yazawa K. Anti-hyperglycaemic effects of the Japanese red maple Acer pycnanthum and its constituents the ginnalins B and C. *J Enzyme Inhib Med Chem.* Apr 2011;26(2):176–80.
7. Wan C, Yuan T, Li L, et al. Maplexins, new alpha-glucosidase inhibitors from red maple (Acer rubrum) stems. *Bioorg Med Chem Lett.* Jan 1 2012;22(1):597–600.
8. Yuan T, Wan C, Liu K, Seeram NP. New maplexins F-I and phenolic glycosides from red maple (Acer rubrum) bark. *Tetrahedron.* 2012;68:959–64.

Navindra P. Seeram, PhD, is an Assistant Professor in the Department of Biomedical and Pharmaceutical Sciences at the University of Rhode Island.

Jialin Xu, PhD, is a Postdoctoral Fellow, Slitt, in the Department of Biomedical and Pharmaceutical Sciences at the University of Rhode Island.

Liya Li, PhD, is a Postdoctoral Fellow, Slitt, in the Department of Biomedical and Pharmaceutical Sciences at the University of Rhode Island.

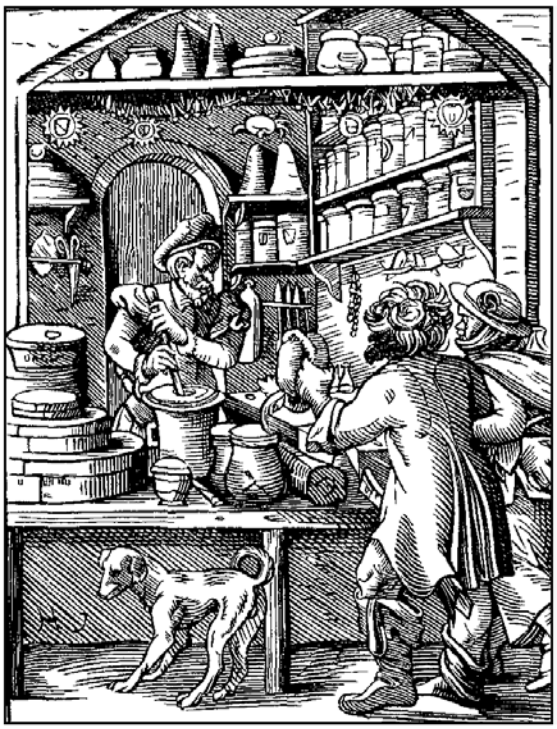
Angela Slitt, PhD, is an Assistant Professor in the Department of Biomedical and Pharmaceutical Sciences at the University of Rhode Island.

Disclosure of Financial Interests

The authors and/or their spouses/significant others have no financial interests to disclose.

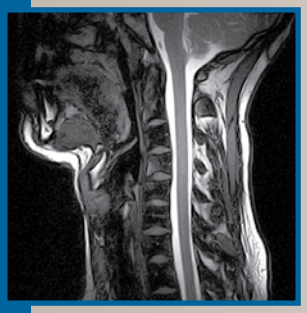
Correspondence

Angela Slitt, PhD
Department of Biomedical and Pharmaceutical Sciences
College of Pharmacy
University of Rhode Island
7 Greenhouse Road
Kingston, RI 02881
phone: (401) 874-5020
e-mail: aslitt@uri.edu



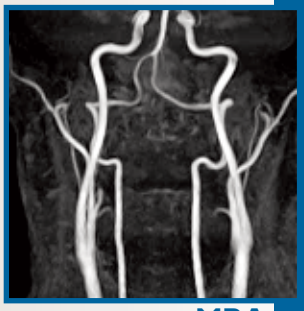
THE IMAGING INSTITUTE

OPEN MRI • MEDICAL IMAGING

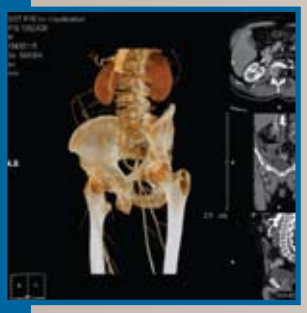


High Field MRI

- **Offering both 1.5T High Field & Higher Field OPEN MRI Systems**
- **Advanced CT with multi-slice technology, 3D reconstruction**
- **Digital Ultrasound with enhanced 3D/4D technology**
- **Digital Mammography with CAD (computer assisted diagnosis)**



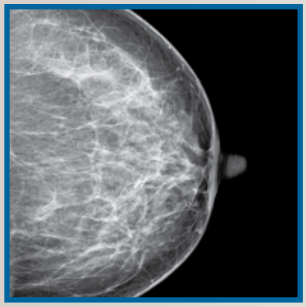
MRA



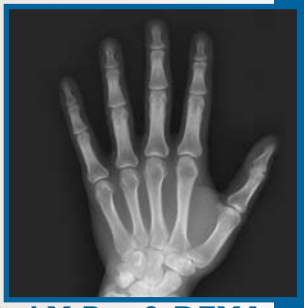
CT • 3D CT

CTA

3D Ultrasound



Digital Mammography



Digital X-Ray & DEXA

- Electronic Medical Record (EMR) Interfaces now available
- Preauthorization Department for obtaining all insurance preauthorizations
- Fellowship, sub-specialty trained radiologists
- Friendly, efficient staff and convenient, beautiful office settings
- Transportation Service for patients

Higher Field OPEN MRI

WARWICK
250 Toll Gate Rd.
TEL 401.921.2900

CRANSTON
1301 Reservoir Ave.
TEL 401.490.0040

CRANSTON
1500 Pontiac Ave.
TEL 401.228.7901

N. PROVIDENCE
1500 Mineral Spring
TEL 401.533.9300

E. PROVIDENCE
450 Vets. Mem. Pkwy. #8
TEL 401.431.0080

A Clearer Vision of Health™

theimaginginstitute.com

We're not LIKE A Good Neighbor,

WE ARE

The Good Neighbor Alliance

Specializing in Employee Benefits since 1982

Health Dental Life Disability Long Term Care
Pension Plans Workers' Compensation Section 125 Plans

The Good Neighbor Alliance Corporation

The Benefits Specialist

Affiliated with

RHODE ISLAND MEDICAL SOCIETY

RIMS-INSURANCE BROKERAGE CORPORATION

401-828-7800 or 1-800-462-1910

P.O. Box 1421 Coventry, RI 02816

www.goodneighborall.com

Pharmacy Research at URI: Bile Acids and Bile Salt Export Pump: Physiology and Pathology

Ruitang Deng, PhD

The long-term objective of our research program is to understand how bile acid homeostasis is regulated in physiological as well as pathological conditions, with a focus on the transcriptional regulation of the **bile salt export pump** (**BSEP**).

As one of the major constituents of bile, bile acids were once considered bodily waste with no useful functions. Now it is well established that bile acids have important physiological functions in animals and human.[1] First, the well-known function of bile acids is to solubilize cholesterol and lipids in an aqueous environment, such as in the bile and the intestines. On the other hand, as biological detergents, too much bile acids are toxic for cells. Second, bile acids are recognized as signaling molecules serving as the endogenous ligands for nuclear receptor **farnesoid x receptor** (**FXR**) and G-protein-coupled receptor TGR5 to regulate cholesterol, bile acids and glucose homeostasis. Finally, recent studies have extended the functions of bile acids into various non-metabolic areas including inflammation, liver regeneration, hepatocarcinogenesis, inhibition of intestine bacterial growth and colon cancer.

Bile acid homeostasis is achieved through coordinately regulated bile acid synthesis and elimination pathways. **Cholesterol 7α-hydroxylase** (**CYP7A1**) is the rate-limiting enzyme for bile acid synthesis while BSEP is the rate limiting-step in the enterohepatic circulation of bile acids.[2] (Figure 1) Modulation of BSEP expression or function by inherited or acquired factors has profound impacts on bile acid homeostasis and subsequently contributes to the risk for various bile acids-associated diseases, including intrahepatic cholestasis, gallstone disease and **hepatocellular carcinoma** (**HCC**). Studying the transcriptional regulation of BSEP will uncover the mechanistic insights in the role BSEP plays in physiological as well as pathological conditions.

BSEP expression is regulated by nuclear receptor liver receptor homolog 1 (LRH-1) and oxysterols.

The expression of BSEP is positively regulated by the bile acid/FXR signaling pathway.[3] Activation of FXR by bile acids strongly induces BSEP expression *in vitro* and *in vivo*. Such feed-forward regulation of BSEP by FXR is considered a major mechanism for preventing excessive accumulation of toxic bile acids in hepatocytes.

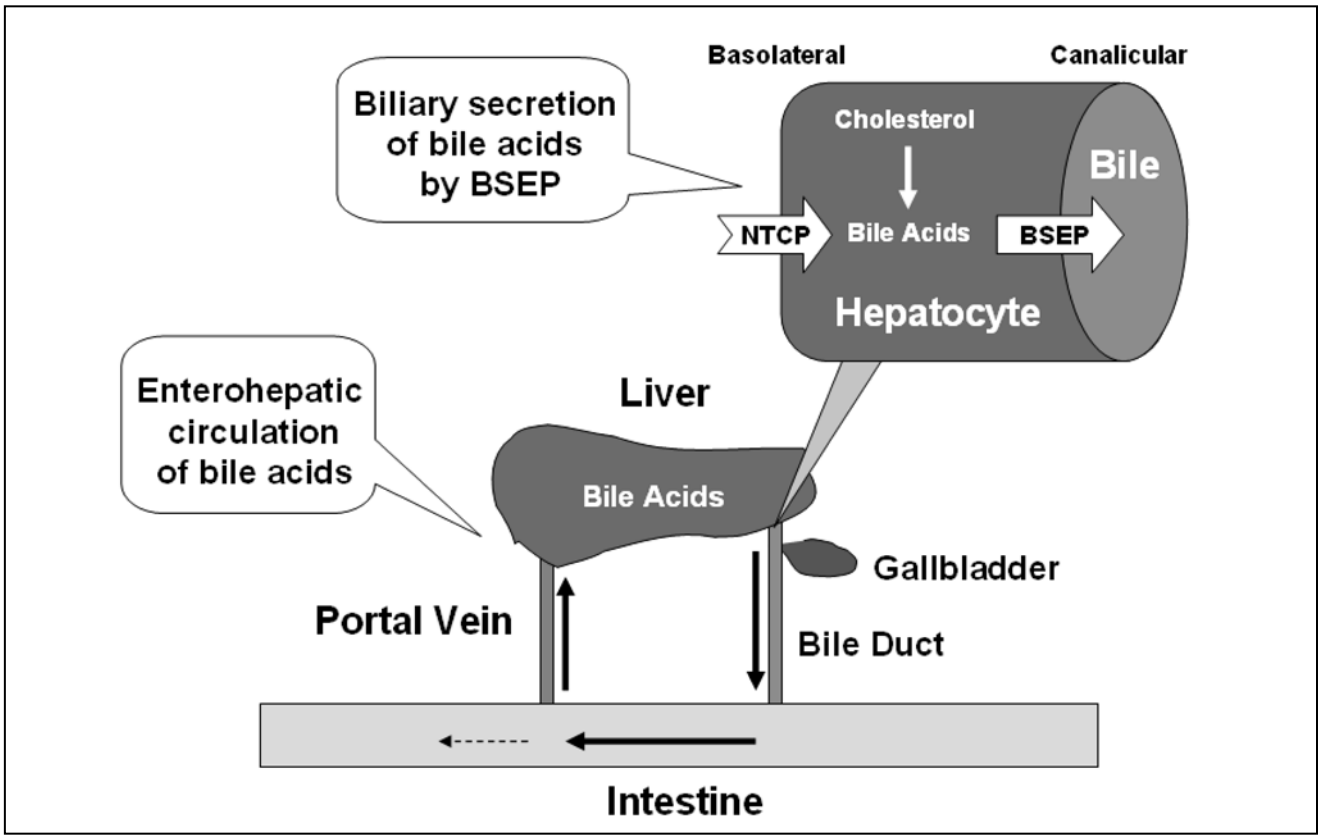


Figure. 1. **Enterohepatic circulation of bile acids**. Bile acids are synthesized in the liver from cholesterol, secreted into the bile through BSEP, reabsorbed in the intestine, and return to the liver via the portal vein. In the liver, bile acids are taken up through Na+/taurocholate cotransporting polypeptide (NTCP) and re-secreted into bile through BSEP, completing the enterohepatic circulation. Through each cycle, 95% bile acids are reabsorbed in the intestine while 5% bile acids are eliminated through fecal excretion.

In addition to the FXR signaling pathway, we have shown that BSEP is transcriptionally regulated by another nuclear receptor **liver receptor homolog 1 (LRH-1)**. LRH-1 activated the BSEP promoter during transcription and functioned as a modulator in the bile acid/FXR-mediated BSEP regulation. Our findings suggest that LRH-1 plays a supporting role with FXR in maintaining hepatic bile acid levels by coordinately regulating CYP7A1 and BSEP for bile acid synthesis and elimination, respectively.[4]

Oxysterols, oxidized derivatives of cholesterol, serve as endogenous ligands for nuclear receptor liver x receptor (LXR) to regulate cholesterol homeostasis. We discovered that oxysterols can also acts as FXR ligands and induce BSEP expression.[5] This finding demonstrates that oxysterols function as dual ligands for both LXR and FXR, and are potentially involved in regulating the biosynthesis, transport and disposition of cholesterol as well as bile acids.

Modulation of BSEP expression by xenobiotics has therapeutic or toxicological effects.

As the rate-limiting step in bile acid disposition, modulation of BSEP expression by xenobiotics, such as drugs and natural products, significantly impacts cholesterol metabolism and intrahepatic bile acid levels. Guggulsterone is a natural product from the *Commiphora mukul* tree and has been used by humans for over several thousands of years. However, the underlying mechanism is unknown. We found that guggulsterone synergistically up-regulates BSEP expression with bile acids and subsequently promotes conversion of cholesterol into bile acids.[6] Such up-regulation of BSEP expression by guggulsterone represents a possible mechanism for the guggulsterone-mediated hypolipidemic effect.

BSEP expression is severely diminished in patients with hepatocellular carcinoma (HCC) associated with altered FXR isoform expression.

A genetic defect of BSEP leads to severe cholestasis and HCC in young children. Clinical studies showed that bile acid homeostasis is disrupted in HCC patients with elevated serum bile acid level as a proposed marker for HCC.[7] However, the underlying mechanisms remain largely unknown. In our study, we found that BSEP expression was severely diminished in HCC patients and was associated with altered FXR isoform (FXRα1 and FXRα2) expression. Further studies showed that proinflammatory cytokines **interleukin-6 (IL-6)** and **tumor necrosis factor-alpha (TNF-α)** were significantly elevated in HCC tissues. Treatment of hepatoma Huh 7 cells with IL-6 and TNF-α resulted in a marked alteration in FXR isoform expression concurrent with a significant decrease in BSEP expression. Thus restoration of BSEP expression through suppressing inflammation in the liver may re-establish the bile acid homeostasis with beneficial effects in HCC patients (submitted for publication).

Cross-talking between bile acid and estrogen signaling pathway in the induction of intrahepatic cholestasis of pregnancy (ICP) and gallstone disease (GD).

Among diseases resulting from the imbalance of bile acid levels, ICP and GD are both associated with estrogen.[8] Although multiple risk factors are linked to those disorders, studies have demonstrated that estrogen may play a key role in the induction of the two diseases. Our research program is directly aimed at investigating the underlying mechanism for the two distinct but related diseases. We showed that estrogen repressed human BSEP expression *in vitro* and *in vivo*, and the repression was mediated by **estrogen receptor α (ERα)** through physically interacting with FXR, indicating a crosstalk between estrogen/ERα and bile acids/FXR signaling pathway (unpublished results). We plan to test the hypothesis that down-regulation of BSEP expression by estrogen is mediated through a novel non-classical transrepression pathway, a direct interaction between ERα and FXR, and as a consequence is a common risk factor for ICP and GD.

Funding Source

This research is supported by a grant from the **National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK),** NIH (R01-DK087755).

References

1. Hofmann AF. The enterohepatic circulation of bile acids in mammals: form and functions. *Front Biosci*. 2009;14:2584–98.
2. Meier PJ, Stieger B. Bile salt transporters. *Annu Rev Physiol*. 2002;64:635–61.
3. Ananthanarayanan M, Balasubramanian N, Makishima M, Mangelsdorf DJ, Suchy FJ. Human bile salt export pump promoter is transactivated by the farnesoid X receptor/bile acid receptor. *J Biol Chem*. 2001;276:28857–65.
4. Song X, Kaimal R, Yan B, Deng R. Liver receptor homolog 1 transcriptionally regulates human bile salt export pump expression. *J Lipid Res*. 2008;49:973-84.
5. Deng R, Yang D, Yang J, Yan B. Oxysterol 22(R)-hydroxycholesterol induces the expression of the bile salt export pump through nuclear receptor farsenoid X receptor but not liver X receptor. *J Pharmacol Exp Ther*. 2006;317:317-25.
6. Deng R, Yang D, Radke A, Yang J, Yan B. The hypolipidemic agent guggulsterone regulates the expression of human bile salt export pump: dominance of transactivation over farsenoid X receptor-mediated antagonism. *J Pharmacol Exp Ther*. 2007;320:1153-62.
7. Chen T, Xie G, Wang X, Fan J, Qiu Y, Zheng X, Qi X, et al. Serum and urine metabolite profiling reveals potential biomarkers of human hepatocellular carcinoma. *Mol Cell Proteomics*. 2011;10:M110 004945.
8. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. *World J Gastroenterol*. 2009;15:2049-66.

Ruitang Deng, PhD, is an Associate Professor in the Department of Biomedical and Pharmaceutical Sciences at the University of Rhode Island College of Pharmacy.

Disclosure of Financial Interests

The author and/or their spouse/significant other have no financial interests to disclose.

Correspondence

Ruitang Deng, PhD
Department of Biomedical and Pharmaceutical Sciences
College of Pharmacy
University of Rhode Island
7 Greenhouse Road
Kingston, RI 02881
phone: (401) 874-4950
e-mail: DengR@mail.uri.edu

Going Deep for Drug Discovery: An Ocean to Bedside Approach to Explore Sub-Seafloor Microbes for the Next Generation of Antibiotics

Stephanie Forschner-Dancause, PhD, Kerry LaPlante, PharmD, David C. Smith, PhD, and David C. Rowley, PhD

The World Health Organization has identified antimicrobial resistance as one of the top three greatest threats to human health. Today, infections by **methicillin-resistant *Staphylococcus aureus* (MRSA)** account for more deaths in US hospitals than both tuberculosis and HIV/AIDS combined.[1] More than 60% of staph infections in intensive care units are due to drug resistant strains,[1] and it is common to encounter those that lack sensitivity to multiple classes of drugs.[2] In addition, pathogenic *Escherichia coli* and *Klebsiella pneumoniae* are increasingly found to produce an extended spectrum of enzymes that significantly decrease drug options for treating infections and often leave patients with limited to no antimicrobial treatment options. Regrettably, antimicrobial research and development is not keeping pace with rising drug resistance.[3] There are currently no novel drugs in late stage development for the treatment of multidrug-resistant Gram-negative pathogens.

This leads scientists and clinicians to ask, "*Where will the next generation of antibiotics come from*?" A crucial component in drug discovery methods should continue to be the proven strategy of screening molecules from nature. Most of our clinically important antibiotics such as penicillins, tetracyclines, and macrolides have been discovered through the study of secondary metabolites produced by terrestrial microorganisms. In recent years, however, the repeated cultivation of the same microbial species from terrestrial soils has resulted in disappointing outcomes.[4] Frontier resources for the discovery of novel molecules are therefore critical to meet the genuine need for new antibiotics.

Exploring the Ocean

More than 70% of the earth's surface is comprised of ocean, and about 60% of the ocean floor is covered by water more than 2000 meters deep. Due to obvious technical challenges, sediments underlying the deep ocean remain one of the least explored environments for microbiology. At all taxonomic levels, there is more diversity of life in the deep sea than initially imagined.[5] Such biodiversity leads one to believe that the deep sea represents the next frontier in the search for exploitable biology.[6]

Collaboration

A new collaboration was formed by URI scientists to capitalize on the potential to discover new antibiotics produced by microbes from deep oceanic sediments. This interdisciplinary collaboration taps existing strengths in the fields of deep ocean microbiology (Smith lab, Graduate School of Oceanography), marine-based antibiotic drug discovery (Rowley Lab, College of Pharmacy), and evaluation (LaPlante Lab, VA Medical Center). It further leverages the opportunity to access deep oceanic sediments collected during expeditions conducted by the **Integrated Ocean Drilling Program (IODP)**. This scientific ocean drilling program, supported by 25 countries, and its predecessors the **Deep Sea Drilling Project (DSDP)** and the **Ocean Drilling Program (ODP)**, has retrieved sediment core samples from around the globe since 1968. Exploration of the subseafloor microbial community began in earnest in the late 1990s.

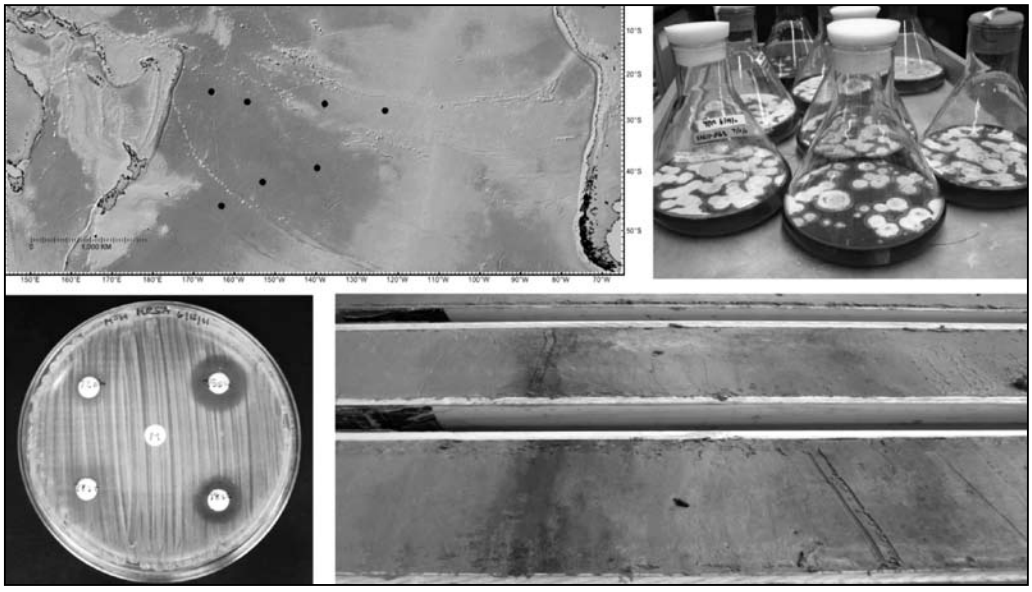


Figure 1. **Discovery of antibiotic compounds from subsurface sediments of the South Pacific Gyre.** Clockwise from top left: Bathymetric map of the South Pacific Gyre with black dots representing sampling sites, large scale static cultivations of a fungal strain isolated from SPG sediments, cross section example of subsurface sediment cores from which the SPG culture collection was isolated, SPG strains were investigated for antibiotic activity using disc diffusion assays.

In 2010, David C. Smith participated in the **Integrated Ocean Drilling Program (DSDP IODP)** Expedition 329 to the **South Pacific Gyre (SPG)**—one of Earth's five major rotating ocean currents—where they cored the sediment stack underlying average ocean depths of 5,057 meters.[7] It possesses the lowest burial rates for organic matter

in the ocean[8] and has been described as the Earth's largest oceanic desert. The sedimentary microbial community has extremely low biomass and metabolic activity and is predicted to be unlike any others of the same depth previously studied by drilling programs.[9] In total, 105 samples were collected from sediment cores within the gyre ranging in depth from 1.3 to 75.3 meters below the seafloor (mbsf) and an additional 27 subcores ranging in depth from 1.4 to 126.9 mbsf were collected from the control site. (Figure 1)

The Rowley group has isolated 150 bacterial and 120 fungal strains from these deep ocean sediments. Taxonomic identification of the bacteria has been undertaken, and many strains identified to date are related to genera and groups recognized to be productive for drug discovery. When grown at atmospheric pressure, room temperature and on standard marine media, a remarkable 60% of bacterial and over 80% of fungal isolates assayed to date from the SPG subsurface sediments produce molecules possessing antibacterial properties against human pathogens, including methicillin-resistant *Staphylococcus aureus, Pseudomonas aeruginosa* PA01, and *Acinetobacter baumannii*.

The next step in this collaborative investigation involves the identification of the exact antibiotics being produced by these microorganisms. Many of the antibiotic producers have been cultured in multi-liter scale, and chemical investigations of their bioactive compounds are underway. Once the antibiotic agents have been purified and the structures have been determined, novel agents will be tested for their growth inhibitory activities against an array of clinically important pathogens at LaPlante's laboratory located at the Providence Veterans Affairs Medical Center.[10, 11]

There are obvious technical challenges to accessing sediments in the deepest regions of the oceans and further difficulties arise in attempting to replicate the extreme environmental conditions of the deep ocean. For example, these microbes are adapted to high pressure, low temperature, and low organic content environments. It is unknown how these parameters may influence the growth of the microorganisms or whether they are critical for the expression of genes leading to antibiotic production. While we can duplicate such conditions in the lab, such cultivations are not conducive to the scale and throughput necessary for drug discovery efforts. Nevertheless, a subset of the deep-sea microbiota can be cultivated under normal laboratory conditions, and these have shown promise for the production of bioactive molecules.

The South Pacific Gyre is just one of five major gyre systems depleted of nutrients year round. The promising antibacterial activities of microbes from the SPG may provide insight into the biomedical potential of similar sedimentary environments underlying other regions of open ocean. Clearly, the deep oceanic subsurface ecosystem should not be overlooked for the discovery of bioactive natural products.

Funding Source

This research is supported by NIH R-15 grant 1R15AI093158-01.

References

1. Boucher HW, Corey GR. Epidemiology of methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis.* Jun 1 2008;46 Suppl 5:S344–9.
2. DeLeo FR, Chambers HF. Reemergence of antibiotic-resistant *Staphylococcus aureus* in the genomics era. *J Clin Invest.* Sep 2009;119(9):2464–74.
3. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis.* Jan 1 2009;48(1):1–12.
4. Jensen PR, Fenical W. Marine microorganisms and drug discovery: Current status and future potential. In: Fusetani N, ed. *Drugs from the sea*. Basel: Karger; 2000:6–29.
5. May RM. Biodiversity - Bottoms up for the Oceans. *Nature.* May 28 1992;357(6376):278–9.
6. Deming JW. Deep ocean environmental biotechnology. *Curr Opin Biotechnol.* Jun 1998;9(3):283–7.
7. Expedition 329 Scientists. South Pacific Gyre subseafloor life. *IODP Prel. Rept. 329.* 2011:doi:10.2204/iodp.pr.2329.2011.
8. Jahnke RA. The global ocean flux of particulate organic carbon: Areal distribution and magnitude. *Global Biogeochem. Cycles.* 1996;10(1):71–88.
9. D'Hondt S, Spivack AJ, Pockalny R, et al. Subseafloor sedimentary life in the South Pacific Gyre. *Proc Natl Acad Sci U S A.* Jul 14 2009;106(28):11651–6.
10. Socha AM, LaPlante KL, Rowley DC. New bisanthraquinone antibiotics and semi-synthetic derivatives with potent activity against clinical *Staphylococcus aureus* and *Enterococcus faecium* isolates. *Bioorg Med Chem.* Dec 15 2006;14(24):8446–54.
11. Socha AM, Laplante KL, Russell DJ, Rowley DC. Structure-activity studies of echinomycin antibiotics against drug-resistant and biofilm-forming *Staphylococcus aureus* and *Enterococcus faecalis*. *Bioorg Med Chem Lett.* Mar 1 2009;19(5):1504–7.

Stephanie Forschner-Dancause, PhD, is a recent graduate of the Pharmaceutical Sciences doctoral program at the University of Rhode Island.

David Smith, PhD, is Professor and Associate Dean at the Graduate School of Oceanography, University of Rhode Island.

Kerry L. LaPlante, PharmD, is an Associate Professor of Pharmacy, University of Rhode Island, Adjunct Clinical Associate Professor of Medicine at the Warren Alpter Medical School of Brown University, and Director of the Rhode Island Infectious Diseases (RIID) Research Program and Infectious Diseases Pharmacotherapy Specialist at the Providence Veterans Affairs Medical Center.

David Rowley, PhD, is an Associate Professor, College of Pharmacy, University of Rhode Island.

Disclosure of Financial Interests

Stephanie Forschner-Dancause, PhD, has no financial interests to disclose.

Kerry LaPlante, PharmD, consults for Cubist Pharmaceuticals, Davol, Inc., TheraDoc, and Forrest Laboratories; receives research grant support from Cubist Pharmaceuticals, Inc., Pfizer Pharmaceuticals, Inc., and Theravance, Inc.; and is on the speakers bureau for Cubist Pharmaceuticals, Inc.

David C. Smith, PhD, has no financial interests to disclose.

David C. Rowley, PhD, has no financial interests to disclose.

Correspondence

David C. Rowley, PhD
College of Pharmacy
University of Rhode Island
7 Greenhouse Road
Kingston, RI 02879
phone: (401) 874-9228
e-mail: drowley@uri.edu

Nanoparticles for Cancer Treatment

Wei Lu, PhD

Particles can be engineered to nanome-ter-size (nm) which are only 1/1,000 the width of a single human hair. Nanoparticles made of gold display strong optical absorption.[1] A special type of gold nanoparticle called hollow gold nanoparticle has a core-shell nanostructure with unique characteristics, including small particle size (~40 nm in diameter), which is an ideal range for particles to be incorporated into living cells; hollow interior, which allows for higher drug loading capacity; and pure gold composition, which is associated with less toxicity.[2, 3] The hollow gold nanoparticles have been proven to convert optical energy into thermal energy, leading to overheating of the local environment around the light-absorbing species. This phenomenon is known as photothermal effect.[4] We have developed a variety of applications of hollow gold nanoparticles in cancer diagnosis and therapeutics, including photothermal ablation therapy, photoacoustic tomography, and light-controlled drug release.

Photothermal ablation therapy

Photothermal ablation therapy is a therapeutic modality in which the light-absorbing nanoparticles are utilized to burn the tumor cells.[5] The heat produced can lead to localized temperatures far above the threshold temperature (~330 K) that causes irreversible cell death.[6] By varying the core radius and shell thickness, the optical absorption of hollow gold nanoparticles can be fine-tuned to the **near-infrared (NIR)** region.[2] Absorbance of NIR light is desirable because it causes minimal thermal injury to normal tissues and deeper tissue penetration, to several centimeters.[7] We have applied this so called "targeted delivery" technology in order to increase the nanoparticles' ability to enter the cancerous cells. In a mouse-bearing melanoma model, the surface of hollow gold nanoparticles was coated with small peptide NDP-MSH, a potent agonist of melanocortin type-1 receptor, which is overexpressed in melanoma cells.[8] Following intravenous injection the NDP-MSH modified nanoparticles were actively located and drawn into cancer cells through the cell membrane. NIR light beamed into tumors with targeted nanoparticles destroyed 66 percent of the tumors, but only destroyed 8 percent of tumors treated with untargeted nanoparticles.[8] (Figure 1) Because of the specific accumulation of nanoparticles in tumor but not in normal tissues, the efficiency of photothermal ablation therapy was vastly improved and side effects were reduced by decreasing the laser dose duration and volume.

Photoacoustic tomography

Photoacoustic tomography is a hybrid technology that visualizes the internal distribution of optical energy deposition in biological tissues through the detection of laser-induced ultrasonic waves.[9] Photoacoustic tomography provides higher spatial resolution than traditional optical imaging in deep biological tissues because ultrasonic scattering in such tissues is two orders of magnitude less than optical scattering. The hollow gold nanoparticles can increase photoacoustic signals because of their light excitation in the NIR spectral region, where the signal ratio of gold nanoparticles to hemoglobin is high and contrast to endogenous chromophores is great.[10] Recently, we developed peptide-based hollow gold nanoparticles to target integrins that are overexpressed in both glioma and angiogenic tumor blood vessels. The targeted nanoparticles permitted accurate photoacoustic imaging of inoculated U87 glioma in nude mice and mediated selective antitumor effect when mice were irradiated with an NIR laser.[11] These findings suggest potential

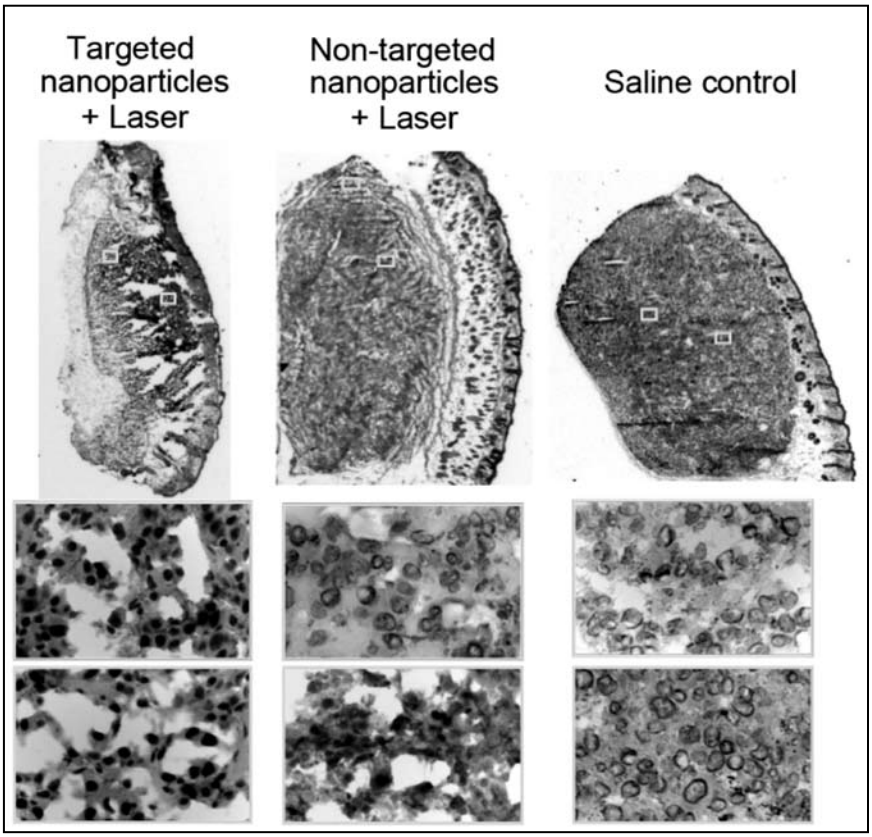


Figure 1. Photothermal ablation with targeted hollow gold nanoparticle-induced destruction of B16/F10 melanoma in nude mice. H&E staining of tumor sections 24 h after NIR laser irradiation. Tumor cells characterized by extensive pyknosis, karyolysis, cytoplasmic acidophilia, and degradation of the extracellular matrix of the tumor in mice treated with targeted nanoparticles plus laser. In mice treated with non-targeted nanoparticles plus laser, such features were observed mostly in areas close to the surface.

applications of hollow gold nanoparticles as a novel diagnostic and therapeutic platform for 1) photoacoustic imaging for pretreatment diagnosis, real-time monitoring of treatment, as well as assessment of treatment outcome; and 2) photothermal ablation therapy of tumor cells under the guidance of photoacoustic imaging. Human malignant gliomas are characterized by their ability to infiltrate and invade surrounding normal brain tissues. Complete tumor resection is often limited by the surgeon's ability to distinguish residual tumor tissue from surrounding brain tissue. Tumors often recur because it is extremely difficult to remove infiltrating tumor cells without affecting vital brain functions. With this technique, it may be possible to achieve NIR laser treatment of the surgical bed through optical fiber for the eradication of residual brain tumor cells.

Light-controlled drug release

The hollow gold nanoparticles can also act as vehicles to get the cancer cells to take the chemotherapy "bait". Because of their hollow interior, each hollow gold nanoparticle can load thousands of chemotherapy "baits". The drug-loaded nanoparticles are like a Trojan horse that can efficiently ferry "toxins" to the tumor cells. The hollow gold nanoparticles with high photothermal conversion efficiency can be exploited for controlled release of doxorubicin from the particles using NIR light as the external stimulus to trigger drug release.[12] Results from both cell and animal experiments showed that NIR light triggered release of doxorubicin from doxorubicin-loaded hollow gold nanoparticles in tumor sites offered temporally and spatially controlled release of the chemotherapeutic agent.[12, 13] This increased the therapeutic efficacy and specificity. The nano-drug delivery system was also found to alter the pharmacokinetic disadvantages of the free drug, avoiding a burst exposure of a large amount of drug to vital organs such as the liver and kidney. In a future study, we will use the hollow gold nanoparticles to load the anticancer drug cisplatin. Conjugated with NDP-MSH peptide, the cisplatin-loaded nanoparticles will target melanoma. The combination of photothermal therapy and chemotherapy, with laser controlled drug release, may produce a synergistic anticancer effect to overcome tumor regrowth and cisplatin resistance.

In summary, nanomedicine with hollow gold nanoparticles represents an innovative field with immense potential for improving cancer treatment. As illustrated in animal models,[8, 10, 11, 13] the novel nano-drug delivery platforms have shown several potential advantages such as tumor targeting, optical imaging and controlled release strategies. Nanomedicine may generate a robust and efficacious therapeutic modality.

References

1. Hirsch LR, Gobin AM, Lowery AR, Tam F, Drezek RA, Halas NJ, West JL. Metal nanoshells. *Ann Biomed Eng.* 2006;34:15–22.
2. Schwartzberg AM, Olson TY, Talley CE, Zhang JZ. Synthesis, characterization, and tunable optical properties of hollow gold nanospheres. *J Phys Chem B.* 2006;110:19935–44.
3. Melancon MP, Zhou M, Li C. Cancer theranostics with near-infrared light-activatable multimodal nanoparticles. *Acc Chem Res.* 2011;44:947–56.
4. Melancon MP, Lu W, Yang Z, Zhang R, Cheng Z, Elliot AM, Stafford J, Olson T, Zhang JZ, Li C. In vitro and in vivo targeting of hollow gold nanoshells directed at epidermal growth factor receptor for photothermal ablation therapy. *Mol Cancer Ther.* 2008;7:1730–9.
5. Hirsch LR, Stafford RJ, Bankson JA, Sershen SR, Rivera B, Price RE, Hazle JD, Halas NJ, West JL. Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. *Proc Natl Acad Sci USA.* 2003;100:13549–54.
6. Hu M, Chen JY, Li ZY, Au L, Hartland GV, Li XD, Marquez M, Xia YN. Gold nanostructures: engineering their plasmonic properties for biomedical applications. *Chem Soc Rev.* 2006;35:1084–94.
7. Weissleder R. A clearer vision for in vivo imaging. *Nat Biotechnol.* 2001;19:316–7.
8. Lu W, Xiong C, Zhang G, Huang Q, Zhang R, Zhang JZ, Li C. Targeted photothermal ablation of murine melanomas with melanocyte-stimulating hormone analog-conjugated hollow gold nanospheres. *Clin Cancer Res.* 2009;15:876–86.
9. Zhang HF, Maslov K, Stoica G, Wang LV. Functional photoacoustic microscopy for high-resolution and noninvasive in vivo imaging. *Nat Biotechnol.* 2006;24:848-51.
10. Lu W, Huang Q, Ku G, Wen X, Zhou M, Guzatov D, Brecht P, Su R, Oraevsky A, Wang LV, et al. Photoacoustic imaging of living mouse brain vasculature using hollow gold nanospheres. *Biomaterials.* 2010;31:2617–26.
11. Lu W, Melancon MP, Xiong C, Huang Q, Elliott A, Song S, Zhang R, Flores LG 2nd, Gelovani JG, Wang LV, et al. Effects of photoacoustic imaging and photothermal ablation therapy mediated by targeted hollow gold nanospheres in an orthotopic mouse xenograft model of glioma. *Cancer Res.* 2011;71:6116–21.
12. You J, Zhang G, Li C. Exceptionally high payload of doxorubicin in hollow gold nanospheres for near-infrared light-triggered drug release. *ACS Nano.* 2010;4:1033–41.
13. You J, Zhang R, Zhang G, Zhong M, Liu Y, Van Pelt CS, Liang D, Wei W, Sood AK, Li C. Photothermal-chemotherapy with doxorubicin-loaded hollow gold nanospheres: A platform for near-infrared light-trigged drug release. *J Control Release.* 2011;158:319–28.

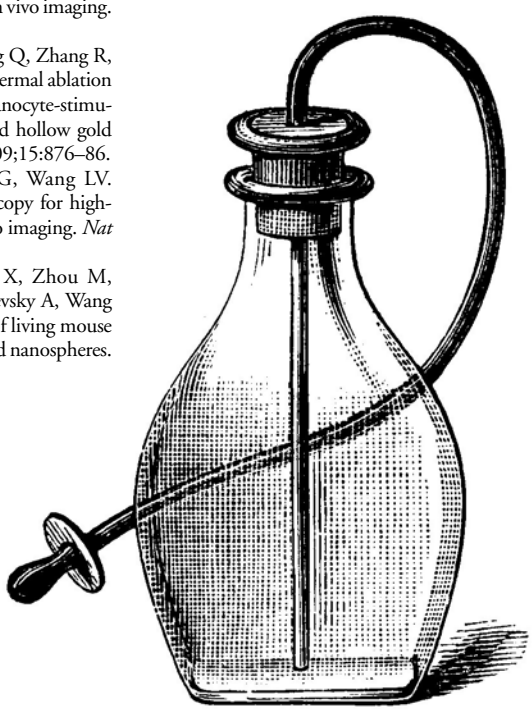
Wei Lu, PhD, is an Assistant Professor of Pharmaceutics in the Department of Biomedical and Pharmaceutical Science.

Disclosure of Financial Interests

The author and/or their spouse/significant other have no financial interests to disclose.

Correspondence

Wei Lu, PhD
College of Pharmacy
University of Rhode Island
7 Greenhouse Road
Kingston, RI 02881
phone: (401) 874-5517
fax: (401) 874-5787
e-mail: weilu@uri.edu



Seasonal Influenza Vaccination Among Pregnant Women in Rhode Island, 2002–2011

Hyun (Hanna) Kim, PhD, Patricia Raymond, RN, MPH, and Rachel Cain, BS

Pregnant women are at increased risk for morbidity and mortality from influenza infection, likely due to the physiologic changes associated with pregnancy.[1] Preventing influenza during pregnancy is an essential component of prenatal care, and vaccination is the most effective strategy. Vaccinating pregnant women for influenza can protect both the women and their infants, especially infants aged less than six months who are not old enough to receive influenza vaccination.[2,3] Since 2004, the **Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP)** has recommended routine vaccination for all pregnant women during influenza season with **trivalent inactivated influenza vaccine** (TIV), at any stage of pregnancy.[2] **The American College of Obstetricians and Gynecologists (ACOG)** and the **American Academy of Family Physicians (AAFP)** also support ACIP's recommendation of routine vaccination of all pregnant women.

This report describes the trends of the influenza vaccination rates among pregnant women in Rhode Island, timing and venues of vaccination, and reasons for not being vaccinated. The report also provides recommended actions for health care providers to improve influenza vaccination among pregnant women.

Methods

We analyzed two different data sets from the **Rhode Island Pregnancy Risk Assessment Monitoring System (PRAMS)**: the 2002-2010 PRAMS calendar year survey data and the 2010-2011 PRAMS flu insert survey data. PRAMS is a collaborative surveillance project of the CDC and 37 state health departments. PRAMS collects state-specific, population-based data on maternal behaviors and experiences before, during, and shortly after pregnancy.[4] Each year, about 1,300 Rhode Island women who have recently given birth (two to six months postpartum) participate in the surveillance through mail or telephone survey.

PRAMS calendar year survey has collected influenza (flu) vaccination data for several years using the following two questions: "At any time during your most recent pregnancy, did a doctor, nurse, or other health care worker offer you a flu vaccination or tell you to get one?" and "Did you get a flu vaccination during your most recent pregnancy?" The 2010-2011 PRAMS flu insert survey collected additional information on flu vaccination during that particular flu season. The additional questions included were: "Since August 1, 2010, did you get a flu shot?", if the respondent said yes, then they were asked: "Did you get this flu shot *during* or *after* your most recent pregnancy?", "During what month and year did you get the flu shot?" and "Where did you get your flu shot?" If the respondents did not get a flu shot since August 1, 2010, they were asked "What were your reasons for *not*

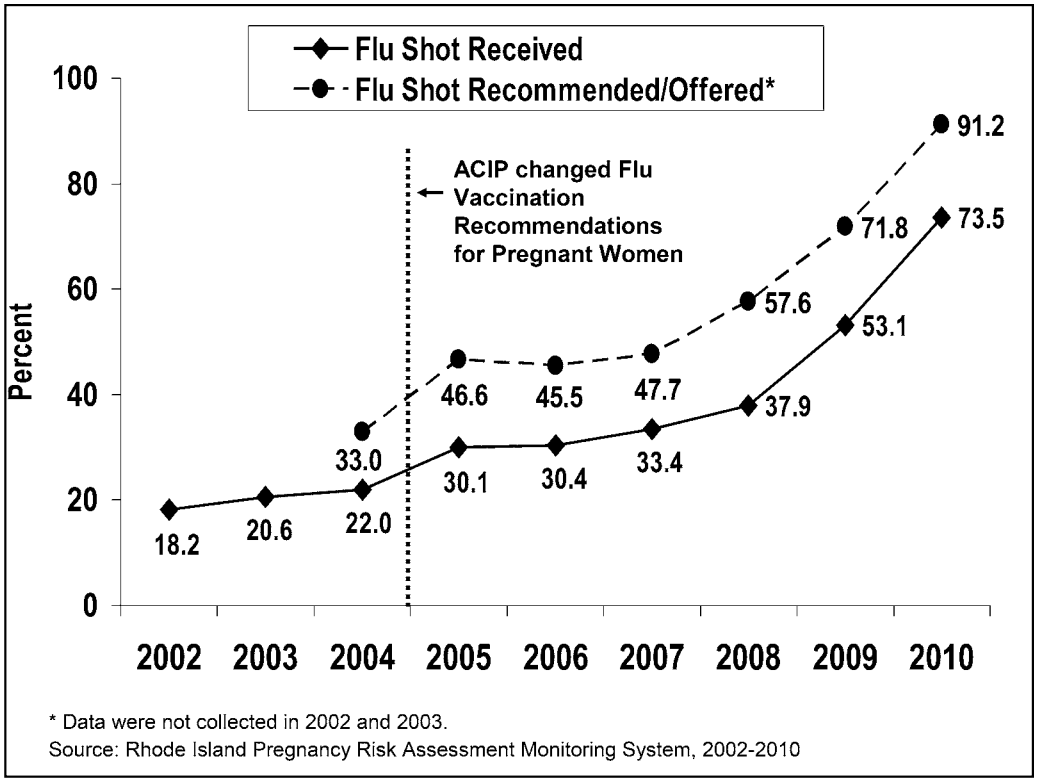


Figure 1. Percentage of women who received influenza vaccination during pregnancy and percentage of women who were recommended/offered influenza vaccine, Rhode Island, 2002-2010.

getting a flu shot since August 1, 2010?" The 2010-2011 flu insert data were collected only from September 2010 to May 2011 (n=888). These data are not directly comparable with calendar year's vaccination coverage data due to the differences in time frames. PRAMS data were weighted to represent all Rhode Island women who have delivered a live infant. The weighted response rates for all the survey years since 2002 were 65% or higher. To make the report simple, we presented only point estimates of the data without confidence intervals.

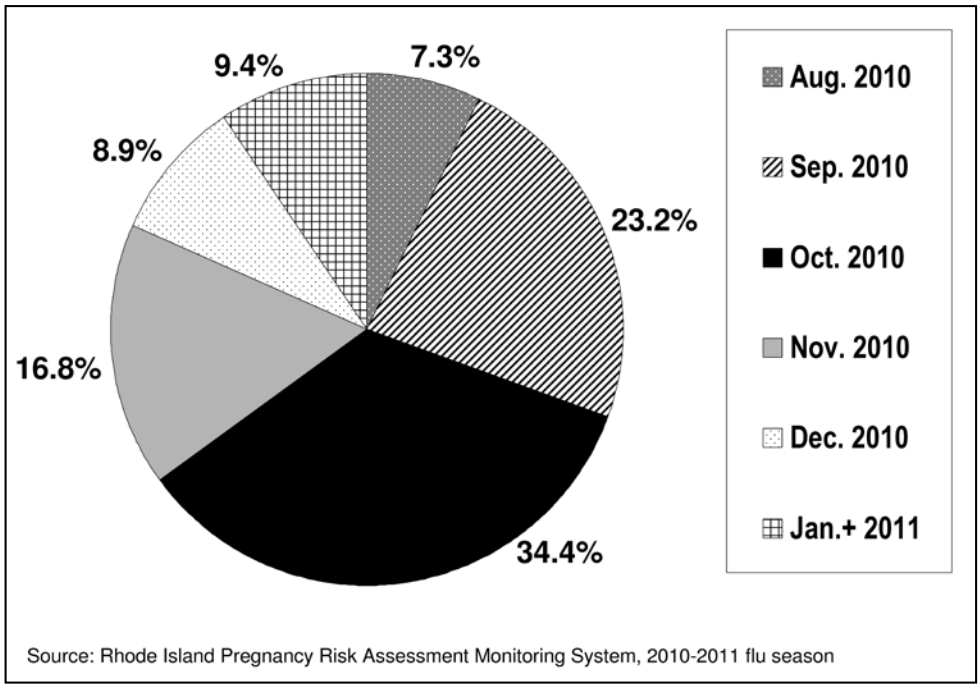


Figure 2. Timing of influenza vaccination among women with a recent live birth, Rhode Island, 2010-2011 flu season.

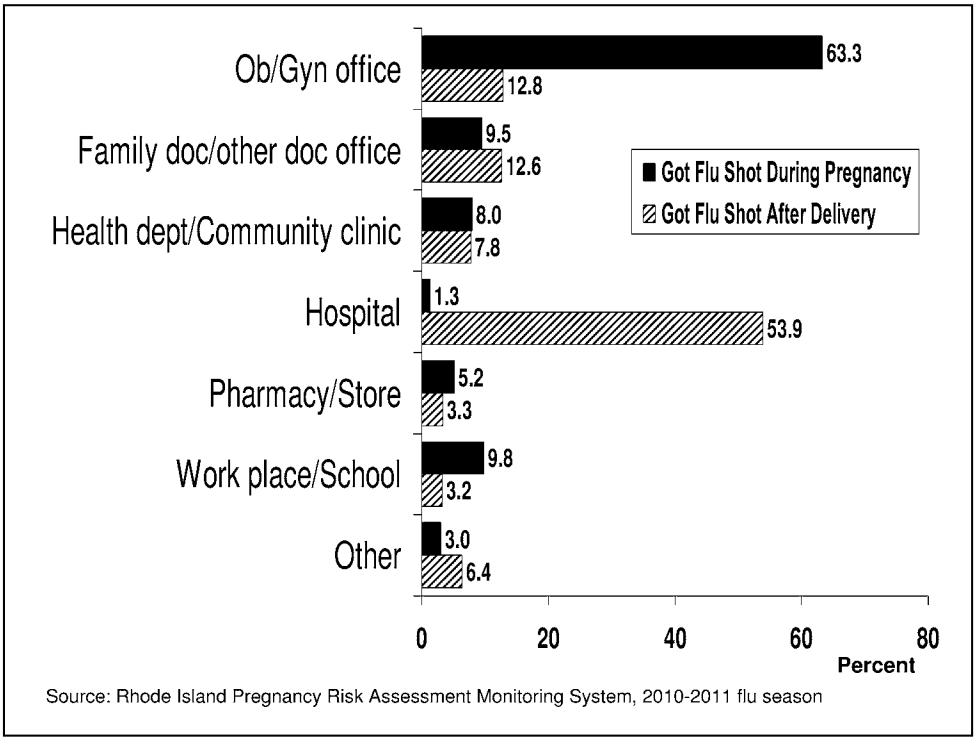


Figure 3. Venues of influenza vaccination among women with a recent live birth, Rhode Island, 2010-2011 flu season.

Results

Data from the PRAMS Calendar Year Survey

The percentage of women who received influenza vaccine during their pregnancy increased significantly from 18.2% in 2002 to 73.5% in 2010 (p<0.0001). Although vaccination coverage rates increased consistently during the period, substantial increases were observed from 2004 to 2005 (8.1 percentage points or 37% increase), from 2008 to 2009 (15.2 percentage points or 40% increase) and from 2009 to 2010 (20.4 percentage points or 38% increase). The percentage of women who reported that their health care provider recommended or offered influenza vaccine during their pregnancy also significantly increased from 33.0% in 2004 to 91.2% in 2010 (p<0.0001). A similar pattern of increases in the provider's recommendations/offers was observed from 2004 to 2010. (Figure 1)

Data from the 2010- 2011 Flu Insert Survey

Timing of Vaccination

The flu insert survey data showed that 71.4% of women with a recent live birth received an influenza vaccination in the 2010-2011 flu season: 61.0% were vaccinated *during* pregnancy and 10.4% were vaccinated *after* pregnancy. Most women reported receiving the vaccine in October (34.4%), followed by September (23.2%), November (16.8%), and December (8.9%). About 9% were vaccinated during January-May, 2011. (Figure 2)

Venues of Vaccination

The venues for receipt of vaccination were significantly different between women who were vaccinated during pregnancy compared to those who were vaccinated during the post-partum

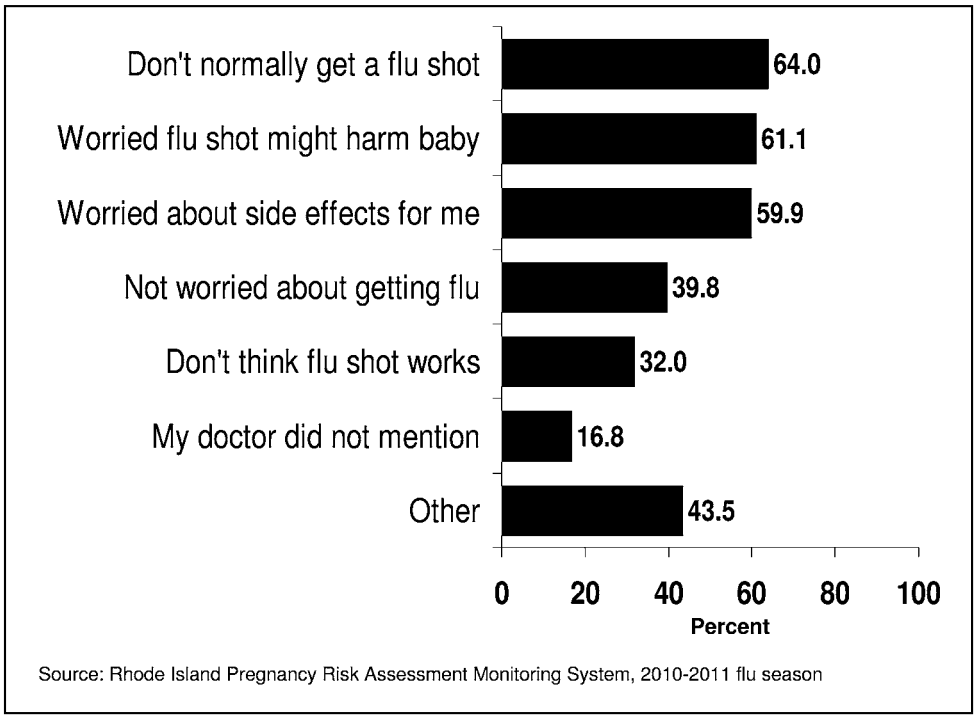


Figure 4. Reasons for not getting influenza vaccination during pregnancy, Rhode Island, 2010-2011 flu season.

period. The most common location for women who were vaccinated during pregnancy was the obstetrician or gynecologist's office (63.3%), followed by work place or a school setting (9.8%), and family doctor or other doctor's office (9.5%). Hospitals (53.9%) were the most common location for women vaccinated during the post-partum period, followed by the obstetrician or gynecologist's office (12.8%), and family doctor or other doctor's office (12.6%). (Figure 3)

Barriers to Vaccination

Women who did not receive flu vaccination during the 2010-2011 flu season were asked to give the reasons (multiple reasons were allowed). The reasons for not getting vaccinated included: I don't normally get a flu shot (64.0%); I was worried that the flu shot might harm my baby (61.1%); I was worried about side effects of the flu shot for me (59.9%); I was not worried about getting sick with the flu (39.8%); I don't think the flu shot works (32.0%); and my doctor didn't mention anything about getting a flu shot (16.8%). (Figure 4)

Discussion

Although the influenza vaccination coverage among pregnant women increased significantly from 2002 to 2010, more than one quarter (26.5%) of women still did not receive an influenza vaccination during their pregnancy in 2010. A substantial increase in influenza vaccination coverage observed from 2004 to 2005 could be, in part, related to changes in ACIP recommendations in May 2004, stating that pregnant women could be vaccinated during any trimester of pregnancy. Prior to this change, influenza vaccination was recommended only for women who would be in their second or third trimester of pregnancy during flu season. The increase in vaccination coverage rates observed since 2008 can be attributed to several factors. These may include, but are not limited to, an overall heightened awareness among pregnant women and prenatal care providers about the risks of influenza during the 2009 H1N1 influenza pandemic. The pandemic led to increased influenza education and outreach efforts targeting health professionals and pregnant women. In addition, the **Rhode Island Department of Health (HEALTH)** engaged in active recruitment of prenatal providers and other vaccine providers into the state-supplied vaccine program to ensure that influenza vaccine was accessible to pregnant women across the state.

The data indicate that the majority of *pregnant women* were vaccinated at their obstetrician or gynecologist's office during their prenatal care visits, while the majority of *postpartum women* were vaccinated at the hospital before they were discharged. The data also indicate that vaccine safety concern was one of the major barriers to vaccination among pregnant women.

The data reported here have several limitations: PRAMS data are self-reported by women two to six months postpartum and therefore their reporting can be subject to recall bias. Data from the flu insert survey are not comparable with annual influenza vaccination coverage data due to the differences in time frames. In the flu insert survey, the respondents who completed the survey during September were less likely to be vaccinated than the respondents who completed the survey during April or May.

It is well documented that when health care providers strongly recommend or offer influenza vaccine, their patients are much more likely to be vaccinated.[5] To improve influenza vaccination coverage among pregnant women, health care providers should use the first prenatal care encounter to educate women about the safety of influenza vaccine, the risk of influenza complications during pregnancy, and the protective effect of influenza vaccination on women and their infants. To prevent missed opportunities for vaccination in the practice setting, health care providers should consider establishing an influenza vaccine reminder system, maintaining standing orders for vaccination, and offering influenza vaccine at the earliest opportunity during influenza season.

Acknowledgments

This publication was made possible by a grant from the Centers for Disease Control and Prevention.

References

1. Centers for Disease Control and Prevention (CDC). Seasonal Flu Vaccination Safety and Pregnant Women. Available at http://www.cdc.gov/flu/protect/vaccine/qa_vacpregnant.htm.
2. Centers for Disease Control and Prevention (CDC). Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR*. August 6, 2010;59(RR08):1–62. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5908a1.htm.
3. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med*. 2008;359:1555–64.
4. Centers for Disease Control and Prevention (CDC), Pregnancy Risk Assessment Monitoring System (PRAMS). Available at http://www.cdc.gov/prams.
5. Rhode Island Department of Health. Influenza Vaccination Among Pregnant and Postpartum Women in Rhode Island: The Importance of the Prenatal Care Provider. Issue Brief, October 2011. Available at http://www.health.ri.gov/publications/issuebriefs/2011InfluenzaVaccinationAmongPregnantAndPostpartumWomenInRhodeIslandTheImportanceOfThePrenatalCareProvider.pdf.

Hyun (Hanna) Kim, PhD, is Senior Public Health Epidemiologist in the Center for Health Data and Analysis, Rhode Island Department of Health, and Clinical Assistant Professor in the Department of Epidemiology, The Warren Alpert Medical School of Brown University.

Patricia Raymond, RN, MPH, is the Team Lead for Preventive Services and Community Practices in the Division of Community, Family Health and Equity, Rhode Island Department of Health.

Rachel Cain, BS, is the PRAMS Program Coordinator in the Center for Health Data and Analysis, Rhode Island Department of Health.

Disclosure of Financial Interests

The authors have no financial interests to disclose.

Correspondence

Hyun (Hanna) Kim, PhD
Rhode Island Department of Health
3 Capitol Hill
Providence, RI 02908-5097
e-mail: hanna.kim@health.ri.gov

Images In Medicine

Thyroid Lymphoma

Barbara J. Nickel, MD, and Kevin J. Chang, MD

A 54 YEAR OLD MAN WITH A RECENT HISTORY OF THYROIDITIS presented to the Emergency Department with subacute onset of shortness of breath, which suddenly worsened on the day of admission, accompanied by fever and a "wet" feeling in the lungs. The patient is a nonsmoker with a remote history of tonsillectomy. His symptoms transiently improved in the ED with conservative treatment, and then acutely worsened, with marked shortness of breath and an episode of suspected aspiration. The patient was felt able to protect his airway at this point, and therefore underwent imaging of the neck for further evaluation.

A lateral radiograph of the neck demonstrated marked soft tissue swelling and possible mass in the infrahyoid region, with narrowing of the trachea. (Figure 1) CT was performed for further evaluation. (Figure 2) Contrast enhanced CT of the neck demonstrated marked enlargement of the thyroid gland, right greater than left. There were multiple areas of hypodensity suspicious for abscess and/or necrosis within the gland. There was abnormal presence of air in the retropharyngeal space. There was mass effect on the trachea, decreasing its diameter to 6 mm.

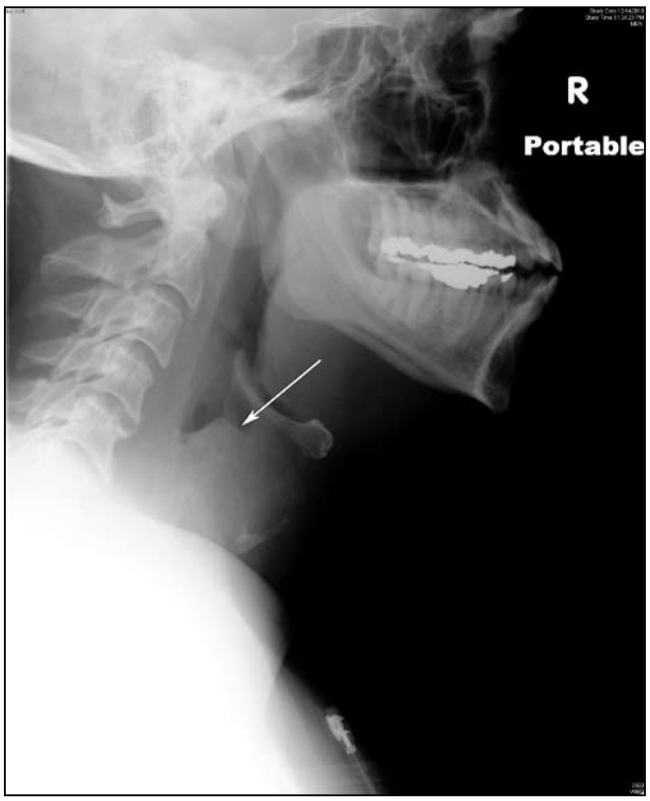


Figure 1. A lateral radiograph of the neck demonstrates marked soft tissue swelling and possible mass in the infrahyoid region (arrow), with narrowing of the trachea.

The patient was taken to the operating room for debridement of the suspected neck abscess and placement of a surgical airway. Specimens sent to Pathology demonstrated necrosis, areas of fibrosis, reactive cells, and no evidence of malignancy.

The patient spent approximately one week in the intensive care unit, after which repeated episodes of aspiration led to concern for undetected abscess, esophageal perforation, and/or

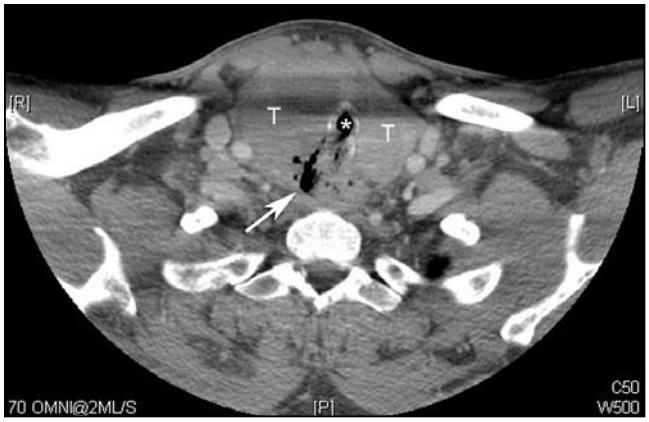


Figure 2. Contrast enhanced CT of the neck demonstrates marked enlargement of the thyroid gland, right side larger than left (T). Internal areas of hypodensity with retropharyngeal space gas are suspicious for abscess and/or necrosis (arrow). There is associated narrowing of the trachea (*).

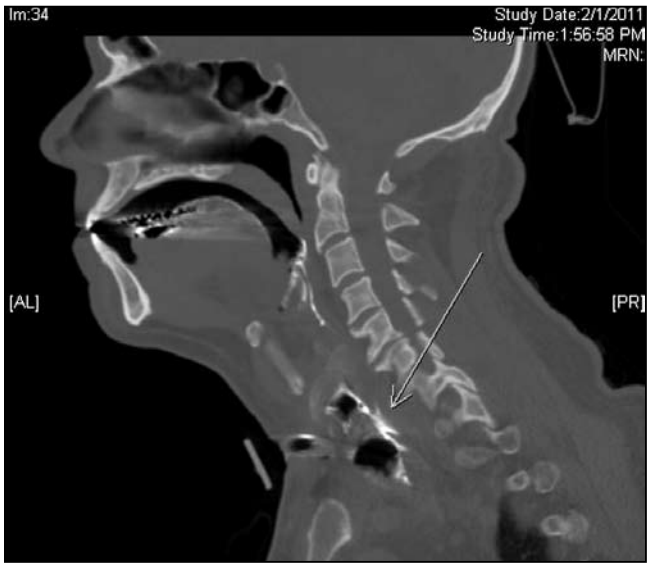


Figure 3. A sagittally reconstructed CT following a barium swallow demonstrates abnormal fistulous connection from the vallecula to the upper trachea. An additional tract was seen between airway and the cervical esophagus (arrow).

tracheal rupture. The patient was again taken to the operating room for bronchoscopy, sternocleidomastoid flap for repair of the trachea, primary repair of the cervical esophagus, and tracheostomy replacement. Specimens at this time demonstrated extranodal marginal zone lymphoma, consistent with B-cell **mucosa associated lymphoid tissue** (**MALT**), with large areas of necrosis and abscess formation, numerous histiocytes and fibrosis. Transformation to diffuse large B-cell lymphoma could not be excluded. Reactive lymph nodes and normal parathyroid tissue were found in the adjacent tissues. Repeat imaging was acquired postoperatively. (Figure 3) A sagittally reconstructed CT following a barium swallow demonstrates abnormal fistulous connection from the vallecula to the upper trachea. An additional tract was seen between the airway and cervical esophagus (green arrow).

Tracheoesophageal invasion and rupture is a rare complication that should be considered when a patient with neck neoplasm develops acute respiratory and gastrointestinal symptoms. Approximately 40% of non-Hodgkin lymphomas occur in extranodal sites, with the majority representing diffuse large B cell lymphomas. Of the small B-cell non-Hodgkin lymphomas, the majority are extranodal marginal zone B-cell lymphomas of mucosa associated lymphoid tissue (MALT lymphomas). Half of MALT lymphomas are located in the GI tract. Common sites of involvement include lung, salivary glands, ocular adnexa, and skin. The thyroid is an uncommon site, involved in 4% of cases. Most cases occur in a middle-aged population with a mean age of 61, and a slight female predominance. Most arise in a background of Hashimoto's thyroiditis, and patients typically present with a rapidly enlarging thyroid mass and sequelae of mass effect on adjacent structures, symptoms which may mimic those of anaplastic thyroid carcinoma. Treatment depends on the histological subtype and stage of the disease and includes radiotherapy and chemotherapy. The prognosis is usually favorable with proper treatment, as compared with that of anaplastic carcinoma. Overlapping cytologic features of thyroid lymphoma and anaplastic thyroid carcinoma make immunocytochemistry an important part of pathologic differentiation of these two entities.

References

1. Jaremko J, Rawat B, and Naik S. Oesophageal and tracheal perforation in thyroid B-cell lymphoma. *Australasian Radiology*. 2007 Dec;51 Suppl:B193–5.
2. Jaffe ES, Harris NL, Stein H, Vardiman JW (eds). *WHO Classification of Tumours. Pathology and Genetics, Tumours of Haematopoietic and Lymphoid Tissues*. IARC Press: Lyon 2001, pp 157–60.
3. Kebapcilar L, Alacicioglu I, and Comlekci A, et al. Primary thyroid lymphoma: case series with literature review. *J BUON*. 2009 Apr-Jun; 14(2):295–9.
4. Daneshbod Y, Omidvari S, and Daneshbod K, et al. Diffuse large B cell lymphoma of thyroid as a masquerader of anaplastic carcinoma of thyroid, diagnosed by FNA: a case report. *Cytojournal*. 2006 Oct 19;3:23.

Barbara J. Nickel, MD is a Radiology Resident at the Warren Alptert Medical School of Brown University.

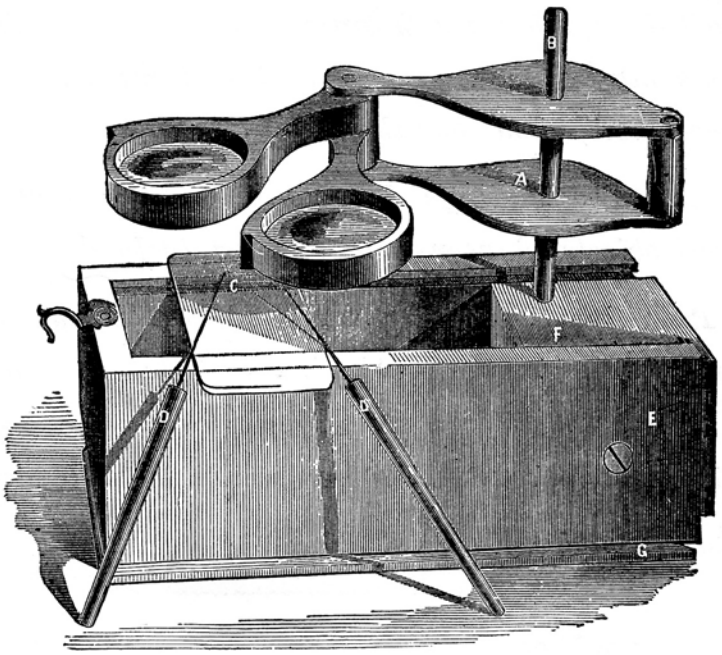
Kevin J. Chang, MD is Assistant Professor of Diagnostic Imaging, Warren Alpert Medical School of Brown University.

Disclosure of Financial Interests

The authors and/or their spouses/significant others have no financial interests to disclose.

Correspondence

Kevin J. Chang, MD
Department of Diagnostic Imaging
Rhode Island Hospital
593 Eddy St.
Providence, RI 02903
phone: (401) 444-5184
e-mail: kchang@lifespan.org



Information for Contributors

Medicine & Health/Rhode Island is peer-reviewed, and listed in the *Index Medicus*. We welcome submissions in the following categories:

Contributions
Contributions report on an issue of interest to clinicians in Rhode Island: new research, treatment options, collaborative interventions, review of controversies. Maximum length: 2500 words. Maximum number of references: 15. Tables, charts and figures should be submitted as separate electronic files (jpeg, tif, or pdf). Each submission should also be accompanied by a short (100-150 words) abstract.

Creative Clinician
Clinicians are invited to describe cases that defy textbook analysis. Maximum length: 1200 words. Maximum number of references: 6. Photographs, charts and figures may accompany the case.

Point of View
Readers share their perspective on any issue facing clinicians (e.g., ethics, health care policy, relationships with patients). Maximum length: 1200 words.

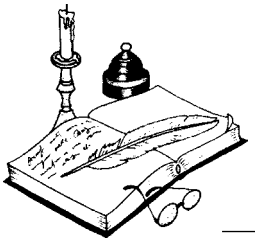
Advances in Pharmacology
Authors discuss new treatments. Maximum length: 1200 words.

Advances in Laboratory Medicine
Authors discuss a new laboratory technique. Maximum length: 1200 words.

Images in Medicine
Authors submit an interesng Image, with a 300-400 word explanation.

For the above articles: Please submit an electronic version (Microsoft Word or Text) with the author's name, mailing address, phone, fax, e-mail address, and clinical and/or academic positions to the managing editor, John Teehan, e-mail: jdteehan@rimed.org. For additional information, phone: (631) 903-3389. Faxes may be sent to (401) 826-1926.

Please be sure to provide complete and up-to-date contact information in order to facilitate communication during the editing process.



Physician's Lexicon
Cerebral Hemispheric Structures

Those privileged to name the many anatomic parts of the body were rarely authorities in the physiology of those structures. As a result, the anatomic nomenclature that we have inherited is quite utilitarian and less a reflection of their assigned biological function.

Consider the names of the four cerebral lobes. The frontal lobe, from the Latin, *frons,* meaning the front of anything, carries a no-nonsense name indicating nothing more complex than its relative position within the calvareum (from the Greek meaning skull and earlier from the Hebrew, *gulgoleth*, meaning skull, and later a skull-shaped hill.). The temporal lobe, from the Latin, *tempus*, meaning pertaining to time, but from an earlier Latin word signifying a place from which to observe, a consecrated place, a sanctuary (and from this variant meaning came English words such as temple and contemplate.) The parietal lobe derives its name from the Latin, *paries,* meaning a wall, and earlier, something seized or fenced in. And the occipital lobe is named from the Latin, *occipitalis*, (toward the rear) and still earlier, from the Latin, *ob-* (a prefix meaning toward or against) and *caput* (meaning the head).

The names of the deeper supratentorial structures are quaintly descriptive, sometimes fancifully so. The hippocampal gyrus, for example, is from the Greek, *hippo-*, meaning horse (and hippopotamus therefore means a river horse—with *potamus,* a Greek word for river, and thus Mesopotamia is a nations between the rivers; and *eohippus*, a prehistoric horse, with *eo*, a Greek word meaning dawn) while campus means something curved (and hence, *campylobacter* means a curved bacterium.)

The thalamus bears a Greek name, meaning a pillow, a bedroom or a vault. The same root is found in the word, ophthalmic, (hence study of the eye-chamber) with the Greek root, *oph-* meaning the eye.

And then there is the putamen, one of the basal ganglia, a word descended from the Latin, *putamen* meaning a shell, a pruning or botanical trimmings. (many English words use the same root including putative, amputate, compute and deputy.) The claustrum is from the Latin, *claustrum*, meaning a bolted place, a monastery, or sometimes a cloister; and thus claustrophobia is a morbid fear of being shut up. It is also related to the Latin, *claudere*, meaning to shut or enclose, and hence the English, claudication, to impair or shut off circulation to a limb. And the globus pallidus is a Latin phrase meaning a pale sphere. *Pallidus*, in Latin, means to extenuate, to make pale, to cloak (and hence, palliation is the therapeutic act of attenuating—of making pale—pain.)

– Stanley M. Aronson, MD

Rhode Island Department of Health
Michael Fine, MD
Director of Health

Vital Statistics

Edited by Colleen Fontana, State Registrar

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

Underlying Cause of Death	Reporting Period			
	September 2011	12 Months Ending with September 2011		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	182	2,449	232.5	3,725.0
Malignant Neoplasms	183	2,270	215.5	5,560.0
Cerebrovascular Diseases	33	440	41.8	737.0
Injuries (Accidents/Suicide/Homicide)	53	677	64.3	9,642.0
COPD	31	548	52.0	507.5

Vital Events	Reporting Period		
	March 2012	12 Months Ending with March 2012	
	Number	Number	Rates
Live Births	963	12,733	12.1*
Deaths	760	10,409	9.9*
Infant Deaths	(6)	(86)	6.8#
Neonatal Deaths	(5)	(66)	5.2#
Marriages	281	6,561	6.2*
Divorces	229	3,620	3.4*
Induced Terminations	344	4,369	343.1#
Spontaneous Fetal Deaths	67	698	54.8#
Under 20 weeks gestation	(56)	(591)	56.8#
20+ weeks gestation	(11)	(107)	8.4#

(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 that 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.*

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

THE RHODE ISLAND MEDICAL JOURNAL
The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publications Committee
VOLUME 1
NUMBER 1
PROVIDENCE, R.I., JANUARY, 1917
PER YEAR $2.00
SINGLE COPY, 25 CENTS

Ninety Years Ago, September, 1922

Frank J. McCabe, MD, looks at the etiology and treatment for glaucoma. He begins by noting how once some thought it was an affection in the vitreous humor, and others in the optic nerve and retina. It was Von Graefe who brought together the various signs and symptoms in a more complete understanding. The author that while there is no clear explanation for the etiology of glaucoma, patients should be considered individually. "Glaucoma simplex with little or no increased tension and fields and vision changing but slowly, I feel that conservative treatment would be the choice. In the inflammatory type, the sooner the operation the better."

L.L. Albert, MD, discusses the treatment of rheumatoid arthritis with reference to radium. He begins by stating that chronic arthritis develops not only because of long continued bacterial infections, but also from metabolic disturbances, gastrointestinal derangements, exposure, diseased teeth, tonsils and "so many other causes too numerous to mention." The main problem is to find a means for the system to eliminate the systemic infection. While using vaccines and proteins, radium treatments for extreme cases have shown the most marked success. "So pronounced have been the results obtained from the use of radium in the therapy of chronic articular rheumatism that I feel certain that a new and wide field of research has been opened to our profession in the use of this substance, and what the future will show as a result of experimentation with radium is indeed beyond our conception.

And editorial states that every effort is made by the advertising management to know that journal advertisements are of ethical character and represent the best in their special line of merchandise; for obvious reasons they must decline, however, to entertain any suggestion of editorial comment or praise of various commodities that are advertised within the journal, however worthy they may be of commendation.

Fifty Years Ago, August, 1962

Charles Rob, MD, presents a piece on the surgical treatment of stenosis and thrombosis of the extracranial portions of the carotid arteries. In a series of 431 patients with proved stenosis or thrombosis of the extracranial cerebral arteries, the cause was atherosclerosis in all but one patient. Two main lines of development were likely to occur. The first concerned the surgery of partial occlusions which were, to a large extent, prophylactic procedures. With complete occlusions, the development of a sense of urgency amongst those who care for those patients so that operation could be performed within a few hours of the onset might well lead to considerable improvement in the results of treatment.

An editorial discusses mechanical medicine, or, "Tender Loving Care By Machine?" "No one can deny the great value of the various mechanical, electrical, and related types of apparatus now in use in the diagnosis and treatment of diseased human beings. Such instruments, developed by modern engineering skill and based on the advancement of knowledge in the fields of physics, chemistry, and other basic sciences, are of the utmost importance in medicine. Radiologic and electrocardiographic examinations, to cite two of the more familiar procedures, yield diagnostic information that saves many lives every day of the year."

In a piece regarding physicians and lobbying, it's suggested that the doctor, as any citizen, certainly has a right to express his views on any and all legislation. But when he speaks on legislative proposals affecting health and welfare he finds himself unduly criticized. Yet, like any person engaged in a specific art or craft, he has an intimate knowledge by reason of his life career that qualifies him eminently as a critic of such proposals which may not be in the best interests of good health for the public.

Twenty-five Years Ago, August, 1987

Seebert J. Goldowsky, MD, provides a brief overview of the 175-year history of the Rhode Island Medical Society citing the charter from the Rhode Island General Assembly at its February session in 1812, and an organizational meeting called by Amos Throop, MD, for April 22, 1812 in the Senate Chamber of the old State House on Benefit Street in Providence. Throop became the first president and the first annual meeting was held on September 1, 1812 at the same location as the organizational meeting.

From that same meeting was read a discourse by Edmund T. Waring. Among his comments was this particular address:

"Gentlemen of the Medical Society of Rhode Island: From the conviction that medical science has been advanced by the united energies of individuals, you have laudably associated yourselves for its diffusion and improvement. As Physicians, you have individually estimated the importance and dignity of the profession which you have embraced; you have realized the weighty responsibilities attached to it; you have been the guardians of the health and lives of your fellow citizens. From the moment that man ushers into being, through the varying and perilous track of life, even to that solemn moment when Nature's mandate is to be obeyed, you have been his hope; the sympathizing colleague of the ministers of peace, to alleviate the agonies of death."

To briefly quote a discourse prepared by an anonymous author published during the tenth year of the Society's existence: "Never was learning more general; sense more common; reason more enlightened; society more refined; the arts more flourishing; and the sciences more diligently cultivated than at the present day. Geniuses are springing up in every direction, and are busily employed in the constructions of fabrics to commemorate themselves to posterity. It seems as if human intelligence were beginning to acknowledge no bounds."

The Name of Choice in MRI

'OASIS' 1.2 Tesla open-sided scanner

Open MRI
of New England, Inc.

- High Field Open-Sided and Short-Bore Systems
- Fast appointments and reports
- Insurance authorization services, physician web portal and EMR system interfaces

Open MRI
of
New England, Inc.

ADVANCED
Radiology, Inc.

- Low dose Multislice CT systems
- Digital xray, bone density and ultrasound
- Insurance authorization services, physician web portal and EMR system interfaces


Brightspeed low dose CT System

ADVANCED Radiology, Inc.

525 Broad St. • Cumberland
T 725-OPEN (6736) F 726-2536

1002 Waterman Ave • East Providence
T 431-5200 F 431-5205

148 West River St • Providence
T 621-5800 F 621-8300

501 Great Road • North Smithfield
T 766-3900 F 766-3906

335 Centerville Rd • Warwick
T 732-3205 F 732-3276

101 Airport Rd • Westerly
T 315-0095 F 315-0092

NUMBERS THAT WORK AS HARD AS YOU DO

22,800 CALLERS ASSISTED IN 2011

1 PHONE CALL IS ALL IT TAKES

24/7 PHONE ACCESS TO LIVE EXPERTS

25,000 CREDENTIALING LETTERS ISSUED

What is great service? For NORCAL Mutual insureds, just 1 phone call is all it takes for great service. That means calling during business hours and immediately reaching a live, knowledgeable, friendly expert. After hours, it means promptly receiving a call back from a professional qualified to help with your issue. No automated telephone tango. Questions are answered and issues resolved — quickly. We're on call 24 hours a day, every day of the year. Great service brings you peace of mind. To purchase your NORCAL Mutual coverage call RIMS Insurance Brokerage at 401-272-1050. **Great service 24/7. Hard-working numbers you can count on.**

CALL 1-800-652-1051 OR VISIT NORCALMUTUAL.COM

Proud to be endorsed by the Rhode Island Medical Society.

NORCAL Mutual Insurance Company®

Our passion protects your practice