Missouri Medicine
The Journal of the Missouri State Medical Association www.msma.org September/October 2014



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Short & Sweet: Make Your Mark on November 2014 Election

by John C. Hagan, III, MD



The state of the state and the state of the nation have grown so perilous and factious that you must invest your precious time, money and vote to elect capable, intelligent, dedicated women and men to our legislative and executive bodies.

Begin by sending a generous check to Missouri Medical Political Action Committee (see form next page). Supporting worthy candidates from all parties, MMPAC has an enviable record in electing women and men that support the profession of Medicine, physicians and the patients they care for.

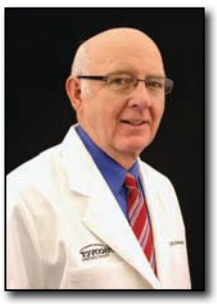
Seek out worthy candidates and become involved in their campaigns. Get to know the candidates and make sure they know you and your opinions and key issues. It will pay dividends beyond measure after the elections as we segue into legislative season.

A word of support and appreciation for **Keith Frederick, DO,** in the Missouri House of Representatives and **Rob Schaaf, MD,** in the Missouri Senate, they have worked effectively and tirelessly for tort reform, prompt pay, fair reimbursement, opposed inappropriate scope of practice expansion by non-physicians through the legislative pathway and economic credentialing.

They are respected by their legislative peers and have important seats on key committees. Drs. Frederick and Schaaf deserve to be re-elected. **Bob Onder, MD,** is unopposed in the Missouri Senate District race; **Jim Neely, DO**, is the physician choice in Missouri House District 8.

Thank you Drs. Frederick, Schaaf, Onder and Neely for your able representation of the medical profession and the citizens of your district.

Who knows the practice of medicine and the needs of your patients better than you?



John C. Hagan, III, MD, FACS, is a Kansas City ophthalmologist and Missouri Medicine Editor since 2000. He is a multi-year Super Diamond Contributor to MMPAC.
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MM

Support Candidates Who Support Medicine

As leaders in the health care community, it is important to inject your voices into the debate over health care reform. Who knows the practice of medicine and the needs of your patients better than you? Your voices - along with your votes - are vital tools that can have a profound impact on the practice of medicine in Missouri.

As the November elections heat up, you need to get to know the candidates who are friendly to medicine. Support those who support you. And support your physician colleagues who want to represent your profession and your patients in the Missouri General Assembly. Contact Jeff Howell at jhowell@msma.org or Kenny Jackson at kjackson@msma.org.

November 2014 Missouri General Election Physician Candidates

[MSMA member names in bold]

- State Senate District 2 (St. Charles): **Bob Onder, MD** (R) will be unopposed.
- State Senate District 34 (St. Joseph): Senator **Rob Schaaf, MD** (R) will face Robert Stuber, MD (D).
- House District 8 (Cameron): Representative **Jim Neely, DO** (R) will face Ted Rights, MD (D).
- House District 121 (Rolla): Representative **Keith Frederick, DO** (R) will be unopposed.

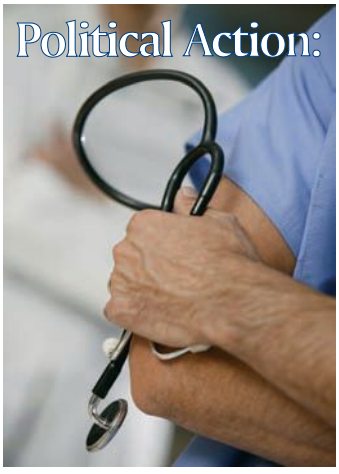
MSMA's Top Legislative Priorities for 2015

Tort Reform - MSMA wants to create a statutory cause of action for medical malpractice claims and reinstate the non-economic damage cap to $350,000. There is no limit under current Missouri law.

Medicaid Transformation - MSMA supports expansion of the Medicaid program, but opposes a proposal to expand the managed care model statewide while only allowing three current insurance contractors to participate under a capitated model.

APRN Scope of Practice/Collaborative Practice - MSMA is fighting a proposal that would allow the Board of Nursing to issue a separate license for APRNs, and create a statutory scope of practice for APRNs. This legislation would change the collaborative practice rules, effectively striking the 50-mile proximity rule, and authorizing what amounts to independent practice for advanced practice nurses.

MSMA White Coat Rally Day at the Capitol
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In the Age of ACOs, the Systems of Measuring Health-Care Quality Remain in Their Infancy

by Joseph A. Craft, III, MD

Our current metrics really just evaluate the system in which a physician works, not the quality of the doctor.



Joseph A. Craft, III, MD, FACC, MSMA member since 2004, is President of the St. Louis Metropolitan Medical Society.
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Since being signed into federal law in March 2010, the Affordable Care Act (ACA) has generated a nearly endless supply of news and speculation. Now, over four years later, the analysis and speculation continues unabated. This article will shed light on some of the ACA impact thus far.

Among its many ambitions, the ACA encourages the formation of Accountable Care Organizations (ACOs). According to www.cms.gov, ACOs are groups of hospitals, doctors and other providers who come together voluntarily to provide high-quality coordinated care to Medicare patients and then share in the savings achieved for the Medicare program. Our issue will highlight some of the early experiences with ACOs in the St. Louis area.

Many had suspected most ACOs would be formed and run by hospitals and large health systems. The June issue of *Health Affairs* provides an early analysis. Colla, et. al from the Dartmouth Institute for Health Policy and the University of California, Berkeley, reveal ACO survey results conducted from October 2012 to May 2013. The authors found that 40% of ACOs were physician-owned, and 51% of ACOs were physician-led. Physicians and hospitals jointly led an additional 33% of ACOs. In total, physicians comprised the majority of the governing boards of 78% of ACOs. The authors assert that the ACO experiment and the fundamental move away from fee-for-service payments in American health care "will not be accomplished without strong, effective leadership from physicians."

Kansas City's Experience with ACOs

Some of our colleagues from Kansas City shared their early ACO experience with attendees at the Missouri State Medical Association (MSMA) Annual Convention in April 2014. The Kansas City Metropolitan Physicians Association (KCMPA) is an independent physicians association (IPA) now composed of more than 40 physician practices in and around the Kansas City metropolitan area. KCMPA works with multiple payers on several different bundled-payment and shared-savings care-delivery models. It leverages information technology consultants and tools to compile data from more than 25 different electronic health records for quality reporting and sharing best clinical practice. Twelve physicians comprise the majority of its 14-member governing board.

A subset of KCMPA was officially designated ACO status in January 2013 with an initial responsibility of more than 12,000 Medicare beneficiaries. Chief Medical Officer Nathan Granger, MD, and CEO Jill Watson reported details of their experience at the MSMA Convention. Ms. Watson reports, "Professionally, it is very empowering" for the doctors to deliver bedside care, direct care models and supervise contracting. As a testament to the physicians' engagement, she reports that board meetings are "standing room only," filled with doctors invested in the success of their practices.

The St. Louis Metropolitan Medical Society (SLMMS) leadership has been following the ACO journey closely, and remains eager to connect interested member physicians with resources. Additionally, the American Medical Association (AMA) website (www.ama-assn.org) presents tools for physicians reassessing practice management in the health reform world, or for those planning Accountable Care Organization (ACO) participation:

- ACOs and other options: A 'How to' Manual for Physicians Navigating a Post-Health Reform World, 4th Edition (www.ama-assn.org/go/aco)
- Evaluating and Negotiating Emerging Payment Reform Options (www.ama-assn.org/resources/doc/psa/x-pub/payment-options.pdf)

Using Metrics Effectively

Fundamental components of health care reform include collection and reporting of quality data. Many experts believe increased reporting and "grading" of physicians are necessary to improve quality and cost of care. However, these processes remain a frustration for many physicians. I personally sit on multiple committees attempting to improve the veracity of reported data—a process that remains imperfect, at best. As many readers know, the feedback generated for physicians about their practice patterns and adherence to guidelines is largely generated from insurance claims data. These reports rely on diagnostic codes or other "discrete data elements," such as medications or allergies, extracted from an electronic health record.

For large populations, myriad data suggests quality improvement programs with reporting of data and goal setting can improve hard health outcomes and decrease cost. However, the data that can be extracted is usually an incomplete accounting of the sophisticated interaction between doctor and patient. For example, a strict blood pressure goal of < 140/90 for a 78-year-old patient with known orthostatic hypotension and falls may not be an appropriate balance of risks and benefits, and it may not be substantiated by any data in that specific patient population. Yet a doctor who does not meet that metric in that one patient would receive negative marks by most reporting programs.

To help lead complicated reporting processes, the Physician Consortium for Performance Improvement (PCPI) was founded by the AMA more than a decade ago. The PCPI is now composed of over 200 member organizations, including many physician specialty societies, the American Board of Medical Specialties (ABMS) and multiple federal agencies. The PCPI gives physicians a substantial voice in the ever-evolving reporting process, and it helps define "quality metrics."

Reporting on Quality Core Measures

Per www.cms.gov, the Physician Quality Reporting System (PQRS) is a reporting program that uses a combination of incentive payments and payment adjustments to promote quality metric reporting by physicians. The ACA of 2010 altered the PQRS. Starting in 2015, the ACA created penalties for physicians who do not participate in the PQRS. To avoid financial loss, doctors must report on quality core measures for their patients in the Medicare and Medicaid programs, as well as the Children's Health Insurance Program (CHIP). Private insurances have similar quality measure achievement goals and reporting requirements.

Physicians are subject to other grading tools. The Physician Value-Based Payment Modifier provides for differential payment to a physician or groups under the Medicare Physician Fee Schedule, based upon the quality of care furnished compared to cost during a performance period, according to www.cms.gov. Medicare payments can be increased or decreased by 0.5–1.5% or more, depending on participation in PQRS and relative performance compared to other physicians or groups. Data collected during calendar year 2013 will affect modified payments in calendar year 2015, for physicians in groups with at least 100 doctors.

Hospitals have many grading requirements as well, some of which attempt to assess the performance of physicians. The HCAHPS (Hospital Consumer Assessment of Healthcare Providers and Systems) Survey evaluates

patients' perceptions of their care in hospital. It asks questions such as, "How often did physicians treat you with courtesy and respect?"

Asking Patients What Makes a Good Doctor

In an ongoing effort to get my head around these developments, I came across an interesting analysis. Dr. Ashish Jha, an internist at the Harvard School of Public Health, cleverly took to social media. On Twitter, he asked the question, "In one word, what makes a good doctor?" The responses: Empathetic, good listener, compassionate, determined, humble, curious, etc. No one responded about Hemoglobin A1C goals, documentation of testing of pharyngitis in kids, or aspirin use for coronary artery disease. Dr. Jha surmised, "Most people assume that physicians meet a threshold of intelligence, knowledge, and judgment, and therefore, what differentiates good doctors from mediocre ones is the 'soft' stuff." He further suggested that our current metrics really just evaluate the system in which a physician works, not the quality of the doctor.

Practice in a health model of the future.

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Although Dr. Jha's methodologies did not exactly employ rigorous scientific method, his data tell an important and honest story. I felt compelled to check this myself. So I asked friends and family on Facebook the same question. I received similar responses.

- The most common answers: judgment and compassion.
- Other responses were: integrity, listener, discernment, empathy, patience, trust, sense of humor.
- Less than 10% of respondents mentioned knowledge or education.
- No one placed importance on where a doctor schooled or trained.
- No one mentioned quality metrics.

Again, my social media survey methods would be laughable to a science journal's editorial board. But I think they support what Dr. Jha concluded. Patients have high character and interpersonal expectations of their doctors. Patients want the chance to share those expectations. Their responses force an important question: Are current quality metrics and physician grading really on target?

Remaining Focused on Health Care Improvement

When pediatrician Dr. Donald Berwick was administrator of CMS, he popularized the "Triple Aim" for health care improvement—improving the patient experience of care (including quality and satisfaction), improving the health of populations, and reducing the cost of health care. SLMMS remains keenly focused on contributing to these goals. But the considerations above suggest our systems of assessing and reporting health care quality may be in their infancy.

To improve health care, physicians must embrace change. We must be open to critique in order to improve the care we offer. Current quality metrics and report cards likely have some value for population and system-based care. Yet, to properly evaluate doctors, we need to focus more on meeting patients' needs, as they define them.

So, as a physician community, let us drive the discussion and lead change. Despite all the excitement and trepidation presented by the ACA, ACOs, and physician report cards, let us always prioritize the patient-doctor relationship. Physicians' resolve is steeled and all the challenges of modern medicine become simpler when we keep patients first. **MM**

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Philology, or What's the Good Word?

by Jeffrey G. Copeland, MD

It is important that we understand the concept that the language we use to talk about what we do can play a rôle in how we act and who gets to direct medical care.



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I love words. More specifically, I love what words do. The ability to express an idea in a small sequence of standardized symbols is an amazing gift that humans uniquely possess. It is a skill and a talent that is not equally present in all persons, but is present enough that it makes most of our sophisticated interactions at least easier to accomplish. My wife reminds me that there are many different modes of communication and that the inflection of a voice or a specific "look" can speak volumes between people, and her point is well-taken, but the ability to very specifically and succinctly convey meaning is really the province of our words. Penultimate, allochthonous, uxorious, philately … they are positively sesquipedalian.

Another feature of words is that there are so many, and if one pays attention, or spends the time to seek it, there is usually one that is best. Choosing that word allows for simple communication of the idea. No circumlocution. I have heard that Ernest Hemmingway would write pages and end up with a paragraph. Accurate, precise, and effective, that's for me.

I have, in my library, a book ("They Have a Word for It" by Howard Rheingold, Saraband Books, 1988) that specifically addresses the point that there are words in various languages which express an idea that is simply not present in other languages. An example of this would be *korinthenkacker,* a German word for "one who is overly concerned with trivial details." Or, to my wife's point, *mamilhapinatapei*, a meaningful look, shared between two people, expressing mutual unstated feelings. So, the culture of the language can make a difference.

Another book I have, but have admittedly never gotten completely through, is Steven Pinker's "The Stuff of Thought" (Viking, 2007). In that book, the unifying theme is that the construction of our language is specific and that the way it is structured controls, to a significant degree, the way we conceptualize.

It is that idea upon which I would like to elaborate. Even with the most extensive, precise vocabulary, we can only conceive what our language allows. Periodically, a new word slips into the collective consciousness to broaden it, but that slow process does not compensate for the conceptual limitations of our language. That dependence on the

structure of language also makes us easy game for those who understand the concept.

There is a phenomenon in our culture in which our thoughts are molded to the purposes of people who receive benefit from doing so. We see examples of this in society in general, with the whole "political correctness" agenda which clearly tries to direct the way we think about things, sometimes in good ways, sometimes not so much. The idea has been well portrayed by the likes of George Orwell, who pointed out that history is controlled by those who write it down. Another categorical example of this that comes rapidly to mind is what I would call "corporate-speak." I have spent some time mingling with administrative officers in various health care systems, and noticed that those organizations are effective at using the mechanism of conceptual speech to control behaviors and to include or exclude certain ways of thinking. I recall clearly hearing about stakeholders, action items, adoption processes (think EMR here), boiling the frog, de-selected (fired), disruptive behavior (outspoken), etc. The extent of this process can be mind-boggling and in some instances quite effective. Think "drinking the Kool-aid." For a more thorough exposition of this topic, see http://www.theofficelife.com/business-jargon-dictionary-B.html. It is at once funny and scary.

I will try my best to not sound like a conspiracy theorist, but I think that we, in medicine, are confronted by such efforts to control our thought processes on a constant basis. There is always some new concept or system which we are asked to "understand" and adopt or risk significant financial misfortune. Think about ICD-10. We are now to adopt a disease description system that is so mired in minutia as to make it ridiculous to use in connection with our payment systems. It is even unwieldy as an epidemiology scheme. Collectively we might benefit from learning some major trends in disease occurrence, but if we fragment that excessively, we lose even that benefit. And we are to begin thinking in ICD-10 terms. To what productive end?

Consider our current EMR systems. They introduce conceptual patterns of work that are designed by and for business entities, not those who deliver care to patients. We are asked to swallow hard and take this giant jagged pill. This problems has not gone un-noticed, but it is a hard thing to fix. (See the recent list, authored by the AMA, of desirable features of EMR systems at http://www.ama-assn.org/ama/pub/ama-wire/ama-wire/post/8-top-challenges-solutions-making-ehrs-usable?&utm_source=BHClistID&utm_medium=BulletinHealthCare&utm_term=091714&utm_content=MorningRounds&utm_campaign=BHCMessageID).

In the current world of corporate medicine,we are now "caregivers, providers, employees" and various other similar monikers, rather than physicians. It is true that we technically fit into those more general categories, but to me it appears that the intention is to devalue physicians as much as to bolster the self-esteem of other persons involved in delivering medical care. The physicians I know, who are paying attention, already give the other people involved in delivering care credit for how important they are, without needing to apply generic terms to them. There is no denying that we physicians are the most thoroughly trained people in the whole system and to me, the most succinct, clearest term to apply to us is "physician." If we settle for the being a "provider," it sets the stage for persons of lesser training to be considered to be equal for purposes of providing medical care to patients. That is a problem.

While it looks to a lot of us that this is the direction where medical care is currently going, there are still decisions to be made about who is in charge of the "medical home" and who may be in charge of various models for providing medical service to patients. I feel that it is important that we understand the concept that the language we use to talk about what we do can play a rôle in how we act and who gets to direct medical care. It is important that we not passively accept linguistic structures that create ambiguity regarding who is qualified to do what and under what circumstances. We live in a world of accelerating change; this is just one place where that change can provide a window of opportunity to those who desire to determine how medical care is delivered. We need to be vigilant and ready to bring our own language to the table. This is worth doing, even if it requires enlisting some professional help.

While we are on the topic of verbal concepts, I was at the Kentucky Medical Association recently when I heard the term "complexivist." The term was introduced during a discussion about what physicians

should be doing in medical care as it evolves. The concept was that it is true that much of what we do is redundant and does not require all the tools that we acquire in training and bring to the daily care that patients receive from us. It is those situations, where the care requires analysis of greater complexity, that our skills are really required and of benefit to the patients above what they might receive from a less completely trained individual. In an ideal world, there would be a very clear understanding that those non-physicians would work in close physical and cognitive contact with the physicians so as situations arose where the greater resources were needed, they would be immediately available with no physical or temporal barriers.

The devil in the detail is that it is very difficult to be sure that is happening and social/economical forces are at play which work to try to get around that most desirable, efficient and safest situation in favor or less well qualified persons working autonomously. During another conversation I had, this time with David Besema, MD, the recently inaugurated president of the Kentucky Medical Association (who has taken the time to not only complete his training in medicine, but to take advanced training in business and in information science), he told me that business theory has addressed the appropriate ratio between a supervisory person and the number of people he or she supervises. The theory runs that the more complex the task, the fewer people who may be safely and effectively supervised. In medical care, a number that is frequently discussed is four. In a practice where the care is very complex, the number may be substantially lower, while in less complex clinical situations it could be a little higher. In no situation was it discussed that the lesser trained person should be granted autonomy because of supply issues. The bottom line of all this was that physicians, like experts in other areas, may leverage their skills and knowledge so they are put to use when it is necessary and can be freed of more mundane, less complex situations. That principle applies to a lot of other situations, but in none other are the stakes as high as in medical care. We have to be very careful to do this in the safest way possible. If we are to be complexivists, we must do it with a compulsion to be safe. **MM**

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Planning the Path to Retirement

by Lenard L. Politte, MD

It is imperative to prepare and plan retirement while still actively working.



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Soon after entering the work force, many people immediately begin to look forward to the time when they can retire. By definition, retirement means withdrawing from one's present employment activities and implies moving in a different, usually less stressful, hopefully equally or more rewarding direction. Many physicians fantasize how great it will be not to have the responsibility of "work"; to have free time to pursue other goals and activities they think they will enjoy more than their profession or job. Most physicians feel their professional life is so much more than a "job." Even if Medicine is a joy, it can't last forever. All long lived physicians must eventually redirect their goals and endeavors.

The road to retirement can be tortuous and sometimes unpredictable. There are many starts, stops and changes of directions. It is important to understand why and when you want to retire and what routes you wish to travel before you start down that path. Individual needs and goals change over time and are influenced by new challenges, opportunities, health problems, financial conditions, family responsibilities and many more expected and unexpected, controlled and uncontrollable events. These circumstances influence how, when and what the transition. After working years toward professional and personal goals how do you walk away from your many responsibilities and enjoy 'the fruits of your labor'? It is imperative to prepare and plan retirement while still actively working.[1] (See sidebar next page.)

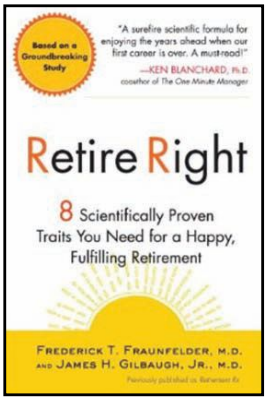
Retirement represents a departure from a lengthy and familiar part of one's life. Retirement affects most people emotionally and physically.[2] Marie Wheatley recommends planning your retirement strategy early; trying leisure and/or interesting alternate pursuits before leaving your practice. See if they are to your liking and expectations. Your medical work daily provides satisfaction, achievements and augments your self-worth. After retirement it will take time to get over a perceived sense of loss.[2]

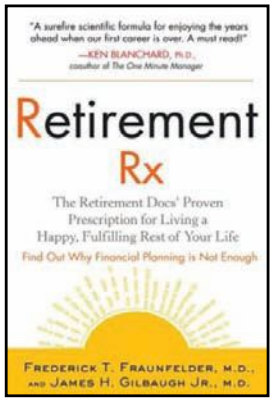
Once you decide to start the process it is difficult to reverse the course. You have been successful in your accomplishments and wonder if what you have a role in developing and maintaining can continue without your participation? Fortunately yes, there is a capable

BOOK REVIEW

Retire Right & Retirement Rx

by Fritz Fraunfelder, MD & Jim Gilbaugh, MD





Over the years, Fritz Fraunfelder, MD, and Jim Gilbaugh, MD, have seen thousands of their patients respond differently to the challenges of retirement. The doctors began to wonder: How do some people maintain their vitality, interests, and zest for life in retirement while others became distant, even depressed? Is there a magic formula for retiring well? To find the answer, they designed a comprehensive study involving more than one thousand patients. The results were surprising but clear. Financial planning is not as important to a fulfilling retirement as many may think-the psychological experience is just as crucial. The happiest retirees shared eight key traits; all of them were able to: plan ahead, maintain a positive attitude, accept change, lean on their support network, have a sense of purpose, keep a healthy lifestyle, engage in leisure activities and enjoy some expression of spirituality.

Retire Right evaluates the reader and provides guidelines for how to develop each key characteristic. The good news? These essential skills can be strengthened, even acquired from scratch, whether the reader is just starting to plan for retirement, is in the early years, or is a seasoned retiree. The first scientifically backed bulletproof prescription, this book is the most concrete guide to a happy retirement.

Author Fritz Franfelder, MD, an internationally known ophthalmologist is the father of Rick Fraunfelder, MD, Chair, Department of Ophthalmology, Mason Eye Institute, University of Missouri.

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younger generation ready to assume your responsibilities. They may not do things the same way you would do them; be satisfied for what you have done. You have had your opportunities and now it's their turn.

There are many reasons that successful people retire; Muggeridge said, "Few men (or women) of action have been able to make a graceful exit at the appropriate time."[3] Why are you retiring? Usually it is a combination of factors that come into consideration: health problems, adverse working conditions, difficulty in staying abreast of new developments, to help with family needs, "physician burn out," and many others. Perhaps the best reason to retire is to have more time and energy to pursue activities enjoyed while in practice. Ideally, the motivation for retirement should a positive goal.

On the opposite side, there are many reasons that may keep you from retiring. The practice of medicine is one of the most gratifying professions in that it serves humanity at the highest level. This has been the physician's life and identity. Physicians find it hard, more so than others, to give up their professional identity. They hold an important and prestigious place in our society. Leaving this position is difficult in that they have worked so hard to achieve such status. One of the most difficult things about quitting medicine is leaving the collegiality of your peers as well as the many patients you have treated for scores of years. Many of these patients become dear friends and part of your extended family.

Can you afford to retire? Financial reasons are becoming a driving force keeping physicians in active practice. In several specialties, the cost of office space, staff, insurance, and other practice expenses leave a smaller margin of take home pay and necessitates continued working. Many physicians cannot afford to retire, especially if they have a luxury lifestyle and/or have not had good retirement-estate planning. Being a fine physician does not translate to being a fine financial wizard. A not uncommon phenomenon in the last decade is retired physicians resuming medical practice because their projections of investment growth and retirement income have not kept pace with inflation and their cost of living.

Retirement demands a re-assessment of a physician's self-image. Solinge and Henkens suggest that retirees from jobs with perceived higher prestige may experience a greater sense of loss with resultant difficulties and require a longer adjustment period.[4] The desire to

continue Medicine or generate income should never outweigh the honest assessment of your capabilities. Self-assessment of one's own capability is never without bias and your colleagues might be reluctant to discuss these problems with you. Consider confidentially asking expert younger colleagues, especially those who can assess your medical and surgical/procedural skills, to frankly discuss any departure from quality, standard-of-care practices and satisfactory interaction with patients, staff and other physicians.[5,6]

Many physicians retire incrementally. They give up the most demanding and stressful parts of their practice and restrict their time to those professional activities that they enjoy most. It gives them additional time to participate with family, friends and community. These might include travel, sports, reading, fishing, golf and other things done for pleasure and health. Physicians have much to offer in the areas of community service and philanthropy. Volunteering in the many community or charity activities can be rewarding and fill as much time as you wish. Be careful and not over commit yourself! Imparting your knowledge and experience by teaching the next generation of health care providers can complement the formal teaching faculty of medical schools.

The trip to retirement takes many turns usually has a few bumps and an occasional crash. Many unanticipated paths branch off and lead to enjoyable and rewarding experiences. Plan this retirement journey while you and your family have the health, the desire and ability to do so. Your legacy is what you have done for others and not yourself. Retire on a high note with dignity and grace.

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MM





The combination of nine lines of evidence converge on the conclusion that near-death experiences are medically inexplicable. Any one or several of the nine lines of evidence would likely be reasonably convincing to many, but the combination of all of the presented nine lines of evidence provides powerful evidence that NDEs are, in a word, real.

Introduction

Near-death experiences (NDEs) are reported by about 17% of those who nearly die.[1] NDEs have been reported by children, adults, scientists, physicians, priests, ministers, among the religious and atheists, and from countries throughout the world.

While no two NDEs are the same, there are characteristic features that are commonly observed in NDEs. These characteristics include a perception of seeing and hearing apart from the physical body, passing into or through a tunnel, encountering a mystical light, intense and generally positive emotions, a review of part or all of their prior life experiences, encountering deceased loved ones, and a choice to return to their earthly life.[2]

Methods

There is no uniformly accepted definition of near-death experience. Definitions of NDE with some variability have been used throughout the 35 plus years that NDE has been the subject of scholarly investigation. For my retrospective investigations, an NDE was required to have both a near-death and experience component.

Individuals were considered to be "near-death" if they were so physically compromised that if their condition did not improve they would be expected to irreversibly die. Near-death experiencers (NDErs) included in my



Jeffrey Long, MD, is a radiation oncologist in Houma, Louisiana and a recognized world expert on near-death experiences. Dr. Long established the nonprofit Near Death Experience Research Foundation and a website forum (www.nderf.org) for people to share their NDEs.
Contact:

investigations were generally unconscious and may have required cardiopulmonary resuscitation. The "experience" component of an NDE had to occur when they were near death. Also, the experience had to be reasonably lucid, which excluded fragmentary or brief disorganized memories. For an experience to be classified as an NDE, there had to be a score of seven or above on the NDE Scale.[3] The NDE Scale asks 16 questions about the NDE content and is the most validated scale to help distinguish NDEs from other types of experiences.

In 1998, a website called the Near Death Experience Research Foundation (NDERF, nderf.org) was established to conduct NDE research and to be a public service. It is NDERF policy that all NDE accounts shared with NDERF are posted on the website if the NDErs give permission to do so. Nearly all NDErs allow their experiences to be posted on the NDERF website. Portions of the NDERF website, including the NDE questionnaire, have been posted in over 20 different languages. The NDERF website has consistently been at or near the top of websites listed from a Google search for the term "near-death experiences." This prominence of the NDERF website provided a unique opportunity to conduct a large-scale study of NDEs, including NDEs from around the world. At the current time there are over 3,700 NDEs posted on the NDERF website, which is by far the largest collection of publicly accessible NDE accounts in the world.

The NDERF website has a form allowing near-death experiencers to share a detailed narrative of their experiences, and includes a detailed questionnaire. Extensive prior studies found that an Internet survey has validity that is equivalent to traditional pencil-and-paper survey.[4] All experiences shared with the NDERF website are reviewed. Sequentially shared NDEs from the NDERF website were studied. NDEs included for study were single NDE accounts, shared in English, and were shared by the individual who personally had the NDE. An investigation of the NDEs shared with NDERF led to nine lines of evidence suggesting the reality of NDE.

Results Suggesting the Reality of Near-Death Experiences

Line of Evidence #1

Lucid, organized experiences while unconscious, comatose, or clinically dead

Near-death experiences occur at a time when the person is so physically compromised that they are typically unconscious, comatose, or clinically dead. Considering NDEs from both a medical perspective and logically, it should not be possible for unconscious people to often report highly lucid experiences that are clear and logically structured. Most NDErs report supernormal consciousness at the time of their NDEs.

The NDERF survey asked, "How did your highest level of consciousness and alertness during the experience compare to your normal, everyday consciousness and alertness?" Of 1,122 NDErs surveyed, 835 (74.4%) indicated they had "More consciousness and alertness than normal"; 229 (20.4%) experienced "Normal consciousness and alertness"; and only 58 (5.2%) had "Less consciousness and alertness than normal."

The NDERF survey also asks, "If your highest level of consciousness and alertness during the experience was different from your normal everyday consciousness and alertness, please explain." In response to this question, NDErs commonly reported that consciousness during their experiences was "clear", "more aware", and often associated with heightened awareness.

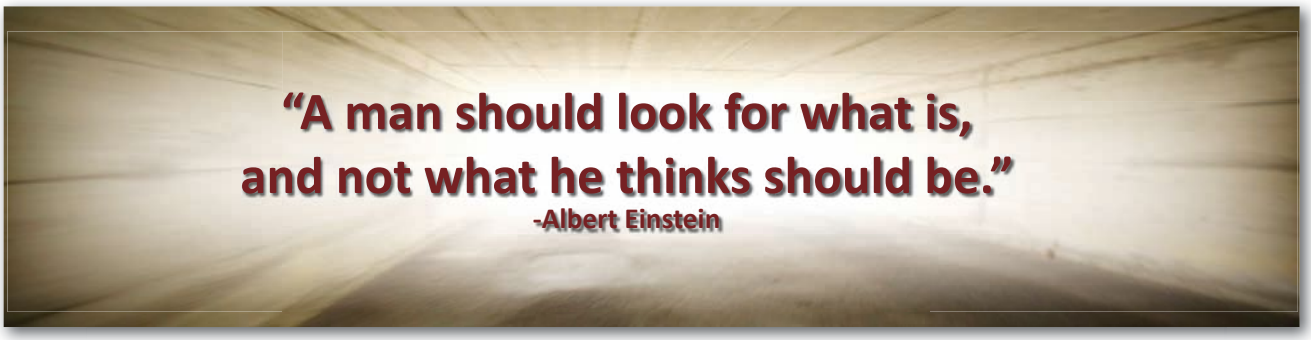
Near-death experiences often occur in association with cardiac arrest.[5] Prior studies found that 10-20 seconds following cardiac arrest, electroencephalogram measurements generally find no significant measureable brain cortical electrical activity.[6] A prolonged, detailed, lucid experience following cardiac arrest should not be possible, yet this is reported in many NDEs. This is especially notable given the prolonged period of amnesia that typically precedes and follows recovery from cardiac arrest.[7]

Line of Evidence #2

Seeing ongoing events from a location apart from the physical body while unconscious (out-of-body experience)

A common characteristic of near-death experiences is an out-of-body experience. An out-of-body experience (OBE) is the apparent separation of consciousness from the body. About 45% of near-death experiencers report OBEs which involves them seeing and often hearing ongoing earthly events from a perspective that is apart, and usually above, their physical bodies. Following cardiac arrest, NDErs may see, and later accurately describe, their own resuscitation.

The first prospective study of the accuracy of out-of-body observations during near-death experiences was by Dr. Michael Sabom.[8] This study investigated a group of patients who had cardiac arrests with NDEs that included OBEs, and compared them with a control group of patients who experienced cardiac crises but did not have NDEs.



Both groups of patients were asked to describe their own resuscitation as best they could. Sabom found that the group of NDE patients were much more accurate than the control group in describing their own resuscitations.

Another prospective study of out-of-body observations during near-death experiences with similar methodology to Sabom's study was published by Dr. Penny Sartori.[9] This study also found that near-death experiencers were often remarkably accurate in describing details of their own resuscitations. The control group that did not have NDEs was highly inaccurate and often could only guess at what occurred during their resuscitations.

Two large retrospective studies investigated the accuracy of out-of-body observations during near-death experiences. The first was by Dr. Janice Holden.[10] Dr. Holden reviewed NDEs with OBEs in all previously published scholarly articles and books, and found 89 case reports. Of the case reports reviewed, 92% were considered to be completely accurate with no inaccuracy whatsoever when the OBE observations were later investigated.

Another large retrospective investigation of near-death experiences that included out-of-body observations was recently published.[11] This study was a review of 617 NDEs that were sequentially shared on the NDERF website. Of these NDEs, there were 287 NDEs that had OBEs with sufficient information to allow objective determination of the reality of their descriptions of their observations during the OBEs. Review of the 287 OBEs found that 280 (97.6%) of the OBE descriptions were entirely realistic and lacked any content that seemed unreal. In this group of 287 NDErs with OBEs, there were 65 (23%) who personally investigated the accuracy of their own OBE observations after recovering from their life-threatening event. Based on these later investigations, none of these 65 OBErs found any inaccuracy in their own OBE observations.

The high percentage of accurate out-of-body observations during near-death experiences does not seem explainable by any possible physical brain function as it is currently known. This is corroborated by OBEs during NDEs that describe accurate observations while they were verifiably clinically comatose.[12] Further corroboration comes from the many NDEs that have been reported with accurate OBE observations of events occurring far from their physical body, and beyond any possible physical sensory awareness.[13] Moreover, NDE accounts have been reported with OBEs that accurately observed events that were completely unexpected by the NDErs.[14] This further argues against NDEs as being a result of illusory memories originating from what the NDErs might have expected during a close brush with death.

Line of Evidence #3

Near-death experiences with vision in the blind and supernormal vision

There have been a few case reports of near-death experiences in the blind. The largest study of this was by Dr. Kenneth Ring.[15] This Investigation included 31 blind or substantially visually impaired individuals who had NDEs or out-of-body experiences. Of the 31 individuals in the study, 10 were not facing life-threatening events at the time of their experiences, and thus their experiences were not NDEs. There were 14 individuals who were blind from birth in this study, and nine of them described vision during their experiences. This investigation presented case reports of those born totally blind that described in NDEs that were highly visual with content consistent with typical NDEs.

The NDERF website has received additional case reports of near-death experiences among those legally blind. For illustration, the following NDE happened to Marta, a five-year-old blind girl who walked into a lake:

"I slowly breathed in the water and became unconscious. A beautiful lady dressed in bright white light pulled me out. The lady looked into my eyes asked me what I wanted. I was unable to think of anything until it occurred to me to travel around the lake. As I did so, I saw

detail that I would not have seen in "real" life. I could go anywhere, even to the tops of trees, simply by my intending to go there. I was legally blind. For the first time I was able to see leaves on trees, bird's feathers, bird's eyes, details on telephone poles and what was in people's back yards. I was seeing far better than 20/20 vision. "[16]

An NDERF survey question asked 1,122 near-death experiencers, "Did your vision differ in any way from your normal, everyday vision (in any aspect, such as clarity, field of vision, colors, brightness, depth perception degree of solidness/transparency of objects, etc.)?" In response, 722 (64.3%) answered "Yes", 182 (16.2%) said "Uncertain", and 218 (19.4%) responded "No". A review of narrative responses to this question revealed that vision during NDEs was often apparently supernormal. Here are some illustrative examples from NDEs:

"Colors were beyond any I had ever seen."

"Everything seemed so much more colorful and brighter than normal."

"My vision was greatly increased. I was able to see things as close or as far as I needed. There was no strain involved it was almost like auto zooming a camera."

"I had 360 degree vision, I could see above, below, on my right, on my left, behind, I could see everywhere at the same time!"

Vision in near-death experiencers that are blind, including totally blind from birth, has been described in many case reports. This, along with the finding that vision in NDEs is usually different from normal everyday vision and often described as supernormal, further suggests that NDEs cannot be explained by our current understanding of brain function. This is also further evidence that NDEs are not a product of what NDErs would have expected to occur during a life-threatening event.

Line of Evidence #4
Near-death experiences that occur while under general anesthesia

Under adequate general anesthesia it should not be possible to have a lucid organized memory. Prior studies using EEG and functional imaging of the brains of patients under general anesthesia provide substantial evidence that the anesthetized brain should be unable to produce lucid memories.[17, 18] As previously discussed, following cardiac arrest the EEG becomes flat in 10 to 20 seconds, and there is usually amnesia prior to and following the arrest. The occurrence of a cardiac arrest while under general anesthesia is a combination of circumstances in which no memory from that time should be possible. Here is an illustrative example of an NDE that occurred under general anesthesia during surgery for a heart valve replacement:

"During my surgery I felt myself lift from my body and go above the operating table. The doctor told me later that they had kept my heart open and stopped for a long time, and they had a great amount of difficulty getting my heart started again. That must have been when I left my body because I could see the doctors nervously trying to get my heart going. It was strange to be so detached from my physical body. I was curious about what they were doing but not concerned. Then, as I drifted farther away, I saw my father at the head of the table. He looked up at me, which did give me a surprise because he had been dead now for almost a year." [19]

I reviewed 613 near-death experiences shared with NDERF, and found 23 NDEs that appeared to have occurred while under general anesthesia. Cardiac arrest was the most common life-threatening event that was described in association with the occurrence of these NDEs. I compared the responses of these 23 NDErs to the 590 non-anesthesia NDErs by reviewing how both groups responded to 33 survey questions that asked about the content of the NDEs. Chi-square statistics was used for this comparison. Due to the large number of questions asked, statistical significance was set at $p=0.01$. The only statistically significant difference between the two groups was that the anesthesia NDEs were more likely to describe tunnels in their experiences.

An NDERF survey question asked, "How did your highest level of consciousness and alertness during the experience compare to your normal everyday consciousness and alertness?" For the NDEs occurring under general anesthesia, 19 (83%) of the respondents answered, "More consciousness and alertness than normal," to this question, compared to 437 (74%) for all other NDEs. The responses to this question by the two

Multiple lines of evidence point to the conclusion that near-death experiences are medically inexplicable and cannot be explained by known physical brain function.

groups were not statistically significantly different. This suggests, remarkably, that the level of consciousness and alertness in NDEs is not modified by general anesthesia.

Other near-death experience investigators have reported NDEs occurring while under general anesthesia. Dr. Bruce Greyson, a leading NDE researcher at the University of Virginia, states:

> "*In our collection of NDEs, 127 out of 578 NDE cases (22%) occurred under general anesthesia, and they included such features as OBEs that involved experiencers' watching medical personnel working on their bodies, an unusually bright or vivid light, meeting deceased persons, and thoughts, memories, and sensations that were clearer than usual.*"[20]

NDEs due to cardiac arrest while under general anesthesia occur and are medically inexplicable.

Line of Evidence #5
Near-death experiences and life reviews

Some near-death experiences include a review of part or all of their prior lives. This NDE element is called a life review. NDErs typically describe their life review from a third-person perspective. The life review may include awareness of what others were feeling and thinking at the time earlier in their life when they interacted with them. This previously unknown awareness of what other people were feeling or thinking when they interacted with them is often surprising and unexpected to the NDErs. Here is an example of a life review:

> "*I went into a dark place with nothing around me, but I wasn't scared. It was really peaceful there. I then began to see my whole life unfolding before me like a film projected on a screen, from babyhood to adult life. It was so real! I was looking at myself, but better than a 3-D movie as I was also capable of sensing the feelings of the persons I had interacted with through the years. I could feel the good and bad emotions I made them go through.*"[21]

In my review of 617 near-death experiences from NDERF, a life review occurred in 88 NDEs (14%). None of the life reviews in these NDEs appeared to have any unrealistic content as determined by my review or based on comments by the NDErs about their own life reviews. Life reviews may include long forgotten details of their earlier life that the NDErs later confirm really happened. If NDEs were unreal experiences, it would be expected that there would be significant error in life reviews and possibly hallucinatory features. The consistent accuracy of life reviews, including the awareness of long-forgotten events and awareness of the thoughts and feelings of others from past interactions, further suggests the reality of NDEs.

Line of Evidence #6
Encountering deceased loved ones in near-death experiences

Near-death experiences may describe encounters with people that they knew during their earthly life. The following is an example of encountering a deceased loved ones in an NDE. This example is also notable as the NDEr was born totally deaf:

> *"I approached the boundary. No explanation was necessary for me to understand, at the age of ten, that once I cross[ed] the boundary, I could never come back—period. I was more than thrilled to cross. I intended to cross, but my ancestors over another boundary caught my attention. They were talking in telepathy, which caught my attention. I was born profoundly deaf and had all hearing family members, all of which knew sign language! I could read or communicate with about twenty ancestors of mine and others through telepathic methods. It overwhelmed me. I could not believe how many people I could telepathize with simultaneously."*[22]

When people known to the near-death experiencers are encountered in NDEs, the great majority are people who are deceased. A study by Dr. Emily Kelly was a comparison

of 74 NDEs with descriptions of encountering deceased individuals with 200 NDEs that did not describe encounters with the deceased.[23] This study found that when NDErs encountered beings known to them from their earthly lives in their NDEs, only 4% described meeting beings that were alive at the time of their experiences. I reviewed 84 NDEs from NDERF that described encounters with individual(s) that they knew in their earthly life.[24] There were only three NDEs (4%) where the encountered beings were alive at the time of the NDEs, consistent with the findings of the Kelly study.

In dreams or hallucinations when familiar persons are present they are much more likely to be living and from recent memory.[25] This is in sharp contrast to near-death experiencers where familiar persons encountered are almost always deceased. Cases have been reported by NDErs of seeing a person who they thought was living, but in fact had recently died.[25, 26] These cases illustrate that NDEs cannot be explained by the experiencer's expectation of what would happen during a life-threatening event. Further evidence that NDEs are not a result of expectation comes from the aforementioned Kelly study where in one-third of the cases the encountered deceased person had a poor or distant relationship with the NDEr, or was someone that had died before the NDEr was born.[23]

Line of Evidence #7

Near-death experiences of young children

Investigation of near-death experiences in very young children is important because at an early age they are less likely to have established religious beliefs, cultural understandings about death, or even an awareness of what death is. Very young children would be very unlikely to have heard about near-death experiences or understand them. I investigated the NDEs in children age five and younger in the same group of 613 NDErs previously discussed in the section on NDEs while under general anesthesia. Two NDEs were excluded as they did not provide their age in the survey. The study groups included 26 NDErs that were age 5 and younger (average 3.6 years old) and 585 NDErs age 6 and older at the time of their NDEs. The NDERF survey included 33 questions about the content of their NDEs. Chi-square statistics was used to compare the responses to these 33 questions between the two groups.[27] There was no statistically significant difference to the responses between the two groups to any of the 33 questions. The NDERF study found that the content of NDEs in children age five and younger appeared to be the same as the content of NDEs in older children and adults. The finding of the NDERF study are corroborated by the investigation of Dr. Cherie Sutherland who reviewed thirty years of scholarly literature regarding the NDEs of children and concluded:

> *"It has often been supposed that the NDEs of very young children will have a content limited to their vocabulary. However, it is now clear that the age of children at the time of their NDE does not in any way determine its complexity. Even prelinguistic children have later reported quite complex experiences.... Age does not seem in any way to affect the content of the NDE."*[28]

Very young children have near-death experience content that is strikingly similar to older children and adults. This is further evidence that NDEs are occurring independently of preexisting cultural beliefs, religious training, or awareness of the existence of NDE.

Line of Evidence #8

Cross-cultural study of near-death experiences

Portions of the NDERF website, including the questionnaire, have been translated into 23 different languages. Over 500 near-death experiences in non-English languages have been shared with NDERF over the years. Dozens of volunteers have translated the non-English NDEs into English. Both the non-English and English translated versions of the NDEs are posted on the NDERF website. Over 60,000 people currently visit the NDERF website each month. Many website visitors are bilingual and this help assure that the NDEs are accurately translated.

My investigation of NDEs from around the world that have been translated into English shows that their content is strikingly similar.[29] If near-death experiences were considerably influenced by pre-existing religious and cultural beliefs, it would be expected that there would be significant differences in the content of NDEs from different cultures around the world. However, in my review of over 500 NDEs from dozens of countries around the world I found impressive similarities in the content of these NDEs.

I investigated 19 non-Western NDEs, where a "non-Western country" was defined as areas of the world that are predominantly not of Jewish or Christian heritage.[30]

These 19 non-Western NDEs were compared to a group of NDEs shared in English from Western countries that were predominantly English speaking. This investigation concluded:

> *"All near-death experience elements appearing in Western NDEs are present in non-Western NDEs. There are many non-Western NDEs with narratives that are strikingly similar to the narratives of typical Western NDEs. At a minimum, it may be concluded that non-Western NDEs are much more similar to Western NDEs than dissimilar."*[31]

Two recent investigations of Muslim near-death experiences in non-Western countries have been reported. An investigation of 19 Iranian Muslim NDEs concluded:

> *"Our results suggest that Muslim NDEs may actually be quite common, as they are in the West, and may not be especially different in their key features from Western NDEs and therefore not heavily influenced by cultural variations, including prior religious or spiritual beliefs."*[32]

Another study of eight Muslim NDEs found:

> *"Although the documentation standard of the available cases is generally low, these accounts indicate that structure and contents of NDEs from many non-Western Muslim communities are largely similar to those reported in the Western NDE literature."*[33]

The lack of significant differences in the content of near-death experiences around the world, including NDEs from non-Western countries, suggests that NDE content is not substantially modified by preexisting cultural influences. This finding is consistent with the previously discussed finding that children age five and under, who have received far less cultural influence than adults during their brief lives, have NDEs with content that is essentially the same as older children and adults. Other common forms of altered consciousness, such as dreams or hallucinations, are much more likely to be significantly influenced by prior cultural beliefs and life experiences. The lack of significant differences in the content of NDEs around the world is consistent with the concept that NDEs occur independently from physical brain function as currently understood.

Line of Evidence #9

Near-death experience aftereffects

Following near-death experiences significant changes in the lives of NDErs are commonly observed. The most recent version of the NDERF survey asked NDErs, "My experience directly resulted in...:"

The responses of 278 NDErs to the question were:

Large changes in my life	152	54.7 %
Moderate changes in my life	68	24.5 %
Slight changes in my life	28	10.1 %
No changes in my life	14	5.0 %
Unknown	16	5.8 %

Changes in beliefs and values following near-death experiences are often called aftereffects. Given that a life-threatening event without an NDE might result in life changes, some of the best evidence for NDE-specific aftereffects came from the largest prospective NDE study ever reported. This study, conducted by Pim van Lommel, MD, divided survivors of cardiac arrest into a group that had NDEs, and a group that did not.[12] The aftereffects of both groups were assessed two and eight years after the cardiac arrests. The group of cardiac arrest survivors with NDEs were statistically more likely have a reduced fear of death, increased belief in life after death, interest in the meaning of life, acceptance of others, and were more loving and empathic. It may take years after NDEs for the aftereffects to become fully manifest. The aftereffects may be so substantial that NDErs may seem to be very different people to their loved ones and family. The consistency, intensity, and durability of NDE aftereffects is consistent with the NDErs' typical personal assessments that their experiences were very meaningful and significant. It is remarkable that NDEs often occur during only minutes of unconsciousness, yet commonly result in substantial and life-long transformations of beliefs and values.

Conclusion of Study

Multiple lines of evidence point to the conclusion that near-death experiences are medically inexplicable and cannot be explained by known physical brain function. Many of the preceding lines of evidence would be remarkable if they were reported by a group of individuals during conscious experiences. However, NDErs are generally unconscious or clinically dead at the time of their experiences and should not have any lucid organized memories from their time of unconsciousness.

It is informative to consider how near-death experiencers themselves view the reality of their experiences. An NDERF survey of 1122 NDErs asked "How do you currently view the reality of your experience?", and received the following responses:

Experience was definitely real	962	95.6 %
Experience was probably real	40	4.0 %
Experience was probably not real	3	0.3 %
Experience was definitely not real	1	0.1 %

The great majority of more than 1,000 near-death experiencers believed that their experiences were definitely real. The 1,122 NDErs surveyed included many physicians, scientists, attorneys, and nurses. These findings suggest that, for the majority of us who have not personally experienced an NDE, we should be very cautious about labelling NDEs as "unreal." Given that such a high percentage of NDErs consider their experiences to be "definitely real," it would be reasonable to accept their assessment of the reality of their personal experience unless there is good evidence that their experiences were not real.

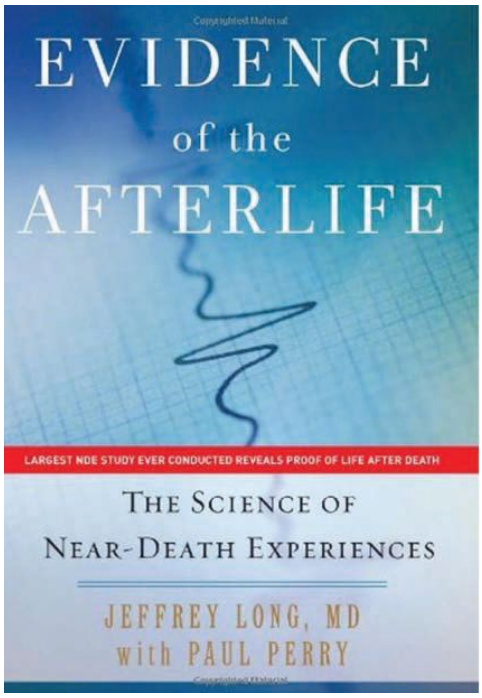
After over 35 years of scholarly investigation of near-death experience, the totality of what is observed in NDEs has not been adequately explained based on physical brain function. It is beyond the scope of this article to review the many proposed "explanations" of near-death experience. Over the years, there have been over 20 different "explanations" of NDE suggested that cover the gamut of physiological, psychological, and cultural causes. If any one or several of these "explanations" were widely accepted as plausible, then there would be no need for so many different "explanations" of NDE. Among those who believe that physical brain function must explain everything that is experienced in all NDEs, there is no consensus whatsoever about how physical brain function produces NDEs.

Conclusion

The combination of the preceding nine lines of evidence converges on the conclusion that near-death experiences are medically inexplicable. Any one or several of the nine lines of evidence would likely be reasonably convincing to many, but the combination of all of the presented nine lines of evidence provides powerful evidence that NDEs are, in a word, real.

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Evidence of the Afterlife: The Science of the Near-Death Experience

BOOK REVIEW

by Jeffrey Long, MD, with Paul Perry

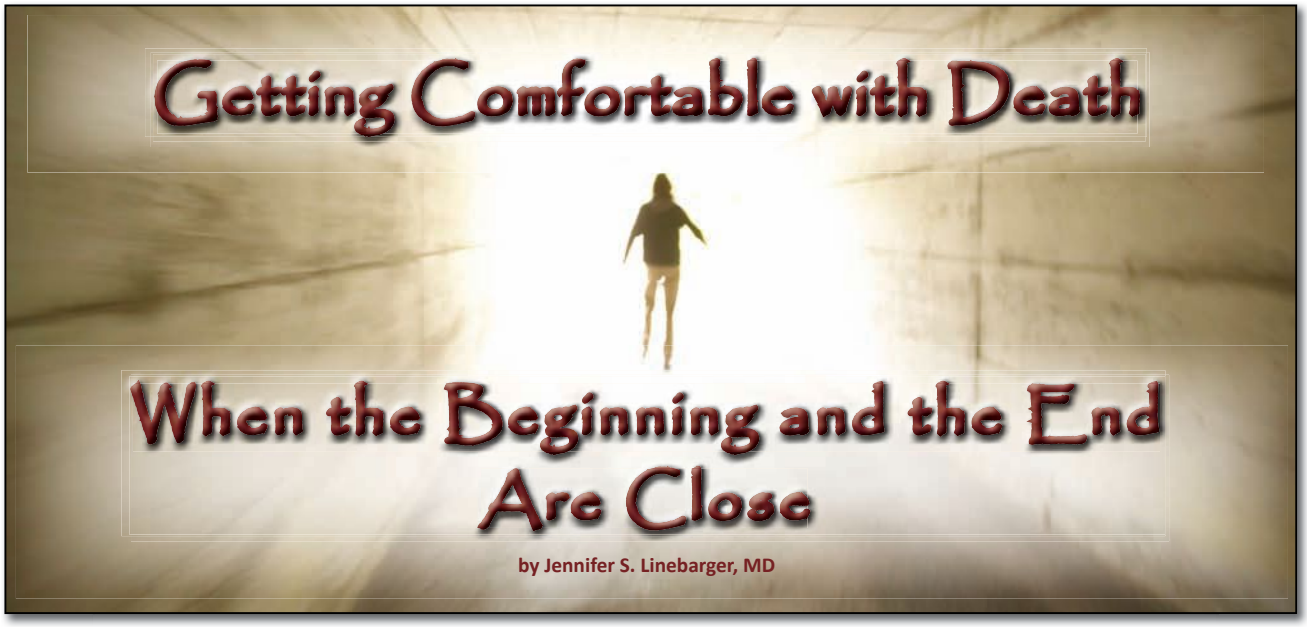
The most compelling scientific evidence for life beyond death ever compiled, Evidence of the Afterlife shares the firsthand accounts of people who have died and lived to tell about it. Through their work at the Near Death Experience Research Foundation, radiation oncologist Jeffrey Long and his wife, Jody, have gathered thousands of accounts of near-death experiences (NDEs) from all over the world. In addition to sharing the personal narrative of their experiences, visitors to the website are asked to fill out a one hundred–item questionnaire designed to isolate specific elements of the experience and to flag counterfeit accounts. The website has become the largest NDE research database in the world, containing over 3,800 NDE accounts. The people whose stories are captured in the database span all age groups, races, and religious affiliations and come from all over the world, yet the similarities in their stories are as awe-inspiring as they are revealing. Using this treasure trove of data, Dr. Long explains how medical evidence fails to explain these reports and why there is only one plausible explanation—that people have survived death and traveled to another dimension.

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None reported.

MM



There are two key questions underpinning pediatric palliative care:
How does the patient and family define quality of life?
What are the goals of care at this time?

Introduction

What does a child represent to you? For most of us, children represent the future, hope, vitality, joy, and playfulness. So when a child is born with a life-shortening condition, develops a life-threatening illness, or dies, it rattles our often presumed order of the world. In these times of duress, the involvement of a pediatric palliative care team may soften the quake. This article aims to define which children may benefit from pediatric palliative care and the role of the palliative care team. It is important to know who these children are and how we can help them, and their families, have the highest quality life possible regardless of a given disease, its trajectory or time course, and anticipated hard times.

Who are These Children?

About 50,000 children die annually in the United States.[1] Even beyond the first year of life, congenital anomalies remain a leading cause of death. Such anomalies may be chromosomal, metabolic, or neurological, and they place children at risk for a shortened life. Palliative care teams may even meet the parents of these children prenatally. So while many may hear "pediatric palliative care" and instantly picture a bald child with cancer, the patient population is really much more diverse.

A group called *Together for Short Lives* helped define the pediatric palliative care patient population using four categories:[2]

1. Conditions for which curative treatment is feasible but can fail, such as cancer;
2. Conditions where premature death is inevitable, such as cystic fibrosis or muscular dystrophy, but a considerable lifespan can be anticipated beforehand;
3. Conditions without curative treatment options, such as many metabolic disorders or complex congenital heart defects, but where many palliative procedures or treatments may offer some benefit for a time; and
4. Irreversible but non-progressive conditions causing severe disability, leading to susceptibility to health complications and likelihood of premature death, such as holoprosencephaly.



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These four categories characterize the various underlying circumstances that can serve to trigger consultation and involvement of a palliative care team. The categories were evident in a prospective multicenter cohort study of pediatric palliative care consult patients seen at six children's hospitals.[3] In that study of new and established patients, the most common conditions were those related to congenital anomalies or genetic conditions (40%), neuromuscular conditions (39%) and cancer (20%). Most of the patients had chronic use of some form of medical technology (feeding tubes, respiratory support, mobility assistance) and were on multiple medications.

When Do They Become Palliative Care Patients?

In the World Health Organization's 1998 definition, palliative care begins when illness is diagnosed and continues regardless of whether or not a child receives treatment directed at the disease, as it aims to alleviate a child's physical, psychological, and social distress.[4] While this definition attempts to normalize the role of palliative care teams, stigma and misconceptions about palliative care still exist.

I recently met a school-age patient who had a brain injury at birth leading to many complications. His mom articulated her hesitancy to meet our team. She shared that meeting us "made it more real" that her son will have a shortened life. At the same time, she welcomed the medically savvy and quality of life-focused decision-making support we could provide as she considered potentially risky surgeries for her son. Her comments highlight the risk-benefit ratio a parent (or a provider) faces when contemplating referral to a palliative care team.

Both a physician and a parent of another palliative care patient referred that mom to our team. The physician who referred this mom had heard her weighing the benefits and the burdens of proposed surgeries. He had not referred her because her son's death was imminent, rather he realized that a palliative care team could support her as she made decisions in the best interest of her son. He had not referred her because he planned to turn all medical care over to someone else, but because of the "neutral sounding board" that a palliative care consult could provide.

What Does Palliative Care Do for These Patients?

Since palliative care is designed to *"meet the patient and their family where they are,"* it can take on many different forms. What palliative care may look like at one moment for a patient may be different than for another; and what it looks like over time for the same patient may evolve as well. In the multicenter cohort study mentioned above,[3] there was often (78%) more than one main goal of the consultation. The top four reasons for a palliative care consult were symptom management (58%), facilitating communication (48%), supporting decision-making (42%), and helping to coordinate care (35%).

There are two key questions underpinning each of those reasons for consult: *How does the patient and family define quality of life? What are the goals of care at this time?*
Quality of life (QOL) has become a bit of a "buzz word" within medicine, and there are many tools aimed at quantifying quality of life for an individual. A more patient-centered definition was proposed by Carr and Higginson:

> *"Quality of life is determined by the extent to which hopes and ambitions are matched by experience, the individuals' perceptions of their position in life, the appraisal of one's current state against some ideal, and the things people regard as important in their lives.*[5]

My favorite question to elicit some notion of QOL is to ask the child (or parent), *"What brings you (your child) joy?"*

Having a clear sense of what makes a person joyful can help guide treatment decisions. Thinking back to the school-age patient I recently met, articulating that he loves going to school, therapy in the pool, and time cuddling with his mom can help shape decision making that lays ahead. Perhaps the burden of respiratory infections on his susceptible lungs is worth the greetings he gets in the hallway at school. Perhaps a tracheotomy or continuous BiPAP support would interfere too much with his time in the pool. Perhaps spinal rods for scoliosis would impair his ability to curl up with his mom the way they both love.

Having a clear sense of what makes a person joyful can also let us know when suffering is becoming too great. At that time we continue thinking about how to manage physical symptoms and address psychosocial or spiritual distress – all while recognizing that in order to best relieve suffering we may hasten death.

As the field of palliative care was first being defined, the American Academy of Pediatrics wrote a statement in support of pediatric palliative care. In it, they stated that the goal is to *"add life to the child's years, not years to the child's life."*[6, p353] Yet, truly focusing on quality of life (at the risk of quantity) can be hard. Sometimes medical teams may feel at odds with a patient, sometimes one parent is at odds with another, sometimes the child is at odds with their parents. One role of the palliative care team is to mediate and facilitate a smooth transition from a primary goal of life extension to a goal of comfort.

Often the pediatric palliative care team gets to know a patient and their family over time. In the multicenter

cohort study, 64% of the patients who were seen by the palliative care team over the course of three months were established patients to the team, and over the 12-month follow-up study period more than two-thirds of the patients were still alive.[3] Such continuity of the relationship allows the palliative care team to articulate the discussions that have occurred over time to others. It also attests to the variability in lifespan of pediatric patients receiving palliative care compared to adults.



Nearly half of all children's hospitals have a palliative care program. Missouri has five pediatric palliative care programs – one in Kansas City, one in Columbia, and three in St. Louis.

The pediatric palliative care team is a resource to provide continuity in the context of the larger inpatient and subspecialty medical teams and consultants. Care coordination and collaboration often includes treatment teams from both the inpatient and the outpatient/community setting. Palliative care teams can smooth transitions across and between care environments, and help to maintain patient and family centered goal directed care that is, at times, subject to inconsistency in specific organ-system or disease focused specialty clinics. For some children receiving palliative care, the community team may include hospice support. Hospice care is a particular form of palliative care defined in the U.S. by federal regulations. Anecdotal evidence suggests the number of hospices caring for children is growing, and in major metropolitan areas there are hospice services designed specifically for pediatrics.

Where Can You Find Pediatric Palliative Care Teams?

The access to pediatric palliative care teams is growing. Feudtner et. al published a cross-sectional national survey pediatric palliative care programs at children's hospitals.[7] Nearly half of all children's hospitals have a palliative care program. Only five of the programs existed before the year 2000, growing to 112 programs as of the summer of 2012 when the survey was conducted. Based on their data, Missouri has five pediatric palliative care programs – one in Kansas City, one in Columbia, and three in St. Louis. Just as the national data showed, each of these programs vary in staffing, funding, and the number of consults staffed annually, but all serve to improve the quality of life and reduce distress for the patients and their families facing a life-shortening or life-threatening illness.

Summary

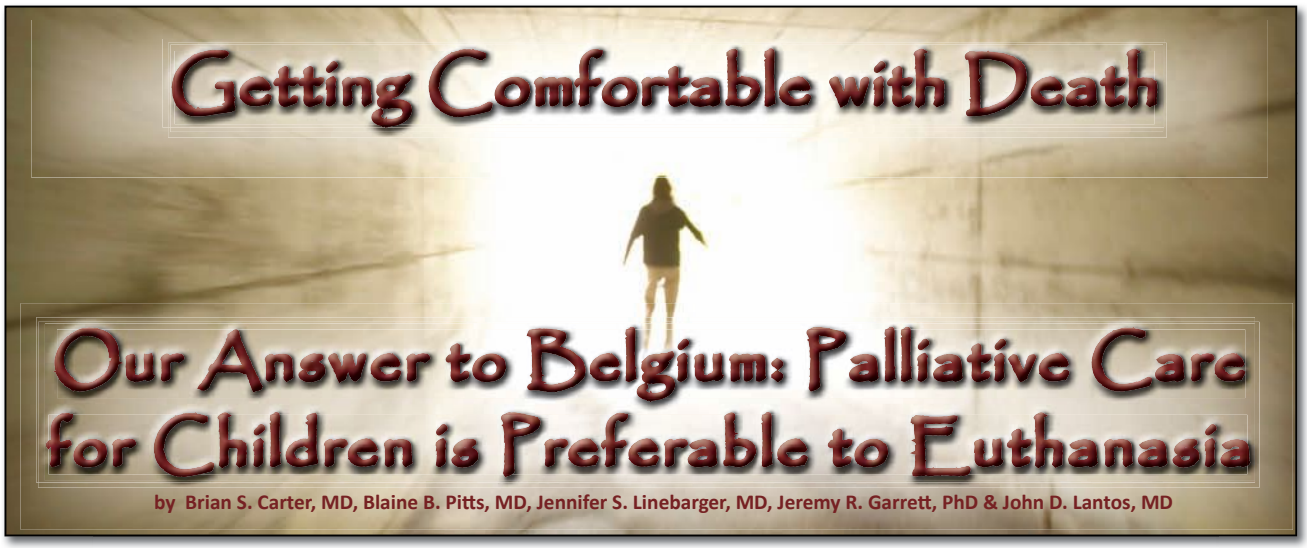
While thinking about the reality that children die can be uncomfortable for many, the role of the pediatric palliative care team is to support the children, families, and providers who care for these children with life-shortening conditions. Such care focuses on enhanced quality of life, and includes symptom management, facilitating communication, supporting decision-making, and helping to coordinate care. The need for such care is clear, and the pediatric palliative care specialty continues to evolve and grow. In 2013, the American Academy of Pediatrics released a policy statement outlining twelve guidelines and recommendations to serve as a touchstone for this evolution and growth, with the promised goal "to care for all children with serious life-threatening and inevitably life-shortening conditions and their families."[8]

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Disclosure

None reported. **MM**



An ethos that focuses on palliative care but that allows the possibility that death might be hastened is preferable to one that focuses on hastening death.

On March 3, 2014, Belgium's King Philippe signed into law an amendment to the country's 2002 Belgium Act on Euthanasia. The original law limited the practice of euthanasia to competent adults. The new law would allow minors to ask for a terminal intervention if they are terminally ill, if they are in great pain and if there is no treatment to alleviate their distress. The request would have to be agreed by the patient's medical team and parents.

The previous law had been in place for a decade. Similar laws exist in the Netherlands and in Luxembourg. They allow for adult euthanasia. Over the decade, the laws in these three countries have been relatively uncontroversial. Estimates are that about 3% of deaths in these countries follow euthanasia or assisted suicide. The extension of the law to children is based upon concern that some children experience constant and unbearable suffering despite all that modern medicine may have to offer.

The law would not allow euthanasia of an infant, since it requires that an individual child who might make such an explicit request for euthanasia do so on his/her own volition (voluntariness).

The new law has some restrictions and safeguards. It does not permit euthanasia for children who are deemed to have a neuro-cognitive impairment. It requires oversight by a multi-disciplinary team whose role is to determine whether the child has decisional capacity and, if so, whether the child's choice of euthanasia seems to be the best option that she or he has.[1, 2]

This approach to end-of-life care raises a number of important concerns. The first has to do with the goals of medicine. The goals of medicine are to restore health, treat disease, and relieve pain and suffering. For millennia, it has been considered beyond (and even contrary to) the goals of medicine to ever deliberately end a patient's life. This principle has been tested in recent decades by approaches to end-of-life care that involve the withdrawal of life-sustaining treatments. Thus, proponents of euthanasia often question whether there is a moral difference between, say, withdrawing fluid and nutrition from a child with severe neurocognitive impairment and giving that same child a terminal intervention. Such dilemmas raise the question of whether or not there are good reasons, today, to change the time honored prohibition on euthanasia.



Children's Mercy KANSAS CITY

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Clearly, advances in medical technology have changed the way we think about end-of-life care. Ventilators, extracorporeal membrane oxygenation (ECMO), dialysis, left ventricular assist devices (LVADs), and other life-supporting technology make it possible today to keep people alive even when they have no hope of recovery and in states characterized by technology-induced pain and suffering. In such cases, physicians face tragic choices about whether to prolong life. In some ways, however, those are the easy cases because, for those patients, there is a life-sustaining technology that can be withdrawn. The tougher cases are the ones in which a child seems to be suffering, in which no palliative treatment seems to relieve that suffering, but in which no life-sustaining treatment is in place that can be withdrawn.3, 4

These choices are not scientific choices. They remain firmly in the domain of the healing arts, not the healing sciences. They require prudential application of science, human wisdom, and a shared intention of benefit for the patient. The healer offers knowledge, skill and wisdom. The vulnerable patient looks to the healer for guidance. The therapeutic relationship depends upon trust and a mutual attention to benefiting the patient.

How, then, does euthanasia fit into this domain of human interaction? The applications of good pain management and comprehensive palliative care have lightened the load for clinicians, patients and families grappling with these tragic circumstances, choices, and residual effects. (See accompanying article on pediatric palliative care page 387.) Most doctors and bioethicists who oppose euthanasia argue that excellent palliative care for children with life-limiting illnesses is almost always able to relieve pain and suffering.5, 6 Palliative care addresses the many facets that comprise all of us as patients (the physical, emotional, spiritual and relational) and it aids and assists families as they travel the varied paths that life-limiting or life-threatening conditions may confer upon a patient and his/her loved ones. In its best sense, palliative care improves upon the quality of life that a patient may enjoy over his/her remaining life-span – be it six days, six months or six years. And even at what some might consider its worst, when comfort seems elusive, time is short, and the disease has mastered the patient, palliative care can almost always control pain and suffering. Sometimes, it unavoidably does so in ways that hasten death. But the goal is never to hasten death, only to treat pain and suffering.7, 8

The difference in goals is crucial. An ethos that focuses on palliative care but that allows the possibility that death might be hastened is preferable to one that focuses on hastening death. Our resistance to euthanasia is rooted in a view of medicine where "healing" and "relief of suffering" are the pre-eminent goals for health care professionals and patients alike. In prioritizing these goals, the medical traditions are in harmony with many religious traditions. Life (and health), in itself, is intrinsically good, while suffering, in itself, is intrinsically bad. This does not entail that extrinsic considerations can never change our all-things-considered judgments about life, or about suffering – such as when a life is incapacitated and filled with suffering, or when suffering serves instrumentally to further some other important good. But, in their own right, life and health are good and suffering is bad, and it is these two value judgments that define the goals of medicine as promoting healing and relieving suffering.

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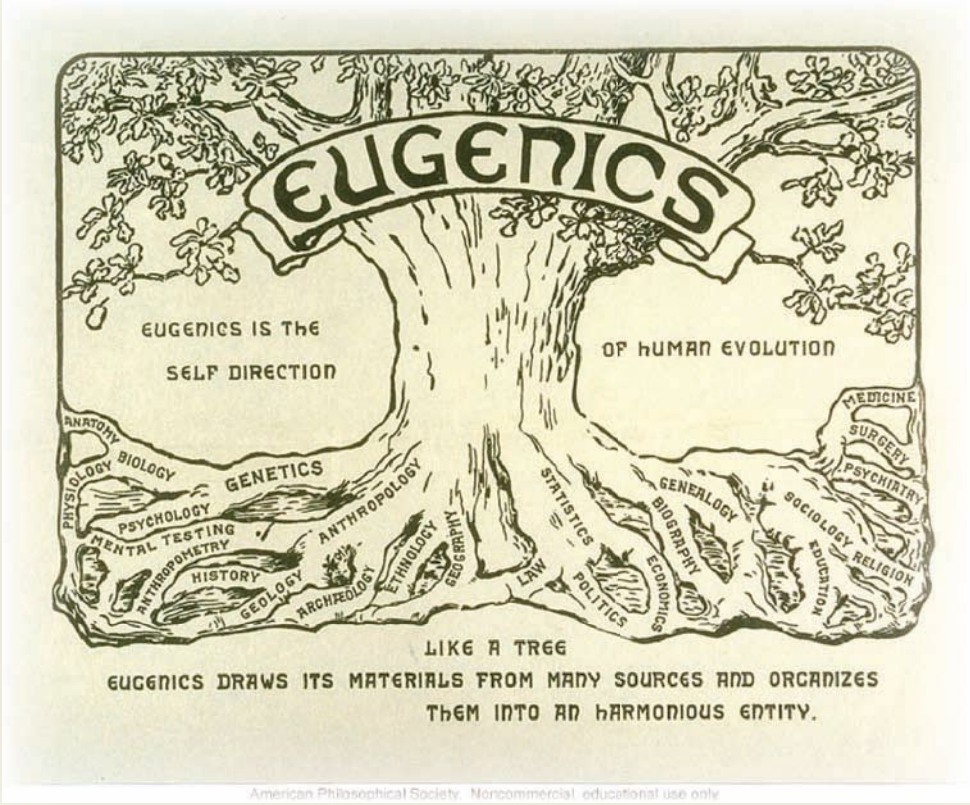
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Our resistance to euthanasia is rooted in a view of medicine where "healing" and "relief of suffering" are the pre-eminent goals for health care professionals and patients alike.

The Role of Eugenics in Research Misconduct

Susan M. Miller MD, MPH



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The demonization of specific populations, medicalization of racial purification, radicalization of racial hygiene, and state-sponsored genocide provided the necessary crucible for the Holocaust.

Introduction

Revisiting history provides a mechanism for medicine to explore the roles racial prejudice, ambition, and indifference played in the Holocaust. Some of the most difficult moral lessons to teach are those we have never learned or those we have ignored from the past. The unanticipated, organized role of physicians and their subsequent radicalization under National Socialism resulted in both medical and research misconduct. This left a legacy which continues to reverberate even though it has been more than sixty years since the Doctors' Trial was held in the occupation zone of Nuremberg, Germany (*United States of America v. Karl Brandt, et al.*). The Doctors' Trial (December 9, 1946 – August 20, 1947) was the first of twelve trials for war crimes which occurred during World War II. [1] Specifically, these defendants were charged with, among other things, the performance of medical experiments on civilians and prisoners of war without the subjects' consent in spite of pre-World War II German guidelines prohibiting such activity.[2] This unethical research and deliberate medical genocide occurred in hospitals, nursing homes, "asylums" and concentration camps.[3] The medicalization of *Rassenhygiene* (racial hygiene) was a pre-condition for the Holocaust and racial purification was considered a step to "heal" society through "killing."[4]

As new moral tensions arise in modern research, it is

time to scrutinize how the German medical system became corrupted by ideology and misplaced utilitarian ethics. Were the cataclysmic events of the Holocaust specifically German, or could they occur in other societies? A partial explanation can be elucidated by exploring how Germany's embrace of eugenics overlapped with its economic collapse. These events were historical precursors to medicine's subsequent misconduct.

Historical Antecedents

In 1867, Germany became a state and by the 1880s, Chancellor Otto von Bismarck (1815-1898) introduced its first social insurance programs. His old-age pensions, accident insurance, medical care access, and unemployment insurance became a model for other countries and were the social-contract basis of the modern German state.[5]

Germany's renowned academic reputation was based on its long-standing tradition of scientific research. Beginning in 1901, German scientists received numerous Nobel Prizes in Chemistry, Physics, and Medicine, and her emphasis on science required a research-based thesis for an M.D. degree. Furthermore, Germany (1931) developed guidelines for human experimentation in response to pediatric deaths from contaminated BCG vaccine research. [6]

So how did Germany's medical system become debased by the Third Reich? In spite of Germany's visionary social and academic policies, physicians abandoned the sanctity of the Hippocratic Oath and willingly participated in genocidal activities. Forty-five percent of German physicians were members of the national Socialist Physicians' League [4] and served as leaders in implementing Hitler's policies.

Eugenics

In 1905, Ernst Rüdin, MD, (1874-1952), a Swiss psychiatrist, co-founded with his physician brother-in-law Alfred Ploetz (1860-1940) the 'Society for Racial Hygiene,'[7] which emphasized the hereditary nature of illness.

In 1921, Erwin Baur, Eugen Fischer and Fritz Lenz first published Human Heredity Teaching and Racial Hygiene. By 1932, formal courses on racial hygiene were incorporated into medical school curricula[7] creating a professional socialization process and established discipline for physicians. Physicians were expected to know this anthropology as part of their medical training but did not have the normative skills to question its validity.

In addition, Alfred Hoche, a neuropathologist, and Karl Binding, a former president of Germany's highest court, published a pamphlet, The Sanctioning of the Destruction of Life Unworthy of Living (1922), which radicalized eugenic ideas by contradicting moral, legal and medical prohibitions against killing using economic and medical arguments to substantiate their claims.[8] Hoche and Binding were "shocked" by the tremendous amount of care provided to "completely worthless creatures" when so many healthy men had died in World War I. Their writings served to support a more "efficient" process than natural selection.

An inflection point in the German historical timeline occurred between 1924-1928 when public health improved in Germany as governmental policies provided expanded health care to all citizens. Physicians received payment from the state's insurance program as employees of the government and as custodians of public health.[9] This resulted in an unintended deterioration in the physician-patient relationship as social policies preferentially emphasized the nation's public health. By 1929, physician loyalties underwent even further change as A) the world economic crisis diminished the amount of available state monies for social expenditures; B) competition for jobs increased; and C) health care became subject to cost-benefit analyses.[10] As six million people became unemployed during the late Weimar period, there were additional pressures to trim the government's budget.[9] When German society began to experience further limitations in its financial revenues, the physician leaders in the eugenics movement argued against the unrestrained use of resources on "inferior" citizens. This collaboration between the medical and public health systems provided an infrastructure for government alignment of eugenics philosophy and subsequent control of physician behavior. Physicians began to shift their fiduciary responsibility and allegiances toward the public health of the body of society (the *Volk*) and away from individual patient needs. [9] Eugenics offered a de facto biomedical solution for societal problems and became a "morally respectable," utilitarian-based justification for subsequent sterilization and euthanasia policies. Ironically, the international reputation of eugenics was already declining in the 1930s as Rüdin and his colleagues used eugenics as a scientific justification for their "applied biology"-racial policies. A comparative analysis of country specific eugenic movements is described by Adams. [9]

German Regulations and Sterilization Research

The Nazification of medical values[6] increased when six months after Hitler became the Chancellor of Germany, the "Law for the Prevention of Progeny of Hereditary

Eugenics is the study of the agencies under social control, that improve or impair the racial qualities of future generations either physically or mentally.

-Sir Francis Galton

Diseases (*Gesetz zur Verhütung erbkranken Nachwuchs*)" (July 14, 1933, co-written by Ernst Rüdin), was passed. [Of interest, U.S. sterilization policies (1907) served as a basis for German law. By the 1920s and 1930s, the "eugenic policy of sterilizing certain mental patients was implemented in a variety of other countries, including Belgium, Brazil, Canada, Japan, and Sweden.[9, 11]

This legislation permitted the forced, involuntary sterilization of "genetically inferior" German citizens who suffered from blindness, hereditary deafness, schizophrenia, epilepsy, manic depression, alcoholism, Huntington's chorea and "feeblemindedness" and allowed for further consolidation of social and medical policies.[12] The Reich Committee required physicians and midwives to register their patients with any of the above disorders and an "independent" Genetic Health Court determined whether forcible sterilization could occur. The patient was not required to be present during this deliberation process. Within four years, 300,000 patients were sterilized, often requiring the use of police force. Many physicians justified the involuntary sterilizations because they thought the sterilization policies served the long-term interests of society. [13] Ultimately more than 1% of the entire German population was sterilized. [14]

Euthanasia

It soon became apparent, however, that eugenic sterilization processes were not enough to rid German society of "unworthy" citizens who were born prior to the 1933 sterilization laws. The next stage in this moral crisis began in the spring and summer months of 1939. An entire infrastructure for "mercy killings" was created under the auspices of Philipp Bouhler (1899-1945) [the director of Hitler's private chancellery] and Karl Brandt (1904-1945) [Hitler's attending physician], mandating reporting of all infants and children under the age of three with severe mental or physical disabilities. These children were admitted to specialized clinics whereby systematic pediatric euthanasia was promulgated (1939-1945). Adolf Hitler signed a secret authorization to protect participating physicians. If any legal actions were taken against a physician, the cases would be thrown out of court. Specialized staff murdered the children via lethal overdoses or through starvation until the last days of World War II.[15] Although participation in sterilizations or killings was "voluntary", individual resistance was rare.[14] Because there were minimal reactions against the killing of children, the scope of the program soon expanded to juveniles and by 1940, the adult euthanasia program, T4, began in earnest (1940-1945). The detainee euthanasia program, known as Action 14f13, (bureaucratic code word for euthanasia), occurred from April 1941 to December 1944 [16] in the concentration camps. It is important to realize that not only did the pediatric euthanasia program predate the more systematic genocide by two years,[8] it served as a rehearsal for Nazi genocidal policies which were activated after the infamous Wannsee conference (1942).

This massive scale of death and dehumanization desensitized the perpetrators, many of whom felt they did nothing wrong. The Hippocratic Oath bled into indifference as individuals ceased to exist. As Micozzi states, "in a system in which so many were routinely condemned to die, the temptation proved strong to use human subjects in medical experimentation prior to their tragic and terrible deaths." [10]

Research Misconduct

Prior to World War II, German guidelines prohibited research where consent had not been given. After 1933, these guidelines were ignored. [6] The German government funded the "academic" research studies on euthanasia populations, especially for physicians who wanted to advance their careers and who also supported Nazi policies. Julius Hallervorden, from The Kaiser Wilhelm Institute, conducted multiple research projects based on these programs. During his interrogation in 1945 Hallervorden said, "if you are going to kill all these people, at least take the brains…there was wonderful material among these brains." [14, 15, 17] Investigators had an endless supply of subjects and requested clinical specimens specific to their

research interests even in advance of the subjects' deaths. This also allowed the collection of clinical information as children selected for "treatment" were observed for a period of time prior to their execution. Once the children were murdered, the organs were collected under the veils of secrecy and the cause of their death was falsified.[18] Another researcher, Hans Nachtsheim, thought it "was ethically permissible to experiment on persons who were going in any case to be killed." [6]

Paradoxically, animals received more research protections than German citizens under the Third Reich. On November 24, 1933, National Socialist Germany enacted the *Reichstierschutzgesetz* (Reich Animal Protection Act), for the protection of animals. In addition, on February 23, 1934, the Prussian Ministry of Commerce and Employment enacted the decree requiring education on animal protection laws at primary, secondary and college levels. [19]

The medical experiments which occurred during the Nazi regime were purported to advance German medicine but the idealism which supported these efforts undermined the moral integrity of their institutions. Ordinary people opportunistically competed for research funding and were propelled into abhorrent behaviors. Their research ideas were not limited to military needs, but also included racially motivated research (e.g. twin experiments) and research which included death as an endpoint. If not for individual physicians and organized medicine, the sterilization programs and T4 program may not have occurred. [20] The medical experiments of the Third Reich would have been prohibited. [21]

The Nuremberg Code (1948) and the Declaration of Helsinki (1964) are international responses emphasizing the prerequisite importance of informed consent, appropriate scientific design, minimization of risk, and qualified research teams. [These same, albeit ignored, concepts were present in pre-WWII Germany.] These virtues were re-emphasized and reinforced in the Belmont Report (September 30, 1978) when beneficence, respect for persons and justice were described. The Belmont principles are reflected in current U.S. regulatory requirements surrounding research oversight and informed consent processes and are required knowledge for modern scientists. In addition, regulatory guidelines provide special protections for vulnerable populations including prisoners, women and children.[22]

Present Day Implications

The challenges of maintaining medical and research ethics are ongoing. Dr. Henry K. Beecher's (1904-1976) *New England Journal of Medicine* article reviewed continued violations of informed consent precepts when he described, for example, hepatitis experiments at Willowbrook (which paralleled Sachsenhausen-Oranienburg) and cancer cell injections in nursing home residents.[23] Up until then, many US scientists thought the Holocaust experiments were anomalous and did not apply to their work. The regulatory aftermath from Jesse Gelsinger's (1981-1999) gene therapy death led to mandatory research ethics training by the OHRP and NIH.

These are just a few examples of how misconduct reveals psychological attitudes, including cognitive dissonance and dehumanization, which continue to persist in spite of regulations. Without self-awareness, investigators are still distracted by personal ambition, prejudice, judgment, efficiency, jealousy and denial. Even today, historical gaps remain in the number of individuals who underwent German experimentation. These final numbers remain unknown. A forensic analysis of academic publications and textbooks based on these activities remains incomplete.[6] Only in August 2012 did the German Medical Association acknowledge and apologize for the role of medicine in the Holocaust. This apology has become known as Nuremberg 2012.[24]

Health care research (e.g. nanotechnology, genetic transfer) requires continued moral inquiry and oversight. Genetic sequencing has the potential ability to be misused especially if social policies identify new populations unworthy of health care. The consequences of stem cell research remain unknown. Which safeguards should society consider?

Certainly regulatory oversight remains essential. Although many countries utilize Institutional Review Boards or Research Ethics Committees, they must be independent and dispassionate to be effective. Furthermore, institutional-based systems need to be in place to manage scientific review, conflicts of interest and research misconduct. Pro-active and integrity-based education and mentoring can provide substantial ethical foundations to protect the rights of individual patients against changing ideology. Scientific inquiry, in most cases, still needs to be subordinate to privacy, confidentiality and voluntary consent.

History shows us how the demonization of specific populations, medicalization of racial purification, radicalization of racial hygiene, and state-sponsored genocide provided the necessary crucible for the Holocaust.[14]

The world can only hope that societal prejudices will

not masquerade as scientific proof. History no longer allows us to hide behind these precepts. Our current system provides checks and balances which were not present or enforced in the 1930s or 1940s, and it is unlikely that a systemic failure could reappear. [17] Bioethics and research ethics have become everyone's responsibility. Whereas eugenicists overlooked the importance of diversity, collaborative partnerships and patient advocacy are becoming more common. An emphasis on subject autonomy and the oversight role of the IRBs provide additional protections. Our professions must continue to learn and teach from our mistakes, and listen to our consciences. Through these insights our virtuous behaviors can mitigate the most egregious harms.

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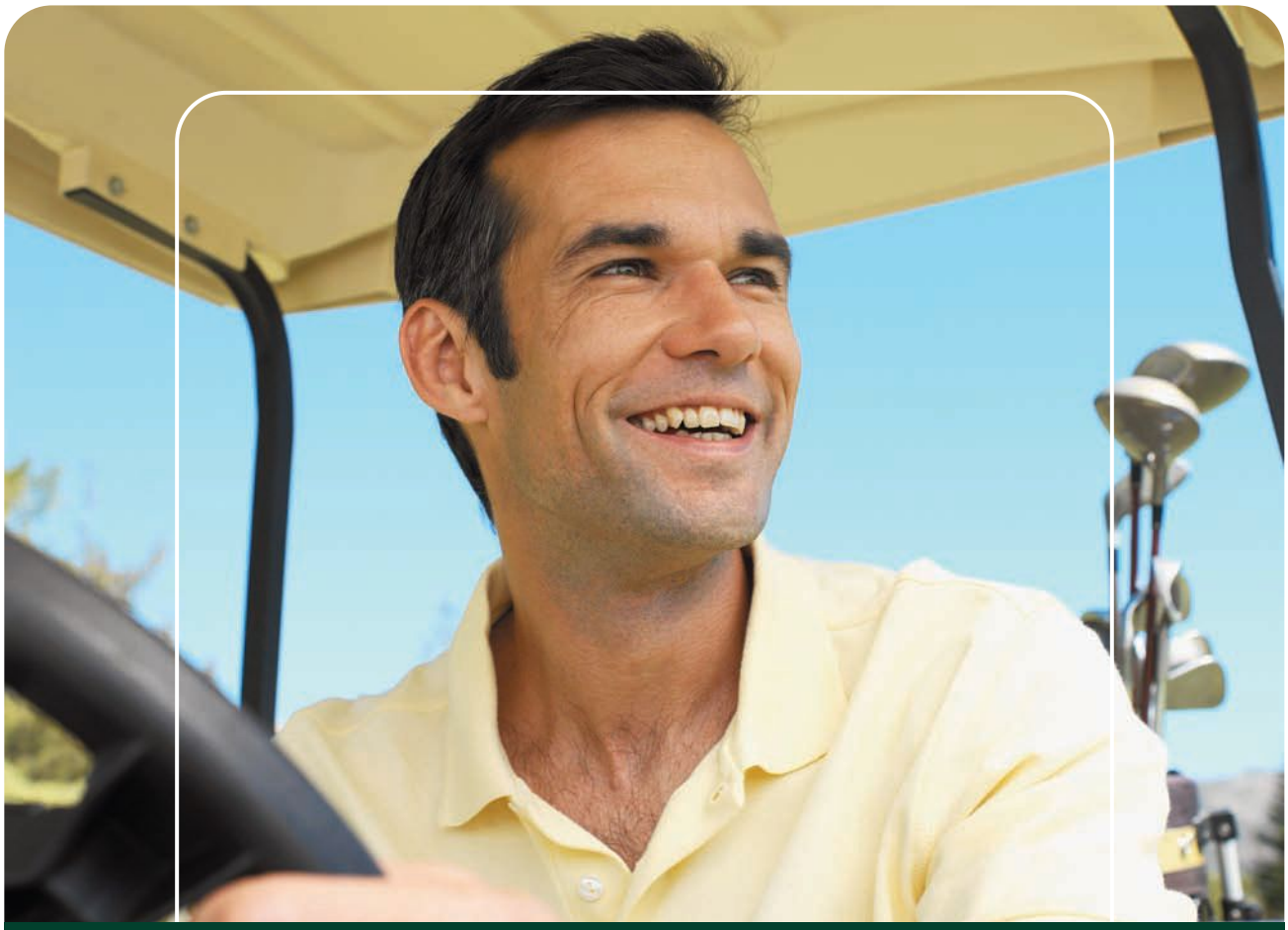
The University of Missouri-Kansas City School of Medicine and Saint Luke's Hospital of Kansas City

Note

This article is based on an abstract presented at the National Conference on Bioethics in Kiev, Ukraine, September 23-25, 2013. **MM**



Susan M. Miller, MD, MPH, is Professor of Clinical Family Medicine at the Institute of Academic Medicine, Houston Methodist Hospital Research Institute in Houston, Texas.
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CORRESPONDENCE

Center for Vaccine Development More Important Now More Than Ever

I think the July/August *Missouri Medicine* is an outstanding publication and I am honored to be a contributor.

Edwin L. Anderson, MD
Center for Vaccine Development
Saint Louis University School of Medicine

Eureka Moment!

I read with interest your "A Eureka Moment-Beta Blocker Eye Drops for Acute Migraines" in the July / August *Missouri Medicine.*

This should be a primer for all medical students, residents and doctors in practice on how to convert a "hunch" into good controlled,prospective, randomized, masked studies. Many times in our everyday practice we see unexpected relationships in our management and therapies in our patients.

As Louis Pasteur stated, "Chance favors the prepared mind." So be prepared for your Eureka moment wherever and whatever you are doing!

George Bohigian, MD
MSMA Member since 1977
Ophthalmologist, St. Louis

Doctor's Desk For Next Generation

I am a fellow MU grad and Family Physician currently practicing in St. Louis. I came across some papers I had stored away, saw a blog post you penned and thought I should send you a note. You wrote the post on medhelp.org in 2009 titled, "The Origins of 'Doctor's Day.'" In it, you describe growing up in Mexico, Missouri, with a special group of physicians.

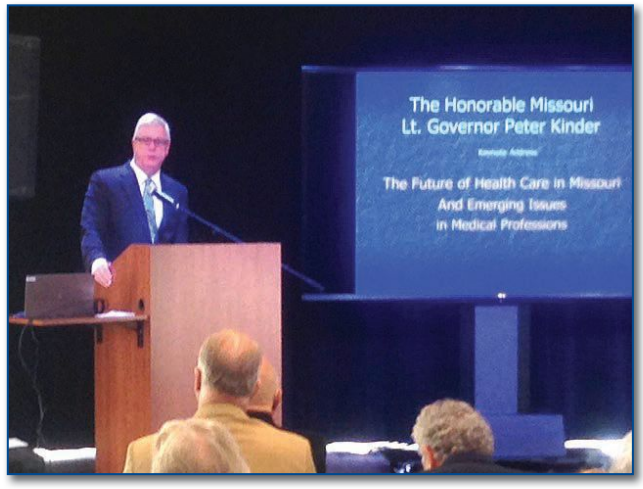
In 2008, I graduated from the MU School of Medicine and my wife wanted to get me a special gift. She contacted Jim Stubblefield, a furniture maker in Mexico. We went to tour his workshop looking for the perfect desk for my future practice. We couldn't find the perfect match until Jim remembered he had an old desk tucked away. It had been the office desk of a Mexico physician for, as he remembered it, most of his career. Jim went on the internet looking for info on the doctor and he came across your post. When it was delivered, your post was in the top drawer. I believe it was Dr. O'Brien's, though I cannot recall at this point if he had said Garcia or O'Brien. The desk was perfect - solid, honest and trustworthy. Jim cleaned the top, painted the body and I inherited what looked like a desk, but what felt like something more profound; the responsibility of carrying on the tradition of the great Missouri physician's you describe in your post.

The desk had been in storage as my practice in Kansas City didn't have a space for it. Last week we moved it into my new office in O'Fallon and I took a deep breath as I thought about the history behind it. It will be an honor to sit behind the desk every day as I continue to work to live up to the example that Dr. O'Brien and yourself have set. I look forward to the challenge.

Christopher Blanner, MD
MSMA Member since 2014
O'Fallon, Missouri



MSMA President Jeffrey Copeland, MD, (center), was special guest of the Kentucy Medical Association during its annual meeting. With him are KMA President David Bensema, MD, (left), and AMA President-Elect Steve Stack, MD.



Missouri Lt. Governor Peter Kinder addresses a full house of physicians at Buchanan County Medical Society's symposium on "Physician Supervision of Allied Health Professionals' Practices."

MSMA Applauds Elimination of Sales of Tobacco in Pharmacies

by Jim Blaine, MD, Family Practice, Springfield, MO
MSMA Public Affairs Commission



When a drug store sells cigarettes they legitimize their use. In April 2014, physicians in the Missouri State Medical Association sent a clear message: those businesses in Missouri that wish to promote the goal of better health should recognize that selling tobacco products contradicts that commitment.

To that end, MSMA applauds the effort by CVS Caremark to eliminate sales of cigarettes and other tobacco products by October 1, 2014. This is especially important because the sale of tobacco products is ethically conflicted with pharmacies providing care and medication to treat hypertension, hyper-lipidemia, heart and lung issues, and diabetes; all conditions exacerbated by smoking. The American Medical Association also joined with MSMA to congratulate CVS for its voluntary action to stop selling tobacco products. And just this past June, the AMA called for stricter e-cigarette regulation; that these products be subject to the same regulations and oversight that the U.S. Food and Drug Administration applies to tobacco and nicotine products.

Almost a half a million people die annually in the United States as a result of smoking. Recent estimates show enormous costs to society: $132 billion in direct medical costs and $157 billion in lost productivity. While increases in tobacco taxation, legislation to create smoke-free public areas, and support in smoking cessation has substantially reduced the prevalence of cigarette smoking, pharmacies are the only health care facilities that continue to make tobacco products available in the same setting where diseases are being diagnosed and treated.

In 2010, the American Pharmacists Association urged pharmacies to discontinue sales of tobacco products and urged state pharmacy boards to discontinue issuing and renewing licenses of pharmacies that sell these products. And more efforts are building: the Affordable Care Act provides for employers to charge smokers higher rates for health insurance, and there is a growing trend for companies refusing to hire smokers. The Centers for Disease Control and Prevention has launched its largest anti-smoking campaign to date. Calls for banning tobacco sales in pharmacies have also come from the American Heart Association, the American Cancer Society, and the American Lung Association. Even the World Health Organization code of practice for health professionals prohibits the sale or promotion of cigarettes.



The removal of tobacco products from the shelves of retailers sends a clear message to tobacco users about the danger of tobacco; most importantly, it models a behavior to children that selling tobacco is inappropriate in a facility that purports to encourage good health. Those who wish to promote the goal of better health should recognize the fact that selling tobacco products contradicts that goal.

Sources

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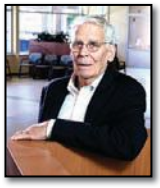
NEWS FROM MISSOURI MEDICINE

Clark Andelin, MD, MSMA member since 2013 from Mexico, has a new office location with Audrain Medical Center, now at 605 E. Promenade Street, Suite A, in Mexico.

Christopher O. Baldwin, MD, of Houston, signed a new three-year contract with Texas County Memorial Hospital and has been an MSMA member for three years now. MSMA wishes him all the best and appreciates his support of organized medicine.

Two valued MSMA members from Hannibal recently returned from a medical mission trip to San Cristobal, Mexico. Welcome back home, **Drs. Deborah Baumann**, member since last year, and **Erik J. Meidl**, member since 1996.

Drs. Sidney B. Belshe of Lohman and **David F. Butler** of Chesterfield were inducted as Fellows into the American College of Radiology during its Annual Convention in Washington, DC, and have been MSMA members for a combined total of 50 years.



John Bentley, MD, MSMA member since 1976 of Springfield, is called the "ideal honoree for this year's Lifetime Achievement Award," by the staff of the Springfield Business Journal. He received the highest honor SBJ has to offer, selected by the Economic Impact Awards independent panel of judges. Dr. Bentley personifies devotion to his profession, community involvement and unremitting service.



After 35-plus years of MSMA membership and surgical practice at Mercy Hospital in Aurora, **Joseph L. Bizek, MD,** was honored with a retirement reception in his name and plaque of appreciation. His loyalty and service to organized medicine has been amazing.



Michael Bukstein, MD, MSMA member since 1976 of Hannibal, now serves as a vpatients in the communities surrounding Hannibal Regional Healthcare System, University of Missouri Health Care in Columbia, Bothwell Regional Health Center in Sedalia, Capital Region Medical Center in Jefferson City and Lake Regional Health System in Osage Beach.



Bradley D. Chrisjohn, DO, has been an MSMA member for a decade now, and was recently appointed to a three-year term on the Board of Directors for Lee's Summit Medical Center.

Kevin Crowe, MD, of West Plains, has been an MSMA member since 2013 and is now using advanced non-surgical techniques to treat abdominal aortic aneurysms at Ozarks Medical Center.

Joseph Dodd, MD, MSMA member since 2010 from Nevada, has joined Cedar County Memorial Hospital, and is now seeing patients in the specialty clinic.

Humam Farah, MD, is a new MSMA member and director of the Hannibal Clinic's Alpha-1 Clinical Resource Center (CRC). He grew up in Jordan and began his medical studies there. Soon he'll be in neighboring nation Israel, where he's partnering with biopharmaceutical company Kamada to create an Alpha-1 testing program for the country.



Ted Garrison, MD, from Lake Ozark, has been an MSMA member since 1959 and was recently honored at a luncheon hosted by Medical Missions for Christ Community Health Center in Camdenton, where a certificate of appreciation from the Board of Directors was presented, thanking him for his years of service to the clinic and community.

Bates County Memorial Hospital hosted a reception and presented **Drs. William Haynie** and **Curtis Long**, both of Butler, with framed proclamations from Missouri Governor Jay Nixon and certificates of appreciation from the board of directors, all of which will be on permanent display at the hospital. Together, they have completed a century of service as family physicians there for 50 years each, as well as supported MSMA as members for 37 years each.



The Cape River Heritage Museum is proud to have nominated **John Holcomb, MD,** for the prestigious Spirit of America award. Dr. Holcomb has been an MSMA member since 1977, which is also when he served as president of Cape Girardeau Area Medical Society.

Bothwell Regional Health Center Board of Trustees Member **David Kuhlmann, MD,** received a Governance Excellence Certificate at the Leadership Forum of the Missouri Hospital Association for completing the voluntary educational program for hospital board members. Dr. Kuhlmann practices in Sedalia and has been an MSMA member since 2007.

Benjamin Lampert, MD, MSMA member since 1985 from Springfield, has been elected to serve as the Missouri Board of Healing Arts president. His term runs through June 30, 2015.

Member since 2012, **Carol R. Martin, MD,** is now accepting new patients at Esse Health in the South County Internal Medicine office in St. Louis

Congratulations goes out to **Gary Mehlhorn, MD,** MSMA member since 1983 from Springfield, who recently joined Mercy Clinic Eye Specialists-Opthalmology-Surgery Center.

Congratulations on your US citizenship, **Drs. Bassem Mikhail** and **Buthaina Richeh,** members of MSMA since coming to Hannibal in 2008 from Syria. Dr. Mikhail presented a free seminar on heart health at the Hannibal Clinic on July 22.



Linda S. Milholen, MD, has been a member of MSMA since 2005 and recently signed a three-year contract with Texas County Memorial Hospital. MSMA wants to wish her all the best in this transition and relocation to Houston, MO.

Jovita Oruwari, MD, MSMA member since 2003 from Ballwin, recently joined Mercy Clinic as a surgical oncologist.



One of MSMA's newest members, **Kavitha Paramanathan, MD,** recently hosted a Lunch & Learn on the Oak Grove Campus in Poplar Bluff. We appreciate her time in educating the public on breast cancer and treatment options.

Luke Pyron, MD, who became an MSMA member last year, recently relocated to Mercy Family Medicine in Carthage after having joined Mercy in Mount Vernon in 2009.

Chris Rosenquist, MD, MSMA member since 1989 from Cape Girardeau, is now providing ob/gyn services at Southeast Health in Dexter.



Mark Shen, DO, MSMA member since 2010 from Osage Beach, recently achieved gold standard credentials from the Hospice Medical Director Certification Board.



Lincoln County Medical Center is pleased to welcome **Ingrid Taylor, MD,** to Troy Medical Group and MSMA is proud to have her as a member since 2011.

Arturo Tenorio, MD, MSMA member since 1979, helped cut the ribbon at a newly-updated Stanberry Rural Health Clinic this summer during a Stanberry Chamber of Commerce-hosted ceremony.

Audrain Medical Center recently welcomed **Reese E. Thompson, MD,** MSMA member since 2003, as their new otolaryngologist.

Continuing the commitment of improving the health of Fayette and surrounding communities, **Hope Tinker, MD,** who is a new MSMA member, has affiliated with Fitzgibbon Hospital in Marshall. The agreement officially changes the clinic name to Fitzgibbon Family Health.

Randall W. Tobler, MD, MSMA member since 1981 from Memphis, has once again been named to the highly-regarded Best Doctors in America List for 2014.

A new MSMA member from Bridgeton and new to the SSM Neurosciences Institute at DePaul Health Center, **Victor G. Williams II, MD,** is a board-certified neurosurgeon specializing in minimally invasive spine surgery, general neurosurgery and other disorders of the back and spine.

For the past 10 years, Mercy Clinic doctors and co-workers in Branson have reached into their own wallets twice each year to help a variety of organizations. This time, their donation goes toward the Gift of Hope Backpack Club, which sends food home with 850 children each weekend. **Adam Wozniak, DO,** who joined MSMA last year, recently helped present a $10,000 check to Gift of Hope.

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The Changing Nature of Academic Health Sciences Libraries

by Paul A. Schoening, MS

Advances in information technology have fundamentally transformed libraries of all kinds, including those serving academic medical centers such as Bernard Becker Medical Library at Washington University in St. Louis.

Thirty years ago we were experts in collecting, cataloging, and searching the expansive journal and book collections housed on our shelves. Our technical services division, whose responsibilities included checking in new journals, requesting duplicates, tracking down missing issues, and maintaining our catalog, was one of the library's largest divisions. Our reference librarians were the primary gatekeepers to the knowledge contained in the library and were essential to anyone needing to search the medical literature. Now, in stark contrast, Becker Medical Library subscribes to fewer than 10 print journals and the technical services division is among the smallest in the library. Specialized online databases such as the National Library of Medicine's PubMed and Internet search engines like Google are increasingly acting as gatekeepers to the literature. So where does this leave academic health sciences libraries and their librarians? It frees them to help their faculty, staff and students navigate the dizzyingly complex and ever-increasing body of biomedical information resources. These resources extend beyond books and journals to include custom databases like those maintained by the National Center for Biotechnology Information, computational software systems for analyzing genetic and proteomic data, and clinical decision support tools integrated within electronic health records. Librarians now include PhD scientists, public health specialists, health communication experts, statisticians and data management professionals, just to name a few, as well as subject expert librarians with intimate knowledge of the published biomedical literature and advanced search techniques. Technological innovation has fostered a flurry of innovation within all libraries, but especially within academic health sciences libraries whose primary mission is to support biomedical research, patient care, teaching and community outreach.



Paul A. Schoening, MS, MBA, is Associate Dean and Director, Bernard Becker Medical Library, Washington University School of Medicine in St. Louis.
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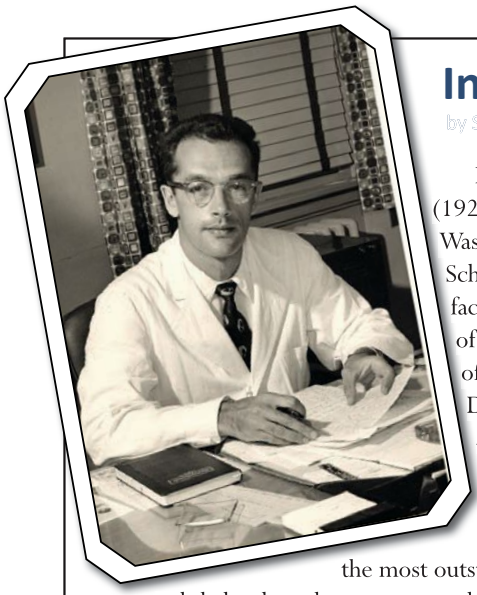
In 2012 Becker Medical Library at Washington University in St. Louis published a report laying out its strategic directions for the next three years.[1] This report identified seven specific areas of future focus while reconfirming Becker Library's commitment to core library competencies. The strategic directions identified are:

- Improve delivery of clinical information at the point of decision making.
- Enhance biomedical informatics support.
- Improve health literacy in the community through partnerships.
- Expand support for authors and focus on measuring research impact.
- Strengthen efforts to preserve the heritage of Washington University School of Medicine.
- Create services to support collaborative science.
- Help researcher share their data.

These directions were influenced by the environmental changes affecting not only the library, but also the School of Medicine, including:

- The changing nature of information, technology and publishing with new models of communicating research results and legislative requirements on public access to research results.
- The changing nature of scientific research with an emphasis on collaboration, demonstrating research impact, and greater attention to accountability.
- The changing nature of patient care with greater emphasis on evidence-based practice, leveraging technology through electronic medical records, emerging requirements stemming from the Affordable Care Act, health literacy, and community health initiatives.

Becker Medical Library is positioning itself to offer resources and services to ensure that our health care



In Memoriam – Bernard Becker (1920-2013)

by Stephen Logsdon, Archivist

Bernard Becker (1920-2013) joined the Washington University School of Medicine faculty in 1953 as Head of the Department of Ophthalmology. During his remarkable 35-year tenure as department chair, Dr. Becker established one of the most outstanding academic ophthalmology departments and residency programs in the country. Under his leadership, the department became internationally known for exceptional research and teaching. Many of his trainees now serve as department heads at other institutions, or hold other prominent positions and leadership roles.

Born and raised in New York City, Dr. Becker attended Princeton University and then Harvard Medical School, both on full academic scholarships. After serving as a captain in the U.S. Army Medical Corps, he joined the Wilmer Eye Institute at Johns Hopkins University as a fellow, and later a resident where he studied with Jonas Friedenwald. By the time of his arrival in St. Louis in 1953, he was already establishing himself as an early leader in academic ophthalmology.

During the course of his outstanding career, Dr. Becker became a world-renowned expert on glaucoma. He discovered one of the first treatments for this disorder when he determined that a drug called acetazolamide, which had been used to decrease pressure in the brain, could also decrease pressure in the eyes. Dr. Becker authored or co-authored nearly 400 articles. He was the co-author of the first two editions of Diagnosis and Therapy of the Glaucomas, one of the classic textbooks in ophthalmology. He was a founding member of the Association of University Professors of Ophthalmology. He served as founder and first editor of Investigative Ophthalmology, and was instrumental in establishing the Association for Research in Vision and Ophthalmology (ARVO). He also played an essential role in the establishment of the National Eye Institute.

Dr. Becker is fondly remembered by colleagues, friends, and library staff for his long-time habit of browsing through the latest medical journals. He would spend hours upon hours reading journals in all branches of science and medicine at the library that would eventually bear his name. Dr. Becker knew the research interests of nearly everyone he was acquainted with, and he would regularly send personalized annotated copies of articles to interested coworkers and students.

Dr. Becker chaired the committee that oversaw the funding, design, and construction of a new library for the medical school. It was completed in 1989, and then renamed the Bernard Becker Medical Library in his honor in 1995. He was a collector of rare medical books, and accumulated over 600 volumes of rare medical books on the sciences of the eye and light. He generously gave his collection to the medical school, where they are housed in the Archives and Rare Books Department of the Becker Library. The Bernard Becker Collection in Ophthalmology and Optics spans some five hundred years and includes works such as Georg Bartisch's 16th century monograph Opthalmodouleia, which was the first comprehensive work on eye diseases and their treatments; two incunabula (books printed prior to 1500), and works by key scientific figures such as Antonio Scarpa and Francesco Redi.

Among the myriad awards bestowed upon Dr. Becker were the Helen Keller Prize, the Mildred Weisenfeld Award for Excellence in Ophthalmology, the Proctor Award, the New York Academy of Medicine Award, and the American Academy of Ophthalmology's Laureate Recognition Award. He also was a recipient of the Washington University Medical Alumni Association's Distinguished Service Award and the School of Medicine's Second Century Award. **MM**

providers, educators, scientists, and administrators all have the information they need to not only succeed, but to excel in carrying out Washington University's mission to "lead in advancing human health through outstanding clinical care, innovative research and the education of tomorrow's leaders in biomedicine."

We are grateful for the opportunity to provide a collection of articles that illustrate the changing nature of medical libraries through the services we provide at Becker Library. Libraries are more important than ever and librarians, whatever their area of expertise, are invaluable partners helping to bridge the gap between need and knowledge.

References

1. The *Strategic Directions 2012-15* document is available to download at https://becker.wustl.edu/sites/default/files/BeckerReport_low.pdf. **MM**

Washington University in St. Louis
School of Medicine

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Measuring Academic Productivity and Changing Definitions of Scientific Impact

by Cathy C. Sarli, MLS & Christopher R. Carpenter, MD

Advances in digital technology afford numerous avenues to disseminate research findings and to document the diffusion of innovations.



Cathy C. Sarli, MLS, AHIP, is the Scholarly Publishing and Evaluation Coordinator, Bernard Becker Medical Library and Christopher R. Carpenter, MD, MSc, FACEP, FAAEM, AGSF, is Associate Professor, Emergency Medicine and Director, Evidence Based Medicine, at Washington University School of Medicine in St. Louis.
Contact: sarlic@wustl.edu

Abstract

This manuscript provides a brief overview of the history of communication of scientific research and reporting of scientific research impact outcomes. Current day practices are outlined along with examples of how organizations and libraries are providing tools to evaluate and document the impact of scientific research to provide a meaningful narrative suitable for a variety of purposes and audiences.

Introduction

As a measure of scientific impact, publication counts alone are an insufficiently descriptive reporting metric of scientific research activities for the public, physicians, scientists, academic institutions and funding agencies. Shrinking biomedical research funding, along with a growing emphasis by key stakeholders to demonstrate tangible and meaningful outcomes, have motivated stakeholders to devise alternative methods that more concretely quantify the impact of scientific research on knowledge diffusion, healthcare professional uptake, and public health outcomes. In order to establish strategic directions, university administrators simultaneously face increased pressure to analyze research productivity and impact, as well as a return on investment from research. Concurrently, funding agencies face public demand via lawmakers to ensure judicious use of taxpayer supported research while promoting the transparency and availability of research findings. The objective of this manuscript is to briefly review existing and emerging means of reporting on and quantifying scientific research impact, ongoing trends towards harmonization of evaluation for reporting of impact, and to present some examples of how academic libraries provide support.

The Historical Context of Scientific Research Communication

Formal reporting of scientific research and the peer review process dates to 1665 with Henry Oldenburg, (See Figure 1), the Secretary of the Royal Society of London, publisher of the *Philosophical Transactions*, the earliest known scientific journal in continuous publication. [See: Philosophical Transactions, Royal Society Publishing: (http://rstl.royalsocietypublishing.org/).]

Scientists during the Renaissance were reluctant to share their scientific discoveries out of concern that others would claim their work. To address this concern, Oldenburg implemented

a series of practices that established the process of modern day peer review. He appointed members of the Royal Society as independent experts to review manuscripts before approving for publication. By registering authors and manuscripts, i.e., "time stamping" of new scientific findings, Oldenburg's methods obligated others to "cite" findings in subsequent manuscripts and ensured a regular schedule for publication of the accepted manuscripts in Philosophical Transactions.[1] The Royal Society of London's practices were the precursors to modern-day principles of scientific communication and peer review, of which scholarly journals operate in their role to communicate scientific research findings.



Figure 1
Henry Oldenburg in a portrait by Johannes van Cleef.
Image courtesy of the National Library of Medicine.

The capacity for physicians and scientists to find applicable scientific literature from the 17th to early 20th century was rudimentary at best. To keep abreast of contemporary scientific discoveries or clinical findings physicians and scientists relied on journal subscriptions, catalogs containing a list of items held by a library, case histories, medical society memberships or correspondence with others in their field.[2] In the United States (U.S.), print bibliographic indexes or bibliographies on a specific subject to locate scientific literature were not available until the latter part of the 19th century. Bibliographic indices are collections of references to the published literature generally arranged by subject and/or by author names. In 1879 Index Medicus (the print precursor to MEDLINE®/PubMed®) was introduced and allowed for an additional means of discovery of scientific research findings.[3]

Bibliometrics: One Step Forward

During the 20th century peer review was a proxy for impact, with the quantity of peer-reviewed journal articles or monographs serving as leading indicators of one's research penetration and professional community recognition for evaluation purposes as exemplified by the "publish or perish" philosophy coined by Logan Wilson in 1942.[4] The large influx of U.S. governmental funding for health research following World War II led to an increase in the number of scientific journals to meet the demand of scientific research reporting. The proliferation of journals and articles spurred the development of bibliographic tools to manage and index peer-reviewed scientific publications. Eugene Garfield in his seminal work from 1955 suggested the possibility of a citation index based on mechanical means to control and track the scientific literature.[5] This led to the development of an index of scientific literature in the early 1960s based not only on indexing of the literature on a specific subject, but also indexing citations to the literature, the Science Citation Index, precursor to the Thomson Reuters Web of Science database.[6] Journal Citation Reports (JCR) followed in 1976, which introduced the Journal Impact Factor score for peer-reviewed journals.

Eugene Garfield and Irving Sher, founders of the Institute for Scientific Information (later absorbed by Thomson Reuters) proposed the JCR Impact Factor score in 1963 as a means of comparing peer-reviewed journals regardless of size. This metric was also used as a journal selection tool for inclusion in the Science Citation Index and later as an acquisitions tool by libraries.[7] The Science Citation Index and Journal Citation Reports were ground-breaking resources that provided new means of quantifying the scientific literature and paved the way for new proxies for impact: citation counts and the JCR Impact Factor score. Tenure and securing external funding gradually became associated with publishing in "high impact" peer-reviewed journals and how frequently an investigator's publications are cited.[8]

The development of automated systems for management of publication data and methods of analysis fostered new areas of study, in particular bibliometrics, a term introduced by Alan Pritchard in 1969.[9] Studies in bibliometrics that outlined the applications of publication and citation data for measuring scientific impact spurred the U.S. government and the National Science Foundation (NSF) to adopt metrics available from Science Citation Reports and Journal Citation Reports for reporting purposes.[10, 11] Academic institutions soon followed suit.

For varied reasons, the JCR Impact Factor score evolved into a proxy for individual author's impact or influence of their published works, however unintentional.[12] The higher the JCR Impact Factor score of a journal, the more prestigious any manuscript in that journal was deemed

to be. Garfield stressed that the JCR Impact Factor score was designed as a metric for journal performance and warned against its use to evaluate scientific articles and authors.[13] One reason for wide-spread use of the JCR Impact Factor score is that it was, and still is, an easy-to-find single numeric score, and does not require extensive knowledge of database searching. Another reason favoring use of the JCR Impact Factor score as a universal metric for author impact is that the interfaces of the early citation databases were crude. Many physicians and journal editors lack any bibliometric database training or familiarity. To construct a search query for citation analysis required third-party mediation from experts (usually medical librarians) who were familiar with formulating queries, reconciling author name variants, data idiosyncrasies, and capable of interpreting the results.[14]

Moving Beyond Citations and the JCR Impact Factor Score

Although citations and the JCR Impact Factor score have been used as an indicator of influence and impact for decades, the landscape is changing.[15, 16] Advances in computer and digital technology along with the general availability of the Internet spurred the development of additional resources. In 2004, two new citation data resources were introduced: Google Scholar (http://scholar.google.com/), and Elsevier Scopus (http://scopus.com). In 2005, Hirsch introduced the h index which is derived from a formula using publications and citations to provide "an estimate of the importance, significance, and broad impact of a scientist's cumulative research contributions."[17] The h index is based on a formula that includes the "X" number of an author's publications and the number of citations that have been cited at least "X" times. For example, an author with an h index of ten has ten publications that have been cited at least ten times. Although the h index is increasingly recognized as a viable and even preferable alternative to the JCR Impact Factor score and raw citation counts to quantify academic productivity, it is not a perfect measure of one's academic portfolio. First, the h index ignores bedside clinical instruction, journal editing, mentoring, and textbook authorship without which academic medicine would cease to exist. Second, the h index is simply a construct based upon citations, which does not necessarily measure clinical relevance.[18]

The attempt to develop one-size-fits all metrics to measure productivity and impact for all disciplines and authors remains elusive despite the numerous attempts to do so. Among the many derivatives are: the v index[19] which includes the proportion of time devoted to research to normalize for clinical academicians who may devote only 40 to 50% of their time to research; the Absolute index (Ab index)[20] which takes into account the impact of research findings while weighting the physical and intellectual contributions of the researcher; and the hi-5 index![21] which is the h index over a five year period, to name a few.

Table 1
Examples of Article-Level Metrics

- Citations from works in bibliographic databases and repositories
- Online downloads of a work
- Online views of a work
- Bookmarks to a work from online reference managers such as Mendeley
- Mentions of a work in social network sites such as Twitter or Facebook
- Discussions of a work in blogs or by mass media technologies
- Favorites/Recommendations of a work in platforms for sharing of works such as in Slideshare, Figshare or YouTube
- Comments/annotations for a work noted in online commenting platforms such as PubMed Commons

Article-Level Metrics

Sophisticated publisher platforms and social media applications have resulted in a new set of metrics beyond citation counts that provide for tracking of a work (journal articles, books, slides, software, conference papers, data sets, figures, etc.) based on usage at the document level unit of analysis. Article-level metrics represent "tallies" based on usage and the social or public engagement of a work that can be captured in order to determine how a work is shared among others, commented upon, recommended, viewed, downloaded, cited in bibliographic databases, or saved in online reference managers.[22, 23] Some article-level metrics are more scholarly in nature, and perhaps more meaningful within the context of end-user uptake since they are documented in the literature (i.e., citations) or either tied with specified technology parameters (i.e., downloads and views). Other article-level metrics remain to a point, anonymous and transient, but nonetheless, can serve as an early harbinger of the potential influence of a work (i.e., comments, mentions, favorites, bookmarks, recommendations). See Table 1 for examples of Article-Level Metrics.

Article-level metrics are available from various publisher sources and platforms, software applications, and databases. These metrics can serve as complementary measures of impact to citations, empowering authors to highlight multiple examples of scholarly output and reach beyond the traditional peer-reviewed journal article.

Recent Trends for Reporting of Scientific Impact by the Government, Funding Organizations and Publishers

The trend from bibliometric-based measures to quantify the overall value of research outputs is slowly shifting towards more meaningful outcomes of measurable impact. The U.S. Government and funding bodies are taking notice of performance and impact measures with an emphasis on outcomes that transcend bibliometrics. The National Institutes of Health (NIH) (http://grants.nih.gov/grants/glossary.htm) currently defines 'impact' as "the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved." In 2012, the NIH began implementation of a new standardized research performance progress report, (RPPR), (http://grants.nih.gov/grants/rppr/), as a means of harmonizing the reporting of federally-funded research across all governmental agencies that disburse extramural funding. One section of the RPPR is "Products" and includes not only publications, but also other products such as websites that disseminate the results of research activities, inventions, technologies, patents, software, databases, etc. Another section is "Impact" and grantees are instructed to report on ways that their research has had an impact. The National Science Foundation's Biographical Sketch includes a section titled "Synergistic Activities" to allow for listing of examples that demonstrate the broader impact of an individual's professional and scholarly activities (http://www.nsf.gov/pubs/gpg/nsf04_23/2.jsp).

Agencies such as the National Institute of Environmental Health Sciences (NIEHS) have implemented strong evaluation programs that emphasize reporting of qualitative-based outcomes and produced a manual: Partnerships for Environmental Public Health: Evaluation Metrics Manual, (http://www.niehs.nih.gov/research/supported/assets/docs/a_c/complete_peph_evaluation_metrics_manual.pdf). The Centers for Disease Control (CDC) has developed the Science Impact Framework, (http://www.cdc.gov/od/science/impact/) which utilizes a combination of quantitative and qualitative indicators to measure impact towards health outcomes, through five levels of influence: disseminating science, creating awareness, catalyzing action, effecting change, and shaping the future. Of particular interest is the inclusion of metrics that reflect indicators of "internal" impact such as new collaborations or partnerships that reflect on the organization and investigators themselves as opposed to external impact indicators such as public health outcomes.

Research organizations and universities also face increased pressure to report on research outcomes and to demonstrate a return on investments. Research organizations and universities have joined with funding agencies to develop methods that enhance the transparency of research findings and to document tangible outcomes for the public. One effort is the Science and Technology for America's Reinvestment: Measuring the Effect of Research on Innovation, Competitiveness and Science, or STAR METRICS project, (https://www.starmetrics.nih.gov/), launched in 2010. STAR METRICS is an effort led by the NIH and the NSF under the auspices of Office of Science and Technology Policy (OSTP), in collaboration with research organizations and universities. The objectives for STAR METRICS are to establish uniform and auditable measures of the impact of science spending and to develop measures of impact on scientific knowledge, social outcomes, workforce outcomes and economic growth. Specific metrics and testing of the metrics are still in development as of this writing.

Publishers are also stressing the need for improving the methods of evaluating and reporting on impact from scientific research. The San Francisco Declaration on Research Assessment (DORA), (http://am.ascb.org/dora/), recently issued a set of recommendations urging funding bodies, publishers and institutions to avoid use of the JCR Impact Factor score as a means of assessing research impact or scientific quality. DORA also stressed the use of other metrics to shift the focus towards the scientific content of an article rather than the publication metrics of a journal. Among other metrics suggested by DORA are article-level metrics, the scientific content of a publication, the influence of a work on policy and practice, and the h index. DORA also emphasizes the recognition of research outputs beyond the peer-reviewed journal article.

The Role of Libraries

Evaluation of scientific research findings and activities is an increasingly important effort by academic medical libraries. New resources and evolving recognition by funding agencies allow medical libraries to demonstrate transformative service models as essential consultants by leveraging expertise of literature searching (published and unpublished) to retrieve information that quantifies scientific impact based on bibliometrics and other measures. Evaluation and consultation to assess productivity and impact can occur at the individual author level; the department level; the research group level, including physical or virtual research groups; the institutional/university level; or for a transient population such as scholars/trainees in which longitudinal tracking is required for reporting purposes. Some libraries are going beyond use of traditional bibliometric evaluation methods by using social network

Note to Readers

If you are not affiliated with an institution that has a subscription to a citation database such as Elsevier Scopus or Thomson Reuters Web of Science, consider using Google Scholar (http://scholar.google.com/), a freely available resource. Google Scholar allows for searching of scholarly literature and citations, and includes a feature for authors to create a personalized profile that contains a listing of publications and citations, affiliation information, and contact information to allow for discovery of your works. By creating a profile, your profile appears when a search of your name is executed in Google Scholar. After a profile is created, publications and citations will automatically be added to your profile and metrics such as the h index and the i10-index are available. Privacy settings for the Google Scholar profile are controlled by the individual.

tools to illustrate impact in the translational environment of the millennial generation.[24]

Medical librarians possess skill sets that are well-suited for conducting evaluation of research findings: familiarity with various database and resources, knowledge of the scholarly processes for dissemination of scientific research, formulating search queries, reconciling author variant names, capturing data from databases, and providing reports based on publication data. Librarians can also provide consultation and reports for specific purposes such as benchmarking, tenure/promotion, recruiting, performance, and funding applications and renewals as well as recommending bibliographic resources or other databases.[25] Some libraries are creating frameworks for scientists to identify qualitative outcomes beyond publication data for documenting and quantifying meaningful health outcomes. One example of a framework developed by a library is the Becker Model, a framework for assessment of research impact that includes a list of over 300 examples of biomedical-based outcomes including bibliometric measures.[26] The outcomes are grouped under five pathways represented by the research cycle with multiple examples noted for some outcomes. Evaluation services provided by libraries have parlayed into invaluable partnerships with campus units with some librarians serving as official members on tracking and evaluation teams affiliated with Clinical and Translational Sciences Awards (CTSA).[27] The Becker Model is currently being used by the Washington University Institute of Clinical and Translational Sciences (http://icts.wustl.edu/) for evaluation purposes. See the Assessing the Impact of Research website: (https://becker.wustl.edu/impact-assessment/) for more information.

Conclusion

Crafting a narrative of scientific research impact is a daunting task. Strides have been made in recognizing that impact transcends publication counts. Impact includes both improvement in public health outcomes and other outcomes correlated with the diffusion of knowledge such as new research collaborations focused on a specific area of study, synthesis into clinical applications, or influence on public policy. These advances in the quantification of "impact" are occurring in tandem with efforts to harmonize reporting of research activities and outputs. The future holds great promise for a more complete and illuminating narrative of the multilevel impact of scientific research. Advances in digital technology afford numerous avenues to disseminate research findings and to document the diffusion of innovations. The capacity to measure and report tangible outcomes can be used for a variety of purposes and tailored for various audiences ranging from the layperson, physicians, investigators, organizations, and funding agencies.

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Libraries and Open Access Support: New Roles in the Digital Publishing Era

by Robert J. Engeszer, MLS & Cathy C. Sarli, MLS

Academic libraries are taking a proactive role by developing service programs to reduce barriers faced by authors and utilizing technology and licensing alternatives to promote accessibility to scholarly works.



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Introduction

The emergence and growth of Open Access (OA) publishing stands as one of the most significant changes to the world of scholarly communication since the migration to digital publishing began over a decade ago. In simplest terms, the definition of OA put forth by Peter Suber in 2004 is still quite accurate – "Open access (OA) literature is digital, online, free of charge, and free of most copyright and licensing restrictions."[1] With an overriding goal of using the Internet to remove barriers to accessing scholarly and, in particular, peer-reviewed scholarly works, early proponents seized upon the potential of OA to transform the scholarly communication process and asserted that sharing of scholarly works would spur innovative scholarly practices, accelerate discovery of research findings, and enhance access to scholarly the scholarly record.

The benefits of OA appear to be mutually beneficial to all of the major participants in the scholarly communication process. Authors could reach a wider audience and share their scholarly works with scholars and the public. Enhanced transparency of research findings would allow funding agencies to report on benefits and return on investment to taxpayers and governments. At the same time, university libraries would be afforded relief to their collection budgets as publishers adopt alternative business models that shift subscription costs from institutional subscribers to a system of fees paid by the author, the author's institution, or the funding agency supporting the work.

But despite all of these advantages and while making great strides over the past decade, OA has yet to establish itself as the predominant model of scholarly communication. Significant barriers still exist to achieving that goal. Publishers are resistant to change of longstanding cost recovery models, authors are apprehensive about publishing in journals that could negatively impact tenure and promotion decisions, and both groups are wary of the implications that OA can have on copyrighted material.

Academic libraries have a vested interest supporting open access

publishing and are playing significant roles in its growth and progress. The fundamental mission of any library is to connect people with information and the goals of OA make librarians a natural advocate for promoting greater access to scholarly works. How advocacy and support for OA has evolved illustrates the creative ways that libraries are adapting to the changes in scholarly communication process and their relationships with publishers and authors, and the dissemination of information.

Libraries and Scholarly Communication

Academic libraries have been involved with issues that fall under the broad category of "scholarly communication" for decades. While many of the initial support programs developed by libraries focused on fair use and copyright restrictions, the scope of activities has since expanded to include topics such as author rights, promoting the use of institutional repositories[2] and, most recently, using publication metrics and other indicators to analyze the impact of research.[3] Interest and demand for information in all of these areas has led many academic libraries to establish formal scholarly communication programs with dedicated librarian positions to develop support programs. For many libraries, initiatives related to OA are a logical extension of their scholarly communication programs which reflect the particular interests, needs and prevailing attitudes of the institution. In the case of OA this is particularly true as its perception as a global movement has created equally passionate advocates and critics within the academic and publishing community. From this perspective, acting as a credible source for useful and objective information is a valuable role for libraries to play and serves as a foundational element of many scholarly communication programs.

The education and guidance libraries provide on OA has assumed many forms. In a 2010 presentation, Brian Rosenblum listed specific ways that librarians are currently supporting OA practices and policies and advising faculty in their roles as instructors, authors, and publishers:[4]

- Assisting with rights and permissions;
- Maintaining scholarly communication websites;
- Organizing workshops on copyright issues and digital scholarship;
- Advocating through university governance and administrative channels, to shape discussions of open access policies;
- Educating and training other librarians and students.

Educating others is a traditional role for libraries to assume with a growing number taking a more proactive role in promoting the benefits of OA. Supported by initiatives such as the Scholarly Publishing and Academic Resources Coalition (SPARC) developed by the Association of Research Libraries and the Harvard University Office for Scholarly Communication, academic libraries are developing mechanisms and services to reduce some of the barriers to OA publishing that confront authors. SPARC has developed numerous education resources including webcasts and podcasts covering a wide range of OA related topics such as author rights, open access funding mechanisms, and public access mandates. At the local level, libraries such as Becker Library at Washington University in St. Louis School of Medicine have established support programs to educate authors on retaining the rights they need to reuse and disseminate their work and providing guidance on alternative and less restrictive licensing models such as Creative Commons.

Reducing Barriers

While education and awareness serves as the foundation for OA support at a majority of academic libraries, a growing number are addressing barriers that authors face when considering OA as a publishing option. These barriers can be financial, institutional, and sometimes, depending on the subject discipline, cultural. It is in this area that libraries are demonstrating their commitment to OA by devising creative strategies and solutions to reduce these barriers in significant ways.

Campus-based Funding Support for OA

Perhaps the biggest barrier that authors face when choosing to publish in an OA journal is the cost. A large number of "gold" OA journals require authors to pay a fee to publish an article. Many funding agencies allow for use of funds to defray article publication charges but the pressures to stretch limited research dollars make this choice unappealing, if not impossible for many authors. To address author inability or

reluctance to pay for article publication charges, campus-based open access author funds are being considered by some academic libraries. The Compact for Open-Access Publishing Equity (COPE) is one example of how academic institutions and libraries are committing to OA by establishing funds to subsidize article publication charges. To date over fifty academic institutions are participating in COPE either as signatories or supporters.[5] Established OA publishers such as PLoS and BioMed Central also provide substantial discounts to authors from institutions that purchase supporting memberships with a number of libraries subsidizing these memberships on behalf of their institutions.

Institutional Repositories

For authors seeking to enhance the visibility of their work to the broadest possible audience, self-archiving through an institutional repository (IR) represents a less costly path to OA. Often described as a form of "green" OA, institutional repositories can contain many types of documents including preprints, postprints, or both. While most institutional repositories do not require peer-reviewed materials they generally host published materials including the final, peer-reviewed manuscript submitted to a non-OA journal. Libraries are at the forefront of advocating for and supporting IRs and the benefits to their authors of self-archiving. The number of academic libraries who maintain an IR on behalf of their institutions has grown dramatically over the past decade. According to the Directory of Open Access Repositories, in 2011 there were over 2,200 open digital repositories worldwide.[6] While the benefits of greater discoverability, accessibility and flexibility in the types of material that can be stored are compelling to many authors, the growth in the adoption of self-archiving practices has been slow. The lack of time, resources, and concerns about copyright issues are often cited as reasons for lack of IR participation by faculty.[7]

Libraries are taking a leadership role in reducing barriers to IR participation. At Washington University School of Medicine's Becker Library staff members assume responsibility for copyright clearance, metadata creation, and submission of all materials to the Digital Commons@Becker IR (http://digitalcommons.wustl.edu/) on behalf of authors. The library's "full service" approach has greatly enhanced faculty interest in using the IR and allowed staff to shift the focus of their efforts from training faculty in the mechanics of building a collection for themselves to collaborating with faculty and research groups to enhance the visibility and scope of their work.

OA and Public Access Mandates

One approach to encouraging OA used by a growing number of institutions, funding agencies, and research programs is the adoption of self-archiving and/or public access mandates. In the biosciences, the mandate most familiar to authors is the Public Access Policy (PAP) implemented in 2008 by the National Institutes of Health (NIH). The NIH PAP requires authors to submit the final, peer-reviewed manuscript version of their NIH-funded works to PubMed Central (PMC) upon acceptance of publication in a journal, with public access to the full text available within 12 months of publication. Works in PMC are protected under copyright laws and access to the works is governed under fair use. While the specific intent of the NIH PAP represents a narrower component of the overall OA movement, its immediate impact on scholarly communication cannot be understated. For many libraries, the NIH PAP provides an opportunity to introduce a number of often misunderstood scholarly communications issues, including OA, and serves as justification for expanding support services that include guidance with compliance and direct submission services to PMC on behalf of authors. One year following the launch of the NIH PAP, almost half of the 123 member institutions of the Association of Research Libraries reported having support programs already in place and the success of these programs has been clear.[8] As one of the more established library-based NIH PAP service programs in the country, Becker Library has provided more than 1,500 individual consultations and over 100 formal presentations and workshops since the program began in 2008. In conjunction with these activities, Becker Library also offers extensive web-based guidance and documents for NIH-funded authors and support staff. These efforts are representative of support programs libraries provide to assist authors with public access mandates.

The impact of the NIH PAP continues to be felt throughout the federal government and has been the

impetus for further initiatives. In 2013, the Office of Science and Technology Policy (OSTP) directed all federal agencies with more than $100 million in R&D expenditures to develop plans to make the published results of federally funded research freely available to the public within one year of publication. As with the compliance support programs for the NIH PAP, efforts are currently underway at many academic libraries to support authors in complying with the OSTP directive.

Government mandates for public access to taxpayer funded research is a highly visible, and much debated, aspect of the OA movement. While not as prevalent, OA mandates by academic institutions are equally controversial and libraries are playing prominent roles in supporting these types of initiatives.

In February 2008, Harvard University's Faculty of Arts and Sciences passed an OA policy granting a license to the university to share their scholarly journal articles openly in an institutional repository and mandating faculty to submit their works. Consequently, other academic institutions in the United States considered similar initiatives. By 2011, 122 institutions worldwide had implemented some form of open access self-archiving mandate.[9] Libraries actively participated in discussions and policy formulations at many of these institutions and while few issued required mandates, most implemented resolutions that highly encouraged authors to consider OA options for dissemination of their scholarly works, as with the resolution passed by the Washington University in St. Louis Faculty Senate in 2011.[10]

Libraries as OA Publishers

The growing acceptance of OA publishing has also afforded libraries with opportunities to assume the role of publisher. While library publishing in itself is not a new activity, the greater availability and affordability of digital publishing platforms are providing libraries the option of working with campus authors to explore new methods of communicating and disseminating their research results. Open source and commercially available publishing platforms are being used to publish OA books and monographs, create OA versions of out-of-copyright works, and to start "in-house" scholarly journals that highlight the works of institutional authors including faculty and students.[11, 12]

Conclusion

Since OA was first introduced ten years ago, traditional publication modes have been supplemented with publishing in OA journals. While many authors recognize the benefits of OA, some authors are deeply vested in traditional publishing practices. Academic libraries often walk a fine line between promoting OA while supporting authors who prefer to publish in non-OA publication modes. Despite this challenge, academic libraries are taking a proactive role by developing service programs to reduce barriers faced by authors and utilizing technology and licensing alternatives to promote accessibility to scholarly works. Libraries have a vested interest in ensuring continued access to the scientific record and are devoted to efforts to increase awareness among authors of the various issues that have an impact on scholarly practices to provide opportunities for dissemination of the scientific record without barriers.

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None reported. **MM**

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Libraries and Genomics: Providing Support to Health Care Providers and Consumers

by Karen E. Gutzman, MA, Marcy L. Vana, PhD & Kristi L. Holmes, PhD

As increasing genomic knowledge continues to lead to dramatic changes in medicine, the responsibility of sifting through the swell of information becomes a heavier burden.



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Introduction

Genetics and genomics play an increasingly important role in many different facets of healthcare. We are all familiar with what might be thought of as typical genetic diseases – those disorders which involve an abnormality in a chromosome or in a specific gene that tend to run in families and result in a rather dramatic phenotype. This is only part of the story, as a patient's genomic information can influence their susceptibility to disease, presentation of symptoms, treatment options, and interventions. As we elucidate the more subtle influences and intricacies in the relationship between genes and health, we will likely see the practical dialog about these topics increase as well. Information support for physicians and patients is a critical need. Some of the biggest challenges physicians face as they begin to integrate genetics into practice are access to and knowledge of information resources to support their own education and to develop an awareness of key issues and concepts in the field. Compounding these challenges for physicians is a patient population that is increasingly aware of the link between genetics and health, but usually untrained in critical appraisal of health information resources and how to find credible health information resources, and support and advocacy resources in the community.

Genetics and Missouri

Missourians are faced with a number of health issues, many of which have a genetic component. The 2012 Missouri Vital Statistics report[1] lists the top twelve causes of death for Missourians (See Table 1). Of these twelve, it is worth noting that every cause has been linked to the concept of genetics in the literature in some manner, with nine out of the top twelve demonstrating a considerable increase in the link of genetics with the disease in the biomedical literature (See Figure 1). This connection in the literature between genetics and disease isn't surprising, given the remarkable rate of advancement in technologies and discovery in this arena. Before the human genome project began in 1990 and since its completion in 2003,[2] there has been a substantial effort to try to understand the influence our genes have on human health.

Genomics already plays a role in how care is provided in a variety of ways and across the lifespan of Missourians. The State of Missouri

requires all newborns be screened for a wide range of diseases and disorders.[3] Maternal screening can also play an important role for mothers in certain risk groups. Most recently, we've seen widespread application of a technique that detects fetal DNA from a small amount of maternal blood. Cell-free DNA testing is most commonly used to detect autosomal aneuploidies[4] and more recently, demonstrates promise for whole-genome sequencing of fetuses for better screening of Mendelian disorders.[5] As these types of non-invasive tests become more widely available – and as their sensitivity and specificity increases – physicians and patients alike are offered an opportunity to detect abnormalities and more effectively shape the way that care is provided.

Pharmacogenomics is a concept that has moved from the research lab to the doctor's office. With pharmacogenomics, individual genomic variations are considered when delivering therapeutics in order to ensure a more targeted and appropriate response from the patient. There are several examples of this in practice, including application of the antiretroviral drug abacavir and administration of Trastuzumab (Herceptin) to breast cancer patients with mutations in the HER2 gene.[6] Genetic screening can also help physicians target interventions for certain cancer signatures (BRCA 1/2 and colon cancer)[7] as well as help identify people who may be at increased risk of developing either early-onset

Table 1. Causes of death of Missouri residents, 2012.[1]

Causes of Death	Percent Of Total
Diseases of heart	24.4
Malignant neoplasms	23.0
Chronic lower respiratory disease	6.5
Unintentional injuries	5.4
Cerebrovascular diseases	5.3
Alzheimer's disease	3.3
Diabetes mellitus	2.5
Nephritis and nephrosis	2.2
Influenza and pneumonia	2.2
Suicide	1.6
Septicemia	1.4
Chronic liver disease and cirrhosis	1.0
All other causes	21.2
Total (All Causes)	**100**

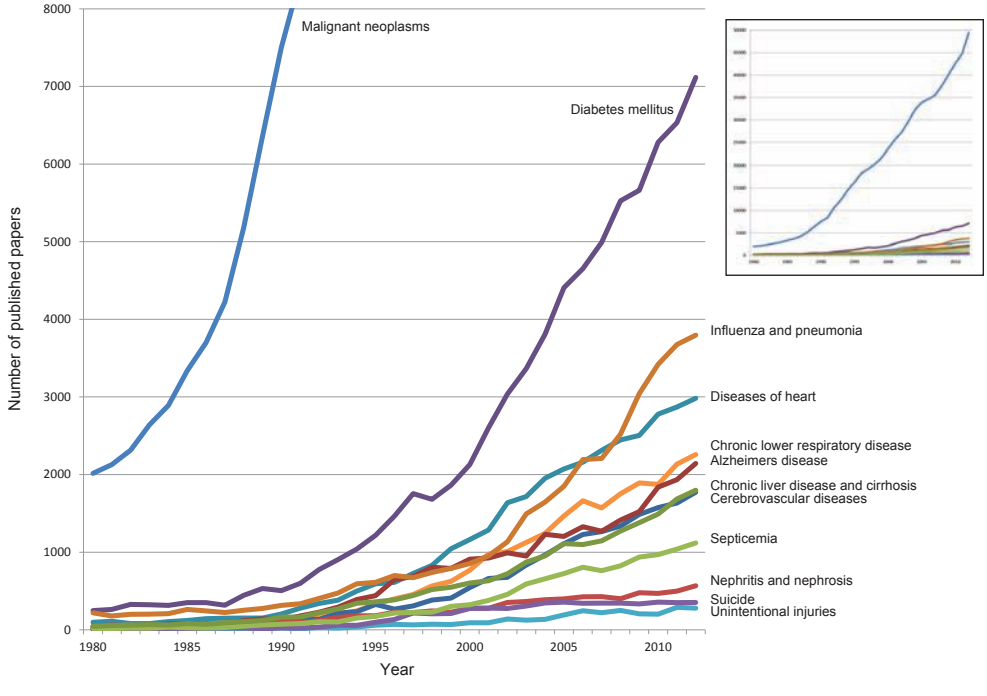


Figure 1

Increased usage of genetic terminology in conjunction with health conditions in primary literature, 1980-2012. Disease areas were selected based on causes of death of Missouri residents in 2012, as shown in Table 1.1 Literature search strategies were created using Medical Subject Headings and Emtree controlled vocabularies as guides to find top-level key words. All searches were run in the Scopus database on 1/31/2014. Search strategies available in DigitalCommons@Becker (http://digitalcommons.wustl.edu/becker_pubs/46/).

or late-onset Alzheimer's disease by looking for variations in a number of specific genes that may increase a person's likelihood of developing the disease.[8]

Knowledge is a very powerful tool for physicians and patients, alike. The ability to understand that one may be at increased risk for developing a disease, or for a family to know they may be caring for a special needs child, offers a rare opportunity for the physician and patient to be proactive. Providers can refer patients to credible information resources and support groups, while patients and their families can consider their personal and family needs and engage with resources that fit their circumstances.

The Pressure for Quality Information

How does a health care provider stay on top of such a challenging aspect of research and medicine? Certainly, there is so much for today's practicing physician to know, and rapidly changing technology and discovery make it difficult to stay current and understand how knowledge in this area can be applied to improve diagnostic and treatment workflows in a practical way. Over the past several years, there has been a significant need for physicians to provide information support for patients around topics such as basic information on a disease or treatment, direct-to-consumer testing, and a real need to be aware of support and advocacy organizations and resources for patients and their families.

While the task of identifying resources to support these information needs might seem straightforward, the critical appraisal and evaluation of key resources in a sea of online information is a daunting task, indeed. Time and patience are required to sift through all of the available information and determine which might provide the most accessible and credible information. Fortunately, numerous agencies, support groups, and organizations are dedicated to providing credible resources and information – at a variety of levels – to support information needs related to genetics in medicine. While some groups focus on either physicians or providers, there are many that offer a wide range of credible resources to support the vast body of information needs in genomic medicine. We'll discuss a few of these resources for physicians and patients and their families more fully below.

Physician Information Needs

Several organizations offer meaningful resources to support information needs physicians may have in topics related to genetics and genomics. The National Coalition for Health Professional Education in Genetics (NCHPEG)[9] is dedicated to education and information support of human genetics and health. Among the site's many resources are targeted education materials, a range of core competencies (ranging from core principles in family histories to principles of genetics in common diseases), and CME materials that can be licensed to hospitals and health systems to support local needs. NCHPEG also makes a suite of point of care tools available which support collecting family history information, communicating risks to patients, addressing ethical and legal issues in the field, and GeneFacts,[9] an ongoing effort to make accessible information about genetic conditions accessible and integrated at the point of care. Another key resource for physicians is GeneTests,[10] a medical genetics information resource which provides current, authoritative information on genetic testing and how it can be applied in the clinic with diagnosis and disease management. GeneTests provides a directory of laboratories offering molecular genetic testing and clinics that provide diagnostic support and genetic counseling. GeneTests also provides a wide range of additional supporting information on genetic panels, individual genes, and substantive information on a large number of disorders.

Patients and Their Families

There are a number of excellent resources for patients and their families or advocates, as well. These resources offer reliable health information in a straightforward and accessible manner. MedlinePlus[11] is one of the best resources for a wide range of consumer health information needs. The resource is made freely available by the U.S. National Library of Medicine, and offers a wide range of information, including information about genetic disorders, genetic counseling, genetic testing, and specific diseases. Genetic Alliance[12] is a nonprofit health advocacy organization committed to transforming health through genetics and promoting an environment of openness centered on the health of individuals, families, and communities. Their website offers many wonderful resources, centered on three main project areas: Biotrust (focused on research participation and ethics), Expecting Health (focused on fetal and childhood genetic screening and testing), and Genes in Life (focused on providing quality information to the public about genetics and genomics, the role of genes in health, and access to a wide variety of support

resources). The site provides access to a wide-reaching network of academic institutions, public policy groups, public and private companies, and over 1,200 disease-specific advocacy organizations. A resource of note is DiseaseInfoSearch,[12] a resource to connect people to information and support resources for more than 13,000 specific diseases and conditions.

Resources for Everyone

The National Human Genome Research Institute (NHGRI)[2] provides a massive amount of information to support a wide range of information needs. The Institute takes their educational mission seriously and, along with their stellar resources for educators and students, they record lectures and educational sessions held on the NIH campus and make them available on GenomeTV.[2] One of the most recent tools made available through NHGRI is the "Talking Glossary of Genetic Terms,"[2] a resource to help anyone understand genetic terms. This resource is particularly helpful if one is uncertain of the proper way to pronounce a term, as well. The Institute provides meaningful information to support information needs and enhance understanding on many complicated ethical, legal, and social issues in genetics. Health care providers and the public can access relevant information targeted to them under the "For You" and "Health" headers on the website. Topics for the healthcare provider include "Genetics 101 for Health Professionals" and "Quick Links for Patient Care" among many others. Similarly, topics for patients include "FAQ about Clinical Research" and "A Brief Guide to Genomics" among many other topics.

Another widely used resource is Genetics Home Reference,[13] provided by the U.S. National Library of Medicine, which offers a "consumer-friendly" resource for anyone wishing to learn more about the relationship between genetics and human health. There is specific information about genetic conditions and individual genes as well as accessible background information and links to support understanding of a wide range of conditions and topics in genetics. This is a great resource for anyone who would like to gain a good foundation-level understanding of topics in this area.

The Role of Libraries

Libraries have a long-standing tradition of supporting the information needs of a variety of stakeholder groups, and we see this commitment to service continue as we move into the era of genomic medicine. Libraries provide meaningful support in a variety of ways:

- Librarians have long-provided advanced literature searches to support diagnosis and treatment and continue to do so on emerging topics related to genomic medicine. Librarians themselves are part of the point of care team, providing information support during rounds.
- Libraries often provide access to diagnostic and other point of care tools and offer support so that these resources can be effectively integrated into the clinical workflow. Clinical information specialists often have advanced training in medical fields (usually RN or MD) and can even help keep clients aware of advancements in diagnosis and treatment options.
- Providing accessible and credible health information to the public is a key area of effort in a number of libraries. Many libraries have a full-time consumer health librarian who can refer the public to information resources or even prepare packets of information on specific topics when ordered by the physician through the electronic health record.
- Librarians can help identify open clinical trials for physicians and their patients.
- Researchers can receive specialty information support from library personnel in areas such as data management, data analysis, and manuscript preparation. A number of libraries license research tools and databases for their affiliated researchers. Library staff members who provide this type of support often have advanced training in the sciences.

Support Efforts at Becker Library

The Bernard Becker Medical Library has two senior support scientists on staff with experience in bench research and data analysis. These staff members provide consultation support for research questions, assist with accessing appropriate databases and datasets, organize training workshops on research resources and software tools, and coordinate site-wide licenses for essential pieces of research software. Though the support scientists' primary support focuses on the basic science research community, the team continues to provide more support to the clinical research and clinical care

communities. Over the last few years, they've reached out in a number of new ways to support growing information needs in genomics on the Washington University in St. Louis School of Medicine campus.

The Library strives to create an enriching environment for the scholars, physicians and researchers at Washington University in support of genomic medicine. As part of this effort the library has facilitated educational programming on campus through the Genomics & the Era of Personalized Medicine seminar series. This series is the first of its kind collaboration between the Departments of Genetics, Medicine, Pathology & Immunology, Pediatrics, and Becker Medical Library. The series offers a practical background in molecular biology, an introduction to genomic research and applications of genomic technologies in the research environment, and an understanding of the clinical application of gained knowledge. The lectures are recorded and made available online, along with supporting materials, at Washington University. The library also provides direct support for the Genomic Medicine program at Washington University through the Institute of Clinical and Translational Medicine in support of the Genomics and Pathology Services (providers of clinical testing, research, and education support) and the Genome Technology Access Center (provider of comprehensive services and data analysis) on campus through training and consultation support services. Additionally the library continues to provide consultation support for researchers working in this area and most recently collaborated with the Washington University Center for High Performance Computing (CHPC) to release an instance of Galaxyv[14] an open web-based research software suite, on the CHPC cluster for the Washington University community.

Looking Ahead

As increasing genomic knowledge continues to lead to dramatic changes in medicine, and the responsibility of sifting through the swell of information becomes a heavier burden, the library hopes to provide information support to both physicians and patients, directing them to the best, most reliable information available. The information resources highlighted here are only a portion of what will hopefully be a vast collection of educational materials for physicians and patients.

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24. Office of Rare Diseases Research (ORDR-NCATS) | Supports rare disease research and information. http://rarediseases.info.nih.gov/.
25. OMIM - Online Mendelian Inheritance in Man. http://omim.org/.

Disclosure

None reported. **MM**

Washington University in St. Louis School of Medicine

BERNARDBECKER MEDICAL LIBRARY
delivering knowledge, informing decisions

Evidence-Based Medicine: Medical Librarians Providing Evidence at the Point of Care

by Lauren H. Yaeger, MLIS & Betsy Kelly, MLS

Clinical librarians anticipate their clinicians' needs, provide education and service, and are proving to be useful members of the clinical team supporting evidence-based medicine in the clinical environment.



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Abstract

Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. . . by best available external clinical evidence we mean clinically relevant research.[1]

Health care reform authorized by the Affordable Care Act is based on the belief that evidence-based practice (EBP) generates cost savings due to the delivery of more effective care.[2]

Medical librarians, skilled in identifying appropriate resources and working with multiple complex interfaces, can support clinicians' efforts to practice evidence based medicine by providing time and expertise in articulating the clinical question and identifying the best evidence.

Introduction

David Sackett wrote in the British Medical Journal in 1996, "Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients... ...by best available external clinical evidence we mean clinically relevant research;"[1] and "Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough."[1] While finding the best evidence requires both time and skill to search the published literature, busy clinicians have little time and are often unsure that their expertise is sufficient to discover the best evidence. Despite the challenges of time and expertise the U.S. Government deemed EBM important enough to pass a law requiring it. "Health care reform authorized by the Affordable Care Act is based on the belief that evidence-based practice (EBP) generates cost savings due to the delivery of more effective care."[2] At the same time, class hours available for bibliographic instruction during medical school is limited and the advent of Google has led to the impression that everything is available, free, and is easy to find. Medical librarians, skilled in identifying appropriate resources and working with multiple complex interfaces are able to provide the two things clinicians lack in their efforts to practice evidence based medicine – time and expertise in articulating the clinical question and identifying the best evidence to support a clinical decision.

According to key Medline indicators last updated in December 2013, 34,052 citations from over

5,600 journals were added to MEDLINE/PubMed in FY2013.[3] The sheer amount of information available coupled with the fact that more than 50% of clinicians are not familiar with using controlled vocabularies such as MeSH makes finding useful, evidence-based information in the clinical environment off-putting and difficult.[4]

A 2011 randomized controlled trial on the impact of librarians working with residents and interns found that having a librarian partner with clinical staff significantly improves their process of searching the literature, selecting appropriate databases, and acquiring evidence for clinical decision making in Pediatrics.[5] Librarian participation in patient centered rounds supports evidence-based medicine (EBM) practice in the clinical environment and promotes residents formulating clear, searchable clinical questions. The librarian uses opportunities during rounds to teach use of controlled vocabulary, keyword searching, resources, and supports critical appraisal of articles.

Evidence-Based Practice at St. Louis Children's Hospital

St. Louis Children's Hospital (SLCH) is the pediatric teaching hospital affiliated with Washington University School of Medicine (WUSM) in St. Louis. The SLCH medical librarian serves students, residents, fellows, and faculty physicians at WUSM as well as nursing and allied health staff.

The Pediatric Residency program at SLCH instituted the Evidence-Based Medicine Quality Improvement project - a multi-step curriculum for residents and interns that teaches research methods, database selection, and critical appraisal necessary to effectively integrate evidence into patient care decisions. The singular goal of the project is for residents to competently practice evidence-based medicine in the clinical setting. It is designed to be an educational experience providing the opportunity to develop skills necessary for forming clinical questions, searching literature, critically appraising articles and applying results to patient care.

In order to better understand the practice of medicine at SLCH the medical librarian asked, in 2010, for permission to be present during patient rounds. As she became comfortable with the language of patient care she was better able to support the information needs of the clinical team as they were identified. Team members recognized the value added by having the librarian present and the medical librarian periodically participates in patient rounds on the general medicine, NICU, and neurology units.

While attending the 2012 McMaster University evidence-based practice workshop led by Gordon Guyatt, the founder of evidence-based medicine, the SLCH chief residents recognized that the SLCH librarian, whose regular presence on the units was already an asset, could provide significant support for the project and invited her to take a more defined and structured role.

As part of the residents' EBM project, the SLCH librarian joins rounds once per week on three different general pediatrics wards. The librarian receives a summary document of the patient's current status and care plan, follows along with the clinicians' discussion and carries an iPad in the event point of care research is needed. Two of the general medicine floors practice Family Centered Rounds and on the third unit, rounds are conducted in a conference room as specialists join and leave throughout to consult on their patients. The librarian listens, may ask for clarification on a question, and the residents gather at the end of rounds to give her any clinical queries they made note of. The librarian works with the senior resident to construct searchable clinical questions based on patient issues seen that day.

After running searches and sending search results to the senior resident the librarian returns to the unit to meet with the clinical team and discuss research methods, breakdown of the clinical question, navigating databases and resources, and constructing search queries to answer the clinical question. Follow up is usually done standing in a meeting room or hallway on the floor; this supports clinician workflow but also reinforces the availability of and access to the librarian. The librarian provides handouts that include the search strategy and controlled vocabulary terms (MeSH and Emtree) and keyword examples, field tags, and information about managing functions of a database such as automatic term mapping. The librarian demonstrates how to run a search similar to the librarian-crafted keyword/controlled-vocabulary search in PubMed Clinical Queries. The librarian may also demonstrate how the search might be done more quickly using basic search terms to locate similar literature, allowing the process to better fit into the clinical workflow. Introduction to different databases, search tips, and time for questions are integral elements of this five to ten minute, face-to-face meeting.

The senior resident then chooses an article from the search results to submit to the chief residents for approval to present at journal club. Using critical appraisial forms the team appraises the article to decide if it could be used to inform future decision making. This process and exercise helps the senior resident and team learn to interpret the literature and apply their own clinical experience in deciding if the research should influence patient care. The residents work with faculty advisors and the chief residents

to gain a deeper understanding of EBM topics. It is noted in the project outline that the librarian is available throughout the senior resident's rotation to answer other clinical questions that may arise. While the focus of the project is to educate the residents it also clearly affirms the librarian's role in clinical support.

The results of research and appraisal are presented formally at resident journal club where peers and advisors discuss whether the article should be used to affect decision making. This final step of presenting at journal club is important because structured support, such as journal clubs, encourages teaching and learning integrated into clinical practice.[6] All physicians attending resident journal club participate in appraising the article and discussing how the information in the article will affect patient care.

The addition of a librarian to the clinical rounding team benefits not only the residents but the also attendings who get to know their librarian and use her as teaching support. Attendings who have had experience with the librarian on rounds are more frequently sending medical students to the library to meet with the librarian for clinical education follow up. Other clinicians, including pharmacists, nurses and consult teams are also made aware of the services provided by and available from the librarian.

EBM Case Report

One example of a clinical question turned into literature search came from a SLCH general medicine unit. A child presented with episodes of abdominal pain, and the resident wanted to know if she should exclude intussusception using ultrasonography. The librarian broke the question into the **PICO** format with ***P***atient/***P***roblem being child with abdominal pain, ***I***ntervention was ultrasonography, no ***C***omparison, and the ***O***utcome was diagnosis or excluding the diagnosis of intussusception. The librarian searched for each concept of the PICO question separately using controlled vocabulary MeSH terms and keywords, limiting to title and abstract fields, and then combined each element using Boolean operators. She also ran a similar query in PubMed Clinical Queries. The team was given examples of each search strategy including the number of results. During subsequent meetings MeSH terms, field tag usage, and PubMed Clinical Queries were all discussed. Questions were asked about why MeSH terms were used, what the field tags did, and why PubMed and not Google Scholar was the first database searched. This entire interaction took place on the clinical floor in under ten minutes; doctors were still able to answer pages and were available to the rest of the team when needed. The residents were then encouraged to search on their own and were reminded that the librarian was available for assistance. One article was selected from the search results for discussion during journal club.

Conclusion

The results of studies support a librarian in the clinical environment working in tandem with clinicians to help identify where evidence based information can be used, provide research assistance and education, and provide ongoing support for critical appraisal and best search methods.[7] Clinical librarians anticipate their clinicians' needs, provide education and service, and are proving to be useful members of the clinical team supporting evidence-based medicine in the clinical environment.[8] Having the librarian involved in clinical rounds allows for all team members to be aware of the importance of listening for clinical queries as well as benefiting from the librarian's expertise in how to formulate well crafted, searchable questions. The SLCH chief residents note "Lauren's integration into the Pediatric Residency EBM curriculum has enhaced the residents' understanding of the practice of evidence-based medicine. Her presence on rounds encourages residents to make evidence-based decisions in their daily practice." Missouri is home to one of the best pediatric hospitals in the country and evidence based medicine supports superior clinical outcomes.

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Disclosures

None reported. **MM**

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MEDICAL LIBRARY
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Evidence-Based Medicine and Systematic Review Services at Becker Medical Library

by Angela C. Hardi, MLS & Susan A. Fowler, MLIS

Resources like systematic reviews, meta-analyses, and practice guidelines can help make it easier to apply current information to patient care.



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The concept of evidence-based medicine has its roots in a group of epidemiologists at McMaster University which, led by David Sackett, wrote a series of articles about how and why clinical evidence needs to be assessed in a critical fashion.[1] The term evidence-based medicine (EBM) was coined by Gordon Guyatt in 1990 in an information document for McMaster residents. It stated that for "evidence-based medicine…the goal is to be aware of the evidence on which one's practice is based, the soundness of the evidence, and the strength of inference the evidence permits."[2] With the passage and implementation of the Patient Protection and Affordable Care Act there has been a greater emphasis on providing patient care that is efficient, cost-effective, and evidence-based.[3] EBM is becoming codified in healthcare legislation and is required to provide the best level of care to patients. Keeping up with recent evidence to answer a clinical question is a key element to practicing evidence-based medicine, however the amount of information published in medical journals, clinical trials, and elsewhere online can make it arduous to find good evidence. It can be difficult for physicians to find the time to search for the best evidence, critically appraise it, and apply it to patient care. Fortunately, resources like systematic reviews and practice guidelines facilitate the acquisition of information and support the practice of evidence based medicine.

Systematic reviews are designed to synthesize information from multiple studies and provide conclusions about the effectiveness, efficacy, or validity of an intervention or treatment and can help medical professionals apply current research to patient care. Medical professionals find them especially appealing because "the recommendations of systematic reviews, instead of reflecting personal views of experts, are based on balanced inferences generated from collated evidence."[4] A quality systematic review includes all appropriate research evidence relevant to the topic. Meta-analysis, within the scope of systematic reviews, is when the data from separate studies have been pooled together using statistical methods. While systematic reviews and meta-analyses synthesize data, critical appraisal is still necessary to determine the strength and clinical applicability of a review. At least one study has shown that there is "an association between training in critical appraisal skills, and the application of evidence-based medicine to patients."[5] Critical appraisal involves carefully reviewing the study results, research methods utilized, and the strength of statistical analysis. Understanding how a systematic review should be conducted can provide a mechanism for practitioners to critically appraise them. There are now guidelines for

Table 1

Systematic Review Guidelines	Critical Appraisal	Reporting Guidelines
Cochrane Handbook for Systematic Reviews of Interventions: http://handbook.cochrane.org	Duke University Worksheets: http://bit.ly/1hFjm8L	PRISMA: http://www.prisma-statement.org
Centre for Reviews and Dissemination: Guidance for Undertaking Reviews in Health Care: http://bit.ly/1b4Maj3	Centre for Evidence Based Medicine Worksheets: http://bit.ly/1b0TVJW	MECIR (Methodological expectations of Cochrane Intervention Reviews): http://bit.ly/1b4KW7w
Systematic Reviews in Health Care: A Practical Guide: http://bit.ly/1nmXApA	*BMJ*'s: How to Read a Paper series: http://bit.ly/1akanon	MOOSE (Meta-Analysis of Observational Studies in Epidemiology: http://bit.ly/Q7pBX7
Introduction to Meta-Analysis: http://bit.ly/1hC4XsT	Secrets to Healthy Skepticism: http://bit.ly/1gmXFtY	

reporting systematic reviews that can be used as critical appraisal tools. They include PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[6], MECIR (Methodological Expectations of Cochrane Intervention Reviews)[7], and MOOSE (Meta-Analysis of Observational Studies in Epidemiology)[8]. There are several rubrics and analysis tools that can make critical appraisal of articles easier to complete, including collections of worksheets from Duke University and the Centre for Evidence Based Medicine. Additional recommended critical appraisal and systematic review resources can be found in Table 1.

The evidence used in systematic reviews is derived from systematic searches of the literature. Without a sound, methodologically rigorous search strategy, the results or findings of the systematic review or meta-analyses should be suspect. Search strategies for a systematic review are carefully documented and should be reproducible.[9] Medical librarians ensure that researchers have the best evidence by creating thorough search strategies and searching multiple databases and grey literature resources. The task of locating all the evidence requires complex search strategies and a thorough knowledge of the literature, indexes and databases. A "high level of expertise is required to understand the technical aspects of data structure and databases" and "it is advisable to have a professional medical librarian or information specialist set up…and conduct the search."[10] Researchers benefit by knowing that their literature searches are methodologically rigorous and created by trained information professionals.

As noted, authors of systematic reviews are encouraged to use the PRISMA guidelines when preparing their findings for publication. This ensures a thorough reporting of each element of a systematic review or meta-analysis.[11] Journals like BMJ, The Lancet, and Chest endorse the use of PRISMA guidelines for publishing systematic reviews and meta-analyses.[12] There are twenty-seven elements that comprise the PRISMA check list, and two call on the particular skills of librarians. Step seven, "information sources," requires the author to "describe all information sources…in the search and date last searched;" and step eight, "Search," asks the authors to "present full electronic search strategy for at least one database, including any limits used, such that it could be repeated."[13] These two steps help inform the methodology section of a complete systematic review. Medical librarians can contribute to this part of the systematic review by writing a statement about the construction and implementation of the search strategy, resources searched, limits used, and the number of results found in the literature search. Librarians can also provide entire search strategies for one or more databases, which are often listed in an appendix. In these ways medical librarians can help researchers fulfill PRISMA guidelines and ensure that their manuscript is complete prior to submission for publication.

Becker Medical Library recognizes the importance of systematic reviews in medical research and clinical care. To help meet the growing demand for systematic review literature searches, the library has developed a comprehensive systematic review service including a standard protocol that articulates

what is required from researchers, and what will be provided by the medical librarians.[14] Librarians work with researchers from the conception of their research question, through the literature search process. Currently four librarians at Becker Medical Library provide systematic review literature searches. As a first step researchers are asked to provide their research question in the PICO (Problem, Intervention, Comparison, Outcome) format, and include a few articles that fit their research and inclusion and exclusion criteria. Next, a medical librarian creates a preliminary search strategy (usually in Medline or Embase) for the researcher to approve. Once the preliminary search strategy is agreed on, it is translated to meet the requirements for searching additional databases and other appropriate resources. Typical systematic reviews will include searches in Medline, Embase, Scopus, and CINAHL. Grey literature resources, like the Cochrane Library and ClinicalTrials.gov, are also reviewed for relevant citations. All of the citations found in the systematic search are exported to a bibliographic management software program (EndNote). Upon completion of the literature search, the researcher receives a methodology document outlining the exact search strategy used in each database, how many citations were retrieved, and the date each resource was searched. Sample methodology text is also included that can be used in a published version of the systematic review. In addition to the methodology document, researchers receive the complete library of citations in a bibliographic management program file, and in an Excel workbook. The systematic review or meta-analysis researchers are then able to move forward with selecting articles to include in their review, analyzing data, and discussing their findings. Becker Medical library also has several computers with a specialized suite of software including SPSS and STATA , which can be utilized to pool and analyze statistics, and Endnote, used to manage citation libraries. Finally, Becker's scholarly communications experts can assist researchers with selecting the best journals to submit their final systematic review or meta-analysis.

The number of published practice guidelines is growing and these can play a significant role in evidence-based medicine if they originate from a foundation of quality studies. The literature search involved for creating guidelines should be as thorough as those done for systematic reviews.[15] The difference between the creation of systematic reviews and patient care guidelines lies mostly with what happens after the literature search is complete. Committees or work groups are usually formed to assess or grade the evidence found, and often have procedures in place to vote on which articles will be included in their final analysis. Practice guidelines are sometimes published by various professional societies or in journals, but often they are designed exclusively for in-house use by a hospital or health system. Though systematic reviews and practice guidelines may serve different purposes, the literature search process used to inform them is similar and the search services that Becker Medical Library offers for systematic reviews can be used in the creation of practice guidelines as well.

Readers interested in learning more about the resources and services available for Evidence-Based Medicine at Becker Medical Library should see our subject guide, Evidence at Becker: http://beckerguides.wustl.edu/ebm. For our systematic review services, please see our subject guide, Systematic Reviews: http://beckerguides.wustl.edu/SystematicReviews

Practicing evidence-based medicine is essential and highly encouraged in the current health care environment. Resources like systematic reviews, meta-analyses, and practice guidelines can help make it easier to apply current information to patient care. Becker Medical library facilitates the creation of quality systematic reviews by offering a comprehensive systematic review service to the Washington University School of Medicine.

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Disclosures

None reported. **MM**

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The William Beaumont Papers: A Life in Letters

by Philip Skroska

The Becker Medical Library holds the correspondence, notebooks and casebooks of William Beaumont, the physician known for his landmark publication on human digestion. Beaumont came to St. Louis, Missouri in 1835. He took part in the creation of the first medical professional society and the first medical school west of the Mississippi. His collection sheds light not only on his research and career, but also on the medical profession in the burgeoning American West.

The Becker Medical Library holds the correspondence, notebooks and casebooks of William Beaumont, the physician widely regarded as the "Father of Gastric Physiology" for his landmark 1833 publication on human digestion: *Experiments and Observations on the Gastric Juice and the Physiology of Digestion*.

In 1822, while stationed at Fort Michilimackinac on Mackinac Island, he treated Alexis St. Martin for a gunshot blast to the abdomen. Alexis survived, but the wound healed into a fistula allowing Beaumont to peer directly into St. Martin's stomach. Being able to observe the workings of human digestion, his experiments settled the debate as to whether digestion was a chemical process.[1]

It was an accident of history which gave Beaumont this scientific opportunity, but it was his inquisitiveness and determination which resulted in his self-published book and his fame. Sir William Osler said of Beaumont, *"[he] is the pioneer physiologist of this country, the first to make an important and enduring contribution to science."*[2]



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The letters and journals which make up the Beaumont Papers offer a unique insight into the man and his life. The challenges he faced throughout his career foreshadow many concerns for today's medical profession. His constant efforts to secure funding for his research, his relationships with would-be collaborators, the efforts to publish, and disagreements with colleagues and professional associations, are very relevant concerns for the modern medical practitioner and scientist.

His writing also touches on his inner thoughts and the times in which he lived. As a physician, military officer, civic leader, husband, and father, Beaumont's life offers a glimpse into the society of the 19th century American West. His writings cover topics as diverse as the War of 1812, life in frontier towns, and modes of travel before the age of railroads.

On Wednesday, June 14, 1820, Beaumont was in Detroit. He was 34, newly re-commissioned as a surgeon in the U.S. Army, and eager to set out after a wait of 10 days for favorable transport. He had been brooding for the last two weeks with nothing to do and little to occupy his time but reading. Before dawn he boarded the steamboat *Walk-in-the-Water* and left for his new posting on Mackinac Island. There was a fine breeze and fair weather, but in his journal Beaumont wrote down what was on his mind.

"Adopted the following maxim this day. 'Trust not to man's honesty . . . Deal with all as though they were rogues & villains, it will never injure an honest person & it will always protect you from being cheated by friend or foe. Selfishness, or villainy, or both combined, govern the world, with a very few exceptions.' "[3]

His dark mood shows his uncertainty of the future and a certain amount of heartbreak. Beaumont had left his fiancé, Deborah Green Pratt, behind in New York while he reported to this new posting and was missing her terribly. On the top of the next page in his journal he wrote a poem.

"Oh D. my heart a vacuum feels,
Your image only I can see;
And wheresoever my body reels
My spirit wings its way to thee"[4]

His earliest notebooks, written just after beginning his medical apprenticeship, reveal his youthful idealism.

"[T]o assist mankind by curing their diseases & and repairing their constitutions, is preferable to being commended by them, & is highly conducive to tranquility of mind, . . ."[5]

In 1810 Beaumont apprenticed himself to Dr. Benjamin Chandler of St. Albans, Vermont as this was then the typical method of medical education. In addition to journaling his personal thoughts he also kept a detailed notebook of his medical training, including case reports and comments on available treatments such as bleedings and "evacuations, by Emetics & cathartics."

"Intermitants [fevers] –

Causes- Marsh Miasmata – damp houses, evening dews, lying on the ground, . . .

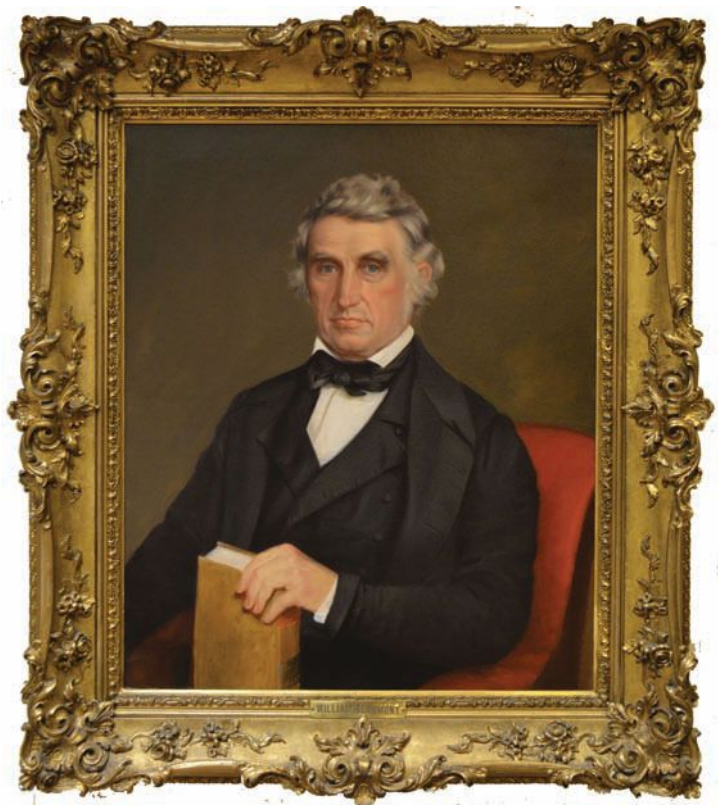
Regimen. Acidulated drinks, mucilages, broths, wine, whey etc. with sometimes, twenty or thirty drops of Laudanum."[6]

After two years of training Beaumont received his medical license from the Vermont Medical Society. When the War of 1812 broke out Beaumont joined the U.S. army as a surgeon's mate and served much of his time treating soldiers at York [now Toronto, Canada] where a major battle occurred in the spring of 1813. On April 28, 1813, he writes:

"Just got time, to suspend capital opperations [sic] whilst I can take a little refreshment to sustain life, for the first time since four o'clock yesterday – return again to the bloody scene of distress to continue dressing, Amputating, & Trepaning. Dressed rising of 50 patients, from simple contusions to the worst compound fractures more than half of the last description – perform'd two cases of Amputation, & one of Trepaning – 12 o'clock PM retired to rest my much fatigued body & soul."[7]

As he prepared to leave Detroit on that day in 1820 he had already served his countrymen in war and would soon marry and begin a family. He could not have suspected what the next fifteen years would bring.

By July 23, 1835, William had married his sweetheart, Deborah Green, and had a daughter and a son. His family had just arrived in Missouri where William had been assigned to Jefferson Barracks outside of St. Louis. The



Portrait of William Beaumont
Along with his papers Beaumont's family also donated a fine portrait of him executed by notable portrait artist, Chester Harding.

publication of his experiments on St. Martin two years earlier had already made him one of the most famous physicians in the country. He was given permission by the Surgeon General to start a private practice in addition to his military duties and was quickly inundated with private cases and pleas by young physicians to enter practice with him. The attention would only grow as the city grew in population. St. Louis was one of the fastest growing cities in the country. From 1835 to 1840 the population of St. Louis doubled to 16,400 residents. In the 1840s the population quadrupled to nearly 78,000. In addition to its permanent residents, St. Louis was the Gateway to the West and incredible numbers of people would pass through the city. Just in April 1836, more than 5,000 newcomers came to St. Louis.[8]

At first, William enjoyed the fellowship and hospitality of his fellow physicians and surgeons. He became a leader and strong supporter of professional camaraderie. On Christmas of 1835 William Beaumont and several other local physicians met at the Masonic Hall where they decided to form a professional society, then called the Medical Society of Missouri.[9] The Society, now known as the St. Louis Metropolitan Medical Society, was also the originating body of the Missouri State Medical Association. In 1850, the Society adopted a resolution to *"devise a plan . . . by which the entire profession of the state can be brought together . . ."* The

result was the Missouri State Medical Society which had its first annual meeting in 1851.[10]

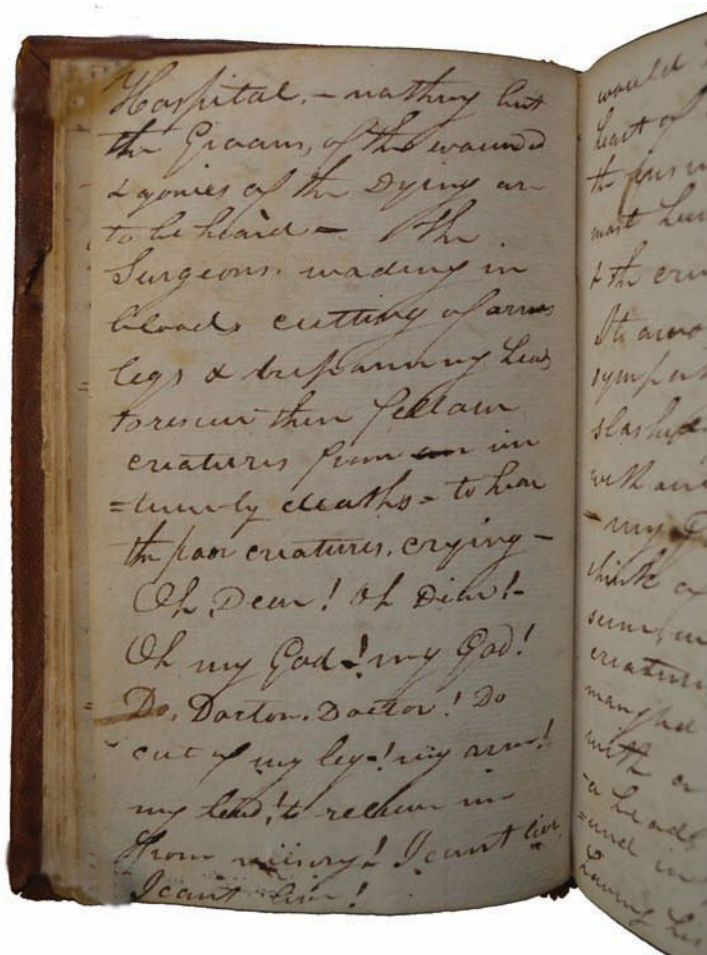
Having finally found a home after years of traveling the country from one military appointment to another, William stayed in St. Louis until his death in 1853. Many of his journals and papers were kept by his daughter, Sarah, and eventually donated to Washington University. The William Beaumont Papers at the Bernard Becker Medical Library is perhaps the largest collection of Beaumontiana in existence, although additional collections can be found at Yale University, the University of Michigan, the University of Chicago, the National Archives, and at smaller, local repositories throughout the upper Midwest. None duplicate the holdings of the others. The dispersion of his writings is the natural result of his correspondence. A good portion of his writing he sent to family, friends and colleagues."[11]

Interest in the fate of Beaumont's papers began in the 1890s, when Sir William Osler championed Beaumont's place in medical history. However, the papers might not have been saved if not for Jesse Myer, MD. Myer was an associate editor for the *Interstate Medical Journal* published in St. Louis by its founder and chief editor, James Moores Ball, MD. It was Ball who first called Myer's attention to the pioneering work of Beaumont. Myer soon learned that Beaumont's daughter, the elderly Mrs. Sarah Beaumont Keim, was still living in St. Louis and had kept two old chests full of yellowing manuscripts and letters. Myer approached her with his desire to write a biography on Beaumont, if the material was made available to him. Working with a small basketful of documents at a time, Myer began going through the letters. Tragically, Myer was diagnosed with leukemia soon after starting. Reading and writing at a feverish pace he was able to complete the biography and lived long enough to see it into print.[12]

After the publication of Myer's biography, the Beaumont Papers were presented to the Washington University School of Medicine by Miss Lucretia Beaumont Irwin, Sarah's daughter, and grand-daughter of William Beaumont. Sarah had once entertained the idea of gifting the papers elsewhere. William Osler had made inquiries with her for procuring the papers on behalf of the Office of the Surgeon General. But in an interesting coincidence, Sarah had been fond friends with Washington University's president, Robert S. Brookings. In the early 1880s, before Brookings had begun his association with the University, he rented an upper floor in Sarah's home. There they co-hosted many parties and society events. Sarah also helped Brookings polish and refine his social graces.[13]

At first the Beaumont Papers were housed in a special room in the Medical School's library, but in the 1940s changes to the library building forced the collection to be moved from one storage area to another. Beginning in 1960, the collection was reassessed and an attempt was made to better describe the letters. If Beaumont had an original order for filing the documents, it had long been lost. His correspondence has now been placed in a chronological order.[14]

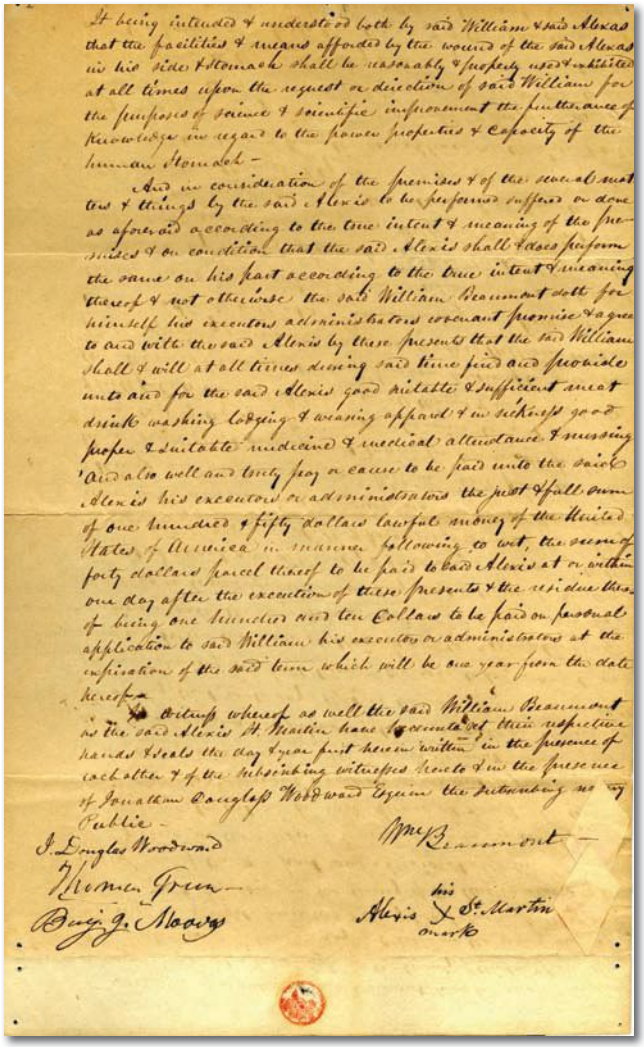
In the late 1960s the Beaumont collection was chosen to test the use of computers in producing indexes for archival collections. At the instigation of Estelle Brodman, PhD, Librarian and Professor of Medical History at the



Beaumont's account of treating the wounded during the Battle of York, April 27, 1813.

Beaumont writes of the scene in the hospital:
" – nothing but the Groans, of the wounded & agonies of the Dying are to be heard – The Surgeons wading in blood cutting [off] arms, legs & trepanning heads to rescue their fellow creatures from untimely deaths – to hear the poor creatures, crying-Oh, Dear! Oh Dear! Oh my God! My God! Do, Doctor, Doctor! Do cut off my leg! My arm! My Head! To relieve me from misery! I can't live! I can't live!"

Source: Beaumont W. Notebook kept by Beaumont during the War of 1812. Series 2, Box 21, Folder 2. William Beaumont Papers. Bernard Becker Medical Library Archives. Washington University School of Medicine, Saint Louis, Missouri.



Contract between William Beaumont and Alexis St. Martin, October 1832

As he was finalizing his research for publication, Beaumont had Alexis St. Martin submit to a legal contract binding him for one year to "obey, suffer & comply with all reasonable & proper orders or experiments," in return for $150 plus "good, suitable & sufficient meat, drink, washing, lodging and wearing apparel." St. Martin, unable to write his own name, signed the document with an "x."

Source: Beaumont W, St. Martin A. Four articles of agreement, October 16, 1832–November 7, 1833. Series 1, Box 3, Folder 23. William Beaumont Papers. Bernard Becker Medical Library Archives. Washington University School of Medicine, Saint Louis, Missouri. http://digitalcommons.wustl.edu/beaumont_1828_1832/6

Washington University School of Medicine, a database with descriptions of Beaumont's correspondence was entered into an automated system devised to output various indexes sortable by name, place, subject, and date. Library staff patiently keypunched hundreds of IBM cards.[15] Those IBM cards, the indexing program and the original database no longer exist. However, the descriptions of the documents live on today in an updated online database. And, unlike in 1960, digital imagery of Beaumont's original correspondence can now be viewed by anyone with access to the internet.

The state of medical publishing in the 1830s presented Beaumont with a number of challenges. Deciding to self-publish and self-promote his book, he astutely gave a few copies away to influential people, including Missouri's first U.S. Senator, Thomas Hart Benton.[16] But he was constantly trying to recover the costs of printing and distributing the book. He even went so far as to give his cousin, Samuel Beaumont, power of attorney and authorized him to

"ask, demand, sue for, recover and receive from Lilly, Wait and Co. now or late Booksellers of Boston, …for the balance due from them for … five hundred copies of a book entitled, "Experiments and Observations on the Gastric Juice and Physiology of Digestion."[17]

Eventually, his private practice in St. Louis was lucrative enough that he was beginning to feel comfortable. Then in September 1839, Surgeon General Thomas Lawson issued special order #48 directing Beaumont to leave St. Louis and to report to Fort Brooks, Florida.[18]

There had been a long simmering animosity between Beaumont and his commanders, in part because of his burgeoning private practice.[19] He threatened to resign his commission unless he was allowed to stay permanently in St. Louis. Behind the scenes he had his friend, U.S. Army Colonel Ethan Allen Hitchcock, press his case. Unfortunately Hitchcock reported, *"The mischief is done. … God bless you in your entrance into civil life."*[20] For his part, Beaumont felt that, *"my pride spirit and indignation were excited at such gross and egregious injustice towards me."*[21]

As his professional stature increased in St. Louis, he also became involved in a number of controversial cases. He was censored by the Medical Society of Missouri for having run an advertisement announcing his new partner, James Sykes.[22] He was also caught up in two cases of medical malpractice.[23] His testimony in the Darnes-Davis Case is in the Beaumont Papers.[24] The experiences left him at times frustrated with his fellow Missouri physicians. *"Invidious, jealous and obsolescent minds … blockheads and dunces,"* he called them.[25]

Near the end of his life Beaumont's fame weighed more on his mind. He began to feel that his original experiments had been a wasted opportunity due to his scientific naivety at the time. *"I must retrieve my past ignorance, imbecility & professional remises of a quarter century, or more … before I die."*[26]

In a letter to his cousin, William refers to *"that old, fistulous Alexis"* and his hope to convince St. Martin to

travel to St. Louis for more experiments.[27] He wrote repeatedly to St. Martin asking him to participate in more experiments. In one letter he address Alexis as *"Mon Ami,"* and ends with this exhortation, *"and now Alexis, I believe this to be the best thing you can do for your family, for yourself, for me and for science."*[28] But he and Alexis would not meet again.

After Beaumont's death in 1853 and into the early 20th century professional medical societies in Michigan, New York and St. Louis continued to honor Beaumont with an almost cult-like reverence. In St. Louis, annual ceremonies were held at Beaumont's gravesite in Bellefontaine Cemetery. Historic sites in Connecticut, New York, and Wisconsin were dedicated to him. Several hospitals throughout the United States would bear his name and in St. Louis, so would a city high school and a medical school (today the Saint Louis University School of Medicine). The Missouri State Medical Association would remember him as a physician, *"beloved by all who knew him."*[29]

Idolized as the first U.S .physician to make a lasting contribution to medical knowledge, he was still a man who knew disappointment, longing, pride, and happiness. His journals and letters found in the Bernard Becker Medical Library leave a lasting insight into the man and his times.

If you would like to read William Beaumont's letters, over 500 of them have been scanned and are available online at the Bernard Becker Medical Library's Digital Commons at http://digitalcommons.wustl.edu/beaumont/

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Disclosures

None reported.

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More than Just Medicine: Hidden Depths in the Becker Library's Rare Book Collections

by Elisabeth Brander, MLS & Martha Riley, MLIS

The importance of our nine collections to scholars working in the humanities illustrates the long-standing connections between developments in medicine and broad culturohistorical trends.

The nine rare book collections at the Becker Medical Library are an invaluable resource for medical historians. Some of the collections – namely the Classics of Medicine and Monuments of Medicine – include works on a variety of medical topics and provide a broad overview of the subject; while others, such as the Becker Collection in Ophthalmology and Optics and the CID – Max A. Goldstein Collection in Speech and Hearing,[1] document the history of a specific medical specialty.

Taken together, the rare book collections hold over fifteen thousand rare medical volumes printed between the late fifteenth and mid-twentieth centuries, including such monumental publications as the 1543 edition of Andreas Vesalius' *De humani corporis fabrica* and the first edition of Sir William Osler's *Principles and Practice of Medicine*. To think of such works strictly as "medical rare books" is, however, to do them a disservice – while these volumes certainly document the history of the medical profession, their relevance is hardly limited to that particular field. Rare books that document the history of medicine are extremely cross-disciplinary in nature, and are an important resource for historians working in a variety of subjects ranging from the visual arts to gender studies. The value of medical rare books in the study of history as a whole is evident in how these collections are used. Visitors to the rare book room are not only medical practitioners, but students and faculty working in traditional humanities subjects.

Many students from Washington University in St. Louis' Danforth Campus and other area institutions are initially exposed to the rare book collections through class visits. In most cases the professor will be the one to contact us and request that we arrange a display of books relevant to the course subject, however there have also been times when we've noticed a particularly relevant class in the course catalog and have contacted the professor ourselves. The classes are all concerned with some aspect of history, whether they approach it through the perspective of the graphic arts, perceptions of the male and female bodies, or even the relationship between magic and medicine. While there is often overlap in the materials chosen for display, the different focus of each class highlights the fact that the rare medical collections can be interpreted and used in a variety of ways.

For example, in November 2012 one of Washington University's professors of art history, Dr. William Wallace, brought his undergraduate seminar on the life and work of Leonardo da Vinci to visit the library. The books that he asked us to pull for his class were a mixture of the expected and the somewhat surprising. Given the seminar's overall emphasis on a great Renaissance artist, Dr. Wallace naturally wanted his students to see a selection of our early modern anatomical atlases. The books he selected therefore included our early 20th century facsimile edition of Leonardo's anatomical drawings, a 1543 Vesalius *Fabrica*, a 1546 French edition of Charles Estienne's anatomical atlas, and a 1560 edition of Juan de Valverde's comprehensive anatomy. In addition to these anatomical works, Dr. Wallace also selected books that were not overtly artistic in nature, such as an early printed edition of Euclid's geometry and a 1496 edition of *De oculo morali*, (See Figure 1) an Italian translation of the second printed work on



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the eye that was more concerned with ethics than medicine.[2] Although this second group of selections is not directly related to art history, their inclusion in the display provided the students with a greater understanding of Leonardo's world. The purely anatomical works highlighted the close connection that existed between anatomy and art in the 16th century, and the other texts helped contextualize the intellectual culture that informed Leonardo's scientific pursuits.

The anatomical works in the rare book collections are also interesting to those studying the history of the male and female body. For a course entitled *Making Sex and Gender: Understanding the History of the Body*,[3] we arranged a display of anatomical milestones ranging from a facsimile of Johannes de Ketham's 1491 anatomical publication, with its highly schematic drawings of the body's interior, to the first American edition of Henry Gray's classic *Anatomy, Descriptive and Surgical*. This broad selection allowed students to see not only how anatomical illustrations grew progressively more realistic and detailed as anatomy's scientific stature grew, but also how the depiction of the human body was influenced by prevailing cultural attitudes. This was particularly striking when it came to anatomical portrayals of the sexual organs. By looking at a selection of anatomical and obstetric works published from the late 15th through 17th centuries, students could observe how depictions of the female reproductive tract evolved through time. The earliest drawings, found in the de Ketham facsimile, are schematic in nature and reflect the period's lack of knowledge about the body's interior. Vesalius' mid-16th century drawings were, of course, much more detailed and realistic; however, they also reflected the classical belief that the female organs were inverted copies of their male counterparts. Finally, the 18th-century obstetric atlases of William Hunter and William Smellie both featured remarkable illustrations by the Dutch artist Jan van Rymsdyk that were more anatomically accurate than anything previously published, a development due at least in part to the increasing prominence of male midwives in the medical profession.[4] Looking at the changes in the depiction of the body through time allowed students of history to observe the close relationship between anatomy and culture, and see firsthand how social ideas influenced the manner in which anatomists and illustrators chose to depict the body.

The library's rare book collections have also been useful to researchers with an interest in magic. The close ties between magic and medicine are particularly evident in the Robert E. Schleuter Paracelsus Collection, which takes its name from the St. Louis surgeon who assembled it. Schleuter began amassing the collection, which consists almost entirely of writings by or about the 16th century Swiss physician and alchemist Paracelsus, in 1909 while traveling in Europe. While the Schleuter collection contains many of Paracelsus' medical works, including numerous editions of his texts on surgery and syphilis, it also encompasses tracts discussing alchemy and mysticism. These include early editions of the *Splendor Solis* and *Pandora*, *Das Ist*, *Die Edleste Gab Gottes*, both of which are known for their magnificent alchemical illustrations; (See Figure 2). Paracelsus' instructions on how to create magical talismans to ward against various ailments, and his writings on mythical creatures such as salamanders, nymphs, and sylphs. When a course on magic and medicine being taught at Washington University's University College came to visit the rare books room, works from the Paracelsus collection were significant part of our display. That said, we were also able to utilize works from collections that are less overtly connected to the occult. For example, we showed our copies of de Ketham and Mondino's anatomies, which have illustrations of medieval Zodiac Men,[5] to highlight the early belief in the power of planetary influences on health; and we also displayed Georg Bartisch's 16th century work on eye disease, *Opthalmodouleia*, because it discusses how black magic can be used to harm the eyes. The combination of traditional medical texts with works from the alchemical and occult traditions created a display that clearly showed the interaction between the worlds of science and magic, a topic that holds a great deal of interest for historians.



Figure 1
Woodcut illustration from De oculo morali by Petrus Lacepiera (Venice: Joannes Rubeus, 1496). The Bernard Becker Collection in Ophthalmology and Optics.

The rare book collections have also been incorporated into meetings and conferences held specifically for advanced scholars in the humanities. One particularly noteworthy event was the symposium "The Enlightenment Pope: Benedict XIV (1675-1758)," which took place from April 30 – May 2, 2012, and was organized and co-chaired by Rebecca Messbarger, Associate Professor of Romance Languages at Washington University.

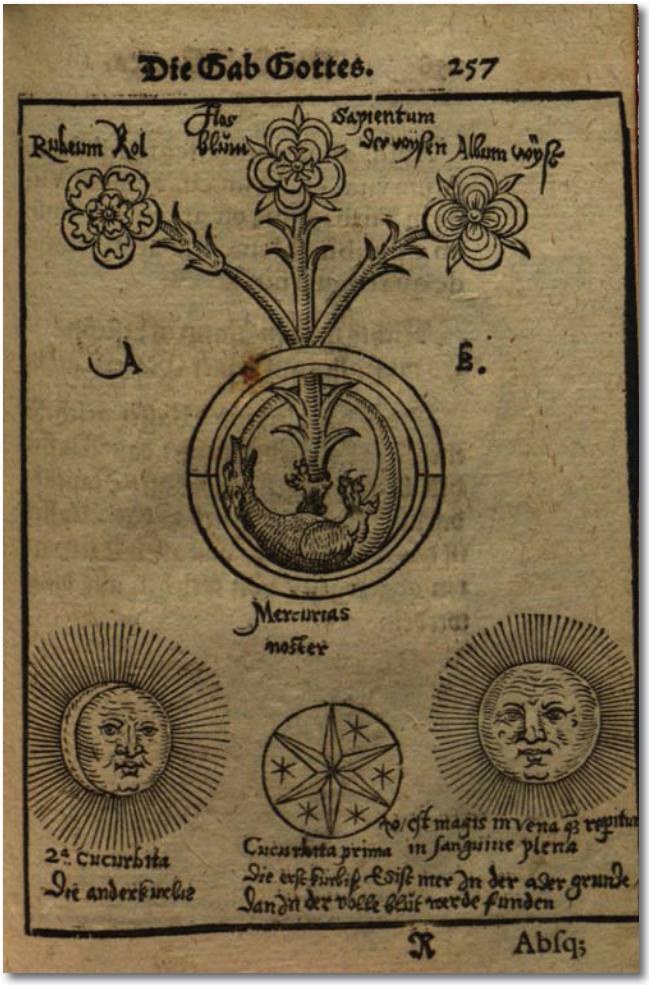


Figure 2
Alchemical illustration from Pandora: Das ist, Die edlest Gab Gottes (Basel: Sebastianum Henricpetri, 1598). The Robert E. Schleuter Paracelsus Collection.

Dr. Messbarger wanted to incorporate the medical library's collections into a special exhibit for the symposium, and provided library staff with a list of medical and scientific works that Benedict XIV cited in his religious writings. Of the 14 books that the medical library contributed to the exhibit, about half were from her list and the rest were large format anatomical atlases published during his lifetime. Although the anatomical atlases were splendid, the Pope Benedict scholars were most fascinated with the lesser known medical textbooks and medical firsts that Dr. Messbarger suggested.

Two textbooks of great interest to the Benedict scholars were Philip Verheyen's 17th century illustrated textbook of anatomy, *Corporis humani anatomia*, and Giralmo Fabrizzi's 16th century textbook of surgery, *Opera chirurgica*. Verheyen's textbook was widely used in 13 editions after its publication in 1693, and, despite the poor quality illustrations, superseded the textbook of Thomas Bartholin in popularity.[6] Giralmo Fabrizzi, also known as Hieronymus Fabricius ab Acquapendente (1533-1619), was a surgeon anatomist who made notable contributions to surgery in the 16th century, particularly in orthopedics.[7] His *Opera chirurgica* was reprinted into the 18th century, and has eye-catching illustrations of surgical instruments and sometimes fantastical prosthetic devices.[8] Its five chapters cover classic surgical techniques, and include a discussion of particular technical procedures Fabrizzi devised.[9]

Also displayed were works by important medical authors cited by Benedict XIV, which include Thomas Willis (1621-1675), Giovanni Borelli (1608-1679), and Pieter van Foreest (1522-1597). Willis' *Pathologiae cerebri*, a work remarkable for its inclusion of psychiatric diseases, epilepsy, and other convulsive diseases;[10] was displayed with Willis' showier work, *Cerebri anatome*, "the most complete and accurate account of the nervous system which had hitherto appeared."[11] The latter includes Willis' descriptions and Sir Christopher Wren's illustrations of the "circle of Willis," a component of cerebral circulation, and the cranial nerve now called the "nerve of Willis."[12] Also on display was Giovanni Borelli's *De motu animalium*, the very first treatise on biomechanics.[13] (See Figure 3) In his capacity as an Iatro-mathematical physicist, Borelli, "treated all physiological happenings as rigid consequences of the laws of physics and mechanics."[14] His work includes amusing and anatomically inexact illustrations comparing human beings to birds and other creatures, showing for example why human beings cannot fly. Finally, a 17th century edition of Pieter van Foreest's publication *Observationum et curationum medicinalium* was also shown to the symposium attendees. This work, which was first published in 1588, is a comprehensive series on diseases in which each ailment is presented by the use of case histories with references to ancient and contemporary authors.[15]

Another significant event for the library was a four week National Endowment for the Humanities seminar titled "Empires and Interactions across the Early Modern World: 1400-1800," held June 3-28, 2013. The seminar was held for the benefit of college and university teachers, and had the goal of "immers[ing] the scholars in the extraordinary age of empire building and the interactions those empires fostered around the world. These interactions include new economics of scale, biological and ecological transformations, global spread of Christianity and Islam, and widespread cultural exchanges."[16] Charles Parker, a professor of history at Saint Louis University and co-chair of the seminar, contacted the library and requested a special display of rare books relevant to the topics being taught.

In response to his request, we organized a display featuring medical and anatomical classics of the early modern period, texts discussing the plague, and works on other diseases spread through the so-called Columbian Exchange; meaning the flow of war, exploration, and trade between the old and new worlds, and east and west. One of the medical classics we selected was a 1593 copy of *Qānūn fī al-ṭibb*, the first Arabic edition

of Avicenna's *Canon* printed in the West, while an anatomical classic was Vesalius' beautiful *Fabrica*. Especially interesting to the seminar attendees, however, were the books discussing the diseases spread through cultural exchange, which included plague, syphilis, the measles, smallpox, and malaria. One book we chose that highlighted this theme was Paracelsus' 1530 *Von der frantzösischen Kranckheit*. This work, a clinical description of syphilis, maintained that the disease could be successfully treated by carefully measured doses of mercury compounds taken internally. Treatment with forms of mercury was used until the advent of penicillin in the 20th century.

The Becker Medical Library's rare book collections appeal to a wide variety of researchers, not just scholars with an interest in tracing the great milestones of medical history. Our holdings have been used to enhance conversations on a variety of subjects including art history, the evolution of gender, and the life of a Renaissance pope. The cross-disciplinary nature of the rare book collections means that they are capable of illustrating more than a series of important developments in medical theory and practice; they are instead vital tools in understanding broader historical trends. Our nine collections might have the overall theme of "medicine," but their importance to scholars working in the humanities illustrates the long-standing connections between developments in medicine and broad culturohistorical trends.

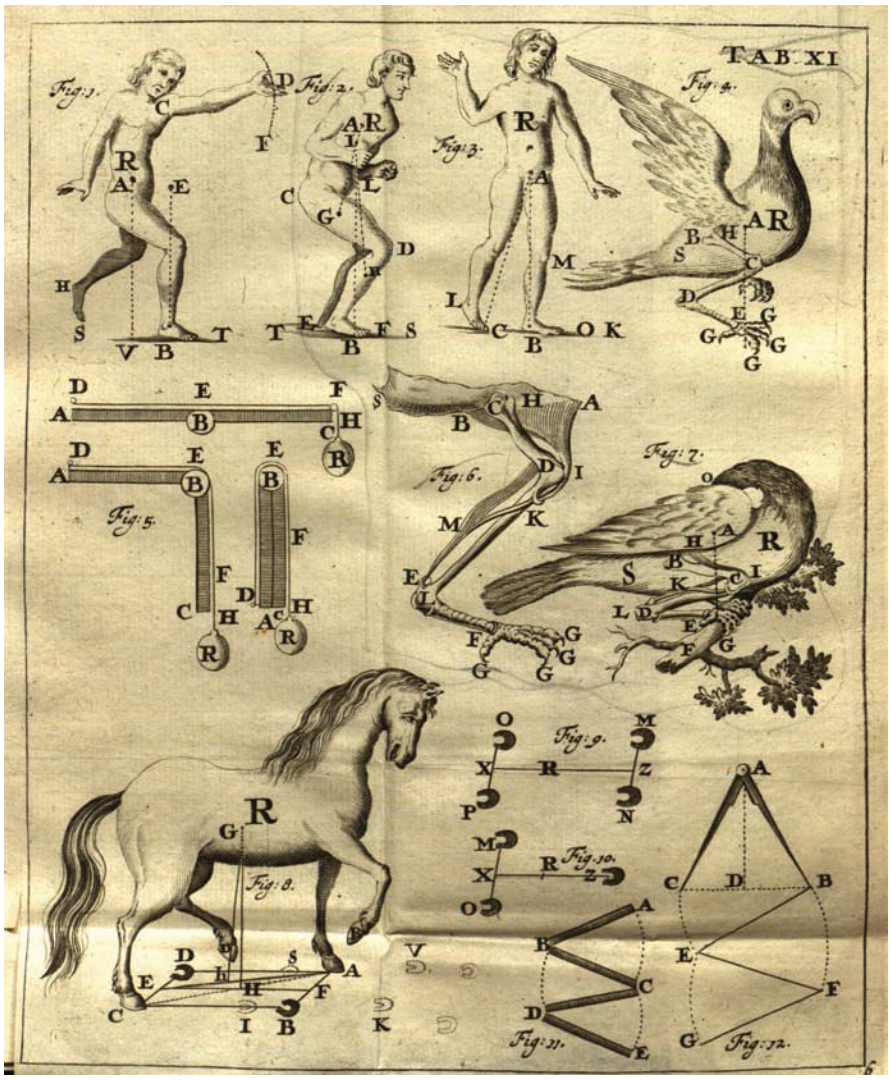


Table XI from De motu animalium by Giovanni Alfonso Borelli (The Hague: Apud Petrusm Gosse, 1743). The CID-Max A. Goldstein Collection in Speech and Hearing

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Disclosures

None reported.

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Epigenetics: Modifying the Genetic Blueprint

by Joel C. Eissenberg, PhD

Environmental stress can impact the way the information in DNA is used, and epigenetic effects can be transmitted through multiple cell divisions and, in some cases, multiple generations.



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Abstract

The sequence of the human genome represents our genetic blueprint. While it is now possible to draw direct connections between specific DNA sequences and specific physical features and to predict disease risk, the effects of certain genes can be masked by a process called "epigenetics." Here, I summarize our current understanding of epigenetics and it affects gene expression, with impacts on health and aging.

Introduction

The 20th century was the 'Century of Genetics' (See Table 1). This march of progress culminated in the first draft of the human genome sequence in 2001, which continues to be refined. The human DNA sequence is regarded as the genetic instructions for our development, our health and our behavior. It contains information about form and function. By inspecting an individual's DNA sequence, it is possible to deduce his or her gender, paternity, eye color, hair color, skin color and blood type, as well as a person's risk for hundreds of single-gene inherited diseases.

When and where each of our genes is expressed is determined by the actions of a complex network of protein and RNA molecules. Thus, each cell type or tissue in our body is distinguished by a unique combination of interactions that activate certain genes and silence others. In most cases, it appears that the decisions dictating whether a given gene is expressed or silent are actively maintained. The loss of the signal or factor responsible for a given state of gene expression will result in a change in expression. But normally, a given gene will function the same way in every cell of a tissue and in every individual who inherits a given state of that gene (dominant or recessive). Indeed, this idea underlies Mendel's first law of inheritance, the "principle of uniformity." Basically, this states that the same combinations of genes will result in the same phenotype in each successive generation.

But we have long known of certain violations of Mendel's first law. For example, human females carry two X-chromosomes in every cell. Yet within any given cell, the genes on only one of the X-chromosomes are expressed, while the genes on the other X-chromosomes are silenced. The decision of whether to silence the paternal or maternal X-chromosome is made randomly on a cell-by-cell basis early in development, but the decision is then clonally inherited

Table I
Landmark events in genetics (http://www.genome.gov/25520238)

Year	*Landmark*
1900	Rediscovery of Mendel's work on inheritance by Hugo DeVries, Carl Correns and Erich von Tschermak.
1902	Archibald Garrod describes the inheritance of alkaptonuria by Mendelian rules
1909	Wilhelm Johannsen coins the word "gene."
1911	Thomas Hunt Morgan and colleagues describe genetic linkage and meiotic recombination
1941	George Beadle and Edward Tatum propose the "one gene, one enzyme hypothesis."
1944	Oswald Avery, Colin MacLeod, and Maclyn McCarty show that DNA is the chemical nature of genes.
1953	Francis Crick and James Watson describe the double helix structure of DNA
1955	Joe Hin Tjio defines the exact number of human chromosomes
1959	Jerome Lejeune and colleagues discover that Down syndrome is caused by trisomy 21
1966	Marshall Nirenberg, Har Khorana, Severo Ochoa and colleagues elucidate the genetic code
1972	Stanley Cohen and Herbert Boyer create the first recombinant DNA molecule using DNA from different species
1983	The gene implicated in Huntington Disease becomes the first disease gene mapped
1987	The first comprehensive molecular genetic map of human chromosome is created
1990	Launch of the human genome project
2001	First draft of the human genome sequence released

by all the descendants of those cells. We know from molecular genetics studies that the genes on the silent X-chromosome have not been mutated, yet their silent state is nearly as faithfully inherited as a mutation. Furthermore, all of the factors necessary for function of the active gene copies are present in the same cell as the silent gene copies. Thus, the X-inactivation mechanism in mammals is said to be "epigenetic," literally "over" or "above" genetics.

The molecular geneticist Mark Ptashne[1] proposes the following working definition of epigenetics: "A change in the state of expression of a gene that does not involve a mutation, but that is nevertheless inherited in the absence of the signal (or event) that initiated the change." While DNA sequence instructions certainly underlie our traits, epigenetics can modify at least some traits.

To extend the metaphor of genetics as a "blueprint," a blueprint for a house (genetic code) may specify the number and positions of exterior windows, but whether those windows are single-pane glass or double-pane insulated glass (epigenetic code) will greatly affect the environment of the building. Below, I summarize some of the evidence that epigenetics impacts human health and disease and the modifications to the DNA code that underlie epigenetic regulation.

Identical twins Are Not Identical

The popular press often adopts the deterministic assumption that a gene exists to explain every human attribute: height, weight, intelligence, social behavior and disease. Indeed, the striking similarities between monozygotic ("identical") twins, which are genetic "carbon copies," testify to the strongly deterministic role of genetics in controlling phenotype. However, twins also tell us that there is more to life than our genes.

Monozygotic twins arise after fertilization when a single early embryo splits in two. The resulting twins are completely matched for genetics, age, sex and pre- and (usually) post-gestational environment. Rates of disease discordance among monozygotic twins are lower than for dizygotic twins (See Figure 1), implicating genetics as an important variable in disease risk. In some cases, differences in mitochondrial makeup, placental differences during gestation or post-partum environmental differences (e.g., diet, drug, alcohol or tobacco exposure) can differentiate monozygotic twines. However, monozygotic twins can show disease discordance rates of over 50%, even for highly heritable conditions,[2-4] suggesting that epigenetics may also contribute to disease risk.[5]

Maternal and Paternal Genes Are Not Necessarily Equivalent

While we know that mothers an fathers can make different genetic contributions to any trait, a corollary to Mendel's first law is that it doesn't matter for the

manifestation of a trait which parent transmits the gene(s) underlying that trait. In most cases, this is the case. But for a small number of our genes, either the maternal or paternal copy is silenced. These genes are said to be "imprinted," as they seem to retain a memory or "imprint" of the gamete that carried them.

Examples of imprinted genes associated with inherited disease include:

Angelman Syndrome

Angelman signs include developmental delay, jerky, ataxic gait, and a happy affect with frequent smiling and laughter. Angelman patients present with such dysmorphic features as microbrachycephaly, maxillary hypoplasia, large mouth, widely spaced teeth and prognathism. The disease is caused by loss of expression of the maternal allele of the UBE3A gene, which is normally silenced (epigenetically imprinted) on the paternal chromosome.

Prader-Willi Syndrome

Prader-Willi Syndrome is the most common form of syndromic obesity, with signs that include hyperphagia, hypotonia and developmental delay. Prader-Willi patients typically present with almond-shaped palpebral fissures, narrow bifrontal diameter, small hands and feet, small genitalia and cryptorchidism in males. The disease is caused by loss of gene activities on the long arm of the paternal chromosome 15 that are normally epigenetically imprinted on the maternal chromosome.

Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann infants typically present with macroglossia, macrosomia, abdominal wall defects and hypoglycemia; they also have a predisposition for certain cancers. While the genetic basis for the disease is complex, in most cases it is the result of unbalanced expression of a small set of epigenetically imprinted genes in one or the other of two regions on the short arm of chromosome 11.

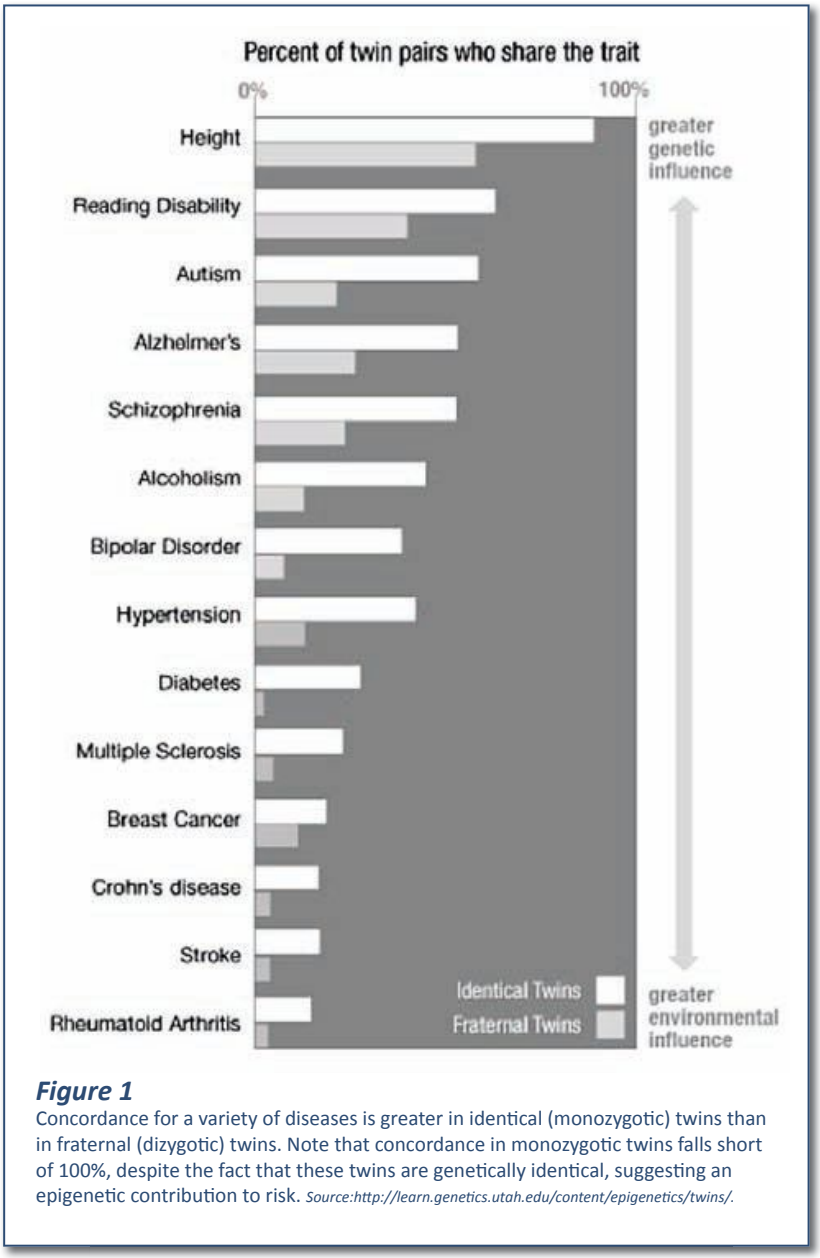


Figure 1

Concordance for a variety of diseases is greater in identical (monozygotic) twins than in fraternal (dizygotic) twins. Note that concordance in monozygotic twins falls short of 100%, despite the fact that these twins are genetically identical, suggesting an epigenetic contribution to risk. *Source:http://learn.genetics.utah.edu/content/epigenetics/twins/.*

The chemical determinant for which parent's allele will be expressed from a woman's X chromosome or from our imprinted genes does not lie in the DNA sequence per se. Rather, a specific chemical modification at specific sites on one or the other gene copy leads to its selective silencing.

5-methyl Cytosine: The "Fifth Base" in the DNA Code

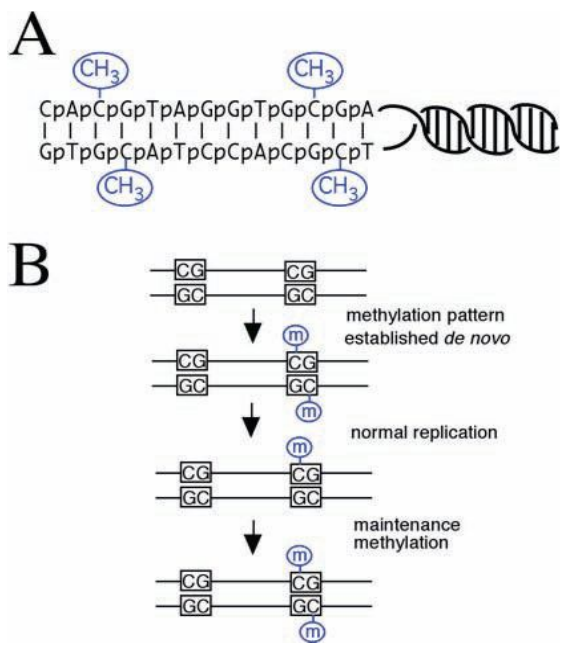
All DNA is comprised of polymers, for which the individual polymer subunits are termed "deoxynucleotides." There are four types of subunits,

distinguished by one of four nitrogenous bases: adenine (A), cytosine (C), guanine (G) and thymine (T). The linear order of these bases in a strand of the DNA double helix constitutes the genetic "code." However, in some regions of the genome, the cytosine base is chemically modified by the enzymatic addition of a methyl group at the fifth position of the pyrimidine ring. Only a small fraction of cytosines are methylated in any particular cell. In mammals, this methylation occurs only in the context of a cytosine immediately followed on the same strand by a guanine (termed "CpG," where the "p" signifies a phosphate that links adjacent nucleotides in the DNA polymer). Note that the occurrence of a CpG sequence on one strand of the DNA double helix implies a CpG (read in the opposite direction) on the other strand, so DNA methylation is symmetrical in chromosomal DNA (See Figure 2A).

The choice of which positions in the DNA will be methylated is made initially by a "de novo" DNA methylase, which can methylate unmethylated CpGs. How the proper CpGs are targeted is not well understood, but probably involves specific DNA binding proteins that recognize and bind specific DNA sequences at or near these target sites. With the next round of DNA replication, each of the methylated DNA strands is copied using unmethylated subunits, creating a "hemi-methylated" site. Such hemi-methylated regions are substrates for "maintenance methylase" enzymes that methylate cytosines only at sites that are paired with a methylated CpG (See Figure 2B). By this mechanism, it is easy to see how the 5-methyl cytosine modification, once established, can be stably propagated, even if the signal or event that initiated the modification disappeared. Indeed, maintenance DNA methyltransferases ensure propagation of CpG methyl marks through mitotic cell divisions with high fidelity.[6,7] Thus, 5-methyl cytosine qualifies as an epigenetic mark.

The inactive X chromosome in each female cell is hypermethylated relative to its active homolog. Similarly, the imprinted and silenced allele of imprinted genes is typically hypermethylated. In the latter case, parental imprints are established during germ cell differentiation. Remarkably, in the early cleavage stage zygote, massive de-methylation occurs on both parental homologs, but some of the methyl marks must survive, since imprinted loci remain faithfully imprinted throughout later development.

The importance of DNA methylation is underscored by the clinical presentation of patients who lack specific methylating enzymes. For example, Immunodeficiency-Centromeric instability-Facial Anomalies Syndrome 1, an autosomal recessive condition associated with facial dysmorphology, mental retardation, immunodeficiency and chromosome centromere instability, is frequently due to mutations in the DNMT3B gene, which encodes a de novo DNA methylase.



Figures 2A & 2B
DNA Methylation

Figure A:
At certain sites in the DNA, cytosines followed by guanines are substrates for methylation (blue). In double-stranded DNA, this is paired with a CpG that is also methylated.

Figure B:
A region of DNA may be methylated during development by the action of a de novo methylase (first step). Upon DNA replication, methylated DNA is paired with newly made, unmethylated DNA. This is a target for maintenance methylases, which recognize hemimethylated DNA and methylate the paired cytosine to restore the fully methylated state.

The silencing associated with hypermethylated regions of chromosomes is programmed in part by proteins with a high affinity for 5-methyl cytosine compared with the unmethylated base, as well as the inability of some gene-activating proteins to bind to the methylated form of their DNA targets. Most patients with Rett Syndrome, an X-linked progressive neurodevelopmental disorder and one of the most common causes of mental retardation in females, carry mutations in the methyl-binding protein MECP2.

CpG methylation is a potential therapeutic target.

The drugs 5-azacytidine and 5-aza-2' deoxycytidine contain chemical analogs of cytosine in which carbon 5 is replaced by an azido group that cannot be methylated. These drugs are used to treat myelodysplastic syndrome, a blood condition characterized by cytopenia, ineffective hematopoiesis, and increased risk of acute myeloid leukemia. Cells that take up these analogs incorporate them into DNA during replication. When DNA methylating enzymes bind a site of analog incorporation, the enzyme becomes covalently trapped at the site. This may result in passive genome-wide demethylation by reducing effective enzyme concentrations as well as active local demethylation by triggering DNA repair to remove the enzyme-DNA complex and replace it with standard—but unmethylated—cytosine. In the context of the pre-cancerous myelodysplastic syndrome, demethylation may act by altering the epigenetic program of cancer cells, promoting derepression of tumor suppressor genes to arrest tumor progression.

In addition to the extensive genome-wide demethylation that occurs shortly after fertilization (mentioned above), developmentally programmed DNA demethylation must also occur during germ line differentiation, to replace the parental methylation pattern with the methylation pattern appropriate to the gender of the zygote. How erasure of the epigenetic DNA methyl mark occurs is still unclear. Some of this could be a passive consequence of DNA replication in the absence of maintenance methylases. However, recent studies have identified a family of enzymes that oxidize 5-methylcytosine to 5-hydroxymethylcytosine.[8] 5-hydroxymethylcytosine may result in the restoration of unmethylated cytosine by one of several mechanisms. It is of particular interest that 5-hydroxymethylcytosine is relatively abundant in neurons of the brain, reaching ca. 1% of all cytosines or ca. 12 million per nucleus, and is associated with expressed genes. In contrast, 5-hydroxymethylcytosine levels are dramatically reduced in cancer cells relative to adjacent normal tissue. TET2, one of the enzymes that catalyzes the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, is mutated in a number of tumor types, suggesting that it normally acts as a tumor suppressor. Similarly, mutations in IDH1, which encodes an enzyme that makes a TET2 cofactor, are particularly frequent in gliomas. Significantly, these tumors show DNA hypermethylation, likely because a failure to convert 5-methylcytosine to 5-hydroxymethylcytosine. However, a major challenge to our understanding of the role of DNA modifications in disease is distinguishing methyl (and hydroxymethyl) marks that are causal from those that are a byproduct of a disease process.

Environment-Associated Epigenetics: Lamarck Lives?

The French biologist Jean-Baptiste Larmarck is most commonly associated with the idea that acquired traits can be genetically transmitted to offspring. The idea of Larmarkian inheritance was largely displaced by Mendelian genetics during the early 20th century. However, epigenetics provides a mechanistic basis to account for observable differences in the transmission of certain traits without invoking environmentally-induced mutations.

Diet and Coat Color in the Agouti^{vy} Mouse

The agouti gene in mice encodes a paracrine-signaling molecule that causes melanocytes to produce yellow rather than black coat pigment and makes mice prone to develop late-onset obesity, non-insulin-dependent diabetes and increased frequency of tumors.[9] In mice carrying the dominant agouti^{vy} mutation, the degree to which the agouti^{vy} allele is methylated regulates its expression and thereby coat color and risk for disease. Dietary supplementation of pregnant mice with methyl donors such as folic acid, vitamin B_{12}, choline, or betaine increases DNA methylation of the gene in their offspring, decreasing agouti^{vy} expression and resulting in brown coat color. The effect of maternal methyl-donor supplementation on coat color is also inherited in the grandchildren of these females through germline epigenetic modifications.

The Dutch Hunger Winter Cohort

The Dutch hunger winter occurred from November 1944 to May 1945, when the Dutch in the German-occupied Netherlands experienced a severe famine. People who were conceived during the Dutch hunger winter had less cytosine methylation on their Insulin-like Growth Factor 2 (IGF2) gene compared to their unexposed same-sex brother or sister six decades later.[10] IGF2 is involved in human growth and development. Less cytosine methylation leads to increased IGF2 expression, so children conceived to starving mothers tend to over-express IGF2. Additional studies on the same cohort found that people conceived during the famine had impaired glucose tolerance, hypercholesterolemia, elevated blood pressure and higher obesity rates in adulthood. A model to explain these observations is that

fetuses of starving moms adapted by increasing their efficiency in storing calories during gestation due to IGF2 over-expression. Even after their starvation ended, the signal to store calories didn't get turned off, resulting in metabolic and cardiovascular problems associated with being overweight.

Epigenetics and Aging

While monozygotic twins have identical DNA sequences and very similar CpG methylation patterns at birth, they diverge epigenetically as they age.[11] Furthermore, different cells within the same tissue show more variation in CpG methylation patterns with age.[12] This could be related to the observation that activities of at least some DNA methylases decline with age.[13] The big questions, of course, are (1) what are the key genes for longevity and aging that are targeted for epigenetic regulation and (2) how does epigenetic regulation of these genes impact longevity and aging normally?[14] Epigenetic therapies to slow aging and mitigate its effects will depend on the answers to these questions.

Future Prospects

While the idea of epigenetic regulation is an old one, our insights into mechanisms of epigenetics are relatively new and still being clarified. In certain cases, the potential for epigenetics-based therapies for treatment of human disease seems promising:

Sickle cell disease and b-thalassemia

In these blood disorders, defective or missing adult b-hemoglobin could be at least partially complemented by the epigenetic activation of the embryonic and/or fetal hemoglobin genes.

Fascioscapulohumeral Muscular Dystrophy

In FSHD, loss of epigenetic silencing of the DUX4 gene (and possibly other genes) results in progressive muscular dystrophy. Drug treatments are currently being investigated that could restore DUX4 silencing in patients prior to the onset of symptoms in the second decade of life.

Cancer

As mentioned above, there is a growing awareness that in some tumors, the loss of tumor suppressor gene expression is the result of epigenetic silencing. Targeted epigenetic therapy to reverse this silencing could lead to tumor cell death.

Conclusion

So does the discovery of epigenetics vindicate the Lamarkian model of inheritance of acquired traits? Partially. Environmental stress (with the exception of known mutagens) does not exert its effect on the DNA as mutations. But is now clear that environmental stress can impact the way the information in DNA is used, and epigenetic effects can be transmitted through multiple cell divisions and, in some cases, multiple generations. However, in all the cases examined to date, intergenerational epigenetic effects are only observed for one or two generations after the environmental stress is withdrawn. Thus, the impact of epigenetics on evolutionary selection is likely to be negligible. Mendelian genetics is enriched by epigenetics,

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Disclosure

None reported. **MM**

Fertility Preservation in Patients Receiving Chemotherapy or Radiotherapy

by Randal D. Robinson, MD & Jennifer F. Knudtson, MD

Referral to a reproductive endocrinologist specialist around the time of cancer diagnosis is important to expand and optimize treatment options for patients receiving chemotherapy or radiation.



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Abstract

The preservation and restoration of fertility are key aspects for enhancing quality of life in cancer survivors. Cytotoxic agents and radiation can produce gonadal dysfunction in both men and women. Survival rates for cancers that occur before or during reproductive age have improved dramatically. Current fertility preservation options are available but limited in males and females. Referral to a reproductive endocrinologist around the time of diagnosis is important to optimize treatment options.

Introduction

The preservation and restoration of fertility are key aspects for enhancing quality of life in cancer survivors.[1, 2] The risk of women developing cancer before the age of 40 is 1 in 49, and more than 99% of cancer diagnoses will occur during the reproductive years.[3] Fortunately, survival rates for cancers that occur before or during the reproductive ages have improved dramatically. Survival rates at five years for patients with testicular cancer, hematologic malignancies, breast cancer and other cancers range from 90 to 95%.[4] As more people survive cancer diagnoses, the survivor quality of life issues are increasing in importance. Unfortunately, the conventional treatments for cancer, cytotoxic agents and radiation, can produce gonadal dysfunction in both men and women. Gonadal dysfunction can lead to premature menopause in women and infertility in men and women. Fertility preservation options are available for interested patients and are becoming increasingly utilized.

In prior surveys, only 57% of cancer patients received information about infertility from their providers[5]. Recently published guidelines, from the American Society of Clinical Oncology (ASCO) and the American Society for Reproductive Medicine (ASRM), are encouraging multi-disciplinary teams for the treatment of survivors including discussion of fertility preservation and referral to reproductive specialists.[6, 7] The ASCO guidelines encourage providers to discuss potential threat to fertility from cancer treatment prior to initiation of therapy. They also recommend providing the patients with information about their options for fertility preservation and that these discussions are documented.[7]

Fertility preservation options are available for males and females. Established fertility preservation options for women undergoing chemotherapy include *in vitro*

fertilization with embryo cryopreservation, or oocyte cryopreservation. Experimental options for women undergoing chemotherapy include gonadal suppression and ovarian cryopreservation. Another option for women undergoing radiation includes ovarian transposition. For males undergoing chemotherapy or radiation, sperm cryopreservation is effective and an approved method. Investigational methods include testicular tissue cryopreservation and hormonal suppression.

Table 1

A review of the randomized trials literature and the outcomes for women who received GnRH agonists prior to chemotherapy, with the principal outcome of return of menses.

Reference (Author and Year)	Number of patients	GnRH Agonist	Cancer Type	Months Follow Up	% with menses-agonist vs control	P value
Blumenfeld 2008	111	triptorelin	hodgkin	24	96 vs 63	0.001
Badaway 2009	80	goserelin	breast	8	90 vs 33	0.001
Sverrisdottir 2009	260	goserelin	breast	24	36 vs 10	0.006
Gerber 2011	60	goserelin	breast	24	70 vs 57	0.28
delMastro 2011	281	triptorelin	breast	12	63 vs 50	0.03
Munster 2012	49	triptorelin	breast	18	88 vs 90	0.36

For women undergoing chemotherapy, their chemotherapy treatment targets rapidly dividing cells not limited to cancer cells. The ovary has follicles which grow every month in response to hormonal activation. These ovarian cells are susceptible to damage and death from cytotoxic agents. Histologic examination of the ovary after exposure to cytotoxic drugs has shown decreased follicle numbers to absent follicles to fibrosis. The effect appears irreversible within the ovary unlike in other rapidly dividing cells.[8] The drugs most associated with ovarian damage are the alkylating agents including cyclophosphamide, busulfan, chlorambucil, nitrogen mustard. Cumulative dose of the cytotoxic drug and age are the key factors concerning permanent premature ovarian failure.[9] Pre-pubertal girls are less susceptible to ovarian damage.[10] Established fertility preservation options for women undergoing chemotherapy include *in vitro* fertilization with embryo cryopreservation, or oocyte cryopreservation. Experimental options for women undergoing chemotherapy include gonadal suppression and ovarian cryopreservation.

In vitro fertilization with embryo cryopreservation is the most successful established option for fertility preservation in women undergoing chemotherapy. During this procedure, a woman undergoes ovarian stimulation by taking injectable medications, the oocytes are removed through an outpatient procedure, the oocytes are fertilized with the sperm and then the embryos formed are cryopreserved for future use. Unfortunately, this is not an option for pre-pubertal girls, some adolescent girls and for many women who do not have a partner or are unwilling to use donor sperm for fertilization. The process can take two to three weeks so chemotherapy may need to be delayed. The live birth rate for infertile women less than thirty-five-years old per embryo transfer from thawed embryos was 38.7% in 2010.[6]

Mature oocyte cryopreservation is a preferred option for many post-pubertal females who do not have a partner and do not desire to use donor sperm. This process is similar to *in vitro* fertilization and begins with ovarian stimulation and retrieval of the oocytes but the freeze occurs without fertilization with semen. Data on pregnancy rates and live birth rates from oocyte cryopreservation is increasing but limited. [6]

Extrapolating from the knowledge that the pre-pubertal ovary is less susceptible to ovarian damage, attempts have been made to achieve medical suppression of the ovary. Gonadal suppression is experimental and controversial. In theory, suppression of the pituitary ovarian axis before chemotherapy could decrease damage via direct suppression, by decreasing ovarian perfusion, or by direct gonadal effect on ovarian apoptosis.[11] Pulsatile gonadotropin-releasing hormone production induces a signaling cascade which results in normal follicular development. Continuous infusion of gonadotropin-releasing hormone, such as by the use of the gonadotropin-releasing hormone(GnRH) agonists, results in an initial increase of gonadotropins, the flare effect,

followed by a progressive decrease in gonadotropins and ovarian suppression.[12] This suppression may take 7-14 days depending upon when the medication is administered in the menstrual cycle. A more rapid suppression occurs if the GnRH agonist is given in the luteal phase, seven days after ovulation. GnRH agonist side effects include menopausal symptoms of hot flashes, reversible bone loss, insomnia and muscle aches. The side effects can be improved by the addition of "add back" therapy such as norethindrone acetate 5 milligrams taken daily.

The data is limited and controversial on the use of these agents for ovarian protection prior to chemotherapy. Animal models have shown that GnRH analogs protect the ovary from damage during chemotherapy. There have been multiple randomized controlled trials which report ovarian protection with GnRH agonists. Our review of the literature of the outcomes for women who received GnRH agonists prior to chemotherapy, with the principal outcome of return of menses, is compiled in Table 1.

The majority of primary outcomes in these studies are return of menses. Overall, the women treated with GnRH agonists have increased return of menses compared to control. However, what is not known is whether return of menses is a suitable surrogate for return of normal fertility and chances of future pregnancies. Additional studies' examining ovarian reserve and pregnancy outcomes in this population of patients is needed.

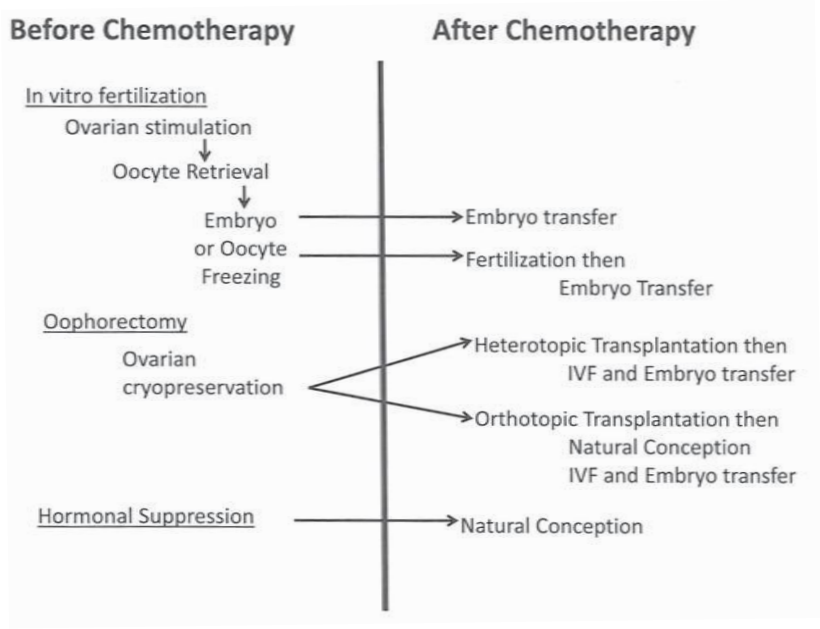
The Cochrane Review currently recommends the use of GnRH agonists to be considered in women of reproductive age receiving chemotherapy.[20] A recent meta-analysis concluded the use of GnRH agonist co-treatment with chemotherapy may be beneficial in preserving future fertility in women treated with chemotherapy. No evidence for improved pregnancy rates has been documented but most studies do not evaluate outcomes long enough for this endpoint to be appropriately evaluated.[21] The discrepancies in the literature are likely promulgated by different regimens and medications used, the different definitions of normal menses and ovulation, and the lack of follow-up.[22] Gonadal suppression may be the only option for some populations including adolescents or women who cannot delay chemotherapy. Additionally these medications are expensive and may not be covered by insurance plans for this off label use.

As mentioned previously, a potential downside to the use of GnRH agonists are that down regulation of the ovary might take up to two weeks causing further delay of chemotherapy initiation. A treatment regimen consideration for patients that need to start chemotherapy quickly and do not have time to wait 7-14 days for the GnRH agonist flare to subside is a combined GnRH agonist and antagonist regimen. This concept utilizes the relatively new option for ovarian down regulation, GnRH antagonists which achieve ovarian down regulation usually within 72 hours of administration and then the GnRH agonist can be added to maintain down regulation. The mechanism for action of GnRH antagonists is similar to the agonist except they directly bind and block the GnRH receptor. The GnRH antagonists do not have the flare effect that is seen with the GnRH agonists. There have been a few studies examining the combination of GnRH agonists and GnRH antagonists in a protocol for rapid suppression. Mardesic et. al reported a combination protocol with GnRH agonist and a GnRH antagonist in six post-pubertal young women with hematological malignancies. This study provided short term follow up but it exhibited how a GnRH antagonist can be used to suppress the flare effect of the GnRH agonists.[23] Another study used a GnRH antagonist and agonist in treatment of precocious puberty. They used the GnRH antagonist and a GnRH agonist together versus the GnRH agonist alone and observed the difference in gonadotropins in the urine. During the first 10 days of treatment, the mean LH concentration in the urine was significantly lower in the combination therapy compared to the agonist only.[24] Another more recent study with 18 to 40-year-old breast cancer patients receiving cyclophosphamide-based chemotherapy had multiple treatment arms which included a subset of women who received GnRH agonist and antagonist. The study concluded that the co-treatment was not protective.[25] However, the study was small and assumed a large difference in the menstrual return when calculating the power. We have designed a randomized, double-blinded blind, placebo controlled trial of GnRH antagonist/agonist pre-treatment versus placebo in adolescent and young females with cancer undergoing chemotherapy that we hope to begin enrollment for soon to try and examine the utility of this combination therapy in this patient population.

Ovarian Cryopreservation, freezing of ovarian tissue, is still investigational. The ovarian tissue is removed by a laparoscopic procedure. When the tissue is ready to be implanted back into the women, it can be reimplanted in a

Figure 1

For women of reproductive age undergoing chemotherapy, our approach is summarized in this algorithm below.



heterotopic, back in the pelvis, or orthotopic, abdomen or arm, site[12]. This can be an option in patients that do not have time to delay chemotherapy, do not have a partner, or cannot have their hormones elevated as part of the *in vitro* fertilization process. Multiple live births have now been reported with this technology.[4]

For women of reproductive age undergoing chemotherapy, our approach is summarized in the algorithm outlined in Figure 1.

Ovarian follicles are very vulnerable to ionizing radiation. The degree of affect is related to the patient's age and the dose of radiation delivered to the ovary.[26] Women undergoing radiation can utilize cryopreservation of embryos, oocytes or ovarian tissue. However, fertility can also be preserved by ovarian transposition. This procedure has been performed for over three decades with excellent results. The best results are with laparoscopic suturing of the ovary lateral and high out of the pelvis. This procedure reduces radiation dose to 10-15% compared to non-transposed ovaries.[27]

Cancer has a negative effect on male fertility even before treatment. It is estimated that around 50% of males treated with chemotherapy have persistent oligospermia, a low sperm count. The extent of gonadotoxicity depends upon the agent, dose and age of the patient.[1] Spermatogenesis is also affected at low doses of radiation. Total body irradiation given for stem cell transplantation causes complete gonadal failure in 80% of males. Adult males have the assessable option of freezing sperm for future use. Unfortunately, it is not an option for some post-adolescent and pre-pubertal boys.[1] Better education concerning fertility issues is now being offered for males undergoing cancer treatment. Males should be encouraged to collect semen prior to initiation of treatment and should freeze as many samples as possible. If production of the sample is problematic then penile vibratory stimulation or electroejaculation can be used. Hormonal suppression prior to chemotherapy in males has been attempted with limited success. Another experimental option for men is testicular sperm extraction and testicular tissue freezing[2] In the future when the male is ready to attempt conception, the couple can undergo assisted reproductive technologies including intrauterine inseminations.

Summary

Referral to a reproductive endocrinologist specialist around the time of cancer diagnosis is important to expand and optimize treatment options for patients receiving chemotherapy or radiation. There are many options available for patients undergoing a treatment that may negatively impact their fertility. Many new experimental techniques show promise but further research is needed before they are offered as standard of care. Sperm banking and cryopreservation of embryos are the best established options. We recommend liberal use of GnRH agonists with GnRH antagonists in those who cannot wait an adequate time prior to chemotherapy for the GnRH agonists to be effective along with

appropriate study approval. Patients who are interested in experimental options should be encouraged to enroll in clinical studies.

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Controversies Surrounding Screening Mammography

by Pamela M. Otto, MD & Christa B. Blecher, MD

Women at average risk should begin screening mammography at age 40. We recommend annual screening for all of our patients. We do not have an upper age limit for screening, but instead recommend that routine mammographic screening continue while a woman remains in good health.



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Abstract

Screening for breast cancer with mammography has been shown in multiple randomized control trials to decrease breast cancer mortality. Despite this, there are ongoing controversies regarding the benefits and risks of mammographic screening. Different professional groups have published conflicting guidelines regarding when to start screening, how often to screen, and when to stop screening which have added to the confusion. In this article we describe the evidence supporting and challenging the efficacy of mammography and review our real world approach to breast cancer screening.

Introduction

Screening mammography has now been in widespread practice in the United States for more than three decades and there is an abundance of data showing improved outcomes over this time. The combination of early diagnosis and better treatment has contributed to a 34% decrease in the breast cancer death rate between 1990 and 2010.[1] This dramatic progress has been a triumph of modern medicine with tens of thousands of women's lives saved.

There are multiple factors contributing to this dramatic success story and not everyone agrees on the degree to which each factor has lowered breast cancer death rates. Patient education and the effects of patient-led breast cancer awareness campaigns, such as those by the Susan G. Koman Foundation, have motivated women both to be screened for breast cancer and to present for evaluation when they develop breast symptoms. There have been advances in breast cancer screening and diagnosis with the advent of digital mammography and the widespread use of breast ultrasound and breast MRI. There has also been major progress in breast cancer treatment, especially in the realm of chemotherapeutic and hormonal therapies, but also in the fields of surgical oncology and radiation oncology. Even with the improvements in treatment, screening mammography alone has been estimated to account for 28-65% of the decline in breast cancer death rates.[2]

The Evidence for the Benefit of Screening Mammography

Any proposed screening test should be examined in terms of its benefits, patient acceptance, safety, and costs both to patients and society as a whole. Mammography is non-invasive, generally well-tolerated by patients, safe, and relatively inexpensive making it an attractive screening test. Given these factors, major studies showing a mortality benefit from mammography have led to widespread acceptance of the test in the U.S. and around the world.

Most of the strongest evidence for the effectiveness of screening mammography in reducing death rates from breast cancer comes from multiple large scale randomized controlled trials (RCTs), the majority of which were performed in the 1970s and 80s. The RCTs of screening mammography which are most often referenced include (start dates in parentheses): New York Health Insurance Plan (HIP) (1963), Malmö (1976), Swedish Two County Trial (1977), Canadian National Breast Cancer Screening Study (1980), Stockholm (1981), Gothenburg (1982), and the UK Age trial (1991).[3,4] Two of the RCTs which show a clear benefit to screening mammography are the Swedish Two County Trial demonstrating a 31% mortality reduction in women aged 40-74 invited to participate in screening mammography[5] and the HIP clinical trial demonstrating a 25% reduction in breast cancer mortality in screened women aged 40-59.[6]

These RCTs have been exhaustively reviewed with meta-analyses of the studies demonstrating a mortality reduction secondary to screening mammography in the range of 15%-26%,[3, 4, 7] with the most recent overview citing a reduction of 20%.[4] The RCTs screened different age groups, used variable screening intervals, utilized different mammographic techniques, and varied as to whether the subjects were actually screened with mammography or just invited to attend screening. All of these factors may account for some of the variability in outcomes.

Outside the RCTs there is also a large amount of data which confirms the mortality benefit of screening mammography. The Breast Cancer Detection Demonstration Project, a combined effort of the American Cancer Society and the National Cancer Institute (1973-1980) showed that 41.6% of all cancers and 59% of non-invasive cancers were found by mammography alone; 8.7% of cancers were found by physical examination alone; 21% of cancers were found in women 40-49 years old; and mammography alone detected 35.4% of the cancers in women in their 40s.[8]

In a follow-up to his original Swedish Two County screening mammography trial, Dr. Laszlo Tabar compared breast cancer mortality within individual counties in the pre-screening and post-screening time periods. Among women invited to undergo mammography, there was a reduction in breast cancer mortality of 50%. Among women who actually underwent regular mammographic screening, he reported an even more impressive 63% reduction in breast cancer mortality. Interestingly, this study also reported no significant mortality reduction in women who were not screened despite new therapies.[9]

Another study published in 2002 utilizing data from Sweden demonstrated a 40-45% decrease in breast cancer mortality in women attending mammography screening compared with a 33% decrease in mortality in all women, screened and unscreened. The authors asserted that their results support the contention that screening mammography is a major factor in breast cancer mortality reduction.[10] Similar mortality reductions have been observed in the Florence Italy screening program study; furthermore, after excluding the breast cancer cases diagnosed at the first screening examination (prevalence screening round), this study reported that the incidence of Stage II or greater breast cancer cases was 42% lower in screened women compared to the unscreened population.[11]

Leading breast radiologist and mammography advocate Dr. Daniel Kopans has written extensively on screening mammography and in particular on screening women in their 40s. He has reported a significant decrease in breast cancer mortality, up to 44%, when mammographic screening is used in women aged 40-49 and long-term follow-up is evaluated. He also emphasizes that many of the RCTs underestimate screening mammography's benefit because their analyses report on women who were "invited" for screening, but did not necessarily actually get screened.[12]

One of the most recent studies assessing the benefits of screening was published in 2013 using a 'failure analysis' approach to breast cancer deaths. Women at a single institution who were either never screened or inconsistently screened accounted for 71%

of breast cancer deaths and the average age at diagnosis of fatal breast cancers in the study was 49 years. The authors emphasize that annual screening is imperative in younger women. They also conceded that, based on their analysis of breast cancer death rates in older women, biennial screening in women aged 70 or greater may be reasonable.[13]

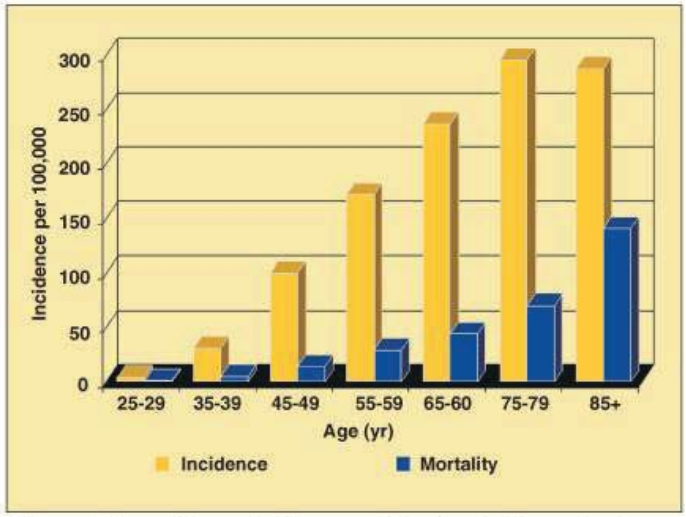


Figure 1: Breast Cancer Incidence and Mortality in Women by Age— US Surveillance, Epidemiology and End Results Registry (SEER) data from 1997–2001.

Studies Questioning the Benefit of Screening Mammography

There are also several well known studies which question the benefit of screening mammography. Perhaps the most well-known of these is the Canadian Trial, a large RCT of screening mammography which initially reported no benefit in women 40-49 years old and question of benefit in women 50-59. Based on these early results, the authors recommended discussion with patients regarding the risks and benefits of screening.[14] The recently released update to this trial showed no mortality benefit for screening mammography in women aged 40-59 when compared with high quality clinical breast exam and standard care.[15]

In 2000, Olsen and Gøtzsche published a paper concluding that the reliable evidence does not indicate any survival benefit of mass screening for breast cancer. They also concluded that screening leads to more aggressive treatment and therefore is not only without benefit, but actually represents a waste of health resources and results in net harm. Of note, in their analysis they excluded five of the seven major screening trials and used all-cause mortality instead of breast cancer mortality as an end point.[16]

In a study comparing women between the ages of 40-49 and women 50 and older undergoing screening mammography at a single institution, the positive predictive value of mammography was lower in the younger women due to overall lower prevalence of disease. Based on this, the authors advocated that screening women in their 40s should be based on risk factors and should not be considered standard for average risk women.[17] The U.S. Preventative Services Task Force (USPSTF) recommendations on screening mammography published in 2009 took a similar view of screening younger women. The panel withdrew its previous support for routine mammographic screening in women aged 40-49 and recommended biennial rather than annual screening for women aged 50-74.[3] The panel's decisions were controversial in part because they changed the recommendations despite there being no new significant data since 1997 when the National Cancer Institute (NCI) issue guidelines recommending screening begin at 40 (See Figure 1).

The Harms of Screening

In addition to the debate about mammography's efficacy in decreasing breast cancer mortality, there are ongoing discussions of the risks of screening which include patient anxiety, radiation, false positives, and overdiagnosis, especially of DCIS and atypias. In the setting of mammography, false positives refer to women called back for extra mammographic images or breast ultrasounds as well as women who undergo biopsies for lesions that turn out to be benign. Overdiagnosis is defined as disease which would have never presented clinically during a woman's lifetime. These harms were addressed by the USPSTF and contributed to the change in mammography guidelines in 2009.[3]

In 2011, Jørgensen and Gøtzsche concluded that one in three breast cancers detected in an organized population-based screening program is overdiagnosed. An underdiagnosis rate of 18-19% was also reported. They stated that it is not possible to distinguish between lethal and harmless cancers; therefore overdiagnosis and overtreatment are inevitable in a mass screening program.[18] Welch and

Bleyer authored a highly publicized article in 2012 which also argued that nearly one-third of breast cancers are overdiagnosed.[19] The UK Independent Review of breast cancer screening published in 2012 pegged the degree of overdiagnosis in women aged 50-70 in the United Kingdom screening program at 19%.[4]

Another often discussed harm of screening mammography is false positives. In most practices in the United States, about 10% of women getting an annual mammogram will be recalled for additional mammographic imaging or ultrasound evaluation.[1] Additionally, the majority of percutaneous breast biopsies result in benign pathology. Therefore, a large number of women who do not have breast cancer will be subject to the additional time, cost, radiation, pain, and anxiety related to false positive findings on mammography. Several recent publications have reported that the stress associated with false positive mammograms can cause long lasting psychosocial harm.[20]

Real World Challenges

Breast cancer remains the most common cancer among women in the U.S. and awareness of the disease has never been higher, partly due to the long term efforts of many breast cancer advocacy groups. However, the USPSTF has narrowed the recommended screening age cohort and suggested biennial screening instead of annual exams. Most major medical groups including the American Cancer Society are recommending against self-breast exams. Guidelines from the USPSTF and National Cancer Institute also report insufficient evidence to show that clinical breast exams decrease breast cancer mortality.[3,21] What do women have left?

What are the real world effects of decreased screening recommendations? Changing from yearly to biennial screening in the U.S., where there is not a centrally organized program inviting women to screening, may result in more inconsistent screening uptake. At current practices where annual screening is recommended, every 18-month or two-year screening is typical. In this environment, will biennial screening become every three- or four-year screening? What will happen if we don't screen women in their 40s when 17-25% of breast cancers are diagnosed in this age group?[1,8,13] How many women will abandon screening altogether due to the confusion and ever changing guidelines?

Approach to Screening

In average risk populations, annual screening mammography is recommended beginning at age 40 according to guidelines published by the American College of Radiology, the Society of Breast Imaging, the American Cancer Society, the American College of Surgeons, and the American College of Obstetricians and Gynecologists. The USPSTF recommends routine biennial screening from 50-74 years and suggest that women between the ages of 40 and 49 should discuss the risks and benefits of screening with their doctor. The American College of Physicians and the American Academy of Family Physicians recommendations mirror the USPSTF guidelines.[3,21,22]

The question of whether to start screening at age 40 or 50 is a philosophical one. The prevalence of breast cancer is clearly lower in women in their 40s compared with women in their 50s or 60s. Still, a significant number of breast cancers are diagnosed in women aged 40-49 and these tend to be more aggressive than those diagnosed in older women. When calculated per year of life saved, the cost of commencing screening at age 40 is nearly the same as starting at 50.[12]

Annual screening is usually recommended for women aged 40-50 years due to aggressiveness of the disease and shorter sojourn time in younger women. Most studies demonstrate that in women aged 50 and older, biennial screening is effective.[23] However, compliance with biennial screening is more of a challenge outside of a centrally organized program.

There is a different approach for screening women identified as having an increased risk for breast cancer. For mammographic screening, the history of a first degree relative diagnosed with breast cancer typically guides the screening protocol. Generally, screening begins 10 years prior to the age at diagnosis of a first degree relative; for example, if the patient's mother was diagnosed at age 45, she should start getting screening mammography at age 35. The main exception to this rule is that screening should not begin prior to age 25-30. It is important to note than for high risk women,

mammography is not the only screening tool available. Ultrasound and MRI have both been shown to increase cancer detection rate and are valuable as supplemental screening tools in women at high risk for breast cancer. Specific screening guidelines which incorporate MRI have been established for women with BRCA1 or BRCA2 mutations, a history of therapeutic chest radiation at a young age, certain familial cancer syndromes, or a 20% calculated lifetime risk of breast cancer.[22]

The topic of when to stop screening is not well studied, but we know based on incidence studies that the rate of breast cancer continues to rise with age. The average life expectancy of women in the United States is 86 years. The American Cancer Society recommends continuing routine mammographic screening as long as women are in good health; in other words, as long as they are healthy enough to undergo treatment if a cancer were to be diagnosed.[1] The USPSTF does not recommend routine screening after the age of 74 due to lack of evidence.[3]

Conclusions

At the University of Texas Health Science Center at San Antonio, we agree with the American College of Radiology, the Society of Breast Imaging, the American Cancer Society, the American College of Surgeons, and the American College of Obstetricians and Gynecologists and recommend that women at average risk begin screening mammography at age 40. Although studies show good results with biennial screening in women over 50, due to compliance issues we recommend annual screening for all of our patients. We do not have an upper age limit for screening, but instead recommend that routine mammographic screening continue while a woman remains in good health.

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Disclosure

None reported.

MM

Hypothyroid Cardiomyopathy Complicated by a Left Ventricular Laminar Thrombus

by Benjamin J. Van Treeck, BS & Amgad G. Masoud, MD

We report a third case of reversible hypothyroid cardiomyopathy complicated by a left ventricular laminar thrombus.





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Abstract

Clinical hypothyroidism is the most common hormone deficiency in the United States and is found in 0.3% of the U.S. population.[1, 2] It is associated with characteristic symptoms that can be readily identified by a careful history and physical examination. Hypothyroidism affects many bodily systems; in particular the cardiovascular system is impacted via multiple mechanisms.[3] Occasionally hypothyroidism leads to transient left ventricular systolic dysfunction, termed hypothyroid cardiomyopathy. A rare sequela of this condition is a left ventricular thrombus, which has been described in two case reports thus far.[4, 5] Here we report a third case of reversible hypothyroid cardiomyopathy complicated by a left ventricular laminar thrombus.

Case Report

A 44-year-old female was admitted to the hospital after suffering a syncopal episode while visiting a friend in the hospital. Blood pressure and pulse were 97/70 mmHg and 75 beats per minute, respectively. Orthostatic hypotension was not present. History revealed cold intolerance, constipation, no chest pain, no heart palpitations, no dyspnea, and no seizure-like activity. Physical exam demonstrated slow mentation, flat affect, hoarse voice, delayed reflexes, no jugular venous distension, and no lower extremity edema. Medical records indicated she had undergone ^{131}I-radioiodine thyroid ablation for Grave's disease two years prior. The patient discontinued her levothyroxine shortly after thyroid ablation because of poor follow-up. Laboratory values were as follows: thyroid stimulating hormone (TSH) 134.18 uIU/ml (normal 0.34-5.6), free T_4 0.18 ng/dl (normal 0.6-1.6), troponin I 0.13 ng/ml (normal 0.0-0.06), creatinine 1.3 mg/dl (patient's baseline 0.8, normal 0.9-1.3), and hemoglobin 15g/dl (normal 12-16). See table 1 for a summary of laboratory results. An electrocardiogram (EKG) revealed new T-wave inversions in leads I and aVL, corrected QT interval of 508 milliseconds, and low voltage QRS. A transthoracic echocardiogram (TTE) was obtained because of

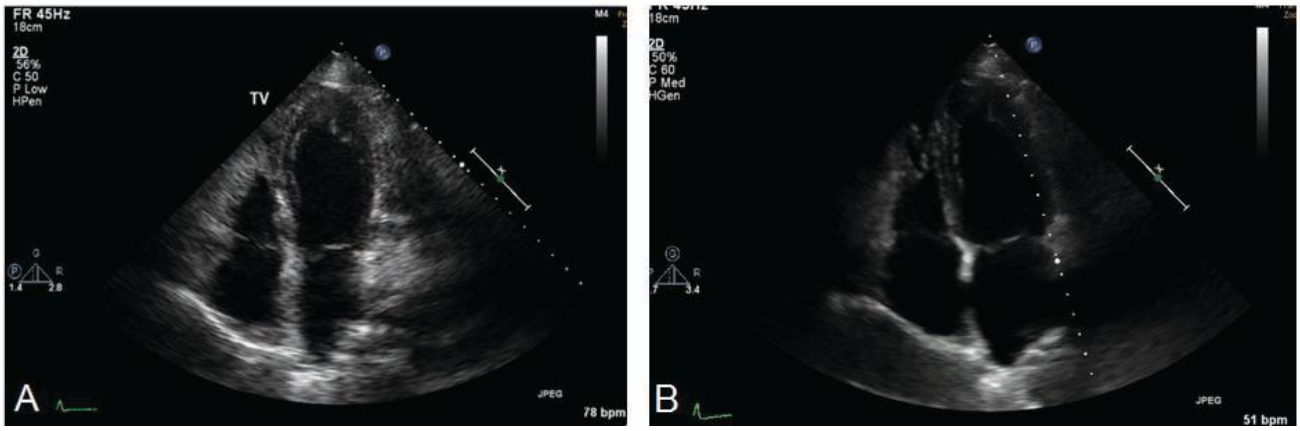


Figure 1. Transthoracic echocardiograms obtained prior to levothyroxine therapy (A) and status post two months of levothyroxine therapy (B). Note the presence of echodensities along the left ventricular apical surface indicating a laminar thrombus and resolution of echodensities after levothyroxine therapy.

the low voltage finding on the EKG and concern for cardiomyopathy and pericardial effusion. The TTE demonstrated a left ventricular (LV) ejection fraction of 25%, global LV hypokinesia, small anterior pericardial effusion without tamponade like features, and a LV laminar thrombus as depicted in Figure 1. Systemic vascular resistance was also calculated, 4,188.8 dynes-sec-cm^{-5} (normal 700-1,600 dynes-sec-cm^{-5}), utilizing variables derived from the TTE and assuming a mean right atrial pressure of 4 mmHg.[6]

The patient's syncope was attributed to a vasovagal reflex in combination with dehydration. Intravenous fluid resuscitation ameliorated the acute kidney injury and diluted the hemoglobin into the anemic range of 10g/dl (normal 12-16). Levothyroxine was initiated and titrated up slowly for the patient's overt hypothyroidism and suspected hypothyroid cardiomyopathy. The LV thrombus was treated with warfarin and an enoxaparin bridge, and there were no signs or symptoms of thromboembolization during or after hospitalization. Troponin I trended down to normal within twenty-four hours of admission deferring the ischemic workup to the outpatient setting. The patient was discharged on levothyroxine and warfarin, and instructed to follow-up with her primary care physician and cardiology for an ischemic workup.

At the patient's two month follow-up appointment, her TSH was 5.82 uIU/ml and her free T_4 1.00 ng/dl. A repeat TTE revealed resolution of the LV laminar thrombus and a normal LV ejection fraction of 51%, thus warfarin was discontinued. Normalization of the LV ejection fraction provided confirmation of the suspected hypothyroid cardiomyopathy. Systemic vascular resistance was calculated to be 2,316.9 dynes-sec-cm^{-5}. The patient's hypothyroid symptoms improved with the continuation of levothyroxine therapy. She continued to deny symptoms of cardiac ischemia and because the patient's low LV ejection fraction resolved with levothyroxine replacement, cardiology decided to omit the ischemic workup that was previously planned.

Discussion

Hypothyroid cardiomyopathy presents with characteristic cardiovascular sequelae that can be explained by attenuation of triiodothyronine (T_3) interaction with the cardiovascular system. T_3 is essential for maintaining cardiovascular homeostasis and has been shown to impact LV systolic function via cardiac contractility, systemic vascular resistance, and total blood volume.[3,7] Hypothyroidism reduces cardiac contractility due to up regulation of phospholamban and beta myosin, dysregulation of cardiac myocyte membrane ion channels, and down regulation of cardiac β_1 adrenergic receptors. Furthermore, low T_3 levels elicit vascular smooth muscle cells to decrease nitric oxide synthase production and alter membrane ion channel conductance thereby increasing systemic vascular resistance and cardiac afterload.[3,7] Elevated systemic vascular resistance down regulates the renin-

angiotensin-aldosterone system, reducing blood volume and cardiac preload. Increasing afterload and decreasing both cardiac contractility and preload ultimately leads to a reduced systolic ejection fraction and contributes to low cardiac output. The reduction in cardiac output explains the narrow pulse pressure observed in hypothyroidism. Depressed T_3 also attenuates erythropoiesis, decreasing the hemoglobin and hematocrit leading to normocytic normochromic anemia.[3]

Dysregulation of the intravascular and extravascular fluid homeostasis, as a result of hypothyroidism, leads to pericardial effusion. However, this finding is not universal among hypothyroid patients. Approximately 38% of hypothyroid patients present with a pericardial effusion.[8] Fluid accumulation is believed to result from diminished lymphatic clearance and increased albumin extravasation and is reversible with levothyroxine replacement.[7] Interestingly, the pericardial effusion almost never presents with tamponade. A possible explanation is the slow accumulation of the pericardial effusion permits the heart time to adapt.[7] Low voltage QRS results from the pericardial effusion. However, the QT prolongation, commonly seen in hypothyroidism, is due to attenuation of potassium channel expression in cardiac myocytes prolonging ventricular repolarization.[9] One report describes a case of torsades de pointes in a hypothyroid cardiomyopathy patient.[1] Therefore, avoiding drugs that may exacerbate a long QT interval should be enforced until the QT interval normalizes with levothyroxine therapy. Surprisingly in hypothyroidism, patients can present with elevated troponin I and EKG changes such as inverted T waves that falsely imitate acute coronary syndrome.[1,10] Thus, it is important to rule out myocardial ischemia.

This report illustrates a patient who developed overt hypothyroidism secondary to neglecting levothyroxine replacement therapy for approximately two years post thyroid ablation. The patient presented with transient hypothyroid cardiomyopathy and LV laminar thrombus. This case is an important reminder that in some instances, severe LV systolic dysfunction with LV thrombus may be reversible and physicians need to be cognizant of this possibility. A TSH level should be ordered when patients present with LV systolic dysfunction to assess for hypothyroid cardiomyopathy. Furthermore, this case also emphasizes the rare association of a LV thrombus with hypothyroid cardiomyopathy. To date, only two cases of hypothyroid cardiomyopathy with concomitant LV thrombus have been described in the literature.[4, 5] In all three cases, including the case presented in this article, the hypothyroid cardiomyopathies reversed with levothyroxine replacement and the LV thrombi resolved with anticoagulation. One case reported by Yang et. al. (2011), documented LV thromboembolization eliciting a cerebral vascular accident.[5] Further reporting of this association increases physicians' awareness of the possible concomitant occurrence of hypothyroid cardiomyopathy and LV thrombus and the need for anticoagulation for thrombus resolution.

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Disclosure

None reported. **MM**

Clues from Hands / Part 2

Personal Details about Patients Revealed by Hand Examination

by Karen Danielle Schilli, MS, Sherea Monica Stricklin, PGY1, Katie Sue Payne, MS1, Ryan Kent Rader, MS2 & William V. Stoecker, MD

The astute clinician has daily opportunities to practice these observational skills, increasing the range of detectable signs well beyond the examples present here, following in the tradition of the famous fictional detective, Sherlock Holmes.



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Abstract

This is the second part of a two-part article on personal details revealed by hand examination. Examining hands to determine daily activities was the focus of Part 1 in the July/August 2014 Missouri Medicine. Personal traits and preferences, including pets, nutrition and psychology are presented here. These articles serve as a guide for visual clues on the hands to discern a patient's daily activities and personal preferences, thereby providing social information that may help establish rapport between patient and physician and may have medical significance.

Introduction

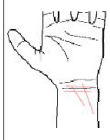
This article is Part 2 of our study of clues obtained from hands, detailing visible signs that yield information about a patient's social and personal history. This article shows personal traits and preferences, including pets, nutrition, and psychology. Not only do these findings enable us to understand our patient better, they may allow us to diagnose nutritional deficiencies and psychological problems at an earlier stage. Additionally, understanding a patient's personal traits can help us focus on more effective prevention. As an example, we will show how finger lengths in males are correlated with risk taking, enabling us to identify those males most at risk for problems associated with risky behaviors. Table 1 provides an overall summary of the activities presented in this article.

Pet Owners

Superficial scratches located from the hand up to the elbow can often be explained by pets. The characteristics of these scratches help identify the type of pet involved. Large dogs can jump high on their owners' arms, or rest their paws near owners' elbows, then slide down, causing vertical scratches down the forearms (See Figure 1). Timing of the injury can also be inferred —the partially healed scratches in Figure 1 are at least one week old. In contrast, small dogs cannot reach their owners' arms while the owner is standing, therefore vertical scratches are not seen. When owners crouch down, the small dog may paw at their forearms, close to the wrist, causing small lateral scratches (See Table 1).

Cat scratches (See Figure 2) are similar to those of small dogs, with short scratches closer to the hands). However, cat scratches are commonly located on dorsal hands, a significant difference from small dog scratches. They are often short, narrow, and

Table 1

Activity	Diagram	Location	Morphology	Explanation	Comments
Big dog owner		Dorsal forearm	Long, axial linear scars	Owner standing, arm straight.	Owners often like the outdoors, exhibit high level of fitness
Small dog owner		Distal dorsal forearm	Circumfer-ential linear scars	Owner crouching, arm bent	
Cat owner		Wrist and hands, may appear elsewhere, especially extremities	2-4 parallel short linear or punctate wounds	Kittens extend all claws and sometimes like to 'hang on'	Can be correlated with preference for quiet indoor activities
Cooking (baking)		Distal extensor (usually dominant) forearm	Short slanted burns	Oven racks burn hands; arms angled at 30°	Lines may persist for months or longer
Black-berry picking		Dorsal hand	Short linear scratches during summer months	Thorns from blackberry vines scratch dorsal side of hands	Summer only
Veget-ables in diet		Proximal volar phalanges, often 3rd/4th digits	Dark yellow to orange pigment (xantho-chromia).	Dietary chromogens include carotenes, lutein, lycopene	Identifying dietary deficiencies can benefit the patient
Forced vomiting due to bulimia (Russell's sign)		Dorsal hand near 2nd-4th MCP and proximal 2nd carpal bone	Callus location varies depending on fingers used	Bulimia: teeth scratch fingers when inducing emesis	Identification can aid earlier diagnosis of eating disorders
Suicidal attempt		Flexor wrist	Scars are linear and predomi-nantly circumfer-ential		Patients who have 'put this behind them' do not want this discussed
Males with detailed analytic approach		2nd and 4th digits (index and ring finger)	Length of index finger vs. ring finger (high 2D:4D ratio)	Ratio of prenatal estradiol:test-osterone correlates with 2D:4D ratio	High 2D:4D: associated with detail-oriented: computer programming and other academic fields.
Compet-itive males with high risk profile		2nd and 4th digits (index and ring finger)	Length of index finger vs. ring finger (low 2D:4D ratio)	Ratio of levels of prenatal estradiol: testosterone correlates with 2D:4D ratio	Low 2D:4D: competitive, sports ability and greater risk taking

clustered, as shown in the figure.

Pets owners risk zoonotic infections, including cat scratch disease (B. henselae infection) and tularemia (F. tularensis) in cats.[1] Dogs in Missouri may acquire and transmit Rocky Mountain spotted fever (R. rickettsii infection). Cat and dog serosurveys elsewhere have expanded the list of pathogens that these animals can potentially transmit.[2]

Nutrition

Signs on the hands can help in the nutritional assessment. A patient with a short linear burn on the dorsal forearm near the wrist could be an avid cook who recently received a burn from an oven. These burns are angled with the radial side more distal, due to the arm being flexed when inserting or removing items from an oven (See Figure 3). These burns can be distinguished from other burns such as fireplace burns, which are wider and more proximal. Patients who bake may be open to healthy dietary information, such as heart-healthy ingredients for bread and other baked dishes.[3,4] In mid-to-late summer, patients who pick blackberries display short linear scratches on the dorsal side of their hands, caused by the thorns on blackberry bushes (See Table 1). These scratches are favorable dietary and exercise indicators, providing an opportunity for reinforcement of this activity.

Mild xanthochromia, suggesting significant amounts of vegetable consumption in the diet, is first seen on the volar surface over the proximal palmar phalanges, most prominently on third and fourth digits, especially with hyperextension. Figure 4A shows the volar orange coloration on the proximal fingers of a person who consumes 4 servings of vegetables/ day. Although commonly attributed



Figure 1
Long scratches oriented axially along the dorsal forearm from a patient's large dog.



Figure 2
Small scratches and small punctures from kitten on forearm.



Figure 3
Short angled burn along distal extensor forearm from an oven rack.

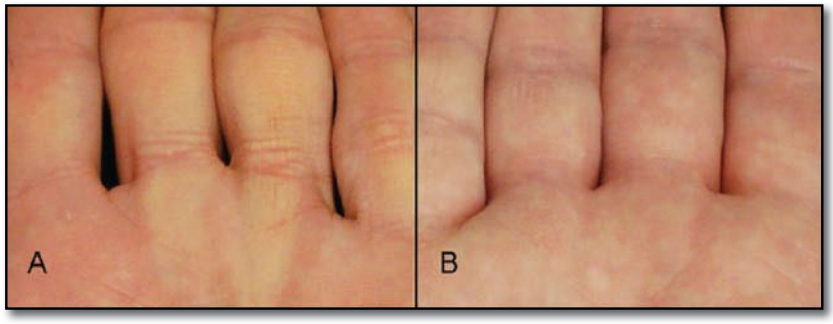


Figure 4
A)vis easiest to detect on volar proximal palmar phalanges, with hyperextension, predominantly on third and fourth digits, in patient who consumes four servings of green and yellow vegetables daily. B) Absence of xanthochromia in patient with vegetable-deficient diet.



Figure 5
Linear and circumferential scars along flexor wrist due to attempted suicide by cutting.

to carotene in carrots, chromogens such as lutein and lycopene also contribute pigment. Figure 4B shows absence of xanthochromia in a patient who consumes about one vegetable serving per day. If on hyperextension, no yellowing is evident, as in Figure 4B, the examiner may be confident that the patient is consuming fewer than two pigment-rich vegetables per day. This provides an opportunity to recommend the DASH (Dietary Approach to Stop Hypertension) diet, long known to benefit hypertension.[4-6] Absence of this volar orange coloration in children with the metabolic syndrome affords an opportunity for intervention. Data from a recent randomized crossover trial shows benefit of the DASH diet for the childhood metabolic syndrome.[7]

Signs of Psychological Disorders

Figure 5 shows the wrist of the non-dominant hand of a patient with a history of attempted suicide via wrist cutting, in an attempt to sever major blood vessels. The scars are linear and predominantly circumferential. These critical findings provide insight to a patient's past psychological history that may not otherwise be voluntarily disclosed.

Russell's sign, characterized by calluses on the dorsal hand or knuckles, although not pathognomonic, is a strong indicator for a patient with purging-type anorexia nervosa (AN) or bulimia nervosa (BN) (Figure 6A).[8,9] These calluses form from teeth repeatedly scraping along the fingers during self-induced purging. While generally prominent over the knuckles,



Figure 6A
Russell's sign on skin over second and fourth metacarpophalangeal joints. Note the abrasion on the fourths proximal phalanx, consistent with a history of recent purging.

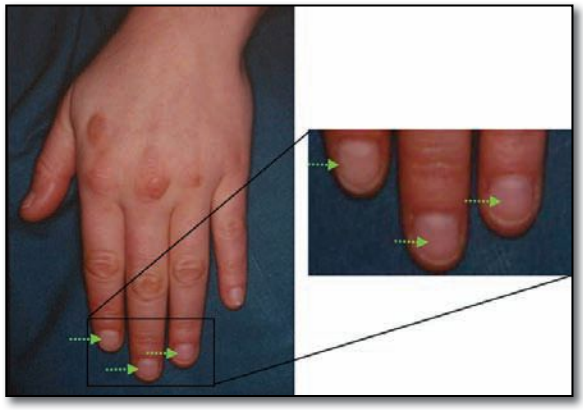
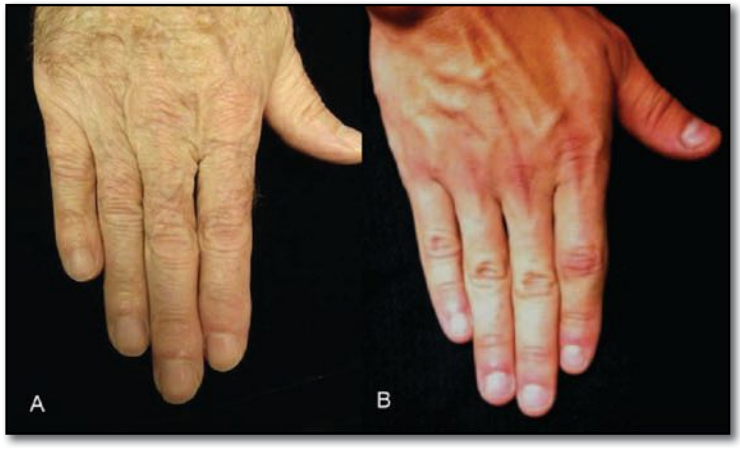


Figure 6B
Russell's sign on skin over second and third metacarpophalangeal joints as well as the prominence over the 2nd metacarpal head. No signs of recent purging such as the abrasion in Figure 6A are present. Barely perceptible grooves in the nail plate reflect starvation status five weeks previously. Nutritional clues in the nails are clearest from a fingertip vantage point. (Photos courtesy of Renata Strumia, MD)



Figures 7A & 7B
A) Longer length of index versus ring finger length (2D:4D) in a computer programmer.

B) Shorter length of index versus ring finger length (2D:4D), in a motorcycle rider and explosive detection expert. The 2D:4D ratio is best assessed with fingers straight.

these BN calluses may also be found near the prominence of the second metacarpal head, as a result of using the index finger to induce emesis (Figure 6B). Calluses at these sites may be accompanied by lateral fingernail ridges (Figure 6B) that indicate nutritional deficiency. Strumia suggested the terminology "anoretic's hand" for identifying a patient with AN, when Russell's sign is absent. Anorectic's hand is comprised of three signs: xerosis, carotenoderma, and cold hands.[8] Xerosis is abnormal dryness of skin with minimal scaling, most likely due to caloric deprivation causing decreased secretion from sebaceous glands. Increased ingestion of carotenoid-rich vegetables can lead to presence of carotenoderma, manifested as xanthochromia, or yellowing of the skin.[8] Elevated carotene levels are found in patients with AN due to the desired ingestion of low calorie foods such as vegetables. If Russell's sign or anorectic's hand is present, they may be accompanied by low BMI, low self-esteem, and distorted perception of body weight.[8] Early identification of AN and BN via either of these signs is potentially life-saving.

Finger Lengths in Men and Personality Traits

Men with a shorter index fingers in comparison to ring fingers (low 2D:4D ratio) have been said to have increased visual-spatial ability and a tendency to excel in physical science.[10] Studies have found a negative correlation of prenatal testosterone/estrogen ratio with a second digit to fourth digit ratio (2D:4D).[11] As Geschwind and Galaburda suggest, "high prenatal testosterone promotes the growth of the right hemisphere and facilitates visual-spatial ability."[10]

Our observations in the clinic support Brosnan's finding that people with a higher 2D:4D ratio thrive in certain detail-oriented professions such as higher

education and computer programming.[12] We found several male computer science faculty members and computer programmers with a high 2D:4D ratio, sometimes exceeding unity (Figure 7A). These men have an analytic approach with great attention to detail, skills that are required for computer programming. They approach decisions analytically, so they often request additional elucidation before they are comfortable with medical advice.

Conversely, a significantly low 2D:4D ratio is associated with a tendency toward competition and risk-taking.[13] Success among high frequency futures traders was greatest among those with lowest 2D:4D ratios.[13] A low 2D:4D ratio was also correlated with success in sports, particularly American football.[14] These studies support the hypothesis that prenatal testosterone promotes the development and maintenance of traits which are useful in activities where aggressiveness and risk-taking are important. The hand of a patient with a preference for taking risks is shown in Figure 7B. He has worked with different military groups, specializing in finding improvised explosive devices (IEDs). He enjoys street racing and motorcycle riding. Note the low 2D:4D ratio (Figure 7B), expected with his high risk profile. This case illustrates how a low 2D:4D ratio is associated with the tendency of a patient to take risks, and especially to engage in sports with breakneck intensity, traits which may generate safety concerns for our male patients. Our observations and the associated 2D:4D hypothesis, has to date been confined to male patients.

Conclusion

As we have shown, the hand examination can reveal details that have medical implications. Astute clinicians strive to incorporate techniques that increase patient trust. Connecting with a patient on a personal level may improve therapeutic compliance and patient satisfaction. For primary care practitioners, trust and confidence in the physician can be developed over an extended period of time. However, for new patient visits, or for some specialists, such as those practicing emergency medicine and dermatology, there may be only one visit to establish a relationship with a patient. If successful, this relationship benefits both physician and patient.

Features found during physical examination and communicated to the patient are helpful in establishing this trust, and as we have shown, can lead to promote earlier significant medical interventions. We submit this to the medical community: clues from observations of hands and forearms can tell us a lot about a patient's daily activities, and these findings increase our effectiveness as clinicians.

As Sir William Osler said, "The good physician treats the disease; the great physician treats the patient who has the disease." We add one caveat—judgment is paramount when disclosing these details, especially those that may reveal self-destructive tendencies or personality traits.

Acknowledgment

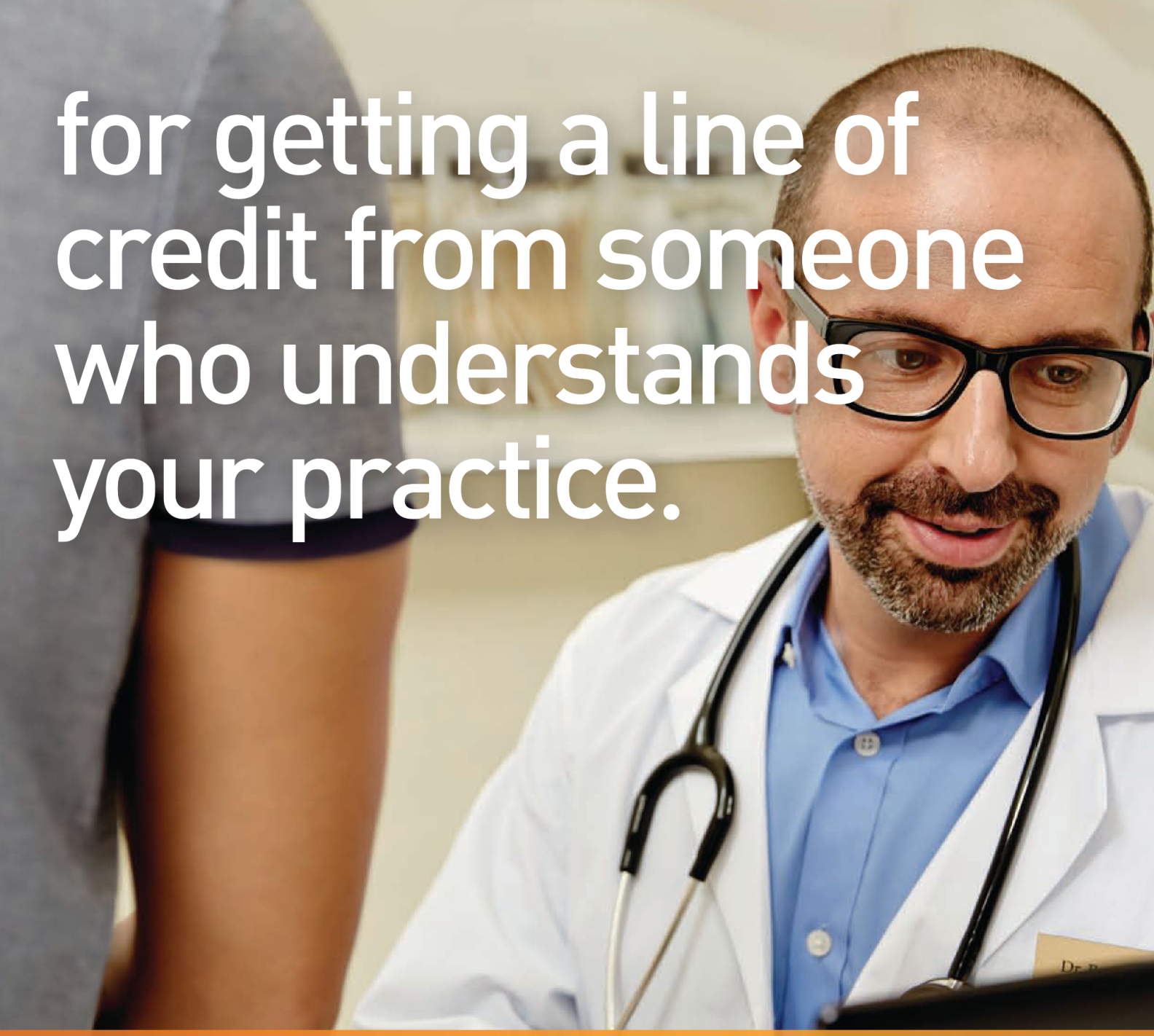
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Disclosure

None reported. **MM**



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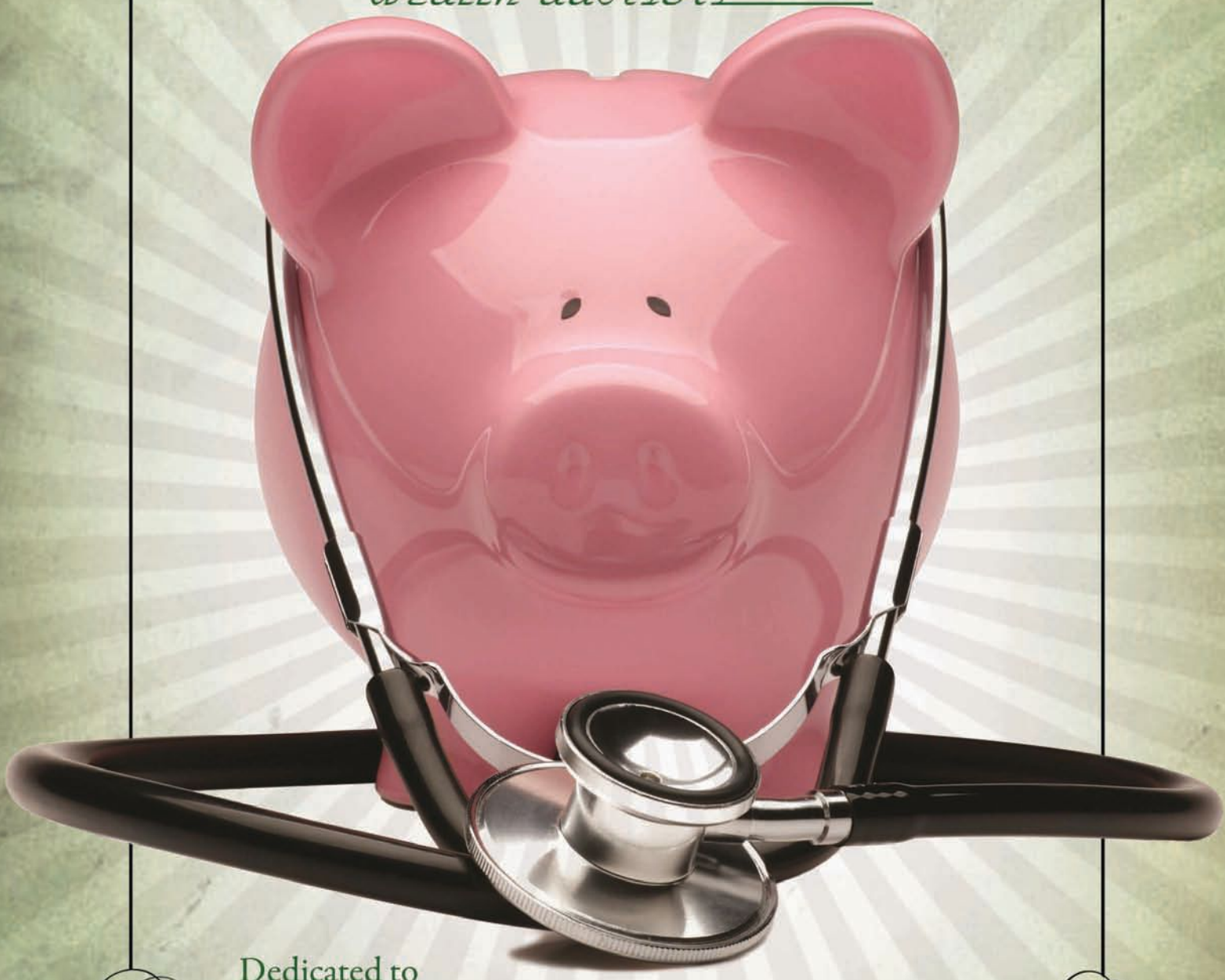
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