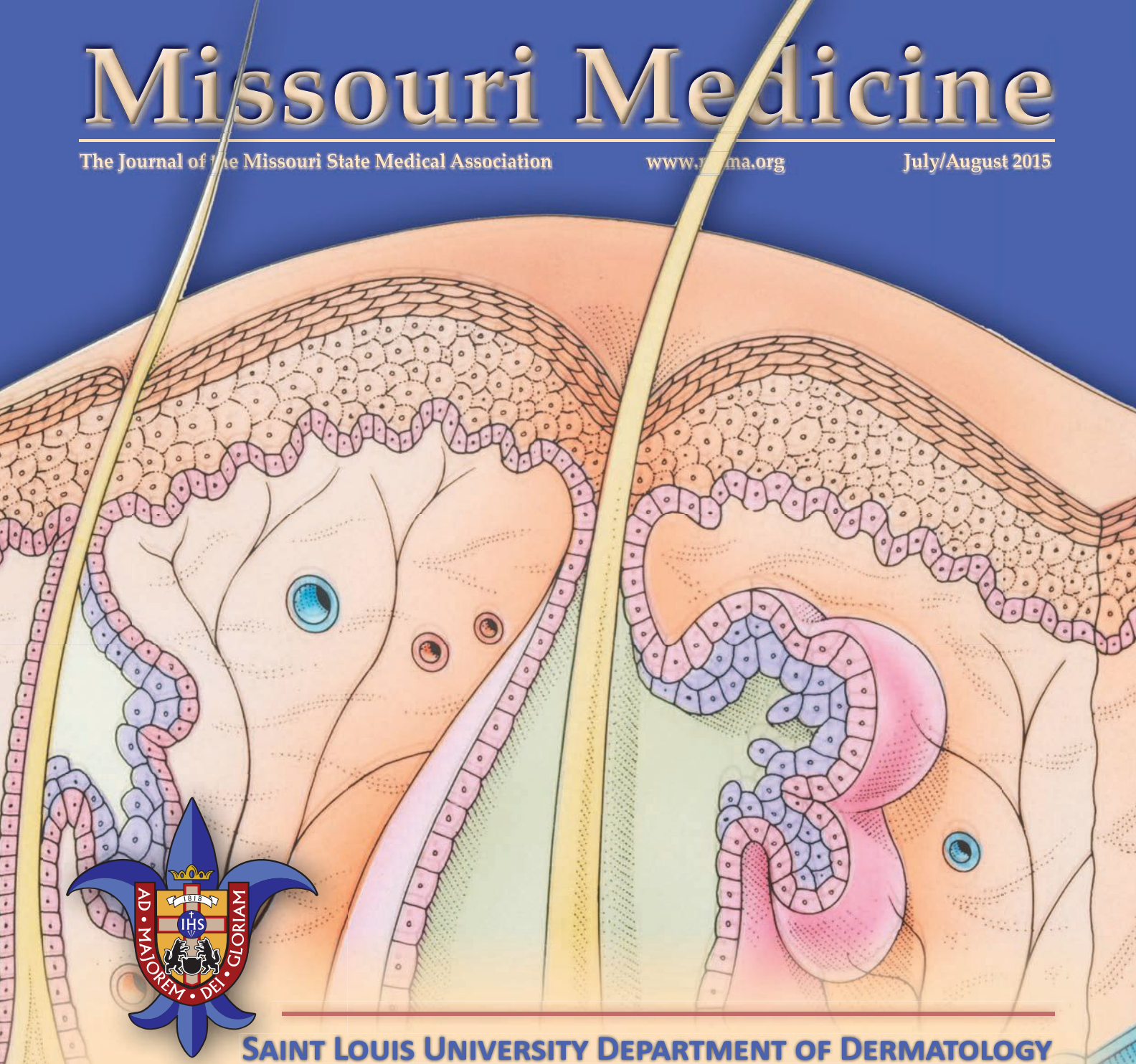
Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org July/August 2015



Saint Louis University Department of Dermatology

The Science of Advancing Skin Care

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Fifty Years of Medicare

Caring for LGBT Patients

World Food Day is October 16

Honoring Military Physicians

ADDITIONAL SCIENTIFIC

How Host Microbiota Contributes to Overall Health

Community, Public Health & Primary Care Linkage

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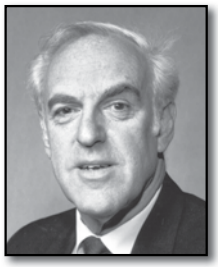
Fifty Years of Medicare



The Good and the Bad

by Arthur Gale, MD

Contributing Editor Arthur Gale, MD, renders his personal opinion about half a century of Medicare and looks into its troubled and uncertain future.



Arthur H. Gale, MD, MSMA member since 1976, is a *Missouri Medicine* Contributing Editor. He practices Internal Medicine in St. Louis.
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The Good of Medicare

July 30, 2015, marked the fiftieth anniversary of Medicare. President Harry Truman first enunciated the need for health insurance for the elderly. President John Kennedy was working on a plan before he was assassinated. Medicare was enacted in 1965 during the Lyndon Johnson administration. The bill was signed by Johnson in Independence, Missouri, the home of Harry Truman who became the first person enrolled in Medicare.

I started practice in 1963, a year and a half before Medicare began. I recall a patient about 65-years-old who came to my office with chest pain. I hospitalized him at a private hospital. He had a myocardial infarction from which he recovered. Several months later he again came to my office with complaints of chest pain. His major concern was not his chest pain but that he had run out of insurance and could not afford private hospitalization.

I arranged for him to be admitted to St. Louis County Hospital. In those days when patients had no insurance they were admitted to a ward service at St. Louis City or St. Louis County Hospital. Medicare was a godsend for patients like the one I just described.

For the first twenty to twenty-five years Medicare worked well with regard to cost to the taxpayer and the quality of care rendered to patients. Journalist Steven Brill showed in a landmark *Time* magazine article how Medicare brought under control the main driver of high health care costs-the hospitals.[1] In contrast to private commercial health insurance companies, Medicare accomplished this feat with very low administrative costs.

The Fee-For-Service (FFS) method of payment under which Medicare operated during this time allowed doctors to act as advocates for patients. Doctors were able to give patients enough time during office visits to express all of their complaints and concerns. The quality of care was good. Until the 1990s most patients were satisfied with Medicare and almost all physicians accepted Medicare.

The Bad of Medicare:

Medicare Advantage, Medicare Acountable Care Organizations, and Medicare Part D

Medicare Advantage

A revolutionary change in Medicare occurred in 1973, during the Nixon administration when the federally-backed Health Maintenance Organization (HMO) Act was passed. This law provided grants and loans to HMOs and required employers with 25 or more employees to offer federally certified HMO options if they offered traditional health insurance to their employees. This law gave HMOs access to the private health insurance market and ultimately to the Medicare population.[2]

This law is, in my opinion, the primary cause of America's problems with cost and quality in health care. The bill was supported by both Republicans and Democrats as a strategy to lower rising health care costs. This was a cruel joke because health care costs in the United States at that time were not out of control and were similar to costs in other Western industrialized democracies.

Caught on Tape

The ostensible reason for introducing HMOs into health care was to lower costs. The real reason was to increase corporate profits. This is borne out by an excerpt from the Nixon tapes in a transcript of a 1971 conversation between President Richard Nixon and his aide, John D. Ehrlichman, that ultimately led to the HMO act of 1973. There are some gaps in these tapes:

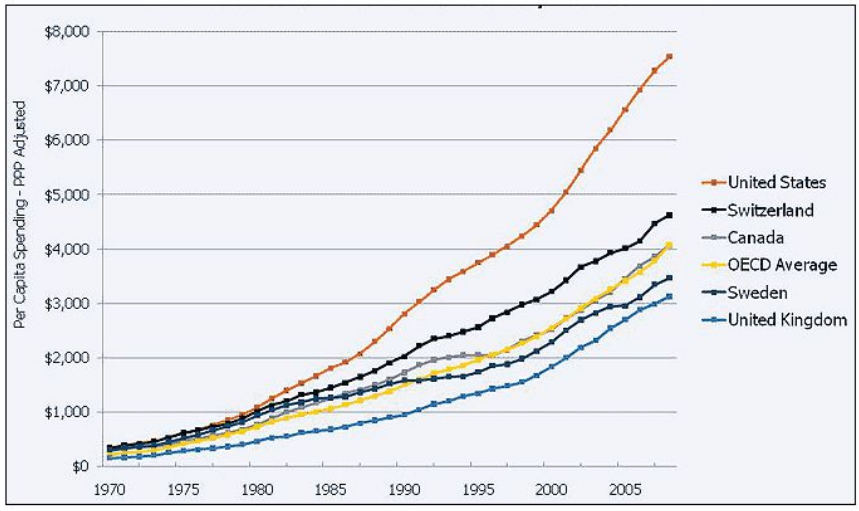
> **Nixon:** … *"You know I'm not too keen on any of these damn medical programs"*
>
> **Ehrlichman:** … *"Edgar Kaiser is running his Permanente deal for profit…And the reason that he can do it…I had Edgar Kaiser come in…talk to me about this and I went into it in some depth…All the incentives are toward less medical care, because…the less care they give them the more money they make"*
>
> **Nixon:** *"Fine…"*
>
> **Ehrlichman:** …*"and the incentives run the right way…"*
>
> **Nixon:** *"Fine…"* [3]

This excerpt neatly sums up the purpose of HMOs from its earliest origins. Nixon told his friends who supported and initiated this law that they could make a lot of money from HMOs. And HMOs have lived up to this expectation in spades. It also explains why health care costs are now so much higher in the United States than in other industrialized nations. Health care costs in the United States were about the same as other industrialized democracies until the 1980s. Then managed care and HMOs took off and so did America's health care costs.



Figure 1 clearly documents this. Health care per capita spending in the United States was about equal to other OECD (Organizations for Economic Cooperation and Development) countries like Canada, the United Kingdom and Switzerland, etc., until about 1980. Then the graph shows a steep rise in health care costs in the USA compared to other countries, which has persisted to the present day. This steep rise coincides with the advent and takeover of the USA health care delivery system by commercial and Medicare managed care.[4]

Figure 1



Source: Organisation for Economic Co-operation and Development (2010), "OECD Health Data", *OECD Health Statistics* (database). doi: 10.1787/data-00350-en (Accessed on 14 February 2011).
Notes: Data from Australia and Japan are 2007 data. Figures for Belgium, Canada, Netherlands, Norway and Switzerland, are OECD estimates. Numbers are PPP adjusted. Break in series: CAN(1995); SWE(1993, 2001); SWI(1995); UK (1997). Numbers are PPP adjusted. Estimates for Canada and Switzerland in 2008.

In the 1980s and 1990s corporate managed care stepped in and "fixed" a system that was not broken. In an Orwellian twist, Medicare policy makers now blame FFS for the high cost of health care despite the fact that standard Medicare which is also known as Medicare FFS annually costs the American taxpayer about $14 billion less than Medicare Advantage, which is Medicare's managed care commercial private for profit plan.[5] It has been estimated that Medicare subsidies to Medicare managed care insurers over the past three decades have amounted to over $280 billion.[6]

Blaming FFS for the high cost of health care is nonsense. Yet everyone involved in health care today, including not just government bureaucrats, policy makers and self-serving insurance cartels, but Congress, hospitals, academics, practicing physicians, residents, medical students, and the general public, all believe this nonsense. Albert Einstein reputedly said any nonsense can attain importance by virtue of its being believed by millions of people.

Medicare Advantage plans are growing and constitute about 30% to 40% of all Medicare enrollees. The public likes them because they get freebees like spectacles, some drug benefits, and gym memberships, and enrollees often do not have to buy a supplemental policy. However, when patients have a serious illness, nursing home and rehabilitation benefits are usually less than in standard Medicare FFS benefits.

Consumers are mainly concerned about how much they pay out of pocket - not what it costs the government and ultimately the taxpayer. So they think that Medicare Advantage is a good deal. The big health insurance companies like UnitedHealth Care and Humana love Medicare Advantage because it is their most profitable product. The corporate executives who run these insurance plans often complain about getting the government out of their lives, but they have no qualms about gouging the government and ultimately the American taxpayer so long as they can make a good profit. Medicare Advantage is a prime example of corporate welfare. The insurance company executives have taken to heart Nixon and Ehrlichman's message about how profitable HMOs can be, "the less care you give them the more profitable they can be."

Accountable Care Organizations

Accountable Care Organizations (ACOs) are the newest government program designed to lower health care costs under Medicare. The easiest way to understand ACOs is to acknowledge that they are just another form of HMO using capitation instead of FFS. Fee-For-Service again becomes the scapegoat for high health care costs even though, as noted above, Medicare FFS on an annual basis is $14 billion per year less expensive than the Medicare HMO, Medicare Advantage. Under ACOs doctors and hospitals will be financially rewarded if they meet certain goals or benchmarks. This is called "shared savings."[7]

The most controversial aspect of ACOs is that doctors will be at financial risk. Financial risk pits the financial

incentives of physicians against the medical interests of patients. The more physicians do for patients the less they get paid. The less doctors do for patients the more they get paid. The physician is no longer the patient's advocate. These financial incentives violate the Hippocratic Oath which states:

> *"I swear…that I… will follow that system which, according to my ability and judgment, I consider for the benefit of patients, and abstain from whatever is deleterious…"*

These perverse financial incentives were tried in the 1990s under the old gate keeper HMOs. Younger doctors probably don't remember gatekeeper HMOs. Under this system the primary care doctor acted as a "gatekeeper" for ordering tests and procedures. For the short time gatekeeper HMOs were in force they did lower health care costs. However when the public found out what actually was going on with their health, i.e., some doctors were padding their own pockets by denying needed care, their fury knew no bounds.

This is best exemplified in the 1997 movie "As Good as It Gets," starring Jack Nicholson and Helen Hunt. In the movie Helen Hunt, a single mother, voices her dissatisfaction in no uncertain terms with an HMO's treatment of her son's asthma. When she says that she is going to obtain the services of a good non-HMO doctor, spontaneous cheering and applause broke out in movie houses all across the nation. These spontaneous public outbursts to "As Good as It Gets" were as bad as it gets for the HMO industry. That movie like no other event signaled the end of gatekeeper HMOs.

I thought that the perverse financial incentives involved in gatekeeper HMOs were gone for good. But I was wrong. The insurance companies apparently never give up on their assumption that doctors are no different from Wall Street traders and that their behavior in treating sick patients can be controlled with financial incentives. Now the same financial incentives they used with gatekeeper HMO are back again under ACOs but with a new name: risk contracts. Because of the bad publicity they received with gatekeeper HMOs the insurance industry wants to conceal its role in developing risk contracts from the public. This is revealed in a recent document released by the American Hospital Association: "One lesson learned from the HMO experiment noted earlier is that providers and patient communities will not accept a system with

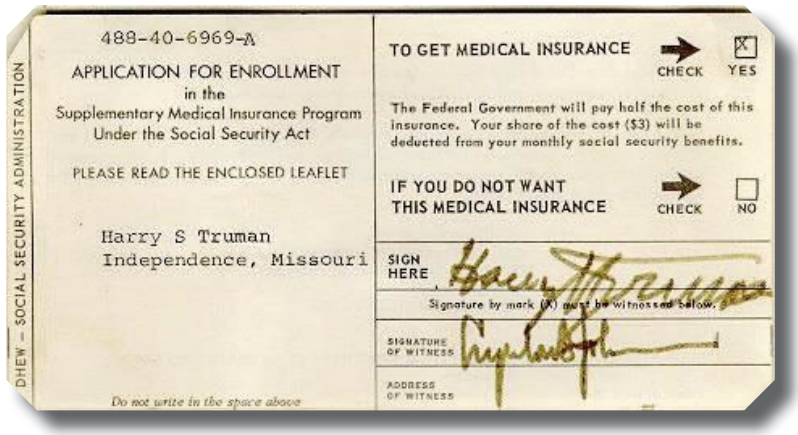
LBJ Signs Bill Establishing Medicare

President Lyndon B. Johnson went to the Truman Library in Independence, Missouri, to have the former president, Harry Truman, join him for the signing of the bill establishing Medicare, or as the record shows then, the "Supplementary Medical Insurance Program Under the Social Security Act."

The Medicare and Medicaid programs were signed into law on July 30, 1965. President LBJ is pictured at the signing ceremony (see page 252). Former President Truman is seated beside him.

LBJ held the ceremony there to honor President Truman's leadership on health insurance, which he first proposed in 1945.

At the bill-signing ceremony President Johnson enrolled President Truman as the first Medicare beneficiary and presented him with the first Medicare card. At right is a photograph of President Truman's application for the optional Part B medical care coverage, which President Johnson signed as a witness


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APPLICATION FOR ENROLLMENT
in the
Supplementary Medical Insurance Program
Under the Social Security Act

PLEASE READ THE ENCLOSED LEAFLET

Harry S Truman
Independence, Missouri

Do not write in the space above

TO GET MEDICAL INSURANCE → CHECK [X] YES

The Federal Government will pay half the cost of this insurance. Your share of the cost ($3) will be deducted from your monthly social security benefits.

IF YOU DO NOT WANT THIS MEDICAL INSURANCE → CHECK [ ] NO

SIGN HERE Harry S Truman

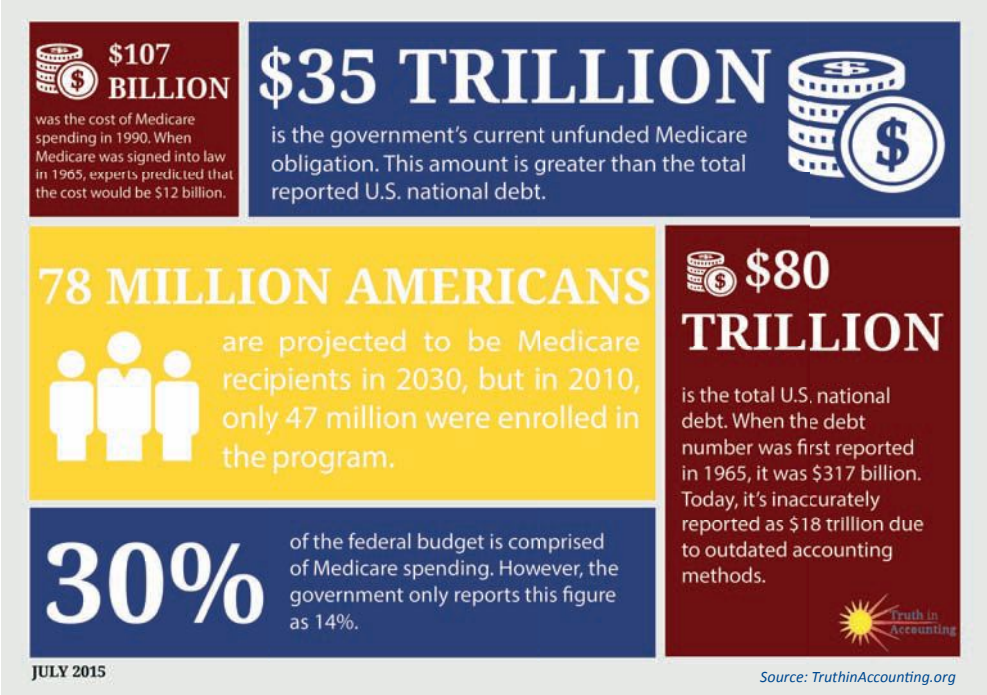
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Photo Credit/Source: SSA History Archives.

medical management from the insurance entity. Consequently there has been an emphasis on physician leadership even when the sponsoring entity, in terms of contracting and investment, is considered the hospital."[8]



What this means in plain English is that now the government and third party insurers with the acquiescence of hospitals and some physicians are going to impose through ACOs physician financial incentives which the American public overwhelmingly rejected in the past. Physicians, unlike insurance companies, are still trusted by the public and they have been chosen to assume a leadership role in ACOs.

This new form of rationing care won't work because ultimately the public will find out what risk contracts really are and again will reject them as they did with old gatekeeper HMOs. And when the trial lawyers find out about them, watch out. It won't be the hospital or insurers or CMS that gets sued. It will be physicians. When a CEO of a hospital network was explaining how risk contracts work to a group of doctors a physician asked, "What if I get sued?" The CEO's response was, "Deal with it," which is another way of saying "it's your problem, not mine."

There is another lesson to be learned about this unholy alliance between commercial health insurance companies and hospitals. In the so-called competitive free market under which our health system operates, hospitals and insurance companies are supposed to be competitors. Now, under ACOs, they are colluding to promote risk contracts. I believe this is a flagrant example of 'crony capitalism.'

By law under Medicare, commercial insurance companies are allowed to skim 20% off the top for administrative costs. And the hospitals will take their cut for administrative and other costs, too. This leaves physicians holding the bag rationing health care to patients. If they don't, their income will suffer. Despite all of the positive hype put-out by CMS, hospitals, and insurance companies, ACOs like all HMOs in the past, will fail in their mission to lower costs. HMOs and capitation have been studied since the 1970s. They have never lowered health care costs. And they never will.

Quality of Care

What about the quality of care in Medicare today? The government, through CMS, is using its new gimmick - the electronic health record (EHR) - to measure "quality" through the Physician Quality Reporting System (PQRS).[9] This is being done in all three modes of health care delivery: Fee-For-Service, Medicare Advantage, and Accountable Care Organizations. Supposedly, by checking boxes on patients' blood pressure, weight, exercise, smoking cessation, cholesterol, LDL, hemoglobin A1C, etc., quality is improved. And physicians are rewarded financially if they check all the boxes correctly. It's as if physicians were not discussing these issues with patients before these EHR metrics were introduced. This payment model for improving quality does not take into account that many, if not most patients, are non-compliant with their physicians' recommendations no matter how many boxes are checked.

Quality of care should be equated with time spent with patients - not box checking. This is especially true in elderly patients with multisystem diseases who have many concerns and need time to express them. I know of

an internist who works for Kaiser Permanente, a staff model HMO, who must see 30 patients per day. He is allotted 10 minutes for each patient. He comes home every night to spend several hours going over lab tests and doing other medical related work. This is not quality care. He advised his children not to go into medicine. In the brave new world of managed care and government edicts, the physician, a once proud professional, has been transformed into an assembly line worker.

Medicare Part D

Medicare Part D is the Medicare drug program passed by Congress. It might be considered an example of padding the bottom line of the pharmaceutical and insurance companies at the expense of Medicare beneficiaries and ultimately the taxpayer. Part D does not allow Medicare to directly negotiate drug prices with health plans as it does with the Veterans Administration. Veterans pay much less for pharmaceuticals than Medicare beneficiaries. Medicare members must pay a price for drugs that is a result of negotiations between drug companies and insurance plans. As a result the cost of drugs to a Medicare patient may be up to 80% more than what a veteran pays for the same drug.[10]

One of the coauthors of this giveaway bill was Representative Billy Tauzin (R-La.), Chair of the House Commerce Committee. After the bill was passed, Tauzin quit Congress and took a job as chief lobbyist for Big Pharma at $2 million per year. The head of CMS at the time, Thomas Scully, defended the giveaway and deliberately understated the cost. He then returned to the private sector and resumed his career as a health care lobbyist. One Congressional representative called it the worst example of lobbying at the expense of the public interest in her 25 years as a member of Congress.[11] Medicare pays physicians directly. Why should the pharmaceutical companies be paid differently? Doctors would be paid far more than they are today if they were allowed to negotiate their reimbursements from Medicare with insurance companies. Right now the doctors can't negotiate and are forced to accept Medicare reimbursement on a "take it or leave it" basis.

Conclusion

If the government, through CMS. was serious about lowering Medicare costs and improving quality, it would stop focusing on physicians and blaming FFS for all of the ills of our health care system. Instead of relying on Medicare Advantage and ACOs, it would eliminate them entirely. The Federal government should also cut out the insurance company middle men in Medicare Part D and purchase drugs directly from the pharmaceutical industry for its Medicare beneficiaries. And of course the hospitals, the main driver of high health care costs, must be reined in. As noted above by Brill, only Medicare has the power to lower out-of-control hospital charges.

None of this is likely to happen, at least in the near future, because our dysfunctional Congress is dominated by the special interests that profit from maintaining the status quo. The non-partisan Congressional Budget Office (CBO) predicts that the Medicare Trust Fund will run out of money in 2030 or in about 15 years.[12] A true financial crisis might force the government to make some of the necessary changes described above. Whether the government and the American people have the will to make these changes remains to be seen.

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MM



Honoring Military Physicians: Taking Care of America's Heroes

by Timothy D. Woods, MD

As I reflect on my time in the military, I realize I was given the unique opportunity to care for some of our nation's finest in their most desperate hours. They are all my heroes. I feel very fortunate that I was put in that role. I will always cherish my time in the military.



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From April 1997 to September 2006, I had the privilege of serving in the United States Air Force (USAF) as a general surgeon. To offset the cost of my medical school training, I chose to accept a scholarship from the military. My service in the military started at the completion of medical school. Since my father served in the United States Air Force for over 28 years, it was an easy choice of which military service to choose. That choice to accept the scholarship proved to be one of the best decisions I ever made!

Despite growing up in the military, I really did not know what to expect as I transitioned into becoming a general surgeon for the USAF. I knew there would be travel. I knew there would be deployments. I knew there would be new friends. I hoped there would be assignments overseas. I hoped the surgical experience would be good. I never thought there would be two major world conflicts during my time in the military. I never thought I would spend over three years taking care of war wounds on our nations finest. September 11, 2001 changed everything. Operation Enduring

Freedom (OEF) and Operation Iraqi Freedom (OIF) ultimately became a focal point of my practice and my life.

At the completion of my residency, I was assigned to a remote tour in Osan, Korea. For those history buffs, the Korean War is officially not over. The Korean Armistice Agreement was signed in 1953, but the "war" continues. The 38th parallel (otherwise known as the Demilitarized Zone) is the most guarded and heavily watched border in the world. There have been occasional skirmishes but essentially the cease-fire has persisted since 1953. Our military base was at a constant ready for any military transgressions from North Korea. My experience in Korea was an excellent time to further develop my surgical skills and increase my overall confidence. We held week-long military exercises every other month. Donning chemical suits became second nature. My wife was even issued a chemical mask and knew the evacuation plan should the situation arise. I was ready for war. Or so I thought. Despite the excellent trauma training in residency and my first year in Korea, I am not sure anything or anyone could have really prepared me for what came next.



Photo 1
Injured soldiers would arrive in Ramstein AFB daily via military transport.



Photo 2
The Critical Care Air Transport Team (CCATT) was comprised of one critical care physician, one ICU nurse, and one respiratory therapist.

I knew early on in my year in Korea that my next assignment would be at Landstuhl Regional Medical Center (LRMC) in Germany. Landstuhl served as the largest tertiary hospital outside of the United States. It also served as the first major hospital for all our injured men and women from the War on Terror. Essentially, every military member injured in the war would get initial treatment in country, and then be transported to Germany as soon as possible. The patient would then receive the critical care and surgical intervention necessary to make the trip back to the United States safely.

The wars in Afghanistan and Iraq were basically in the early stages of conflict when I arrived in Germany. Landstuhl had been busy since the start of the wars, but the heavy fighting was yet to come. During non-combat times, LRMC essentially functioned as a small suburban hospital with practically no trauma, a four-bed ICU, and bread and butter general surgery cases. The wars transformed LRMC into a fully functional trauma center capable of taking 50 to 100 trauma patients per day. It was a remarkable surge in capabilities. The ICU capability tripled overnight. The medical/surgical ward capability increased five-fold.

I was thrown in to the mix immediately. The surgery department was fairly short staffed when I arrived so they quickly put me to work. The trauma surgeons were responsible for the overall care of every trauma admission which basically meant every admission. Although there were some medical admissions every day, the great majority of admissions were due to trauma, both accidental and combat. It always amazed me how many patients were injured doing non-combat operations. It became apparent that accidents really do just happen, regardless of where or what one is doing.

Injured soldiers would arrive in Ramstein AFB daily via military transport. (See Photo 1.) The typical aircraft utilized for transport was the versatile C-17. It had the capabilities of landing in most places, transporting essential supplies to areas of conflict, and evacuating injured soldiers out of harms way. It is a great plane. The wounded were divided in to the walking wounded and the seriously wounded. Walking wounded did not imply that they were not badly injured. It just meant that they were relatively stable. The critically injured patients would be transported with a Critical Care Air Transport Team (CCATT). The CCATT team could take up to three ventilated patients. Many times, these patients were just hanging on to life. The CCATT was comprised of one critical care physician, one ICU nurse, and one respiratory therapist. (See Photo 2.)



Photo 3
The CCATT teams carried all essential equipment so they could provide ventilator support, acute surgical interventions, and life supporting measures.

These teams carried all essential equipment so they could provide ventilator support, acute surgical interventions, and life supporting measures. (See Photo 3.) During my time in Germany, no soldier lost their life under the care of a CCATT team despite life threatening injuries. Although my primary responsibilities were to be a trauma surgeon in Germany, I was also tasked to be a CCATT team leader. This was one of the highlights of my career in the Air Force. Not only did I provide critical care to soldiers as they were flown out of Iraq and Afghanistan, I also flew many patients from Germany to the United States to continue their recovery from their horrific injuries. In addition, I made multiple other CCATT missions to include Kazakhstan, Ukraine, Crete, Italy, and Greece.

My workload in Germany was quite intense, both physically and emotionally. Nothing made me more proud, however, than when I was able to get a critically injured soldier back to the United States to continue the recovery with his or her family. I wasn't able to save everyone as would be expected. Those who gave the ultimate sacrifice will always remain with me. I remember many of them like it was just yesterday. The hardest part of their death was often the conversation with their spouse or parent. Despite their death, almost every family stated how happy they were that their loved one died on "American soil" next to an American physician.

My hours were long and full of intensity. Our mission at LRMC was to provide life saving therapy, continue the surgical treatment, and also prepare them for transport to the United States. During my three years at LRMC, over 30,000 patients were moved by aero-medical evacuation. Of those, over 10,000 patients were admitted to LRMC. Although not all were injuries, the shear number of patients required aggressive and prompt treatment as well as prompt disposition. Plans for disposition often started before the patients had arrived. Landstuhl had limited physical resources, so continued movement was necessary to keep the system working.

I will always remember the bravery and positive attitude of our injured military members. Despite overwhelming injuries, their concerns and comments were almost always the same. "When can I get back to my squad?" "How are the rest of the guys doing?" "I am glad it was me and not my buddies!" "Get me patched up because there is more work to be done." This is fairly hard to hear especially when it comes from someone who just lost both of his arms or legs. If I heard it once, I heard it 100 times.

The injuries were something that no surgery residency really prepares you for. The utter destruction that military weapons and improvised explosive devices (IEDs) inflict was truly indescribable. The first responders and first medical teams who provided initial care did an awesome job. The survival rate in OEF and OIF far exceeds any survival rate from any prior armed conflicts. Many factors have contributed to this marked increase in survivability. Body armor, Kevlar helmets, tourniquets, massive transfusion adjustments, ventilator techniques, and rapid transport have all played an integral role. Soldiers can now survive injuries that in previous wars would have most likely progressed to death. I recall one evening when I was preparing 12 critically injured soldiers for transport back to the United States. All of the 12 soldiers were expected to survive their injuries despite the fact that there were a total of 25 limbs missing. 25 limbs! I was both proud and sad at the same time.

In June 2005, I was called in to my commander's office for an emergent meeting. Not sure if something was wrong, I reported as ordered. I was soon asked to sign a letter of nondisclosure and was informed of a mission in Afghanistan that had gone awry. I was told that over 19 special operators were killed on the mission and there was just one survivor. The mission was so top secret at the time that a nurse and I were the only medical professionals tasked to care for the wounded operator. We arranged for the patient to be boarded in an unused part of the hospital. Guards were placed at all entrances to maintain operation security. The two of us provided 100% of his care. He stayed with us for just under two weeks.

The patient was Navy Seal Marcus Luttrell, otherwise known as the "Lone Survivor." (See Photo 4) He stayed at LRMC significantly longer than most injured soldiers, and I assume that was due to the sensitive nature of his mission. His injuries were quite impressive, but he responded very

well to our surgical care. Due to his almost two-week stay at LRMC, I got to know him fairly well. Our conversations were initially focused on his injuries but soon evolved like any other friendship. He ultimately left LRMC, and I honestly thought our paths would never cross again.

Several years ago, a colleague asked if I had read this new book about a Navy Seal who was the lone survivor after an incredible mission. I hadn't, so he gave me the book to read. I did what most people do and flipped to the picture section of the book. It took me five seconds to recognize Marcus in several of the pictures. I read the book with great interest. Much of what was in the book I learned for the first time, but other parts I had kept secret for all these years. I never told the story to anyone other than my wife until I realized that the book had been published. I remember being very happy for Marcus that he was able to tell his amazing story and the story of the 19 heroic military members who paid the ultimate sacrifice.



Photo 4
The "Lone Survivor" Patient: Navy Seal Marcus Luttrell, (left) otherwise known as the "Lone Survivor" was a patient of Dr. Woods (right).

Several months ago, I had the opportunity to meet up with Marcus for the first time since 2005. He was speaking at a charity event in Branson, Missouri. Now that his story is out and a movie has been made, "Lone Survivor," he has been a highly sought out speaker. Our meeting was an emotional experience for both of us. We shared some stories in private and truly enjoyed our own personal memories of that short time. I will always keep him in very high regard. Interestingly, he is the only patient from my time in Germany that I have had the opportunity to reconnect.

As I reflect on my time in the military, I realize I was given the unique opportunity to care for some of our nations finest in their most desperate hours. Just like Marcus, they are all my heroes. I feel very fortunate that I was put in that role. I will always cherish my time in the military. **MM**



Advancing Health Care for Lesbian, Gay, Bisexual, and Transgender Patients in Missouri

by Jane A. McElroy, PhD, Jenna J. Wintemberg, MPH & Kenneth A. Haller, MD

We all went into our health professions to help people. The lesbian, gay, bisexual, transgender community has frequently been marginalized, stigmatized and victimized, yet the vast majority of their health concerns are the same as anyone else's.







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Sexual and gender minorities (SGM), the new umbrella term used for LGBT, (lesbian, gay, bisexual, queer, other non-heterosexual sexual orientations, transgender and gender variant identities) persons represent three to four percent of the population[1] with one in 37 children living with a gay parent.[2] SGM patients and parents may feel reluctant to disclose their sexual and gender identities to their providers due to confidentiality concerns, fear of discriminatory reactions and stigmatization, and either personal or known negative experiences due to SGM status within the health care system.[3, 4] Needless to say, this lack of disclosure limits the provider's ability to truly know their patients and potentially negatively affects care.

The authors hope to make physicians aware that there is a significant community of LGBT patients and families in Missouri who feel alienated from the health care system, not so much by lack of trust in the competency of their doctors to meet basic health needs, but by fear of being turned away if they are honest about the circumstances of their lives. In this paper the authors review the history of this marginalization and offer physicians effective strategies for reaching out to SGM patients and communities.

Over time, various strategies have been employed to address the needs of SGM patients seeking welcoming providers. Each strategy has advantages and disadvantages.

Local listings maintained at LGBT community centers and organizations have the advantage of including patient-driven recommendations and knowledge of the local community. However, lack of coverage for non-urban areas, concerns about the currency of the list, community access to the list, who maintains it, and any personal biases that might impact entries to the list are all significant disadvantages.

Having practices or health care systems identify LGBT-friendly providers allows for each system to integrate SGM competency into their health care mission. Resources to train frontline staff as well as health care professionals on culturally relevant issues could be integral to this working environment. Disadvantages include inconsistences of documentation of safe providers in that some systems might have a listing whereas other systems might not. This strategy requires an internet presence, and smaller practices, particularly in rural areas, might not use this resource. How LGBT-friendly providers are identified might also vary by system.

A national referral directory provides the huge potential advantage of a national database which would allow patients to find providers throughout the U.S., including in both urban and rural areas and for all manner of specialty care. A disadvantage of this strategy is that the viability of a national directory depends upon providers' willingness to populate the list. Assuring that providers, as well as patients, even know that such a directory exists as a resource is also a challenge. The most comprehensive directory is administered by GLMA: Health Professionals Advancing LGBT Equality, formerly known as the Gay and Lesbian Medical Association. Their Provider Referral Service (PRS) can be accessed online at www.glma.org and is searchable by specialty, city, state, and ZIP code.

GLMA was founded in 1981 as the American Association of Physicians for Human Rights (AAPHR) and was an offshoot of the Bay Area Physicians for Human Rights (BAPHR), a San Francisco-based physician organization founded to fight discrimination faced by gay and lesbian physicians in the workplace based upon their sexual orientation. AAPHR was founded to take this mission to a national level.

As the original name American Association of Physicians for Human Rights implies, in the 1980s physician members still had valid concerns about the possibility of being fired or losing their practice if their SGM status were publicly known. AAPHR maintained a member directory to alert its members to advances in gay and lesbian, and later LGBT health, as well as to communicate with members about upcoming events like the Annual AAPHR Symposium, the first of which was held in 1982. A Member Directory was printed and mailed to all dues-paying members. However, members had to Opt-In to agree to their contact information being included in the Member Directory, again because of fears of loss of livelihood if their SGM status were known publicly.

Over time, the focus of AAPHR grew to include, not just confronting homophobia faced by physicians, but also discrimination that lesbian and gay patients encountered in the health care environment. As such, AAPHR instituted its first Physician Referral Program (PHP) in 1993. Here, as with the Member Directory, physician members were always required to Opt-In to be included in the PRP. In order for patients to find a physician, they would have to call the AAPHR office during business hours and talk to a staff person about where they lived and what specialty they were seeking. The following year, 1994, AAPHR finally "came out" as an organization and changed its name to the Gay and Lesbian Medical Association.

Here in Missouri, through the work of the state-based organizations, PROMO and SAGE, (Missouri organizations that advocate for lesbian, gay, bisexual, and transgender equality though advocacy and education) and funded by the Missouri Foundation for Health, the number of health care institutions that have scored 100% on the HEI and been designated "Leaders of LGBT Healthcare" has gone from three in January 2014 to 19 in October 2014.

Eventually, patients were able to obtain referrals by email, which still needed to be handled by a GLMA staff person. Even with little promotion or advertising, the service caught on with LGBT patients. A GLMA Executive Director's (ED) Report from late 1999 states, "during the last fiscal year, the average number of calls per week increased from 40 to 70. Last year we began to investigate ways to [expand] the program, speed up response time, and minimize the labor-intensive nature of the current operation."[5] A December 1999 ED Report notes further progress and addresses GLMA members' confidentiality concerns: "…the Physician Referral Service… will be online at the beginning of February [2000]. A letter is going to the membership telling of the move and allowing members who do not wish to continue, to remove their names. It will also allow new members to join."[6] An ED Report from June 2000 reports that, "after… the new web site was launched [in February], we saw the number [of referral searches] jump to more than 140 per week… In the two weeks ending June 22 [2000], there have been more than 250 physician referral searches per week – more than five times the base number…"[7]

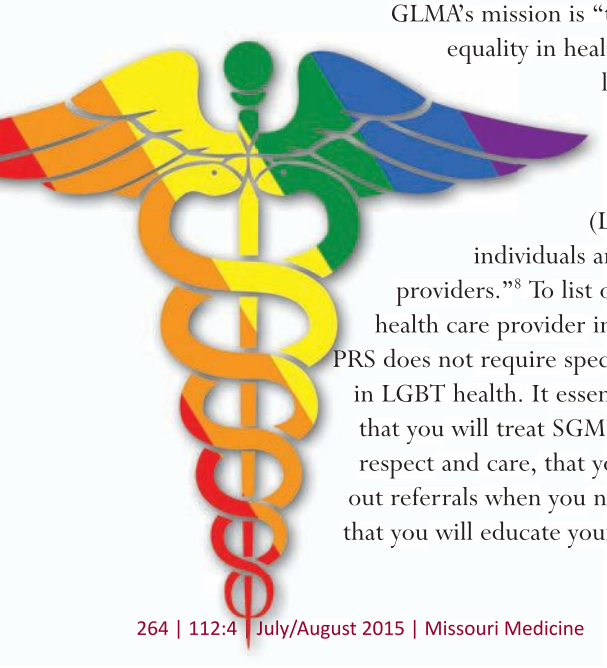
Since that time, GLMA has expanded its scope in terms of both its membership reach and its Provider Referral Service. As there has been more awareness of SGM identities beyond gay and lesbian in the medical community and as GLMA expanded its membership to health care providers beyond

Joining the GLMA Provider Referral Service means being a doctor who will say, "I'm glad you're here. How can I help you?" That is where healing truly begins.

physicians, the name "Gay and Lesbian Medical Association" was seen as inadequate to encompass the scope of GLMA's work and mission. However, since the GLMA name and brand had been established over many years, both in health policy circles and among LGBT-focused advocacy organizations, in 2010 the board decided to change the organization's designation to "GLMA (pronounced "glamma"): Health Professionals Advancing LGBT Equality."

The GLMA Provider Referral Service (PRS) has expanded in two ways: As GLMA has broadened its professional membership base beyond MDs and DOs, the PRS also includes non-physicians as of the mid-2000s. By 2008 the PRS had been opened to health care providers who are not members of GLMA yet wished to provide services to SGM patients. Therefore, any health care provider currently wishing to serve SGM clients may be listed in the GLMA PRS.

As of January 2015, there are 2,497 health care providers listed in the GLMA PRS. Forty percent (997) of those providers are listed as MDs or DOs. (However, 765 of the providers in the PRS do not have degrees listed by their names in the directory so the percentage of physicians may be higher.) Just under 10% (245) of the providers on the PRS are GLMA members, and the GLMA PRS gets between 2,800 and 3,200 referral searches per month.



GLMA's mission is "to ensure equality in healthcare for lesbian, gay, bisexual and transgender (LGBT) individuals and health care providers."[8] To list oneself as a health care provider in the GLMA PRS does not require special training in LGBT health. It essentially means that you will treat SGM patients with respect and care, that you will seek out referrals when you need them, and that you will educate yourself over time about the particular health care concerns facing persons who identify as LGBT. GLMA encourages any health care provider who has an interest in providing care to SGM patients to add his/her name on this referral list.

To be listed in the PRS, GLMA requires a provider to have a current license in one's health care profession in the jurisdiction where one practices, but GLMA does not require a level of professional certification for membership. This is because, while the University of Pennsylvania[9] and a few other academic institutions offer certificate programs in LGBT health, there are no full residency or fellowship programs specific to LGBT health and thus no metrics for certification in this field. This, then, presents a challenge to creating a "safe" Provider Referral Service for SGM persons.

Further, when as a public service, the GMLA PRS was opened to providers who are not GLMA members, the question was raised of how to assure that providers who want to victimize and/or stigmatize vulnerable LGBT patients cannot enter the directory? When the service was only open to GLMA members, the burden of paying $300 or more a year for membership was felt to be a strong disincentive to those who would think of joining the service to cause mischief for SGM clients. Patients accessing the directory are given a caveat emptor message on the cover page that states, "We do not screen providers and therefore cannot make any guarantees." They are also given contact information for the GLMA office in case they wish to report a problem with a provider. [11]

The Out, Proud, and Healthy (OPAH) project at University of Missouri has been working with GLMA to increase provider listings on the GLMA's PRS. In 2012, there were barely more than 20 providers listed in the GLMA PRS for the entire state of Missouri, with those 20 providers only representing the St. Louis, Kansas City, and Columbia areas. Today, there are 168 providers listed for Missouri including some rural areas of the state. In addition, these Missouri safe providers represent a wide range of professions and over 15 medical specialties such as: therapy and psychiatry, women's health/OBGYN, family practice, transition counseling, infectious disease, pediatrics, reproduction and fertility, dentistry, hospice, emergency

medicine, addiction treatment, dermatology, acupuncture, and surgery. Much of this increase is due to the work of the Out, Proud, and Healthy project which has spent the last two years seeking out SGM patient recommendations for culturally competent providers and systematically contacting those providers to give them information about joining the GLMA PRS.

In 2011 the Institute of Medicine released a report entitled, "The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding."[12] The 17-member committee that authored the report conducted a review assessing the state of the science on the health status of LGBT populations, identified research gaps and opportunities, and outlined a research agenda that will assist NIH in enhancing its research efforts in this area. In essence they found that work in LGBT health was far behind that in other marginalized populations due to funding priorities that for decades ignored LGBT persons as populations worthy of study.

That same year the Joint Commission, an independent, not-for-profit organization that accredits and certifies more than 20,500 health care organizations and programs in the United States, [13] released the report "Advancing Effective Communication, Cultural Competence, and Patient- and Family-Centered Care for the Lesbian, Gay, Bisexual, and Transgender (LGBT) Community"[13] which called upon health care institutions "to create a more welcoming, safe and inclusive environment that contributes to improved health care quality for lesbian, gay, bisexual, and transgender (LGBT) patients and their families."

Since 2007, the Human Rights Campaign (HRC), a national LGBT civil rights organization, has been using the Healthcare Equality Index (HEI) to rank health care institutions on the basis of patient non-discrimination, equal visitation, employment non-discrimination, and training in LGBT-centered patient care[14] Here in Missouri, through the work of the state-based organizations, PROMO and SAGE, and funded by the Missouri Foundation for Health, the number of health care institutions that have scored 100% on the HEI and been designated "Leaders of LGBT Healthcare" has gone from three in January 2014 to 19 in October 2014.[15]

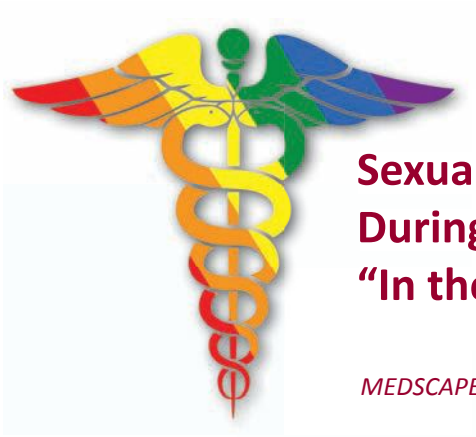
As professional certifying and governmental regulatory organizations make LGBT health a priority, it is imperative that physicians be on the forefront of providing a welcoming space for SGM patients and their families. Furthermore, from a business and marketing standpoint, as more hospitals seek out HEI Leadership designation, it will behoove physicians and other health care providers to proactively solicit LGBT clients in their communities. While it will be essential to include an LGBT-friendly designation on one's system-wide Physician Profile Page, it will be even more important for physicians to reach beyond the directory of the workplace to attract new patients in the larger community. The GLMA Provider Referral Service, after more than two decades of service to the LGBT community, has a level of credibility among SGM persons nationwide that is unmatched.

Finally, we all went into our health professions to help people. The LGBT community has frequently been marginalized, stigmatized, and victimized, yet the vast majority of their health concerns are the same as anyone else's. As the increasing searches of the GLMA PRS indicate, these patients are looking for compassionate health care providers. They simply need a place where they can be fully themselves without fear of judgment or mistreatment. Joining the GLMA Provider Referral Service means being a doctor who will say, "I'm glad you're here. How can I help you?" That is where healing truly begins.

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Sexual and Gender Minority Identity Disclosure During Undergraduate Medical Education: "In the Closet" in Medical School

MEDSCAPE 2/18/2015

by Mansh, Matthew; White, William MA; Gee-Tong, Lea; Lunn, Mitchell R. MD; Obedin-Maliver, Juno MD, MPH; Stewart, Leslie MD; Goldsmith, Elizabeth MD, MS; Brenman, Stephanie MD; Tran, Eric MFA; Wells, Maggie; Fetterman, David PhD; Garcia, Gabriel MD

Overview

Of sexual minority respondents, 29.5% said they concealed their sexual identify in medical school. Although most (67.5%) were "out" about their identity, the authors note that this is not all that much better than the estimate of 44% 2 decades ago. (Some respondents declined to answer this question).

Sexual identity concealment was lowest among gay and lesbian (14.7%) and queer (22.2%) respondents. Most bisexuals (53.9%) and questioning (92.0%) respondents reported concealing their sexual identify in medical school

Abstract

Purpose

To assess identity disclosure among sexual and gender minority (SGM) students pursuing undergraduate medical training in the United States and Canada.

Method

From 2009 to 2010, a survey was made available to all medical students enrolled in the 176 MD- and DO-granting medical schools in the United States and Canada. Respondents were asked about their sexual and gender identity, whether they were "out" (i.e., had publicly disclosed their identity), and, if they were not, their reasons for concealing their identity. The authors used a mixed-methods approach and analyzed quantitative and qualitative survey data.

Results

Of 5,812 completed responses (of 101,473 eligible respondents; response rate 5.7%), 920 (15.8%) students from 152 (of 176; 86.4%) institutions identified as SGMs. Of the 912 sexual minorities, 269 (29.5%) concealed their sexual identity in medical school. Factors associated with sexual identity concealment included sexual minority identity other than lesbian or gay, male gender, East Asian race, and medical school enrollment in the South or Central regions of North America. The most common reasons for concealing one's sexual identity were "nobody's business" (165/269; 61.3%), fear of discrimination in medical school (117/269; 43.5%), and social or cultural norms (110/269; 40.9%). Of the 35 gender minorities, 21 (60.0%) concealed their gender identity, citing fear of discrimination in medical school (9/21; 42.9%) and lack of support (9/21; 42.9%).

Conclusions

SGM students continue to conceal their identity during undergraduate medical training. Medical institutions should adopt targeted policies and programs to better support these individuals.

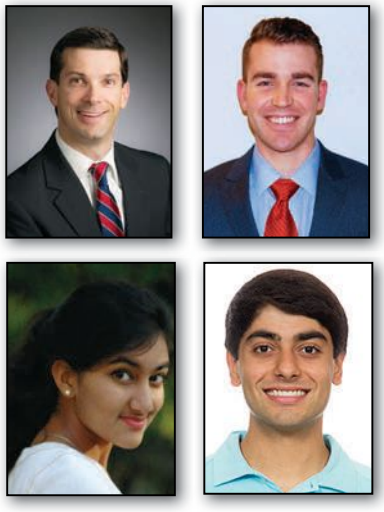
Source: http://journals.lww.com/academicmedicine/Abstract/publishahead/Sexual_and_Gender_Minority_Identity_Disclosure.98848.aspx

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World Food Day: Taking a Bite Out of Hunger at Home and Abroad



by Joseph A. Craft III, MD, Andy Hayden, MS-2, Radhika Jain, MS-2 & Kavon Javaherian, MS-2



Joseph A. Craft III, MD, MSMA member since 2004, (left top) is a cardiologist at The Heart Health Center in St. Louis. Andy Hayden. MS-2, MSMA member since 2014, (right top) is at Saint Louis University, and Radhika Jain, MS-2, (left bottom) and Kavon Javaherian, MS-2, MSMA member since 2014, (right bottom) are at the Washington University School of Medicine.
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Co-Published with St. Louis Metropolitan Medicine.

Food insecurity has significant effects on physical, psychological, social, and economic well-being and should be considered a serious public health problem.

Although undernourishment impacts more than 790 million individuals in developing nations,[1] food insecurity and malnutrition are not unique to the developing world. Food insecurity, defined as limited or uncertain access to adequate food, affected more than 17 million American households in 2013.[2] Furthermore, 5.6 million U.S. households in 2013 had very low food security, with inconsistent eating patterns and reduced food intake due to limited resources—a situation classically known as "hunger."[2] Food insecurity has significant effects on physical, psychological, social, and economic well-being and should be considered a serious public health problem.

Missouri is not immune from this issue. In fact, amongst the fifty states Missouri had the single largest jump in the number of households with food insecurity and hunger between 2000 and 2010.[3] In 2013, 16.9 percent of Missourians lived in households with food insecurity and 8.1 percent lived in homes with hunger.[4] This need is amplified in the city of St. Louis, where approximately one in five households experienced



Members, staff, and families of the St. Louis Metropolitan Medical Society during Wold Food Day in 2014.

food uncertainty and households spent an average of 18.7 percent of total income on food in 2010.[3]

The health ramifications of this level of need can be severe. Households with very young and very old inhabitants are particularly likely to experience health and behavioral setbacks. For example, American children in food-insecure families experience more frequent stomachaches, headaches, and viral infections than children in food-secure homes.[5] These children are also twice as likely as their food-secure counterparts to experience iron-deficiency anemia, thereby causing weakness and fatigue and limiting activities necessary for child development. Additionally, studies demonstrate that food-insecure children perform worse in school. In one multi-state study, children from food-insecure homes were more likely to experience irritability and have difficulty concentrating;[6] these findings mirror other studies that have linked food insufficiency to poor academic performance. [7,8] These behavioral and developmental setbacks can persist into adolescence, during which food insufficiency has been shown to correlate with a higher incidence of depressive disorders and suicidal tendencies.[9]

Older adults are also susceptible to hunger-associated health and behavioral consequences. A joint study conducted by Feeding America and the National Foundation to End Senior Hunger found that food-insecure seniors are 40 percent more likely to experience congestive heart failure, 53 percent more likely to have a heart attack, and twice as likely to develop asthma than individuals with stable and sufficient access to healthy foods. Additionally, food insecure seniors are 60 percent more likely to be diagnosed with depression.[10]

Amanda Hilmer, MD, an internist at Family Care Health Center in St. Louis, believes that access to quality food is a "top three issue" for her patients, many of whom are homeless, uninsured, or on Medicaid, and usually suffering from mental illness. Her patients consume inexpensive, non-perishable options rather than fresh fruits and vegetables. They must allocate a large portion of their income to purchasing food, leaving little for clothes and medicine. Indeed, in Missouri an estimated 60 percent of households utilizing food banks have unpaid medical bills; 80 percent have purchased inexpensive, unhealthy food in the last 12 months to

try and secure food for themselves and their families; and 65 percent have had to choose between paying for food and paying for medicine or medical care.[11] According to Dr. Hilmer, this phenomenon yields the "paradoxical effect of poorly nourished, overweight patients at high risk for diabetes and cardiovascular disease."

To address this reality, Dr. Hilmer assigns her patients to teams of social workers and psychologists who help the patients take advantage of food resources; she also organizes a bi-monthly group to enable her patients to cook healthy, tasty, and affordable food. She says she has learned as much as her patients "about good choices on a very restricted budget," and encourages physician colleagues to spearhead their own medical teams knowledgeable about navigating food insecurity.

Many public and private programs in the United States are also attempting to address food insecurity. The United States Department of Agriculture Food and Nutrition Service operates thirteen nutrition assistance programs, including the Supplemental Nutrition Assistance Program (SNAP), formerly known as the federal Food Stamp Program. Missourians rely heavily on SNAP, with approximately 89 percent of eligible Missouri residents and nearly one-third of all St. Louis residents taking advantage of the program in 2012.[3,12] The National School Lunch Program (NSLP) funds nutritious lunches at free or reduced cost for eligible children in schools across the nation. More than 224 billion lunches have been served by NSLP since 1946.[13] Additionally, the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) provides nutritious food, education, counseling, and health referrals for pregnant women and children under the age of five.

When these federal programs lack funds and time, community organizations often step up to fill in the gaps. For instance, food banks collect donations from individuals, food manufacturers, farmers, and grocery stores, and then distribute these items to local hunger relief agencies, such as dedicated food pantries, homeless shelters, places of worship, and community centers. Missourians can use websites like www.feedingamerica.org and www.foodpantries.org to find their closest food bank or distribution location. The immediate support offered by hunger relief agencies can be a critical resource for individuals who do not qualify for federal assistance, are unable to complete the documentation required for financial support, or are experiencing a temporary loss of food security.

Project Bread's FoodSource Hotline, a phone-in service, refers individuals to emergency food banks, screens callers for SNAP eligibility, and provides information on other government programs. Locally, the City of St. Louis opened three new and affordable



St. Louis World Food Day 2015 is Friday, October 16, in the Field House at John Burroughs School, St. Louis, Missouri. The St. Louis Metropolitan Medical Society has been a proud corporate sponsor of this event for the last three years, and SLMMS invites physicians across Missouri to volunteer with their family and friends.

Please register or inquire at www.stlwfd.org, or with SLMMS at www.slmms.org or 314-989-1014.

grocery stores in areas designated as food deserts in early 2014 to improve access to healthy food.[14] The St. Louis Healthy Corner Store Project provides grocery store owners with strategies to increase their healthy food inventory, and as a result, healthy food content has increased by 25 percent in participating stores since the program's inception in 2011.[15]

World Food Day is an annual, global event featuring grassroots activities and public awareness campaigns aimed at reducing hunger around the world. Locally, St. Louis World Food Day (STLWFD) was founded in 2012 by high school student Donald Soffer and his parents Allen Soffer, MD and Mary Beth Soffer to provide Missourians with the opportunity to take action against hunger both at home and abroad. On World Food Day, volunteers come together in St. Louis to package nutritious, vitamin-fortified meals. These meals are then shared with hungry families in St. Louis and Tanzania, through partnerships with the St. Louis Area Foodbank and the Outreach Program, respectively. More than 1800 people participated in 2014. Their registration fees, along with sponsorships and donations, helped defray the cost of the food packaging ingredients. Working together in one-hour assembly line shifts, participants packaged 384,000 meals in a single day.

Dr. Soffer reports that "participants are overwhelmingly enthusiastic both during and after the event. We have a diverse population of participants, ranging in age from 7 to 90+. In any given hour, you will find third graders, church groups, local celebrities, and executives—all in hairnets and aprons—working together assembling meal packets.... After the event we get letters from participants, describing how much the sense of community in that gym—people working together towards a common goal to help the hungry—moved them, and how they realized that when individuals work cooperatively, they can make a real difference."

St. Louis World Food Day 2015 will be held on Friday, October 16th in the Field House at John Burroughs School, St. Louis, MO. The St. Louis Metropolitan Medical Society (SLMMS) has been a proud corporate sponsor of this event for the last three years, and SLMMS invites physicians across Missouri to volunteer with their family and friends. As Dr. Soffer explains, doctors "have lots of talents beyond the bedside or bench, and with their leadership and organizational skills and resources they are in a unique position to help others, whatever their passion or interest."

Please register or inquire at www.stlwfd.org, or with SLMMS at www.slmms.org, 314-989-1014.

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Proud to Meet to Our Members



by John O. Stanley, MD

It's been three months since I embarked upon my yearlong journey as your MSMA President. I continue to be humbled by the position, and hope I can build upon the excellent work my predecessors have done. At the MSMA Annual Convention, several past presidents made reference to the amount of travel I'd be doing this year as president. One even recommended that I go ahead and get a set of new tires for my car. I haven't done that, but I'll probably need to before the year is out. I'm proud to reach out to members as it has been fun, informative, and enlightening. I'm happy to represent MSMA, and I am learning a great deal about the problems medical societies face, and the creative solutions they are implementing.

Though MSMA's quarterly council meetings in Jefferson City are excellent, the heart and soul of the MSMA lives at the local level, where grassroots energy and promotion of organized medicine begins. A good example of this is the Tri-County Medical Society, based in Washington, Missouri. I participated in a spirited discussion about the medicine-related bills passed during this legislative session. The members were well-informed and enthusiastic about their role in the political process. Thanks to **David Chalk, MD,** and **Keith Ratcliff, MD,** for hosting this excellent meeting.

Part of the fun of traveling is experiencing our beautiful state. I was scheduled to attend the Quad County Medical Society's meeting in Poplar Bluff. Part of the plan was to hike in one of the nearby state parks; it was spoiled by a torrential rainstorm, but I was most excellently received by **Charles Lawson, MD**, Quad's president, and I enjoyed meeting with the society members, discussing recent legislation, and brainstorming about ways to increase membership.

At the AMA's June Annual Meeting in Chicago, Missouri announced that in 2016, one of our own MSMA Past Presidents, **David Barbe, MD**, will be a candidate for president-elect of the AMA. This is such a prestigious honor for Dr. Barbe, and for MSMA, as we residents of the Show-Me State get a chance to "show" what Missouri physicians are made of. My experience at the meeting was enhanced by the camaraderie displayed by our delegation members, and by the outstanding behind-the-scenes work done by our MSMA staff. To me, they outshone their counterparts from all the other states.

In another out-of-state trip, I traveled to the Iowa Medical Society's Annual Meeting in Cedar Rapids. This was a fascinating meeting for me, because Iowa has dissolved its House of Delegates, and has begun to use the Policy Forum method to create and amend official policy. Iowa is among several states, including Maine, Montana, New Hampshire, Oregon, and others, that has taken this step in order to increase participation at the state level, increase the number of resolutions submitted to the HOD, and improve attendance at society meetings. Much of the policy-making work that was previously done at the Iowa society's quarterly meetings will now be done using "virtually enabled forums." Policymaking steps begin with the "Call for Action," where members are invited to submit resolutions to the society. After the "Call for Action" period, members may participate in the "Testimony Forum," during which testimony is contributed on the resolutions via a members-only online discussion. The final phase, "Policy Forum," takes place at the semi-annual physical meetings, and directs action at the policy resolutions (called Policy Request Statements in Iowa).

Even more than informing Missouri members about how a neighoring state is shaping its HOD, the Iowa society believed that its previous, more traditional House of Delegates process was not understood by younger physicians, and that physicians were discouraged from participating in the society because of the need to travel long distances to meetings. Their new system is more flexible, and appeals to physicians who are accustomed to and comfortable with "virtual" communication. Incidentally, the AMA has been using virtual reference committees since 2010.

As my travels continue, I look forward to meeting more physicians from Missouri and from neighboring states. I'm stressing the importance of involvement in organized medicine every chance I get, and will also keep my ears open to new and innovative ideas that will help us increase medical society membership. **MM**

John O. Stanley, MD, MSMA 2015-2016 President and member since 1993, is a Family Physician from North Kansas City, Missouri.
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Your Missouri Delegation Continues In Leadership Roles at the AMA Meeting

by the Missouri Delegation to the AMA

Most physicians recognize the value of Maintenance of Certification, both to maintain competence, and to reassure the public that physicians are maintaining their skills. The AMA will continue to work to ease the burden on practicing physicians.



Charles W. Van Way, III, MD, MSMA member since 1989, is a Missouri Alternate Delegate to the American Medical Association, Professor of Surgery at the University of Missouri - Kansas City School of Medicine, and Director of the UMKC Shock Trauma Research Center.
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Your Missouri Delegation was very active at the Annual Meeting of the American Medical Association House of Delegates on June 6-10, 2015, in Chicago. David Barbe, MD, Mountain Grove, is currently serving as Immediate Past Chair of the AMA Board of Trustees. He has announced his candidacy for AMA President Elect in 2016. Edmond Cabbabe, MD, of St. Louis, is the Chair of the Missouri Delegation and the Heart of America Caucus, which includes Missouri, Kansas, Oklahoma, and Arkansas. Like most other states, we join forces with other state delegations in our region to ensure that our voice is heard in all of the reference committees and deliberations.

After years of pressure from the AMA and many other medical organizations, Congress has finally repealed the Sustainable Growth Rate formula. Our outgoing president, Robert Wah, MD, said he was very proud to have this happen on his watch. As well he should be. The legislation carries with it a small annual increase (2%) in reimbursement for the next several years. But it also mandates an increase in the timetable for adoption of alternative payment schemes, among other provisions. Still, it is good news. Besides being beneficial in itself, it will free up the time and efforts of medical organizations to fight for things which will actually help patients.

This year, as many as 1,500 MD and DO graduates from U.S. schools, plus about 3,000 American graduates of international schools, were unable to find residency positions after graduation. There simply aren't enough jobs to go around. This year's group adds to the growing pool of young physicians who cannot continue in their training. There was extensive concern and much discussion about the mismatch between residency positions and new graduates, both American and international. The AMA passed several resolutions on this point. All resolutions supported the idea that more positions are needed; the unresolved questions are where they can be created, and how to pay for them. Only about 600 of the 5,000 acute care hospitals sponsor residencies. The Federal government doesn't want to pay for new residency positions, nor does anyone else. The pending merger of the residencies under the American Osteopathic Association with the Accreditation Council on Graduate Medical Education is a Good Thing, but it will not by itself create new residencies. The AMA recognizes that it needs

30+ Year MSMA Member David Barbe, MD, Announces Bid for AMA President Elect



David O. Barbe, MD, MHA, a board-certified family physician from Mountain Grove, Mo., past Chair of the American Medical Association Board of Trustees, is running for the position of AMA President Elect in June 2016.

A 30+ year MSMA member and past MSMA President, Dr. Barbe served six years on the AMA Council on Medical Service, and was then elected to the AMA Board of Trustees in 2009, where he has served as Secretary, Chair-Elect, and Chair. He is proudly endorsed by the Missouri State Medical Association and the American Academy of Family Physicians.

to take the lead with specific proposals to increase the number of residency positions, and finance them. We are already short of physicians. No new graduate should go untrained.

In an ongoing effort to improve medical schools, 11 schools received $1 million grants from the AMA for several new initiatives. This effort will continue over the next several years, in the hope that medical education can be updated to meet the needs of new physicians. See the website www.changemeded.org . It was reported that the Liaison Committee on Medical Education, our credentialing body, is simplifying its accreditation requirements, and that 15 new medical schools are now accredited or on the path to accreditation. Unfortunately, few of these schools are starting up new residency programs.

There is always keen interest in defining needs for medical education. There were multiple resolutions calling for provision of training opportunities, either in medical school or residency, in many areas. These include use of EMR and other technology, health policy, and public health issues such as obesity, sex trafficking, eldercare, and veterans' care. While the AMA cannot legislate curriculum changes in medical education, its advice is heard in both undergraduate and post-graduate education.

The Code of Medical Ethics continues to be revised, something which has become an annual event. While the current revision is an improvement over last year's, it was sent back to the Council on Ethics and Judicial Affairs for further revision.

Maintenance of certification (MOC), is still contentious. There were several resolutions, and much discussion. The American Board of Internal Medicine came in for particular criticism for its heavy-handed implementation of MOC. The AMA has existing policy opposed to linking maintenance of licensure with MOC. The AMA is working with the credentialing organizations to ease the burden of MOC on practicing physicians. Most physicians recognize the value of MOC, both to maintain competence, and to reassure the public that physicians are maintaining their skills. But there was general agreement that MOC has become overly burdensome. The AMA will continue to work in this area, to ease the burden on practicing physicians.

There were a number of recommendations for Congressional lobbying. Care in the Veterans Affairs health care system continues to be of concern. Several resolutions urged Congress to make it easier for veterans to seek care out of the increasingly dysfunctional VA system. There was opposition to Congressionally-proposed changes in the way the Environmental Protection Agency forms its scientific panels. The chemicals used in hydraulic fracturing should be more completely disclosed, so that effects on groundwater and runoff water can be better assessed. There was opposition to the use of coal for energy. There was concern about funding in the prison health systems across the country for treating hepatitis C. This is said to be present in some 30% of prison populations, and cannot be treated because of the great expense of the drugs required. The effectiveness of lobbying for many of these objectives has not been great, but there is a continuing desire by the House of Delegates to see the AMA involved in national policy in any such area which affects the health of the public at large.

A resolution was adopted urging the elimination of the three-day inpatient requirement for long-term care under Medicare. This requirement is outmoded, and now results in a considerable wastage of hospital days simply to qualify for subsequent care.

Implementation of ICD-10 appears to be unstoppable, despite the firm opposition of the AMA. The best that can be hoped for will be a two-year phase-in of requirements. In this way, and others, the AMA will continue to try to minimize the negative impact on medical practice.

Brain damage to young athletes continues to be a matter of great public health concern. There was a resolution concerning the use of helmets in women's lacrosse, something which is opposed by those who supervise that sport. Women's lacrosse is played helmetless, while helmets are required for men's' lacrosse. The rationale for this was not made clear in the discussion, and the resolution passed without difficulty.

E-cigarettes continue to be a matter of concern. The Food and Drug Administration continues to drag its collective feet. The consensus of the several resolutions considered was that the FDA should regulate e-cigarettes, and that they pose particular dangers to children and teen-agers.

The AMA has decided once again to maintain dues at their present level. Dues have remained the same for the past 11 years. The AMA has increased membership over the last five years, and has convincingly reversed its long decline. This, together with the obvious increase in the involvement of medical students and residents in the organization at all levels, is very good news.

There is a new president of the AMA. Stephen Stack, MD, an Emergency Medicine physician from Lexington, Kentucky, was inaugurated on June 9. He is the first EM physician to be president, as well as the youngest president in 160 years. He has been particularly active in working with medical schools to improve medical education (see above). He has considerable expertise in health information technology, and will continue his ongoing work in making the electronic health record both safer and more useable. **MM**

Leading the Way: Your Missouri Delegation to the AMA



Missouri is represented by MSMA physicians from all over the state to represent Show-Me Medicine at the national level.

Top photo, from left: St. Louis physicians Bill Huffaker, Nathaniel Murdock, Edmond Cabbabe, and Elie Azrak.





MIddle photo, from left: Kansas City physicians Michael O'Dell, MSMA President John Stanley, Charles Van Way, and Rebecca Hierholzer.

Bottom photo, from left: Medical Student Kavon Javaherian, St. Louis, and Dr. O'Dell.

Additional Missouri Delegates and representatives to the AMA not pictured are physicians James Conant, Ted Groshong, Lent Johnson, Warren Lovinger, Jerry Kennett, and Larry Rues.

Near-Death Experiences

The Last Word

by Eben Alexander, III, MD

The phenomenological properties and transformative power of NDEs are totally different, and, in many ways, the opposite of dream content.

Toward a More Comprehensive Scientific Paradigm

> *"I maintain that the human mystery is incredibly demeaned by scientific reductionism, with its claim in promissory materialism to account eventually for all of the spiritual world in terms of patterns of neuronal activity. This belief must be classed as a superstition. . . . we have to recognize that we are spiritual beings with souls existing in a spiritual world as well as material beings with bodies and brains existing in a material world."*
>
> — Sir John C. Eccles, PhD (1903 – 1997), neurophysiologist, Nobel Prize in Medicine and Physiology, 1963

Any evaluation of reports of near-death experiences must involve a mindset that is suitable to the task. These experiences challenge our understanding about the fundamental nature of consciousness, indeed of all of existence, at the most basic of levels, and if the mindset is too limited, we compromise our ability to approach the grander truth underlying our observations and attempts to understand them. The more broadly we can open our minds to the possibilities, the more readily we will come to a deeper understanding.

Kevin Nelson, MD's article in *Missouri Medicine*'s series on near-death experiences (NDEs) demonstrates the hazards of approaching near-death experiences with too limited a view of the possible explanations (Editor's note: Neuroscience Perspectives on Near-Death Experiences, 2015; 112(2:92-98) The danger lies in missing the forest for the trees, for being too myopic in scope and thus falling woefully short of the mark. This is an inherent problem when one is shackled, as is Dr. Nelson, within the narrow confines of the physicalist world view (i.e. that the physical world is all that exists; that consciousness is an epiphenomenon of the workings of the physical constituents of the brain following natural laws). By accepting the unproven assumption that the physical brain creates consciousness, his approach is doomed from the start. The brain is clearly related to consciousness — the fallacy is in believing the brain creates consciousness out of purely physical matter.



Eben Alexander III, MD, is a former neurosurgeon who spent 15 years on faculty at Harvard Medical School, the Brigham & Women's and the Children's Hospitals in Boston, MA. He wrote a memoir about his near-death experience entitled "Proof of Heaven: A Neurosurgeon's Journey into the Afterlife" (2012), and has written a comprehensive sequel entitled "The Map of Heaven: How Science, Religion and Ordinary People are Proving the Afterlife," published 10/7/14.
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Spiritually transformative experiences of all sorts, including NDEs, are usually described as much more real than our daily reality in the physical realm.

Entitled "Neuroscience Perspectives on Near-Death Experiences," Dr. Nelson's paper demonstrates many of the difficulties inherent in the scientific investigation of something as profoundly complex as near-death experiences when one's starting (physicalist) assumptions are false. The fog of confusion overwhelms his efforts to make sense of such deep experiences limited entirely to the confines of the physical brain, from a purely physicalist point of view.

In the teaser for his article, Dr. Nelson purports to "explore near-death experiences through the lens of science and discovers that near-death fits within the conventional neuroscience as securely as the Germ Theory of Disease and Evolution stand in other branches of science."

This teaser, and his ensuing article, address NDEs through a most distorted lens, indeed. First and foremost, Dr. Nelson seems to believe that conventional neuroscience has a firm enough understanding of the mechanism of consciousness to weigh in on all of the facets of near-death experiences. In fact, the "neuroscience of consciousness" is an oxymoron — no such entity exists. No neuroscientist on earth, nor philosopher of mind, can offer even a few sentences in an effort to describe in broad strokes the mechanism by which the human brain might create consciousness — not even vague hand-waving. No one has a clue, and yet the mantra of conventional physicalist proponents like Nelson is that the brain creates consciousness, said with the conviction that it is such a well-established fact as to be beyond the necessity for any evidence.

Part of the unfathomable enigma of the relationship between brain and mind is reflected in what is known in scientific and philosophical circles as the "Hard Problem of Consciousness" (HPC), and many believe it is the most profound enigma in all of human thought. The HPC was defined by David Chalmers PhD as the challenge to physicalism in explaining "qualia," or the phenomenological aspects of human perceptions, and their integration into consciousness as a whole.[1] From a scientific perspective, it is challenging to even entertain possible questions that might lead towards experiments to better elucidate the mechanism of consciousness. The problem becomes less "hard" when one abandons the simplistic falsehoods of physicalism (i.e. that the brain creates consciousness). I believe that addressing the issue of consciousness more fully, as we do in this kind of discussion about near-death experiences, will lead us into fruitful territory in our understanding of the nature of reality and of humanity's place in it.

The conventional neuroscientific assertion that the brain creates the "illusion" of consciousness through the physical action of the subatomic particles, atoms, molecules and cells of the brain, so fundamental to Dr. Nelson's point of view, is, as the Australian neurophysiologist and Nobel Laureate Sir John C. Eccles (quoted at beginning of article) famously said, "a superstition." Dr. Nelson and other physicalists are incapable of meeting the empirical challenges posed by the empirical data from NDEs, out-of body experiences (OBEs) and all manner of related mystical experiences. They neglect or deliberately ignore these "inconvenient" empirical facts, or attempt to explain away the basic rudiments through simplistic elementary explanations that cannot even begin to elucidate the rich landscape of the actual experiences.

As astrophysicist Paul Willard Merrill, PhD, wrote in his book on long-period variable stars, when faced with facts that contradict one's expectations, "if discordant values be omitted the others agree very well."[2] This humorous observation of science gone awry applies well to the approach of members of the conventional scientific community (like Nelson) who dismiss and deny any data from NDEs that do not fit rigidly into the conventional brain-creates-consciousness (physicalist) model.

A common error in this standard physicalist reasoning results from observing that some aspect x of NDEs (or OBEs) has some similarities to neurological condition y; therefore, explaining y explains those aspects x of NDEs, OBEs or other mystical experiences. This kind of oversimplification is guaranteed to lead to gross misinterpretation of the experiences.

Debunkers like Dr. Nelson don't acknowledge the differences between true OBEs and illusions of leaving

the body. They then claim that explaining the illusions explains the real experiences. Most of the sources Nelson cites as explaining OBEs in fact explain a variety of somatic illusions that have nothing to do with OBEs, but are simply distortions of bodily perception that do not involve perception from an out-of-body perspective, to say nothing of cases of veridical perception from an out-of-body perspective.

"If all you have is a hammer, everything looks like a nail" also applies to modern neuroscience. Dr. Nelson has taken the physiology he feels he understands and applied it to these other phenomena, offering generic explanations based on weak analogies. One's tools and methodologies can confine one's ability to elucidate the underlying truth. It is better to stay focused on explaining the full experience as much as possible, remaining cognizant of the limitations of our tools and methodologies.

Nelson also ignores much of the relevant literature, including a voluminous amount of research on psi phenomena, the entire literature on survival of the soul after bodily death, the argument about deep general anesthesia presented in Irreducible Mind, the copious literature on cardiac arrest cases, and the transformative power of NDEs. [3] In addition, Nelson's discussion of OBEs focuses on illusory experiences, with no mention of the large literature on veridical OBEs. [4] The reasoning often implies that one non-veridical case means they all are.

In his discussion of how near-death is "often a misnomer," Dr. Nelson argues that in assessing the experiences in a mixed group of those who were medically near death and others who were not, that the experiences were quite similar between the two groups.[5] His interpretation misses the main point of that paper: the more dramatic changes in mentation occurred in patients who were medically closer to death, which directly confronts the notion that "brain creates mind." Nelson then tries to explain all NDEs as due to decreased cerebral blood flow. This shotgun approach is typical among the debunker/denier pseudo-skeptics — he can't have it both ways.

Nelson's claim that syncope produces features indistinguishable from an NDE reveals a fundamental misunderstanding of what an NDE actually is. I would compare this to claiming that the experience of viewing a partial eclipse of the sun is similar to that of viewing a total solar eclipse. Anyone who has witnessed the latter will understand what folly it is to assume that one can extrapolate the experience of a total eclipse from having viewed a partial eclipse.

Nelson's discussion of the mystical sense of Oneness (the "transcendent" aspect being the main contributor to an NDE's depth according to the Greyson scale) as being completely explicable through understanding the serotonin-2a receptor function in the brain is another example of how extreme oversimplification leads to erroneous conclusions. Correlation does not equal causality. If one is able to demonstrate changes in the brain through imaging with functional MRI, pharmacologic blockade or similar means of evaluating brain function that occur during a specific phenomenal experience, that observation of putative correlation does not necessarily imply causality. Nelson's attempt to conflate fear and mystical experience is also erroneous and artificial.

Dr. Nelson claims that "much of the neuroscience behind mystical experience is understood" — a pretty bold claim, when in fact no neuroscientist on earth can offer even the most rudimentary statement about the neuroscience of consciousness, i.e. the mechanism by which the physical brain might give rise to consciousness.

The Inadequacy of REM Intrusion

Serious challenges to Dr. Nelson's proposed role of REM Intrusion in explaining the phenomena of NDEs have been pointed out by Bruce Greyson, MD and Jeffrey P. Long, MD.[6]

1. Volunteers who share their NDEs on the internet, which comprise Nelson's study population, are probably more likely than most NDE experiencers in their willingness to publicly discuss unusual experiences
2. Nelson's control group, comprised of medical center personnel and their contacts, would have reservations about endorsing pathologic symptoms such as hallucinations, diminishing their value as a true control group (note their endorsement rate of only 7% for hypnagogic hallucinations, approximately one-fourth the rate in the general population).
3. Specific features such as fear, which is quite typical in sleep paralysis but rare in NDEs, as well as the occurrence of typical NDEs under general anesthesia and other drugs that inhibit REM, rule against any explanation of NDEs through REM intrusion.
4. The etiology of phenomena as complex as NDE is likely multi-factorial, making it unlikely that a single, simple physiologic explanation such as REM intrusion will suffice.

The phenomenological properties and transformative power of NDEs are totally different, and, in many ways, the opposite of dream content. Spiritually transformative experiences of all sorts, including NDEs, are usually described as much more real than our daily reality in the physical realm. They are also life-altering, and much more persistent than the memories of dreams or hallucinations. To equate NDEs and dreams in the REM intrusion hypothesis is once again indicative of how one's prejudices and biases can lead one far astray.

Physicalism is Inadequate for the Task

In his comments about my coma experience,[7] Dr. Nelson incorrectly states that I "provided no answer to the question about when" in my coma the experience occurred. In fact, such an analysis was a crucial part of my investigation (as those who have actually read my book realize), and the clues within my odyssey revealed it all had to have occurred between days one and five of my seven-day coma, a period during which my neurologic examinations, imaging studies and laboratory values all revealed my neocortex to be incapacitated by my meningitis.

Nelson concludes that "the influence of near-death experience can be powerful enough to conflate faith and science even in the mind of a neurosurgeon." In fact, the experience was powerful enough for this neurosurgeon to realize the brain does not create consciousness, to see the failure of pure physicalism as a worldview, to realize that mind or consciousness is primary (not brain or the physical realm), and to see the emergence of a natural synthesis of science and spirituality. It is our science that must expand its boundaries beyond the simplistic falsehoods of physicalism to more fully grasp the extreme mystery of consciousness as revealed through NDEs and similar experiences.

Nelson also claims this neurosurgeon to be "anti-scientific," then erroneously pits me against the "sage words of a brilliant Canadian neurosurgeon from the mid-20th century," Wilder Penfield, MD.[8] Dr. Nelson appears to have also completely misinterpreted Dr. Penfield's book and message, which, in fact, are closely aligned with my own view that the brain does not create the mind:

- "But to expect the highest brain-mechanism or any set of reflexes, however complicated, to carry out what the mind does, and thus perform all the functions of the mind, is quite absurd." Penfield, p. 79
- "And yet the mind seems to act independently of the brain in the same sense that a programmer acts independently of his computer, however much he may depend upon the action of that computer for certain purposes." Penfield, p. 79
- "Taken either way, the nature of the mind presents the fundamental problem, perhaps the most difficult and most important of all problems. For myself, after a professional lifetime spent in trying to discover how the brain accounts for mind, it comes as a surprise now to discover, during this final examination of the evidence, that the dualist hypothesis seems the more reasonable of the two possible explanations." Penfield, p. 85 [i.e. that brain does not create mind, and the two should be considered as existing in their own right]
- "What a thrill it is, then, to discover that the scientist, too, can legitimately believe in the existence of the spirit!" Penfield, p. 85
- "The mind conditions the brain." Penfield, p. 86
- "It is an observation relevant to any inquiry into the nature of man's being, and in conformity with the proposition that the mind has a separate existence. It might even be taken as an argument for the feasibility and the possibility of immortality!" Penfield, p. 87
- "What is the reasonable hypothesis in regard to this matter, considering the physiological evidence? Only this: the brain has not explained mind fully." Penfield, p. 88
- "I worked as a scientist trying to prove that the brain accounted for the mind and demonstrating as many brain-mechanisms as possible hoping to show how the brain did so. . . . In the end I conclude that there is no good evidence, in spite of new methods, such as the employment of stimulating electrodes, the study of conscious patients and the analysis of epileptic attacks that the brain alone can carry out the work that the mind does. I conclude that it is easier to rationalize man's being on the basis of two elements than on the basis of one." (Penfield, pp. 113-114)

Of note, Christof Koch, PhD, Chief Scientific Officer at the Allen Institute for Brain Science (Seattle), long a very determined physicalist neuroscientist, has recently followed Penfield in explicitly abandoning any hope of explaining consciousness as a product of brain processes.[9]

Nelson claims that "a central tenet of neuroscience holds that all human experience arises from the brain," which he erroneously concludes is aligned with the views of Penfield, whereas Penfield's (and my) position is exactly

"What a thrill it is, then, to discover that the scientist, too, can legitimately believe in the existence of the spirit!"
-Wilder Penfield

the opposite. Nelson claims that "a plausible neuroscience explanation has always been found in 'unexplained' cases" (especially of consciousness outside, or independent of, the brain) — another patently false assertion.

If one reads Dr. Penfield's book, and mine, they find we are congruent in many ways - certainly in stating that the brain does not create consciousness (the exact point Nelson is erroneously trying to contradict with his quote). Dr. Penfield's main limitations from that point, in my opinion, were not knowing enough about the implications of the measurement problem in quantum mechanics (not to mention the current experimental evidence supporting the "weirdness" of quantum reality, such as the recent "delayed choice quantum eraser" and related experiments [10,11]), that it is information and not energy that is "conserved," and the fact that the current controversies in physics about the nature of causality that call into question our very notions of time itself [12,13] had not yet emerged when Penfield wrote his insightful book in 1975.

Nelson demonstrates just how crippling blind faith in physicalism, the notion that "brain creates consciousness," can be. Others like him who widely trumpet this claim are guilty of an unsupported faith-based belief system, and of being willfully ignorant when they deny the data concerning the rich tapestry of mystical experiences, including NDEs.

In fact, the challenge of understanding NDEs from this brain-based perspective becomes even greater when one considers the realm of shared death experiences (SDEs), first described by Raymond Moody, MD, PhD, and Paul Perry in their fascinating book, Glimpses of Eternity. [14] The experiential aspects of SDEs closely resemble those of NDEs, but they occur in physiologically normal people. SDEs occur when the soul of a completely healthy bystander at the bedside of a dying patient is drawn along on the journey with the soul of the dying patient, even to the point of witnessing a full-blown life review of the departing soul, before the bystander soul returns to the earthly realm. In the hundreds of talks I give on these topics, I encounter numerous people who share their own stories of NDEs and after-death communications. A small but significant percentage of the stories I hear from the general public are actually of SDEs — they are not rare.

Rejection of the Data Results in Willful Ignorance

Dr. Nelson is a neurologist who professes an interest in spiritual experiences. As such, one might expect him to demonstrate interest in the case of a neurosurgeon who was driven into coma over three hours due to gram-negative bacterial meningitis as severe as that which I reported in Proof of Heaven,[7] spent seven days in coma to the point where doctors had abandoned hope and were recommending termination of antibiotics, returned to this world with his mental faculties devastated, but then went on to a full recovery over eight weeks — to the point where he could participate in this deeply intellectual discussion about NDEs in *Missouri Medicine*. Yet Nelson's accusation that my book [7] "falls into a slick and clever literary genre," was based not on his having read the book, but on a book review article in the New York Review of Books by a literary critic (R Gottlieb) who was completely ignorant of the relevant scientific issues.[15] This reveals Nelson's unwillingness, or inability, to consider the relevant data, and to actually participate in this very deep discussion about the nature of consciousness and of all reality as revealed through NDEs and similar spiritually-transformative experiences. Such willful ignorance is rampant among the debunkers and deniers of the physicalist camp, which renders their contribution to this deeper dialogue to be largely irrelevant.

Nelson also does not appear to be familiar with the Handbook of NDEs,[4] Irreducible Mind,[3] or any other such books that responsibly address the full constellation of features found in NDEs, and in fact present a far more robust discussion of consciousness, and notably of non-local consciousness (i.e. consciousness independent of the here-and-now of the physical brain and body's immediate environs), than are found in any of the physicalist sources.

It is crucial to realize that the only thing any human being has ever experienced is the inside of his or her own consciousness, a model created within mind, but not external "objective" reality itself.

Part of the problem is that this is not simply a discussion about a few interesting and unusual phenomena that paradoxically appear around the time of death or near-death. Given that we are all essentially prisoners within our own consciousness, this discussion is actually about the very nature of all existence — a fundamental investigation into the nature of reality. A more comprehensive, top-down approach, one that takes all of the relevant data into account, and addresses the profound mystery of our conscious existence itself might lead to a deeper understanding. Seeking answers is no small task: any significant progress will influence not only the realms of neuroscience and philosophy of mind, but the entire scientific community (notably physics and cosmology), and all of humanity.

Science Beyond Physicalism

If one is too confined by physicalist prejudices, e.g. believing at the outset that one is trying to fit the empirical observations into one's model of reality (i.e. that the brain creates the mind), they risk completely missing the deeper lessons of the journey. As with any attempt to gain a deeper understanding of something as fundamental as "consciousness," any partitioning of the subject matter is guaranteed to lead to confusion and misinterpretation. The problem is in our mindset, and is an inherent problem with the conventional scientific approach of reductive materialism.

The brain is clearly related to consciousness — the fallacy is in believing the brain creates consciousness out of purely physical matter. The emerging scientific view, far more powerful in its explanatory potential, relates to the notion of the brain as a reducing valve, or filter that limits primordial (infinite?) consciousness down to the minuscule trickle of the apparent here-and-now of our physical human existence. This idea (filter theory) enables the possibility that the soul survives bodily death, and is attributed to the brilliant masters of the human psyche who worked mainly in the late 19th and early 20th centuries, notably Frederic W.H. Myers, Henri Bergson, and William James.[3]

Physicalism and atomism (the idea of the separation of objects within the universe) often go hand in hand - and both introduce distortions in trying to understand how humans fit into the universe as a whole. The act of separating parts of the universe from the whole is artificial and detracts from approaching the deeper truth of reality. This is one of the fundamental problems with our predominant scientific model of reductive materialism that relies largely on such false separations.

In spite of the wonders the world has seen from the advances of modern science and technology, there is a dark underbelly related to that progress in the form of the destruction of our planetary ecosystems, modern warfare, thoughtless homicide and suicide, etc. — much of it due to the artificial removal of human spirit from the predominant physicalist worldview.

The false conclusion of physicalist science that consciousness is manufactured by physiological processes occurring in the brain, that we are nothing more than "meat computers," automatons or zombies, that free will itself is a complete illusion, are vastly destructive as a predominant worldview. The emerging scientific view of consciousness as fundamental in the universe also incorporates the Oneness of all consciousness,[16] and the importance of appreciating the connectedness of all elements of the universe in reaching fundamental truth. I foresee this top-down approach to understanding as being much more fruitful.

For those with a serious interest in understanding the emerging science, I recommend especially the book Beyond Physicalism: Toward Reconciliation of Science and Spirituality (February 2015), edited by Edward F. Kelly, Adam Crabtree and Paul Marshall, et. al from the Esalen Institute and the Division of Perceptual Studies at the University of Virginia. [17] This landmark opus, from the same group that published the world-changing Irreducible Mind: Toward a Psychology for the 21st Century, [3] offers a theoretical framework that will "hopefully contribute to blowing away the fog of ignorance and confusion that materialists have imposed on the scientific community and humanity at large," as stated by one of the prominent endorsers of the book, B. Alan Wallace, physicist, Buddhism scholar and teacher, and the president of the Santa Barbara Institute for Consciousness Studies. I agree wholeheartedly

with Dr. Wallace's endorsement, which goes on to opine that Beyond Physicalism might allow us to "free ourselves from the ideological straitjacket of physicalism so that modern civilization can emerge from the dark age of ignorance and delusion about consciousness and return to the true spirit of open-minded empiricism that heralded the rise of modern science."

It is this open-minded empiricism to which I aspire, and which I encourage other scientific investigators to pursue. That is the spirit of this NDE series in Missouri Medicine — thus I felt compelled to respond to Dr. Nelson's article so that the physicalist/materialist camp was not claiming the final "scientific" word in this forum.

As much as Dr. Nelson claims to be holding up the light of science and reason, his physicalist view simply supports the "dark age of ignorance and delusion about consciousness," when true light and understanding are available — we must maintain an open mind and address all of the empirical data, not just that which we feel fits our dominant theoretical model. NDEs are just the tip of the iceberg in this evolving scientific view of the phenomena of non-local consciousness (proving the reality of phenomena such as near-death experiences, after-death communications, shared death experiences, telepathy, remote viewing, precognition, déjà vu, past-life memories in children indicative of reincarnation, psychokinesis, etc.). [3, 17]

A Masterful Illusion

It is crucial to realize that the only thing any human being has ever experienced is the inside of his or her own consciousness, a model created within mind, but not external "objective" reality itself. Increasingly refined experiments in quantum mechanics suggest that there is no underlying objective reality — that all experience depends fundamentally on consciousness to allow its manifestation. [10,11] There is no "clockwork universe" unfolding through pure natural laws, the object of natural science's attention during the Scientific Revolution (which began centuries ago, when they were less likely to tread on the sacred ground of mind and consciousness claimed by the powerful church, lest they be burned at the stake). All that is must be observed by mind in order to exist. As much as this defies our everyday assumptions, and the intentions of four centuries' of increasingly powerful probing by those pursuing investigations in the natural sciences, this is the way the universe works according to the most proven theory in the history of science (quantum mechanics). This is not some form of dogma, but in fact what is revealed in the most sophisticated efforts to probe the workings of the world, the very fabric of reality, at a subatomic level, through quantum physics.

The human brain and mind elaborate an astonishingly masterful illusion: every speck of our human experience and memory since before our birth has been our witnessing of an internal construct, of our mind's model of "reality," but not of reality itself. The profound consequences of this trick can lead us into a simplistic, unquestioning acceptance of the physicalist perspective, i.e. that only material stuff exists.

Given that our human perspective is always from within "mind," the greatest difficulty with assessing phenomena associated with near-death experiences is not having a broad enough field of view to get the full picture. The discussion rapidly converges around the fundamental nature of consciousness itself. This is the Mind-Body debate, an earnest and rigorous discussion that has been ongoing for ages, and formally for at least 2,600 years (since the likes of Plato, Aristotle and Democritus weighed in with their often astonishingly prescient views). It is not surprising that over a hundred generations of human beings have mused over the deep issues involved, but I find it astonishing that so little progress has been made. I also believe that that is about to change, and will involve a synthesis of the greatest wisdom from Eastern and Western spiritual traditions over millennia and the very frontiers of our current investigations in physics and cosmology.

In fact, the discussion goes far beyond the purview of just neuroscience and philosophy of mind — given that all of us are witnesses to our own mind only, it is about the fundamental nature of all reality and of our universe. All of physics and cosmology will participate in the emerging revelations from this discussion.

Pondering the Unknown

> *"Try and penetrate with our limited means the secrets of nature and you will find that, behind all the discernible concatenations, there remains something subtle, intangible and inexplicable. Veneration for this force beyond anything that we can comprehend is my religion. To that extent I am, in point of fact, religious."*
>
> — Albert Einstein (1879 – 1955)

The only safe assumption about the unknown is that it is infinite. Scientific inquiry over the last few centuries has proven that everyday human experience is often misleading in our effort to understand the true nature of reality. Proposing a "theory of everything" is a guaranteed source of embarrassment for the person foolish enough to believe they are close to such knowledge. Given that our modern society places scientists in such high esteem as the arbiters of truth, it is incumbent on scientists to fully admit the scope of the unknown in their endeavors.

The human pursuit of such deep understanding requires opening our minds broadly to explain all of our empirical observations. As Carl Sagan, PhD so wisely pointed out, we are "not smart enough to know which pieces of knowledge are permissible" — thus scientists, first and foremost, should not suppress any knowledge, yet in the current discussion around NDEs the formal scientific community often actively denies and debunks everything that doesn't fit the very narrow physicalist model of "brain-creates-mind." Their unwarranted assumption that the brain creates consciousness renders their contribution to any meaningful discussion of NDEs as woefully impotent.

Much of our knowledge about the nature of reality must derive from all of human experience, not just the limited flow from strict application of the scientific method in a controlled environment. Anecdotes provide a rich source of understanding, if they are carefully scrutinized and combined with other knowledge. In fact, all of scientific discovery has involved anecdotes and individual experience as the seed from which knowledge emerges.

The good news is that many scientists around the world fully appreciate the depth of the mystery of consciousness, and how NDEs and similar mystical experiences offer profound clues in approaching a deeper understanding of the underlying reality. [18] This dialog sows the seeds for the destruction of the purely physicalist model of the universe. Likewise, the startling enigma of the measurement problem in quantum mechanics, which suggests that consciousness is primordial in the universe, calls for a fundamental reworking of our worldview. [10] Current scientific understanding must be greatly expanded to fully incorporate the unfathomably deep mystery of consciousness itself, and its role in manifesting all of emergent reality.

Nelson closes his article with: "Medical professionals who tout spiritual shortcuts by forsaking science seriously risk debasing near-death experiences in the minds of many who hold science in esteem… Clinicians have an ethical responsibility to clearly differentiate the domains of science and faith." In fact, Nelson is the one guilty of "forsaking science." The emerging scientific view will be one that fully embraces these extraordinary conscious experiences and provides a far more realistic model of the universe than the paltry and barren fiction provided by lame physicalism.

I believe that medical professionals like Nelson who claim to have purely materialist explanations of phenomena that are far beyond the ken of those simplistic "scientific" physicalist assumptions do great damage in pretending they know things they do not, such as the mechanism of consciousness itself — therein lies the real damage that can be done in the interaction between medical professionals and their patients who report these amazing journeys.

We ought rather to foster an environment where these stories are widely shared and discussed — they are gems that reward us with great riches in a deeper understanding of all of existence. The expanding boundaries of this emerging science will fully embrace our spirituality and allow medical professionals who are more enlightened to offer greater healing than the purely physicalist mindset ever allowed.

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Former *Missouri Medicine* Editor Jordan W. Burkey, MD, Dies

Dr. Burkey was Editor of the MSMA Journal from 1982-1988



Jordan W. Burkey, MD, former *Missouri Medicine* Editor, and MSMA member for 37 years, died on Friday, June 12, 2015, at The Neighborhoods of Quail Creek in Springfield, Missouri. He was 92.

He was born on July 7, 1923, in Arkansas City, Kansas, and after graduating from Arkansas City High School, he edited the town newspaper's sports page while attending the local community college. The U.S. Army took Dr. Burkey out of Kansas in 1943 and moved him around the Midwest and then to India at the end of World War II.

Dr. Burkey earned his undergraduate and medical degrees from Kansas University. While in medical school he met Ruth Jean Wolf, a KU nursing student, and they married in 1951. They lived in Kansas City while Jordan interned at Bethany Hospital and finished his residency at the KU Medical Center. They settled in Springfield where he practiced ear, nose, and throat medicine for forty years, retiring in 1995. During 1971-1983 he was also a clinical assistant professor of surgery at the University of Missouri.

Maintaining his interest in journalism, Dr. Burkey served several years as editor of the *Journal of the Greene County Medical Society*, and also *Missouri Medicine*, replacing Wilfred W. Woolridge, MD, in 1982.

MSMA Members in the News





MSMA District Two Councilor **Sandra Ahlum, MD**, and Past President **Lent Johnson, MD**, both of Hannibal, recently recertified as clinical densitometrists. They have supported organized medicine in Missouri for a combined total of 66 years.



MSMA has a new member in its young physician section, **Jennifer Blair, DO**, and she is also new to the staff at Wright Memorial Hospital in Trenton.

MSMA member since 2012, Travis **Brawner, MD, FACS**, co-sponsored a back-to-school drive in Branson, contributing school supplies and backpacks to more than 1,000 children.

MSMA member since 2011, **Matthew A. Brown, MD**, has been awarded the Degree of Fellow of the American Academy of Family Physicians.

After teaming with leading investigators from top institutions around the nation, **Michael Bukstein, MD**, MSMA member since 1976, and **Humam Farah, MD**, MSMA member since 2014, are credited with breakthrough research in the development of a genomic signature to help patients battling the diagnosis of lung disease.

MSMA Members Drs. **Robert Carter, Scott Kujath, Karl Stark,** and **Jonathan Wilson** are now seeing patients at CRMC Westside Medical in Cameron. Together, they have supported MSMA for nearly 50 years with their memberships.



MSMA member since 2011, **James Day, DO,** now sees patients in Parkville and in Smithville.

Gerald Lee Early, MD, of Kansas City, has been an MSMA member since 1982, and was recently honored with the Distinguished Alumni Award from Central Methodist University.



Congratulations goes out to **Arthur Freeland, MD**, FAAFP, MSMA member since 1997, who was recently presented with the MAFP 2015 Family Physician of the Year Award.



Margaret "Meg" Gibson, MD, MSMA member since 2010, has been named official marathon medical director this year for the Waddell and Reed Kansas City Marathon.



Doug Girod, MD, MSMA member since 2001, and **Bridget McCandless, MD**, member since 2011, made the Kansas City Business Journal's list of Power 100.

MSMA member since 1983, **Michael Handler, MD**, gave the keynote address on May 15 at the second annual Vijay Babu Rayudu Quality & Patient Safety Day program at UMKC.



The Distinguished Reviewer Award for 2014 from the medical journal Diabetes Care, a journal of the American Diabetes Association has been awarded to MSMA member since 1976, **Richard Hellman, MD**, from Kansas City.



A superhero in his own right, **Timothy Isakson, MD,** was a proud Omega Sponsor of the 3rd Annual Superhero 5k, hosted by Phelps County Regional Medical Center Relay for Life team on June 13.

Physicians at Phoenix Urology of St. Joseph have a long history of supporting organized medicine. Drs. **Mike Kozminski, Mark Lierz,** and **Krikor Partamian** have been members of MSMA for a combined total of 86 years. MSMA would like to congratulate the newest addition to the team, **Bradley Moore, MD**, and recognize him as a valued young physician member of MSMA since joining just last year. Dr. Moore's services span from Phoenix Urology, to Putnam County Memorial Hospital's outreach clinic, to Northwest Medical Center, and into Kansas.

Earlier this summer, **Erik Meidl, MD**, of Hannibal, joined 24 missionaries from all across the country and spent eight days treating patients in San Cristobal and other small communities in Mexico. **Dr. Meidl** has been an MSMA member since 1996.

MSMA appreciates the support of **Bassem Mikhail, MD**, since 2008, of Hannibal. He has been named a Fellow of the Society for Cardiovascular Angiography and Interventions.

A new member of MSMA from Osage Beach, **Jenny Powell, MD, FAAFP**, attended the National Physicians Coalition for Freedom in Medicine in Washington, DC, and visited with Congressional legislators about a proposal titled "How Practicing Physicians Would Restore Affordability, Promote Patient Choice, and Retain Quality in Health Care."



MSMA wishes to congratulate **Ben Reine, DO**, on his new position in his hometown at the Savannah Medical Clinic, and for becoming an MSMA member.

Roark Family Health and Medical Spa, along with **Lisa Roark, MD**, MSMA member since 2011, announced the grand opening of their Direct Primary Care medical clinic at a ribbon cutting on May 29 in Cassville.

Jonathan Roberts, MD, MSMA member since 1994 in Jefferson City, is providing top-notch services with the introduction of new MarginProbe technology. Dr. Roberts is the first in Missouri to utilize this system during a removal procedure.

MSMA is happy to have **Heather Savedra, MD**, as a new young physician member, and Southland Primary Care has the recent honor of bringing her on staff in Belton.

MSMA member of 20 years, **Shahid Waheed, MD**, gave the keynote address for unveiling a new linear accelerator at SSM Health in Mexico.

New MSMA member and resident **Dylan Werth, MD**, recently joined the physician staff of Pleasant Hill Medical Clinic.

MM

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Dermatology at Saint Louis University: Offering the Most Advanced Skin Care in the Area

by Scott W. Fosko, MD

Where excellence in patient care drives education, research, and innovation in skin disease.



Scott W. Fosko, MD, is Professor and Chair of the Department of Dermatology at Saint Louis University School of Medicine in St. Louis.
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It is with tremendous pride that our Department of Dermatology at Saint Louis University is featured in *Missouri Medicine*. The Department has evolved over the years to what is today, a comprehensive and subspecialty approach to the broad range of dermatologic conditions our patients present with each day.

Our Department began its formal development in 1992 when our inaugural Chair, Neal S. Penneys, MD, recruited by the late Coy Fitch, MD, Chair of Internal Medicine, arrived from Miami University to begin a formal academic dermatology program. Dermatology was first established as a Division of Internal Medicine, and in 1996 became a Department of Dermatology at Saint Louis University School of Medicine. Within the first year, a core group of six faculty was established, and our Residency Program approved with Drs. Dobbin Connor and Mary Gibney, our first two residents. At the end of this academic year, we will have graduated 45 residents who practice across the United States, both in private practice and academic settings. Several graduates have remained in the St. Louis and midwest region and contribute to our tradition of excellence in patient care. In 2001 I became the second Chair of the Department. We have grown to 12 faculty and two physician assistants.

The Department's mission statement is "To provide excellence in all aspects of patient care, while furthering the field of Dermatology through the education of trainees and the advancement of research." This statement has been our roadmap to establishing a premier academic department and our growth and expansion continues. Let me highlight several areas of our department. Clinically, we have two practice sites, one on the midtown medical center campus in the Anheuser-Busch Institute building, and our more recent expansion in 2012, on the grounds of Des Peres Hospital. At each site we offer medical dermatology, phototherapy, Mohs surgery and cutaneous oncology, cosmetic and laser dermatology, contact dermatitis and patch testing. We also offer a full service reference dermatopathology laboratory with faculty expertise in reading skin

While clinical excellence defines our daily focus, it is our patient care foundation that has allowed us to expand into areas of clinical research.

pathology. Our dermatopathology specimens are received from all over the United States. Pediatric dermatology is based in the Department of Pediatrics in our Cardinal Glennon Children's Hospital.

From our clinical practice we have developed outstanding and deep educational programs. Medical student education is robust with nine clinical rotations offered and classroom and laboratory sessions provided. Graduate Medical Education has flourished and has grown from two residents a year to now four. Subspecialty fellowship training followed with programs in Mohs surgery and cutaneous oncology, dermatopathology and clinical research.

While clinical excellence defines our daily focus, it is our patient care foundation that has allowed us to expand into areas of clinical research. Our research unit oversees a broad range of clinical trials, both industry and investigator initiated and focuses on the areas of cutaneous oncology, cosmetic dermatology, hyperhidrosis, biologic therapy for psoriasis and immunobullous conditions and other dermatologic disorders. We support two clinical research fellows a year. In the past four years we have initiated 33 funded trials, and since 2002, we have had approved over 100 IRB research protocols.

So welcome to the Department of Dermatology at Saint Louis University. More information can be found about our faculty, and Department's activities at http://dermatology.slu.edu/ web address. In this issue of *Missouri Medicine*, you will find a range of articles highlighting the spectrum of dermatologic conditions that impact our patients. Dr. Glaser, our Director of Cosmetic and Laser Surgery and Vice Chairman, and President of the International Hyperhidrosis Society, shares her knowledge and experience with the piece, "Use of Systemic Therapies to Manage Focal Hyperhidrosis." Dr. Hurley, Director of Dermatopathology, and Co-Director of our multidisciplinary cutaneous lymphoma clinic, highlights her area of clinical and research interest with, "Clinical Practice Guidelines for Cutaneous Lymphomas." Dr. Burkemper, our Residency Program Director and Director of our contact dermatitis program, discusses the role of patch testing and how we can assist in the evaluation of patients who may be encountering a cutaneous allergen in "Contact Dermatitis, Patch Testing and Allergen Avoidance." Dr. Mary Guo, Director of our Women's Health, discusses the often overlooked and difficult to diagnose and manage, and unfortunately at times quite debilitating, cutaneous conditions of the female genitalia in "Vulvar Dermatoses: a Review and Update." Dr. Vidal, a member of our Dermatopathology Division, and Director of Medical Student Education, highlights the complexity of hair loss and making a pathologic diagnosis in "Alopecia: a Dermatopathologist's Perspective." Dr. Maher, Associate Director of Mohs Surgery and Cutaneous Oncology, reports on the safety and high quality experience of outpatient surgery that can be offered to our patients with "Aesthetic Reconstruction in the Outpatient Setting."

As you can see, the specialty of Dermatology is broad in scope and deep with expertise in many areas. These articles are just a sampling of the many areas dermatologic conditions impact our patients. We as your colleagues can assist you and your patients in their care. Dermatology continues to evolve as a specialty, with our research and innovations helping us advance this area of medicine. I hope you enjoy this issue and if there is any way that our Department can be of assistance to you, please contact us at http://dermatology.slu.edu. **MM**

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Use of Systemic Therapies to Manage Focal Hyperhidrosis

by Dee Anna Glaser, MD & Katherine Glaser, MS-5

Oral therapies can play an important role in treating hyperhidrosis of all types. Although monotherapy is sometimes useful, combining systemic treatments with more focally-based therapy may provide superior results.



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Abstract

Primary hyperhidrosis (excessive sweating) commonly affects the axillae, palms, soles, scalp, face, and the groin. Patients may have multiple areas involved making localized therapy challenging. Systemic therapy may be necessary and can be used as monotherapy or combined with other hyperhidrosis treatments for optimal outcomes. Systemic therapy can also be used to treat secondary hyperhidrosis and compensatory hyperhidrosis. Patient selection and counseling are key, and monitoring for side effects is required throughout therapy.

Introduction

Hyperhidrosis (HH) is a common disorder, affecting approximately 3% of the US population. It is a disabling condition that significantly impacts quality of life (QOL) and can cause considerable emotional stress. Primary HH presents with focal areas of excess sweating such as the axillae, palms, soles, scalp, face and groin. Although some patients have only one focal area of excessive sweating, it is common for patients to have more than one body site producing excessive amounts of sweat.[1] In addition, patients may present with more generalized forms of HH which are usually secondary in nature. In these cases, treatment or removal of the offending cause can be very beneficial, but may not always be feasible. Compensatory hyperhidrosis following sympathectomy occurs in 50-80% of patients and can affect very large areas such as the chest, abdomen and back.[2] Systemic therapy can be beneficial in all of these patients.

There are no oral agents that have an FDA-approved indication to treat HH and there is a paucity of studies on the use of systemic medications for treating HH.

Treatment Indications

In general, treatment for primary HH should be as specific and focal or localized as possible to insure good response and minimize side effects and interactions with other medications. Topical therapies such as aluminum chloride are usually first line treatment but can be ineffective and produce skin irritation. More focally targeted therapies such as botulinum toxin injections, iontophoresis, or microwave thermolysis are focal treatments that should be considered. However, when these treatments are ineffective, intolerable, or not feasible, systemic therapies may be warranted. In addition, oral medications can be added to the above treatments to enhance therapeutic outcomes. This is especially beneficial when patients have multiple areas of HH. In such

individuals, a multi-pronged approach might be needed with the use of botulinum toxin A injections for the axilla, iontophoresis for the hands and feet, and an oral agent to help manage other areas such as the groin, face, or submammary sweating.

Generalized sweating presents a challenge. If a specific etiology is identified, that agent or cause should be removed. However, it is common that an offending agent can't be removed. Patients with psychiatric disease frequently can't lower or change the medications that are controlling their mental illness. In these instances, other options such as oral medications to treat the HH have to be considered.[3] Some patients will have multiple co-founding factors that can induce or worsen HH, and oral therapy may be very helpful.

There are groups of patients that should be considered very carefully before initiating therapy with oral medications, especially anticholinergics which decrease sweating from the entire body. Athletes and individuals who work or play a lot outdoors may become overheated if they are unable to cool their bodies without sweat evaporation, and may have an increased risk of hyperthermia. Small children or individuals who have difficulty self monitoring their body temperature, mentation, and urine output may not be good candidates for oral anticholinergic agents. Allergies, other medications, or health issues need to be reviewed to avoid interactions or worsening of other diseases or health concerns. As an example, beta blockers are generally not given to patients with psoriasis.

It is important to counsel patients on what therapy is being used, how it works, and what to monitor. It is also critical that patients are counseled on realistic expectations. Most patients can expect an improvement but not complete resolution of their HH symptoms. Patients should be warned that they will most likely still have episodes of excessive sweating, and they may be the first to sweat and even sweat more than their counterparts during activity. Setting a step-wise plan for the patient can be very helpful so they don't discontinue therapy. Improvement in symptoms is usually possible to achieve, but anhidrosis is not, nor is it desirable.

Anticholinergic Agents

Since the sweat glands are innervated by the sympathetic postganglionic nerves and have acetylcholine as the primary neurotransmitter, the use of anticholinergic agents is a logical choice to treat hyperhidrosis.[4] Anticholinergic agents work by competitive inhibition of acetylcholine at the muscarinic receptor. Muscarinic receptors are present throughout the central and autonomic nervous system, accounting for the widespread and varied side effects that can develop.

There are several anticholinergic agents available; however there are differences in the side effect profile. Glycopyrrolate as a quaternary amine, has limited passage across lipid membranes such as the blood-brain barrier. This is in contrast to agents such as atropine or scopolamine, which are tertiary amines and can easily penetrate lipid barriers. This is probably the reason why glycopyrrolate has fewer central nervous system side effects and may have less effect on the heart rate at lower doses.[5] The most common side effect is dry mouth due to inhibition of salivary glands. There are many potential side effects (See Table 1), and concurrent use with other medications with anticholinergic activity such as phenothiazines,

Table 1
Anticholinergic Therapy Side Effects

Gastrointestinal
- Dry Mouth
- Constipation
- Nausea
- Vomiting
- Bloated Feeling
- Loss of Taste

Ocular
- Mydriasis
- Cycloplegia
- Dry or Gritty Eyes
- Blurred Vision
- Photophobia

Respiratory
- Bronchodilation
- Reduced Secretions

Genitourinary
- Urinary Retention
- Slow Voiding
- Urinary hesitancy
- Erectile Dysfunction
- Loss of Libido

Cardiac
- Bradycardia (lower doses)
- Tachycardia (higher doses)
- Arrhythmias
- Palpitations

Central Nervous System
- Headache
- Dizziness
- Insomnia
- Drowsiness
- Mental confusion and/or excitement (usually in elderly)
- Seizures

Skin
- Decreased sweating
- Urticaria
- Pruritus

antiparkinson drugs or tricyclic antidepressants, intensify the antimuscarinic effects and increase side effects. Anticholinergic therapy may be contraindicated in patients with glaucoma, obstructive uropathy, obstructive diseases of the GI tract, paralytic ileus, severe ulcerative colitis, and myasthenia gravis.

Glycopyrrolate

Glycopyrrolate is the authors' most commonly used anticholinergic drug to treat HH. Dosing is variable and is usually started at a dose of 1 mg twice daily. The patient is asked to increase the dose by 1 mg per day at two-week intervals based on the therapeutic response and side effects. Dry mouth is the most common side effect and usually the limiting factor in dosing. If side effects are minimal, management can allow patients to continue their medication. Managing dry mouth could include use of artificial saliva preparations, increasing water intake, keeping candy or mints available, etc., and increased fiber consumption and light exercise can help to improve mild constipation. Over the counter eye drops can improve dry eye symptoms, but many patients will have to discontinue therapy due to intolerable side effects. The side effects of therapy are generally dose-dependent.

Walling published a retrospective review of 45 patients who used glycopyrrolate to treat HH of various body sites. Overall 67% were responders and 33% failed treatment.[6] Of the treatment failures, 40% were nonresponders and the rest had adverse effects requiring medication cessation (xerostomia, GI disturbance, headache, rash, and mental status change). Only one-fourth of these patients used it as monotherapy, while the majority of patients combined therapy with topical aluminum chloride, botulinum toxin, and iontophoresis. These patients most commonly took 1 mg daily and the highest dose that was used was 3 mg BID. Bajaj and Langtry reported on 19 patients treated with glycopyrrolate and found that 80% responded to therapy.[5] The most common dose was 2 mg twice daily or three times daily but one patient took 4 mg BID. Side effects were reported in 80% of the patients and about one-third of their patients had to stop the glycopyrrolate due to side effects. Typically my patients will require daily maintenance, but a few will take on a "as-needed basis." Doses range from 1 mg BID to 8 mg BID and does not seem to correlate significantly with age, gender or body mass.

Oxybutynin

Oxybutynin is another common anticholinergic drug that can be used to treat hyperhidrosis. It is classified as a tertiary amine. It comes in several different preparations including a tablet, slow-release tablet, topical gel, and a transdermal patch. For oral administration, 5-10 mg daily is usually required for relief of HH, but doses up to 15 or 20 mg daily may be required.[7, 8] Wolosker did a randomized placebo-controlled trial using oxybutynin for palmar and axillary HH. Fifty patients were enrolled, and the drug was initiated at 2.5 mg daily, increased to 2.5 mg BID during weeks two and three, and then treated with 5 mg BID. Approximately 70% of the patients reported improvement in their axillary and palmar HH, while 90% of patients with plantar involvement reported improvement in their plantar sweating. The majority of treated-patients reported improvement in their QOL, while one fourth had no change in their QOL. Side effects were limited to dry mouth that was rated as moderate to severe by 30% of the subjects during the first three weeks (lower dose) and reached 35% by six weeks with the higher dose of oxybutynin.[9] Tupker reported 13 patients with generalized HH and one with paroxetine-induced HH that were treated with oxybutynin (2.5 mg TID, and 5 mg TID), with all of the generalized HH patients responding (the drug-induced HH patient did not respond). Therapy was well tolerated with the most common side effects being dry mouth, urinary difficulty, GI complaints, headache, and lassitude; although 30% had to discontinue therapy due to side effects. Therapy seems to work well in both men and women, as well as overweight and obese individuals.[10, 11]

There are no guidelines to use when choosing which anticholinergic drug to use for hyperhidrosis. Because of the more limited penetration into the CNS, glycopyrrolate is a good option. Patients may respond to one anticholinergic drug better than another, or may experience fewer or different side effects with one drug compared to other anticholinergics.[6] Additionally, there may be better compliance with the once-daily slow release oxybutynin. It is reasonable to switch anticholinergic drugs when faced with nonresponse. Another option is to try a topical formulation.

Other Anticholinergic Agents

Different options are available in various parts of the world. One of the best studied is methantheline bromide, which is a quarternary amine available in Germany. A multicenter placebo-controlled randomized study of 339 patients with axillary or palmar-axillary HH was performed.[12] Methantheline 50 mg or placebo was used TID: gravimetric measurements of sweat, Hyperhidrosis Disease Severity Scale (HDSS) and QOL was measured. At day 28, there was a reduction of sweat production of

40% compared to the placebo-treated group who had a 19% reduction in sweat production. The measured reduction in sweat was greater in the axilla compared to the palms. The researchers hypothesized that the decreased efficacy in the palmar sweating may be due to the fact that a significant proportion of methantheline is excreted through the sebaceous glands and these are lacking in the palms. Tolerability was good, with dry mouth, impaired accommodation, and dry eyes reported. There was a statistically significant decrease in the HDSS and an improvement in QOL in the methantheline-treated subjects compared to placebo-treated subjects.

Anticholinergic Use in Pediatric Patients

In general, I avoid the use of systemic anticholinergic therapy for my young patients with HH since they have less control of their environment at school, may be exposed to heat stresses during playtime, and may not be able to monitor themselves for signs or symptoms of hyperthermia. However, Amy Paller, MD, reported on 31 pediatric patients that were treated with glycopyrrolate and found that 90% had improvement while 10% had no improvement in their hyperhidrosis. Most of her patients were teens with the average age at the time that the glycopyrrolate was prescribed being 14.8 years ± 2.9. The mean dose for these teens was 2 mg daily but ranged from 1-6 mg daily. Approximately 30% had side effects including dry mouth, dry eyes, and blurred vision. One patient had to stop therapy due to palpitations.[13] Oxybutynin has been studied extensively in children for urologic problems with a good safety profile, although there is a higher number of CNS adverse event cases reported in pediatric patients as compared with adult patients.[14, 15] Glycopyrrolate is FDA-approved to treat children with sialorrhea and in this population side effects are dose-dependent and include behavioral changes, constipation, excessively dry mouth, urinary retention, facial flushing, nasal congestion, vomiting, and diarrhea.[16]

Beta Adrenergic Blockers

The use of beta blockers to treat patients with HH stem from their use to improve symptoms of social phobias and performance anxiety.[17] Performance anxiety can affect anyone in a multitude of situations but studies are often aimed at those who are frequently in the "spotlight" such as actors, musicians, or surgeons.[18] Sweating may develop throughout the day, but many HH patients complain that severe episodes develops at times of performance-related stress or when just a perception that sweating may interfere with performance, such as meetings, public speaking, school performance. In these instances the use of a beta blocker such as propranolol can be helpful. Propranolol is a highly lipophilic drug that binds to both β1 and β2 receptors with equal affinity. Peak concentration is 1 to 1.5 hours post ingestion, although food may delay peak concentration.[19] Contraindications to therapy are numerous (See Table 2), and a thorough history needs to be obtained, but low doses are generally used infrequently, making this therapy well tolerated. A resting blood pressure and heart rate should be taken in the office prior to prescribing the drug.

Table 2

Contraindications for Propanolol Therapy

- Bradycardia*
- AV block*
- Asthma
- COPD
- Depression
- Diabetes Mellitus
- Heart Failure
- Hepatic Disease
- Hypotension
- Hypoglycemia
- Cerebrovascular Disease
- Myasthenia Gravis
- Psoriasis
- Renal Disease
- Thyroid Disease

** Absolute Contraindication*

Small doses such as 10 mg of propranolol taken approximately one hour prior to the planned performance may be very helpful. For patients with low resting blood pressure, slow baseline heart rates or very small body mass index, 5 mg may be used initially. Patients should take a "test run" at home to monitor for hypotension, orthostatic hypotension, depressed cognition, or poor performance in general before using in a "real" performance situation.

Alpha Adrenergic Agonist

Clonidine is a sympatholytic medication used to treat hypertension as well as some anxiety/panic disorders. It is classified as a centrally acting α2 adrenergic agonist and has been successfully used to treat some patients with HH, and with flushing and sweating associated with menopause.[6, 20, 21,22] Doses used to treat menopausal hot flashes are low, ranging from 0.025 mg to 0.1 mg BID. Walling reported on 13 patients with HH that were treated with Clonidine with an average dose being used 0.1 mg BID. Overall there was a 46% response rate and the

majority of his patients used Clonidine as monotherapy. Interestingly, the patients with craniofacial HH comprised most of his responders. Of the seven patients who failed treatment, 3 were non-responders and four had to discontinue due to side effects, all were related to decreased blood pressure.[6] Other side effects seen with the use of clonidine are dry mouth, dizziness, constipation, and sedation.

As with propranolol, a thorough history and exam including blood pressure, should be performed prior to initiating therapy. Doses of 0.1 mg BID are most commonly used and the drug can be combined with other therapies to treat HH. [6, 22] Anecdotally, I have found it most useful in my middle-aged patients with craniofacial HH and sweating associated with flushing. I have prescribed it for generalized HH especially when there are several factors contributing to the overall sweating and to those patients with anxiety disorders requiring anti-anxiety medications.

Benzodiazepines

Benzodiazepines are sometimes listed as a treatment for HH, social anxiety disorders, and performance anxiety.[17, 23] Diazepam 5-20 mg/day is recommended, but there is no real primary literature supporting the efficacy in patients with HH. Since HH is a chronic disease, one has to carefully weigh the risks of addiction or dependence. Propanolol would be the authors' first choice to treat performance-based sweating. If anxiety appears to be the over-riding problem, referral to psychiatry for cognitive therapy or other drug management is prudent.

Conclusions

Oral therapies can play an important role in treating HH of all types. Although monotherapy is sometimes useful, combining systemic treatments with more focally-based therapy may provide superior results. Due to side effects and drug interactions, a thorough assessment should be performed prior to initiating systemic therapy, and working with other health care team members can be valuable to monitor for and reduce the risks of systemic therapies.

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Disclosure

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Clinical Practice Guidelines for Cutaneous Lymphomas

by Angela M. Sutton, DO & M. Yadira Hurley, MD

Communication between primary care physicians, dermatologists, dermatopathologists, and oncologists is essential for accurate and early diagnosis.



Angela M. Sutton, DO, is a Resident at Saint Louis University Department of Dermatology. M. Yadira Hurley, MD, (above), is an Associate Professor of Dermatology and Pathology at the Saint Louis University School of Medicine.
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Abstract

Primary cutaneous lymphomas are non-Hodgkin lymphomas, which are broadly divided into cutaneous T-cell lymphomas and cutaneous B-cell lymphomas. These classifications include numerous distinct entities, all with varying clinical presentations and disease courses. Herein, we will review the cutaneous T-cell lymphomas, including Mycosis Fungoides, Sézary syndrome, CD30+ lymphoproliferative disorders, as well as other less common entities. Cutaneous B-cell lymphomas will also be discussed, including primary cutaneous marginal zone lymphoma, cutaneous follicle-center lymphoma, diffuse large B-cell lymphoma, leg type, as well as other less common entities. Accurate and early diagnosis is key, as the treatment and prognosis varies significantly between conditions.

Introduction

Primary cutaneous lymphomas are defined as non-Hodgkin lymphomas that present in the skin without evidence of extracutaneous involvement at the time of diagnosis. The skin is the second most common site of involvement for non-Hodgkin lymphomas, and is characterized by an estimated annual incidence of 1:100,000.[1] Primary cutaneous lymphomas can be broadly divided into cutaneous T-cell lymphomas and cutaneous B-cell lymphomas. Clinical course and prognosis varies significantly between entities, thus proper diagnosis and classification is of the utmost importance. The objective of this article is to provide the primary care physician with an understanding of the clinical presentation, diagnosis, prognosis, and treatment of several primary cutaneous lymphomas and other lymphoproliferative disorders that often present in the skin.

Cutaneous T-cell Lymphomas

Cutaneous T-cell lymphomas comprise approximately 75-80% of all primary cutaneous lymphomas in the Western World.[2] Included in this classification are Mycosis Fungoides and its variants, Sézary syndrome, CD30+ lymphoproliferative disorders, and other more rare entities including subcutaneous panniculitis- like T-cell lymphoma, extranodal NK/T-cell lymphoma nasal type, primary cutaneous peripheral T-cell lymphoma not otherwise specified, and adult T-cell leukemia/lymphoma.

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma and accounts for almost 50% of all primary cutaneous lymphomas.[2] Mycosis fungoides primarily affects middle age to older adults, with a recent study reporting

a mean age at diagnosis of age 53.7, with a range of 8 to 91 years.[3] Clinical presentation may be varied, with patients presenting with multiple hypopigmented to pink to hyperpigmented patches, plaques, or tumors, which may or may not ulcerate as the disease progresses. The tumor cells are typically CD3+, CD4+, and usually CD8-. There is often predilection for "bathing suit" or "double covered" distribution of lesions early on in the disease course. The disease follows an indolent course, with progression typically occurring over many years. In later stages of the disease, lymph nodes, hematologic, and other visceral organ involvement may occur. Prognosis depends on stage and extent of disease. For those patients with limited body surface area of patch or plaque stage lesions their life expectancy is unchanged from matched controls. Prognosis worsens in patients with extensive body surface area of involvement, those with tumor stage lesions, and as expected those with extracutaneous involvement.

Treatment is guided by stage and degree of body surface area involvement. (See www.cancer.gov/cancertopics/pdq/treatment/mycosisfungoides/HealthProfessional) Early stage MF (Stage IA-IIA) is managed with skin directed therapies, including topical corticosteroids and phototherapy.[4] In cases unresponsive to the above, topical nitrogen mustard, bexarotene, local radiation, and PUVA are often employed.[4] Treatment options for more advanced disease includes, total skin electron beam therapy, interferon therapy (IFNα and IFNγ), systemic bexarotene, extracorporeal photopheresis, biologic therapies including Alemtuzumab, a monoclonal antibody against surface antigen CD52, histone deacetylase inhibitors including vorinostat and romidepsin, as well as single and multiagent chemotherapy.[4] Investigational therapies including lenalidomide, toll-like receptor agonists, interleukin-12 and interleukin-2, zanolimumab, a monoclonal antibody against CD4, proteasome inhibitor bortezomib, anti-PD1 agents, protein kinase C inhibitors, and phosphoinositide 3-kinase inhibitors.[4] Variants of mycosis fungoides have been classified based on their own unique clinical and histopathologic features. Folliculotropic MF is characterized by lymphocytic infiltrates that are tropic to hair follicle structures with relative sparing of the epidermis and clinical lesions exhibiting predilection for the head and neck. Lesions are often folliculocentric papules or plaques/tumors, often with associated alopecia. Eyebrow involvement is especially characteristic. Prognosis is similar to patients with classic tumor stage MF, with disease specific five-year survival studied at 70-80%.[2] Treatment of this condition is often challenging, and skin directed therapies are often ineffective.[2] Pagetoid reticulosis is a variant of MF with very localized, slowly growing patches and plaques of intraepidermal neoplastic T-cells. Extracutaneous involvement and disease related deaths have never been reported in this condition, and treatment is focused on the individual lesions and typically includes radiotherapy, excision, topical steroids or topical nitrogen mustard.[2] Granulomatous slack skin is a rare subtype in which there is development of localized loose skin in areas of skin folds with a granulomatous infiltrate on histopathology. Clinical course is often indolent, and treatment with radiotherapy is suggested to be effective, although studies are limited.[2]

Sézary syndrome is an advanced stage cutaneous lymphoma classically consisting of erythroderma, lymphadenopathy, and circulating neoplastic T-cells. The International Society for Cutaneous Lymphomas (ISCL) recommends that for diagnosis, an absolute Sézary count of greater than 1000 cells/mm^3, or presence of immunophenotypical abnormalities confirming a T-cell clonality in the peripheral blood, must be present.[5] Clinically patients often present with erythroderma, and may or may not exhibit exfoliation, edema, alopecia, lymphadenopathy, hyperkeratosis of palms and soles, and/or pruritus.[2] Prognosis is often poor, with disease specific five-year survival noted to be 24%, with most patients dying of infections in the setting of immunosuppression.[2] Treatment strategies are similar to those of advanced stage mycosis fungoides including extracorporeal photopheresis, interferons, PUVA, oral retinoids such as bexarotene, anti-folates such as methotrexate, and biologic targeted therapies.[4]

Primary cutaneous CD30+ lymphoproliferative disorders are the second most common group of cutaneous T-cell lymphomas, and account for approximately 30% of cases.[2] Included in this classification is primary cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis. These entities share similar histopathologic features of a dense inflammatory infiltrate of CD30+ cells. Although some characteristic features on histopathology may aid in diagnosis, often times clinical history, disease course, and follow up are the main determinants of a final diagnosis. Primary cutaneous anaplastic large-cell lymphoma most often affects adults, with a male predominance.[2] Most lesions are solitary nodules or tumors that often ulcerate, however multiple lesions can occur in up to 20% of patients. The lesions may spontaneously regress but local recurrence is common and extracutaneous involvement may occur in up to 10% of patients.[2, 6] Prognosis has been shown to be excellent in these patients with 5-and 10- year disease-related survival rates over 90%.[6] Recommended treatment for solitary lesions is local radiotherapy or excision.[6] Multiagent chemotherapy has been suggested for those with disseminated disease; however, local skin recurrence after treatment cessation is common and not necessarily

associated with a more aggressive course.[6] Lymphomatoid papulosis is a chronic, recurrent and self-limiting condition characterized by papules, papulonecrotic, or nodular lesions that characteristically regress with atrophic scarring in weeks to months, and frequently occur on the trunk and limbs.[2] The duration of the disease can last months to over 40 years.[2] In approximately 20% of patients, another lymphoma is diagnosed at some point, either before, during, or after the course of their disease.[2, 6] Prognosis is excellent, with a recent study citing a 100% five- and ten- year disease related survival.[6] Given that no treatment has been shown to be curative or to affect the natural course of the disease, the benefits of temporary improvement with active treatment must be balanced against the potential side effects of various treatment modalities.[6] If few lesions are present, no active treatment may be necessary.[6] When treatment is desired, in patients with many lesions or those in cosmetically sensitive areas, low dose methotrexate or PUVA are typically the treatments of choice with radiotherapy or excision as options for larger, localized lesions.[6]

Other entities included within the cutaneous T-cell lymphoma classification include subcutaneous panniculitis-like T-cell lymphoma, extranodal NK/T-cell lymphoma, nasal-type, adult T-cell lymphoma/leukemia, and primary cutaneous peripheral T-cell lymphoma, unspecified. Subcutaneous panniculitis T-cell lymphoma is characterized by an infiltrate of T-cells and macrophages in the subcutaneous tissue, and presents as nodules or deep subcutaneous plaques which may demonstrate ulceration, most often involving the extremities and trunk.[7] This condition exhibits an α/β phenotype, and follows an indolent clinical course.[7] A similar condition with a γ/δ phenotype, which exhibits an aggressive clinical course and poor prognosis, has since been designated under the category of peripheral T-cell lymphoma, unspecified.[7] Hemophagocytic syndrome is an uncommon, but potentially fatal condition associated with this disease.[7] Extranodal NK/T-cell lymphoma, nasal-type is an EBV+ associated lymphoma of NK-cells or T-cells that commonly occurs in the nasal cavity/oropharynx or skin, and often presents as lesions on the trunk and extremities or as a midline destructive facial lesion.[2] Systemic symptoms, extracutaneous involvement, and hemophagocytic syndrome may also be present.[2] This condition follows an aggressive clinical course, and systemic chemotherapy is the recommended treatment.[2] Adult T-cell leukemia/lymphoma is a T-cell neoplastic disorder associated with human T-cell leukemia virus 1 (HTLV-1) and most commonly occurs in regions with high prevalence of this virus.[2] Often patients present with the acute form of this condition, demonstrating leukemic involvement, lymphadenopathy, diffuse cutaneous lesions, and other systemic signs and symptoms.[2] In rare cases, smoldering forms of this condition have been reported with primarily limited skin involvement only.[2] Prognosis and treatment is dependent on the clinical subtype and degree of systemic involvement.[2] Primary cutaneous peripheral T-cell lymphoma, unspecified is an heterogeneous group of conditions that encompasses all other cutaneous T-cell neoplasms that do not fit into another defined category. Previously included in this group was primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, cutaneous gamma-delta T-cell lymphoma, and primary cutaneous small-medium CD4+ T-cell lymphoma; however these entities have recently been given their own distinct provisional classifications.

Cutaneous B-cell Lymphomas

Cutaneous B-cell lymphomas comprise approximately 25% of all cutaneous lymphomas and are divided into three main morphologic groups, primary cutaneous marginal zone lymphoma, cutaneous follicle-center lymphoma, and diffuse large B-cell lymphoma, leg type.[2] Less common entities included in this classification include diffuse large B-cell lymphoma, other type, and intravascular large B-cell lymphoma.[2]

Cutaneous marginal zone lymphoma is a lymphoma arising from cells of the marginal zone, including centrocytes, lymphoplasmacytoid cells, and plasma cells, as well as centroblasts, immunoblasts, and reactive T-cells.[2,8] Lesions are often red to violaceous, scattered papules, nodules, patches, or plaques often on the trunk and upper extremities.[2, 8] European cases have been reported in association with Borrelia burgdorferi; however, this has not been reported in cases elsewhere.[2, 8] Phenotypically cutaneous marginal zone lymphoma is classically bcl-2 positive and bcl-6 negative. This condition has an excellent prognosis, with five-year disease related survival noted to be >95%.[2, 9] First line treatment of localized lesions includes radiotherapy and excision.[9] For more wide spread lesions, close observation, radiotherapy for focal symptomatic lesions, systemic chemotherapy and/or the monoclonal antibody rituximab may be used.[9] For those cases associated with Borrelia infection, treatment with antibiotics should be considered.[9]

Primary cutaneous follicle-center lymphoma is a lymphoma of cells of the follicle center, usually including a combination of centrocytes and centroblasts.[2] Clinically this condition often presents with solitary or grouped papules, nodules, or plaques, usually on the head or

scalp and trunk.[2, 8] Lesions typically enlarge locally, but extracutaneous disease is uncommon.[2] Phenotypically, the neoplastic follicle cells express bcl-6, and expression of bcl-2 is typically absent or faint.[2] Prognosis is again excellent, with five-year disease related survival noted to be over 95%.[2] Treatment is very similar to that of cutaneous marginal zone lymphoma, with surgical excision or radiotherapy being the recommended treatment for solitary lesions. [9] For more widespread involvement, rituximab is the first line therapy, however, in severe or refractory cases systemic chemotherapy may be considered.[9]

Primary cutaneous diffuse large B-cell lymphoma, leg type is neoplastic disorder of centroblasts and immunoblasts, which typically presents as a red to violaceous nodules or tumors on the lower extremities.[2] Phenotypically, bcl-2 and bcl-6 are often expressed, as is MUM-1. Extracutaneous disease is common, with these tumors having a relatively high propensity to disseminate.[10] Prognosis is variable with disease related 5-year survival being 40-50% in patients with multiple lesions at time of diagnosis, to 100% in those patients that present with a single lesion. [2, 10] Given the propensity of this lymphoma to disseminate, and its clinical course being similar to that of systemic diffuse large b-cell lymphoma, it is recommended that first line treatment be multi-agent CHOP chemotherapy, with or without rituximab.[9] In those patients where systemic chemotherapy is not an option, radiotherapy to individual lesions or rituximab alone can be considered.[9] Other, rare large B-cell lymphomas can also present in the skin. For those cases that do not fit into another previously mentioned category, the term primary cutaneous diffuse large B-cell lymphoma, other, has been designated. Included in this classification are morphologic variants of diffuse large B-cell lymphoma including anaplastic or plasmablastic subtypes and T-cell/histiocyte rich large B-cell lymphoma.[2] The presentation of these particular lymphomas on the skin is often a manifestation of systemic disease.[2] Intravascular large B-cell lymphoma is a subtype in which neoplastic B-cells have accumulated within blood vessels and often affect many organ systems, however rarely cutaneous disease only can occur.[2]

Plasmacytoid/Dendritic Cell Neoplasms

Not included in any of the above classifications is an entity known as blastic plasmacytoid dendritic cell neoplasm, an aggressive neoplastic process of plasmacytoid origin. This condition exhibits frequent leukemic, lymph node, and bone marrow involvement with an extremely high propensity for cutaneous lesions, which may be the presenting finding.[11] Skin lesions are often asymptomatic, with variable morphology from papules, nodules, and plaques to bruise-like lesions that may be solitary or multiple.[11] Phenotypically these lesions are positive for CD4 and CD56. This condition offers a poor prognosis, with a median 5-year survival to be noted at 12-14 months. [2, 11] Systemic, multi-agent, chemotherapy is often attempted for treatment, however relapse is quite common.[11]

Conclusions/Recommendations

In summary, cutaneous lymphomas are a heterogenous group of disorders with variable presentations, which can often pose a diagnostic conundrum to clinicians. A multidisciplinary approach is recommended, and communication between primary care physicians, dermatologists, dermatopathologists, and oncologists is essential for accurate and early diagnosis.

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Disclosure

None reported. **MM**

Contact Dermatitis, Patch Testing, and Allergen Avoidance

by Nicole M. Burkemper, MD

Most contact dermatitis is irritant in nature and recommending avoidance of irritating substances as well as dry skin care measures with gentle skin cleansers and regular moisturizer use can control most of these patients' dermatitis.



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Abstract

In patients presenting with a complaint of rash, contact dermatitis is often the underlying diagnosis making it an entity with which health care providers should be familiar. Contact dermatitis can be divided into irritant contact dermatitis and allergic contact dermatitis. In a patient suspected of having allergic contact dermatitis, patch testing can be done to identify specific allergens. Education focused on allergen avoidance and safe products is an integral part of treatment for the contact dermatitis patient. Knowledge of the most common allergens is helpful for clinicians to be able to provide this education.

What Is Contact Dermatitis?

Contact dermatitis is inflammation of the skin induced by chemicals when they come in contact with the skin. In the acute phase contact dermatitis has the appearance of erythema, vesiculation (blister formation), weeping, and crusting (See Figure 1). In the chronic phase contact dermatitis demonstrates scaling, fissuring (cracking), and lichenification (accentuated skin lines) (See Figure 2). There are four general categories of contact dermatitis including irritant contact dermatitis, allergic contact dermatitis, photocontact dermatitis, and contact urticaria. The vast majority of contact dermatitis falls into the first two categories of irritant or allergic contact dermatitis.

Irritant Contact Dermatitis

Irritant contact dermatitis accounts for approximately 80 percent of contact dermatitis. It is a non-immunologic form of contact dermatitis meaning it causes damage to the skin without prior sensitization of the immune system. Irritant contact dermatitis can occur in any member of the population; however, there is variation in individual susceptibility with those in high-risk occupations being the most susceptible. High-risk occupations include caterers, furniture industry workers, hospital employees, hairdressers, chemical industry workers, dry cleaners, metal workers, and florists. The mechanism by which irritant contact dermatitis causes inflammation of the skin is through denaturation of epidermal keratins, removal of skin surface lipids, damage to cell membranes and direct cytotoxic effects. Irritant contact dermatitis is usually caused by the chronic effect of exposure to a weak irritant. The most common

causative agents are solvents such as alcohol, xylene, turpentine, acetone and ketones; metalworking fluids; surfactants such as sodium lauryl sulfate; alkalis in soap; and acids. Hands are the most commonly affected area in irritant contact dermatitis.

Allergic Contact Dermatitis

Allergic contact dermatitis makes up most of the remaining 20 percent of contact dermatitis. It is a type IV delayed hypersensitivity reaction which requires prior sensitization with a genetic predisposition. Allergens are usually of low molecular weight and are lipid soluble which allows them to penetrate the skin barrier. There are two phases to a type IV hypersensitivity reaction: the sensitization phase and the elicitation phase.[1] The sensitization phase starts with an unprocessed antigen, called a hapten, penetrating the skin barrier and being taken up by an antigen-presenting cell, typically the epidermal Langerhans' cell. As the Langerhans' cell migrates to the draining lymph node the hapten is chemically altered within the cell and is conjugated with an HLA-DR molecule to form the complete antigen. The complete antigen is then expressed on the surface of the Langerhans' cell and presented to CD4+ helper T-cells in the regional lymph nodes. The helper T-cells clonally expand and these memory T-cells migrate to the skin. The elicitation phase occurs when there is re-exposure to the allergen (hapten). It is again taken up by Langerhans' cells and presented to the specific memory T-cells in the skin via HLA-DR.[2] Cytokines are produced including IL-1, IL-6 and GM-CSF leading to mast cell and macrophage activation with subsequent inflammation, cellular destruction and repair. After sensitization, skin inflammation develops 24 to 48 hours after re-exposure.

Figure 1
Acute contact dermatitis to poison ivy demonstrating erythema, vesiculation and crusting.



Figure 2
Chronic contact dermatitis to a preservative in shampoo demonstrating scaling and lichenification.



Patch Testing

Although clinicians may biopsy rashes to try and determine whether contact dermatitis is irritant or allergic in nature, there are no histologic features that have been shown to consistently favor one over the other.[3] Instead, patch testing is used to produce in miniature an eczematous reaction by applying allergens under occlusion on intact skin of patients suspected of being allergic. The T.R.U.E. (Thin-layer Rapid-Use Epicutaneous) Test is a pre-made patch test that consists of 35 allergens incorporated into hydrophilic gels. The T.R.U.E. test is widely used by Dermatologists and Allergists due to its convenience and ease of use. The disadvantages of the T.R.U.E. test include the limited number and somewhat outdated nature of the allergens in the panel. Studies have shown that extended patch testing reveals 37-76 percent more positive reactions and 50% have positive

reactions only to non-T.R.U.E. test allergens.[4, 5] More extensive patch testing typically requires manual loading of allergens into wells which is more time and labor intensive as well as costly. Various allergen panels are available; the North American Contact Dermatitis Group standard series of 65 allergens is one such panel.

Regardless of the panel used, allergens are affixed to intact skin on the patient's back (See Figure 3). After occlusion for 48 hours (day 3) the patches are removed for the first reading. The patient then returns in another 48 hours (day 5) for the final reading. Patients must avoid showers, wetting the site, ultraviolet irradiation, and excessive sweating for the entire five days of patch testing. In addition, patients cannot use topical steroids on the back until after the final reading. Positive reactions are scored in the following way: ?/+: doubtful (macular erythema), +: weak (papular erythema), ++: strong (edematous or vesicular), +++: extreme (bullous or ulcerative). True allergic reactions should persist or appear at the day 5 reading.

Figure 3
Allergen panels being placed on the back of a patient undergoing patch testing.



Allergen Avoidance

The most crucial part of patch testing is the patient education that occurs once the final reading has taken place. It is important to provide the patient with written information on all of the allergens with a positive reaction. This written information should include the allergen name, synonyms, typical uses, and strategies on ways to avoid the chemical. The American Contact Dermatitis Society's (ACDS) website (www.contactderm.org) provides helpful handouts for many of the more common allergens. These handouts are available to members of the Society. Another resource available to members of the ACDS is the Contact Allergen Management Program (C.A.M.P.). This database provides a list of products that are safe for a patient to use once the patient's allergens have been entered into the system--in essence, the patient's "shopping list."

When reviewing allergens with the patient it is important to try to determine relevance of each allergen to the patient's dermatitis. An allergen is clinically relevant if there is existence of an exposure and the patient's dermatitis is explainable (totally or partially) with regard to that exposure. Strategies to help establish relevance include taking a comprehensive clinical history especially as it relates to occupational or non-occupational exposures. Examples of non-occupational exposures include skin care products, hobbies, and jewelry. Another strategy to establish relevance is an environmental evaluation with research into the composition of products to which the patient has been exposed. This information may come from ingredient lists, Material Safety Data Sheets (MSDS) and manufacturers.

It is helpful to know the most common allergens based on current patch test data in an effort to provide some proactive counseling even prior to formal patch testing. Following are the most common allergens detected in patients undergoing patch testing as identified by the North American Contact Dermatitis Group (NACDG) from 2011-2012 and published in the journal Dermatitis in 2015.[6]

Metals (Nickel and Cobalt)

Nickel sulfate is the most common allergen with 18.5% of patients that are patch tested having a positive reaction. This high rate of sensitivity is attributed to the common practice of ear and body

piercing. Nickel dermatitis can present as earring dermatitis, dermatitis under a necklace or watch back (or more recently a Fitbit®.)[7] Dermatitis of the mid-abdomen can be caused by nickel in a belt buckle or snap. Sweating can increase the amount of metal leached from a product. The dimethylglyoxime test can detect the presence of nickel in metal objects for a patient suspected of or proven to have nickel allergy. In order to avoid nickel, patients should be counseled to look for high-quality stainless steel, copper, sterling silver, yellow or rose gold of at least 12 carats (white gold actually does contain nickel), platinum, aluminum, brass and titanium.

Cobalt is a metal used for its hardness and often combined with other metals. Because of this, 80 percent of patients allergic to cobalt are also found to be allergic to chrome and/or nickel.[8]

Fragrance (Balsam of Peru, Fragrance Mix I, Fragrance Mix II)

Fragrance allergy can be detected using a variety of allergens. Balsam of Peru is a common screening fragrance; however it only detects approximately 50% of fragrance-allergic patients. It is the resin of the Myroxylon pereirae tree native to Central America and is used as a fragrance or preservative in a variety of personal use products. Fragrance mix I and II are more complete allergens used to detect fragrance allergy in patch test patients. Although not as prevalent as nickel allergy, (7.9% for Balsam of Peru, 12.1% for fragrance mix I and 5.2% for fragrance mix II) allergy to fragrance is found to be relevant to the patient's dermatitis a staggering 87 percent of the time. It is important for patients with fragrance allergy to use "fragrance-free" products rather than "unscented" products since "unscented" products may actually contain masking fragrance to cover unpleasant odors![9]

Topical antibiotics (Neomycin and Bacitracin)

Neomycin (positive in 9.1% of patch test patients) and bacitracin (positive in 7.8% of patients tested) are both topical antibiotic preparations found in common over-the-counter products such as Neosporin® Original (neomycin and bacitracin) and Polysporin® Original (bacitracin). Co-reactivity between these two allergens is common since they are often found in the same or similar products. Caution should be employed in patients with chronic leg ulcerations as these patients show a high degree of sensitization to these topical antibiotics. Bacitracin is especially dangerous because of the real, although low, risk of anaphylaxis with topical exposure. Neomycin and bacitracin can remain in fabric even after washing so it is best to discard any fabrics that were in contact with the antibiotic once allergy is discovered. Prescription topical antibiotic preparations, such as mupirocin are much less allergenic and can be used with patients in need of topical antibiotics. Of note, clean skin surgery procedures such as biopsies and excisions have a low rate of infection and topical antibiotics do not need to be used for wound care. Instead petrolatum ointment is adequate in this setting.[10]

Formaldehyde (and Quaternium-15)

Formaldehyde, positive in 6.6% of patch test patients, is used as a preservative in cosmetics, medications, textiles, paints, cigarette smoke, paper, and plastic bottles. Textile dermatitis can be caused by formaldehyde in wash-and-wear, permanent press or wrinkle-free clothes. Formaldehyde allergy in this setting can present as axillary dermatitis with sparing of the axillary vault since the fabric does not directly contact this area. One hundred percent polyester clothing contains the least amount of formaldehyde and washing clothing in one cup of powdered milk can remove excess formaldehyde; however, the formaldehyde will never be completely depleted. Formaldehyde-free undergarments can also be worn under clothing in an attempt to avoid this allergen.

Today, formaldehyde is rarely used in its pure form in personal use products; however a variety of formaldehyde-releasing preservatives are used in these items. Quaternium-15, positive in 6.5% of tested patients, is the most common cause of preservative-induced dermatitis and is found in products such as shampoo, moisturizer, conditioner, and soap. It is found to be relevant in 89 percent of patients allergic to it. There are non-formaldehyde-releasing preservatives used in personal use products and a safe product list proves to be extremely helpful for these patients.[11]

Table 1
Safe Products Using the Most Common Allergens

Soap
- Aveeno® Active Naturals Moisturizing Bar
- CeraVe® Hydrating Cleanser

Hair Conditioner
- Cleure® Replenishing Conditioner
- DHS® Conditioning Rinse with Panthenol

Hair Shampoo
- Cleure® Volumizing Shampoo SLS Free
- Free & Clear® Shampoo for Sensitive Skin & Scalp

Moisturizer
- Aveeno® Eczema Therapy Moisturizing Cream
- CeraVe® Moisturizing Cream

Antiperspirant/Deodorant
- Speed Stick® Power Unscented Antiperspirant & Deodorant Solid

Sunscreen
- Neutrogena® Pure and Free Baby Faces Ultra Gentle Sunblock SPF 50

Laundry Detergent
- 7th Generation® Free & Clear Natural Laundry Detergent
- Ultra Tide® Free Powdered Detergent

Para-phenylenediamine

Para-phenylenediamine (PPD) is a black dye found in not only black, but also brown hair dyes. It can be relevant to both people that color their hair as well as hairdressers. PPD is also found in black henna tattoos, which can lead to sensitization and subsequent dermatitis with re-exposure. Bleach and PPD-free hair dyes (such as vegetable dyes or Elumen by Goldwell®) are alternatives for patients found to have PPD allergy.[12]

Recommended Products

In patients suspected of having contact allergy and in whom patch testing has not been performed, it can be helpful to recommend products that contain the least amount of potential allergens in an attempt to either improve the patient's condition while they are awaiting Dermatology or Allergy consultation for patch testing or to completely resolve the patient's dermatitis, thereby eliminating the need for patch testing altogether. "Safe" products in Table 1 was generated using the most common allergens found in personal use products taking into account the clinical relevance of each of those allergens.[13]

Conclusion

Contact dermatitis is often the underlying diagnosis in patients presenting with complaint of rash. Most contact dermatitis is irritant in nature and recommending avoidance of irritating substances as well as dry skin care measures with gentle skin cleansers and regular moisturizer use can control most of these patients' dermatitis. However, in about 20 percent of patients, the contact dermatitis is allergic in nature and may require referral to Dermatology or Allergy for formal patch testing and subsequent education targeted at allergen avoidance and alternatives. In the absence of formal patch testing, products can be recommended that contain low numbers of potential allergens to see if the dermatitis can be alleviated in this way and thus avoid the need for patch testing in some individuals.

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Disclosure

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DEPARTMENT OF DERMATOLOGY
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Vulvar Dermatoses: A Review and Update

by Cassandra Simonetta, MD, Erin K. Burns, MD & Mary A. Guo, MD

Psoriasis, lichen sclerosis, lichen simplex chronicus and lichen planus are common vulvar conditions that cause pruritis and/or pain. Plasma cell vulvitis and desquamative inflammatory vaginitis are rare and challenging to diagnose.



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Abstract

The purpose of this article is to review six important inflammatory dermatoses of the vulva and to update readers on the new advancements in treatment of these mucosal conditions. Psoriasis, lichen sclerosis, lichen simplex chronicus and lichen planus are common vulvar conditions that cause pruritis and/or pain. Plasma cell vulvitis and desquamative inflammatory vaginitis are rare and challenging to be recognized, which often remain undiagnosed.

Vulvar Psoriasis: Pathophysiology and Epidemiology

Psoriasis is a chronic, inflammatory skin condition that affects approximately 2% of the general population.[1] The pathophysiology is multifactorial, with polygenetic factors playing a role in abnormal T cell activation favoring the T_H17 profile. Vulvar psoriasis (VP) often occurs in the setting of generalized plaque psoriasis or inverse psoriasis. Involvement of the genital skin occurs in 29-46% of patients with psoriasis.[2] Only 2-5% of psoriatic patients present with involvement limited to the genital area.[1] Psoriasis has a bimodal onset with peaks in the third and sixth decades, however, vulvar psoriasis occurs in patients of all ages.

History and Clinical Presentation-VP

Vulvar psoriasis may present with classic plaque type or inverse psoriasis with mild to severe pruritis. Vulvar psoriasis often presents with a nonspecific, poorly demarcated erythema. Scale can be difficult to appreciate in this location. Pain and/or burning may become more severe in the setting of increased inflammation secondary to friction, perspiration and maceration at this site. Vulvar psoriasis may be associated with considerable morbidity, discomfort and embarrassment that may impair psychosexual wellbeing.[2]

Diagnosis-VP

Diagnosis is based on clinical morphology. It often affects hair-bearing cutaneous vulva including the mons pubis and labia majora while sparing the vulvar mucosa, with poorly demarcated erythematous plaques with minimal to no scale. Maceration or fissures may also be appreciated.[2] Clinical confirmation is often provided by whole-body cutaneous exam, which reveals features of generalized or inverse psoriasis. Patients with genital psoriasis are more likely to have nail



Figure 1
Vulvar psoriasis complicated with contact dermatitis.

findings compared to those who lack genital involvement.[3] Diagnosis may be complicated by superimposed infection, contact dermatitis or changes of lichen simplex chronicus[4] (See Figure 1). Differential diagnosis includes vulvovaginal candidiasis, dermatophyte infection, lichen simplex chronicus, extramammary Paget's disease, and contact dermatitis.[4] If clinical diagnosis is unclear or lesions are unresponsive to treatment, skin biopsy may be warranted.

Pathology-VP

Histologic features of vulvar psoriasis are similar to those from non-genital psoriasis, however, typical characteristics may be subtle.[1] It features parakeratosis, collections of neutrophils within the stratum corneum (Munro microabscesses), collections of neutrophils within the epidermis (spongiotic pustules of Kujol), regular epidermal acanthosis, thinning of suprapapillary plates, loss of the granular layer and dilatation of vessels in the papillary dermis.

Treatment-VP

Guidelines for treatment of intertriginous psoriasis including vulvar psoriasis were recently published.[5] First-line treatment includes topical steroids. Topical vitamin D analogs or calcineurin inhibitors are a good option for long term therapy and do not carry the risks of atrophy, telangiectasia, striae, and ulceration. Topical steroids and steroid-sparing agents are often used in combination to minimize irritation. Any concomitant infection should be treated accordingly. Second-line treatments include emollients and topical tar-based products. Severe vulvar psoriasis may require systemic therapy, such as methotrexate, oral retinoids or biologic agents.[5]

Lichen Sclerosis: Pathophysiology and Epidemiology

Lichen sclerosis (LS) is a chronic inflammatory condition with an unknown pathophysiology. It appears to be multifactorial involving genetic, autoimmune, and environmental factors.[4] Circulating antibodies directed against extracellular matrix protein 1 have been identified in 74% of patients with lichen sclerosus.[6] There is a bimodal age peak at premenarche and postmenopausal, however most patients are 50 years and older.[4] Malignant transformation to squamous cell carcinoma has been reported in 2%–5% of patients.[4, 7]



Figure 2
Lichen sclerosus with shiny glistering cigarette paper-like texture.
Photo courtesy of Libby Edwards, MD

History and Clinical Presentation-LS

Most patients complain of pruritus, burning and/or pain, however some may be asymptomatic. Dyspareunia may occur in the setting of scarring that leads to narrowing of the vaginal introitus. Perianal involvement may lead to pain on defecation with resultant constipation.[8] Symptoms may be progressive or relapsing and remitting, and spontaneous remission is rare.[6] Extragenital involvement occurs in less than 20% of patients.[7] One should consider screening for a history of autoimmune disease, such as thyroid disease, alopecia areata and vitiligo.[6,8]

Diagnosis-LS

Lichen sclerosus may involve the labia minora, labia majora, clitoris, clitoral hood, perineum and perianus, characteristically forming a figure-of-eight around the vulva

and anus[6, 7] (See Figure 2). It presents as circumscribed or widespread pallor with a wrinkled texture. Additionally, fissures, erosions, ecchymoses, and pigmentary alteration may be present. Scarring may result in shrinkage or loss of the labia minora, stenosis of the vaginal introitus and scarring of the clitoral hood.[7] Of note, the vagina and cervix are typically spared. Differential diagnosis includes lichen planus, psoriasis, lichen simplex chronicus, vitiligo, immunobullous disease and mucous membrane pemphigoid.[4, 6] Biopsy can aid in distinguishing lichen sclerosis from lichen planus and in ruling out malignant transformation to squamous cell carcinoma.[6, 7]

Pathology-LS

Histologic features can vary depending upon the chronicity of the lesion, however, a lichenoid inflammatory infiltrate is characteristic. Early lesions often reveal interface or lichenoid dermatitis. In contrast, well-developed lesions typically have a thin atrophic epidermis, superficial dermal edema with a wide band of hyalinization just below the dermoepidermal junction.[7] Dilatation of blood vessels and red blood cell extravasation are also features. Hyperkeratosis may also be appreciated in some specimens. Superimposed changes of lichen simplex chronicus can also be seen.[4]

Treatment-LS

First line treatment includes potent and ultrapotent topical corticosteroids. Established guidelines recommend daily application of ultrapotent topical corticosteroid for one month, followed by every other day application for one month and then twice weekly application for an additional month.[6, 7] Maintenance therapy with less frequent application is recommended. Second-line therapies include topical calcineurin inhibitors [6, 7] For severe disease, systemic retinoids and other immunosuppressant medications may be considered.[6]

Lichen Simplex Chronicus: Pathophysiology and Epidemiology

Lichen simplex chronicus (LSC) is one of the most common causes of vulvar pruritus and is seen in patients of all ages.[7] The cause of LSC is unknown. While many patients have a personal or family history of atopy, the mechanism by which an atopic diathesis results in the development of LSC is not clear. In most circumstances, pruritus occurs secondary to irritation. Common causes of irritation include warmth, moisture, excessive cleaning, and friction from tight clothing. Rubbing or scratching provides immediate yet temporary relief, however ultimately results in skin thickening, which in turn leads to continued rubbing and scratching. This pattern has been coined "the itch-scratch cycle," which defines LSC. LSC can occur primarily or secondary to underlying dermatoses affecting the vulva.



Figure 3
Lichen simplex chronicus with hyperpigmented lichenified plaques secondary to rubbing.

History and Clinical Presentation-LSC

Patients complain of chronic or intermittent pruritus of the vulva that has been present for weeks to years. Many patients identify an inciting event that coincided with onset of pruritus, commonly a yeast infection or other stress, however, note that pruritus persisted after resolution of the triggering event.[9] Most patients are conscious of the itch-scratch cycle and are able to minimize rubbing and scratching throughout the day.[9] Pruritus is often worse in the evening or during the night, when scratching provides pleasure and relief of symptoms. Frequent nightly rubbing and scratching leads to erosions that cause burning and pain. Patients may try various topical medications or use more aggressive hygiene routines in effort to relieve symptoms; however, these practices often exacerbate irritation and pruritus. (See Figure 3.)

Diagnosis-LSC

Diagnosis of LSC is based on history and clinical findings. LSC typically affects the hair-bearing portion of the labia majora.[7] Examination shows epidermal thickening or lichenified papules and plaques with accentuation of skin markings. Ill-defined erythema, linear excoriations, erosions, ulcers, fissures and crusting may also be appreciated. Scale may or may not be present in the warm, moist environment of the vulva. Pubic hair in the affected areas may be broken or decreased in density as a result of chronic friction. Depending upon the patient's natural skin color and the severity and chronicity of the symptoms, pigment alteration including post-inflammatory hyper- and/or hypopigmentation may also be appreciated.[7]

Differential diagnosis of LSC includes psoriasis, extramammary Paget's disease, candidiasis, dermatophytosis and Streptococcus A infection. A thorough whole-body mucocutaneous exam can aid in the diagnosis if the patient has lesions characteristic of other dermatoses elsewhere. Biopsy can also provide valuable information if the clinical diagnosis is unclear or if the patient is not responding to treatment as expected.

Pathology-LSC

Histology reveals hyperkeratosis, parakeratosis, acanthosis, a prominent granular layer, lengthened rete ridges and a variable chronic inflammatory infiltrate. In addition, lamellar thickening of the papillary dermis and perineural fibrosis may be seen.[7]

Treatment-LSC

There is no evidence-based data concerning the treatment of LSC.[7] However, most experts agree that treatment of LSC requires a multi-faceted approach. First and foremost, identifying and eliminating suspected irritant and allergic contact exposures should be discussed with the patient. A bland skin care regimen is highly recommended. Secondly, the itch-scratch cycle that perpetuates symptoms must be interrupted. This is often accomplished by application of potent or ultrapotent topical corticosteroid. Topical corticosteroids applied once daily for three to four weeks often results in significant improvement in pruritus. While some experts use a tapering schedule over three to six months or transition to a lower potency steroid to help prevent relapse, others advise use of topical corticosteroids as needed. Sedating antihistamines help prevent scratching during sleep and topical anesthetics are alternative options if topical corticosteroids do not provide significant symptomatic relief. Topical calcineurin inhibitors are second-line treatment for patients who are unable to tolerate or are resistant to topical corticosteroids.[7] Lastly, it is important to identify underlying conditions or infections that may result in secondary LSC and treat appropriately.[8] Patients should be followed closely with monthly exams initially while using daily high potency topical corticosteroids, with less frequent follow-up during maintenance treatment.



Figure 4
Erosive Lichen planus with significant scarring and agglutination.

Lichen Planus: Pathophysiology and Epidemiology

Lichen planus (LP) is a mucocutaneous inflammatory disease of unknown etiology, which may affect the skin, hair, nails, and mucosal surfaces including the oral cavity and genitalia. It is estimated that approximately 50% of women affected by oral LP have vulvar involvement.[10,11] The pathogenesis of LP is poorly understood, although increasing evidence suggests it is autoimmune in nature, governed by CD8+ cytotoxic T lymphocytes.[12,13] Antigenic triggers remain unknown.

History and Clinical Presentation-LP

Vulvar LP presents as one or more of three clinical patterns: classic papulosquamous, hypertrophic and

erosive.[14] Classic lesions usually occur on the labia majora in a similar presentation to other sites of cutaneous LP with pruritic, polygonal, violaceous flat-topped papules with lacelike reticulated white patches called Wickham's striae.[15] The hypertrophic form shows lesions of classic LP with overlying features of lichen simplex chronicus.[14] The erosive type is the most common genital form of LP in women and typically affects the labia minora and vaginal introitus.[14] (See Figure 4) Its clinical appearance demonstrates bright erythema and erosions and may be surrounded by a white reticular rim. Chronic erosions may lead to scarring in up to 95% of affected patients and subsequent vaginal stenosis, strictures and agglutination.[11,15] Erosive LP is frequently characterized by vulvar pain, pruritus, burning and associated dysuria and dyspareunia.[16] Rare cases of malignant SCC transformation have been reported, however the link between LP and vulvar neoplasia is not well established.[17,18]

Diagnosis-LP

Clinical diagnosis of vulvar LP is complex, and should always be suspected given bright red and painful vulvar erosions. According to a recent consensus, diagnosis of erosive LP requires at least three of the following: 1) scarring, 2) hyperkeratotic border or Wickham's striae, 3) other mucosal involvement, 4) well-demarcated erosions at the vaginal introitus, 5) pain/burning symptoms, 6) vaginal inflammation, 7) band-like infiltrate at the dermal-epidermal junction, 8) lymphocyte predominance, and 9) evidence of basal degeneration.[19]

Pathology-LP

Classic LP lesions show compact orthokeratosis, wedge-shaped hypergranulosis, acanthosis of the epidermis, necrotic keratinocytes within the epidermis (colloid bodies/Civatte bodies), basilar vacuolization, rete ridges with a "saw-tooth" appearance, and a dense band-like lymphocytic infiltrate in the papillary dermis obscuring the dermal-epidermal junction. When located in mucosal sites, LP may feature parakeratosis and a thinned epidermis, while the "saw tooth" rete ridge appearance and "wedge-shaped" hypergranulosis may be attenuated.[14] Hypertrophic LP displays similar features to those mentioned above, in addition to pronounced irregular epidermal acanthosis. Erosive LP shows epidermal erosion or ulceration with prominent underlying inflammation; a clue to diagnosis includes typical LP changes at the edge of the ulcer.[15] For this reason, a biopsy obtained to help aid in the diagnosis of erosive LP should be taken from the edge of an eroded area.

Treatment-LP

High-potency corticosteroids are first-line treatment; however, monotherapy is rarely sufficient.[20] Topical calcineurin inhibitors have also shown good response in select case series.[17,21] Alternative therapies to consider in treatment-resistant disease include systemic corticosteroids, immunosuppressants, retinoids and in rare cases, biological agents. Vaginal dilators may be employed to treat introital narrowing.

Plasma Cell Vulvitis: Pathophysiology and Epidemiology

Plasma cell vulvitis (PCV), also known as Zoon's vulvitis and vulvitis circumscripta plasmacellularis, was first described in 1957 by Garnier and is known as the female counterpart to Zoon's balanitis.[22] It is a rare, benign, chronic inflammatory condition, which is aptly named for its plasma cell rich infiltrate. It tends to affect middle age and elderly postmenopausal women. The origin is unclear, though several hypotheses have been put forth suggesting a triggering factor such as trauma, virus, hormones, and autoimmunity. Its pathogenesis predominantly relies on distinct histopathologic features.

History and Clinical presentation-PCV

Lesions of PCV present as red or orange-brown, glistening, sharply demarcated patches or plaques, and may mimic punctate purpur (See Figure 5). Distribution is most often bilateral and symmetrical, most commonly found on the vestibule and labia minora. Erosions and tissue fragility/friability has been seen.[23] It is typically associated with vulvar pruritus, pain, burning, bleeding and discharge. The natural course of disease is characterized by recurrent periods of relapse and remission.

Diagnosis-PCV

Diagnosis is suggested by clinical examination and confirmed by biopsy. Definitive diagnosis of PCV is based on distinct histologic findings.

Pathology-PCV

The characteristic histopathological features of PCV include superficial erosions with sparse neutrophils scattered in the upper epidermis, moderate spongiosis, effacement of rete ridges, red blood cell extravasation and a mixed lichenoid infiltrate in the papillary dermis rich in plasma cells. This high density of plasma cells is a key feature; they must comprise over 50% of the inflammatory infiltrate, or be accompanied by epidermal atrophy and hemosiderin deposition when comprising only 25-50% of the infiltrate.[24] Over time, epidermal atrophy may ensue and subepidermal clefts along with dermal fibrosis may develop. Suprabasilar keratinocytes are notably "diamond-" or "lozenge-shaped." [25] Vertically oriented dermal blood vessels may be another diagnostic clue.

Treatment-PCV

Asymptomatic patients do not require treatment. When symptoms ensue, potent topical corticosteroids are the first-line treatment.[26] Alternative treatments consist of intralesional corticosteroids, imiquimod and topical cyclosporine.[27] Topical tacrolimus has not been shown to be effective.[28]

Desquamative Inflammatory Vaginitis: Pathophysiology and Epidemiology

Desquamative inflammatory vaginitis (DIV) is a relatively common sterile inflammatory vaginitis causing vulvovaginal irritation with accompanying purulent discharge. It was first described by Scheffey, et al. in 1956.[29] DIV was initially believed to be a presentation caused by any noninfectious erosive mucosal skin disease, particularly lichen planus, manifesting in the vagina. Current opinion, however, favors that DIV is a distinct clinical entity in itself, characterized by vaginal wall erythema and copious discharge in the absence of infection, erosions or other mucosal involvement.[30] The cause of DIV is unknown, though autoimmune etiology has been purported. DIV occurs in both pre- and post-menopausal women.[31]

History and Clinical Presentation-DIV

Patients with DIV often complain of vulvar burning, irritation and dyspareunia. A yellow or green vaginal discharge is common. Unlike lichen planus, the oral mucosa is spared. Physical examination demonstrates variable erythema of the vestibule, caused by irritation from purulent secretions. Erosions and scarring are absent. The vagina may display red macules and micropapules, mimicking the "strawberry cervix" of trichomonas.[30] Vestibular edema may be present in severe cases.

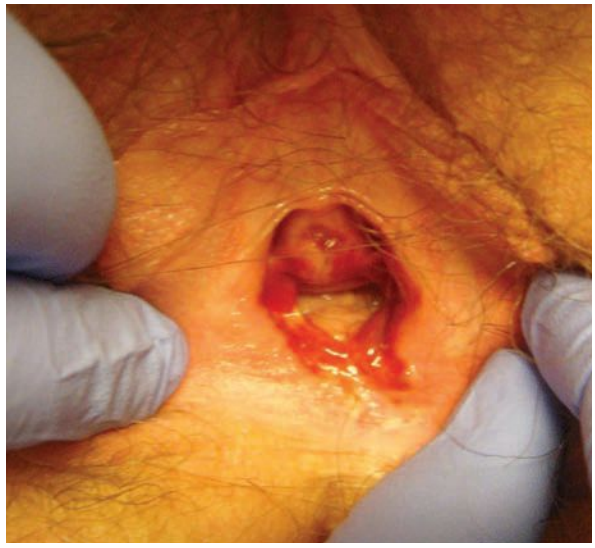


Figure 5
Rusty red, glistering well demarcated plaques of plasma cell vulvitis.

Diagnosis-DIV

Diagnosis of DIV is based on clinical findings of vaginal erythema and purulent vaginal secretions in a female with no other mucous membrane involvement, normal estrogen levels and cultures negative for bacteria, viruses and yeast. In addition, it is necessary to rule out trichomoniasis. Wet mount shows parabasal cells, increased polymorphonuclear leukocytes, and decreased lactobacilli, with an elevated vaginal pH greater than 5.[30] Vaginal cultures may show group B streptococcus, however their pathogenic role is unclear. The diagnosis may be missed if a speculum exam to visualize the vaginal vestibule is not performed, and it is often misdiagnosed as dysesthetic vulvodynia.

In all cases of suspected DIV, an investigation for infection and estrogen deficiency should be sought and corrected if identified.

Pathology-DIV

Biopsy of the vaginal wall mucosa may show one of two histologic patterns. In one study, the majority displayed a lichenoid infiltrate without basilar cell damage, while others

showed a nonspecific mixed inflammatory infiltrate with lymphocytes, eosinophils and plasma cells.[31]

Treatment-DIV

First-line therapy for DIV includes topical clindamycin and/or hydrocortisone acetate 25mg rectal suppositories per vagina.[31] Sobel reported improvement of symptoms in over 95% of subjects with clindamycin 2% suppositories, however relapse rate was 30%.[32] For recalcitrant disease, potent topical corticosteroids may be used. Post-menopausal patients with DIV may require estrogen therapy to achieve remission. [32] It is advised to consider weekly fluconazole to prophylactically prevent secondary candidiasis.[30]

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Overview of Alopecia: A Dermatopathologist's Perspective

by Claudia I. Vidal, MD, PhD

A Dermatopathologist can be an invaluable resource to the clinician.



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Abstract

Hair loss affects men and women of all ages and frequently has significant social and psychologic consequences. An awareness and understanding of the various microscopic tests that can be performed is helpful in making an accurate diagnosis. A Dermatopathologist can be an invaluable resource to the clinician.

Introduction

Hair loss (alopecia) can be caused by many factors ranging from genetics to the environment. While androgenetic alopecia is by far the most common form of alopecia, other forms including those related to underlying diseases are also frequently encountered. This review will highlight the roles of microscopic evaluation in the management of alopecia with Table 1 summarizing its importance.

Tests

Although not enough can be said for the importance of history and physical examination, the various tests that require microscopic evaluation can provide additional information to aid the clinician in making an accurate diagnosis.[1]

Hair Pull Test, Hair Pluck Test and Trichogram

Hairs, whether they are pulled, plucked or spontaneously shed, can be examined under the microscope without any special processing. A hair pull test can give a rough estimate as to how much hair is being lost. Gentle traction is placed on a small portion of hair by sliding the fingers down the hair on three separate areas of the scalp. The extraction of less than three hairs is considered a negative pull test, whereas extraction of greater than six is considered a positive test.[2] Before performing the test, the physician should remember to ask if the patient recently washed their hair since the results of the hair pull test may not be as accurate if the patient recently washed their hair. A forceable hair pluck is performed by grasping approximately 50 hairs with a rubber-tipped surgical clamp and quickly jerking the hairs from the scalp. Hairs may be placed on a slide for visualization (trichogram). Tape or clear nail polish may be used to keep the hairs in place. A few drops of immersion oil can be placed on the hairs and a second glass slide or cover slip is placed on top. Taping the slides together may help the ends of the hair to lie flat especially if the hair is curly.[3] Although a trichogram may be performed by the clinician, a dermatopathologist can be utilized to help with interpretation.

In the normal situation, the only hairs that can be gently and easily pulled from the scalp are those that are in the telogen phase of the hair cycle. If another type of hair is easily removed from the scalp, it can be

Table 1
Contribution of Microscopy to Alopecia Management
- Accurate Diagnosis
- Helps in Determining Prognosis
- Helps in Determining Treatment

regarded as an abnormal situation. Under the microscope, telogen hairs have completely cornified which prevents bending relative to the long axis, a process that can be seen in anagen hairs. Telogen hairs have an expanded, club shaped bulb. Anagen hairs have a pigmented bulb, characteristically in the shape of a triangle that results from the hair tearing away from the hair papilla. Due to plucking, the outer root sheath or both sheaths remain in the dermis and can give the plucked anagen hair a dysmorphic (bent) appearance. Plucked catagen hairs resemble telogen hairs characteristically shows a translucent epithelial sac surrounding the club.[3]

Biopsy

Biopsy, a Greek-derived word (bio-life; opsia-to see) loosely translated as "view of the living",[4] is used to support the clinical findings in alopecia by narrowing or making a diagnosis. It can also serve as an indicator of prognosis – Is there a chance of hair recovery and re-growth? Is there inflammation that can be treated and hopefully slow or halt the progression of disease? It is important for the clinician to never underestimate the importance of dialogue with the dermatopathologist as it is only through this partnership that the patient can really be helped.

Although the number of biopsies performed and selection of the most fruitful site is somewhat dependent on the disease process, typically the best place to biopsy is the leading edge of the process, where there is some hair loss and some erythema. It is generally not recommend to biopsy an area with complete hair loss, as there is limited information that can be gained by performing a biopsy in this area.

A 4 mm punch biopsy oriented in the direction of hair growth is advised.[5] A 4mm punch biopsy is recommended because hair counts that are performed on horizontal sections are standardized. Performing a smaller punch biopsy can lead to the misperception on histology that the number of follicular units are diminished.[3] Additionally, as a dermatopathologist I cannot stress the importance of orientating the biopsy in the direction of hair growth such that the hairs are cut transverse rather than tangential on horizontal sectioning. It is equally important for the clinician to remember to handle tissue gently. Although often unintentional, crushing of tissue with tissue forceps during the procedure or rough handling of tissue can destroy the histological features, rendering accurate microscopic assessment difficult.

Additional biopsies may be required if there are more than one clinical presentation or if direct immunofluorescence (DIF) studies are desired. Biopsies obtained for DIF should be placed in the appropriate medium, such as Michel's solution, and it is generally not advisable to perform one punch biopsy and submit half of the specimen for routine processing and the other half for DIF studies. The importance of an adequate clinical history and description on the pathology requisition sheet cannot be emphasized enough and will enable the pathologist to provide the best clinicopathological correlation.

There are various manners a biopsy for alopecia can be processed. Visualization of the epidermis requires vertical section, making it appropriate for entities such a lichen planopliaris (LPP) and lupus erythematosus (LE). Vertical sections are limited, however, on the number and types of hairs visualized and thus have considerable sampling error.[6] Hair counts can only be performed on horizontal sections. Horizontal sections also allow for better evaluation of the hair cycle and the ability to see the entire hair follicle including the level / location of inflammation.[7,8] Ideally, it is best for the clinician to seek an experienced laboratory for processing of an alopecia biopsy since performing and interpreting horizontal sections is unfamiliar to many laboratories and pathologists.

The following sections will discuss a few alopecias with emphasis on special considerations for microscopic evaluation (summarized in Table 2).

Non-Scaring Alopecias

Androgenetic alopecia

Androgenetic alopecia (AGA) is also referred to as common balding, hereditary balding and male or female-pattern alopecia. It is extremely common and mediated by the effects of androgens on susceptible hairs. Aside from genetic factors, conditions that lead to the overproduction or exogenous administration of androgens can also cause or worsen androgenetic alopecia. The typical clinical pattern observed in AGA begins with recession of the frontal hair line followed by thinning of the vertex scalp with ultimate fusion of the two areas as the disease progresses.[9] In women there is widening of the central part of the frontal scalp with a pattern that has been likened to a Christmas tree. The sparing of the frontal hair line is also characteristic in women.[3]

Hair pull test can be useful in distinguishing AGA from telogen effluvium. Biopsy is typically helpful when the pattern of AGA is not typical or to exclude telogen effluvium or early scarring alopecia. In early disease, the ideal specimen should be 4mm punch biopsies of involved and uninvolved areas such that a comparison of follicular size and

Table 2
Special Consideration for Microscopic Evaluation of Alopecia

Alopecia	Special consideration(s)
Androgenetic alopecia (AGA)	Hair pull test - useful in differentiating AGA from TE Biopsy: Early disease: Two 4mm punch biopsies (lesional - frontal or vertex scalp and uninvolved - occiput scalp) processed horizontally so that hair counts can be performed Late disease: One 4mm punch biopsy from involved scalp processed horizontally so that hair counts can be performed
Telogen effluvium (TE)	Hair wash test / Hair pull test followed by trichogram - numerous clubbed hairs (if dysmorphic anagen hairs think of AA) Hair pull test followed by trichogram - telogen count must exceed 20% for diagnosis Biopsy: 4mm punch biopsy from edge of involved scalp processed horizontally
Alopecia Areata (AA)	Hair pull test followed by trichogram - telogen and pencil point shafts Biopsy: 4mm punch biopsy processed horizontally at the active / advancing margin of alopecia
Fungal alopecia	KOH preparation of scaly area with broken hairs Hair pull often not useful Biopsy: If clinical suspicion is high and biopsy is not diagnostic, still culture
Trichotillomania (TT)	Trichogram - to exclude hair shaft disorders Biopsy: 4mm punch biopsy of lesional area processed horizontally; helpful in establishing and convincing of diagnosis
Scarring alopecias	Biopsy: 4mm punch biopsy of the active boarder; clinical consideration can be given to submission of additional biopsies including biopsy for DIF

DIF - direct immunofluorescence

hair number can be performed. A single 4mm punch biopsy can be performed from the involved scalp if the disease is more advanced.[3]

Telogen Effluvium

When an abnormally large number of anagen hairs on the scalp enter the telogen phase, a telogen effluvium (TE) occurs. This may be caused by a variety of conditions - physiological, pathological, endogenous and exogenous resulting in stress on the follicle. The stressed follicle prematurely enters catagen which commits them to proceed to the telogen phase after which they are shed. The stress event typically occurs 3-4 months prior to a TE. Interestingly, the majority of TE cases likely do not come to clinical attention as an apparent reduction in hair density is only appreciated if a substantial number of hairs are lost. Additionally, since TE is reversible, the disease may be undetected clinically once the recovery phase begins, especially in cases where the patient is not seen by a physician prior to the recovery phase. If alopecia is present in TE, it diffusely affects the scalp. Complete hair loss is unusual in TE, however, if severe, it can effect non-scalp hair including the eyebrow hair and pubic hair.[10]

Patients may present to the clinic with a mound of hair, usually collected from the shower drain or hair comb (referred to as the "wash test") that can be evaluated microscopically.[11] A hair pull test followed by microscopic evaluation will reveal several clubbed hairs. If a hair pluck is performed, telogen hair counts should exceed 20% for a diagnosis of TE to be made.[3] Of note, the diffuse variant of alopecia areata can be a deceptive clinical mimic of TE.[12] Lack of stressor, dysmorphic anagen hairs on hair pull test and 4mm punch biopsy processed horizontally can be helpful. An important point to remember is that TE can unmask early androgenetic alopecia. Thus, if this is a clinical concern for AGA paired biopsies form the frontal and occipital scalp can be performed.[3]

Alopecia Areata

Alopecia areata (AA) is another common non-scarring alopecia. Aside from the scalp, alopecia areata can affect hair in any area of the body. The pathogenesis is believed to be a multifactorial autoimmune process of unknown etiology. The clinical presentation of AA can be quite varied, with the degree of involvement ranging from a small, well-defined, circular, smooth bald patch to total scalp hair loss (alopecia totalis) to total body hair loss (alopecia universalis).[13] Because the inflammation in AA is deep in the skin, there are typically no visible changes, such as erythema, to the patch of alopecia. Additionally, there is typically no surface change that is appreciated. "Exclamation point" hairs (short hairs that taper as they approach the scalp) are characteristic and found most often at the edge of the active / advancing margin of alopecia. The hair pull test in AA reveals many telogen and pencil point shafts (hairs with tapered ends).[3] 4mm punch biopsy at the active / advancing margin of alopecia can be helpful in quantifying the degree of inflammation and distinguishing AA from other alopecias.

Dermatophyte-induced alopecia (tinea capitis)

Tinea capitis is an infectious form of alopecia caused by pathogenic fungus infecting the superficial portions of the skin and hair shaft. Worldwide, the fungus *Microsporum audouini* is a very common cause of tinea capitis, but increasingly *Trichophyton tonsurans*, a large-spore endothrix infection, can also cause tinea capitis, especially in the United States and Latin American countries. The disease is caused by invasion and subsequent proliferation of the fungus within the hair shaft leading to hair fragility and breakage leaving a bald patch of skin.[13]

Although many clinical presentations are possible, including mild scaling within an alopecic plaque to intense erythema, induration, pustules and purulent discharge, the classic presentation is a bald, scaly patch where the follicular ostia are filled with keratinous debris.[13] "Black dots" may be seen resulting from the residua of the broken, pigmented hair. An important clinical clue that can be helpful in distinguishing tinea capitis from other forms of alopecia is the presence of post-auricular and cervical lymphadenopathy.[3]

Diagnosis can be made by scraping the scalp in the area of the broken hairs for potassium hydroxide (KOH) preparation. An attempt to visualize abnormalities of hairs obtained by hair pull test is often not useful, as the long hairs obtained are not those infected. Interestingly, infected hairs can be difficult to find on biopsy, thus if the clinical suspicion is high, fungal culture may yield better results.[3]

Trichotillomania

Trichotillomania (TT) is recognized by the DSM IV as an impulsive behavior disorder. It is also linked to many mood and anxiety disorders. The typical age of onset is 12-13 years of age with most patients being selective with the areas of hair pulling.[12] Common areas of involvement include the scalp, eyebrows, eyelashes, body hair, facial hair, and pubic hair. The alopecic areas are typically sharply demarcated and unusually shaped. Any hairs that are present are of varying length. There is no scale or erythema; however, excoriations may be present.[13]

The role of light microscopy lies in excluding other hair disorders, including those of the hair shaft that can cause hair fragility. Biopsy can be crucial for establishing the diagnosis and convincing the patient, especially since patients frequently deny hair plucking.[3] Of note, it has been reported biopsies taken within eight weeks of onset of TT have the highest yield.[17]

Scarring Alopecias

Scarring alopecia, also known as cicatricial alopecia, refers to a collection of hair loss disorders including entities such as lichen planopilaris, central centrifugal cicatricial alopecia folliculitis decalvans, and dissecting cellulitis. Scarring alopecia may also be part of a systemic condition such as lupus erythematosus. While many forms of scarring alopecia exist, they all share a common premise of potentially permanent and irreversible destruction of hair follicles with replacement of scar tissue. Most forms of scarring alopecia tend to first occur as small patches of hair loss that may progress over time Inflammation causing redness can be an associated finding. The loss of follicular openings or ostia is a key clinical finding that differentiates scarring from non-scarring alopecia.[18] Because the scarring alopecias can progress to permanent hair loss, the importance of early diagnosis and treatment strategies to forestall permanent hair loss is of greatest significance with biopsy playing a crucial role.

Lichen Planopilaris

Lichen Planopilaris (LPP) is the most common cause of scarring alopecia and typically affects middle aged women, with an average of onset of 51 years, and without racial predilection.[19] Tumor necrosis factor-alpha, interferon-alpha and the peroxisome proliferator-activated receptor-gamma pathway have been implicated in the pathogenesis.[20-22] The follicular keratotic lesions result in inflammation and destruction of the hair follicle with secondary hair loss. Presentation may vary depending on the stage of the disease. In general, patients typically present with scaling, perifollicular erythema, and an area of atrophic scarring with peripheral follicular papules.[19]

Biopsy for routine processing (hematoxylin and eosin) and direct immunofluorescence testing can be helpful in nailing down the diagnosis and determining the stage of disease. The latter can be important to the clinician in guiding treatment and prognosis counseling. Direct immunofluorescence in LPP is associated with Civatte / colloid bodies and can be useful in distinguishing LPP from alopecia caused by lupus erythematosus.[3]

Lupus Erythematosus

Hair loss is lupus erythematosus (LE) is common. Although the most common pattern of hair loss seen in LE is the scarring type, LE may also cause non-scarring patterns. Both the non-scarring and scarring form of alopecia secondary to LE are discussed in this section since the nonscarring plaques of LE alopecia can progress to a scarring form if left untreated.[23]

The nonscarring form of alopecia secondary to LE presents clinically as patches of partial or total hair loss throughout the scalp. Mild erythema may be present.23 Interestingly; the residual hairs in the balding patch are almost all telogen hairs or dystrophic anagen hairs making trichogram useful in this situation. Biopsy is also beneficial in making the diagnosis, but should be used in

conjunction with serology as distinction from other causes of alopecia, such as alopecia areata and syphilitic alopecia can be difficult on histopathological grounds alone.3 Some dermatopathologists advocate performing two biopsies so that one can be processed horizontally and the other vertically, with the latter allowing visualization of the dermoepidermal junction. Certain laboratories, such as our own, use an alopecia protocol that allows for visualization of the epidermis vertically following horizontal evaluation.

Chronic cutaneous lupus erythematosus (CCLE) is the term used to encompass a variety of clinical expressions of cutaneous LE. The lesions of discoid chronic cutaneous lupus erythematosus are a cause of inflammatory scarring alopecia. Discoid lupus erythematosus (DLE) is more likely to occur in adults, predominately in women. Some patients are asymptomatic, while others can experience itching or tenderness. On physical examination, this disease presents with dilated keratotic follicular plugs, erythema, epidermal atrophy and alopecia. A common finding in darker-skinned patients is central hypopigmention with peripheral hyperpigmentation.25

Histological evaluation following hair pull test can shows an increased anagen count in active disease. Biopsy of the active edge of alopecia can help make the diagnosis. Performing an additional biopsy for direct immunofluorescence can also be helpful with granular IgG and C3 along the dermoepidermal junction seen in 70-90% of cases.[3]

Central Centrifugal Cicatricial Alopecia

Central centrifugal cicatricial alopecia (CCCA) is the most common form of scarring alopecia in African American patients, with adult females being three times more likely to suffer from this disease than males. The average of onset is the mid-30s. There is a close association of the disease with the use of various hair care practices. CCCA is predominately located in the vertex or on the crown and spreads in a centrifugal pattern. Common symptoms include pruritus and tenderness.[25] Pustules and crusting can also be found in some patients as it takes on what some consider the inflammatory variant of this entity, Folliculitis Decalvans.[3]

Biopsy is helpful in confirming the diagnosis. Importantly, horizontal sections should be requested as even a 4mm biopsy that is taken from the periphery of the alopecic area may contain only one or two "diagnostic" follicles since the involved follicles are selectively destroyed. The utility in performing a biopsy for direct immunofluorescence is variable, with direct immunofluorescence serving to exclude other entities.[3]

Conclusions

The approach to a patient with alopecia begins with a complete history and physical, but also involves the use of ceratin tests that require microscopic evaluation. A carefully selected, performed and interpreted trichogram or biopsy can be critical in rendering an accurate diagnosis.

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Disclosures

None reported.

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Aesthetic Reconstruction in the Outpatient Setting

by Ian A. Maher, MD

Skin cancer care and cutaneous complex reconstruction can be safely and cost-effectively delivered in an outpatient setting allowing for maximization of precious health care resources.



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Abstract

We face a skin cancer epidemic in our country that presents our health care system with challenges both to provide and pay for necessary care. Outpatient skin cancer surgery has been proven to be safe and effective. By delivering care in the outpatient setting, patient access is increased and health care costs minimized.

Introduction

We have a skin cancer epidemic in this country. The number of non-melanoma and melanoma skin cancer are increasing year-on-year as a result of an aging population as well as the effects of indoor tanning. While it is difficult to precisely define the true burden of non-registry skin cancers, the number of skin cancers in the Medicare and Medicaid populations alone exceeded two million in 2008. The profound number of skin cancers is creating a strain on health care resources. The U.S. government paid over $633 million dollars for direct costs alone of skin cancer in 2008.

While many non-melanoma skin cancers due not represent an immediate danger to life and health skin cancers on the head and neck can cause profound negative effects on the appearance of skin cancer patients. While previously thought to be a purely cosmetic concern, appearance is being increasingly recognized as an important functional outcome after facial surgery. Appearance is one of the most important functions of the face as evidenced by a 2010 study.[1] In fact appearance was rated behind only breathing, vision, speech and eating in terms of importance. Additionally study participants when asked to choose which body part they would want restored after an injury or disfigurement overwhelmingly chose the face. Increased rates of depression and body image dysfunction are associated with facial disfigurement.[2] Further, patients with facial scars are perceived as having negative traits by observers – including being less intelligent, less trustworthy and less employable.[3] Given the steep penalties of abnormal facial appearance, every effort must be made to restore normal aesthetics after skin cancer surgery.

While historically a primarily diagnostic specialty, the development of Mohs Micrographic surgery has greatly expanded dermatologist's role in the surgical care of skin cancers.[4] Fellowship-trained Mohs surgeons receive a year of intensive post-residency training focused on

Mohs surgery and advanced facial reconstruction. A recent analysis of Medicare claims data showed that dermatologists are performing over 70% of all head and neck closures and more flaps than any other specialty.[5]

The vast majority of dermatologists operate in outpatient offices, and while there has been some concern regarding the safety of office-based procedures those have been shown to be unfounded.[6,7] Very large studies encompassing tens of thousands of patient encounters have shown a vanishingly low rate of adverse effects.[8-11] In fact, even advanced cutaneous reconstructive techniques including interpolation flaps and cartilage grafts have been demonstrated to be safe, and have a low rate of complications when performed in an outpatient setting.[12,13]

Given the proven safety of outpatient skin cancer surgery, as well as the increasing cost pressures in the current health care environment, it is reasonable to treat even advanced skin cancers in the outpatient setting provided the comfort of the patient and operating surgeon can be assured. Avoiding anesthesia and hospital costs can represent a significant cost-savings for the patient. It is likely that, given the increasing percentage of care costs that are being borne by patients that providers will be pressured to do a greater percentage of cutaneous procedures under local anesthesia.

This paper will briefly review the general philosophical approach to facial reconstruction and present a representative case study of an advanced cutaneous malignancy treated and reconstructed in the outpatient setting.

Approach to Reconstruction

There is a fundamental hierarchy of needs for any facial reconstruction. Higher priority items must be satisfied first and foremost with attention paid to the lesser items only after the higher priority needs have been satisfied. All repair options should be judged by their ability to satisfy the four criteria below:

- Any repair should first and foremost maintain the functional integrity of the body part. Thus eyelid function, oral competency and nasal airflow are all examples of highest order priorities. If functionally critical areas of the face are affected by a tumor or repair the functional integrity of that body part must be assured prior to working to satisfy.
- Distortion of free margins such as the eyelid margin, the alar rim of the nose, the eyebrows, or the vermillion border of the lip. Asymmetry resulting from free margin distortion is noticeable and will have a higher aesthetic penalty than even a very complex series of scar lines.[14]
- Place suture lines in areas where the eye is used to perceiving lines. Scars placed in areas of the face that represent natural transitions between facial cosmetic unit (e.g. the lips, nose or cheek) will camouflage more easily than scars placed in other areas. This is known as the cosmetic unit theory.[15] Thus a longer scar placed at the junction between the nose and cheek will most often yield a better cosmetic result than a shorter scar placed away from the this natural tissue transition. When possible scars should be placed in cosmetic unit boundaries.
- Finally, and only if the above criteria have been satisfied should scars be placed in the relaxed skin tension lines (RSTL). RSTL generally run perpendicular to the direction of the underlying musculature. Thus placing scar lines within the RSTL, tension on the wound will be minimized and scar spread mitigated.

Case Study

A 60-year-old Caucasian male presented for consultation with a biopsy proven BCC of the right nasal ala and medial cheek. The lesion had been present for ten years and during that time had eroded away the patient's right ala. He noted intermittent shooting pain in the lesion. His past medical history was otherwise unremarkable. Physical exam revealed a 2 cm ulcer encompassing the right ala, apical triangle of the upper lip and medial cheek. The tumor was partially mobile over the underlying tissue. There was no palpable head and neck lymphadenopathy.

The patient was counseled on his therapeutic options including Mohs surgery, wide local excision, and radiation therapy. Given his desire to have the lesions treated without general anesthesia and to be reconstructed post-cancer removal he opted to undergo Mohs surgery. He was counseled on the likelihood of the need for a multi-stage reconstruction, and the likely requirement for a paramedian forehead flap to reconstruct his nasal ala.

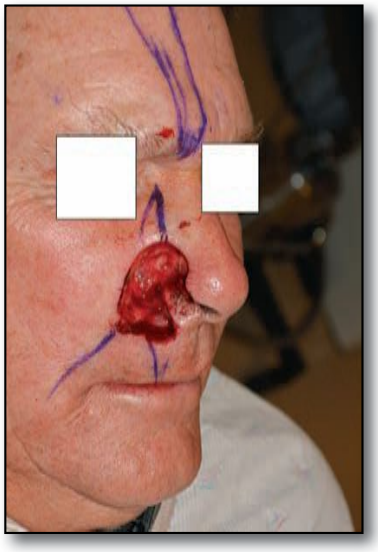


Figure 1
A 3.5 cm defect encompassing the full thickness of the right ala, as well as the skin and subcutaneous tissue of the nasal sidewall, medial cheek and upper cutaneous lip.



Figure 2
Immediately after repair with a rotation flap to repair the upper lip, an advancement flap to repair the cheek, and the first stage of a three-stage paramedian forehead flap to repair the nose.

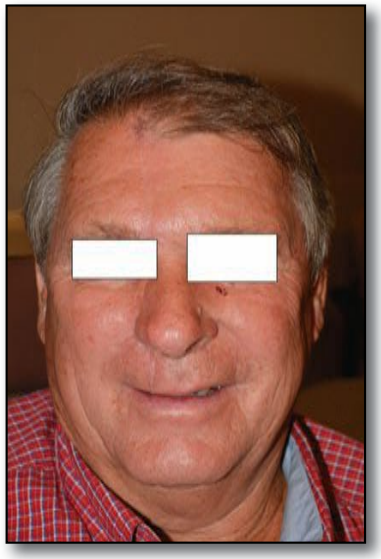


Figure 3
Frontal view at 12-week follow-up. The patient has a good aesthetic and functional result even in the early post-operative period.

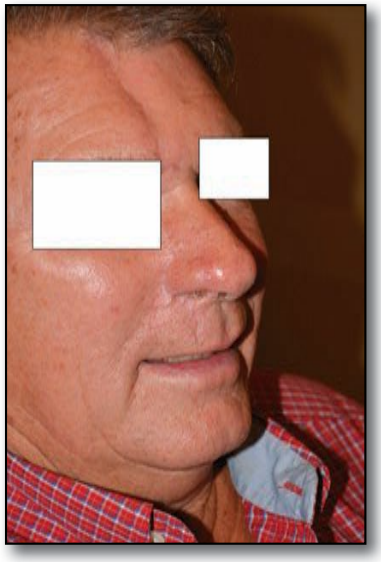


Figure 4
Side view at 12-week follow-up.

The tumor was successfully excised after 3 stages of Mohs surgery leaving a 3.5 cm wound involving the full thickness of the right ala, as well as portions of the ipsalateral nasal sidewall, cutaneous upper lip and the cheek (See Figure 1). In order to successfully reestablish normal appearance for the patient, the lip, cheek and nose components of the defect all had to be reconstructed separately. Furthermore, reconstruction of the cheek and lip portions was imperative to provide a stable base for the newly reconstructed ala, and allow for normal nasal airflow.

After discussion with the patient the following reconstructive plan was arrived at; rotation flap to repair the cutaneous upper lip component, an advancement flap to repair the cheek component, and a three-stage paramedian forehead flap to repair the nasal portion of the defect. The repair of the para-nasal tissues and the first stage of the paramedian forehead flap were performed immediately following the Mohs extirpation of the tumor (See Figure 2). By utilizing the nasolabial fold as a common incision line for the lip rotation and cheek advancement flaps a substantial proportion of the incision lines were kept within a natural tissue boundary. The use of distinct repairs for the three distinct facial areas involved by the wound (nose, lip and cheek) allowed for a more natural appearance.

The three-stage paramedian forehead flap is a versatile repair that allow for the reconstruction of complex full-thickness nasal defects – those missing both cutaneous covering and nasal lining.[16,17] In the

first stage a flap is elevated along the course of one of the forehead's paired supratrochlear artery. It is then turned down into the nasal defect and folded on itself so as to replace both the missing cutaneous covering and nasal lining. The flap is allowed to heal for three weeks, during which time neovascularization from the surrounding nasal tissues begins to contribute additional perfusion to the flap. Three weeks after the first stage the flap is partially elevated from the nose, sculpted and any necessary cartilage support can be placed, prior to the flap being sewn back in place. After an additional three weeks the flaps pedicle is divided, final sculpting is performed, and the flap is fully sewn into its new home on the nose.

While living with the forehead flap pedicle is certainly difficult, especially for those who are very reliant on glasses, these flaps are intended to repair devastating defects. In this setting it is important to remind patients that they are trading the temporary disfigurement of the flap pedicle to avoid permanent disfigurement (and possibly functional impairment) resulting from failure to reconstruct a critical facial structure.

In this patients case the second and third stages of the reconstruction were accomplished without incident. A cartilage graft harvested from the right antihelix was placed to support the nostril rim during the second stage. He returned at three months following the final stage, pleased with the aesthetic result, and with normal airflow in his right nostril. Photos of the patient can be seen in Figures 3 and 4.

Discussion

Our health care system faces a collision of forces. We have an ever-growing skin cancer epidemic. In addition to an increasing incidence of skin cancers due to an aging population, tumors are occurring in ever younger patients. Restoration of normal facial appearance is of paramount importance, especially in patients who are still working and require normal social functioning in order to earn a living. Failure to do so results in economic loss not only for the patient, but for the economy as a whole.

The increasing demands on the health care system with an aging population have also resulted in an increasing focus on cost control. Skin cancer care, and cutaneous reconstruction can be safely and cost-effectively delivered in an outpatient setting allowing for maximization of precious health care resources. Even complex reconstructions can be reliably and safely performed in an outpatient setting. Provided that patient comfort can be assured, the vast majority of cutaneous defects can be reconstructed under local anesthesia.

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Disclosure

None reported. **MM**

SAINT LOUIS UNIVERSITY

Host Microbiota Contributes to Health and Response to Disease

by Rajeev Aurora, PhD & Thomas Sanford, MD

Microbiota is a non-heritable host factor that contributes to maintaining and restoring health by maintaining homeostasis (balance).



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Abstract

Recent studies have revealed that normal microbiota interacts with the host through four mechanisms: the normal microbiome acts as a barrier against pathogens; second, as modulators of the permeability of host mucosa; third, as modulators of energy extraction from, and metabolic utilization of ingested food; and lastly, as modulators of the immune system. An alteration of the normal microbiota increases predisposition of the host to diseases through these four mechanisms.

Introduction

The discovery of the human microbiota has broadened our understanding of germs. Infections by microbes, collectively termed germs (i.e. bacteria, fungi, viruses and helminthes), have been a persistent cause of morbidity and mortality in humans for thousands of years. Pasteur and others developed the Germ Theory over 150 years ago, which posits that eliminating germs eliminates disease. Germ Theory has contributed immensely to human health. For a thousand years prior to the construction of Germ Theory the average life expectancy had been 20 years or less. As a consequence of improved sanitation, hygiene and public health efforts to minimize the transmission of germs, life span doubled.[1] New culturing techniques were established to grow and identify pathogens. Development of methods to culture pathogens led to the development of new antibiotics and tests for sensitivity to antibiotics. In addition to culturing, development of staining and structural techniques identified a number of virulence factors, products made by a microbe that determines the degree of pathogenicity to the host.

More recently, organisms could be identified without culturing because of the advent of polymerase chain reaction (PCR) amplification and decreased cost of DNA sequencing. Culture independent identification has revealed communities of microbes colonize many anatomical surfaces, such as skin and mucosa (oral, respiratory, urogenital and gastrointestinal) of healthy individuals.[2] These results show that very few germs are harmful (i.e. pathogens), while the majority of microbes are neutral (commensals) and some are beneficial to the host (symbionts).

One shortcoming of Germ Theory is the inability to explain the variance of host response to infections. Typically, the risk of, and ability to survive, an infection has been attributed to host genetics. Surprisingly, recent research shows that the configuration and constituents of a host's normal germ flora

influences the risk for disease. An abnormal flora, called dysbiosis, can increase the risk of obesity and inflammatory diseases. Additionally, recent studies make a compelling argument for dysbiosis increasing risk of autoimmune and cognitive diseases. Thus, the unexpected finding that the normal flora plays a crucial role in maintaining health (homeostasis) has emerged. In this review, we analyze recent studies where an abnormal microbial flora promotes disease by four different mechanisms. We argue that an abnormal microbial flora appears to be a risk factor for disease. Moreover, the spectrum between a normal and abnormal microbial flora may contribute to disease risk as much as the genetics (allelic differences) in the population.



Figure 1: Structure of 16S ribosomal RNA gene in kingdom *Bacteria*. Primers in the conserved (green) regions are used to amplify segments of the gene and are subject to DNA sequencing. The sequence of the variable regions (V1 through 9) varies between species, but is nearly identical within species (and similar between related species, e.g. Staphylococcus aureus and S. epidermis). The sequence of the variable region is thus used to identify the organism present in the sample. Although, any variable region can be sequenced for identification, sequencing of V4 segment provides robust results.

Definitions, Nomenclature, and Methods for Measuring the Microbiota

Microbial communities exist within any given environment. The collection of microbes is referred to as the microbiota. The collective genomes of the microbiota are referred to as the microbiome. Such communities could not be identified previously because less than 1% (but 40 to 50% of pathogens) bacteria can be currently cultured. Shotgun sequencing of the microbiome is termed metagenomics. In some instances, it is desirable to simply identify the bacterial and fungal species (i.e. "who is present?"), rather than sequencing entire genomes. This is accomplished by amplification of the 16S ribosomal RNA (16S rRNA) gene. The 16S rRNA is an essential component of the small subunit of the ribosome that performs protein translation in bacteria. The 16S rRNA gene can be readily amplified because there are invariant blocks (See green segments in Figure 1) of sequences surrounding variable regions. Primers for PCR amplification designed for the invariant regions can amplify (nearly) all species in the kingdom *Bacteria*. The variable regions (See gray segments in Figure 1) vary between species but are conserved within a species, and thus the sequence can be used to identify the organism. Massively parallel sequencing (also called next generation sequencing) of the PCR amplicons is used to identify bacterial species and the number of times a sequence is observed is used to quantitate the amount of bacteria present, in any collected sample requiring no culturing.

Using these culture-independent techniques, investigators have shown that the skin, upper airway mucosal surfaces, the mouth, gums, tongue, the entire digestive and urogenital tract have a unique community of microbes at each anatomical site. The communities are dynamic and respond to non-physiological (e.g. infections, trauma and antibiotics) and physiological (e.g. pregnancy) changes in the host. For instance, the gut microbes change with age, fiber intake,[3] and the vaginal microbiome changes during pregnancy and with the gestational age of the fetus.[4-6] There are now several examples where changes in the microbiota lead to disease states. We review a few of these studies because they document that the microbiota plays an important role in nutrient uptake and utilization (conversion of food to usable calories for the host), in altering permeability of barriers that exist within the host and in altering the immune system.

The Microbiota Influences Energy Extraction and Utilization Leading to Obesity

The relationship between the gut microbiota and diet has been an area of interest for many years. For instance, it was noted in the 1960s that germ-free mice (referred to as Gnotobiotic mice, these mice are born by Cesarean section, then maintained under a sterile environment, including being fed autoclaved sterile food and water) require 30% more calories to maintain the same weight as their conventionally raised siblings.[7] Theses studies with mice suggested that efficient energy extraction from food requires a gut microflora. In the last decade, the role of gut microbiota in modulation of energy extraction in humans has been elucidated in the context of obesity and is described next.

Obesity is a multifactorial process that includes, but is not limited to, host genetics, environment, socioeconomic and dietary variables.[8,9] It is associated with a number of

comorbidities including fatty liver disease, cardiovascular disease, insulin resistance and diabetes. Within this complex set of interactions lies the microbiota. A number of recent reviews have discussed the role of the microbiota in obesity. [10-12] The hypothesis that the microbiota and obesity are correlated is supported by observations by Turnbaugh et al. which demonstrated that the microbiomes of lean and obese monozygotic twins were different.[13,14] Further, the obesity–associated microbiota could be transferred from human host to individual germ-free mice as well. Observations such as these have lead to studies that have uncovered potential pathways for the microbiota to support obesity. Such pathways include the breakdown of food to usable nutrients (e.g. plant starch to sugars), the release of metabolic products by bacteria that aid absorption of nutrients and the production of cofactors (e.g. vitamins B and K) that are needed by the host.

In addition to the bacterial metabolic products directly affecting the host metabolism, increased immune activity has been recognized in obesity and associated with the microbiota. Lipopolysaccharides (LPS) from gram-negative bacteria in the microbiota are found to increase in obesity. LPS activates host's immune system through Toll-like receptors on monocytes. Lean individuals have lower concentrations of LPS in the blood compared to obese individuals[15,16]. Furthermore, there is an association between elevated LPS and decreased insulin sensitivity.[15,16] These studies establish a fundamental link between obesity and insulin sensitivity through inflammation.

Endocrine functions have also been identified as a mechanism by which the gut microbiota can lead to obesity. Bacterial fermentation products can induce the secretion of hormone peptide YY and leptin, by signaling through G protein–coupled receptors (GPCR) which are present in the small intestine, colon and adipocytes. Changes in these hormones can affect caloric intake. As an example, genetically obese mice have distinct differences in the microbiota resulting in different leptin levels.[17] Together, these studies have established a number of mechanisms by which dysbiosis (directly or indirectly) leads to risk of obesity. These mechanisms include short chain fatty acid (SCFA) byproducts, inflammation, endocrine functions, endo-cannabinoid tone and bile acid production.

The Host Microbiota Acts as a Barrier or Deterrent for Pathogens

Clostridium difficile infection (CDI) is an example of how the intestinal microbiota acts as a barrier. Loss of a healthy microbiota leads to conditions that allow *C. difficile* to infect and to cause disease. In 1977, it was noted that CDI required previous antibiotic exposure of the patient.[18,19] Multiple studies in humans and mice have subsequently shown that antibiotics can have a profound and sometimes long standing effect on the gastrointestinal (GI) microbiota. These changes are produced by alterations in the metabolites from both GI enterocytes and the microbiota,[20,21] as well as by the overall structure of the microbiota.[22] The mechanisms by which antibiotics cause dysbiosis (abnormal microbiota) and subsequent CDI have been shown to include toll-like receptor (TLR) signaling, changes in T-helper 17 T-cells (T_H17), and changes in epithelial permeability.[23] Supporting the idea that changes in the microbiota lead to CDI is the compelling evidence that restoring the diversity of the microbiota by fecal transplantation can lead to resolution and resistance to CDI. Patients with CDI can eliminate *C. difficile* after transplantation of healthy microbiota[24]. Studies are currently evolving to define how healthy microbiota from different individuals with considerable variability can have the same result of resolution of CDI. It is possible that fecal transplant may support the growth of suppressed indigenous microbiota leading to CDI resolution and resistance[22].

The Gut Microbiota Can Influence Mucosal Barrier Permeability

All biological systems are organized into smaller subsystems. For example, the human body anatomically consists of five critical subsystems or organs, viz. heart, lungs, liver, kidneys and brain. Indeed, there are over 60 organs. Each of these anatomical subsystems are separated or compartmentalized by a barrier, connected by lymphatic and circulatory subsystem. Flow of materials across the barrier is highly regulated. For instance, ingested food is broken down and digested in the stomach and some of the resulting nutrients are absorbed in the stomach and intestines to be used by the rest of the body. It has become evident that species within the gut microbiota not only play an important role in metabolizing the ingested food but some of the resident bacteria, directly or through the immune system, regulate the permeability of the gut mucosa to determine the absorption of the nutrients. Additionally, species within the microbiota encode for a number of enzymes, whose products alter gut permeability. For example, production of histamine via microbial encoded histidine decarboxylase increases mucosal permeability.[25] Altering the permeability not only affects that transfer of nutrients and bacterial metabolites, but also affects the immune system. A rather spectacular example of how gut

dysbiosis can affect the central nervous system, across several barriers, is in autism spectrum disorders (ASD).

ASD is a disease of unknown origin but it has been linked to several triggers including pre- or post natal exposure to chemicals and drugs, air pollutants, maternal infection, stress and dietary factors.[26] Several comorbidities have also been associated with ASD including gastrointestinal distress.[27] Studies in both murine and human systems have defined potential pathways that connect ASD to changes in the microbiota of the gut. Mouse strains that have symptoms of ASD behavior have been shown to have gut barrier functional defects and dysbiosis.[28] In one study the authors showed that providing *Bacteriodes fragillis* to the microbiota of these same mice early in development reduced autism behavior. This same study implicated microbiota produced metabolic products such as 4-ethylphenylsulfate were directly linked to symptoms of ASD in mice.[28] Pregnant mice treated with valproic acid, a compound shown to change the murine gut microbiota, resulted in ASD phenotypes in offspring.[29,30] Gnotobiotic mice have reduced sociability, social cognition deficits and repetitive grooming, similar to behaviors observed in ASD. These symptoms can be at least partially reversed by colonization of the germ free mice.[31]

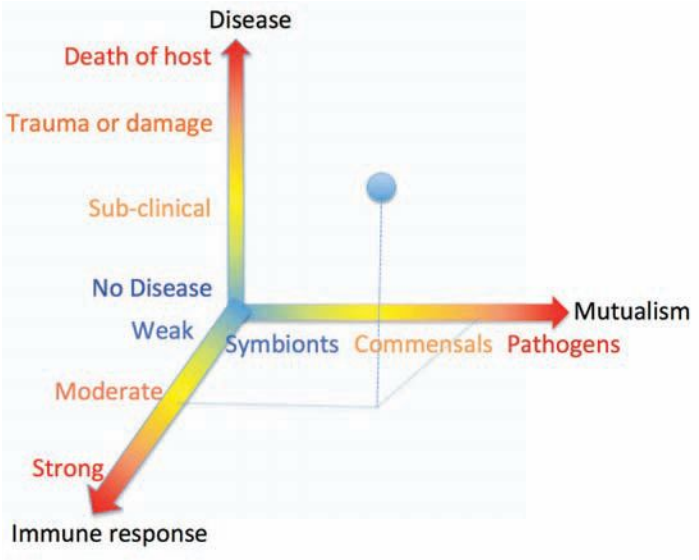


Figure 2: The relationship between germs, immune response and disease: Germs (viruses, bacteria, fungi, helminthes) are shown as a spectrum of mutualism: on one end of the spectrum are the symbionts (in blue) and one the other extreme, the pathogens (red). Pathogens can be more or less pathogenic. Between the two extremes (in yellow) of the spectrum are commensals, which are neither beneficial nor harmful. The other axis depicted at the bottom is the host immune response, which maintains the normal flora and responds to pathogens. The vertical axis depicts the disease states, which can vary from healthy (no disease) to death of host. A healthy immune response to a moderate pathogen (shown by dashed lines) can eliminate the pathogen or lead to subclinical disease (shown as blue dot). This representation also shows that an aberrant immune response to commensals (or self antigens) can also lead to chronic inflammation and disease.

In human studies, children with ASD have a distinct and less diverse gut microbiota and gut community structure.[32] In one study, children with ASD were found to have lower levels of the species *Bifidobacterium* and higher levels of *Lactobacillus* leading to change in the metabolites acetate, propionate and valerate.[33] Another set of studies have shown changes in metabolites, LPS and potential neuromodulating compounds such as IL-6 in ASD patients.[34] IL-6 has been shown to increase permeability of the blood brain barrier and LPS has been linked to an increase in GI permeability. Interestingly, children with ASD treated with antibiotics directed against bacteria that produce LPS resulted in improvement of some of their cognitive skills.[35] Taken together the above examples indicate that the gut microbiota contributes to the development of ASD by affecting the barrier permeability of the gut and possibly the blood-brain barrier.

Direct Link Between Microbiota and the Host Immune System

The host immune system regulates the constituents and the abundance of the microbiota through a number of mechanisms. First, epithelial cells produce a number of anti-microbial proteins (AMP). These peptides belong in three families: the defensins, cathelicidins, and histamins[30]. Second, IgA secreted by B-cells or plasma cells shapes the abundance of the microbes.[31, 32] T-cells, like B-cells are part of the adaptive immune system, are educated during early development to recognize self-antigens. Similarly, exposure to bacterial and viral antigens during early development leads to education of the adaptive immune system. As a consequence, the immune system does not respond to these organisms. Moreover, these bacterial antigens are needed for the development of a normal immune system as is evident in germ-free mice.[36] The commensal gut microbes produce low-level activation of both the innate and adaptive immune system.[37] This low-level activation sets the threshold that must be exceeded to produce an appropriate immune response to pathogens. Perhaps simplistically, in the absence of a normal microbiome the activation of the immune system is set to a too low threshold, and consequently the immune system is hyper-responsive.

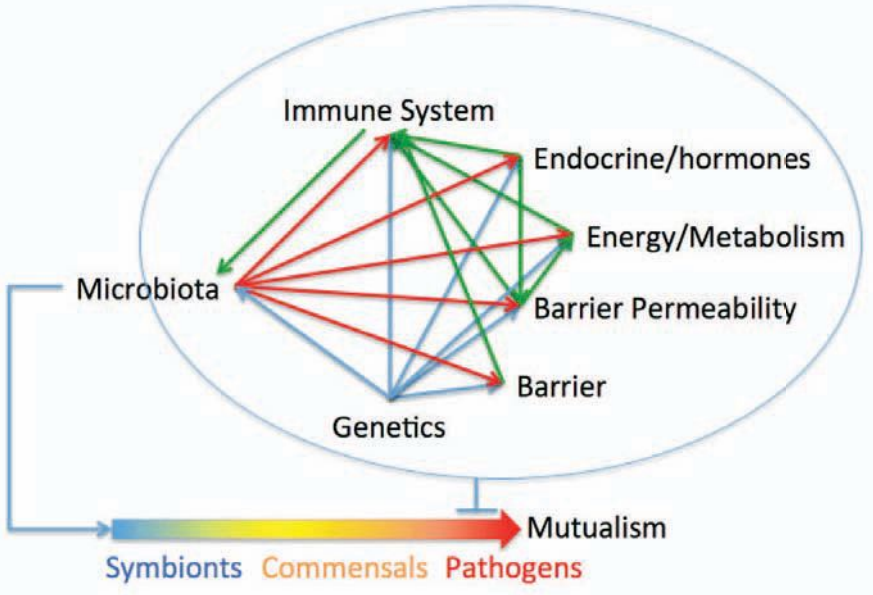


Figure 3: Interactions between the microbiome and amongst the host subsystems that may account for variability in response to pathogens. The response of different individuals to pathogens can vary from being resistant, to asymptomatic carriers, to completely sensitive. Host genetics only partially account for this variability. Additional non-heritable influences such as prior exposure to related pathogens and nutritional status of the host could also factor into the response. We argue that the microbiota, because it influences the host health status, also influences the health of the host. Thus, dysbioses is a host risk factor that determines susceptibility to pathogens such as C. difficile infections, and to obesity and autism. The crosstalk between the subsystems provides robustness and maintains health. The crosstalk provides robustness because other subsystems can compensate for the transient loss of one subsystem. The contribution of genetics is shown by blue lines, physiological interactions are shown in green and the influence of microbiota is shown in red.

Correspondingly, epidemiological evidence over the last three decades indicates that changes in the microbiota can alter the risk factors for allergies, autoimmune and other inflammatory diseases.[38] These epidemiological studies parallel the so-called hygiene hypothesis[39-41] further supports the important role of the normal microbiome in maintaining homeostasis of the immune system.

Interactions Between These "Host-Factors"

As we have documented above, the normal microbiome affects the host through a number of mechanisms. The main four mechanisms are: first, by modulating calorie extraction from the diet and nutrient utilization; second, by acting as a deterrent to pathogen colonization; third, by modulating the immune response; and finally, and by modulating barrier permeability directly through secretion of chemical mediators and indirectly through the immune system. Moreover, there is considerable crosstalk between the immune system and barriers and metabolism, which are in turn influenced by genetics and the environment (See Figure 3). The crosstalk increases the complexity of the system in the sense that we must understand each subsystem (e.g. how an immune response is regulated; See Figure 2), but also in the sense that risk or benefit cannot be assigned to any one factor or component (e.g. how effective the immune response is). This crosstalk evolved to increase the overall robustness of the system because transient loss or decrease in function in one subsystem can be compensated for by the other subsystems.

Conclusion

We began this review by pointing out the strengths and shortcomings of Germ Theory. The strength of Germ Theory is that it produced an increased awareness of pathogens that led to some relatively simple solutions like sewers, clean water sources, and improved hygiene to prevent the spread of these pathogens. The primary shortcoming of Germ Theory has been that it cannot readily explain the variation in host response (e.g. why some individuals are asymptomatic carriers and others succumb to the infections). Conventionally, it has been argued that host genetics (heritable alleles) are in large part responsible for this variation. However, emerging data indicates that epigenetics and environmental factors that are non-heritable contribute significantly. The variation occurs through both heritable and non-heritable factors. We propose that the normal (healthy) microbiota composition, although influenced by genetic factors is a non-heritable component that contributes critically to preventing disease in three significant ways: first, it contributes to setting thresholds of the immune response. As we note above, a weak or overly strong response is harmful to the host because it causes damage. Second, the microbiota forms a barrier by competing for nutrients and space in the host, and further by altering the permeability of mucosa, which prevents pathogens from colonizing, crossing the mucosa and dissemination. Third, the microbiota modulates the extraction and utilization of energy and nutrients from

food consumed. As undernourished and overnourished hosts have hypo- or hyper-responsive immune activation respectively, the healthy microbiota contributes to response to a pathogen. Together, these factors contribute to the ability of the host to fight pathogens and to recover from pathogens. Thus, the microbiota is a non-heritable host factor that contributes to maintaining and restoring health by maintaining homeostasis (balance). Given that different populations of patients could have different and unique microbiota, it is interesting to consider how the measurements of microbiota will be incorporated into the practice of precision medicine in the future.

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Disclosure

None reported. **MM**

Missouri Community, Public Health, and Primary Care Linkage

2011-2012 Pilot Project Results & Evaluation

by Shumei Yun, MD, Ellen Ehrhardt, MS, Lisa Britt, BS, Barbara Brendel, Janet Wilson, MPA, Anita Berwanger, LD

The project helped a good number of participants gain control of their high blood pressure, and improvements are needed to make the intervention more effective.



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Abstract

This pilot project worked to establish linkages among community-based organizations, health care providers, and public health systems. The partnerships were created to help ensure identification, referral, and follow-up for community members with uncontrolled high blood pressure or pre-hypertension to lay the groundwork for sustainable referral and health education support systems in rural communities. The evaluation shows the project helped some participants control their blood pressure and change their blood pressure management behaviors.

Introduction

About 2.23 million of over six million Missouri residents live in rural areas of the state. Rural Missourians as a whole have lower levels of income, education, and access to health care, as well as a higher prevalence of risk behaviors that lead to adverse health status and decreased life expectancy.

Cardiovascular disease is the number one killer among rural residents in Missouri, similar to the rest of the state. However, the age-adjusted heart disease and stroke death rates were significantly higher among rural residents than among urban residents. Among rural residents, the prevalence of cardiovascular disease risk factors is higher than that among urban residents. For example, in 2011, a higher percentage of rural residents were obese (32.2% in rural vs 28.9% in urban) and had high blood pressure (37.4% in rural vs 32.6% in urban) than urban residents. A higher percentage of rural residents than urban residents were also current smokers (24.6% in rural vs 21.6% in urban) and had not engaged in any leisure-time physical activity in past 30 days (26.4% in rural vs 22.0% in urban).[1]

To reduce the urban and rural gap in cardiovascular disease risk, the Missouri Heart Disease and Stroke Prevention Program (HDSP) collaborated with 10 county health departments in 2011-2012 to establish linkages among community-based organizations, health care providers, and public health systems. The partnerships were created to help ensure identification, referral, and follow-up for community members with uncontrolled high blood pressure or pre-hypertension to lay the groundwork for sustainable referral and health education support systems in the communities.

The objective of this study is to evaluate the effectiveness of the project in helping community members modify their behaviors and improve their high blood pressure management and control. The Missouri Department of Health and Senior Services Institutional Review Board reviewed and approved the project.

Methods

Project Description

Ten county health departments were selected to participate in the project based on their proven track records in working with community partners, some pre-established relationships with the health care community and serving low income rural communities. In addition, they had existing health educators or registered nurses who are knowledgeable about high blood pressure to carry out the intervention, and therefore no additional training was necessary. The 10 county health departments participating in the project were Ozark, Reynolds, Texas, Pemiscot, McDonald, Douglas, Carter, Oregon, Dunklin, and Newton.

For the intervention, each county health department established partnerships with community-based organizations to help the members control blood pressure. The health educator or registered nurse from the county health department went to the community-based organizations to provide group education for the organizations' members about the cause, classification, prevention and management of high blood pressure. Blood pressure was measured during education sessions. Participants with pre-hypertension and uncontrolled HBP were referred to partnering health care providers for medical care and invited to participate in the follow-up intervention. Informed consent was obtained from each participant for completing an initial (pre-) and a final (post-) questionnaire and to allow the health educator or nurse to contact them periodically to provide education and support for up to one year. The health educator or nurse contacted participants periodically to provide lifestyle education, identify barriers to high blood pressure control, and assist participants with overcoming barriers. These services were provided at no cost to participants. However, the cost of physician care and medications were not covered by this project. Participants had to use whatever resources were available to them to pay for their medical care and medications.

Data Collection and Analysis

Data were collected using several instruments including the attendance sheet, presentation planning form, pre- and post-questionnaires, and the follow-up documentation form. Information on the program operation was collected through monthly reports, quarterly conference calls, and periodic site visits.

The pre- and post-survey data and other data were entered into an Excel spreadsheet and analyzed using SAS. For 121 participants who completed both pre- and post-questionnaires, the percentage of participants with different risk behaviors (e.g. smoking, physical inactivity), blood pressure management behaviors (e.g. taking medication, seeing doctors, changing diets), and blood pressure status were calculated and compared before and after the intervention. Chi-square test was used to determine if the post-intervention change was statistically significant.

External Comparison Group

Because it was not feasible to have a control group, we compared the percentage of blood pressure control among participants of this project with that among Missouri WISEWOMEN Program participants.[2] The Well-Integrated Screening and Evaluation for Women Across the Nation (WISEWOMAN) Program is supported by CDC and designed to reduce the risk of heart disease and stroke among low-income, underinsured, or uninsured women through clinical screenings, risk factor assessment, and lifestyle interventions. During June 30, 2005 through June 29, 2012, 515 women with high blood pressure were enrolled in the Missouri WISEWOMAN Program. After participating in the program for 11 to 18 months, 41.2% of these participants gained control their blood pressure.[2]

Results

Program Reach and Socio-Demographic Characteristics of Participants

A total of 287 education sessions were held in 199 community organizations in which 4405 community members attended, 815 attendees (18.5%) were referred for medical care, and 243 (5.5%) were recruited to participate in the follow-up interventions. All 243 participants completed the pre-questionnaire, and 121 participants completed both pre- and post-intervention questionnaires. Those who completed both the pre- and post- questionnaires were similar to those who only completed the pre-questionnaire in terms of age, sex and weight status. However, those who completed both questionnaires were more likely to be white, college graduates, and with household incomes of $15,000 or more than those who only completed the pre-questionnaire (See Table 1).

Duration of Follow-up and Documentation

Participants were followed up for various lengths of time. Among 121 participants who completed both pre- and post-intervention questionnaires, 23 (19%) were followed for six months or more, 70 (58%) were followed for one to six months, 28 (23%) were followed for less than one month or had no follow-up information. Intervention intensity varied across counties. In some counties, health educators met participants monthly, while in other sites they only met once during the entire follow-up period. The level of detail in documentation of the follow-up education and problem-solving varied across sites. While a few counties kept very detailed documentation, records kept in other counties were sketchy.

Table 1
Characteristics of project participants

Characteristic	Participants completed pre-and post- questionnaires	Percent	All participants	Percent
Number of Participants	121	100	243	100
Age				
<25	3	2.5	10	4.1
25-34	10	8.3	22	9.0
35-44	19	15.7	41	16.9
45-54	23	19.0	49	20.2
55-64	28	23.1	59	24.3
65+	30	24.8	54	22.2
unknown	8	6.6	8	3.3
Gender				
Male	41	33.9	75	30.9
Female	80	66.1	168	69.1
Race and Ethnicity				
White	109	90.1	210	86.4
African American	3	2.5	21	8.6
Hispanic	1	0.8	2	0.8
unknown, other	9	7.4	12	4.9
Education				
No High School		0.0	11	4.5
Some High School	10	8.3	16	6.6
High School	39	32.2	96	39.5
Some College or Technical	25	23.1	52	21.4
College degree	40	33.0	54	22.2
unknown	7	5.8	14	5.8
Income				
< $15,000	17	14.0	72	29.6
$15,000 -$35,000	26	21.5	27	11.1
$ 35,000 +	33	27.3	61	25.1
unknown	45	37.2	83	34.1
Medical Insurance				
Yes	87	71.9	171	70.4
No	19	15.7	47	19.3
unknown	15	12.4	25	10.3
Weight Status				
Underweight	6	4.9	5	2.0
Normal	20	16.5	53	21.8
Overweight	37	30.6	72	29.6
Obese	48	39.7	101	41.6
unknown	10	8.3	12	4.0

Self-reported and Measured Blood Pressure during Education Sessions

Among 121 participants, 53 (43.8%) self-reported that they had previously been told they had high blood pressure on two or more occasions by health care professionals, 20 (16.5%) reported they had been told on only one occasion, and 13 (10.7%) reported they had been told they had pre-hypertension (See Table 2). The blood pressure measured during the education sessions showed that 18 of the 121 participants (14.9%) had stage II hypertension (BP≥ 160/100), 44 (36.4%) had stage I hypertension (140/90≤ BP<159/99), and 45 (37.2%) had blood pressure within pre-hypertension range (120/80≤ BP<139/89), of which 30 had been diagnosed as having hypertension before (See Table 2) .

Blood Pressure Management Behavior and Life-style Changes after the Intervention

Among 121 participants who completed both pre- and post-intervention questionnaires, 43.0% (52 people) reported they were taking HBP medication all the time or most of the time before the intervention. After the intervention, the proportion increased significantly to 57.9% (70 people), a net increase of 14.9% (18 people, p=0.020) (Table 2). Similarly, the number of participants who were seeing doctors for high blood pressure increased significantly from 41.3% pre-intervention to 62.8% post-intervention, a net increase of 21.5% (p=0.002). The percentage of participants who reported they were trying to change behaviors to control their blood pressure also increased significantly after the intervention. The participants who prepared more meals at home increased from 33.9% to 57.0% (p<0.001), participants trying to reduce salt intake increased from 38.8% to 57.0% (p=0.005), participants trying to maintain weight increased from 14.0% to 31.4% (p=0.001), and participants trying to eat more fruits and vegetables increased from 33.8 to 55.4% (p=0.010). In terms of physical activity, seven additional participants (an increase of 5.8%, p=0.481) were engaging in leisure-time physical activity, and among those who were engaging in leisure-time physical activity, seven additional participants were physically active five or more times per week (p=0.020) (Table 2). Smoking status and frequency of eating high sodium foods did not change after the intervention.

Blood Pressure Change after the Intervention

Among 107 participants from whom both pre- and post-intervention blood pressure data were collected, 62 had stage I or II hypertension, and 45 had blood pressure between 120/80 and 139/89, having either controlled high blood pressure or pre-hypertension before the intervention (See Table 3). Among the 62 participants with hypertension before the intervention, 40 (62.5%) gained control at the end of the intervention, compared to 41.2% among the Missouri WISEWOMAN Program participants. Among the 45 participants with pre-hypertension, 10 (22.2%) became normal, 9 (20.0%) deteriorated to stage I and 3 (6.7%) changed to stage II hypertension. The net increase in the number of controlled or normal blood pressure among 107 participants was 38 (35.5%) (Table 3).

Barriers for Care and Management of High Blood Pressure

Seventy-four participants reported barriers to caring for their HBP in the pre-intervention questionnaire. The most frequently reported barriers to seeing their health care provider or taking their medication to control HBP were the cost of medicine (42%), lack of medical insurance (37%), side-effects of the medication (17%), lack of time (6%), the cost of doctor (4%), falling out of habit or forgetting (4%), and lack of transportation to clinic or pharmacy (4%).

Discussion

Cardiovascular disease is the number one killer in Missouri.[3] Hypertension is one of the major risk factors for cardiovascular disease. Therefore prevention and control of blood pressure is very important for reducing cardiovascular events and associated health care costs.[4]

In this project, health educators linked community organizations and clinics, and provided health education and follow-up counseling to community members. The evaluation data show that the intervention is effective in changing high blood pressure care and management behaviors and lifestyle factors. Following the intervention, an increased number of participants visited doctors and took medications to control their blood pressure. More participants were motivated and intended to increase physical activity and eat a healthier diet for blood pressure control. In addition, more people gained control of their blood pressure.

Based on the data from 107 participants from whom both pre- and post-intervention blood pressure data were collected, 38 (35.5%) additional participants gained control of their high blood pressure or changed from pre-hypertension to normal blood pressure. If we assume the intervention had the same effect on all 243 participants, then 86 participants would have gained control at the end of the intervention period. However, 86 may be a high estimate because we know those from whom both pre-and post-intervention blood pressure data were collected tended to have a higher level of education and household income, and a longer duration of follow-up than those participants with only pre-intervention data. Therefore, it would be reasonable to project that the intervention may have helped between 38 and 86 participants either gain control of high blood pressure or return to normal blood pressure from pre-hypertension.

Table 2
Blood pressure and behavior changes after intervention among participants who completed pre- and post-intervention questionnaires.

	Pre N=121		Post N=121		Difference Post-Pre		Chi-squared Test
	n	percent	n	percent	n	percent	p value
Self-report blood pressure							
Ever been told having HBP on 2+ occasions	53	43.8	-	-	-	-	-
Ever been told having HBP on one occasions	20	16.5	-	-	-	-	-
Ever been told having pre-hypertension	13	10.7	-	-	-	-	-
Normal BP or HBP only during pregnancy	0	0.0	-	-	-	-	-
No answer	35	28.9					
Measured blood pressure							
<120/80	0	0.0	18	14.9	18	14.9	
120/80 – 139/89	45	37.2	55	45.5	10	8.3	
140/90 – 159/99	44	36.4	19	15.7	-25	-20.7	p<0.001
160/100 or greater	18	14.9	15	12.4	-3	-2.5	
Unknown	1	0.8	13	10.7	12	9.9	
Taking HBP medication							
All or most of the time	52	43.0	70	57.9	18	14.9	
Only occasionally	5	4.1	4	3.3	-1	-0.8	P=0.020
Not on medication	61	50.4	45	37.2	-16	-13.2	
No answer	2	1.7	2	1.7	0	0.0	
Seeing doctor for HBP							
Yes	50	41.3	76	62.8	26	21.5	P=0.002
No	66	54.5	45	37.2	-21	-17.4	
No answer	5	4.1	0	0.0	5	4.1	
Changing behavior to control HBP (multiple choices)							
Preparing more meals at home	41	33.9	69	57.0	28	23.1	P<0.001
Reducing salt	47	38.8	69	57.0	22	18.2	P=0.005
Reducing alcohol	6	5.0	9	7.4	3	2.5	P=0.424
Exercising	46	38.0	54	44.6	8	6.6	P=0.296
Eating more fruit and vegetables	47	38.8	67	55.4	20	16.5	P=0.010
Taking medication as prescribed	37	30.6	59	48.8	22	18.2	p<0.004
Trying to lose weight	45	37.2	53	43.8	8	6.6	P=0.295
Trying to maintain weight	17	14.0	38	31.4	21	17.4	P=0.001
Trying to quit smoking	8	6.6	11	9.1	3	2.5	P=0.473
No answer	27	22.3	10	8.3	-17	-14.0	
Total number of changes	294	-	429	-	135	-	
Smoking Cigarettes							
Every day	17	14.0	16	13.2	-1	-0.8	
Some days	4	3.3	5	4.1	1	0.8	P=0.931
Not at all	98	81.0	99	81.8	1	0.8	
No answer	2	1.7	1	0.8	-1	-0.8	
Leisure-time physical activity							
Yes	78	64.5	85	70.2	7	5.8	P=0.481
No	36	29.8	32	26.4	-4	-3.3	
No answer	7	5.8	4	3.3	-3	-2.5	
Physical activity among those with leisure-time physical activity							
5 or more times per week	21	26.9	28	32.9	7	-	P=0.020
Less than 5 times a week	41	52.6	52	61.2	11	-	
Unknown frequency	16	20.5	5	5.9	-11	-	
Total	78	-	85	-	7	-	

Table 3
Blood pressure among project participants who completed both pre- and post-intervention questionnaires and with known initial and final blood pressure data.

Initial Blood Pressure	*Number of participants*	*Final Blood pressure*			
		<120/80	120/80 – 139/89	140/90 – 159/99	160/100 or greater
120/80 – 139/89	45	10	23	9	3
140/90 – 159/99	44	7	26	4	7
160/100 or greater	18	1	6	6	5
Total	107	18	55	19	15

The overall annual cost of the project, including project management and evaluation, was approximately $300,000. Of the $300,000, about $50,000 covered partial salaries and benefits of the DHSS project manager and program evaluator and the remainder was awarded to the LPHAs to support salaries and benefits of the health educators and nurse practitioners.

Therefore, we estimate on average the cost of gaining control of blood pressure was between $3,488 and $7,895 per person. In addition to helping the follow-up participants gain control of their blood pressure, the project provided education to more than 4,000 community members and referrals to more than 800. There were several limitations in the implementation and evaluation of this pilot project that may have affected the results. The health educators and nurses involved in the project were required to conduct project activities in addition to their regular responsibilities. Therefore, the time that some were able to devote to the project was limited. Staff turnover was quite frequent, which impacted the county health departments' ability to complete project activities and data collections as specified in the contract. In addition, there was no concurrent comparison group. Therefore, determining whether the improvement was completely a result of the project is not possible. However, we believe the program was at least partially responsible for the findings.

Although the project helped a good number of participants gain control of their high blood pressure, improvements are needed to make the intervention more effective. First, the change in smoking behavior is limited. Second, although the project helped many participants with stage I and stage II hypertension gain control, a high proportion (12 out of 45) with pre-hypertension range blood pressure deteriorated to stage I or stage II hypertension, which shows additional efforts are needed to address behavior change. Third, this project is limited to high blood pressure prevention and control. In the future, other chronic diseases and conditions should be included in the intervention because of interconnectedness among chronic diseases. Finally, although the most frequently reported barrier to taking medication to control HBP was the cost of medicine (42%), no effort was made to collect information on the types and costs of medications prescribed. In the future, the information should be collected to better understand and help participants overcome cost barriers.

We are aware of only one similar project that has been conducted in resource-limited rural communities. The Community Health Educator Referral Liaison Project conducted in one rural and two urban/suburban communities in Michigan showed that the community health educator referral liaisons helped patients reduce risky health behaviors (e.g., drinking, smoking, physical inactivity) by linking them with community resources, offering counseling and encouragement over the telephone, and providing feedback to referring physicians.[5]

Conclusions

The pilot project helped some participants control their high blood pressure and change their blood pressure management behaviors. It looks like a promising approach if we include other chronic diseases in the intervention and improve local capacities in chronic disease prevention and control.

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